Neuroimaging in dementia

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Abstract

Neuroimaging contributes to dementia assessment by detecting structural lesions, characterizing neurodegenerative and vascular injury, identifying molecular pathology, and monitoring treatment safety. These functions require different acquisitions and support different levels of inference. Computed tomography remains useful when magnetic resonance imaging is unavailable, contraindicated, or poorly tolerated, whereas magnetic resonance imaging provides more complete assessment of regional atrophy, small vessel disease, diffusion restriction, and hemorrhagic lesions. Fluorodeoxyglucose positron emission tomography and perfusion single photon emission computed tomography characterize regional dysfunction; dopamine transporter imaging addresses nigrostriatal degeneration. Amyloid positron emission tomography identifies fibrillar amyloid burden, while tau positron emission tomography provides information about the distribution and severity of Alzheimer type tau aggregates. Neither a positive molecular scan nor an atrophy pattern independently establishes the cause of every cognitive symptom. The interpretation of imaging therefore requires integration with the cognitive phenotype, functional status, disease tempo, comorbidity, and the consequences of diagnostic uncertainty. This narrative review examines acquisition, interpretation, diagnostic criteria, differential diagnosis, tracer characteristics, quantification, and clinical algorithms. It also evaluates emerging biomarkers of synaptic density, neuroinflammation, astrocyte reactivity, microstructural injury, perfusion, blood–brain barrier dysfunction, susceptibility, and network organization. Particular attention is given to biological versus clinical definitions of Alzheimer disease, the limitations of early tau detection, and the distinction between amyloid clearance and clinical benefit. Imaging for antiamyloid therapy introduces an additional requirement: reproducible magnetic resonance surveillance for amyloid related imaging abnormalities. Future clinical adoption of emerging measures depends on analytical reproducibility, external validation, representative populations, and evidence that their use improves decisions or outcomes.

Keywords: dementia; magnetic resonance imaging; computed tomography; positron emission tomography; amyloid; tau; imaging biomarkers

Introduction

Dementia is a clinical syndrome defined by acquired cognitive impairment that interferes with independent function. It is not a single pathological entity. Alzheimer disease, Lewy body disease, frontotemporal lobar degeneration, cerebrovascular injury, and combinations of these processes can produce overlapping syndromes. Imaging contributes most effectively when the clinical question is explicit: exclusion of an alternative structural explanation, identification of the anatomical basis of a syndrome, assessment of a candidate pathology, estimation of progression risk, or evaluation of treatment safety. A scan that answers one question may leave the others unresolved. A structural magnetic resonance imaging examination can show hippocampal atrophy without identifying its protein substrate, and an amyloid scan can demonstrate plaques without proving that plaques explain the presenting syndrome (Dickerson et al., 2025; Jack et al., 2024).

The relation between imaging and diagnosis has changed with the development of molecular biomarkers and amyloid targeting treatments. Structural imaging was initially used predominantly to exclude mass lesions, hydrocephalus, and cerebrovascular disease. Contemporary practice also uses regional atrophy and metabolic patterns to support syndrome classification, amyloid testing to establish a treatment target, and serial magnetic resonance imaging to detect treatment associated edema and hemorrhagic injury. The 2024 Alzheimer's Association criteria and 2025 appropriate use criteria for amyloid and tau positron emission tomography formalize several of these applications, while retaining the need for clinical interpretation (Jack et al., 2024; Rabinovici, Knopman, et al., 2025).

This review addresses computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT), with particular emphasis on amyloid and tau ligands and emerging biomarkers. It treats diagnostic accuracy, prognosis, and clinical utility as separate evidentiary domains. Pathological validation supports an inference about tissue abnormalities; prospective prediction supports an inference about future outcomes; a change in clinician management does not by itself establish improved patient function or quality of life. This distinction is necessary when evaluating both established techniques and research methods.

Review approach and evidentiary scope

This paper is a narrative review, not a systematic review or meta-analysis. Its evidence base comprises peer reviewed diagnostic criteria, consensus procedure guidelines, imaging to autopsy studies, prospective cohorts, clinical trials, and methodological investigations. Priority is given to publications from 2020 onward; earlier studies are retained when they establish still used diagnostic criteria, tracer validation, quantification standards, or measurement methods. Literature retrieval used PubMed indexed records and Europe PMC metadata and abstracts, supplemented by accessible full texts and citation tracing. The review does not claim exhaustive retrieval, duplicate screening, or a formal risk of bias assessment.

Evidence is interpreted according to the population, reference standard, acquisition, and intended use. Studies of terminally ill participants with autopsy confirmation are particularly informative about tissue specificity but can over-represent advanced disease. Studies comparing clinically diagnosed Alzheimer dementia with healthy controls often provide a less demanding classification problem than the mixed and uncertain presentations encountered in memory clinics. Prognostic studies require a defined time horizon and an outcome that is not circularly determined by the index scan. These distinctions also inform the assessment of automated imaging systems (Borchert et al., 2023; Fleisher et al., 2020; Soleimani-Meigooni et al., 2020).

Clinical algorithms presented below are a synthesis of the cited recommendations and evidence. They are not a newly validated prediction rule. Treatment monitoring is discussed using published clinical trials and appropriate use recommendations; drug specific prescribing information and local protocols remain the operational authority for dosing and surveillance. This distinction is especially relevant when a published research protocol and subsequent clinical practice recommendations differ (Cummings et al., 2023; Rabinovici, Selkoe, et al., 2025).

Biological interpretation and diagnostic frameworks

Syndromes and pathology

Imaging should be interpreted across three related axes: cognitive functional stage, anatomical syndrome, and underlying disease. An amnestic syndrome may be associated with Alzheimer pathology, limbic predominant age related TDP-43 encephalopathy (LATE), hippocampal sclerosis, or combinations of these. A language led presentation may reflect Alzheimer pathology or frontotemporal lobar degeneration. The same proteinopathy can affect different networks and therefore produce different clinical phenotypes. Conversely, the same anatomical pattern can arise from more than one pathology (Gorno-Tempini et al., 2011; Nelson et al., 2019).

MRI atrophy and fluorodeoxyglucose (FDG) PET hypometabolism are downstream indicators of tissue injury and dysfunction. They are useful for assessing the distribution of disease but are not specific assays of amyloid, tau, TDP-43, or alpha-synuclein. This distinction explains why an Alzheimer compatible FDG pattern should be described as supportive of an etiological hypothesis rather than as direct evidence of Alzheimer protein deposition. The 2018 amyloid, tau, and neurodegeneration framework explicitly placed neurodegeneration measures in parentheses to indicate their lack of specificity to Alzheimer disease (Jack et al., 2018).

Alzheimer disease definitions

The 2024 Alzheimer's Association criteria define Alzheimer disease biologically and distinguish early changing Core 1 biomarkers from later changing Core 2 biomarkers. Amyloid PET is a Core 1 measure. Selected cerebrospinal fluid assays and sufficiently accurate blood assays also fall in this group. Tau PET belongs to Core 2 and provides information about aggregated tau distribution and biological stage. The distinction matters because soluble phosphorylated tau measures and tau PET do not represent interchangeable observations of the same temporal process (Jack et al., 2024).

Under these criteria, an abnormal validated Core 1 result can establish biological Alzheimer disease, but clinical stage remains separately assessed. Biological staging by PET ranges from amyloid positivity without measurable tau PET abnormality, through medial temporal tau involvement, to increasing neocortical tau burden. These PET stages are not equivalent to neuropathological Braak stages, because ligand sensitivity, spatial resolution, and thresholds limit detection. A negative tau PET study, particularly with a visual reading method optimized for advanced neocortical pathology, does not exclude earlier Alzheimer disease (Fleisher et al., 2020; Jack et al., 2024; Soleimani-Meigooni et al., 2020).

The International Working Group takes a different position on clinical nomenclature. Its 2021 recommendations require an appropriate clinical phenotype together with biomarker evidence, and its 2024 update retains Alzheimer disease as a clinical biological construct. Most cognitively unimpaired people with biomarker abnormalities are described as at risk, with more specific consideration of presymptomatic states when the biomarker profile indicates closer proximity to symptoms. The disagreement concerns how disease terminology should be applied clinically, not whether amyloid and tau can be measured before dementia develops (Dubois et al., 2021; Dubois et al., 2024).

The practical implication is that reports and research papers should identify the framework being used. "Amyloid positive," "biological Alzheimer disease under the 2024 criteria," and "dementia due to Alzheimer disease" are related but different statements. Reporting a molecular result without describing clinical status can obscure that distinction. Likewise, an apparently typical clinical syndrome should not be assumed to be biomarker confirmed when molecular testing has not been performed.

