Advances in Dementia with Lewy Bodies 3

Diagnostic and other biomarkers of dementia with Lewy bodies: from research to clinical settings

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Dementia with Lewy bodies is characterised clinically by visual hallucinations, fluctuating cognitive function, parkinsonism, and rapid eye movement sleep behaviour disorder, and can cause more frailty than other dementias. The disease is heterogeneous in presentation and progression, and misdiagnoses are common. In people with dementia with Lewy bodies, other brain copathologies are frequent, limiting the usefulness of some diagnostic biomarkers. This heterogeneity, together with the scarcity of diagnostic and prognostic biomarkers, has hindered the implementation of therapeutic trials. However, novel neuroimaging techniques have emerged with high sensitivity to brain tissue composition and microstructure. Fluid biomarkers are being developed to detect very low concentrations of neuropathological proteins. These biomarkers could soon be adopted in clinical practice and incorporated as outcome measures in clinical trials. These advances will pave the way for early diagnosis, disease monitoring, and prognosis, and will facilitate the implementation of disease-modifying trials.

Lancet Neurol 2025; 24: 1053–65

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This is the third in a **Series** of three papers about advances in dementia with Lewy bodies

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Introduction

Dementia with Lewy bodies is the second most common cause of neurodegenerative dementia after Alzheimer's disease, accounting for up to 24% of dementia cases.[1] Dementia with Lewy bodies causes more frailty and higher mortality than other dementias, and a greater economic burden.[2] Diagnostic criteria have changed little over the past 30 years,[3] and a reassessment of the role of biomarkers in dementia with Lewy bodies seems timely for three reasons. First, dementia with Lewy bodies remains under-recognised, with many patients receiving alternative diagnoses. Second, biological frameworks for the diagnosis of Parkinson's disease and other synucleinopathies have been proposed[4,5] that replace the emphasis on clinical syndromes with biological markers. How dementia with Lewy bodies fits within these classifications is not resolved, and will need to be defined if these frameworks become widely applied. Finally, new imaging and fluid biomarkers have emerged with strong potential for application in clinical practice to diagnose and monitor dementia with Lewy bodies.

In this third paper in a Series on dementia with Lewy bodies,[6,7] we describe these new imaging and fluid biomarkers, and the evidence on how they can complement established biomarkers for diagnosis of dementia with Lewy bodies. We also cover the evidence on new imaging and fluid biomarkers of disease progression and severity. Finally, we examine how fluid and imaging biomarkers provide information on underlying pathophysiology, how they could be used to target specific interventions, and challenges in the translation of this evidence into clinical practice.

Clinical and neuropathological features

Dementia with Lewy bodies is clinically characterised by prominent attentional, executive, or visuospatial deficits, plus recurrent visual hallucinations, cognitive fluctuations, motor parkinsonism, and rapid eye movement (REM) sleep behaviour disorder.[3] Supportive clinical features include autonomic dysfunction, falls, delusions, anxiety, and depression,[3] which can precede core clinical symptoms.[8] Mean disease duration varies between 5 years and 7 years, depending on underlying pathology. Dementia with Lewy bodies is distinguished from Parkinson's disease dementia by the timing of dementia onset. Parkinson's disease dementia is diagnosed when dementia occurs in patients with established Parkinson's disease,[9] and dementia with Lewy bodies is diagnosed if dementia occurs before or within 12 months of motor symptoms onset.[3]

Lewy body dementia is an umbrella term, comprising both dementia with Lewy bodies and Parkinson's disease dementia. Lewy body dementia reflects the overlap in clinical symptoms and underlying neuropathology, and can be applied to patients when the timing of dementia onset, in relation to motor parkinsonian symptoms, is not known. Although there are calls for these conditions to be unified[10] based on common symptomatology, underlying neuropathology, and genetic architecture, some specialists remark their distinct pathophysiology, such as differences in cholinergic dysfunction,[11] and argue that these conditions should not be grouped.[12] The 12-month cutoff is arbitrary as, in people with Parkinson's disease, dementia can start at any point after diagnosis rather than only at advanced disease stages.

The neuropathological hallmark of dementia with Lewy bodies is the presence of Lewy bodies and Lewy neurites comprised of misfolded α-synuclein. However, a high proportion of patients have substantial copathologies,[13] most commonly Alzheimer's disease pathology with amyloid plaques, and less frequently tau neurofibrillary tangles. The presence of copathology seems the norm, with Alzheimer's disease pathology

observed in up to 77% of patients with dementia with Lewy bodies at postmortem. Patients with Parkinson's disease have shorter progression times to dementia if they have higher concentrations of amyloid β and tau pathology.[13] Patients frequently have more than two copathologies, including TDP-43 pathology, which has a higher prevalence in cases in whom Alzheimer's disease pathology is also present.[14] A synergistic effect is seen between copathologies, with high concentrations of tau tangles and amyloid plaques correlating with cortical Lewy body burden.[13,15] Cerebrovascular disease is also frequent,[13] usually with an inverse relationship to Lewy pathology severity, potentially suggesting that cerebrovascular disease lowers the threshold for clinical manifestation in people with dementia with Lewy bodies.

A major challenge in diagnosing and managing dementia with Lewy bodies is variability in clinical presentation, timing of dementia onset, and rates of progression. Heterogeneity in clinical presentation and insidious onset means that dementia with Lewy bodies is frequently under-recognised. The prediction of an individual's clinical course is difficult and clinical trial design is challenging due to an absence of objective outcome measures.[16,17] Clinical variability is underpinned by heterogeneity in underlying neuropathology. With promising anti-amyloid emerging treatments,[18] there are opportunities to treat this copathology in people with dementia with Lewy bodies. Biomarkers are therefore required to: (1) enable accurate and early diagnosis; (2) monitor disease progression and predict outcomes; and (3) detect and quantify underlying pathologies, to improve the design of clinical trials and predict therapeutic response.

See Online for appendix

Panel 1: **Biomarkers in the diagnostic criteria for dementia with Lewy bodies**

Current diagnostic criteria are largely clinical, with biomarkers playing a supportive role. Diagnosis requires presence of dementia with cognitive deficits mostly affecting attention, executive functions, and visuoperceptive ability, rather than memory.[3] Core clinical features include fluctuating cognition, recurrent visual hallucinations; rapid eye movement (REM) sleep behaviour disorder; and motor parkinsonism. Probable dementia with Lewy bodies is diagnosed when two or more core clinical features are present.[3] See the appendix (p 1) for the diagnostic criteria in full.

