

Functional imaging beyond anatomy: The emerging role of magnetic resonance spectroscopy and metabolic biomarkers in monitoring targeted cancer therapy

Hao Sun¹, Xiaojun Dong², Jinze Yu³, Yuanyin Teng⁴, Gaoyang Guo⁵, Liangyu Li⁵, Wei Wang⁶, Bing Liu⁷, Yuquan Li⁸ & Keyang Xu⁹

¹ ZJU-Xinchang Joint Innovation Centre (TianMu Laboratory), Gaochang Hi-Tech Park, Xinchang 312500, China; College of Animal Sciences, Zhejiang University, Hangzhou 310058, China; Wolfson Institute for Biomedical Research, Division of Medicine, University College London, Gower St, WC1E 6BT, London, United Kingdom

² Hunan Provincial Key Laboratory of Novel Antibody Drugs and Their Intelligent Transportation Systems, Hunan Provincial Key Laboratory of Synthetic Biology Research of Traditional Chinese Medicines, School of Medical Information and Engineering, Hunan University of Medicine, Huaihua, China

³ Computer Science and Communication Engineering, Global Center for Science and Engineering, Faculty of Science, Waseda University, Tokyo, Japan

⁴ Institute of Hematology, Zhejiang University, Hangzhou 310003, China

⁵ Faculty of Information Science and Technology (FTSM), Universiti Kebangsaan Malaysia (UKM), 43600 UKM Bangi, Selangor, Malaysia

⁶ Center for Precision Health, School of Medical and Health Science, Edith Cowan University, Perth, WA, 6027, Australia; The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, 515041, China

⁷ College of Animal Sciences, Zhejiang University, Hangzhou 310058, China; ZJU-Xinchang Joint Innovation Centre (TianMu Laboratory), Gaochuang Hi-Tech Park, Xinchang 312500, China

⁸ State Key Laboratory of Public Big Data, College of Computer Science and Technology, Guizhou University, Guizhou, China

⁹ Faculty of Chinese Medicine, State Key Laboratory of Mechanism and Quality of Chinese Medicine, Macau University of Science and Technology, Macau, China

Correspondence: Hao Sun, ZJU-Xinchang Joint Innovation Centre (TianMu Laboratory), Gaochang Hi-Tech Park, Xinchang 312500, China; College of Animal Sciences, Zhejiang University, Hangzhou 310058, China; Wolfson Institute for Biomedical Research, Division of Medicine, University College London, Gower St, WC1E 6BT, London, United Kingdom. E-mail: hao.sun@ucl.ac.uk

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Abstract

Anatomical imaging — measurements of tumour size on computed tomography or conventional magnetic resonance imaging (MRI) — remains the backbone of oncologic response assessment, yet it is structurally blind to the earliest events of treatment action. Targeted anticancer agents, by definition, act on specific molecular pathways whose blockade alters tumour metabolism within hours to days, long before any measurable change in tumour dimensions. Magnetic resonance spectroscopy (MRS) and spectroscopic imaging (MRSI) are uniquely positioned to capture these pharmacodynamic events non-invasively, repeatedly and without ionising radiation, by quantifying endogenous metabolites that report on membrane phospholipid turnover (total choline, phosphomonoesters), aerobic glycolysis (lactate), neuronal and tissue integrity (N-acetylaspartate, citrate), oncometabolite production (2-hydroxyglutarate in IDH-mutant glioma) and, with hyperpolarised ¹³C and deuterium (2H) tracers, real-time metabolic fluxes. This review synthesises the principles, biomarker repertoire and clinical evidence for MRS-based monitoring of targeted cancer therapy across glioma, breast, prostate and

abdominal malignancies; examines how metabolic readouts document on-target pathway modulation for kinase, PI3K/AKT/mTOR, IDH, antiangiogenic and endocrine agents; surveys the maturing technologies of hyperpolarised ^{13}C MRSI and deuterium metabolic imaging; and discusses the integration of MRS with multiparametric MRI, artificial intelligence and nanotheranostic drug development. We argue that the field is transitioning from proof-of-principle pharmacodynamic studies toward standardised, biomarker-guided adaptive therapy, and that the principal barriers — technical harmonisation, quantification standards and prospective validation — are now well defined and addressable. Functional imaging beyond anatomy, anchored in MRS-detectable metabolic biomarkers, offers a practical route to earlier response assessment, reduced exposure to ineffective therapy and more informative oncology drug development.

Keywords: magnetic resonance spectroscopy, metabolic biomarkers, targeted cancer therapy, hyperpolarized ^{13}C MRI, deuterium metabolic imaging.

Imagem funcional além da anatomia: O papel emergente da espectroscopia por ressonância magnética e dos biomarcadores metabólicos no monitoramento da terapia direcionada contra o câncer

Resumo

A imagem anatômica — baseada na mensuração do tamanho tumoral por tomografia computadorizada ou por ressonância magnética (RM) convencional — permanece como o principal pilar da avaliação da resposta oncológica, mas é estruturalmente incapaz de detectar os eventos mais precoces da ação terapêutica. Os agentes antineoplásicos direcionados, por definição, atuam sobre vias moleculares específicas, cujo bloqueio altera o metabolismo tumoral em questão de horas a dias, muito antes que qualquer mudança mensurável nas dimensões do tumor possa ser observada. A espectroscopia por ressonância magnética (MRS) e a espectroscopia por imagem (MRSI) estão particularmente bem posicionadas para capturar esses eventos farmacodinâmicos de forma não invasiva, repetida e sem radiação ionizante, por meio da quantificação de metabólitos endógenos que informam sobre o metabolismo dos fosfolipídios de membrana (colina total, fosfomonoésteres), a glicólise aeróbica (lactato), a integridade neuronal e tecidual (N-acetilaspártato, citrato), a produção de oncometabólitos (2-hidroxi-glutarato em gliomas com mutação em IDH) e, com o uso de traçadores hiperpolarizados de ^{13}C e deutério (2H), os fluxos metabólicos em tempo real. Esta revisão sintetiza os princípios, o repertório de biomarcadores e as evidências clínicas relacionadas ao monitoramento, baseado em MRS, da terapia direcionada contra o câncer em gliomas, neoplasias de mama, próstata e tumores abdominais; examina como as leituras metabólicas documentam a modulação de vias-alvo por agentes inibidores de quinases, PI3K/AKT/mTOR, IDH, antiangiogênicos e endócrinos; apresenta as tecnologias em amadurecimento de MRSI com ^{13}C hiperpolarizado e de imagem metabólica com deutério; e discute a integração da MRS com a RM multiparamétrica, a inteligência artificial e o desenvolvimento de fármacos nanoteranósticos. Argumentamos que o campo está passando de estudos farmacodinâmicos de prova de conceito para uma terapia adaptativa padronizada e orientada por biomarcadores, e que as principais barreiras — harmonização técnica, padronização da quantificação e validação prospectiva — estão agora bem definidas e podem ser enfrentadas. A imagem funcional além da anatomia, fundamentada em biomarcadores metabólicos detectáveis por MRS, oferece uma estratégia prática para uma avaliação mais precoce da resposta, menor exposição a terapias ineficazes e um desenvolvimento mais informativo de novos tratamentos oncológicos.

Palavras-chave: espectroscopia por ressonância magnética, biomarcadores metabólicos, terapia direcionada contra o câncer, RM com ^{13}C hiperpolarizado, imagem metabólica com deutério.

1. Introduction

The evaluation of cancer therapy has historically been an exercise in morphometry. From the World Health Organization criteria through RECIST 1.1, response has been defined by the shrinkage of measurable lesions — an approach that served cytotoxic chemotherapy reasonably well but fits the modern therapeutic era poorly (Glunde; Bhujwalla, 2011; Kauppinen; Peet, 2011). Targeted agents — tyrosine kinase inhibitors, pathway-selective small molecules, monoclonal antibodies, antibody–drug conjugates and endocrine therapies — are frequently cytostatic rather than cytoreductive: they may arrest tumour growth, induce metabolic quiescence or trigger differentiation without producing early volume change, and their clinical benefit is measured in progression-free survival rather than in rapid regression (Serrao; Brindle, 2016; Woitek; Gallagher,

2021).