Table 1: Diagnostic frameworks and the role of imaging

Framework	Core diagnostic requirement	Imaging contribution and limit
Alzheimer's Association 2024	Biological Alzheimer disease may be established by a validated abnormal Core 1 biomarker. Clinical severity is assessed separately.	Amyloid PET is Core 1; tau PET is Core 2 and contributes to biological staging. MRI atrophy and FDG hypometabolism are nonspecific injury measures.
International Working Group 2021 and 2024	Clinical diagnosis combines an appropriate phenotype with biological evidence. Most biomarker positive cognitively unimpaired people are considered at risk.	Molecular imaging supports the clinical biological construct; positivity alone does not establish dementia.
DLB Consortium 2017	Dementia plus at least two core clinical features, or one core feature with an indicative biomarker, supports probable DLB. Biomarkers alone do not establish probable DLB.	Reduced striatal dopamine transporter uptake is indicative; occipital hypometabolism and relative medial temporal preservation are supportive.
Behavioural variant FTD 2011	Possible disease requires three of six specified clinical features. Probable disease adds functional decline and characteristic imaging.	Frontal or anterior temporal atrophy, hypometabolism, or hypoperfusion supports probable disease; it does not determine the protein substrate.
Primary progressive aphasia 2011	Progressive language led impairment is classified by variant specific language features.	An expected regional pattern supports an imaging supported variant; definite pathology requires pathological or genetic evidence.
VASCOG 2014	Objective cognitive disorder with evidence supporting a vascular etiology, interpreted through clinical course and lesion distribution.	MRI or CT establishes vascular injury; lesion burden alone does not prove causation or exclude Alzheimer copathology.
Boston criteria version 2.0	Probable CAA requires an eligible clinical presentation at age 50 or older and a specified combination of lobar hemorrhagic and white matter features, without deep hemorrhagic lesions or another cause.	Use the complete criteria. Multiple strictly lobar hemorrhagic lesions, or a lobar lesion plus a qualifying white matter feature, can support probable CAA.

Note. Sources: (Charidimou et al., 2022; Dubois et al., 2021; Dubois et al., 2024; Gorno-Tempini et al., 2011; Jack et al., 2024; McKeith et al., 2017; Rascovsky et al., 2011; Sachdev et al., 2014). Abbreviations: CAA, cerebral amyloid angiopathy; DLE

Structural imaging with computed tomography

Clinical indications and diagnostic yield

Noncontrast CT is an appropriate structural examination when MRI cannot be obtained or when rapid assessment of hemorrhage, mass effect, or another acute intracranial process is required. It can identify large infarcts, extensive white matter hypoattenuation, substantial regional atrophy, ventricular enlargement, subdural collections and intracranial masses. Its acquisition is short and less susceptible than a lengthy MRI protocol to intolerance or sustained motion. These advantages are relevant in patients with advanced cognitive impairment or substantial medical instability (Dickerson et al., 2025).

CT has lower soft tissue contrast than MRI for subtle regional atrophy and small vascular lesions. It does not provide the susceptibility sensitive assessment needed to characterize cerebral microbleeds and cortical superficial siderosis adequately. A CT examination that excludes a mass therefore does not answer the separate question of hemorrhagic small vessel burden. This limitation becomes clinically consequential when considering an amyloid targeting antibody: CT cannot replace the MRI examination required for baseline risk assessment and subsequent detection of amyloid related imaging abnormalities (ARIA) (Cummings et al., 2023; Duering et al., 2023; Rabinovici, Selkoe, et al., 2025).

Interpretation and limitations

Atrophy should be assessed for anatomical distribution, symmetry, and proportionality to age, while recognizing the limited specificity of each feature. Medial temporal volume loss, widening of the temporal horns, and posterior cortical volume loss may support a neurodegenerative syndrome, but the combination must be interpreted against the presenting deficits. Marked frontal or anterior temporal atrophy can suggest frontotemporal degeneration, whereas extensive infarction may establish a substantial vascular contribution. Neither finding excludes coexisting Alzheimer pathology (Rascovsky et al., 2011; Sachdev et al., 2014).

Ventricular enlargement requires distinction between tissue loss and a hydrocephalic configuration. An enlarged ventricular system accompanied by disproportionate sulcal changes can justify further assessment for normal pressure hydrocephalus when the clinical presentation is compatible. CT can raise this possibility, although MRI better characterizes associated tissue abnormalities and alternative diagnoses. The imaging finding alone does not establish shunt responsiveness (Nakajima et al., 2021).

The report should state the examination's limitations when the clinical question exceeds its capabilities. In a patient with progressive cognitive impairment and an unrevealing CT, MRI or molecular imaging may still be indicated because absence of a gross structural abnormality is not evidence against early neurodegeneration. Routine repetition of CT without a change in the clinical question offers little etiological clarification; subsequent imaging should address a defined unresolved problem (Dickerson et al., 2025).

Magnetic resonance imaging acquisition and analysis

Core sequences

A dementia MRI protocol should combine volumetric structural assessment with vascular and diffusion sensitive sequences. A three dimensional T1 weighted acquisition supports multiplanar inspection and volumetry. T2 weighted and fluid attenuated inversion recovery (FLAIR) images characterize white matter lesions, edema, lacunes, and other abnormalities. Diffusion weighted imaging with apparent diffusion coefficient maps detects restricted diffusion. A susceptibility sensitive sequence, either T2 star gradient echo or susceptibility weighted imaging, assesses hemorrhagic lesions. Sequence selection should follow the clinical question and local technical capabilities (Dickerson et al., 2025; Duering et al., 2023).

These acquisitions are complementary. A small lesion that appears bright on diffusion weighted imaging requires assessment on apparent diffusion coefficient maps to distinguish true restriction from T2 shine through. A susceptibility focus requires correlation with anatomy and other sequences to distinguish hemorrhagic products from vessels, calcification, or artifact. FLAIR hyperintensity should not automatically be labeled ischemic: distribution and associated findings can suggest inflammatory, demyelinating, infectious, or treatment related processes. An abbreviated examination can preserve diagnostic value if it retains the sequences necessary for the actual decision.

Contrast enhancement is not routinely required to characterize uncomplicated degenerative atrophy. It becomes relevant when a neoplastic, inflammatory, infectious, or meningeal process is suspected. Similarly, angiographic, venographic, perfusion, and vessel wall acquisitions should be added selectively rather than treated as mandatory components of every dementia examination. The technical aim is adequate coverage of the differential diagnosis without imposing acquisitions that the patient cannot tolerate or that will not inform management (Dickerson et al., 2025; Duering et al., 2023).

Visual assessment and quantitative morphometry

Visual assessment should describe medial temporal, posterior, frontal, and anterior temporal involvement, asymmetry, ventricular configuration, and vascular injury. Structured visual ratings can make observations more reproducible, but age, disease stage, and reader training affect their interpretation. An atrophy score should not be treated as a binary assay for Alzheimer disease. A relatively preserved hippocampus also does not exclude Alzheimer pathology in a posterior cortical or language led phenotype (Gorno-Tempini et al., 2011; Jack et al., 2018).

Automated morphometry estimates regional volumes, cortical thickness, and deviation from reference populations. These measures can reveal subtle anatomical differences and support longitudinal analysis, but they are vulnerable to segmentation errors, motion, acquisition differences, and inappropriate normative comparisons. Visual review of the source images and the segmentation is therefore part of interpretation. A numerically low hippocampal percentile is not sufficient evidence of a specific proteinopathy, and a normal percentile cannot override a convincing clinical progression.

Multisite work illustrates the need to separate biological differences from scanner effects. Fortin and colleagues showed that harmonization can reduce nonbiological variance in cortical thickness measurements, while large lifespan reference charts offer a framework for age dependent interpretation. Neither approach removes the need to validate measurements in the population and scanner configuration in which they will be used. Normative centiles summarize deviation from a reference distribution; they do not independently provide an etiological diagnosis (Bethlehem et al., 2022; Fortin et al., 2018).

Longitudinal measurement

Serial MRI can document progressive regional tissue loss, but the interpretation depends on acquisition consistency, scan interval, and measurement uncertainty. Scanner replacement, software updates, changes in sequence parameters, and head motion can produce apparent differences unrelated to progression. An observed volume change should exceed plausible technical variability before it is interpreted as an individual biological effect. Longitudinal pipelines should maintain registration and segmentation consistency while preserving sensitivity to genuine change (Fortin et al., 2018).

Treatment studies introduce additional complexity. A meta-analysis reported accelerated volume changes with several antiamyloid drug classes, including ventricular enlargement associated with ARIA inducing antibodies. The biological explanation and long term clinical implications of these changes are not fully resolved. Consequently, volume loss during treatment cannot simply be equated with the untreated rate of neuronal death, and MRI volume change is not an established stand alone surrogate for cognitive benefit or harm (Alves et al., 2023).

Structural patterns across dementia syndromes

Alzheimer phenotypes

Typical amnestic Alzheimer presentations frequently involve medial temporal structures and temporoparietal association regions. The relative contribution of hippocampal and neocortical abnormalities varies across patients. Young onset and atypical presentations can show disproportionate posterior cortical or language network involvement. Structural imaging is therefore interpreted against the dominant deficits: visuospatial dysfunction directs attention to posterior association regions, while language impairment requires careful analysis of perisylvian and temporal anatomy (Gorno-Tempini et al., 2011; Jack et al., 2018).

Atrophy is a measure of accumulated tissue injury and may be absent or subtle early in a molecularly positive individual. Conversely, pronounced hippocampal atrophy can occur without Alzheimer amyloid pathology. This is particularly relevant in advanced age, when LATE and hippocampal sclerosis may produce an amnestic syndrome. The appropriate inference from hippocampal atrophy is evidence of limbic injury, followed by an etiological assessment that considers molecular results, disease tempo, and competing explanations (Nelson et al., 2019; Wolk et al., 2025).

Frontotemporal degeneration and primary progressive aphasia

In behavioural variant frontotemporal dementia, frontal and anterior temporal abnormalities support the clinical syndrome. The revised consensus criteria distinguish possible disease based on clinical features from probable disease, which additionally requires functional decline and characteristic imaging. The imaging requirement increases etiological confidence but does not identify whether the underlying substrate is tau, TDP-43, or another pathology. An apparently normal early scan also requires consideration of disease stage and alternative psychiatric or neurological explanations (Rascovsky et al., 2011).