Indicative biomarkers inform the diagnosis if only one core feature is present. These biomarkers include reduced dopamine transporter uptake in the basal ganglia; reduced uptake on cardiac [^{123}I]metaiodobenzylguanidine myocardial scintigraphy; and video polysomnographic evidence of REM sleep without atonia. However, these indicative biomarkers are not specific to dementia with Lewy bodies, and do not provide information on underlying pathological processes.

Additional supportive biomarkers are included in the diagnostic criteria, but they have lower sensitivity and specificity than the three measures mentioned above (appendix p 1).

Diagnostic criteria for prodromal dementia with Lewy bodies define three syndromes based on clinical features:[8] mild cognitive impairment with Lewy bodies, a delirium-onset syndrome, and a psychiatric-onset syndrome. Supportive biomarkers are only defined for mild cognitive impairment with Lewy bodies. See the appendix (p 2) for diagnostic criteria for prodromal dementia with Lewy bodies.

Recent staging systems have been proposed for Parkinson's disease and related conditions, based on biological measures.[4,5] For instance, the neuronal synuclein disease staging is based on the presence of synucleinopathy (using CSF α-synuclein biomarkers) and dopaminergic neuron degeneration (using dopamine transporter SPECT). These criteria are not yet approved for clinical use, and it is not clear how dementia with Lewy bodies could be incorporated into them.

Indicative diagnostic biomarkers

According to current criteria, indicative biomarkers can be used to inform the diagnosis of dementia with Lewy bodies in patients in whom only one core clinical feature is present (panel 1). In this section, we describe these diagnostic biomarkers in order of their clinical relevance.

FP-CIT SPECT

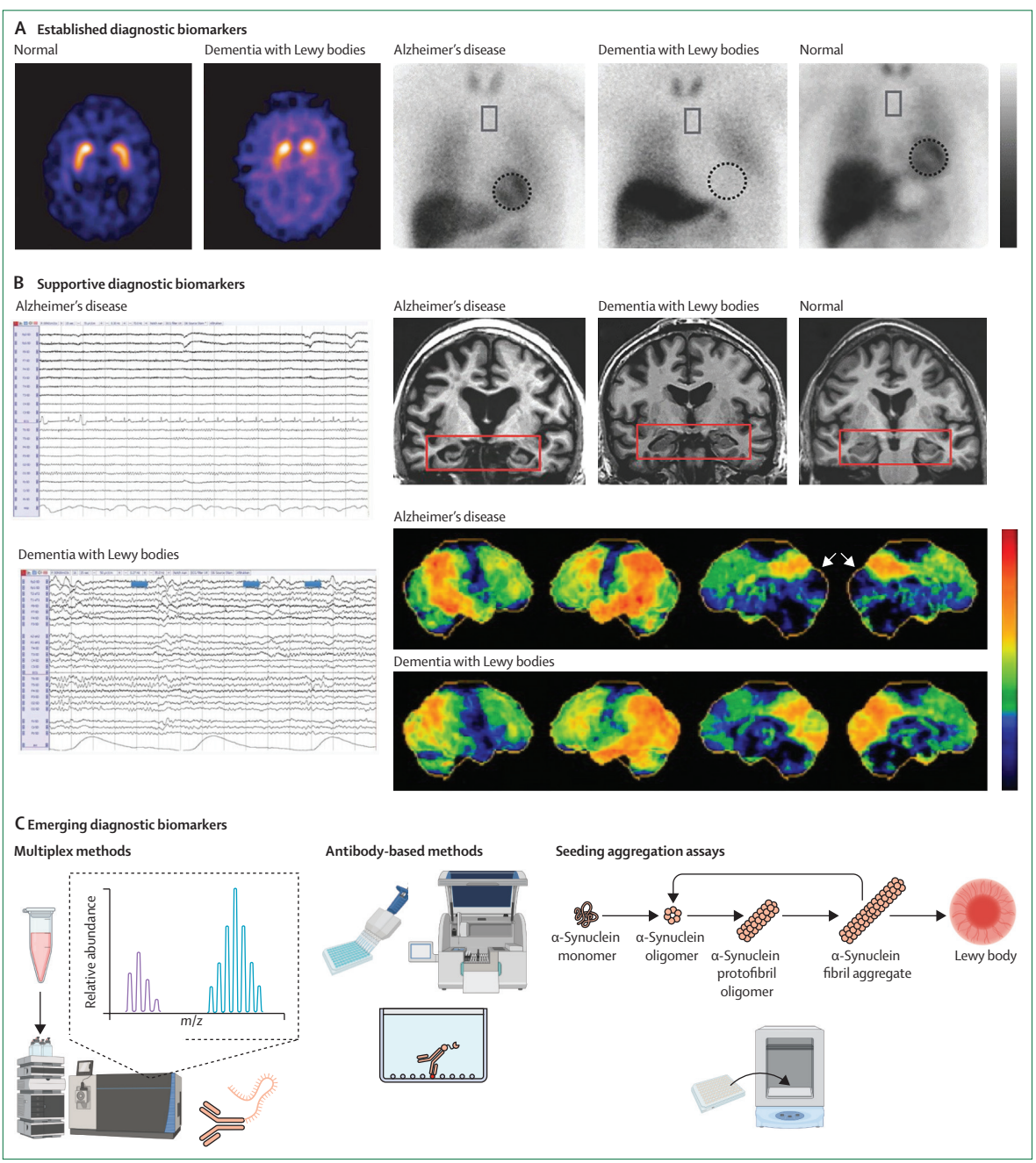
Dopamine transporter neuroimaging using [^{123}I] ioflupane ([^{123}I]FP-CIT) SPECT is established as an indicative biomarker for the diagnosis of dementia with Lewy bodies in the current criteria.[3] The radioligand is a cocaine analogue that binds to presynaptic CNS dopamine transporters, allowing the detection of nigrostriatal pathway denervation (figure 1). Abnormal FP-CIT SPECT differentiated dementia with Lewy bodies from Alzheimer's disease and other dementias with 78% sensitivity and 90% specificity in a large multisite study that included 326 patients with dementia with Lewy bodies and 147 patients with other forms of dementia

