

Perspective

Functional Imaging in Osteoarthritis: Bridging Mechanistic Insight and Therapeutic Translation

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ABSTRACT: Functional imaging provides a decision-oriented framework for evaluating osteoarthritis (OA) beyond late structural morphology. OA is a heterogeneous, aging-associated whole-joint disease in which cartilage matrix disruption, synovial inflammation, subchondral bone remodelling, altered mechanics, and pain-circuitry changes may evolve before radiographic end-stage features dominate. Conventional radiography and symptom scores remain indispensable, but they provide limited information about active biological processes and are often poorly aligned with pain, progression risk, or treatment response. In this Perspective, we argue that functional imaging should be selected according to a defined decision context rather than technical novelty alone. Quantitative and compositional magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI, selected positron emission tomography (PET)-based approaches, procedure-linked optical coherence tomography, neurofunctional imaging, mass spectrometry imaging, and isotope-informed spatial methods occupy different positions along the translational pathway. Near-term clinical and trial value is most plausible for risk enrichment, mechanistic phenotyping, longitudinal monitoring, and target-engagement assessment; discovery platforms remain essential for target nomination and endotype refinement. We therefore propose a restrained roadmap that separates candidate signals from qualified biomarkers and prioritises reproducibility, biological specificity, and clinical utility.

Keywords: Imaging, Biomarker, Molecular Imaging, Osteoarthritis, Microenvironment, Function

1. Introduction

Osteoarthritis (OA) is an escalating global health burden, fuelled by population aging and rising obesity rates, with major consequences for disability and health-service demand. The latest Global Burden of Disease estimates

suggest that ~595 million people were living with OA in 2020 (7.6% of the global population), with case numbers increasing by ~132% since 1990 and projected to rise further to 2050 across major joint sites [1]. Despite growing recognition of OA as a whole-joint disease, routine diagnosis and staging remain largely symptom-led

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and radiography-dependent. While radiographs capture mineralised changes such as osteophytes and joint space narrowing, they are insensitive to non-mineralised tissues and early biological activity. MRI and ultrasound are typically reserved for specific indications [2]. Patient-reported outcome measures (PROMs) [3], including Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), standardise the assessment of pain and function; however, they neither localise active tissue pathology nor reliably identify pre-radiographic disease, and symptoms often correlate only weakly with structural change—particularly early in the course of OA [4]. Consequently, management remains predominantly symptom-directed (education, exercise, topical/oral nonsteroidal anti-inflammatory drugs (NSAIDs)) [5], with arthroplasty as the definitive option for end-stage, refractory disease, underscoring the limited clinical uptake of disease-modifying therapies [5]. These constraints support a shift from late structural diagnosis towards earlier, mechanism-informed detection of joint dysfunction and treatable phenotypes—integrating evidence of synovial inflammation, altered subchondral perfusion and vascular changes, aberrant joint mechanobiology, metabolic dysregulation, and altered pain processing [6].

Functional imaging extends OA assessment beyond static structural morphology by measuring biological function alongside anatomy. In this Perspective, we use the term broadly to encompass imaging and image-linked analytical approaches that capture molecular, physiological, biomechanical, metabolic, or neurobiological activity rather than structural appearance alone. These methods commonly rely on dynamic acquisition, quantitative modelling, targeted tracers or probes, or spatial chemical mapping to capture processes relevant to OA biology [7, 8]. In OA, functional imaging can interrogate several complementary domains, including synovial inflammation and perfusion, cartilage composition and microstructure, subchondral bone metabolism and turnover, and central pain-network processing [7, 8]. Examples considered here include functional mass spectrometry imaging (MSI), which maps the spatial distribution of lipids, metabolites, and proteins within joint tissues [8, 9]; functional magnetic resonance imaging (fMRI), which characterises brain activity and connectivity relevant to pain phenotypes and central sensitisation [10–12]; in vivo molecular imaging approaches, including positron emission tomography (PET), single-photon emission computed tomography (SPECT), and targeted probes that visualise inflammatory or bone-remodelling processes [13–15]; stable-isotope tracing, which quantifies pathway fluxes and turnover that cannot be inferred from steady-state abundance alone [16, 17]; and dynamic time-series methods, such as dynamic

contrast-enhanced magnetic resonance imaging (DCE-MRI), which derive quantitative perfusion and synovitis-related kinetic measures [18]. Because these approaches differ in biological target, spatial scale, and translational maturity, functional imaging should not be treated as a single technology or biomarker class [19–21]. Each modality samples a different level of OA biology, and its clinical interpretation depends on the intended use case, such as risk enrichment, prognostication, stratification, or treatment monitoring, as well as the strength of analytical and clinical validation [8, 19, 20]. To avoid overstating clinical maturity, we use the term biomarker only when an imaging-derived measure has been evaluated in a defined context of use and supported by an appropriate validation process. Where such a qualification remains incomplete, more cautious terms such as functional signal, imaging measure, or candidate biomarker are used instead. Accordingly, this Perspective distinguishes exploratory functional signals, candidate biomarkers for defined trial contexts, and qualified biomarkers that have sufficient analytical and clinical evidence for a specified use.

The most defensible role for functional imaging in early OA is not routine early diagnosis, but risk enrichment and mechanism-informed phenotyping. Quantitative imaging can capture compositional, perfusion, metabolic, mechanical, or neural readouts that complement symptoms and morphology when the clinical question is explicit. For example, cartilage compositional MRI may support pre-radiographic risk assessment, dynamic or contrast-enhanced approaches may interrogate synovial activity and perfusion, and load-informed methods may clarify biomechanical drivers. These signals should be interpreted as candidate biomarkers until their repeatability, biological specificity, and longitudinal relevance have been demonstrated in the intended context of use [21–24].

This Perspective therefore organises the field by translational readiness rather than by modality catalogue. We distinguish in vivo clinical or near-clinical imaging, procedure-linked imaging, ex vivo spatial biology platforms, and discovery-stage mechanistic methods. For each category, the central question is what decision the signal can support: cohort enrichment, endotype assignment, target engagement, response monitoring, or hypothesis generation (Fig. 1).

2. From joint biology to imaging endotypes and decisions

OA is best framed as a heterogeneous, whole-joint disorder rather than an isolated cartilage disease. Pathobiology encompasses cartilage, synovium, subchondral bone, meniscus, ligaments, and periarticular muscle, and, particularly in early disease, often presents

as functional dysregulation (altered tissue mechanics, vascular and inflammatory activity, and nociceptive processing) before irreversible structural loss becomes radiographically evident [25-27] (**Fig. 2**). This biology–time mismatch helps explain why symptoms and plain

radiography can be weakly aligned with contemporaneous disease activity, and why short-term responses to intervention may be difficult to capture using static morphology alone [28, 29] (**Table 1**).