The consequence is a temporal blind spot of weeks to months during which clinicians cannot distinguish response from resistance, patients may be exposed to ineffective and toxic therapy, and clinical trials must wait for anatomical endpoints that arrive long after the pharmacology has already declared itself (Day et al., 2007; Kashif et al., 2024).

Metabolism offers a way out of this blind spot. Malignant transformation rewires cellular metabolism — aerobic glycolysis (the Warburg effect), accelerated membrane phospholipid synthesis, glutamine addiction and, in genetically defined subsets, production of oncometabolites such as 2-hydroxyglutarate (2-HG) (Glunde; Bhujwala, 2011; Lodi; Ronen, 2011). Because targeted therapies act directly on the signalling nodes that drive these metabolic programmes — receptor tyrosine kinases, PI3K/AKT/mTOR, RAF/MEK/ERK, mutant IDH — pathway inhibition produces rapid, pathway-specific metabolic consequences (Liu et al., 2024; Ward et al., 2010). A metabolic readout is therefore, in principle, the most proximal pharmacodynamic biomarker of targeted drug action short of invasive tissue sampling (Andronesi et al., 2018; Day et al., 2007).

Magnetic resonance spectroscopy is the only modality that can quantify a repertoire of such metabolites in vivo, non-invasively, repeatedly and without radiation exposure (Andronesi et al., 2018; Kauppinen; Peet, 2011). Single-voxel ^1H -MRS and multivoxel MR spectroscopic imaging (MRSI) detect choline-containing compounds, creatine, N-acetylaspartate (NAA), lactate, mobile lipids, citrate, glycine and 2-HG; ^{31}P -MRS reports on phosphomonoesters, phosphodiesteres, inorganic phosphate and intracellular pH; and tracer-based methods — hyperpolarised ^{13}C MRSI and deuterium metabolic imaging (DMI) — now measure metabolic flux through glycolysis and the tricarboxylic acid cycle in real time (De Feyter et al., 2018; Kashif et al., 2024; Serkova; Brown, 2012). Parallel progress in the biology of therapy resistance has underscored why such biomarkers matter: metabolic reprogramming is itself a mechanism of acquired resistance to targeted and endocrine therapies, meaning that MRS-visible metabolites can report not only initial response but also the emergence of escape routes (Kreis et al., 2020; Lodi; Ronen, 2011).

The historical arc is instructive. MRS entered oncology in the 1980s and 1990s through ^{31}P studies of tumour energetics and ^1H studies of brain and breast tumours, and by the early 2000s the core empirical observation — that effective treatment normalises tumour spectra — had been replicated across organs and modalities (Glunde; Bhujwala, 2011; Kauppinen; Peet, 2011; Sharma; Jagannathan, 2022). What the field lacked then was not evidence but context: chemotherapy response was adequately tracked by size, and there was no pressing clinical question that only a metabolic answer could settle.

Targeted therapy changed the question. When a drug's action is defined as pathway blockade rather than cell kill, the clinically decisive events — target engagement, pathway suppression, adaptive escape — are metabolic events, and the size endpoint becomes a lagging indicator of a process that spectroscopy can observe directly (Day et al., 2007; Liu et al., 2024; Ward et al., 2010). The economic argument reinforces the scientific one: a failed targeted-therapy course costs months of progression-free life and tens of thousands of dollars per patient, so an early, cheap, radiation-free futility assessment carries value for patients, payers and trial sponsors alike (Serrao; Brindle, 2016; Woitek; Gallagher, 2021).

This review examines the emerging role of MRS and MRS-detectable metabolic biomarkers in monitoring targeted cancer therapy. We first summarise the technical foundations and the biomarker repertoire (Figure 1), then review organ-specific clinical evidence, dissect how metabolic imaging documents on-target effects across the major targeted-therapy classes, appraise the tracer-based flux methods that are redefining sensitivity, and consider translational infrastructure — from three-dimensional tumour culture platforms and nanotheranostic agents to artificial intelligence — that is accelerating the path from spectroscopy to clinical decision-making (Figure 2). Throughout, we adopt a critical stance: the promise of MRS has been articulated for three decades, and an honest account must address why routine adoption has lagged and what has now changed (Kauppinen; Peet, 2011; Serrao; Brindle, 2016).

In Figure 1, MRS Detectable Metabolic Biomarkers in Tumour Metabolism, Magnetic resonance spectroscopy (MRS) offers a unique window into tumour biochemistry, enabling non-invasive detection of key metabolites that reflect oncogenic pathway activity. As summarised in Figure 1, these MRS-visible signals can be mapped onto distinct metabolic reprogramming events, collectively providing a pharmacodynamic panel for monitoring targeted therapy response.

A hallmark of aggressive tumours is aerobic glycolysis (the Warburg effect), which elevates lactate production. This can be detected both by conventional ^1H MRS at 1.33 ppm and, with greater sensitivity and specificity, by hyperpolarised ^{13}C MRS measuring the lactate to pyruvate exchange rate—a direct readout of glycolytic flux.

Another major signature is increased membrane phospholipid turnover, reflected by elevated total choline (3.2 ppm on ^1H MRS) and ^{31}P phosphomonoesters. These signals correlate with cell proliferation and are among the earliest responders to effective targeted inhibition.

In specific tumour subtypes, tissue context markers add diagnostic and monitoring value. For instance, mutant isocitrate dehydrogenase (IDH) produces the oncometabolite 2-hydroxyglutarate (2-HG), detectable at 2.25 ppm—a critical marker for IDH mutant gliomas and cholangiocarcinomas. Conversely, metabolite losses also serve as indicators: prostate cancer typically shows citrate depletion (due to altered zinc metabolism and citrate oxidation), while gliomas exhibit N-acetylaspartate (NAA) loss, reflecting neuronal integrity and tumour infiltration. These contextual markers help distinguish tumour from normal tissue and can track treatment-induced metabolic normalisation.

Beyond static pool measurements, advanced isotope-labelled methods—using ^2H or ^{13}C tracers—enable quantification of metabolic fluxes rather than steady-state concentrations, offering dynamic insights into pathway utilisation and real-time drug effects. Together, these MRS-detectable signals form a comprehensive, non-invasive pharmacodynamic toolkit. They capture early metabolic shifts that precede anatomical changes, empowering clinicians to stratify responders, detect resistance early, and adapt therapy promptly—a paradigm that aligns perfectly with the principles of precision oncology.