Figure 1: **Diagnostic biomarkers for dementia with Lewy bodies**
(A) Established diagnostic biomarkers included in current diagnostic criteria[3] to inform the diagnosis of probable dementia with Lewy bodies when only one core clinical feature is present. Left: dopaminergic imaging (FP-CIT SPECT) showing bilateral, asymmetrical reduction in DLB compared with a normal scan. Reproduced from McKeith and colleagues, with permission from Wolters Kluwer Health.[19] Right: ^{123}I-meta-iodobenzylguanidine scintigraphy showing pronounced cardiac denervation (dotted circle) in a patient with dementia with Lewy bodies compared with a patient with Alzheimer's disease and a healthy individual. Reproduced from McKeith and colleagues, with permission from Wolters Kluwer Health.[3] The rectangle indicates the mediastinum, which is used as a control region, where low uptake of 123I-meta-iodobenzylguanidine is expected and used as a comparison with uptake within the heart. (B) Supportive diagnostic biomarkers can provide additional information but lack sensitivity and specificity to inform the diagnosis of dementia with Lewy bodies. Left: EEGs showing a normal recording in a patient with Alzheimer's disease and a recording with pronounced abnormalities, particularly posteriorly, in a patient with dementia with Lewy bodies. Reproduced from van der Zande and colleagues[20] with permission from Frontiers. Top right: structural T1-weighted imaging of a patient with Alzheimer's disease, followed by a scan showing preserved hippocampal volume in a patient with dementia with Lewy bodies, and that of a healthy individual. The red rectangle indicates the hippocampi in each image. Reproduced from McKeith and colleagues, with permission from Wolters Kluwer Health.[3] Bottom right: differential FDG-PET profiles in patients with Alzheimer's disease (autopsy-confirmed) or those with dementia with Lewy bodies. Adapted from Minoshima and colleagues, with permission from John Wiley and Sons.[21] (C) Emerging biomarkers, that can detect α-synuclein aggregation, amyloid and tau co-pathology, and changes in multiple protein profiles in CSF or plasma. Multiplex methods like proximity extension assays can detect multiple proteins at once in CSF or plasma. Antibody-based applications like ELISA are well established for markers of amyloid co-pathology and might play a role in the diagnosis of dementia with Lewy bodies. α-Synuclein aggregates can be reliably detected in the CSF by seeding aggregation assays and are being developed to detect aggregates in plasma. Subpanel created with BioRender.com.

(including Alzheimer's disease and vascular dementia), in which diagnoses were clinically established by a consensus panel.[19] This indicative biomarker was later validated in an autopsy study that showed 80% sensitivity and 92% specificity of FP-CIT SPECT against neuropathological diagnosis of dementia with Lewy bodies.[22] However, dopaminergic imaging is also atypical in other disorders affecting dopaminergic transmission—eg, corticobasal degeneration and progressive supranuclear palsy. Additionally, the diagnostic value of FP-CIT SPECT for prodromal dementia with Lewy bodies is lower, with 54–66% sensitivity and 88–89% specificity.[23,24] However, even at these lower sensitivities, FP-CIT SPECT provides useful additional diagnostic information, particularly for differentiating dementia with Lewy bodies from Alzheimer's disease.

MIBG scintigraphy

[^{123}I] metaiodobenzylguanidine (MIBG) is a physiological analogue of norepinephrine used to detect cardiac sympathetic denervation in myocardial scintigraphy.[3] Cardiac sympathetic denervation is quantified using the



heart-to-mediastinum ratio, which compares uptake of the analogue between the heart and mediastinum. A 3-year prospective study found a 77% sensitivity and 97% specificity for baseline MIBG in the differentiation of dementia with Lewy bodies from Alzheimer's disease;[25] and in an autopsy validation study, MIBG differentiated patients with Lewy body brain pathology from those with other pathologies, with 70–80% sensitivity and 85–96% specificity.[26] Therefore, in people with dementia, MIBG can help to differentiate dementia with Lewy bodies from other dementias. However, atypical MIBG is also seen in people with heart failure,[27] a common comorbidity in people with dementia.[28] Additionally, the diagnostic value of MIBG is lower in prodromal disease, with only 59% sensitivity and 88% specificity in differentiating prodromal dementia with Lewy bodies from prodromal Alzheimer's disease.[29]

Video polysomnography

Video polysomnography is an indicative biomarker that can identify REM sleep without atonia and REM sleep behaviour disorder. REM sleep behaviour disorder strongly correlates with α-synuclein pathology. In an autopsy study of 652 cases enrolled in a brain donation programme, α-synucleinopathy was more frequent in patients with REM sleep behaviour disorder (73·7%) than in those without (35·8%, p<0·001).[30] However, REM sleep behaviour disorder is not specific to dementia with Lewy bodies, and video polysomnography findings can be similar in people with Parkinson's disease, Parkinson's disease dementia, or atypical parkinsonian syndromes.[31]

Supportive diagnostic biomarkers

Supportive biomarkers are currently included in the diagnostic criteria, but are neither necessary nor sufficient for the diagnosis of dementia with Lewy bodies in the absence of clinical features of dementia with Lewy bodies, due to their low sensitivity and specificity.

Preserved medial temporal lobe on MRI

Cortical atrophy is consistently seen in people with dementia with Lewy bodies, involving the insula, posterior cingulate, frontal, inferior parietal, temporal, and occipital lobes. However, atrophy patterns are not specific, and can coincide with those seen in normal ageing and Alzheimer's disease. In a multicentre study of 333 patients with dementia with Lewy bodies, 352 patients with Alzheimer's disease, and 233 healthy controls that used visual rating scales, global cortical atrophy was seen in both dementia with Lewy bodies and Alzheimer's disease, compared with controls.[32] This atrophy pattern is also seen using quantitative measures,[33] with reduced medial occipital and posterior temporal lobe volumes, and nucleus basalis of Meynert, even in prodromal dementia with Lewy bodies compared with healthy controls.[34] In patients with dementia with Lewy bodies, the medial temporal lobe and the hippocampus are usually relatively spared (figure 1), in comparison with patients with Alzheimer's disease,[32] including in cohorts with neuropathological confirmation of Alzheimer's disease or dementia with Lewy bodies. However, grey matter imaging has only about 65% sensitivity to discriminate between dementia with Lewy bodies and Alzheimer's disease, and even less sensitivity in people with mild cognitive impairment.[35] The detection of atrophy in the nucleus basalis of Meynert might be more useful than medial temporal atrophy to detect patients with prodromal dementia with Lewy bodies from patients unlikely to progress to dementia.[34]

Hypometabolism on FDG-PET

[^{18}F] fluorodeoxyglucose ([^{18}F]FDG)-PET is a supportive diagnostic biomarker for dementia with Lewy bodies that measures cerebral metabolic glucose consumption.[3] [^{18}F]FDG-PET shows generalised low uptake and parieto-occipital hypometabolism in people with dementia with Lewy bodies, but only with 70% sensitivity and 74% specificity.[3] In people with dementia with Lewy bodies, [^{18}F]FDG-PET shows a characteristic pattern of relative preservation of mid-cingulate metabolism—ie, the cingulate island sign—which has some prognostic value, especially when using semiquantitative analyses. Patients with dementia with Lewy bodies with coexisting Alzheimer's disease pathology do not usually have this sign.[36]

[^{18}F]FDG-PET has diagnostic potential also in prodromal dementia with Lewy bodies, with the cingulate island sign showing 90% specificity, but only 59% sensitivity in distinguishing mild cognitive impairment due to dementia with Lewy bodies from that due to Alzheimer's disease. Notably, a higher medial temporal to substantia nigra ratio was 94% sensitive and 83% specific in differentiating these groups.[37] In summary, although the cingulate island sign is not particularly sensitive, if present, it is useful in differentiating dementia with Lewy bodies (including prodromal stages) from Alzheimer's disease.