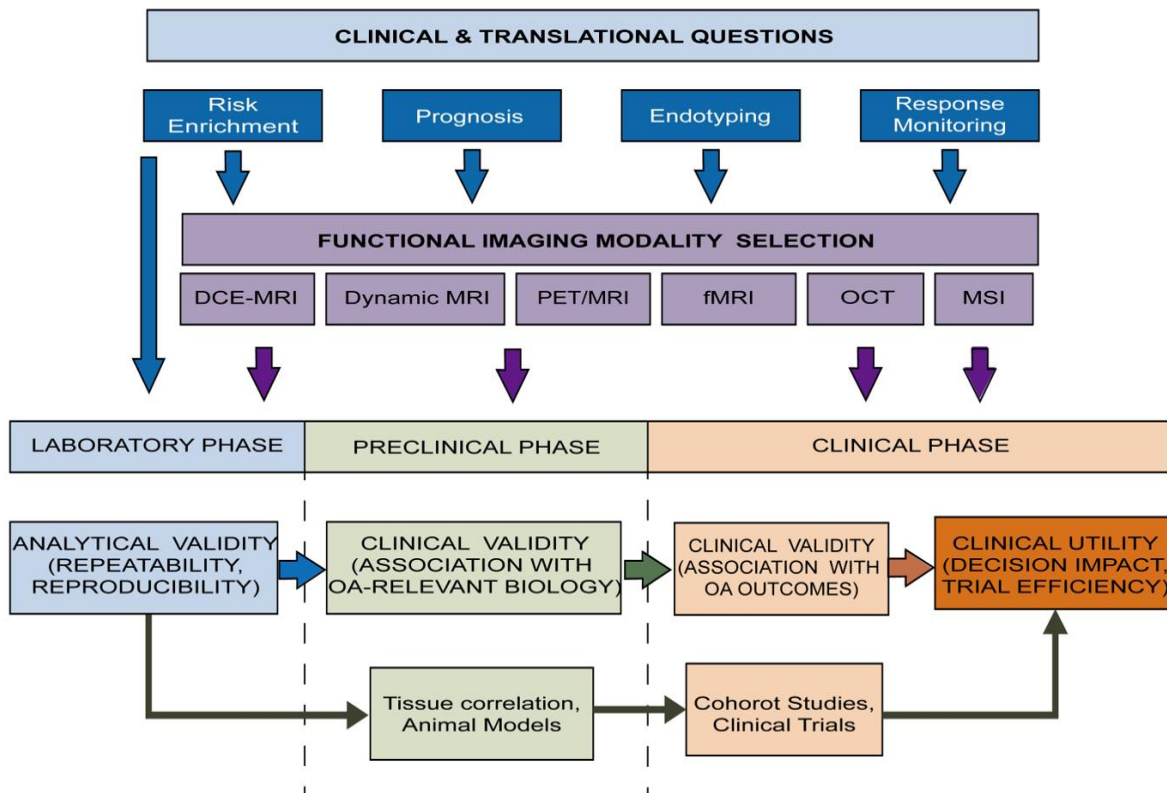


Figure 1. Decision-first research design for functional imaging biomarkers in osteoarthritis. Functional imaging modalities are selected based on specific clinical and translational questions, including risk enrichment, prognosis, endotyping, and response monitoring. Biomarkers progress from laboratory and preclinical validation (analytical validity: repeatability and reproducibility) to clinical validation (association with OA-relevant biology and outcomes), ultimately supporting clinical utility through decision impact and improved trial efficiency. DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; MRI: magnetic resonance imaging; PET/MRI: positron emission tomography/magnetic resonance imaging; fMRI: functional magnetic resonance imaging; OCT: optical coherence tomography; MSI: mass spectrometry imaging; OA: osteoarthritis.

2.1 What decision is the imaging-derived measure meant to support?

Functional imaging in OA should not be appraised as a universally “better scan”; rather, its utility is contingent on whether it addresses a clearly defined clinical or translational decision problem, since distinct applications require distinct evidentiary thresholds [30, 31]. For risk enrichment or early mechanism-informed assessment, identifying individuals most likely to progress requires longitudinal evidence, preferably with external validation and incremental predictive value beyond established risk factors and conventional imaging. Longitudinal MRI-derived features, including bone marrow lesion trajectories and radiomics-based signatures, have been

associated with incident or progressive OA outcomes [32, 33]. By contrast, mechanistic stratification asks whether imaging can identify which tissue compartment or biological process predominates in a given patient. This requires the imaging signal to be anchored to relevant biology, such as synovial inflammation, bone remodelling activity, or cartilage microstructural disruption, and supported by reproducible associations with structural, symptomatic, biochemical, or tissue-level features of OA through convergent validation using histology, biochemical markers, or orthogonal imaging modalities [13, 34, 35]. For mechanism-matched trial enrichment, the evidentiary standard is higher still: the signal should support effect modification or enrichment in clinical trials, meaning that an imaging-defined subgroup derives

greater benefit from a mechanism-aligned therapy than an unselected population. In practice, this may begin with feasibility or pilot data showing that imaging-defined inflammatory activity correlates with symptomatic response, thereby motivating enrichment strategies in subsequent trials [36, 37]. Finally, for response monitoring, including assessment of whether an intervention engages its target and alters disease activity, evidence should include short-interval sensitivity to

change, test/retest reliability, and interpretable links to clinically meaningful outcomes; quantitative dynamic results, such as dynamic contrast-enhanced MRI (DCE-MRI) synovitis kinetics, illustrate how repeatability and responsiveness can be explicitly evaluated for experimental medicine. Overall, a central implication is that an imaging biomarker may be scientifically informative yet clinically unhelpful if it is not interpreted within a defined decision context [30, 31].

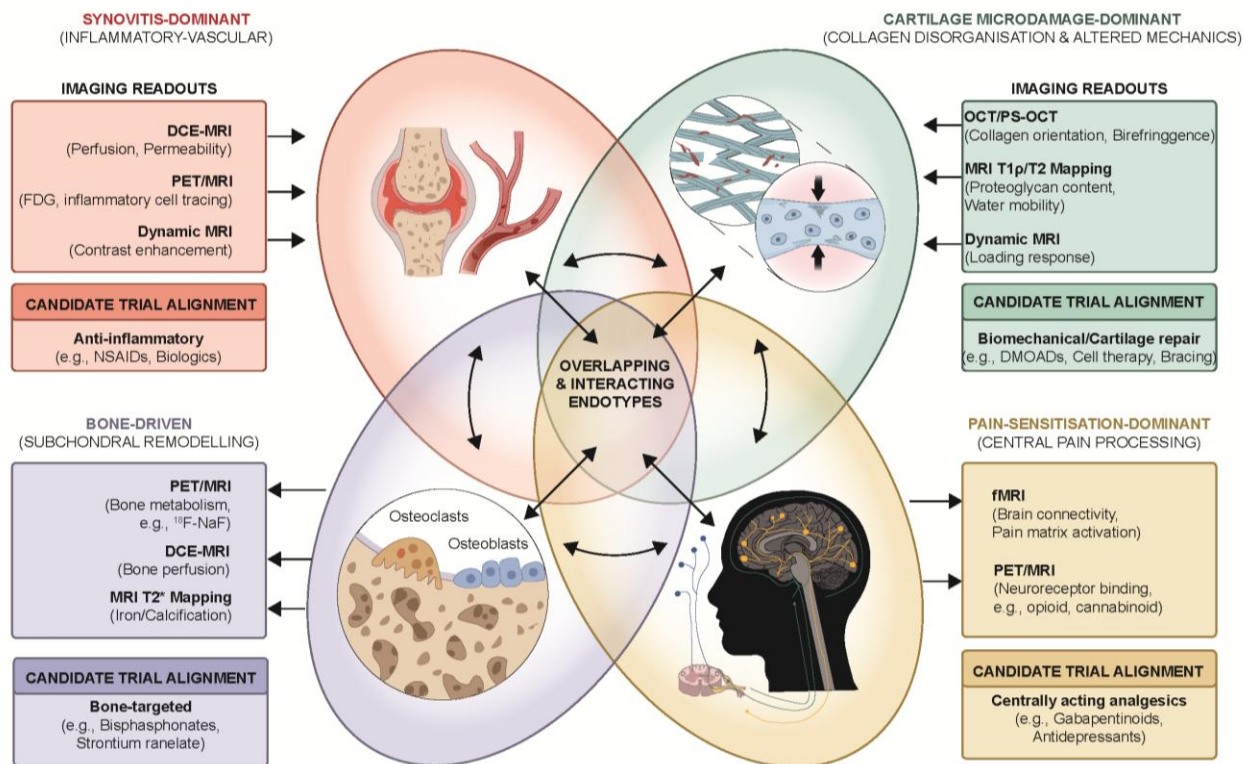


Figure 2. Mechanistic mapping of functional imaging domains to osteoarthritis endotypes. Osteoarthritis can be stratified into partially overlapping endotypes based on dominant biological processes, including synovitis-dominant (inflammatory-vascular), cartilage microdamage-dominant (collagen disorganisation and altered mechanics), bone-driven (subchondral remodelling), and pain-sensitisation-dominant (central pain processing) phenotypes. Each endotype is linked to functional imaging readouts and candidate trial-alignment hypotheses, which require prospective validation. DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; PET/MRI: positron emission tomography/magnetic resonance imaging; FDG: fluorodeoxyglucose; NSAIDs: non-steroidal anti-inflammatory drugs; OCT: optical coherence tomography; PS-OCT: polarisation-sensitive optical coherence tomography; MRI: magnetic resonance imaging; T1ρ: spin-lattice relaxation in the rotating frame; T2: transverse relaxation time; DMOADs: disease-modifying osteoarthritis drugs; ^{18}F -NaF: fluorine-18 sodium fluoride; fMRI: functional magnetic resonance imaging.