Primary progressive aphasia is initially a clinical diagnosis, with imaging supported classification based on the expected anatomical distribution. Nonfluent or agrammatic presentations commonly direct attention to left posterior frontal and insular regions; semantic presentations to anterior temporal regions; and logopenic presentations to left temporoparietal regions. The association between logopenic aphasia and Alzheimer pathology is useful for test selection but is not absolute. Molecular confirmation is particularly valuable when the pathology will determine treatment eligibility or research enrollment (Gorno-Tempini et al., 2011; Rabinovici, Knopman, et al., 2025).

Lewy body disease

Relative preservation of medial temporal structures can support dementia with Lewy bodies (DLB) compared with an amnestic Alzheimer presentation, but structural MRI is not an indicative biomarker under the DLB consensus criteria. Greater medial temporal atrophy may reflect concomitant Alzheimer pathology. The main structural contribution is assessment of vascular disease, other lesions, and the extent of tissue injury, while the syndrome is defined through clinical features and, when appropriate, dopaminergic or other indicative biomarkers (McKeith et al., 2017).

Prodromal DLB requires particular caution because clinical features and imaging abnormalities may be incomplete. The 2020 research criteria operationalize mild cognitive impairment with Lewy bodies, while recognizing insufficient evidence for equally formalized delirium onset and psychiatric onset categories. A later systematic review supported the clinical features and the potential utility of dopaminergic imaging, but emphasized limitations in the biomarker evidence. Dementia stage estimates of test sensitivity should therefore not be transferred directly to prodromal populations (Donaghy et al., 2023; McKeith et al., 2020).

LATE and non Alzheimer limbic injury

The inability to image TDP-43 directly limits the specificity of MRI in an older patient with an amnestic syndrome. LATE can produce marked medial temporal atrophy and coexist with Alzheimer pathology. Proposed clinical criteria use clinical characteristics and available biomarkers to identify suspected cases, but this is an inferential classification rather than direct visualization of TDP-43. A negative amyloid result may reduce the probability of Alzheimer disease while leaving several non Alzheimer causes of limbic degeneration unresolved (Nelson et al., 2019; Wolk et al., 2025).

A 2026 memory clinic investigation examined operationalized clinical LATE categories and found different trajectories between probable LATE, Alzheimer disease, and co-occurring categories. This provides evidence that multimodal profiles can identify clinically distinct groups, but it does not establish a pathology specific imaging assay. Classification performance in a specialist cohort also requires validation in other settings before the same operational definitions are used for individual prognostication (Groot et al., 2026).

Vascular injury and mixed dementia

Lesion characterization

MRI should document the type, location, and burden of cerebrovascular injury. Relevant findings include recent small subcortical infarcts, lacunes, white matter hyperintensities, enlarged perivascular spaces, cerebral microbleeds, cortical superficial siderosis, and larger cortical or subcortical infarcts. STRIVE-2 updates terminology and acquisition considerations and extends attention to quantitative measures of tissue injury. Standard terminology reduces ambiguity when comparing reports, research cohorts, and longitudinal examinations (Duering et al., 2023).

Lesion burden is not interchangeable with clinical attribution. A strategically located infarct can have disproportionate cognitive consequences, while extensive white matter abnormality may produce a gradual executive and processing speed syndrome. Temporal association with stroke, lesion distribution, cognitive phenotype, and functional consequences all inform whether vascular disease substantially contributes. The VASCOG criteria explicitly address a spectrum of mild and major vascular cognitive disorders and acknowledge frequent coexisting Alzheimer pathology (Sachdev et al., 2014).

Hemorrhagic small vessel disease

Strictly lobar hemorrhagic lesions and cortical superficial siderosis can support cerebral amyloid angiopathy (CAA), whereas deep hemorrhagic lesions suggest a different arteriopathy distribution. The Boston criteria version 2.0 combine clinical eligibility, hemorrhagic findings, selected white matter features, and exclusion of other causes. Their use requires the full set of conditions; finding a single lobar microbleed is insufficient to diagnose probable CAA. The criteria were developed and validated against neuropathological assessment in a multicentre study (Charidimou et al., 2022).

CAA is relevant both as a contributor to cognitive impairment and as a treatment safety consideration. Amyloid PET does not reliably distinguish vascular amyloid from parenchymal plaque amyloid at the individual level. A positive scan therefore cannot substitute for susceptibility sensitive MRI when estimating hemorrhagic risk. Conversely, the absence of visible hemorrhagic markers does not prove the absence of microscopic vascular amyloid. Treatment decisions must use the modality that measures the relevant safety concern (Charidimou et al., 2022; Cummings et al., 2023; Rabinovici, Selkoe, et al., 2025).

Quantitative vascular biomarkers

White matter hyperintensity volume captures only part of small vessel injury. Diffusion based measures can quantify abnormalities in normal appearing tissue and the aggregate effect of tract injury. Peak width of skeletonized mean diffusivity was developed as an automated measure associated with processing speed across several small vessel disease cohorts. It provides a useful example of a quantitative biomarker whose intended target is distributed vascular injury, not a specific dementia proteinopathy (Baykara et al., 2016).

STRIVE-2 places such measures within a broader research agenda that includes subvisible tissue injury, higher field imaging, and lesion symptom relationships. Translation requires reproducibility across scanners and acquisition schemes, appropriate handling of motion, and demonstration that the added measurement improves a relevant decision. A stronger association with a cognitive score does not automatically establish an advantage over conventional MRI for routine diagnosis or treatment selection (Duering et al., 2023).

Functional imaging with FDG PET

Physiological basis and acquisition

FDG PET measures the distribution of a glucose analogue whose transport and phosphorylation provide an index of regional glucose utilization. In dementia, the observed signal reflects regional neuronal and synaptic activity together with contributions from other metabolically active cells. It is a functional measure of tissue state rather than a direct count of neurons or synapses. Reduced uptake can precede readily visible atrophy, but this temporal advantage does not confer pathological specificity (Guedj et al., 2022).

Patient preparation and the uptake environment influence interpretation. Fasting status, blood glucose, medication exposure, sensory stimulation, and sedation should be documented. Hyperglycemia reduces tracer uptake and can alter image quality and regional contrast. Sedation can change cerebral metabolism and should be timed and administered according to a validated procedural protocol when necessary. A patient who is restless during acquisition may also have motion induced abnormalities that resemble focal hypometabolism or compromise registration (Guedj et al., 2022).

PET/CT provides attenuation correction and anatomical localization; the low dose CT used for correction is not necessarily a complete diagnostic structural examination. PET/MRI can combine metabolic information with structural and other MRI acquisitions, although attenuation correction and motion remain potential sources of error. In both configurations, the metabolic findings should be interpreted alongside an adequate structural study. A focal metabolic deficit adjacent to an infarct, tumor, or severe atrophy requires a different explanation from the same apparent pattern without a structural correlate (Guedj et al., 2022).

Patterns and differential diagnosis

The usual Alzheimer associated pattern includes temporoparietal, precuneus, and posterior cingulate hypometabolism, with extension depending on stage and phenotype. Frontal involvement may become more evident with progression, and asymmetry can accompany language or visuospatial presentations. The anatomical pattern should be compared with the cognitive syndrome rather than scored solely against a canonical template. FDG PET can support an Alzheimer hypothesis, but confirmation of amyloid pathology requires an appropriate molecular or fluid biomarker (Guedj et al., 2022; Rabinovici, Knopman, et al., 2025).

Frontotemporal degeneration often produces frontal, anterior cingulate, insular, or anterior temporal abnormalities, with the distribution determined by the clinical phenotype. Semantic and nonfluent aphasic syndromes have different expected patterns. Overlap with Alzheimer and psychiatric presentations limits the specificity of an isolated frontal reduction. The source images, structural findings, disease tempo, and clinical examination remain necessary to establish whether the metabolic result provides coherent evidence for a progressive neurodegenerative syndrome (Gorno-Tempini et al., 2011; Guedj et al., 2022; Rascovsky et al., 2011).

DLB can show occipital hypometabolism with relative preservation of posterior cingulate metabolism, the cingulate island sign. This pattern is supportive, not an indicative biomarker under the consensus criteria. It also overlaps with posterior cortical presentations and is influenced by concurrent Alzheimer pathology. The distinction between relative preservation and normal absolute metabolism is important: a region may appear preserved only because adjacent regions are more severely affected (Guedj et al., 2022; McKeith et al., 2017).

Quantification and uncertainty

Semiquantitative analysis compares regional uptake with a reference region or a normative database. Surface projection and statistical maps can help identify subtle patterns, but they depend on registration, smoothing, age matching, scanner characteristics, and the choice of normalization. A reference region affected by disease can distort the apparent distribution of abnormalities. Thresholded color maps should therefore be interpreted as aids to visual assessment rather than as independent diagnostic outputs (Guedj et al., 2022).

Partial volume effects are especially relevant in an atrophic brain because a PET voxel contains mixtures of gray matter, white matter, and cerebrospinal fluid. Apparent hypometabolism may partly reflect loss of tissue volume. Correction can improve estimation of tissue activity but introduces dependence on segmentation and registration and may amplify noise. The report should distinguish a robust distributed metabolic pattern from findings dominated by focal atrophy, technical limitations, or equivocal statistical deviations (Guedj et al., 2022).