Slow-wave activity on EEG

In patients with dementia with Lewy bodies, diffuse slowing is seen on EEG, and over 90% of patients have an abnormal EEG.[20] EEG abnormalities are predominantly the slowing of background rhythm with increase in theta and delta and reduced alpha and beta bands. In a systematic review that included 42 studies comparing dementia with Lewy bodies with Alzheimer's disease, a dominant frequency of less than 8 Hz differentiated dementia with Lewy bodies from Alzheimer's disease in over 85% of participants.[38] This slowing is particularly prominently seen in posterior brain regions in patients with dementia with Lewy bodies, a finding which was not commonly seen in patients with Alzheimer's disease.

Emerging diagnostic biomarkers

Diagnostic biomarkers are now emerging with potential for improving early and accurate diagnosis of dementia with Lewy bodies. α-Synuclein seeding aggregation assays (SAAs) of CSF showed high sensitivity and specificity to detect α-synucleinopathy in analyses from the Parkinson's Progression Markers Initiative.[39] These assays are also highly accurate in detecting the presence of α-synuclein in dementia with Lewy bodies. In a study of 47 patients with dementia with Lewy bodies and 101 patients who were neuropathologically confirmed to be Lewy body negative, SAA had 95% sensitivity and 98% specificity.[40] Compared with Parkinson's disease, SAAs in dementia with Lewy bodies show faster seeding kinetics and stronger fluorescence signals.[41] Kinetic parameters seem to detect or predict the presence and development of dementia in people with dementia with Lewy bodies or Parkinson's disease.[42] A longitudinal study examined 196 patients with positive SAAs across the spectrum of Lewy body dementia, including 26 participants with negative SAAs at baseline, but converted to positive SAAs over the 2-year follow-up, testing CSF samples in four replicates. The study found that the number of positive replicates predicted subsequent dementia, providing some quantitative metrics relating to conversion. By contrast, the longer time difference needed for the signal to reach the positivity threshold between baseline and subsequent visits was negatively associated with progression to dementia.[42] However, other studies show lower SAA-positivity in people with dementia with Lewy bodies than in those with Parkinson's disease, with only 137 (72%) of 191 patients with dementia with Lewy bodies having a positive SAA.[43] Notably, patients with dementia with Lewy bodies who were α-synuclein SAA-positive had poorer cognition, higher motor scores, and higher incidence of REM sleep behaviour disorder and hyposmia than patients with dementia with Lewy bodies who were SAA-negative.[43]

In patients with Parkinson's disease, α-synuclein SAAs can be measured also in other fluids and tissues, such as skin biopsies, submandibular gland biopsies, and serum.[44,45] However, sensitivities and specificities are lower than for CSF measures; serum measures of α-synuclein SAAs are not yet widely validated, and data for other fluids and tissues from patients with dementia with Lewy bodies are scarce. Overall, CSF α-synuclein SAAs can reliably differentiate patients with dementia with Lewy bodies from healthy controls, although a substantial proportion of patients with dementia with Lewy bodies are SAA negative.[43] Additionally, different strains of α-synuclein can be seen in dementia with Lewy bodies than those in other α-synucleinopathies,[46,47] and in vitro derived fibril strains differ structurally from brain-derived ones,[47] potentially limiting applicability of the α-synuclein SAAs in detecting the presence of α-synuclein in dementia with Lewy bodies. These assays are available in research settings, but more work is needed in different populations and disease stages before they can be incorporated into clinical practice.

Diagnostic accuracy for CSF measures could be increased when used in combination. For example, a model combining amyloid β 42, total tau, total α-synuclein, oligomeric α-synuclein, age, and sex could differentiate patients with dementia with Lewy bodies from healthy controls (sensitivity 68% and specificity 93%) and Alzheimer's disease (sensitivity 81% and specificity 74%).[48]

Finally, omic approaches might identify new diagnostic biomarkers. In a proteome analysis based on proximity extension assay technology, 665 proteins were assessed in CSF samples from patients with dementia with Lewy bodies, Alzheimer's disease, and healthy controls, revealing over 50 dysregulated proteins in dementia with Lewy bodies. Dopamine biosynthesis enzyme dopa-decarboxylase (DDC) distinguished patients with dementia with Lewy bodies from controls; and a panel of six markers (DDC, corticotropin-releasing hormone, MMP-3, ABL1, MMP-10, and THOP1) was consistently able to differentiate dementia with Lewy bodies from Alzheimer's disease (area under the curve [AUC] greater than 0·90) in four validation cohorts.[49]

α-Synuclein PET radioligands to directly image α-synuclein accumulation are highly desirable, but there are major challenges to their development. These challenges include low density of α-synuclein fibrils in brain tissues relative to amyloid β and tau copathologies, and the intracellular location of pathological α-synuclein.[50] The [^{18}F]F0502B PET tracer might be a promising biomarker, as it shows high affinity and specificity for α-synuclein in animal models and human brain sections.[51]

Biomarkers of disease progression

In addition to their usefulness in diagnosis, biomarkers can also help to monitor disease progression and predict clinical outcomes. Although fluid prognostic markers are established for other neurodegenerative diseases, such as Alzheimer's disease, their role in dementia with Lewy bodies is less clear. MRI shows potential as a prognostic biomarker, especially sequences with sensitivity to brain tissue composition.[52,53]

Fluid biomarkers

Fluid biomarkers that correlate with disease activity and have prognostic potential are emerging. Patients with dementia with Lewy bodies have higher CSF neurofilament light chain (NfL) concentrations compared with healthy controls, and patients with dementia with Lewy bodies with Alzheimer's disease copathology have the highest concentrations of CSF NfL. NfL concentrations are increased in patients with prodromal dementia with Lewy bodies compared with healthy controls; and are increased in patients with dementia with Lewy bodies compared with patients with prodromal dementia with

Lewy bodies.[54] A multicentre study examining several plasma measures in people with dementia with Lewy bodies showed an association between higher NfL and GFAP concentrations in plasma with lower Mini-Mental State Examination scores and faster cognitive decline.[55] However, NfL and GFAP are non-specific biomarkers that are also increased in other neurodegenerative conditions. More promising than NfL and GFAP are fluid biomarkers for Alzheimer's disease, which could also influence cognitive outcomes in dementia with Lewy bodies. Abnormal CSF amyloid β concentrations and higher concentrations of tau phosphorylated at Thr181 (p-tau181) in plasma are associated with worse cognition[55,56] and with disease progression in people with dementia with Lewy bodies.[56] However, more longitudinal studies using these fluid biomarkers across different laboratories are needed to assess their validity.