2.2 From pathobiology to measurable domains

We define four interacting domains to organise functional imaging targets in OA; each domain aligns with a distinct set of biological processes and, consequently, requires different measurement strategies. First, cartilage matrix integrity and mechanics can change early through collagen disorganisation, proteoglycan-associated shifts in tissue properties, microdamage, and spatially localised abnormalities in load-related deformation and strain,

often emerging before overt morphological loss [23, 38, 39]. Accordingly, microstructural and procedure-linked methods, such as polarisation-sensitive optical coherence tomography (PS-OCT), provide a practical route to collagen-sensitive assessment in contexts where arthroscopy is already clinically indicated [39, 40].

Moreover, subchondral bone physiology and adaptation may plausibly drive progression in a subset of patients through altered turnover, mineralisation patterns that reflect chronic loading, microdamage repair, and

changes in osteochondral perfusion. In this setting, tracer-based approaches and hybrid platforms enable quantification of metabolically active bone remodelling while simultaneously assessing cartilage composition

within the same joint [35, 41, 42]. Meanwhile, evidence syntheses indicate that SPECT/CT-derived bone activity metrics may contribute to OA phenotyping and prognosis, albeit with recognised limitations [43].

Table 1. Decision-oriented OA imaging endotypes and required functional information.

Clinical question/decision context	Dominant biological driver	Required functional information (not modality-specific)	Spatial focus	What structural imaging alone cannot resolve	Decision enabled
Is pain driven by joint inflammation or central sensitisation?	Synovial inflammatory activity vs. altered pain processing	Inflammatory activity dynamics vs. nociceptive network engagement	Joint vs. CNS	Pain–structure discordance; normal radiographs despite severe pain	Stratification for peripheral anti-inflammatory vs. centrally acting interventions
Is disease progression primarily load-driven?	Abnormal joint mechanics and subchondral bone adaptation	Load-dependent tissue response; dynamic contact behaviour	Whole joint under motion or load	Static morphology underestimates mechanical drivers	Selection of biomechanical corrections (bracing, osteotomy, rehabilitation)
Is cartilage matrix undergoing early biochemical failure?	Collagen disorganisation and proteoglycan depletion	Matrix integrity and compositional change prior to thickness loss	Cartilage zonal structure	Morphology remains preserved in early degeneration	Early identification of candidates for disease-modifying trials
Is there ongoing molecular activity despite minimal structural change?	Enzymatic activity, inflammatory or catabolic signalling	Spatially localised molecular activity	Tissue or joint subregions	Structural imaging is insensitive to molecular processes	Target engagement assessment; biological enrichment of trial cohorts
Is tissue viability compromised by metabolic stress or hypoxia?	Altered cellular metabolism and oxygenation	Metabolic flux and oxygen availability	Cartilage–bone interface	Structural changes lag behind metabolic dysfunction	Identification of metabolically vulnerable tissue and early intervention

CNS: central nervous system; OA: osteoarthritis.

Furthermore, synovial and osteochondral inflammation/metabolism encompass dynamic, low-grade processes, such as synovial inflammation and vascularity, immune activation, enzymatic activity, oxidative stress, and metabolic rewiring across synovial and osteochondral compartments, which may better reflect symptom variability and response to anti-inflammatory therapy than static structural measures [34, 44]. Therefore, functional imaging techniques such as quantitative DCE-MRI, with explicit evaluation of repeatability and sensitivity to change, are particularly relevant [18]. In parallel, molecular imaging is expanding to more specific inflammatory targets [13]. Finally, pain processing from peripheral and central nerves integrates nociceptive input from joint tissues with central modulation and sensitisation, thereby accounting for the frequent mismatch between pain severity and structural findings. As a result, neurofunctional endpoints can usefully complement joint-tissue measures, particularly in analgesic trials and pain endotyping [10, 45, 46].

2.3 Imaging “endotypes” as a unifying storyline

OA heterogeneity is a key explanation for why disease-modifying trials have frequently underperformed: even among patients with comparable radiographic severity, the dominant biological drivers and subsequent trajectories can differ substantially. In this context, functional imaging is most impactful when it enables endotyping and delineates biologically coherent subgroups that carry distinct risks of progression and, ultimately, exhibit differential responsiveness to treatment [36, 47, 48].

A pragmatic, hypothesis-driven framework can include several endotypes. First, a synovitis-dominant endotype is characterised by elevated perfusion- or inflammation-associated signals and more variable symptom patterns; consequently, it provides a candidate rationale for testing anti-inflammatory or immunomodulatory strategies in trial designs that enrich for inflammatory activity [35, 42, 43]. Second, a bone-driven endotype exhibits heightened subchondral

metabolic activity or adaptive signals, which may plausibly align with more rapid structural deterioration. Therefore, it represents a candidate subgroup for bone-targeted interventions, provided that phenotyping is rigorous and outcomes are carefully validated [23, 38, 39]. Third, a cartilage microdamage–dominant endotype features focal collagen disorganisation and early mechanical compromise, accompanied by relatively limited synovitis; accordingly, it may generate candidate hypotheses for evaluating biomechanical unloading, alignment approaches, or cartilage repair strategies in appropriately stratified studies [23, 38, 39]. Fourth, a pain-sensitisation–dominant endotype presents with pain disproportionate to structural joint findings, alongside sensitisation or neurofunctional signatures; thus, it may provide a candidate rationale for evaluating centrally acting analgesics or multimodal pain-management strategies in stratified studies, with neurofunctional readouts serving as complementary exploratory or pharmacodynamic endpoints [10, 45, 46]. Critically, these endotypes should not be treated as mutually exclusive, because overlap is expected and biologically plausible. Therefore, the near-term priority is not to establish a definitive taxonomy, but rather to develop a clinically usable stratification approach that improves prognostic precision and increases trial signal-to-noise [25, 47].

2.4 What turns a functional signal into a qualified biomarker?

A recurring limitation in the field is the premature designation of an imaging contrast or derived feature as a “biomarker” before it has undergone even minimal qualification [30, 31]. Therefore, for functional imaging biomarkers in OA, explicit and consistent evidentiary expectations should be stated. First, analytical validity should be demonstrated through repeatable acquisition and robust quantification, including test/retest, reader reproducibility, and inter-site comparability, ideally supported by pre-specified pipelines. In this context, quantitative DCE-MRI measures of synovitis provide a practical example of how repeatability and sensitivity to change can be evaluated directly [18]. Second, clinical validity should be established by showing a reproducible association with OA-relevant states, such as early disease, risk of progression, flare-related biology, or treatment response, in independent cohorts; accordingly, evidence that synovitis can be detected in pre-radiographic or early OA illustrates how functional signals may precede structural changes visible on radiographs [34, 49]. Third, clinical utility should be demonstrated by evidence of improvement in clinical decision-making, patient outcomes, or trial efficiency relative to standard measures; however, this remains the most stringent

criterion and is frequently absent, even when analytical and clinical validity appear promising [31]. In parallel, OA-specific validation should address confounding and causal interpretation, because vascular-derived signals may reflect systemic influences, tracer uptake can vary with activity, and pain-network signatures are often shaped by comorbid mood and sleep disturbances. Consequently, rigorous studies should incorporate appropriate control conditions, conduct sensitivity analyses, and define preregistered endpoints to strengthen interpretability and support translation [28, 31].