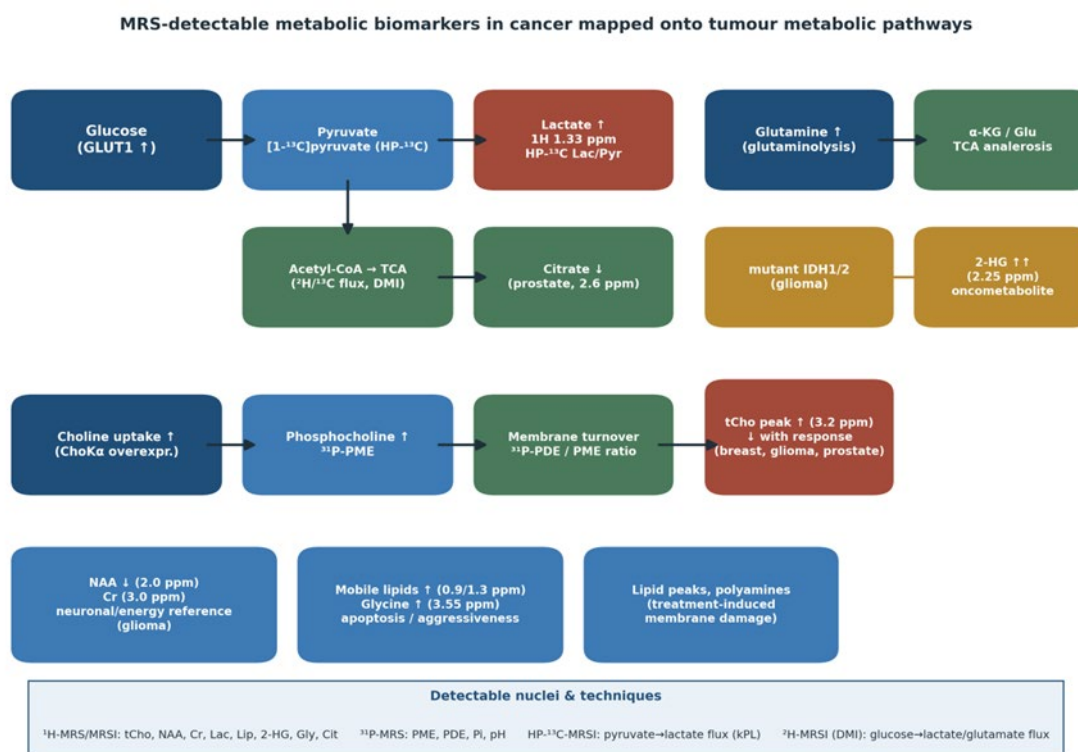


Figure 1. MRS-detectable metabolic biomarkers mapped onto tumour metabolic pathways. Aerobic glycolysis elevates lactate (^1H -MRS, 1.33 ppm; hyperpolarised ^{13}C lactate/pyruvate ratio); membrane phospholipid turnover elevates total choline (3.2 ppm) and ^{31}P -phosphomonoesters; mutant IDH generates the oncometabolite 2-hydroxyglutarate (2.25 ppm); prostate citrate depletion and glioma NAA loss provide tissue-context markers; and $^2\text{H}/^{13}\text{C}$ tracer methods quantify fluxes rather than pools. Together these signals constitute a non-invasive pharmacodynamic panel for targeted therapy monitoring. Source: Authors, 2026.

2. Technical Foundations: What MRS Measures and why it is Pharmacodynamic

2.1 Proton MRS and MRSI

Proton MRS exploits the chemical shift — the parts-per-million displacement of resonance frequency produced by each metabolite's electronic environment — to resolve and quantify tissue metabolites at millimolar sensitivity (Andronesi et al., 2018). In oncologic practice the dominant signals are: total choline (tCho, 3.2 ppm), the composite of choline, phosphocholine and glycerophosphocholine that reports on membrane phospholipid

turnover; creatine (3.0 ppm), a reference for cellular energetics; NAA (2.0 ppm), a neuronal marker whose displacement or destruction signals glioma infiltration; lactate (1.33 ppm), the end-product of aerobic glycolysis; mobile lipids (0.9 and 1.3 ppm), associated with membrane breakdown and apoptosis; and tissue-specific markers such as citrate in prostate (2.6 ppm) and glycine in high-grade glioma (3.55 ppm) (Cheng et al., 2005; Chetta; Zadra, 2021; Glunde; Bhujwalla, 2011).

Technical developments — higher field strengths (3 T and 7 T), phased-array coils, adiabatic pulses, improved water and lipid suppression, and three-dimensional MRSI with whole-tumour coverage — have progressively converted these signals from research curiosities into quantifiable biomarkers with defined coefficients of variation (Andronesi et al., 2018; Tiwari et al., 2020).

The pharmacodynamic logic rests on timing. Choline phospholipid metabolism is driven by growth-factor signalling through choline kinase α and phospholipase activation; lactate accumulation is driven by PI3K/AKT/mTOR- and MYC-dependent glycolytic enzyme expression (Day et al., 2007; Glunde; Bhujwalla, 2011). Blockade of these pathways therefore lowers phosphocholine synthesis and glycolytic flux within hours to days — before cell death, and long before volume loss (Day et al., 2007; Liu et al., 2024). *Ex vivo* and *in vivo* studies established this sequence directly: MRS-detectable metabolic fingerprints of drug action appear within the first treatment cycle and correlate with downstream efficacy (Branzoli; Marjańska, 2020; Day et al., 2007).

Two methodological notes complete the proton picture. First, spectral editing — MEGA-PRESS and related J-difference techniques — separates metabolites whose signals overlap in conventional spectra, and it was editing that converted 2-HG from an aspirational target into a quantifiable clinical signal at 3 T (Jagannathan et al., 2001; Tiwari et al., 2020). Second, the choice between single-voxel MRS and multivoxel MRSI is not merely technical: tumours are heterogeneous, and the metabolically most aggressive subvolume — highest Cho/NAA, highest kPL — may be the subvolume that determines outcome, and that should guide biopsy, dose-painting and response assessment (Cheng et al., 2005; Pope et al., 2012; Ward et al., 2010). Three-dimensional MRSI sequences with clinically acceptable acquisition times (under ten minutes at 3 T) have made the heterogeneous, whole-tumour approach realistic in routine workflows (Tiwari et al., 2020).

2.2 Phosphorus-31 and multinuclear MRS

^{31}P -MRS resolves phosphomonoesters (PME; phosphocholine and phosphoethanolamine, the synthetic arm of membrane turnover) and phosphodiester (PDE; the degradative arm), together with inorganic phosphate, phosphocreatine, nucleoside triphosphates and intracellular pH (Glunde; Bhujwalla, 2011; Kauppinen; Peet, 2011). The PME/PDE ratio captures the balance of membrane anabolism and catabolism and shifts predictably with growth arrest and treatment response; in breast cancer, ^{31}P -detectable changes in phospholipid metabolism have been tracked during neoadjuvant chemotherapy with response-associated trajectories (Kauppinen; Peet, 2011). Although limited by lower sensitivity and coarser resolution than ^1H -MRS, ^{31}P methods remain uniquely informative for energy status and pH, and are experiencing a renaissance at ultrahigh field (Andronesi et al., 2018).

2.3 Tracer-based flux imaging: hyperpolarised ^{13}C and deuterium MRSI

Steady-state metabolite pools are ambiguous — a stable lactate level may reflect high production balanced by high clearance. Flux methods resolve this ambiguity. Dissolution dynamic nuclear polarization increases ^{13}C signal by four to five orders of magnitude, enabling injection of hyperpolarised $[1-^{13}\text{C}]\text{pyruvate}$ and imaging of its conversion to $[1-^{13}\text{C}]\text{lactate}$ within a one-to-two-minute window; the apparent exchange rate constant kPL quantifies glycolytic flux *in vivo* (Cao et al., 2012; Kashif et al., 2024). The seminal demonstration that hyperpolarised ^{13}C MRS detects tumour response to treatment — a fall in lactate labelling within 24 h of drug exposure, preceding size change — established the pharmacodynamic credentials of the technique (Kashif et al., 2024).

Deuterium metabolic imaging takes the complementary route: oral or intravenous $[6,6\text{'-}^2\text{H}_2]\text{glucose}$ is traced into ^2H -labelled lactate and glutamate/glutamine using ^2H MRSI, offering a technically simpler, lower-cost and readily translatable flux measurement without hyperpolarisation hardware (De Feyter et al., 2018; Serkova; Brown, 2012). A systematic review of DMI confirms rapid methodological maturation and expanding oncologic applications (Hesketh; Brindle, 2018).

2.4 Quantification, standardisation and quality assurance

A biomarker is only as good as its measurement chain. MRS quantification requires attention to voxel placement, partial-volume effects, T1/T2 relaxation, referencing strategy (internal water versus external standards), and fitting algorithms (LCModel, jMRUI and successors), each a documented source of inter-site variability (Andronesi et al., 2018). Consensus efforts now define acquisition and reporting standards, and quantitative frameworks have been articulated specifically for translating MRS metabolic profiles into clinically usable biomarkers (Andronesi et al., 2018). These standardisation themes recur in Section 8, because they constitute the principal reason that MRS response criteria have not yet entered formal guidelines (Woitek; Gallagher, 2021).

2.5 MRS in the functional-imaging landscape: complementarity with PET and DWI

MRS does not compete in a vacuum. FDG-PET measures glucose uptake with high sensitivity and whole-body coverage; diffusion-weighted imaging (DWI) reports on cellularity and treatment-induced cell death; perfusion MRI and CT capture vascular effects (Pan et al., 2024; Woitek; Gallagher, 2021). The comparative profile of MRS is distinctive in four respects. First, specificity: where FDG uptake conflates glycolytic tumour cells with inflammatory infiltrate, MRS metabolites carry pathway-specific meaning — phosphocholine for membrane synthesis, 2-HG for IDH genotype, pyruvate-to-lactate exchange for glycolytic flux (Jagannathan et al., 2001; Liu et al., 2024; Ward et al., 2010).