Neuroimaging biomarkers

Higher rates of global atrophy (measured by annual increase in ventricular volume) are associated with worse functional performance in people with dementia with Lewy bodies, and reduced cortical thickness in the insula, medial frontal, middle temporal, inferior frontal, and inferior parietal lobes is associated with worse cognition.[57] However, patterns of grey matter atrophy are highly heterogeneous between individuals and are less useful for risk stratification. Neuroanatomical normative modelling captures between-patient heterogeneity by mapping individual differences from expected norms at each brain region using very large reference datasets. When applied to cortical thickness, normative modelling has shown greater atrophy in individuals with dementia with Lewy bodies compared with healthy controls, and an association with poorer cognition,[58] with potential to be adopted in clinical settings.

White matter integrity can be assessed in vivo using diffusion-weighted imaging. Diffusion tensor imaging is the best established analysis method, with several studies showing widespread group-level changes in people with dementia with Lewy bodies, compared with healthy controls, particularly posteriorly, even in the absence of grey matter atrophy.[59] Degeneration of cholinergic white matter projections from the nucleus basalis of Meynert can also be detected, together with volume loss in both people with dementia with Lewy bodies and those with Alzheimer's disease, with tract integrity more strongly associated with cognition than volume loss.[60]

It is unclear whether white matter alterations can track longitudinal progression in people with dementia with Lewy bodies, with only one longitudinal study to date (including only 14 patients). This study showed baseline loss of white matter integrity, but no additional changes after 1-year follow up.[59] This lack of longitudinal change could reflect limited diffusion tensor imaging sensitivity. Instead, more advanced diffusion-weighted imaging techniques can predict dementia in patients with Parkinson's disease[53] and track disease progression in Alzheimer's disease,[61] but there are few applications of this technique in patients with dementia with Lewy bodies. A cross-sectional study using neurite orientation dispersion and density imaging compared 45 patients with dementia with Lewy bodies with 45 healthy controls and showed widespread white matter changes.[52]

An alternative method of diffusion-weighted imaging analysis is free water imaging. This method estimates fractional volume of free water within each voxel, thought to represent extracellular space and possibly reflect inflammation. Increased free water is seen in both dementia with Lewy bodies and Alzheimer's disease in projections between the nucleus basalis and the cortex, compared with healthy controls, with increased free water in tracts between the pedunculopontine nucleus and thalamus in people with dementia with Lewy bodies, but not in those with Alzheimer's disease.[62] Free water imaging can also track disease progression. In a small longitudinal study of 23 patients with dementia with Lewy bodies, progressive increases in free water were seen over time within multiple grey and white matter regions, with increases more pronounced in the temporal lobes.[63] The increases correlated with motor and cognitive severity.[63] However, longitudinal studies in larger populations are needed to show the value of this technique in tracking disease severity, and studies are needed that examine the relationship between loss of white matter and grey matter integrity as disease progresses.

Loss of neuromelanin-containing dopaminergic neurons and subsequent loss of pigmentation in the substantia nigra are major pathological hallmarks of dementia with Lewy bodies. This loss can be detected in patients by use of neuromelanin-sensitive MRI, a technique in which signal results from the interaction between neuromelanin and chelated iron. Most neuromelanin-sensitive MRI studies have been done in individuals with Parkinson's disease, and found a pooled 89% sensitivity and 83% specificity to distinguish individuals with Parkinson's disease from healthy controls calculated using bivariate random-effects modelling in a meta-analysis.[64] A study in seven patients with dementia with Lewy bodies found reduced signal on neuromelanin-sensitive MRI within the substantia nigra, compared with healthy controls.[65] However, in people with dementia with Lewy bodies, neurodegeneration is more widespread outside neuromelanin-containing regions than in Parkinson's disease, and this neurodegeneration is not captured using neuromelanin-sensitive MRI, so this technique might have limited use in clinical practice.

Iron accumulates within the substantia nigra with ageing, a process that is accelerated in people with synucleopathies[66] particularly within nigrosome-1 (a region within the substantia nigra). MRI techniques sensitive to tissue susceptibility, such as quantitative susceptibility

mapping (QSM) and R2*, can detect iron accumulation in vivo. Three small cross-sectional studies assessed loss of nigrosome-1 in people with dementia with Lewy bodies,[67] described radiologically as loss of the swallow's tail appearance on susceptibility-weighted imaging. All three studies showed loss of nigrosome-1 in people with dementia with Lewy bodies, which distinguished these participants from people with Alzheimer's disease or other dementias. However, no study assessed the correlation of nigrosome-1 loss with disease progression or severity.[65,67] A cross-sectional QSM study of 36 patients with dementia with Lewy bodies showed higher susceptibility in the substantia nigra compared with 102 healthy controls and 15 people with mild cognitive impairment due to Lewy bodies, but this susceptibility did not correlate with clinical severity.[68] A study comparing QSM in Lewy body dementia subtypes showed increased QSM in widespread cortical regions in Lewy body dementia compared with healthy controls, but with higher QSM in Parkinson's disease dementia compared with dementia with Lewy bodies, and correlations with disease severity mainly in Parkinson's disease dementia.[69]

Iron accumulation was also seen in cortical regions in people with dementia with Lewy bodies using R2*. In 46 patients with prodromal dementia with Lewy bodies, lower R2* signal was seen than in 20 healthy older people in the bilateral superior frontal, left superior temporal and right fusiform gyrus; with correlations in the thalamus between R2* and cognitive fluctuations.[70] In summary, neuroimaging techniques sensitive enough to detect brain microstructure show promise for monitoring disease severity in people with dementia with Lewy bodies, but longitudinal data are not available.