2.5 A modality-to-decision mapping principle

Because no single imaging approach can comprehensively interrogate every relevant biological domain, a practical principle is to align modality selection with the biological proximity of the research or clinical question. Thus, when the focus is on cartilage microstructure or collagen organisation, modalities with strong microstructural sensitivity should be prioritised, such as PS-OCT in procedure-linked settings and, where appropriate, compositional quantitative MRI (qMRI) [23, 39, 40]. When the focus shifts to bone turnover or subchondral activity, tracer-based methods or bone-adaptation indicators are more informative, including ^{18}F -NaF PET, SPECT/CT in carefully defined contexts, and PET–MRI for integrated assessment [35, 42, 43]. Similarly, when the key question concerns synovial activity and dynamic inflammation, emphasis should be placed on perfusion- and inflammation-linked measures, notably DCE-MRI, complemented by emerging molecular tracers when adequately justified [13, 18]. In contrast, when interrogating pain mechanisms or analgesic responses, neurofunctional endpoints should be incorporated as complementary measures that augment, rather than replace, joint-tissue assessment [10, 45]. Finally, an important controversy to foreground is the commonly cited pain–structure discordance: rather than representing a “failure” of imaging, a functional framework renders it a tractable biological question, thereby motivating parallel evaluation of joint tissues and pain processing instead of relying on any single structural metric to account for symptoms [28, 29].

3. Functional imaging modalities for OA: a translational-readiness framework

Functional imaging methods in OA differ not only in technical principle, but also in biological proximity, clinical accessibility, and readiness for trial use. These differences determine the biological question each approach can address, the decision context in which it is most useful, and the evidentiary boundary that should

guide cautious interpretation and wording (Table 2). Accordingly, the field is best organised not as a catalogue of modalities, but as a translational-readiness framework. Here, we group functional imaging strategies into near-

clinical and trial-enabling approaches, procedure-linked and clinical-adjacent approaches, pain-mechanism imaging, and discovery-oriented spatial and molecular platforms (Fig. 3).

Table 2. Functional imaging modalities in OA: principles, spatial characteristics, and translational relevance.

Modality / readout	Primary OA question	Best-fit use	Translational status	Key constraints	Evidence boundary	Recommended wording
Quantitative/compositional MRI; DCE-MRI	Cartilage composition, synovitis, perfusion, early tissue activity	Risk enrichment; longitudinal monitoring/target-engagement	Near-clinical / trial-enabling	Protocol harmonisation; kinetic modelling; contrast safety	Not a stand-alone early diagnostic replacement	Candidate biomarker when repeatability and context of use are defined
PET-MRI, ¹⁸F-NaF PET, selected PET/SPECT	Bone turnover, inflammatory activity, bone-cartilage coupling	Mechanism-focused studies; selected trial enrichment/target-engagement assessment	Specialised trial-adjacent/mechanism-focused	Cost, access, radiation, tracer specificity, threshold validation	Use for defined hypotheses rather than broad screening	Specialised mechanism-focused candidate readout
OCT / PS-OCT	Cartilage surface, collagen organisation, microstructural mechanics	Arthroscopy-adjacent lesion assessment; repair monitoring	Procedure-linked	Limited depth; procedural access; limited biochemical specificity	Not suitable for population-level screening	Procedure-linked microstructural assessment
fMRI and pain-network imaging	Central pain processing and sensitisation-related phenotypes	Pain-mechanism stratification; pharmacodynamic endpoints	Trial-enabling for selected pain studies	Task design, medication, sleep, mood, scanner/preprocessing effects	Not joint-region diagnostic imaging	Complementary pain-circuit phenotyping
MSI and isotope-informed spatial platforms	Spatial molecular heterogeneity; metabolic flux; target nomination	Endotype refinement; tracer and target development	Ex vivo discovery/early translational	Small cohorts, semi-quantitation, matrix effects, reproducibility	Requires orthogonal and cross-cohort validation	Discovery-stage mechanistic platform
AI-enabled quantification	Segmentation, harmonisation, reproducible feature extraction	Workflow support across imaging modalities	Enabling layer	Dataset shift, shortcut learning, external validation, reporting quality	Does not substitute for biological validation	Analytical support tool

OA: osteoarthritis; AI: artificial intelligence; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; fMRI: functional magnetic resonance imaging; ¹⁸F-NaF: fluorine-18 sodium fluoride; MRI: magnetic resonance imaging; MSI: mass spectrometry imaging; OCT: optical coherence tomography; PET: positron emission tomography; PET-MRI: positron emission tomography–magnetic resonance imaging; PS-OCT: polarisation-sensitive optical coherence tomography; SPECT: single-photon emission computed tomography.

3.1 Near-clinical and trial-enabling approaches

The most mature near-term opportunities lie in methods that already sit close to clinical imaging or trial workflows. Quantitative and compositional MRI, including T2, T1ρ and related cartilage mapping approaches, can detect matrix-associated changes before overt morphological cartilage loss becomes dominant [19–23, 50, 51]. These measures are most relevant when the question concerns early cartilage biochemical change, risk enrichment, or longitudinal monitoring. However, their value depends on standardised acquisition,

reproducible segmentation, and interpretation within a defined context of use. They should therefore be framed as candidate biomarkers for specific trial or cohort-enrichment settings, rather than as stand-alone replacements for radiography or conventional MRI [19, 21, 23].

DCE-MRI provides a complementary functional readout by quantifying synovial perfusion and inflammation-related enhancement kinetics. This is particularly relevant in OA because synovitis and vascular activity may contribute to symptoms, flare biology, and treatment response even when structural change is modest

[18, 34, 44]. Prospective work has also shown that DCE-MRI measures can be evaluated for repeatability, discrimination, and sensitivity to change, making this approach suitable for experimental medicine and inflammatory enrichment designs [18]. At the same time, DCE-MRI remains sensitive to acquisition timing, kinetic modelling, and contrast use. Its strongest near-term role is therefore as a candidate pharmacodynamic or enrichment readout when the inflammatory question is prespecified, not as a general-purpose OA scan.

Selected PET-based strategies, particularly PET/MRI and ^{18}F -NaF PET, are best positioned as specialised trial-adjacent approaches rather than as broadly near-clinical tools. By measuring bone turnover, subchondral

metabolic activity, and bone-cartilage coupling, they can address mechanism-focused questions that are not captured by structural MRI alone [14, 35, 42, 52, 53]. Their most defensible use is selected trial enrichment, target-engagement assessment, or multimodal studies in which cartilage, synovium, and subchondral bone are interrogated within the same joint. Nevertheless, cost, access, radiation exposure, tracer specificity, kinetic modelling, and threshold validation currently limit broad deployment. PET/MRI and ^{18}F -NaF PET should therefore be described as specialised mechanism-focused candidate readouts for defined OA questions, rather than as routine clinical endpoints or fully qualified trial biomarkers.