Second, multiplicity: a single examination quantifies a panel of metabolites rather than a single tracer's uptake, enabling ratio-based and pattern-based interpretation (Day et al., 2007; Kashif et al., 2024). Third, repeatability: the absence of ionising radiation permits the dense serial sampling that pharmacodynamic monitoring demands — weekly or even daily measurements that would be untenable with PET (Kashif et al., 2024; Sharma; Jagannathan, 2022).

Fourth, synergy: the strongest practical implementations are multiparametric, combining MRS with DWI and perfusion in one MRI session, and head-to-head studies in breast cancer have shown early MRS tCho changes to complement, and in some analyses outperform, FDG-PET for early response prediction (Cho et al., 2016; Pan et al., 2024). The tracer-based MR methods sharpen the comparison further: hyperPET studies combining hyperpolarised ^{13}C -pyruvate MRS with FDG-PET in the same animals demonstrated that the two modalities report related but non-identical aspects of glycolytic metabolism, arguing for complementary rather than redundant roles (Cao et al., 2018; Woitek; Gallagher, 2021).

3. Tumour Metabolic Reprogramming: The Biological Basis of MRS Biomarkers

The biomarkers of Section 2 are not arbitrary signals; each corresponds to a node of the metabolic reprogramming that targeted therapies aim to reverse (Glunde; Bhujwalla, 2011; Lodi; Ronen, 2011). Four programmes dominate.

Aerobic glycolysis. Constitutive growth-factor signalling and HIF-1 α stabilisation drive glucose uptake and lactate export even under normoxia. Glycolytic flux sustains biosynthetic intermediates and acidifies the microenvironment, promoting invasion and immune evasion; it is read out by ^1H -detectable lactate, by hyperpolarised pyruvate-to-lactate exchange, by DMI lactate labelling and, in the PET domain, by FDG uptake (De Feyter et al., 2018; Kashif et al., 2024; Pan et al., 2024). Because PI3K/AKT/mTOR and MAPK signalling sit immediately upstream of glycolytic enzyme expression, their pharmacological inhibition produces among the fastest metabolic responses measurable — the basis for using hyperpolarised ^{13}C lactate labelling as a same-day pharmacodynamic readout of PI3K pathway inhibitors (Liu et al., 2024).

Choline phospholipid metabolism. Choline kinase α overexpression and altered phospholipase activity elevate phosphocholine and tCho in most solid tumours; the tCho signal correlates with grade, proliferation and malignant transformation across glioma, breast and prostate (Chetta; Zadra, 2021; Cho et al., 2016; Glunde; Bhujwalla, 2011). Growth-factor pathway blockade suppresses choline kinase and lowers tCho within days, while effective cytotoxic or targeted therapy collapses membrane turnover altogether; conversely, a persistent or rising tCho signals a resistant, proliferating tumour (Sharma; Jagannathan, 2022; Zhu et al., 2024).

Glutaminolysis and the TCA cycle. MYC-driven tumours are glutamine-addicted, and flux through glutaminolysis supports TCA anaplerosis, redox balance and nucleotide synthesis (Glunde; Bhujwalla, 2011). DMI is particularly well suited to this axis, resolving ^2H label from glucose into both lactate (glycolysis) and glutamate/glutamine (oxidative metabolism), thereby capturing the glycolytic-oxidative balance that shifts with

therapy and resistance (Serkova; Brown, 2012; Peng et al., 2025). Metabolic reprogramming along these axes is now recognised as a driver of therapeutic resistance in breast cancer and as a general contributor to anticancer drug resistance, which gives MRS flux readouts a second role: surveillance for the metabolic escape routes that announce emerging resistance (Lodi; Ronen, 2011).

Microenvironmental acidification and lipid signalling. Two further programmes complete the biomarker map. Lactate export and carbonic anhydrase activity acidify the extracellular space, and the resulting pH gradient — alkaline inside, acidic outside — is invertible by ^{31}P -MRS and pH-sensitive methods and is druggable by antiangiogenic and metabolic agents (Glunde; Bhujwala, 2011; Kauppinen; Peet, 2011). Separately, *de novo* lipogenesis and lipid-droplet accumulation generate the mobile-lipid resonances at 0.9 and 1.3 ppm that ^1H -MRS detects; these signals increase with apoptosis and treatment-induced membrane remodelling, providing a spectroscopic correlate of cell death that complements the flux readouts (Glunde; Bhujwala, 2011; Kashif et al., 2024). Lipid metabolism is also a recognised axis of endocrine resistance, connecting the spectroscopic lipid panel to the endocrine-monitoring application discussed below (Krei et al., 2020; Taglang et al., 2022).

Oncometabolite production. Neomorphic mutations of isocitrate dehydrogenase (IDH1/2) convert α -ketoglutarate to D-2-hydroxyglutarate, which accumulates to millimolar levels and becomes directly MRS-detectable at approximately 2.25 ppm (Jagannathan et al., 2001; Tiwari et al., 2020). 2-HG is the paradigm genotype-specific imaging biomarker: its presence non-invasively identifies IDH-mutant glioma, its concentration tracks tumour burden, and its fall documents target engagement by mutant-IDH inhibitors (Jagannathan et al., 2001; Ward et al., 2010). Mutant-IDH gliomas additionally remodel phospholipid metabolism, downregulating phosphocholine and phosphoethanolamine synthesis — an MRS-visible phenotype that links genotype to the choline axis (Gul et al., 2025).

4. Organ-Specific Clinical Evidence

4.1 Glioma: the most mature MRS application

Neuro-oncology has been the natural home of MRS because conventional MRI is least informative there: blood–brain barrier disruption, oedema and treatment-related change confound contrast enhancement, and pseudoprogression after chemoradiation mimics true progression in up to a third of glioblastoma cases (Kauppinen; Peet, 2011; Tiwari et al., 2020). MRSI metabolite ratios — elevated Cho/NAA and Cho/Cr in viable tumour, their normalisation with response — have long been used to distinguish tumour recurrence from treatment effect, to guide biopsy and radiotherapy targeting, and to grade gliomas preoperatively (Cheng et al., 2005; Kauppinen; Peet, 2011). Glycine detectable by MRS has been validated as an imaging biomarker of glioma aggressiveness, correlating with proliferation and grade (Cheng et al., 2005).

The IDH era has transformed the field. Non-invasive MRS detection of 2-HG identifies IDH-mutant glioma with high specificity, enabling genotype-informed surgical and therapeutic planning without tissue (Jagannathan et al., 2001). Critically for this review's theme, serial 2-HG MRSI has been used as a pharmacodynamic endpoint in trials of mutant-IDH inhibitors: three-dimensional MRSI documented significant on-treatment reductions in tumoural 2-HG, constituting direct *in vivo* evidence of target engagement in patients (Ward et al., 2010).

Current reviews of MRS in IDH-mutant glioma converge on 2-HG quantification as the benchmark genotype-specific metabolic biomarker and highlight remaining technical requirements — edited sequences, 3 T standardisation — for routine deployment (Tiwari et al., 2020). Metabolic subtyping adds a further layer: deuterium MRS distinguishes glioblastoma metabolic subtypes with differential treatment sensitivity, and MRS metabolite panels carry prognostic information beyond conventional imaging (Peng et al., 2025).

The pseudoprogression problem deserves separate emphasis because it is where MRS already changes management in practice. After temozolomide chemoradiation, enlarging contrast-enhancing lesions may represent either true progression or treatment effect, and anatomical MRI cannot reliably separate them for months (Kauppinen; Peet, 2011; Tiwari et al., 2020). Spectroscopy addresses the distinction directly: viable tumour retains high Cho/NAA and Cho/Cr ratios and detectable lactate/lipid signals, whereas treatment-related necrotic and inflammatory change shows globally depressed metabolites (Cheng et al., 2005; Kauppinen; Peet, 2011; Tiwari et al., 2020).

In the targeted-therapy context — bevacizumab and, increasingly, IDH inhibitors and immunotherapeutic combinations — the same logic applies with greater force, because these agents normalise vascular permeability and thereby mask the enhancement on which anatomical assessment depends (Jagannathan et al., 2001; Tiwari et al., 2020). Serial MRSI, interpreted alongside perfusion and diffusion, is currently the most credible non-invasive strategy for this distinction, and its incorporation into response-assessment frameworks for glioma

trials is an active standardisation effort (Peng et al., 2025; Tiwari et al., 2020).