[18F]FDG-PET can also be used to examine metabolic changes in dementia with Lewy bodies. Longitudinal decline in [18F]FDG-PET using a standardised uptake value ratio (SUVR) predicted progression from mild cognitive impairment to dementia with Lewy bodies in a study of 35 patients with dementia with Lewy bodies, 37 with mild cognitive impairment, and 100 healthy controls.[71] Additionally, using a combined region including FDG-SUVR data from frontal, cingulate, and insula areas, rates of FDG-SUVR correlated with rates in cognitive performance (measured using the Clinical Dementia Rating Sum of Boxes score), suggesting potential for monitoring disease activity.[71]

Biomarkers used in research settings to quantify copathologies

Biomarkers of underlying pathology are essential for identifying the patients who have specific pathologies to be included in clinical trials of disease modifying treatments. The identification of copathology is particularly relevant for research on dementia with Lewy bodies, given the high prevalence of copathologies, which can influence disease severity more than Lewy body-related pathology,[13] and the individual heterogeneity. Pathology-specific biomarkers might also have a role in clinical trials to measure target engagement and as outcome measures in early phase trials without the statistical power to detect benefits on clinical outcomes.

Amyloid and tau biomarkers

Amyloid-PET is an established biomarker for the diagnosis of Alzheimer's disease, with several amyloid-PET tracers available to image amyloid plaques that have been validated in autopsy studies.[72] Amyloid brain deposition is found in at least 50% of patients with dementia with Lewy bodies, and more plaques of amyloid β are linked with more rapid clinical progression.[13,73] The longitudinal trajectory of amyloid accumulation in dementia with Lewy bodies follows a sigmoid-shaped functional curve, similar to that of Alzheimer's disease, and correlates with cognitive decline.[74] Although amyloid-PET cannot be used to differentiate dementia with Lewy bodies from Alzheimer's disease, it might have a research role in stratifying patients with more rapid progression and for clinical trials of anti-amyloid therapies.

Tau-PET uses ligands that bind to tau-containing neurofibrillary tangles. Tau neuropathology mirrors the progression of Alzheimer's disease pathology and correlates well with Alzheimer's disease severity. However, studies in dementia with Lewy bodies that measure presence of tau have generally included small sample sizes, resulting in varied results. A study using the tau-PET tracer [18F] flortaucipir compared ten patients with dementia with Lewy bodies, 27 patients with Alzheimer's disease, and 14 healthy controls, and showed minimal deposition of [18F] flortaucipir in dementia with Lewy bodies.[75] Medial temporal lobe [18F] flortaucipir distinguished dementia with Lewy bodies from Alzheimer's disease, with an AUC of 0·87.[75] By contrast, a study including 24 patients with dementia with Lewy bodies, 43 patients with Alzheimer's disease, and 18 healthy controls found increased tau-positivity concentrations in patients with dementia with Lewy bodies, with 13 (54%) patients showing spatial patterns similar to Alzheimer's disease, and four (17%) patients showing a distinct pattern.[76] Another study using a different tracer ([8F]PI-2620), which binds to tau and neuromelanin, compared 43 patients with Lewy body dementia (including 14 patients with dementia with Lewy bodies) with 28 patients with Alzheimer's disease and 70 healthy controls, and found similar burden of tau in Lewy body dementia and healthy controls, which was much lower than in Alzheimer's disease.[77] Tau burden was associated with poorer cognitive performance in patients with Lewy body dementia.[77] Similarly, a small [18F] flortaucipir longitudinal study of 22 patients with dementia with Lewy bodies found faster tau accumulation in dementia with Lewy bodies than in healthy controls, with higher rates of tau accumulation associated with accelerated temporal atrophy and disease progression.[78]

These findings imply that tau copathology has important negative effects on cognition. Similar to amyloid-PET, tau-PET has potential for identifying patients with dementia with Lewy bodies who are tau positive and could be candidates for emerging anti-tau treatments. Longitudinal studies are needed to determine the sensitivity of these techniques in people with dementia with Lewy bodies, especially now that new disease-modifying therapies are available for Alzheimer's disease and might have future applications for dementia with Lewy bodies.

Fluid biomarkers of underlying pathology are well established in Alzheimer's disease and are likely to have relevance in dementia with Lewy bodies to identify copathologies and predict disease progression. Longitudinal analysis of Alzheimer's disease-related pathology using the established amyloid, tau, and neurodegeneration (ATN) classification assessed via fluid biomarkers (amyloid β42-to-amyloid β40 ratio [Aβ42/40], p-tau, and total tau) showed lower concentrations of amyloid β42/40 and higher p-tau181 and total tau in Alzheimer's disease and dementia with Lewy bodies, compared with healthy controls, reflecting Alzheimer's disease copathology in dementia with Lewy bodies. Notably, a distinct evolution was seen in the different subtypes of dementia with Lewy bodies.[79] Some patients who were amyloid positive, tau negative, and had dementia with Lewy bodies transitioned to amyloid-negative status after 12 months, whereas patients who were amyloid positive, tau positive, and had dementia with Lewy bodies remained amyloid-positive. Furthermore, tau-positive status was correlated with advanced Braak stages postmortem.[79]

Plasma biomarkers have the important advantage of being minimally invasive, and could enable population-based screening and repeated measurements for clinical monitoring and trials. However, they are less likely to be useful in distinguishing dementia with Lewy bodies from Alzheimer's disease.

A highly sensitive single-molecule immunoassay in plasma samples enabled analysis of p-tau181, amyloid β42, amyloid β40, NfL, and GFAP in 117 patients with Lewy body dementia (110 with dementia with Lewy bodies and seven with Parkinson's disease dementia), 63 with Alzheimer's disease, and 73 healthy controls. This analysis revealed elevated GFAP concentrations in patients with Lewy body dementia and those with Alzheimer's disease, compared with controls, but plasma biomarkers could not differentiate patients with Lewy body dementia from those with Alzheimer's disease, or patients who were amyloid-PET positive from those who were negative.[80] Although the Lewy body dementia cohort included both individuals with dementia with Lewy bodies or Parkinson's disease dementia, the majority (110 patients) had dementia with Lewy bodies. Higher plasma GFAP concentrations were also found in people with mild cognitive impairment-related Lewy body dementia and dementia with Lewy bodies, compared with healthy controls, and were associated with brain amyloid-PET positivity. The amyloid and tau positive PET profile was predicted by plasma p-tau181.[81]

An analysis of 371 patients with dementia with Lewy bodies showed higher plasma p-tau181 and tau phosphorylated at Thr231 compared with 205 healthy controls, but lower than in 207 patients with Alzheimer's disease, and no differences between those with dementia with Lewy bodies and Parkinson's disease (204 patients).[56] Both p-tau markers were increased in dementia with Lewy bodies subgroups with reduced CSF amyloid β42 concentrations.[56] Combined biomarker analysis can have additional benefits over individual biomarkers. An analysis of combined plasma p-tau181, amyloid β, and NfL distinguished patients who were amyloid positive from those who were amyloid negative in a group of patients with dementia with Lewy bodies or frontotemporal lobar degeneration. However, results were not reported separately for each disease.[82] It is likely that plasma biomarkers will be eventually used in combination, with a panel of different biomarkers examined concurrently, to provide information on underlying amyloid, tau, and other copathologies.