A normal or nonspecific FDG study may reduce confidence in a currently active, widespread degenerative process, but its prognostic meaning depends on disease stage and follow-up horizon. It does not exclude molecular Alzheimer pathology or all future neurodegeneration. FDG PET is most useful when the unresolved question concerns the functional anatomy of a symptomatic syndrome and the result is expected to change the differential diagnosis or management.

SPECT and dopaminergic imaging

Cerebral perfusion SPECT

Perfusion SPECT commonly uses technetium labeled radiopharmaceuticals to estimate regional cerebral blood flow. Because perfusion and metabolism are coupled under many physiological conditions, regional patterns can resemble those on FDG PET. The biological quantities are nevertheless different, and vascular disease, altered transit, acquisition, and reconstruction can affect the relationship. Perfusion SPECT should therefore be interpreted as a perfusion measure with its own technical and clinical limitations (Guedj et al., 2022).

Where FDG PET is unavailable, perfusion SPECT can provide functional information in a clinically selected patient. Its interpretation requires attention to spatial resolution, attenuation and scatter correction, head positioning, and the normative database. Apparent posterior or frontal reductions are not intrinsically specific for a proteinopathy. Choosing between modalities should consider local expertise and the unresolved question, rather than assuming that every functional technique is interchangeable. The FDG procedure guideline also discusses perfusion SPECT as an alternative in selected circumstances, including problematic glycemic conditions (Guedj et al., 2022).

Dopamine transporter imaging

Dopamine transporter SPECT, typically with iodine-123 ioflupane, addresses presynaptic nigrostriatal integrity. It does not measure cerebral perfusion and should not be grouped with perfusion SPECT as if the tests answer the same question. Reduced striatal uptake is an indicative biomarker in the DLB consensus criteria, interpreted in conjunction with the clinical features. It supports a degenerative dopaminergic deficit but does not directly demonstrate alpha-synuclein (McKeith et al., 2017; Morbelli et al., 2020).

A reduced dopamine transporter signal is not specific to DLB among all neurodegenerative Parkinsonian disorders. Interpretation requires consideration of progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, and other causes of nigrostriatal degeneration. Structural lesions can also affect regional striatal appearance, and medications that interact with transporter binding require review. Procedural guidance emphasizes acquisition quality, age appropriate reference data, semiquantification, and the limitations of visual and quantitative assessments (Morbelli et al., 2020).

Cardiac iodine-123 metaiodobenzylguanidine scintigraphy assesses sympathetic cardiac innervation and is another indicative biomarker in the DLB criteria. Cardiac disease, diabetes, and medication effects can complicate interpretation. It is an extracerebral autonomic measure, not a brain perfusion examination. Polysomnographic confirmation of REM sleep without atonia supplies another diagnostic route and illustrates why an imaging result must be integrated with the full set of diagnostic evidence (McKeith et al., 2017).

Table 2: Comparison of structural and functional modalities

Modality	Principal measurement	Best matched question	Main limitation
Noncontrast CT	Gross anatomy and attenuation	Mass lesion, major infarction, hemorrhage, hydrocephalus; structural assessment when MRI is impractical	Limited small lesion and tissue contrast; inadequate for ARIA surveillance
Conventional MRI	Anatomy, tissue signal, diffusion, susceptibility	Regional injury, vascular disease, alternative diagnoses, treatment safety	Atrophy is not protein specific; motion and protocol affect sensitivity
FDG PET	Regional glucose analogue utilization	Functional pattern in a clinically uncertain progressive syndrome	Metabolic dysfunction is nonspecific; preparation and normalization matter
Perfusion SPECT	Regional tracer distribution related to blood flow	Functional assessment where appropriate and locally available	Perfusion is not metabolism; resolution and correction influence interpretation
Dopamine transporter SPECT	Presynaptic striatal transporter availability	Evidence of nigrostriatal degeneration in suspected DLB	Abnormal in other degenerative Parkinsonian disorders; no direct synuclein measurement
Amyloid PET	Fibrillar amyloid retention	Presence of target pathology and selected treatment decisions	Positivity does not assign all symptoms to Alzheimer disease
Tau PET	Ligand dependent aggregated tau retention	Alzheimer tau distribution, biological stage, selected prognosis	Limited early sensitivity and variable binding across tau conformations

Note. Sources: (Dickerson et al., 2025; Duering et al., 2023; Guedj et al., 2022; Morbelli et al., 2020; Rabinovici, Knopman, et al., 2025; Soleimani-Meigooni et al., 2020). ARIA, amyloid related imaging abnormalities.

Amyloid PET tracers and interpretation

Molecular target and established ligands

Amyloid PET detects aggregated fibrillar amyloid with sufficient density to generate a measurable retention pattern. Carbon-11 Pittsburgh compound B (PiB) established the feasibility of in vivo amyloid imaging and remains a research reference ligand. Its short radioactive half-life limits distribution compared with fluorine-18 labeled agents. Florbetapir, florbetaben, and flutemetamol are established fluorine-18 amyloid tracers with imaging to pathology validation. Their acquisition protocols and visual interpretation rules are ligand specific (Clark et al., 2012; Curtis et al., 2015; Klunk et al., 2004; Sabri et al., 2015).

The ligands differ in kinetics, nonspecific retention, imaging windows, and reading procedures. These differences mean that an uptake ratio cannot be transferred uncritically from one tracer to another. The broad clinical inference is common: a positive cortical retention pattern supports a clinically meaningful burden of amyloid deposition. It does not identify soluble oligomer concentration, establish a complete neuropathological diagnosis by itself, or determine how much of an individual's disability is attributable to Alzheimer disease (Rabinovici, Knopman, et al., 2025).

Imaging to autopsy validation

In a prospective florbetapir study, sensitivity for moderate to frequent neuritic plaques was 92% and specificity was 100% among participants with autopsy within two years of imaging. The corresponding confidence intervals were 78%–98% and 80%–100%, respectively, reflecting the limited sample. These values validate detection of a defined pathological category in the studied population; they should not be presented as universal sensitivity and specificity for the clinical syndrome of Alzheimer dementia (Clark et al., 2012).

Florbetaben validation included 74 deceased participants with matched imaging and tissue assessment. The reported subject level sensitivity was 97.9% and specificity 88.9% for the defined neuritic plaque classification. Flutemetamol validation similarly demonstrated an association between visual scan interpretation and neuritic plaque density in an end of life population. Reader variation and differences between subject level and regional tissue matched analyses require attention when comparing results across ligands (Curtis et al., 2015; Sabri et al., 2015).

Autopsy studies provide a strong reference standard but have selection and temporal limitations. Terminally ill volunteers differ from typical patients with mild cognitive impairment, and pathology can progress between imaging and death. The reference category also matters: none or sparse versus moderate or frequent neuritic plaques is not the same comparison as presence versus absence of every microscopic amyloid deposit. A negative PET result is therefore compatible with low density pathology below the detection threshold (Clark et al., 2012; Jack et al., 2024).

Visual reading and technical pitfalls

A negative amyloid scan typically retains gray white matter contrast, with prominent nonspecific white matter signal. A positive scan shows cortical retention that reduces this contrast in characteristic regions. Tracer specific training is required because region selection and positivity rules differ. Atrophy, motion, low count statistics, and misregistration can blur the cortical boundary. Correlation with MRI or CT is helpful when cortical thinning makes the anatomical assignment of uptake uncertain (Rabinovici, Knopman, et al., 2025).

Borderline scans should not be forced into unwarranted certainty. Quantification can support review, but a result near a threshold requires consideration of technical quality and the purpose of testing. A second trained read, review of the reference region, or an independent biomarker may be appropriate when the result will determine a consequential treatment decision. The uncertainty should be reflected in the report and in the subsequent clinical explanation (Jack et al., 2024; Rabinovici, Knopman, et al., 2025).

Centiloid quantification

The Centiloid system was developed to place amyloid PET results on a common scale anchored by young controls and typical Alzheimer participants. It is a calibrated measurement scale, not a percentage of neurons affected or a percentage of maximum possible amyloid. Values may fall below zero or above 100. Valid conversion depends on the tracer and processing pipeline, including region definitions, reference tissue, registration, and scanner characteristics (Klunk et al., 2015).

Florbetapir to Centiloid conversion illustrates this dependence. Navitsky and colleagues derived a conversion for a specified analytical method and identified a pathology based discrimination threshold in their validation data. Applying that equation to a different pipeline without validation would defeat the purpose of standardization. Similarly, a threshold chosen to detect early amyloid accumulation need not equal one used for visual positivity or treatment completion (Navitsky et al., 2018).

Longitudinal quantification is useful for measuring target engagement in treatment trials, but changes in cerebral blood flow, reference region behaviour, scanner performance, and partial volume can influence standardized uptake value ratios. A numerical decline is most persuasive when acquisition and analysis are consistent and the magnitude exceeds expected measurement variability. Standardization supports comparison; it does not eliminate the need for quality control.

Clinical role and clinical utility

Amyloid PET is valuable when Alzheimer pathology is a meaningful diagnostic possibility and knowing amyloid status is expected to change management. Examples include early onset or atypical presentations, unresolved mixed syndromes, and confirmation of a target before amyloid directed treatment. The updated appropriate use criteria assess amyloid and tau PET separately across 17 clinical scenarios. They do not support an indiscriminate molecular imaging sequence for every patient with a cognitive complaint (Rabinovici, Knopman, et al., 2025).