4.2 Breast cancer: choline as a response biomarker in the neoadjuvant setting

Breast MRS rests on the most extensive clinical response dataset outside the brain. The foundational observation that locally advanced breast cancers exhibit elevated tCho, and that tCho falls with neoadjuvant chemotherapy in responders, dates to volume-localised 1H-MRS studies that demonstrated response monitoring within the first treatment cycles (Sharma; Jagannathan, 2022). Subsequent prospective work confirmed that quantitative MRI plus MRS changes after one or two cycles predict final pathological response earlier than size criteria (Baek et al., 2008), that internal-reference tCho quantification tracks response across the full course of neoadjuvant therapy (Zhu et al., 2024), and that early tCho decline is competitive with — and complementary to — FDG-PET for early response prediction (Pan et al., 2024).

High-resolution magic-angle-spinning MRS of intact tissue extended the concept to prognostic metabolic profiling: MR metabolic profiles of breast tumours predicted long-term survival and treatment response in patients receiving neoadjuvant chemotherapy (Branzoli; Marjańska, 2020). Contemporary reviews of MRI/MRS methods in breast cancer management frame tCho and its quantitative derivatives as validated pharmacodynamic markers awaiting multicentre standardisation (Cho et al., 2016), and integrative analyses argue that coupling metabolic imaging with an understanding of metabolic reprogramming improves prediction of breast cancer treatment response (Taglang et al., 2022).

Two features of the breast literature generalise to the whole field. First, the temporal design: the informative measurement is the change between baseline and an early on-treatment scan (after one or two cycles), not any single timepoint — a principle that should be written into every MRS monitoring protocol (Baek et al., 2008; Sharma; Jagannathan, 2022; Zhu et al., 2024). Second, the quantification lesson: studies using internal-referenced, absolute or semi-absolute tCho quantification achieved better inter-patient comparability than ratio-only approaches, prefiguring the standardisation agenda of Section 8 (Andronezi et al., 2018; Zhu et al., 2024).

Ex vivo HR-MAS profiling of biopsy tissue has added a bridge between *in vivo* spectroscopy and molecular subtyping, demonstrating that metabolic profiles carry subtype- and prognosis-related information recoverable from small samples (Branzoli; Marjańska, 2020). The unresolved step is scale: no multicentre trial has yet embedded quantitative breast MRS as a decision-driving biomarker, and the technology assessment literature frames this, rather than biological doubt, as the remaining obstacle (Cho et al., 2016).

4.3 Prostate cancer: citrate, choline and the hyperpolarised frontier

Prostate tissue is metabolically distinctive: normal peripheral-zone epithelium accumulates citrate, which is lost in malignancy, while choline and the (choline+creatine)/citrate ratio rise — a spectroscopic signature established by tissue MRS and translated to *in vivo* MRSI for localisation, staging and recurrence detection (Chetta; Zadra, 2021). Reviews of prostate MRS metabolism document the maturity of these pool-based markers and their integration into multiparametric MRI (Chetta; Zadra, 2021). The flux frontier has moved fastest here: the first-in-human hyperpolarised [1-¹³C]pyruvate studies were performed in prostate cancer, and subsequent work demonstrated that hyperpolarised ¹³C-pyruvate MRI detects real-time metabolic flux in prostate tumours, with elevated kPL in cancerous versus benign tissue and dose-responsive changes under androgen-axis therapy (Pope et al., 2012). Because androgen receptor signalling directly regulates prostate tumour metabolism, MRS and hyperpolarised flux readouts are mechanistically aligned pharmacodynamic markers for androgen-targeted agents (Pope et al., 2012; Serrao; Brindle, 2016).

4.4 Abdominal and other malignancies

Body applications have historically been limited by motion, susceptibility heterogeneity and lower signal, but are advancing rapidly (Woitek; Gallagher, 2021). In hepatocellular carcinoma, multiparametric approaches combining hyperpolarised ¹³C MRSI with conventional imaging have characterised tumour metabolism and therapy response in preclinical and translational settings (Cao et al., 2012). Deuterium metabolic imaging has demonstrated feasibility in abdominal tumours, and early-response studies using [2H7]glucose DMI have detected chemotherapy-induced glucose-metabolic alterations in bladder cancer models, extending flux imaging

to urothelial disease (Hesketh; Brindle, 2018; Serkova; Brown, 2012). Renal, ovarian and pancreatic applications are emerging within the body-imaging programmes of the hyperpolarised ^{13}C community, which has articulated clinical roles spanning diagnosis, characterisation and response assessment across body tumours (Serrao; Brindle, 2016; Woitek; Gallagher, 2021).

5. Monitoring the major targeted-therapy classes

5.1 Receptor tyrosine kinase and MAPK-pathway inhibitors

Tyrosine kinase inhibitors of EGFR, HER2, VEGFR and ALK, and RAF/MEK/ERK inhibitors, act upstream of both the glycolytic and choline programmes. Preclinical and translational studies show that pathway inhibition lowers phosphocholine and lactate within days — an MRS-detectable pharmacodynamic signature of on-target action that precedes tumour regression (Day et al., 2007; Liu et al., 2024). Hyperpolarised ^{13}C MRSI documented this principle with particular clarity: inhibition of PI3K signalling produced rapid suppression of pyruvate-to-lactate flux *in vivo*, establishing KPL as a same-week pharmacodynamic biomarker of pathway engagement (Liu et al., 2024). The same logic extends to resistance: because tumours escape targeted inhibition partly through metabolic rewiring — for example, the metabolic reprogramming observed in metastatic melanoma and breast cancer with acquired resistance — serial MRS offers a non-invasive means to detect the metabolic phenotype of resistance as it emerges (Lodi; Ronen, 2011).

5.2 PI3K/AKT/mTOR inhibitors

This class is the best validated for MRS pharmacodynamics. Beyond the hyperpolarised demonstration of rapid flux suppression (Liu et al., 2024), conventional MRS studies have shown that PI3K-pathway blockade reduces phosphocholine synthesis through effects on choline kinase and lipid metabolism, producing measurable tCho and ^{31}P -PME declines within days of dosing (Day et al., 2007; Glunde; Bhujwala, 2011). The reproducibility of these signatures across tumour types and inhibitors makes PI3K/AKT/mTOR agents the reference class for metabolic pharmacodynamic assay development in early-phase trials (Andronesi et al., 2018; Day et al., 2007).

5.3 Mutant-IDH inhibitors: the paradigm of genotype-specific metabolic monitoring

IDH inhibitors (ivosidenib, enasidenib, vorasidenib) reverse the neomorphic production of 2-HG. *In vivo* 3D MRSI in glioma patients demonstrated measurable falls in tumoural 2-HG during mutant-IDH1 inhibitor therapy — a direct, quantitative, non-invasive confirmation of target engagement that has informed dosing and development decisions (Ward et al., 2010). This is the cleanest example in oncology of an imaging biomarker that is simultaneously diagnostic (genotype identification), pharmacodynamic (target engagement) and prognostic (residual metabolic tumour) (Jagannathan et al., 2001; Tiwari et al., 2020). It illustrates the template toward which other genotype-metabolite pairs are being sought (Gul et al., 2025).

5.4 Antiangiogenic and vascular-targeted therapy

Antiangiogenic agents produce a complex metabolic picture: vascular normalisation may transiently improve oxygenation and glucose delivery, while sustained anti-VEGF pressure can drive glycolytic, hypoxia-adapted phenotypes (Glunde; Bhujwala, 2011; Kauppinen; Peet, 2011). MRS studies in preclinical models have tracked lactate, choline and pH changes under antiangiogenic treatment, and multinuclear approaches combining ^{31}P energy-status readouts with ^1H metabolites have been used to dissect vascular from metabolic effects (2). The lesson for monitoring is that antiangiogenic metabolic response is time-dependent and potentially biphasic — a caution against single-time-point biomarker interpretation (Serrao; Brindle, 2016).