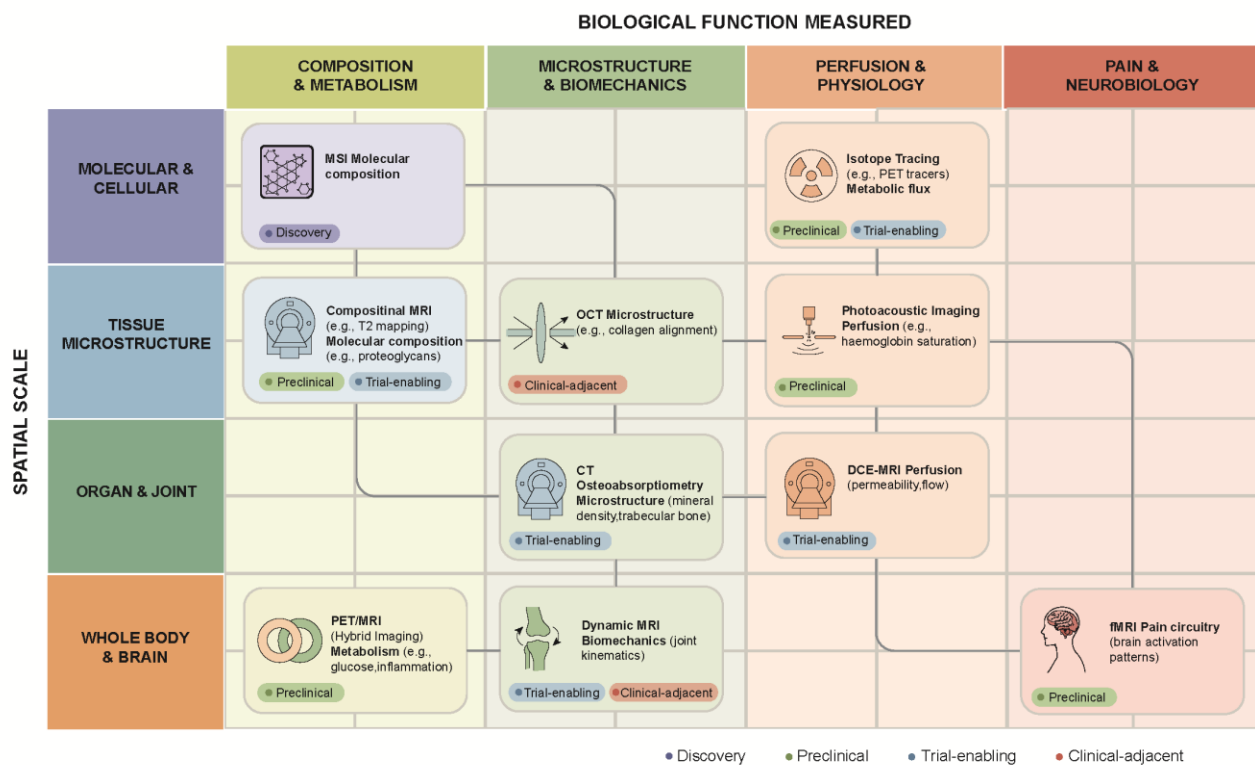


Figure 3. Translational hierarchy of functional imaging modalities across spatial and biological scales in OA. Different methods provide complementary views across biological layers, time windows, and spatial scales, but they do not occupy the same translational position. The figure uses four cautious, non-exclusive readiness labels: ex vivo discovery, preclinical/early translational, procedure-linked/clinical-adjacent, and near-clinical/trial-enabling. Some modalities may span more than one readiness category depending on tracer or probe design, acquisition protocol, validation status, and context of use. These labels should therefore be read as translational positioning rather than biomarker qualification. Here, “clinical-adjacent” includes procedure-linked approaches that are close to existing clinical workflows but are not suitable for broad screening or routine clinical deployment. Functional imaging techniques are positioned according to the biological processes they probe, including composition and metabolism, microstructure and biomechanics, perfusion and physiology, and pain and neurobiology, as well as their relevant spatial scales from molecular and cellular levels to whole-joint and brain-level readouts. This hierarchy emphasises that mass spectrometry imaging and isotope-linked spatial methods remain primarily discovery-oriented, optical coherence tomography is procedure-linked, and quantitative or compositional MRI, as well as dynamic contrast-enhanced MRI, are closer to defined trial-enabling contexts. MSI: mass spectrometry imaging; MRI: magnetic resonance imaging; OCT: optical coherence tomography; CT: computed tomography; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; PET: positron emission tomography; PET/MRI: positron emission tomography/magnetic resonance imaging; fMRI: functional magnetic resonance imaging.

3.2 Procedure-linked and clinical-adjacent approaches

Procedure-linked approaches occupy a different translational niche. They may be close to clinical workflows, but only in selected settings where access to the joint is already justified. OCT provides real-time, high-resolution cross-sectional imaging of cartilage microstructure using backscattered light [54, 55]. In OA, its main value is not broad screening, but arthroscopy-adjacent assessment of cartilage surface integrity, subsurface disruption, and repair tissue quality [55, 56]. PS-OCT adds further biological relevance by detecting collagen organisation through birefringence changes, which makes it attractive for early cartilage microdamage assessment and repair monitoring [39, 40, 57].

The key limitation is practical rather than conceptual. OCT and PS-OCT can reveal microstructural features that may be underestimated by surface inspection alone, but they are constrained by penetration depth, procedural access, and limited biochemical specificity. They do not directly quantify proteoglycan loss or whole-joint disease activity [40, 55, 56]. Their most defensible positioning is therefore procedure-linked microstructural assessment: useful when arthroscopy, needle-based assessment, or cartilage repair monitoring is already being considered, but not suitable for population-level screening.

CT osteoabsorptiometry (CT-OAM) and related CT-based density-mapping approaches provide another clinical-adjacent route by assessing subchondral mineralisation as a surrogate of long-term mechanical loading and adaptation [58, 59]. This is relevant because OA progression may be shaped by malalignment, meniscal pathology, altered compartmental loading, and subchondral bone response [58, 60-64]. Compared with generic claims about “functional CT”, CT-OAM is more defensible because it capitalises on CT’s strength in mineralised tissue and links the readout to a plausible biomechanical process. However, its role should remain narrow. Radiation exposure, region-of-interest definition, limited soft-tissue contrast, and threshold standardisation restrict its use to load-informed phenotyping, surgical planning, or mechanism-focused studies rather than broad OA diagnosis.

3.3 Pain-mechanism imaging

Pain-mechanism imaging should be separated from joint-tissue imaging because it addresses a different biological level. fMRI does not image OA pathology in the joint; rather, it measures haemodynamic correlates of brain activity, commonly through blood oxygen level-dependent signals and resting-state or task-based functional connectivity [10-12, 65, 66]. This distinction is

important because OA pain often reflects a combination of peripheral nociception, synovial or subchondral activity, biomechanics, mood, sleep, and central pain modulation [28, 29, 45, 46]. In this context, fMRI and pain-network imaging are best positioned as complementary tools for pain-mechanism stratification. They may help identify patients whose pain is disproportionate to structural joint findings, distinguish nociceptive-dominant from centrally amplified pain phenotypes, and provide pharmacodynamic readouts for centrally acting or neuromodulatory interventions [10, 46, 67]. This role is particularly relevant for analgesic trials, where structural imaging alone may not explain treatment response.

However, fMRI should not be framed as a routine OA diagnostic modality. Its outputs are sensitive to task design, medication exposure, mood, sleep, comorbid pain conditions, scanner effects, and preprocessing choices [10, 46]. Therefore, its near-term translational value lies in selected pain studies and mechanistic phenotyping, not in primary joint diagnosis. In a decision-oriented framework, fMRI complements tissue-focused imaging by addressing pain–structure discordance, rather than replacing joint imaging.

3.4 Discovery-oriented spatial and molecular platforms

Discovery-oriented platforms are essential for understanding OA mechanisms, but their current role should be distinguished from trial-ready imaging endpoints. MSI enables spatially resolved mapping of lipids, metabolites, glycans, proteins, and other molecular features directly in tissue sections [68-71]. This is particularly valuable in OA because molecular changes are spatially organised across cartilage zones, lesion margins, synovium, infrapatellar fat pad, and the osteochondral interface [9, 72-77]. MSI can therefore support endotype refinement, target nomination, and spatial interpretation of disease mechanisms. At present, however, MSI remains mainly an ex vivo discovery platform. Many OA studies are relatively small, technically intensive, and semi-quantitative. Matrix effects, molecular annotation uncertainty, batch variation, and cross-platform reproducibility remain important barriers [73, 78]. Consequently, MSI-derived signals should be described as spatial molecular features or candidate mechanisms unless supported by orthogonal validation, quantitative calibration, and replication across independent cohorts.

Isotope-informed spatial methods provide a related but distinct mechanistic bridge. Stable-isotope tracing and isotope-enabled mass spectrometry can test whether metabolic pathways are functionally active, rather than

merely showing that metabolites are present [16, 17, 79-84]. In OA, these approaches may clarify chondrocyte metabolic dysfunction, synovial macrophage activity, and osteochondral metabolic stress [16, 79-83]. When combined with autoradiography, PET, or stable-isotope MSI, they can connect flux hypotheses to spatial molecular patterns and support rational tracer or target development [13, 84, 85]. Their current strength is mechanistic interpretation and tracer development, not routine clinical imaging.