The IDEAS study found changes in a composite management outcome in 60.2% of patients with mild cognitive impairment and 63.5% of patients with dementia after amyloid PET. Because the design lacked a randomized control group, these results establish association with management change rather than a causal improvement in patient outcomes. The AMYPAD-DPMS randomized trial addressed a different outcome: early PET increased the proportion receiving a high confidence etiological diagnosis at three months compared with later imaging. Diagnostic confidence remains distinct from preserved cognition, reduced institutionalization, or improved quality of life (Altomare et al., 2023; Rabinovici et al., 2019).

Tau PET tracers and biological staging

Tau conformations and ligand specificity

Tau aggregates differ in isoform composition, conformation, and anatomical distribution across diseases. Alzheimer disease contains paired helical filament tau with both three repeat and four repeat isoforms, while progressive supranuclear palsy and corticobasal degeneration have predominantly four repeat pathology. A ligand that recognizes Alzheimer type tau cannot be assumed to bind all tauopathies with comparable affinity. This molecular constraint limits the use of an Alzheimer validated tracer as a general diagnostic assay for frontotemporal degeneration (Brendel et al., 2020; Soleimani-Meigooni et al., 2020; Tagai et al., 2021).

The Braak neuropathological scheme describes a characteristic progression of neurofibrillary changes from transentorhinal through limbic to widespread isocortical regions. PET can estimate a related regional distribution, but its spatial resolution and detection threshold prevent exact substitution for histological staging. A PET based stage should therefore be identified as such. In particular, microscopic early medial temporal pathology can be present when a clinical visual read remains negative (Braak & Braak, 1991; Jack et al., 2024).

Flortaucipir

Flortaucipir is the most extensively established clinical tau ligand in the evidence reviewed here. An imaging to autopsy study demonstrated high sensitivity for advanced Alzheimer type tau pathology, with reader dependent specificity. The validation target included Braak V–VI disease, not uniformly sensitive detection of early transentorhinal tangles. The study's advanced age and terminal illness population also limits direct transfer of performance estimates to younger patients or those with subtle impairment (Fleisher et al., 2020).

A separate PET to autopsy series found good correspondence with advanced Alzheimer tau pathology but inconsistent correspondence in non Alzheimer tauopathies and limited detection of earlier Braak stages. This supports a restricted inference: an appropriate neocortical flortaucipir pattern can provide strong evidence of Alzheimer type tau burden, while a negative result does not exclude early Alzheimer disease and a subcortical signal does not establish progressive supranuclear palsy or corticobasal degeneration (Soleimani-Meigooni et al., 2020).

Off target retention can occur in structures adjacent to regions of interest, including choroid plexus and subcortical structures. Spillover can complicate medial temporal quantification, particularly in small or atrophic structures. Clinical visual interpretation and research regional quantification may also apply different positivity definitions. A study described as tau negative under a validated visual method may nevertheless contain quantitative medial temporal signal; these observations should not be treated as contradictory without examining the methods (Rabinovici, Knopman, et al., 2025).

RO948 and MK 6240

RO948 and MK-6240 are research ligands developed to improve measurement of Alzheimer type tau. In the BioFINDER-2 diagnostic study, RO948 discriminated Alzheimer dementia from non Alzheimer neurodegenerative disorders with high area under the receiver operating characteristic curve. The findings support its diagnostic potential, but the result depends on the studied populations, region definitions, and reference diagnoses. It does not establish equal performance in all prodromal or mixed pathology presentations (Leuzy et al., 2020).

Early MK-6240 kinetic work compared simplified uptake ratios with full kinetic modeling and identified an acquisition interval in which the measures were robust. This illustrates why tracer validation includes more than visual similarity to expected disease anatomy. Delivery, clearance, binding reversibility, reference tissue assumptions, and scan timing determine whether a regional value is an interpretable estimate of specific retention. Extracerebral or meningeal signal and spillover also require review with research tau ligands (Pascoal et al., 2018; Rabinovici, Knopman, et al., 2025).

PI 2620 and PM PBB3

PI-2620 has been investigated in progressive supranuclear palsy, including a multicentre study that found elevated binding in expected subcortical targets and reported discrimination from control groups. This is evidence of biomarker potential, not a definitive individual level assay for all four repeat tauopathies. The interpretation of low level subcortical retention requires careful consideration

of kinetics, control selection, and the degree of neuropathological corroboration (Brendel et al., 2020).

PM-PBB3, also known as APN-1607, has been studied for imaging a broader range of tau deposits. Experimental and clinical work reported retention patterns in Alzheimer disease and non Alzheimer tauopathies, with neuropathological support in selected cases. These findings justify further validation but do not make all positive uptake in a clinically suspected tauopathy pathology specific. The need for wider autopsy confirmation, standardized acquisition, and independent replication remains material (Tagai et al., 2021).

Prognosis and treatment stratification

Tau burden is more closely related to clinical expression than amyloid burden in many Alzheimer cohorts. A multicohort study found that baseline tau PET predicted subsequent cognitive change and provided stronger prognostic associations than the compared amyloid PET and MRI measures. This supports tau PET as a prognostic marker at the group level and as a potential aid to counseling, while leaving uncertainty about calibrated individual trajectories, competing pathology, and the influence of cognitive reserve (Ossenkoppele et al., 2021).

Among cognitively unimpaired participants, combined amyloid and tau positivity was associated with increased short term risk of cognitive decline and progression to mild cognitive impairment. Risk differed by tau distribution. These findings do not imply inevitable dementia within a fixed interval for every positive individual: hazard ratios describe relative rates in a cohort, and absolute risk depends on age, follow-up, competing mortality, and the population studied (Ossenkoppele et al., 2022).

Tau PET can also support trial stratification. TRAILBLAZER-ALZ 2 incorporated tau PET to characterize participants and analyze treatment effects by baseline pathology. That research role should not be confused with a universal requirement for clinical eligibility. Published donanemab appropriate use recommendations state that tau PET is not required for eligibility, while amyloid confirmation and MRI assessment remain necessary components of the clinical pathway (Rabinovici, Selkoe, et al., 2025; Sims et al., 2023).

Table 3: Amyloid and tau tracers and evidentiary boundaries

Tracer	Target and established evidence	Interpretive boundary
Carbon 11 PiB	Fibrillar amyloid; foundational human amyloid imaging and quantification reference	Short half-life constrains distribution; research reference rather than a universal clinical acquisition standard
Fluorine 18 florbetapir	Amyloid; prospective imaging to autopsy validation	Tracer specific visual rules and calibrated quantification are required
Fluorine 18 florbetaben	Amyloid; phase 3 imaging to histopathology validation	Regional and subject level accuracy estimates answer different questions
Fluorine 18 flutemetamol	Amyloid; phase 3 comparison with neuritic plaque density	End of life validation does not directly establish prognosis in mild cognitive impairment
Fluorine 18 flortaucipir	Alzheimer type tau; autopsy validation strongest for advanced pathology	Negative clinical visual read does not exclude early tau; off target retention requires review
Fluorine 18 RO948	Alzheimer type tau; strong discrimination in a specialist cohort	Research cohort performance requires independent clinical validation
Fluorine 18 MK 6240	Alzheimer type tau; kinetic and quantitative validation	Scan timing, modeling, and extracerebral signal influence measurement
Fluorine 18 PI 2620	Tau ligand studied in Alzheimer disease and four repeat tauopathies	PSP cohort findings do not establish universal pathology specific individual classification
Fluorine 18 PM PBB3	Broader tau binding investigated with experimental and selected pathological corroboration	Further standardized and independent validation is necessary

Note. Sources: (Brendel et al., 2020; Clark et al., 2012; Curtis et al., 2015; Fleisher et al., 2020; Klunk et al., 2004; Leuzy et al., 2020; Pascoal et al., 2018; Sabri et al., 2015; Soleimani-Meigooni et al., 2020; Tagai et al., 2021). PSP, progressive supranuclear palsy. Entries distinguish validation evidence from research potential and do not constitute a global regulatory status list.

Table 4: Clinical algorithm for etiological imaging

Decision point	Imaging action	Consequence
Establish syndrome and tempo	Select structural imaging after clinical and cognitive assessment; expand urgently for rapid or focal presentations	Identify a defined differential diagnosis and actionable structural causes
Obtain structural baseline	MRI with T1, T2 or FLAIR, diffusion and susceptibility sensitive sequences; CT if MRI is impractical	Characterize atrophy, vascular injury, hemorrhage and alternative lesions
Resolve uncertain functional anatomy	Consider FDG PET; perfusion SPECT may be an alternative in selected settings	Assess whether the regional pattern supports the suspected degenerative syndrome
Evaluate suspected DLB	Consider dopamine transporter imaging when the result would change diagnostic confidence	Interpret with core features and alternative causes of dopaminergic loss
Establish Alzheimer pathology when consequential	Use an appropriately validated fluid biomarker or amyloid PET within a specialist pathway	Clarify etiology or confirm a treatment target; avoid redundant confirmation without a reason
Refine selected stage or prognosis questions	Consider tau PET after defining the decision and expected incremental value	Integrate tau distribution with clinical stage and competing pathology
Investigate discordance	Review technical quality, thresholds, biomarker timing and mixed pathology; use an independent test selectively	Explain disagreement before repeating or expanding testing
Disclose integrated result	Combine clinical phenotype, structural injury and molecular findings	State diagnosis, contribution of each process, uncertainty and management consequences

Note. Clinical synthesis based on (Dickerson et al., 2025; Guedj et al., 2022; Jack et al., 2024; Morbelli et al., 2020; Rabinovici, Knopman, et al., 2025). This sequence is not a validated prediction rule or a requirement to perform every test.