5.5 Endocrine therapy and metabolic resistance

Endocrine therapy in breast and prostate cancer engages metabolic pathways directly: oestrogen and androgen signalling regulate lipid synthesis, glycolysis and mitochondrial metabolism. Metabolic reprogramming has been defined as an emerging mechanism of resistance to endocrine therapy, with resistant tumours adopting distinct metabolic states (Kreis et al., 2020). MRS-detectable lipid and choline signals, and flux readouts of oxidative versus glycolytic balance, are candidate surveillance biomarkers for this transition (Kreis et al., 2020; Taglang et al., 2022). In prostate cancer specifically, androgen-axis therapy alters the citrate-choline economy that ^1H -MRSI measures, aligning spectroscopic monitoring with the dominant targeted modality of the disease

(Chetta; Zadra, 2021; Pope et al., 2012).

5.7 Antibody–drug conjugates, radioligands and combination regimens

Newer targeted modalities create new monitoring demands. Antibody–drug conjugates combine target-specific delivery with cytotoxic payloads, so their metabolic signature is expected to mix pathway-modulation and cell-death components — early tCho and flux changes from target engagement, followed by lipid and necrosis markers from payload action — a composite pattern that MRS panels are structurally suited to resolve (Chetry et al., 2025; Day et al., 2007; Kashif et al., 2024).

Radioligand therapies and external-beam radiotherapy produce analogous sequences, and hyperpolarised fumarate imaging of necrosis offers a direct spectroscopic window on treatment-induced cell death in these settings (Chetry et al., 2025). Combination regimens — targeted agent plus chemotherapy, or targeted agent plus immunotherapy — multiply the interpretive burden on anatomical imaging while leaving the metabolic logic intact: each component's expected metabolic signature is known, and deviations from the expected sequence can flag which component is failing (Chetta; Zadra, 2021; Woitek; Gallagher, 2021). Prospective work formalising these composite signatures is a clear priority (Chetta; Zadra, 2021; De Feyter et al., 2018).

5.6 Immunotherapy and the immune–metabolic interface

Immune checkpoint blockade creates distinctive monitoring problems — pseudoprogression from immune infiltrate, delayed response, and hyperprogression — that anatomical criteria handle poorly (Serrao; Brindle, 2016). Metabolic imaging is beginning to contribute: hyperpolarised [1-¹³C]pyruvate MRS has been reported to evaluate immune potential and predict response to immunotherapy, reflecting the tight coupling between tumour-cell glycolysis and the immune microenvironment (Pope et al., 2012). The broader principle is that tumour metabolism shapes, and is shaped by, antitumour immunity — comprehensive characterisation of T-cell subtypes in lung adenocarcinoma, for instance, has defined prognostic and predictive immune phenotypes whose metabolic correlates are spectroscopically accessible (Viswanath et al., 2018).

Neuron–tumour crosstalk represents a further frontier of microenvironmental biology with metabolic and translational dimensions that imaging biomarkers may eventually capture (Manton et al., 2006). MRS-based immunotherapy monitoring remains the least mature but potentially most differentiating application, because it addresses the class of therapy for which anatomical response criteria fail most visibly (Serrao; Brindle, 2016).

6. Tracer-Based Flux Imaging Comes of Age

The defining technical trend of the past decade is the shift from pools to fluxes (Cao et al., 2012). Hyperpolarised ¹³C MRSI has progressed from the landmark demonstration of treatment-response detection in lymphoma models (Kashif et al., 2024) through first-in-human prostate studies to multicentre-capable acquisition protocols and quantitative kPL modelling (Pope et al., 2012; Woitek; Gallagher, 2021). Key pharmacodynamic validations now span cytotoxics, targeted agents and radiotherapy: early response detection with hyperpolarised [1-¹³C]pyruvate has been replicated across tumour models (Liu et al., 2021); hyperpolarised ¹³C-fumarate MRS reports on necrosis through malate production, adding a cell-death dimension to the flux panel (Chetry et al., 2025); and brain-tumour applications have demonstrated that hyperpolarised ¹³C metabolic imaging is feasible across the blood–brain barrier (Chen et al., 2020). Clinical role definitions for body imaging now explicitly include therapy-response assessment (Serrao; Brindle, 2016; Woitek; Gallagher, 2021).

Deuterium metabolic imaging offers a pragmatic parallel path. The original demonstration of three-dimensional DMI *in vivo* (Serkova; Brown, 2012) was followed by fast deuterium MRI measurements of tumour glycolytic flux (De Feyter et al., 2018), by applications distinguishing glioblastoma metabolic subtypes and their therapeutic implications (Peng et al., 2025), and by systematic-review confirmation of the field's trajectory (Hesketh; Brindle, 2018). DMI's advantages — no hyperpolariser, inexpensive tracer, long signal lifetime, simultaneous glycolytic and oxidative readouts — suit it to repeated pharmacodynamic measurement in exactly the serial-monitoring scenario this review describes (Hesketh; Brindle, 2018; Serkova; Brown, 2012). Chemical exchange saturation transfer (CEST) and ³¹P flux methods occupy adjacent niches, extending the MRS family toward pH mapping and energy-metabolism kinetics (Glude; Bhujwalla, 2011; Kauppinen; Peet, 2011).

The probe repertoire beyond pyruvate is expanding in directions directly relevant to therapy monitoring.

Hyperpolarised $[1-^{13}\text{C}]$ fumarate reports on necrosis through malate labelling (Chetry et al., 2025); hyperpolarised ^{13}C -bicarbonate measures extracellular pH, targeting the acidified microenvironment that antiangiogenic and metabolic therapies perturb (Cao et al., 2012; Cetta; Zadra, 2021); hyperpolarised $[1-^{13}\text{C}]$ glutamine and $[5-^{13}\text{C}]$ glutamine probe glutaminolysis, the resistance-associated axis highlighted in Section 3 (Cetta; Zadra, 2021; Lodi; Ronen, 2011); and hyperpolarised $[2-^{13}\text{C}]$ fructose and ^{13}C -urea extend the panel to alternative fuel use and perfusion (Cao et al., 2012; Chetta; Zadra, 2021).

Each new probe converts another metabolic programme into an imaging endpoint, and the multi-probe exam — pyruvate plus fumarate, or pyruvate plus bicarbonate, in a single session — is technically demonstrated and clinically plausible (Chetta; Zadra, 2021; Chetry et al., 2025). For trial design, this means pharmacodynamic panels can be assembled to match a drug's mechanism: a glycolysis-targeted agent monitored with pyruvate flux, an apoptosis-inducing regimen with fumarate, a pH-directed therapy with bicarbonate (Cao et al., 2021; Chetta; Zadra, 2021; Kashif et al., 2024).

7. Translational infrastructure: models, delivery systems and analytics

7.1 Preclinical platforms that de-risk metabolic biomarker development

The credibility of an MRS pharmacodynamic biomarker depends on preclinical models in which drug-metabolism relationships can be established under controlled conditions. Three-dimensional tumour cultures — spheroids, organoids and patient-derived models — have emerged as the intermediate fidelity tier between cell monolayers and xenografts, enabling drug-resistance mechanisms to be dissected and therapeutic candidates to be screened under clinically relevant architecture (Liu et al., 2025).

For MRS specifically, such platforms permit direct correlation of spectroscopic signatures with pathway inhibition, dose and resistance phenotype, and their compatibility with high-resolution and HR-MAS spectroscopy makes them efficient biomarker-development engines (Day et al., 2007; Liu et al., 2025). A pragmatic development pipeline follows: establish the drug-spectrum relationship in 3D culture, where metabolite changes can be directly attributed to pathway inhibition without haemodynamic or stromal confounders; validate in xenograft or patient-derived xenograft models with *in vivo* MRSI; then transfer to early-phase trials with predefined metabolic endpoints (Andronesi et al., 2018; Day et al., 2007; Liu et al., 2025). Each tier adds biological realism at the cost of spectroscopic cleanliness, and the discipline of predefined endpoints — which metabolite, which direction, what magnitude, by which day — is what distinguishes a pharmacodynamic biomarker from an exploratory measurement (Andronesi et al., 2018; Woitek; Gallagher, 2021).

