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PERSPECTIVE

Clinical criteria for limbic-predominant age-related TDP-43 encephalopathy

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Abstract

Limbic predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) is highly prevalent in late life and a common co-pathology with Alzheimer's disease neuropathologic change (ADNC). LATE-NC is a slowly progressive, amnestic clinical syndrome. Alternatively, when present with ADNC, LATE-NC is associated with a more rapid course. With the emergence of anti-amyloid therapeutics, discrimination of LATE-NC from ADNC is critical and will lead to greater clinical recognition of amnestic patients without ADNC. Furthermore, co-pathology with LATE-NC may influence outcomes of these therapeutics. Thus there is a need to identify patients during life with likely LATE-NC. We propose criteria for clinical diagnosis of LATE as an initial framework for further validation. In the context of progressive memory loss and substantial hippocampal atrophy, criteria are laid out for probable (amyloid negative) or possible LATE (amyloid biomarkers are unavailable or when amyloid is present, but hippocampal neurodegeneration is out of proportion to expected pure ADNC).

KEYWORDS
Alzheimer's disease, dementia, limbic predominant age-related TDP-43 encephalopathy, mild cognitive impairment, multi-etiology dementia

Highlights

- Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a highly prevalent driver of neuropathologic memory loss in late life.
- LATE neuropathologic change (LATE-NC) is a common co-pathology with Alzheimer's disease neuropathologic change (ADNC) and may influence outcomes with emerging disease-modifying medicines.
- We provide initial clinical criteria for diagnosing LATE during life either when LATE-NC is the likely primary driver of symptoms or when observed in conjunction with AD.
- Definitions of possible and probable LATE are provided.

1 | INTRODUCTION

Individuals with limbic predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) at autopsy often presented with an amnestic cognitive disorder that is difficult to distinguish during life from amnestic mild cognitive impairment (MCI) or dementia due to Alzheimer's disease (AD).[1] The term LATE describes the clinicopathologic entity associated with the pathologic finding of TDP-43 proteinopathy (LATE-NC) with or without the presence of amyloid plaques and neurofibrillary tangles (pathognomonic of AD neuropathological change, or ADNC) in the aging brain.[2] Multiple studies have shown that LATE-NC is very common in aging, affecting approximately a third of individuals 85 years of age and older, and related to a decline in memory independent of ADNC.[3–5] Recent advances in the in vivo detection of amyloid plaques and tau tangles[6] have amplified the need to find ways to diagnose and treat LATE-NC separately from ADNC. This need has become even more urgent in the setting of U.S. Food and Drug Administration (FDA)–approved therapeutics specifically targeting AD pathophysiology.[7] Adding substantial complexity is the problem that ADNC and LATE-NC often co-occur in the same brain, including in overlapping limbic brain regions, where the co-pathologies markedly accelerate cognitive decline.[8,9] In contrast, when LATE-NC is present without concomitant ADNC, the amnestic syndrome appears to be significantly slower than that of "pure" AD, increasing the prognostic importance of accurate diagnosis.[5] Although there has been tremendous growth in biomarkers for both amyloid and tau, molecularly specific and sensitive LATE-NC biomarkers are not yet available, and clinical diagnostic guidelines have not been developed.

In May 2023, a group of experts convened to discuss the need and potential for clinical diagnostic guidelines for LATE. The committee was composed of expert clinicians, trialists, pathologists, neuroimagers, neurochemists, basic scientists, and community researchers. This group (reflected in the authorship of this article) agreed on the need for guidelines for several reasons. First, the absence of LATE clinical diagnostic criteria impedes clinical and basic research into the pathogenesis and treatment of this common form of dementia in aging. Second, with the FDA approval of anti-amyloid agents for AD, we expect that many of the patients deemed ineligible for treatment based on the absence of "positive" AD biomarkers may instead have LATE-NC. This creates an opportunity for testing and developing other treatments, and to provide a clinically useful diagnosis to the patient, family, and their clinician. Third, in those persons with concomitant LATE and AD pathophysiology have a faster progression and it is currently unclear whether anti-amyloid agents will show similar benefits in the setting of mixed pathology. A clinical diagnosis of AD with possible LATE-NC will not only advance knowledge in the therapeutic space, but may also benefit patients, families/caregivers, and clinicians in sharing prognoses and making informed decisions regarding the potential usefulness of these agents. Finally, combination and new therapies for multiple pathologies are on the horizon. We reiterate that LATE-NC, both with and without concomitant AD, is common, affecting >10% of all individuals ≥65 years of age and ≈25%–40% of those ≥85 years of age, respectively and that for each patient, there is a glaring need to make an accurate diagnosis during life.

2 | CRITERIA

We propose criteria for two primary contexts in which LATE-NC may occur. The criteria are applied based on clinical findings and the suspicion of coexisting AD pathobiology as determined by biomarkers. In either case, the diagnosis of LATE as a clinical entity should include an understanding of the clinical likelihood of AD.