Integrated clinical algorithms

Initial evaluation and test selection
The initial assessment establishes whether there is objective cognitive decline, whether independence is impaired, and which cognitive behavioural syndrome is present. The clinical evaluation also identifies delirium, medication effects, psychiatric illness, sleep disturbance, sensory impairment, and systemic contributors that can affect both symptoms and test interpretation. Structural imaging follows as part of an etiological assessment, with MRI preferred when feasible and CT used when MRI is impractical or unavailable (Dickerson et al., 2025).

The next test should address the uncertainty that remains after structural imaging. FDG PET is useful when the question concerns the distributed functional pattern of a progressive syndrome. Dopamine transporter imaging is useful when a DLB hypothesis remains uncertain and demonstration of nigrostriatal degeneration would change diagnostic confidence. Amyloid testing addresses whether Alzheimer pathology is present, while tau PET can refine biological stage or the likelihood that Alzheimer pathology substantially contributes to symptoms. These questions may overlap, but the tests should not be ordered as an automatic panel (Guedj et al., 2022; Morbelli et al., 2020; Rabinovici, Knopman, et al., 2025).

Discordant multimodal findings
Discordance is often biologically informative. Amyloid positivity with limited tau burden and a strongly non-Alzheimer phenotype may indicate coincident amyloid deposition. Marked hippocampal atrophy with negative amyloid testing can prompt consideration of LATE, hippocampal sclerosis, vascular injury, or another limbic process. A convincing Alzheimer clinical phenotype with a negative molecular result requires review of scan quality, threshold effects, alternative assays, and alternative diagnoses before any conclusion that the test is erroneous (Dubois et al., 2021; Jack et al., 2024; Wolk et al., 2025). The interpretation should distinguish a technical disagreement from a biological one. Motion, segmentation failure, an abnormal reference region, or inappropriate application of a threshold can generate an apparent discrepancy. When each measurement is technically credible, different biomarker timing and mixed pathology may explain the findings. Repeating several tests without first specifying the mechanism of disagreement can increase complexity without resolving the clinical question.

A practical multimodal conclusion states the syndrome, the observed abnormalities, their likely contribution, and the remaining uncertainty. For example, an amnestic dementia with amyloid positivity, extensive neocortical tau, and concordant temporoparietal injury provides a different degree of etiological support from isolated amyloid positivity in a patient with hallucinations, fluctuations, and reduced striatal dopamine transporter uptake. Both patients can have amyloid pathology, but the explanatory role of that pathology differs (Jack et al., 2024; McKeith et al., 2017).

Rapid progression and alternative structural explanations
Rapid or subacute cognitive decline requires an expanded differential diagnosis. Diffusion abnormalities, enhancement, edema, seizures, mass effect, and inflammatory or infectious patterns may redirect the investigation away from a routine degenerative pathway. The diagnostic value of MRI in this setting derives from its ability to identify a different mechanism and guide targeted clinical and laboratory testing. A dementia label should not delay the evaluation of an acute or potentially treatable process (Dickerson et al., 2025; Guedj et al., 2022).

Normal pressure hydrocephalus provides a different example of a potentially actionable imaging pattern. Disproportionately enlarged subarachnoid space hydrocephalus includes ventricular enlargement with characteristic sulcal disproportion. The finding is interpreted alongside gait and other clinical features and followed by appropriate specialist assessment. Imaging supports the pathway; it does not establish that every cognitive symptom will improve with cerebrospinal fluid diversion, particularly when neurodegenerative comorbidity is present (Nakajima et al., 2021).

Imaging in amyloid directed treatment

Confirmation and baseline risk assessment
Amyloid directed treatment requires confirmation of the target pathology in an appropriately selected clinical population. In the lecanemab phase 3 trial, participants had early Alzheimer disease with amyloid evidence by PET or cerebrospinal fluid testing. The donanemab trial incorporated both amyloid and tau imaging in its eligibility and analysis strategy. The imaging result must be integrated with clinical stage and other eligibility conditions; demonstration of amyloid is not sufficient to establish that treatment is appropriate (Sims et al., 2023; van Dyck et al., 2023).

Baseline MRI identifies hemorrhagic and vascular findings relevant to safety and provides a comparator for subsequent scans. Susceptibility sensitive imaging establishes the pre-existing microbleed and superficial siderosis burden, while FLAIR and diffusion imaging assist with edema, infarction, and alternative diagnoses. Published appropriate use recommendations specify exclusions and surveillance requirements for each agent. These are drug specific recommendations, and a threshold used in one protocol should not be generalized to every amyloid directed therapy (Cummings et al., 2023; Rabinovici, Selkoe, et al., 2025).

The donanemab recommendations, for example, advise excluding patients with more than four cerebral microbleeds, cortical superficial siderosis, or a major

vascular contribution to cognitive impairment. They also specify baseline MRI timing and additional monitoring for higher risk individuals. These criteria concern the studied treatment pathway; they are not diagnostic criteria for dementia or a universal definition of acceptable vascular burden (Rabinovici, Selkoe, et al., 2025).

ARIA detection and management implications

ARIA-E comprises edema or sulcal effusion, generally assessed on FLAIR. ARIA-H comprises hemorrhagic abnormalities including new microhemorrhages and superficial siderosis, assessed using susceptibility sensitive imaging. The two can occur together. MRI interpretation requires comparison with baseline because pre-existing lesions and treatment emergent lesions have different implications. A consistent acquisition technique is important when counting small susceptibility foci (Cummings et al., 2023; Rabinovici, Selkoe, et al., 2025; Salloway et al., 2022).

ARIA can be asymptomatic or associated with headache, confusion, visual symptoms, seizures, focal deficits, or other neurological changes. Published aducanumab safety analyses demonstrated that many events occurred early in treatment and that APOE epsilon 4 status influenced risk. These findings inform the broader understanding of ARIA but should not be used as a substitute for agent specific incidence estimates. Severity assessment combines radiographic extent and clinical symptoms (Salloway et al., 2022).

New neurological symptoms during treatment require prompt evaluation rather than reliance on the date of the next scheduled scan. FLAIR and susceptibility findings should be interpreted with diffusion imaging and the clinical presentation because infarction, hemorrhage, and other acute conditions may overlap. Decisions to continue, pause, or discontinue treatment depend on the agent's protocol, symptoms, radiographic severity, and evolution. CT can identify major acute hemorrhage but cannot reliably exclude the full ARIA spectrum (Cummings et al., 2023; Rabinovici, Selkoe, et al., 2025).

Target engagement and clinical response

Lecanemab and donanemab trials demonstrated substantial amyloid reduction together with statistically significant slowing of decline on clinical outcomes. The clinical effect should be described as reduced decline over the studied interval, not restoration of normal cognition. Amyloid clearance is a pharmacodynamic measure, while clinical benefit is assessed through cognition and function. Their association does not make the magnitude of PET reduction a direct individual measure of treatment success (Sims et al., 2023; van Dyck et al., 2023).

Repeat amyloid PET can have a treatment specific role, including consideration of treatment completion in a donanemab pathway. This is different from serial imaging to track untreated dementia severity. Tau PET, MRI atrophy, and fluid biomarkers may contribute to research on downstream effects, but changes in these measures require independent validation as surrogates for patient outcomes. Treatment decisions should not be inferred from an imaging biomarker's change without an established clinical interpretation (Alves et al., 2023; Rabinovici, Selkoe, et al., 2025).

Emerging MRI biomarkers

Diffusion microstructure

Diffusion MRI estimates water displacement within tissue and is sensitive to changes in white matter and gray matter microstructure. Conventional diffusion tensor measures, including fractional anisotropy and mean diffusivity, are influenced by axonal organization, extracellular water, crossing fibers, and partial volume. A reduced fractional anisotropy value is therefore not a histological diagnosis of demyelination or axonal loss. Its biological interpretation depends on anatomy, model assumptions, and complementary measurements (Bergamino et al., 2021).

Free water models separate an extracellular isotropic compartment from tissue related diffusion. In an Alzheimer study using OASIS-3 data, free water correction changed the pattern and consistency of several diffusion measures, demonstrating that extracellular water can materially influence conventional tensor estimates. The approach improves characterization of the measured signal but does not uniquely identify the cellular mechanism producing an abnormal compartment fraction. Model stability and acquisition sufficiency remain necessary for individual interpretation (Bergamino et al., 2021).

Neurite orientation dispersion and density imaging and related multicompartment methods attempt to characterize tissue complexity more specifically than a single tensor. A systematic review and meta-analysis of in vivo microstructural abnormalities in mild cognitive impairment and Alzheimer disease illustrates the breadth of diffusion investigations. Group differences support biological sensitivity, but cross-study heterogeneity and overlapping causes of microstructural injury limit direct diagnostic thresholds. Advanced diffusion currently complements research characterization more readily than it supplies a stand alone clinical etiological assay (Duering et al., 2023; Zhong et al., 2023).

Arterial spin labeling

Arterial spin labeling (ASL) uses magnetically labeled arterial blood water as an endogenous tracer to estimate perfusion without ionizing radiation or an injected contrast agent. It can be incorporated into MRI and offers a route to repeated physiological measurements. Consensus implementation recommendations favour standardized labeling, background suppression, acquisition, and cerebral blood flow calculation, because signal intensity alone does not provide a reliable comparable perfusion value (Alsop et al., 2015).