The adaptive-evolution dimension of resistance deserves emphasis: just as adaptive substitutions at defined residues can increase the fitness of viral variants under selective pressure — demonstrated mechanistically in plant-virus chimera systems (Bushra et al., 2024; Jia et al., 2026) — tumour populations under targeted-therapy pressure evolve metabolic escape states that serial MRS may detect before they become anatomically manifest (Lodi; Ronen, 2011).

7.2 Nanotheranostics and targeted delivery

MRS-based monitoring intersects with drug development at the level of formulation as well as target. Stimuli-responsive and targeted delivery systems — exemplified by chitosan-based hydrogels engineered for drug and gene delivery, phototherapy and immunotherapy in cancer — create pharmacokinetic profiles whose metabolic consequences can be followed spectroscopically, closing the loop between delivery and pharmacodynamics (Saito et al., 2015).

Gold-based nanomaterials, whose synthesis and biomedical applications have been comprehensively reviewed, serve as radiosensitisers, photothermal agents and imaging probes in theranostic constructs (Mignon et al., 2014); redox-active cerium oxide nanoparticles, produced by diverse synthesis strategies, modulate tumour oxidative balance and interface with the metabolic phenotypes that MRS measures (Najac; Ronen, 2016); and precisely targeted nanomachines — such as systems engineered to reverse pathological cardiac remodelling — illustrate the maturing art of organ- and pathway-specific nanodelivery whose oncologic analogues will require pharmacodynamic biomarkers of exactly the kind MRS provides (Peng et al., 2025).

Bismuth- and vanadate-based nanomaterials add CT-contrast and catalytic functionality to this engineering repertoire (Sun et al., 2022), while metal-organic frameworks, now advancing from electrocatalytic

fundamentals toward device integration, represent a further materials class with biosensing and catalytic-therapy potential (Sun et al., 2024). The synthesis and characterisation methodologies developed across doped oxide and composite nanomaterials — manganese-doped bismuth oxide, iron-doped copper oxide, Fe/Ti-codoped strontium oxide, NiO–Co₃O₄ nanocomposites and nickel-doped strontium oxide catalysts — provide the materials-science foundation on which such theranostic agents are built (Gul et al., 2025; Jamil et al., 2025; Muhammad et al., 2026; Zhu et al., 2024; Wang et al., 2026). For the metabolic-imaging field, the practical implication is direct: every engineered therapeutic agent needs an engineered pharmacodynamic readout, and MRS metabolites are among the few readouts compatible with serial, non-invasive, whole-tumour assessment (Andronesi et al., 2018; Day et al., 2007).

7.3 Artificial intelligence and computational spectroscopy

Two computational trends are reshaping MRS practice. First, machine-learning spectral analysis — automated fitting, artefact detection, quality classification and metabolite-pattern recognition — is reducing the operator dependence that has limited reproducibility (Andronesi et al., 2018). Second, deep learning is demonstrating across oncologic imaging that subtle, multiparametric patterns predictive of diagnosis and outcome can be extracted at scale; deep supervised learning frameworks for accurate early breast-cancer detection exemplify the analytical paradigm now being transferred to spectroscopic and multiparametric data (Zhang et al., 2026).

The integration of MRS metabolite maps with radiomic features from anatomical and diffusion MRI, analysed jointly, is a foreseeable route to composite response classifiers (Cho et al., 2016; Zhang et al., 2026). Complement-system and inflammatory biomarkers — highlighted by analyses of complement protein changes in retinal vascular disease — remind us that imaging biomarkers will ultimately be interpreted alongside circulating molecular panels rather than in isolation (Jamal et al., 2024).

In Figure 2, Conceptual Framework and Clinical Workflow for Metabolic Monitoring of Targeted Therapy, Targeted therapy has become a cornerstone strategy for multiple malignancies; however, its therapeutic response assessment has long relied on anatomical imaging (e.g., CT or MRI) to detect changes in tumor volume, which often take weeks to months to become evident. This temporal lag severely constrains early adjustment of treatment decisions, potentially leading to ineffective drug exposure or missed opportunities for therapy switching. To address this, Figure 2 proposes a metabolic monitoring strategy based on magnetic resonance spectroscopy (MRS), aiming to capture response signals much earlier than morphological changes.

Panel A illustrates the critical temporal difference: after initiation of an effective targeted agent, MRS-detectable metabolic biomarkers—including total choline (reflecting cell proliferation), hyperpolarized lactate/pyruvate exchange (reflecting glycolytic activity), and 2-hydroxyglutarate (a specific oncometabolite in IDH-mutant tumors)—show significant decreases within days to two weeks. In contrast, anatomical tumor shrinkage typically lags by weeks to months. This "early window" provides a valuable decision-making gap for clinicians, making adaptive therapy based on metabolic response feasible.

Panel B further outlines a complete MRS-guided monitoring workflow: first, baseline multiparametric spectroscopic acquisition to establish the patient's metabolic profile; then, an early MRS scan (recommended within 1–2 weeks after treatment initiation) to obtain the early metabolic readout; subsequently, stratification of patients into metabolic responders and non-responders based on predefined thresholds—for non-responders, immediate regimen switching or dose escalation should be implemented to avoid ineffective treatment as much as possible; later, conventional anatomical imaging confirms tumor shrinkage, while MRS helps differentiate pseudoprogression (i.e., volume enlargement caused by treatment-related inflammation or necrosis) from true progression, thereby reducing unnecessary treatment interruptions.

This framework elevates metabolic imaging from a "research tool" to a "clinical navigator." It not only promises to shorten the response evaluation cycle but also provides dynamic, quantitative decision-making support for individualized targeted therapy—particularly suitable for scenarios such as immunotherapy-combined targeted therapy or neoadjuvant therapy, where rapid benefit assessment is critical. In the future, with the increasing clinical availability of hyperpolarization techniques and multi-nuclear MRS, this metabolic monitoring strategy may reshape the response evaluation criteria for solid tumors.

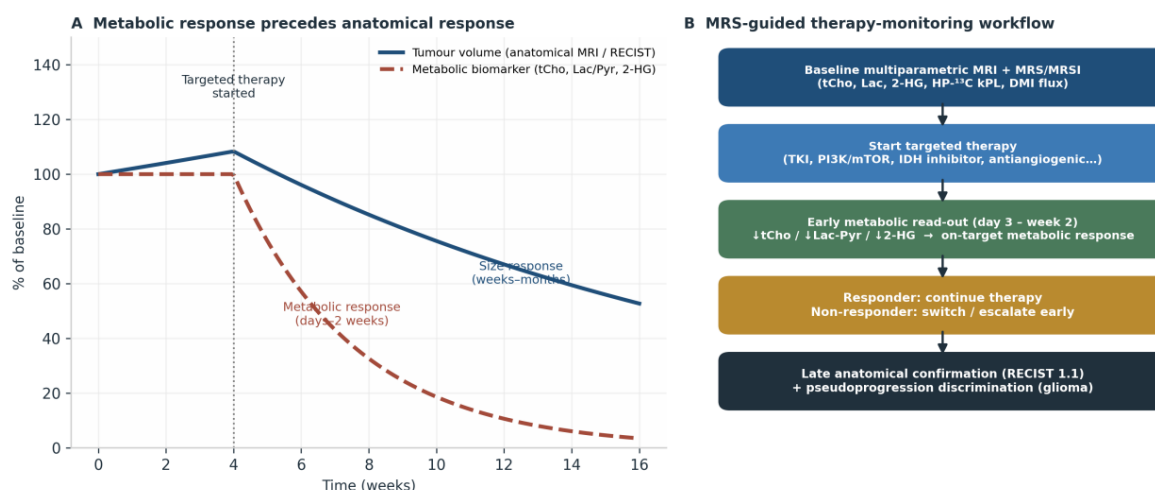


Figure 2. The conceptual case for metabolic monitoring of targeted therapy. (A) After initiation of an effective targeted agent, MRS-detectable metabolic biomarkers (total choline, hyperpolarised lactate/pyruvate exchange, 2-hydroxyglutarate) fall within days to two weeks, whereas anatomical tumour shrinkage lags by weeks to months; the shaded early window is where adaptive decisions become possible. (B) An MRS-guided monitoring workflow: baseline multiparametric spectroscopy, early metabolic read-out after treatment start, responder/non-responder stratification with early switch or escalation for non-responders, and later anatomical confirmation with spectroscopic discrimination of pseudoprogression. Source: Authors, 2026.