Photoacoustic imaging (PAI) and activatable probes also belong primarily in the discovery or early translational category. PAI can capture haemoglobin-related vascular and oxygenation signals, whereas activatable probes are designed to report target-dependent processes such as enzymatic activity, oxidative stress, or matrix-related change [86-88]. Experimental OA studies suggest that synovial hypoxia, vascular remodelling, and cartilage-related contrast signals may track aspects of disease activity or tissue damage. These signals are biologically informative because they address dynamic microenvironmental processes that conventional structural imaging does not directly capture.

Nevertheless, these approaches should remain hypothesis-generating rather than trial-ready. Broader translation will

require safety evaluation, probe validation, reproducible acquisition and quantification, and benchmarking against established clinical imaging workflows or better-validated functional readouts in the same decision context [89]. Their most defensible near-term role is target validation, mechanism testing, probe development, and candidate-signal discovery. This cautious positioning helps preserve the central argument of this Perspective: functional imaging should be valued according to the biological question it can answer and the decision it can realistically support, rather than by technical novelty alone.

4. From images to decision-relevant biomarkers: quantification, modelling, and validation

Functional imaging is unlikely to influence OA practice or trials unless candidate readouts are reliable across settings, interpretable to end users, and linked to concrete decisions. Translation therefore requires an end-to-end workflow: define the decision context, standardise acquisition, document preprocessing and segmentation, quantify the candidate signal, and then test analytical validity, clinical validity, and clinical utility separately (Fig. 4; Table 3) [8, 30, 31].

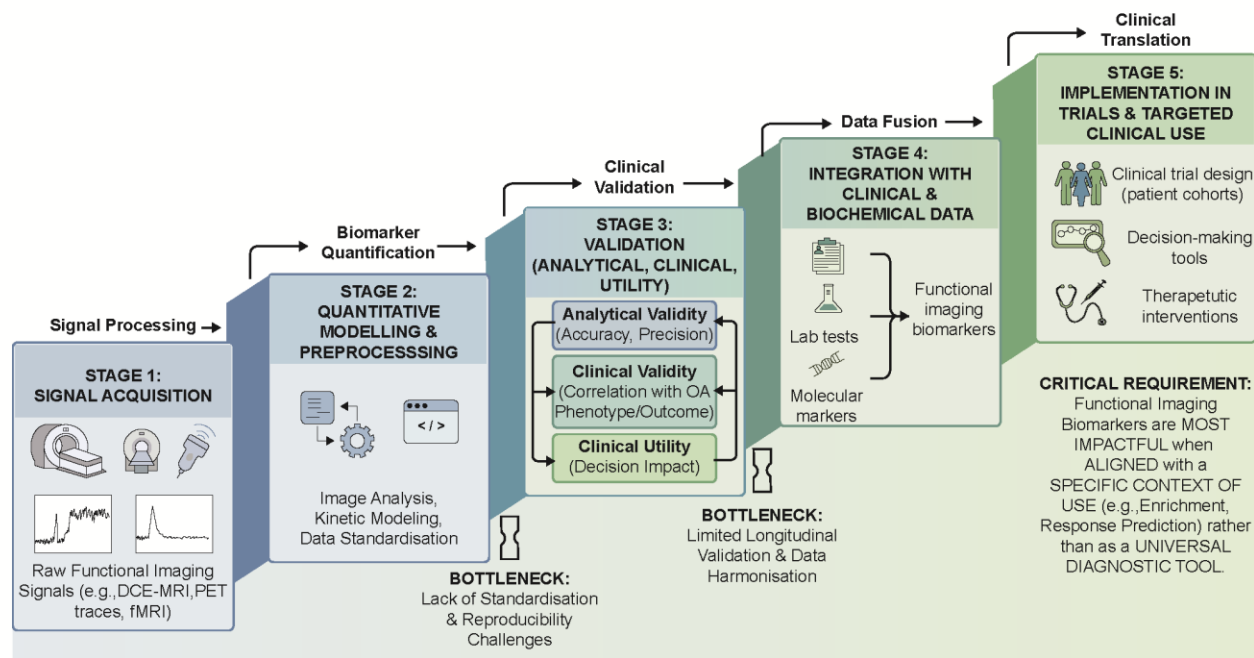


Figure 4. Translation roadmap from functional imaging signals to qualified biomarkers. Candidate functional imaging signals progress through sequential stages, including signal acquisition, quantitative modelling, validation of analytical and clinical performance, assessment of clinical utility, and integration with clinical and biochemical data, before they can be considered qualified biomarkers for targeted clinical or trial use. Key translational bottlenecks include a lack of standardisation, limited longitudinal validation, and challenges with data harmonisation. Functional imaging biomarkers are most impactful when applied within a clearly defined context of use. DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; PET: positron emission tomography; fMRI: functional magnetic resonance imaging; OA: osteoarthritis.

Table 3. Qualification and reporting framework for functional imaging signals as candidate biomarkers in OA.

Qualification stage	Core question addressed	Minimum evidence required	Typical study design	OA-specific pitfalls	Representative functional imaging examples*
Analytical validity	Is the signal technically reliable and reproducible?	• Test/retest reliability (e.g., ICC ≥ 0.75) • Intra-/inter-site reproducibility • Standardised acquisition and preprocessing pipeline • Sensitivity to change exceeds measurement noise	• Repeatability studies in stable OA cohorts • Phantom or calibration studies (where applicable) • Cross-scanner or cross-centre comparisons	• Motion artefacts during pain or dynamic tasks • Activity-dependent variability (loading, gait, recent exercise) • Scanner- and protocol-dependence	• Dynamic contrast-enhanced MRI measures of synovitis • Quantitative compositional MRI (T2, T1ρ) • Dynamic musculoskeletal MRI for joint kinematics
Clinical validity	Does the signal reflect a relevant biological process or disease phenotype?	• Association with clinically meaningful outcomes (pain, function, progression) • Discrimination of OA endotypes or disease states • Biological plausibility supported by joint biology	• Longitudinal cohort studies • Correlation with structural, molecular, or histological markers • External validation in independent cohorts	• Pain–structure discordance • Central sensitisation confounds peripheral signals • Systemic factors influencing local joint function (vascular, metabolic)	• Neurofunctional imaging of pain processing networks • Perfusion or vascular imaging of inflamed synovium • Subchondral bone functional imaging linked to mechanical loading
Clinical utility	Does the use of the signal improve decisions or outcomes?	• Demonstrated impact on trial efficiency or patient stratification • Predictive value for treatment response or disease trajectory • Actionability linked to a specific decision point	• Embedded biomarker-stratified clinical trials • Enrichment or responder-identification designs • Decision-analytic or cost-effectiveness modelling	• Overinterpretation of associative signals • Limited scalability, cost, or accessibility • Regulatory and standardisation barriers	• Neuroimaging-guided stratification in pain-modulating trials • Functional imaging endpoints for DMOAD evaluation • Multimodal imaging used to define treatable OA subgroups

*Examples are illustrative rather than exhaustive and do not imply qualification for routine clinical use. DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; DMOAD: disease-modifying osteoarthritis drug; ICC: intraclass correlation coefficient; MRI: magnetic resonance imaging; OA: osteoarthritis; T1 ρ : spin-lattice relaxation in the rotating frame, an MRI-derived compositional measure sensitive to cartilage matrix changes; T2: transverse relaxation time, an MRI-derived measure related to cartilage water content and collagen organisation.

4.1 Defining the imaging target: “What decision will this measure support?”

Early OA-relevant imaging targets may be fundamentally biomechanical, capturing strain, stress, or inferred material properties, when image-derived features are integrated with numerical modelling. However, in practice, each proposed endpoint should be anchored in a specific decision context, as the evidentiary threshold differs depending on whether the goal is risk enrichment, prognosis, mechanistic stratification, or response monitoring [90].