Table 5:: Clinical algorithm for imaging during amyloid directed therapy

Stage	Required imaging question	Interpretive action
Before treatment	Is target pathology established, and is MRI adequate for baseline risk assessment?	Confirm amyloid by the accepted pathway; assess microbleeds, siderosis, infarction, white matter disease and other exclusions
Scheduled surveillance	Is there new ARIA-E or ARIA-H compared with baseline?	Use the agent specific surveillance schedule and a reproducible MRI protocol
New neurological symptoms	Could ARIA, stroke, hemorrhage or another acute process explain symptoms?	Arrange prompt clinical assessment and appropriate imaging; do not await the next routine surveillance scan
ARIA identified	What are the clinical and radiographic severity and temporal evolution?	Communicate directly with the treatment team; apply the agent specific continuation, suspension or discontinuation rules
Follow-up after an event	Has edema resolved, and are hemorrhagic findings stable or progressive?	Compare FLAIR and susceptibility imaging with baseline and intervening scans before treatment decisions
Target engagement or completion	Would repeat amyloid quantification change the treatment plan?	Use only an established treatment specific pathway; distinguish plaque reduction from cognitive response

Note. Clinical synthesis based on (Cummings et al., 2023; Rabinovici, Selkoe, et al., 2025; Salloway et al., 2022; Sims et al., 2023; van Dyck et al., 2023). Published appropriate use recommendations inform this table; current drug specific

ASL is sensitive to labeling efficiency, arterial transit time, postlabeling delay, motion, and partial volume. Delayed arrival of blood can resemble low perfusion if the acquisition does not account for transit effects. These issues are especially relevant in older patients with vascular disease. A posterior perfusion deficit may be compatible with an Alzheimer associated pattern but is not a direct amyloid or tau measure, and its incremental diagnostic value depends on comparison with structural and other available biomarkers (Alsop et al., 2015).

Functional connectivity

Resting state functional MRI estimates temporal associations in blood oxygenation dependent signals. Alzheimer disease research has examined default mode and medial temporal network abnormalities, including both reduced and increased connectivity. Longitudinal work showed related changes in posterior medial and anterior temporal hippocampal networks associated with cognitive decline. Such findings indicate that network dysfunction is not adequately represented by a single model of uniformly reduced connectivity (Dautricourt et al., 2021).

The blood oxygenation signal depends on neurovascular coupling as well as neuronal activity. Head motion, vigilance, respiratory effects, vascular disease, preprocessing, and global signal treatment can alter connectivity estimates. An apparent increase may reflect compensation, disinhibition, altered network segregation, or methodological effects; the interpretation requires direct evidence rather than an automatic compensatory label. Clinical adoption requires reliable individual estimates and demonstrated value beyond standard assessment.

Susceptibility and tissue composition

Quantitative susceptibility mapping estimates local magnetic susceptibility and has been used to study tissue iron related changes. An AIBL study found that higher regional susceptibility was associated with faster cognitive deterioration among amyloid positive participants. This supports investigation of susceptibility as a modifier of risk, but it does not make the measure specific to iron concentration or establish a causal effect of iron on decline (Ayton et al., 2017).

Susceptibility is influenced by several tissue constituents, orientation, acquisition, and reconstruction. Hemorrhagic products and myelin also affect the signal, and regional values depend on the chosen reference. Susceptibility mapping should therefore be distinguished from conventional microbleed detection, even though both use susceptibility sensitive information. Its potential contribution is quantitative tissue characterization; validation must address reproducibility and the specificity of the proposed interpretation.

Spectroscopy and metabolic MRI

Proton magnetic resonance spectroscopy assesses metabolites such as N-acetylaspartate, myo-inositol, choline containing compounds, and creatine. Changes may provide information about neuronal metabolism and glial related processes, but metabolite concentrations and ratios are influenced by tissue composition, acquisition, spectral fitting, and the stability of the denominator. A metabolite ratio is not automatically a quantitative measure of one cell population.

A 2025 hybrid three dimensional spectroscopic imaging and amyloid PET study examined 174 participants and reported regional relationships between amyloid, lower N-acetylaspartate, and higher myo-inositol. The work supports the value of spatially matched metabolic and molecular measurements. Improved classification within a study, however, requires external validation before the combined protocol can be treated as a clinical diagnostic standard. Research on functional spectroscopy of lactate similarly remains limited by measurement and biological interpretation challenges (Shirbandi et al., 2023; Zhang et al., 2025).

Blood brain barrier imaging

Dynamic contrast enhanced MRI can estimate contrast transfer related to blood–brain barrier permeability. In a human study of APOE epsilon 4 carriers, hippocampal and medial temporal barrier dysfunction was associated with genotype and cognitive impairment, while cerebrospinal fluid evidence of pericyte injury predicted subsequent decline. The findings support a vascular pathway that is not simply reducible to measured amyloid and tau burden (Montagne et al., 2020).

Low level leakage measurements are technically demanding. Temporal resolution, acquisition duration, arterial input estimation, baseline relaxation measurements, vascular volume, and pharmacokinetic modeling influence the result. Contrast exposure also changes feasibility for repeated measurement. A group level association with cognitive impairment does not yet define a clinically transferable threshold or establish whether measuring permeability improves an individual diagnostic decision. The main current contribution is mechanistic characterization and research stratification.

Emerging molecular imaging biomarkers

Synaptic density

Synaptic vesicle glycoprotein 2A (SV2A) PET provides a molecular approach to estimating a presynaptic protein associated with synaptic density. Carbon-11 UCB-J studies have shown reduced binding in medial temporal and neocortical regions in early Alzheimer disease. In one study, regional reductions persisted after correction for volume loss and were more extensive than the observed gray matter volume differences. This indicates sensitivity to information that is not fully captured by morphometry (Mecca et al., 2020).

SV2A binding is not a literal count of all functional synapses. The signal depends on protein availability, tracer delivery, modeling, and potentially medications occupying the target. Synapse type and function also cannot be inferred from a single regional binding value. These considerations

are important when proposing SV2A PET as a treatment response biomarker: a change in target availability requires interpretation before it can be equated with synapse gain or loss.

A 2025 study compared cerebrospinal fluid SV2A with UCB-J PET in a small early Alzheimer and control sample and found correspondence between the measures within the Alzheimer group. The study illustrates how imaging can validate the spatial and biological interpretation of fluid markers. It also shows why different "synaptic" biofluid proteins should not be assumed to index the same process; several other measured proteins did not show the same relationship with PET (Mecca et al., 2025).

Microglial and other inflammatory targets

Translocator protein (TSPO) PET has been used to study inflammatory responses in Alzheimer disease. The biological signal is broader than a unique detrimental microglial state, and binding is affected by tracer properties and, for several ligands, TSPO genotype. Appropriate interpretation therefore requires careful participant characterization and kinetic analysis. A high signal should not automatically be labeled evidence that inflammation is causing faster clinical decline.

Longitudinal DPA-714 work reported different relationships between baseline binding, subsequent binding change, and clinical progression. Higher initial binding was associated with a more favorable course, whereas increasing signal over follow-up was associated with worsening. These observations argue against a single monotonic interpretation of TSPO binding across all patients. A later multimodal study found spatial relationships among microglial activation, tau propagation, and amyloid, supporting interaction among these processes without proving that a particular PET signal identifies a uniquely causal cell state (Hamelin et al., 2018; Pascoal et al., 2021).

New inflammatory targets may eventually provide more selective information than TSPO, but clinical translation requires demonstration of target specificity, brain penetration, adequate specific binding, test retest reliability, and pathological or biological validation. The evaluation should distinguish expression of a target from a full cellular phenotype. A tracer can accurately measure a protein while still supporting only limited inference about whether the underlying response is protective, harmful, or stage dependent.

Astrocyte reactivity

Astrocyte related PET research includes targets such as monoamine oxidase B and other proteins associated with reactive states. Target expression is not restricted to a single pathological interpretation, and cellular specificity must be demonstrated rather than assumed. Fluid and imaging combinations can help test whether astrocyte related processes modify the relationship between amyloid and tau.

Bellaver and colleagues studied more than 1,000 cognitively unimpaired individuals across three cohorts and found that astrocyte reactivity, assessed with a fluid marker, modified the association between amyloid and tau measures. Tau PET provided information about downstream regional accumulation. The study supports a multimodal model of interacting pathology; it is not direct validation of an astrocyte specific PET ligand. Keeping those roles separate prevents a fluid defined biological association from being misreported as tracer validation (Bellaver et al., 2023).

Unmet proteinopathy targets

The reviewed clinical pathways still lack an established broadly available PET assay for TDP-43 or alpha-synuclein comparable with established Alzheimer amyloid imaging. Dopamine transporter imaging identifies a functional consequence of nigrostriatal degeneration, and clinical LATE criteria infer a likely underlying process from phenotype and other biomarkers. Neither directly visualizes the relevant protein aggregate (McKeith et al., 2017; Morbelli et al., 2020; Wolk et al., 2025).

This limitation affects mixed pathology assessment. An amyloid negative result can exclude a substantial Alzheimer plaque burden while leaving uncertainty among several non Alzheimer disorders. Development of a new ligand requires more than an anatomically plausible retention pattern in a clinically diagnosed cohort. Binding should be established in tissue, specificity tested against competing aggregates and off target substrates, and in vivo performance confirmed with independent biological or neuropathological evidence.