Cholinergic-PET

Various cholinergic-PET tracers have been investigated in dementia with Lewy bodies, from acetylcholine transporter to nicotinic and muscarinic acetylcholine receptors, to acetylcholine-esterase, and vesicular acetylcholine transporter, which has specificity for cholinergic terminals. These tracers show differences between Alzheimer's disease and dementia with Lewy bodies, suggesting a potential diagnostic role. Although decreased cholinergic PET signal at terminal projections from the cholinergic basal forebrain (Ch1–4), with neocortical losses, can be detected both in patients with Alzheimer's disease and those with dementia with Lewy bodies, greater occipital loss of cholinergic terminals is seen in people with dementia with Lewy bodies.[11,83] Furthermore, terminal losses from pedunculopontine (Ch5) and lateral dorsal tegmentum (Ch6) projections to the thalamus are seen in people with dementia with Lewy bodies, but not in people with Alzheimer's disease.[84] Whether Alzheimer's disease copathology contributes to these changes in cholinergic terminals is not yet established.[84]

Studies using the [^{18}F]FEOBV vesicular tracer suggest potential of this PET method as a biomarker of disease progression, as there is a gradient of terminal projection involvement from the posterior (Ch4) to the anterior (Ch1 and Ch2) basal forebrain.[11] The most pronounced differences in cholinergic terminal loss between patients with dementia with Lewy bodies and those with Parkinson's disease are in the amygdala, hippocampus, and cingulate.[11] Whether increasing cholinergic loss occurs in these regions during disease progression requires further investigation.

MRI measures of cerebrovascular disease

In people with Lewy bodies, cerebrovascular disease is an important copathology that is detectable on MRI, by use of which four features can be recognised: white matter hyperintensities, lacunes, cerebral microbleeds, and enlarged perivascular spaces. In these patients, larger white matter hyperintensity volume is associated with worse cognition.[85] Cerebral microbleeds are more prevalent in dementia with Lewy bodies than in Alzheimer's disease, with a 36% prevalence compared with 32% in Alzheimer's disease, and 5–15% in healthy controls, according to a 2024 meta-analysis.[86] Interestingly, although the regional distributions of microbleeds on MRI[86] and neuropathology[87] are similar between dementia with Lewy bodies and Alzheimer's disease, and lobar microbleeds in Alzheimer's disease are related to cerebral amyloid angiopathy, a meta-analysis suggested that microbleeds in dementia with Lewy bodies were associated with hypertension, but not amyloid brain deposition,[86] implying distinct mechanisms. Enlarged perivascular spaces in basal ganglia are associated with worse executive function in people with dementia with Lewy bodies.[88] Whether the presence of small vessel disease in dementia with Lewy bodies acts in combination to aggravate effects of other copathologies is not yet known, and future trials are needed to test whether interventions targeting vascular risk factors improve outcomes. Ultimately, these biomarkers sensitive to specific pathologies are likely to be used as a panel, providing information about each pathology. These biomarkers could inform prognosis and could be used to test therapies as these become available; however, further validation is required before they are ready for clinical use.

Fluid measures of inflammation

Inflammatory processes might also be relevant in dementia with Lewy bodies. In a study using an electrochemiluminescence immunoassay (ECLIA) in plasma samples from patients with dementia with Lewy bodies or Parkinson's disease, and healthy controls, protein panels including the inflammatory markers IL-6, CRP, TNFα, and FABP could differentiate dementia with Lewy bodies and Parkinson's disease from controls, and dementia with Lewy bodies from Parkinson's disease.[89] Using ELISA and ECLIA, increased concentrations of macrophage inflammatory protein 3α, IL-17A, and IL-2, and lower concentrations of IL-8 were seen in dementia with Lewy bodies compared with healthy controls.[90] However, these measures are still exploratory and further work is needed for their application in clinical practice and to understand whether they can have a role to identify patients for treatments targeting inflammatory pathways.

Conclusions and future directions

Several biomarkers of Lewy body dementia are available that could be used in diagnosis, prognosis, and disease monitoring (figure 2). However, substantial challenges to bring some of these biomarkers into clinical practice remain (panel 2).[91] An important challenge in dementia with Lewy bodies is the presence of mixed pathology, which is more common in older people (80 years or older),[92] in whom secondary pathological accumulations might not be driving clinical presentation or severity. The presence of mixed pathology is also relevant for interpreting SAAs, which might be positive in people with very low levels of misfolded α-synuclein but also other pathologies. Validated quantification of these assays could help resolve these issues.