In practical terms, decision-relevant targets can be grouped into four partially overlapping domains. First, for earlier mechanistic detection and risk enrichment, functional imaging may help recognise biologically active joint dysfunction before clear radiographic change. At

present, however, its most realistic role is to enrich prevention or early-intervention trials rather than to serve as a population-level screening tool [91]. Second, for prognosis and progression prediction, functional readouts may help identify patients who are more likely to progress rapidly, particularly when the signal reflects active subchondral remodelling, sustained synovial inflammation, or other compartment-specific disease drivers [90, 92]. Third, for stratification or endotyping, functional imaging may support biologically plausible subgrouping, such as synovitis-dominant, bone-driven, cartilage microdamage-dominant, or centrally amplified pain phenotypes. This may help pathway-targeted interventions avoid being diluted across heterogeneous cohorts [8, 93, 94]. Fourth, for response monitoring, functional measures may provide early pharmacodynamic findings in settings where structural endpoints evolve

slowly, including quantitative synovitis measures that may shift over shorter time horizons than cartilage morphometry [18, 93].

This decision-first framing clarifies the validation pathway from technical performance to clinical validity and, ultimately, clinical utility [95]. It also helps avoid overinterpretation: a signal that is useful for mechanistic stratification may not yet be sufficient for treatment selection, and a pharmacodynamic endpoint in an early-phase trial may not automatically qualify as a routine clinical biomarker.

4.2 Acquisition and harmonisation: controlling the dominant source of variance

Across modalities, between-site and between-protocol variability can exceed the biological effects of interest, especially when biomarkers are quantitative and intended for multicentre studies. Therefore, guidance from the quantitative imaging biomarker literature consistently prioritises designing for repeatability and reproducibility from the outset, since measurement variance directly diminishes statistical power and increases required sample sizes [95, 96].

A pragmatic harmonisation core should include pre-defined acquisition parameters (for example, MRI field strength and sequence specifications, or PET reconstruction settings), systematic capture of acquisition metadata (scanner model, coil/probe configuration, calibration status, contrast dose and timing, and motion or loading conditions), and, where feasible, test/retest or phantom-based procedures to quantify drift and longitudinal stability [96]. In knee OA trials, expert recommendations for efficient, standardised MRI protocols further emphasise the selection of contrasts and endpoints that remain both biologically informative and operationally feasible across sites [97].

Notably, dynamic techniques are particularly vulnerable to protocol deviation because their quantitative outputs depend on multiple tightly coupled steps. In synovitis assessment, for example, DCE-MRI parameters reflect acquisition timing, signal processing, and pharmacokinetic modelling choices; even modest inconsistencies can propagate into meaningfully different parameter estimates, thereby compromising cross-centre comparability [18]. Similarly, for compositional cartilage MRI, standardisation initiatives and the Quantitative Imaging Biomarkers Alliance (QIBA) profiling demonstrate how protocol and analysis guidance can be formalised to improve reproducibility and strengthen multicentre translation [19, 98].

4.3 Preprocessing and segmentation: reproducibility before sophistication

Preprocessing can be framed as the set of operations that stabilise raw data for downstream quantification, including denoising, motion correction (particularly relevant for dynamic acquisitions and joint kinematics), intensity normalisation, and attenuation/scatter correction for nuclear imaging. In parallel, registration should be treated as a separate methodological layer, spanning both longitudinal alignment (baseline versus follow-up) and multimodal co-registration when localisation depends on cross-modality workflows. Segmentation should then be reported transparently as manual, semi-automated, or automated, with minimum reporting that includes inter- and intra-rater reliability for human annotation, as well as sensitivity to boundary definitions and acquisition variability for automated pipelines. In knee MRI, reproducibility studies of automated cartilage segmentation underscore that segmentation stability is quantifiable and should be reported rather than presumed [99]. Meanwhile, contemporary deep-learning approaches are increasingly enabling subregional cartilage quantification that can be evaluated for its downstream predictive value [100]. This leads to a practical implication: without reproducible segmentation, “advanced” analytics such as radiomics, modelling, and AI risk functioning as high-variance amplifiers rather than genuine improvements, a limitation repeatedly highlighted within the radiomics reproducibility literature [101].

4.4 Quantification models: biomechanics, physiology, and molecular signals

Functional imaging quantification models can be organised into three broad classes, each with characteristic vulnerabilities. For biomechanics (strain, stress, and material properties), strain is often derived more directly from deformation measured across serial images, whereas stress and material parameters typically depend on modelling assumptions and boundary conditions; therefore, model-derived metrics should be accompanied by sensitivity analyses and explicit reporting of assumptions, including constitutive model selection, loading conditions, and constraints, in line with broader calls for standardised, reproducible quantitative imaging pipelines [102]. For physiology and perfusion in dynamic imaging, pharmacokinetic parameters from DCE-MRI are notably sensitive to temporal sampling, arterial input function specification, and fitting stability; consequently, parameter identifiability and test–retest repeatability should be treated as primary outcomes rather than relegated to technical footnotes. In knee OA synovitis, prospective studies that directly evaluate repeatability, discrimination, and sensitivity to change

provide a practical template for defining what “analysis-ready” should mean for OA dynamic imaging [18]. For molecular distributions using MSI and targeted probes, it should be stated clearly that matrix-assisted laser desorption/ionisation mass spectrometry imaging (MALDI-MSI) is frequently not fully quantitative and that many studies rely on semi-quantitative relative-abundance comparisons; therefore, any claims about biomarker “magnitude” should be anchored to calibration strategies, internal standards where feasible, batch controls, and, ideally, orthogonal validation such as targeted mass spectrometry or immunoassays. Where available, practical methodological guidance for quantitative MALDI-MSI—including calibration and standardisation considerations—should be explained explicitly [78].

4.5 Statistical validation and requirements before clinical application

To support biomarker qualification, validation should follow a stepwise pathway from technical reliability to clinical usefulness. In this framework, analytical validity refers to whether an imaging-derived measure can be consistently acquired and quantified. It should include test/retest repeatability within the same scanner or site, reproducibility across scanners, sites, and operators, and robustness to preprocessing and segmentation choices. It should also assess sensitivity to key pre-analytical factors, such as recent physical activity, analgesic exposure, time of day, contrast timing, and loading conditions [18, 27]. These issues are especially important for dynamic and quantitative methods, because small differences in acquisition or modelling can materially affect parameter estimates.

Clinical validity refers to whether the measure is reproducibly associated with OA-relevant tissue states, disease features, or outcomes within a defined context of use. Relevant examples include synovial inflammation, subchondral bone metabolic activity, pain and function trajectories, and structural progression [94, 103]. Where possible, these associations should be tested under prespecified confounder control. Candidate biomarkers should also show added value beyond established clinical, imaging, or biochemical measures, using prespecified models and appropriate validation strategies [90, 92]. Clinical utility represents the highest evidentiary threshold. It refers to evidence that using the biomarker can improve clinical or trial decisions, patient outcomes, or trial efficiency beyond existing measures. In OA studies, this may include enriching trials for rapid progressors, identifying mechanism-aligned subgroups, reducing sample size, shortening the time to go/no-go decisions, or providing pharmacodynamic endpoints that

predict durable benefit [92, 93]. This distinction is particularly important in OA, because endpoints across tissue and time scales do not always change in parallel. Structural cartilage loss may correlate only weakly with worsening pain, whereas inflammatory features such as synovitis can contribute meaningfully to symptom trajectories [104, 105]. Therefore analytical validity, clinical validity, and clinical utility should be stated clearly and interpreted separately. This helps distinguish functional signals that are technically measurable from those that are biologically informative, and from those mature enough to support clinical or trial decisions.

4.6 AI and machine learning: useful, but not a substitute for biology or validation

Artificial intelligence (AI) should be positioned as an enabling layer rather than a substitute for biological reasoning. Near-term value is clearest in segmentation, quality control, harmonisation, and reproducible feature extraction [100]. Progression prediction and endotype classification require external validation, transparent reporting, and careful assessment of shortcut learning, site effects, and cohort shift, in line with updated AI-imaging reporting guidance [106-112].