Table 6: Emerging biomarkers and requirements for translation

Measure	Biological information	Main validation requirement
Advanced diffusion MRI	Microstructure, extracellular water and tract injury	Model robustness, multisite reproducibility and specificity of interpretation
ASL perfusion MRI	Regional cerebral blood flow	Control of transit time, labeling and partial volume effects
Resting state functional MRI	Network organization through hemodynamic correlations	Motion control, neurovascular confounding and reliable individual prediction
Quantitative susceptibility mapping	Tissue susceptibility influenced by iron and other constituents	Reconstruction standardization and separation of competing tissue effects
MR spectroscopy	Regional metabolite concentrations or ratios	Spectral quality, tissue correction and externally validated incremental value
Dynamic contrast enhanced MRI	Barrier transfer and vascular permeability estimates	Reliable low leakage measurement and clinically interpretable thresholds
SV2A PET	Presynaptic protein availability associated with synaptic density	Target occupancy review, kinetic reliability and outcome validation
TSPO PET	Inflammation related protein expression	Genotype and cellular specificity, modeling, and stage dependent interpretation
Astrocyte related imaging	Selected proteins associated with astrocyte biology	Direct target and cellular validation; separation from fluid defined associations
AI and normative modeling	Patterns and deviation from reference anatomy or combined measurements	Independent, representative validation; calibration and clinical decision benefit

Note. Sources: (Alsop et al., 2015; Ayton et al., 2017; Bellaver et al., 2023; Bergamino et al., 2021; Bethlehem et al., 2022; Borchert et al., 2023; Dautricourt et al., 2021; Hamelin et al., 2018; Mecca et al., 2020; Montagne et al., 2020; Pascoal et al., 2021; Zhang et al., 2025; Zhong et al., 2023).

Multimodal integration and blood biomarkers

Blood based biomarkers can alter the sequence and frequency of imaging without eliminating its distinct spatial and safety functions. A prospective clinical study found high diagnostic accuracy for plasma percentage phosphorylated tau 217 and an amyloid probability score in symptomatic primary and secondary care populations. These results support blood testing as a potentially efficient route to assessing Alzheimer pathology when the assay and intended population are appropriately validated (Palmqvist et al., 2024).

The relation to imaging is conditional. A sufficiently accurate assay may establish a biological category under a specified framework, while PET remains useful for resolving equivocal or discordant findings and quantifying spatial pathology. MRI remains necessary for structural causes, vascular injury, and ARIA assessment because blood testing does not supply an anatomical map of hemorrhage or edema. Tau PET also provides regional staging information that cannot be reconstructed directly from a single blood concentration (Jack et al., 2024; Rabinovici, Knopman, et al., 2025).

A two threshold blood testing strategy can separate clearly low and high probability results from an intermediate zone that requires further evaluation. Its performance depends on prevalence, assay calibration, and comorbid influences. The downstream pathway should specify which result warrants PET or cerebrospinal fluid confirmation and why. Combining multiple correlated biomarkers without a defined decision rule can increase apparent certainty while adding little independent information.

For a multimodal model, incremental value should be measured against the best feasible existing pathway. Adding PET to a weak clinical comparator may appear beneficial even when the same gain could be achieved with a more complete clinical assessment or an accessible validated fluid assay. Conversely, a blood assay may be efficient for amyloid classification while leaving a major unresolved question about the anatomical distribution of tau, vascular comorbidity, or treatment safety. The value of each modality is determined by the decision it improves (Dickerson et al., 2025; Palmqvist et al., 2024; Rabinovici, Knopman, et al., 2025).

Artificial intelligence and quantitative implementation

Clinical questions and validation

Machine learning systems can estimate diagnosis, progression, regional abnormality, and patterns of heterogeneity from structural and molecular imaging. These are different tasks and require different reference standards. A classifier trained to distinguish Alzheimer dementia from healthy controls does not establish performance for differentiating Alzheimer disease from DLB, LATE, depression, or mixed vascular disease in a memory clinic. The intended population and decision should be defined before choosing a performance metric.

A systematic review of 255 neuroimaging artificial intelligence studies found heavy dependence on the Alzheimer's Disease Neuroimaging Initiative and limited independent validation. This concentration creates a risk that reported performance reflects features of a selected research sample, acquisition environment, or diagnostic labeling procedure. External validation should therefore include other institutions, scanner configurations, demographic groups, disease severities, and clinically relevant alternatives (Borchert et al., 2023).

Data leakage can occur when repeated scans from one participant appear in both training and test sets, preprocessing uses information from the full dataset, or feature selection is performed before partitioning. A high area under the curve does not resolve these design problems. Prospective evaluation should also assess calibration, failure modes, missing data, and the consequences of acting on false positive and false negative predictions.

Harmonization and normative interpretation

Harmonization methods aim to reduce scanner dependent variation while retaining biological differences. Their validity depends on the study design: if diagnostic groups and sites are strongly confounded, separating site from disease is difficult. The method and its parameters should be fitted within the training data in predictive studies and assessed on independent data. A statistical correction cannot replace an adequate acquisition and quality assurance protocol (Borchert et al., 2023; Fortin et al., 2018).

Normative brain charts provide age related centiles, but their clinical application requires an appropriate reference population and uncertainty estimates. The large lifespan dataset assembled by Bethlehem and colleagues demonstrates the scale needed to model anatomical variation, while also acknowledging uneven population representation. A low centile indicates an unusual measurement relative to that reference; it does not state whether the cause is developmental, vascular, degenerative, or technical (Bethlehem et al., 2022).

Deployment and accountability

A clinically deployed imaging system should make its input requirements, intended use, and failure conditions explicit. Segmentation overlays should be available for review, and numerical results should be traceable to a processing version. Quality assurance should detect motion, incomplete coverage, unexpected anatomy, and out of distribution inputs. An algorithm that cannot produce a dependable output should identify that failure rather than issue an apparently precise diagnostic probability.

Monitoring after deployment is necessary because scanner software, referral patterns, and population characteristics change. Performance should be evaluated through decisions and outcomes as well as discrimination metrics. The immediate clinical responsibility remains interpretation of the complete case, including symptoms and competing pathology. Automation can improve consistency and throughput, but its value requires evidence that its use improves the actual diagnostic pathway (Borchert et al., 2023).

Reporting standards and clinical communication

A useful imaging report distinguishes observations from etiological interpretation. The technical section identifies the modality, tracer where relevant, acquisition limitations, and comparison studies. The findings describe regional anatomy or uptake, vascular lesions, and incidental abnormalities. The conclusion states what the findings support, what they do not resolve, and whether an additional test could answer a specific remaining question. This structure avoids converting a compatible pattern into an unsupported pathological diagnosis (Guedj et al., 2022; Morbelli et al., 2020; Rabinovici, Knopman, et al., 2025).

For molecular imaging, the result should be expressed using the validated reading method, with quantification identified as supplementary or as part of an explicitly validated analysis. If a Centiloid value is reported, the analytical pipeline and its relevant interpretation should be clear. For tau PET, the distinction between an approved visual classification and research regional staging should be stated. For treatment surveillance, new lesions and change from baseline require explicit comparison, together with the imaging severity assessment used by the treatment team.

Disclosure should connect the result to the original question. A positive amyloid scan means amyloid pathology is present above the relevant detection threshold; it does not provide an exact date of future decline or establish that all symptoms arise from that pathology. A negative scan may narrow the differential diagnosis without identifying the alternative. The specialist should explain how the result changes diagnostic confidence, treatment options, and the need for further evaluation (Dubois et al., 2024; Rabinovici, Knopman, et al., 2025).

Limitations of the evidence and priorities for research

The evidence base is uneven across modalities and disease stages. Amyloid ligands have substantial pathological validation, whereas several emerging targets are supported by smaller mechanistic studies. Clinical tau PET has a stronger basis for advanced Alzheimer type pathology than for early microscopic disease or all non Alzheimer tau conformations. MRI and FDG patterns are widely used but remain biologically nonspecific. These differences should determine the strength of the language used in diagnosis and research conclusions (Clark et al., 2012; Fleisher et al., 2020; Soleimani-Meigooni et al., 2020).

Mixed pathology is a central limitation of single target interpretation. Multiple processes can contribute to one clinical syndrome, and the availability of an assay for one process can bias attention toward it. Greater neocortical tau burden can strengthen an Alzheimer attribution, while vascular MRI and dopaminergic imaging may demonstrate additional mechanisms. The absence of established direct assays for other common proteinopathies leaves a residual uncertainty that should not be concealed by a positive Alzheimer biomarker (Jack et al., 2024; McKeith et al., 2017; Nelson et al., 2019).

Research priorities include imaging to autopsy validation across disease stages, prospective studies with representative clinical populations, reproducible quantification, and comparisons against realistic diagnostic pathways. Emerging biomarkers should be evaluated for incremental prognosis and treatment response, not only separation of cases from controls. Therapeutic studies should distinguish target engagement, safety markers, and validated clinical outcomes. For imaging driven management pathways, randomized or otherwise, well controlled outcome studies are needed to determine whether greater diagnostic certainty translates into benefit for patients and care partners (Altomare et al., 2023; Borchert et al., 2023; Rabinovici et al., 2019).

Conclusion

Neuroimaging in dementia is most informative when each modality is matched to a specific inference. CT and MRI identify structural disease and injury; functional imaging characterizes regional dysfunction; amyloid and tau PET assess defined molecular targets with different temporal and pathological sensitivities. Clinical interpretation requires an explicit diagnostic framework and recognition of mixed pathology. In amyloid directed treatment, MRI also has a separate safety function that molecular or blood biomarkers cannot replace. Emerging techniques broaden measurement of synapses, glial responses, microstructure, perfusion, barrier integrity, and network function, but their clinical use requires reproducible individual measurements and evidence of added decision value.

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