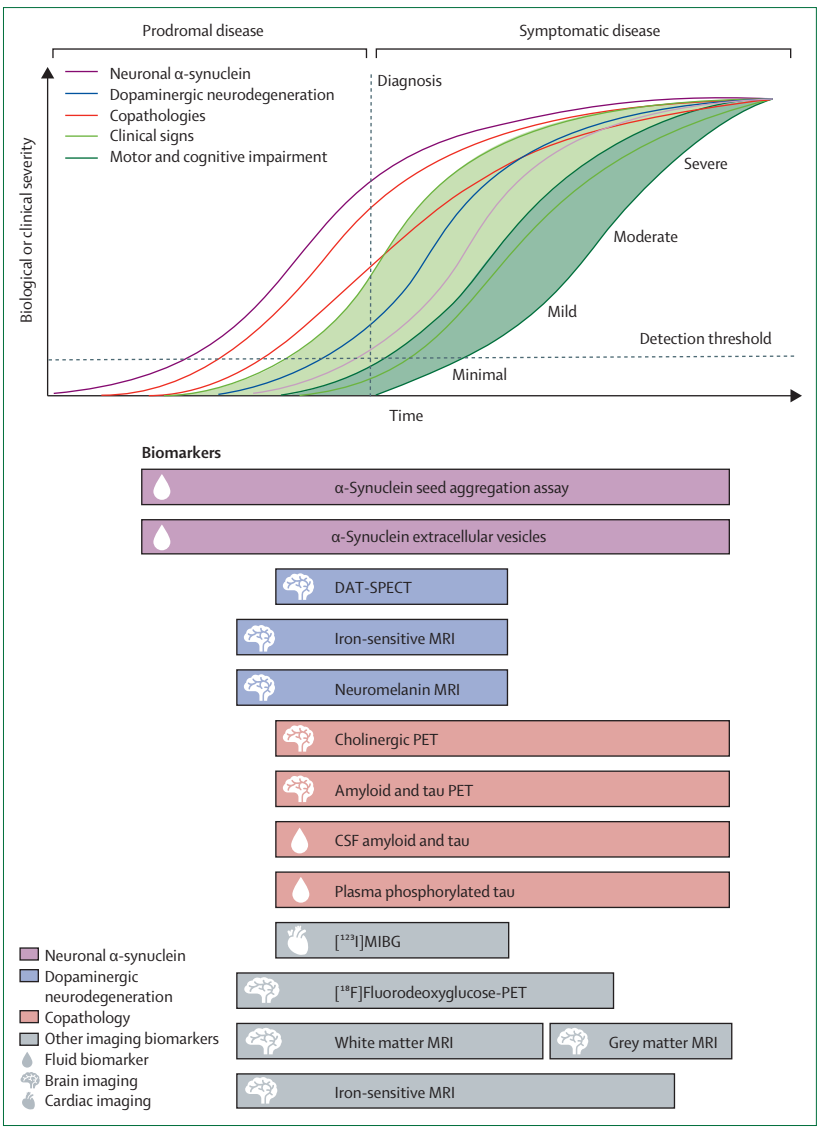


Figure 2: **Biomarkers of Lewy body dementia and their potential use along the disease course**
Top: a hypothetical model of α-synuclein accumulation, dopaminergic neurodegeneration, co-pathologies, and clinical signs and symptoms. The shapes and slopes of the curves and their temporal relationship are qualitative. Dopaminergic degeneration and other co-pathologies are likely to overlap, and their temporal relationship in each individual can be different. Bottom: available biomarkers with specificity for pathological processes, and how they relate to different disease stages, colour-coded according to their corresponding pathways. DAT-SPECT=dopamine transporter SPECT. [^{123}I]MIBG=[^{123}I]metaiodobenzylguanidine myocardial scintigraphy.

Panel 2: Challenges in the translation of imaging and fluid biomarkers into clinical settings

- High prevalence of comorbid bystander pathologies in ageing populations
- Reconciling clinical syndromes with underlying pathological processes
- Incorporating new staging systems of α-synucleinopathies
- Scarcity of multimodal longitudinal studies that compare the ability of different biomarkers to track disease progression
- Imaging biomarkers are derived from protocols that are not widely available in clinical practice, processing is time-consuming and not automated, and replication across scanners is scarce
- Fluid biomarkers do not have clinically relevant cutoffs and standardisation across centres
- There are no validated outcome measures that encompass the heterogeneous clinical presentation and progression in patients with dementia with Lewy bodies

There are conceptual challenges regarding blurred clinical and neuropathological boundaries between dementia with Lewy bodies and Parkinson's disease dementia, with increasing calls to unify these conditions[4,10] although some specialists emphasise the distinct pathological processes between the two diseases.[12] Recent staging systems[4,5] could provide frameworks to improve clarity, but have important limitations[93] and will need validation before they can be widely applied.

We still lack evidence for the use of biomarkers to track dementia with Lewy bodies progression, which are required for clinical trials. This evidence will require the study of large longitudinal cohorts with diverse participants, and careful validation before implementation.

There are practical challenges for translating neuroimaging biomarkers into routine clinical practice. Advanced neuroimaging techniques require considerable preprocessing and analysis. These techniques need to be streamlined and validated across different scanners. Fluid biomarkers similarly require standardisation and validation in large cohorts, and different laboratories.[94] They require careful interpretation and clinically relevant cutoffs before they can be more widely used. Increased resources are needed to enable fluid biomarker testing of many patients in clinical facilities.

All these challenges are amplified in low-income and middle-income countries, with low density of MRI scanners compared with high-income countries, and scarcity of skilled operators.[95] Although blood-based biomarkers have potential to be widely used, there are nonetheless challenges with implementation in low-income and middle-income countries due to less widely available access to phlebotomy, equipment, storage facilities, and laboratories. Some challenges could be overcome with new technologies that are cheaper and scalable. For example, low-field MRI could be an accessible neuroimaging alternative[95] and skin prick tests with point-of-care testing could be easier to implement, once available. As targeted treatments are adopted for other dementias, the need for biomarkers of diagnosis, subtyping, and progression is warranted. Different biomarkers might be required at different disease stages, and biomarkers of underlying pathology to stratify patients in clinical trials are needed. These biomarkers are likely to be used in combination, to provide a multidomain profile for each individual with dementia with Lewy bodies. Multimodal approaches will enhance our understanding of underlying disease processes and enable personalised treatments.

Search strategy and selection criteria

We searched PubMed for publications in English from Jan 1, 2018, to Feb 20, 2025, and reviewed references from relevant articles to identify further papers. We used the following search terms: "Lewy" [title] and "dementia" and "biomarker" and "imag*", with "DAT" or "MRI" or "PET"; and without "imag*", but with "CSF", or "cerebrospinal fluid"; or "blood", or "plasma" or "serum" or "fluid". The final reference list was generated on the basis of originality, methodological rigour, and relevance to this Series.

Contributors
All authors planned the manuscript, conducted the literature search, contributed to the figures, and wrote, edited, and approved the manuscript. All authors accept full responsibility for the decision to submit for publication.

Declaration of interests
LCST has received speaking honoraria from Eisai. NCF has received honoraria for consultancy and educational presentations from Eisai, Hoffmann-La Roche, Eli Lilly, and Biogen. BM has received honoraria for consultancy and educational presentations from GE Healthcare, Bial, Roche, Biogen, AbbVie, and Amprion. RSW has received speaking and writing honoraria from GE Healthcare, Bial, Omnix Pharma, and Britannia; consultancy fees from Accenture and Therakind; and is the principal investigator for an EIP Pharma neflamapimod trial. All other authors declare no competing interests.

Acknowledgments
AZ is supported by an Alzheimer's Research UK Clinical Research Fellowship (number CRF2021B-001), Rosetrees, and Parkinson's UK. MB has received funding from the Deutsche Forschungsgemeinschaft (413501650) and Else Kröner-Fresenius-Stiftung (2025_EKEA.03). LCST is supported by the Singapore Ministry of Health's National Medical Research Council under its Open Fund Large Collaborative Grant (MOH-OFLCG24may-0026). BM is member of the executive steering committee of the Parkinson Progression Marker Initiative of the Michael J Fox Foundation for Parkinson's Research; and has received research funding from Aligning Science Across Parkinson's disease (Collaborative Research Network). NCF is supported by the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre and the UK Dementia Research Institute. RSW is supported by a Wellcome Career Development Award (number 225263/Z/22/Z), Parkinson's UK, the Lewy Body Society, Michael J Fox Foundation, and the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre.

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