4.7 Minimum reporting standards for functional imaging OA studies

A minimum reporting checklist for functional imaging OA studies should include: a clearly stated use case and hypothesis; replicable acquisition parameters; transparent preprocessing, registration, and segmentation; test/retest or reader-reliability metrics where applicable; a prespecified statistical plan; confounder handling; external validation for predictive models; and data or code sharing when feasible [95, 101, 106-108]. The key transition is from technically measurable signals to qualified candidate biomarkers with a defined context of use.

4.8 Best-fit applicability of functional imaging strategies

After acquisition and validation requirements are defined, modality selection should be guided by biological process and decision context rather than technical sophistication. For synovitis-focused studies, DCE-MRI is one of the more actionable near-term approaches because quantitative synovitis measures have repeatability and sensitivity-to-change evidence [18, 94]. For bone-driven phenotypes, ^{18}F -NaF PET and selected PET/MRI strategies are better suited to mechanism-focused studies of turnover and bone-cartilage coupling [42, 53]. OCT

and PS-OCT are most credible in arthroscopy-adjacent cartilage assessment, while MSI and isotope-informed platforms should remain discovery-oriented unless linked to validated in vivo surrogates [9, 40, 55, 56, 73]. fMRI is most appropriate for pain-mechanism stratification and pharmacodynamic endpoint development [10, 45, 67]. This best-fit mapping reinforces the central Perspective: functional imaging signals should be judged by reproducibility, biological interpretability, and decision impact, not by novelty alone.

5. Challenges, controversies, and verification priorities

Functional imaging can shift OA assessment from late-stage morphology toward mechanistic characterisation, but only if interpretive limits are made explicit. Candidate readouts may indicate activity, adaptation, compensation, or incidental change; they do not by themselves prove causality or clinical utility.

5.1 What a functional signal can and cannot mean

Correlation alone cannot establish a causal mechanism. Perfusion dynamics, tracer uptake, cartilage deformation, and neural activation can be associated with OA severity or symptoms, but longitudinal cohorts and interventional studies are required to determine whether the measured process drives progression, reflects compensation, or functions as a response marker [113].

Meanwhile, OA heterogeneity challenges any single-biomarker narrative. OA is more accurately framed as a syndrome comprising multiple, partially overlapping phenotypes/endotypes, including inflammatory or synovitis-dominant disease, meniscus–cartilage-dominant patterns, subchondral bone–dominant forms, and atrophic or hypertrophic trajectories [114, 115]. As a result, biomarker performance may differ significantly across these subgroups and between disease stages and clinical applications. Accordingly, a given functional biomarker is best interpreted within the population, disease stage, and decision context in which it is expected to provide incremental value.

The mismatch between pain symptoms and structural abnormalities should be recognised as a core area of contention rather than dismissed as a mere nuisance variable. In OA, two paradoxical presentations are frequently observed: severe pain paired with only mild structural changes, and conversely, significant structural damage accompanied by minimal pain. This pattern aligns with the combined contributions of peripheral nociceptive generators and altered central pain-processing pathways [113, 116]. Here, functional imaging can help disentangle this discordance by distinguishing peripheral tissue

activity (for example, synovitis, bone marrow lesion activity or turnover, and osteochondral vascular alterations) from processes related to central pain modulation. Nevertheless, no single modality should be positioned as a comprehensive measure or explanation of OA pain [117]. Overall, functional imaging is most informative when anchored to an explicit, testable hypothesis and a clearly defined clinical decision. With that framing in place, the next major barrier becomes methodological, namely harmonisation, reproducibility, and cross-site comparability.

5.2 Overcoming reproducibility and standardisation barriers

In the short term, progress is often limited by insufficient analytical validity. Notably, variations in data acquisition protocols, segmentation practices, and kinetic or biomechanical modelling techniques can produce results that are challenging to replicate across different research centres—and in some cases, even within the same centre when using different scanning equipment. For this reason, trial preparedness must be grounded in explicit minimum standards, including: consistency in results when tests are repeated (test/retest reliability), stability of assessments both between different evaluators and within the same evaluator (inter- and intra-rater robustness), suitable calibration processes where applicable, and predefined frameworks for data analysis [18].

Meanwhile, confounding and nuisance variability remain substantial and are highly modality-dependent. For example, perfusion-derived endpoints may be perturbed by systemic vascular status, recent physical activity, analgesic exposure, and inflammatory comorbidities. Likewise, tracer-based measures depend on acquisition timing, kinetic behaviour, clearance, and non-specific uptake. In parallel, cartilage mechanical outcomes can vary with different loading protocols and limb alignments, whereas neurofunctional changes are often influenced by factors such as mood, sleep patterns, medications, and non-OA pain conditions.

Although AI and radiomics may increase statistical power, they also introduce predictable vulnerabilities. In particular, dataset shift, scanner or site effects, and shortcut learning can yield strong apparent performance in internal datasets that diminishes when external validation is performed [109, 110]. Therefore, clinical translation should prioritise transparent reporting, careful calibration, independent external validation, and standardised, reproducible feature definitions [107, 111, 112]. Ultimately, without harmonised acquisition and analysis pipelines, functional signals are unlikely to meet the evidentiary threshold required for biomarker qualification. Moreover, even when technical rigour is

achieved, real-world impact will still be shaped by feasibility constraints, notably safety, cost, and access.

5.3 Clinical and implementation constraints: feasibility, safety, and utility

Implementation must be evaluated in terms of scalability, safety, and actionability. Procedure-linked OCT is not a screening tool; PET/MRI is more plausible for targeted trial enrichment than routine care; repeated CT, PET, or SPECT requires explicit radiation justification; and DCE-MRI must follow contemporary gadolinium safety guidance [118-120]. Even technically robust readouts will matter only if they improve trial efficiency or clinical decisions beyond current clinical, biochemical, and conventional imaging measures.

6. From late-stage structural OA to early mechanistic phenotyping

The field should now move from late-stage structural confirmation toward early mechanistic phenotyping. Functional imaging is not a competitor to radiography or standard MRI; it is a biomarker strategy for quantifying active processes in defined trial or clinical decision contexts [30, 91, 113, 121].

Three priorities are most realistic. First, quantitative and compositional MRI, DCE-MRI, and selected PET/MRI approaches should be developed as trial-facing tools for risk enrichment, synovitis or bone-turnover phenotyping, longitudinal monitoring, and target-engagement assessment [18, 42, 53, 103]. Second, OCT should be evaluated in procedure-linked niches where high-resolution cartilage assessment can influence lesion interpretation or repair monitoring [40, 57]. Third, MSI, isotope tracing, and probe-based optical methods should remain upstream discovery platforms until their signals are linked to validated in vivo surrogates or clinically measurable biomarkers [72, 74, 122].

Progress over the next 3 to 5 years is unlikely to be uniform. Near-term impact is most plausible for validated quantitative/compositional MRI, DCE-MRI in defined inflammatory settings, selected PET/MRI strategies, and multimodal frameworks that combine imaging with clinical and biochemical data. Discovery-stage approaches should be valued for target nomination and endotype refinement, not presented as ready for broad clinical deployment.

7. Conclusion

Functional imaging will be most useful in OA when it is tied to specific decision points: risk enrichment, mechanistic phenotyping, longitudinal monitoring, target-

engagement assessment, and trial-context stratification. In practical terms, approaches already close to clinical or trial workflows should be prioritised for near-term OA trial enrichment and monitoring, whereas ex vivo spatial, isotope-informed, and probe-based platforms should be framed mainly as discovery tools until their signals are validated in clinically actionable contexts. The promise of functional imaging does not lie in replacing radiography or conventional MRI, nor in becoming a generic early OA detector. Rather, its value is to make active biological processes measurable in patients or tissues where structural appearance alone is insufficient. Progress will require consensus acquisition protocols, multicentre reproducibility studies, prospective cohorts linking candidate signals to progression and symptoms, and pathway-targeted trials with pre-specified imaging endpoints. With restrained interpretation, functional imaging can help move OA research from late structural description toward mechanism-informed classification and therapeutic translation.

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Competing Interests

The authors declare no conflict of interest.

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