8. Challenges, limitations and the standardisation agenda

An honest appraisal must acknowledge that MRS has been “emerging” for a long time (Kauppinen; Peet, 2011). The obstacles are identifiable and, encouragingly, mostly engineering rather than biological. Sensitivity and resolution: millimolar detection limits restrict coverage and force trade-offs between voxel size and signal-to-noise; whole-tumour 3D MRSI at 3 T mitigates but does not eliminate the constraint (Andronesi et al., 2018; Tiwari et al., 2020). Technical heterogeneity: differences in field strength, sequences, referencing and fitting produce inter-site variability that has impeded pooled analyses and guideline acceptance; harmonised protocols and quantitative phantoms are the documented remedy (Andronesi et al., 2018).

Biological confounders: necrosis, inflammation, treatment-related change and partial-volume averaging can mimic or mask metabolic response, particularly in glioma, where spectroscopy must be interpreted within a multiparametric framework (Cheng et al., 2005; Kauppinen; Peet, 2011). Tracer logistics: hyperpolarised ^{13}C studies require on-site polarisers, rapid injection and specialised acquisition, constraining throughput and cost, although clinical programmes have demonstrated feasibility across multiple centres (Woitek; Gallagher, 2021; Pope et al., 2012); DMI relaxes these requirements substantially and may prove the more scalable flux modality (Hesketh; Brindle, 2018; Serkova; Brown, 2012).

Evidence level: most response data remain single-centre, and prospective-validation cohorts with hard endpoints are scarce; the breast neoadjuvant tCho literature shows both the promise and the fragmentation that multicentre standardisation must overcome (Baek et al., 2008; Pan et al., 2024; Sharma; Jagannathan, 2022; Zhu et al., 2024). Finally, regulatory qualification of metabolic-imaging biomarkers as drug-development tools — the context-of-use definitions, analytical validation and clinical qualification pathway — is a defined but incomplete agenda whose completion would unlock trial incorporation at scale (Andronesi et al., 2018; Serrao; Brindle, 2016).

Two further, practical barriers deserve mention because they are solvable by organisation rather than science. Workflow and cost: an MRS or DMI add-on extends an MRI session by five to fifteen minutes; in stretched clinical schedules this requires explicit justification, which the adaptive-therapy argument of Figure 2 supplies — a small scanning cost against months of potentially futile targeted therapy (De Feyter et al., 2018; Woitek; Gallagher, 2021). Expertise: spectral quality control and interpretation have historically required physicist support that most oncology centres lack; automation, cloud-based fitting pipelines and AI-assisted quality assessment are eroding this barrier and are prerequisites for the multicentre evidence the field needs (Andronesi et al., 2018; Zhang et al., 2026). The standardisation agenda can thus be summarised in one sentence: agree the protocols, automate the pipeline, and run the prospective trials — none of which requires a single new biological

discovery (Andronesi et al., 2018; Serrao; Brindle, 2016; Tiwari et al., 2020).

9. Future directions

Several convergent developments plausibly define the next decade. First, standardised quantitative MRSI embedded in multiparametric protocols: as whole-tumour 3D MRSI and automated quality control mature, metabolic metrics can join diffusion and perfusion parameters in routine reporting, with the glioma and breast use-cases leading (Cho et al., 2016; Tiwari et al., 2020). Second, flux imaging as a pharmacodynamic default: the complementary economics of hyperpolarised ^{13}C and DMI suggest a two-tier future — hyperpolarised studies for maximal sensitivity at specialist centres, DMI for scalable serial monitoring — with harmonised kPL and flux reporting (De Feyter et al., 2018; Serkova; Brown, 2012; Woitek; Gallagher, 2021).

Third, genotype-specific metabolic surveillance: the IDH–2-HG paradigm will be generalised as further genotype–metabolite links are validated, and MRS-visible resistance phenotypes will be monitored as part of adaptive therapy strategies (Gul et al., 2025; Lodi; Ronen, 2011; Ward et al., 2010). Fourth, integration with immunotherapy monitoring, where metabolic readouts of the tumour–immune interface may resolve the pseudoprogression problem that anatomical imaging cannot (Manton et al., 2006; Viswanath et al., 2018). Fifth, closed-loop theranostics, in which engineered delivery systems are developed together with their MRS pharmacodynamic readouts from the outset (Mignon et al., 2014; Peng et al., 2025; Saito et al., 2015). Underpinning all five is the computational layer — AI-assisted spectral analysis and multimodal fusion — that will determine whether metabolic imaging scales beyond expert centres (Andronesi et al., 2018; Zeng; Sun, 2025; Zhang et al., 2026).

Hardware trajectories point the same way. Ultrahigh-field (7 T) systems improve spectral dispersion and signal-to-noise, shrinking voxels and acquisition times and improving detection of low-concentration metabolites such as 2-HG and glycine (Cheng et al., 2005; Cho et al., 2016; Tiwari et al., 2020). Cryogenic and high-temperature-superconductor coil technologies, parallel-transmit pulses and motion-robust sequences extend body MRSI toward the robustness that abdominal monitoring demands (Andronesi et al., 2018; Woitek; Gallagher, 2021).

On the tracer side, next-generation polarisers with higher throughput and lower per-dose cost, and the emergence of DMI as a hardware-light alternative, together suggest that flux imaging will follow the diffusion-MRI path from exotic to routine over the coming decade (De Feyter et al., 2018; Hesketh; Brindle, 2018; Serkova; Brown, 2012). If that trajectory holds, the limiting factor for metabolic monitoring of targeted therapy will soon be neither physics nor biology but the will to standardise and validate — a conclusion that is, for a field accustomed to technical excuses, an unusually optimistic place to stand (Serrao; Brindle, 2016; Woitek; Gallagher, 2021).

10. Conclusions

Magnetic resonance spectroscopy has matured from a research technique into a coherent biomarker platform whose value proposition is precisely aligned with the needs of targeted oncology: it measures the pathway-proximal metabolic consequences of drug action, non-invasively and repeatedly, at a timepoint when therapeutic decisions are still reversible. The evidence base now spans genotype-specific oncometabolite tracking in glioma, choline-based response prediction in breast cancer, flux imaging of androgen-targeted therapy in prostate cancer, and pathway-pharmacodynamic validation across kinase, PI3K/mTOR, IDH, antiangiogenic and endocrine agents.

The remaining barriers — harmonisation, quantification standards, prospective multicentre validation and regulatory qualification — are concrete and addressable. Functional imaging beyond anatomy, anchored in MRS-detectable metabolic biomarkers, is best understood not as a replacement for size-based criteria but as the early-decision layer above them: the modality that answers, within days of the first dose, the question every targeted therapy poses — is the drug hitting its target, in this patient, now?

11. Authors' Contributions

Hao Sun: conceptualization, methodology, investigation, data curation, writing – original draft, writing – review & editing, project administration, and corresponding/submission administration. *Xiaojun Dong*: methodology, investigation, data curation, and writing – review & editing. *Jinze Yu*: investigation, data curation, and writing – review & editing. *Yuanyin Teng*: investigation, formal analysis, and writing – review & editing. *Gaoyang Guo*:

methodology, investigation, and writing – review & editing. *Liangyu Li*: investigation, formal analysis, and writing – review & editing. *Wei Wang*: validation, investigation, and writing – review & editing. *Bing Liu*: supervision, validation, and writing – review & editing. *Yuquan Li*: supervision, conceptualization, and writing – review & editing. *Keyang Xu*: conceptualization, supervision, project administration, and writing – review & editing.

12. Conflicts of Interest

No conflicts of interest.

13. Ethics Approval

Not applicable.

14. Artificial Intelligence Statement: Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

Generative AI and AI-assisted tools were used solely to assist with English and Portuguese grammar and language editing during the preparation of this manuscript. No AI tools were used to generate or modify the scientific content, figures, images, schemes, or tables. All AI-assisted text was reviewed, verified, and approved by the authors, who assume full responsibility for the accuracy, integrity, and final content of the manuscript. AI tools are not authors and do not assume any responsibility for the content.

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