The first context is when LATE-NC is presumed to occur independently of significant (more than low ADNC) AD pathology and is being considered as the possible primary driver of the clinical presentation. In this scenario, either probable or possible LATE may be diagnosed. The second context is when LATE-NC is being considered in the presence of suspected or biomarker-confirmed ADNC and both disease processes are being considered as contributors to the clinical features. In this scenario, because of current limitations in LATE biomarkers, we recommend a designation of possible LATE (Figure 1).

Of note, the core clinical syndrome and required supportive features differ when LATE-NC is being considered as the primary driver versus being considered in the presence of ADNC (Table 1). Probable LATE can only be diagnosed when LATE-NC is considered the primary

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the existing literature of limbic predominant age-related TDP-43 encephalopathy, as well as relevant manuscripts prior to the coining of this condition in 2019. Focus was on studies that described clinical and imaging features to develop the criteria described. These relevant citations are appropriately cited.
2. **Interpretation**: Based on this review and discussion of the authors, a consensus set of criteria were developed and proposed that would likely enrich identified patients as having underlying LATE neuropathologic change (LATE-NC).
3. **Future directions**: This manuscript provides initial criteria for diagnosis of LATE either when it is the primary driver of cognitive symptoms or when it co-occurs with symptomatic Alzheimer's Disease. These criteria reflect a first step and further validation in practice will be needed, as well as integration with emerging biomarkers for TDP-43 as they are developed.

driver of the clinical presentation. By contrast, possible LATE can be diagnosed either as a primary driver or when suspected in conjunction with a diagnosis of AD. This designation of possible and probable is to denote the likelihood of underlying LATE-NC. In this context, *definite* LATE can only be established at this time by autopsy revealing LATE-NC

2.1 | Clinical criteria for LATE as the primary disease driver of cognitive decline (probable or possible LATE)

In a significant proportion of individuals, particularly in those ≥80 years of age, clinical presentations of a primarily amnestic syndrome in the absence of positive AD biomarkers is frequently associated with LATE-NC as the primary (presumed disease-driving) pathology (≈20% of individuals ≥85 years of age with an amnestic syndrome have LATE-NC as the dominant pathology).[3,5] Other pathologies may be present to varying degrees, but the salient clinical features are highly likely to be associated with LATE-NC.[1,10,11] One caution is that many studies are limited in diversity with respect to demographic, cultural, and socioeconomic parameters that should be considered in future work.[12]

The following criteria (Table 1) are proposed to identify such individuals during life. These criteria follow the logic of the Dementia Nomenclature committee and first define a clinical syndrome prior to use of biomarkers which, in turn, aid in linkage to pathoetiology.[13] Although the described clinical syndrome will frequently be associated with LATE-NC, it is not specific and other pathologies, particularly ADNC, may produce overlapping clinical features. To further link the syndrome to a specific etiology, additional biomarker studies are required. As there currently is no well-validated molecular biomarker linked directly to TDP-43 pathology, AD biomarker studies are used to assess for the presence or absence of the primary competing or comorbid etiology (i.e., ADNC) for the described clinical syndrome. Finally, some neuroimaging findings have been found to be promising in their association with LATE-NC in distinction from ADNC, and, thus, would offer further support of the diagnosis. These neuroimaging findings can be considered reasonable surrogate biomarkers for LATE-NC in the context of an amnestic syndrome until more protein-specific markers become available.

2.1.1 | Core clinical syndrome

The most salient cognitive feature of LATE is progressive episodic memory loss.[8] The memory loss has features described as a temporo-limbic amnesia or "an amnestic syndrome of the hippocampal-type."[14] This type of memory loss is characterized by relatively preserved immediate memory, or encoding, but the presence of a significant deficit in delayed recall that is generally not substantially improved with cueing or recognition memory. Temporo-limbic memory loss can be distinguished from subcortical or frontal dysexecutive mediated memory impairment in which, due to diminished attention, immediate memory measures are relatively poor, along with delayed recall, but with largely intact recognition memory. Notably, this temporo-limbic memory profile is also associated with the typical amnestic syndrome of AD,[15] reflective of the overlapping topographic pattern of pathology in ADNC and LATE-NC.

In addition to the amnestic profile, patients with LATE-NC confirmed at autopsy will commonly have evidence of mild semantic memory deficits, often detected as a mild relative decrement in performance on measures of category fluency (e.g., generating names of animals) versus more preserved lexical fluency (e.g., words beginning with the letter F).[5,16–18] Subtle confrontation naming deficits may also be present.[19] Some have reported saliency of more specific semantic deficits in relation to famous events or people.[18]

Outside of the above, other cognitive domains are largely spared until later in the course of LATE. This characteristic is somewhat distinct from typical clinical AD, which is generally an amnestic, multi-domain syndrome. However, AD can present with greater limbic predominance or be a primarily limbic syndrome, also sparing other domains. It is important to note that with the current evidence, *cognitive profiles may be helpful but are generally not adequate* to differentiate AD and LATE with a high degree of confidence.

Another helpful, but incomplete, distinguishing feature of LATE is the tendency to have a relatively indolent course, in which an amnestic syndrome predominates often for several years. Although a specific cutoff for the number of years of a relatively isolated amnestic syndrome is not clear, 2 or more years of such a presentation is very common and supports the diagnosis.[5,17,20] The longer the course without the development of significant additional cortical cognitive

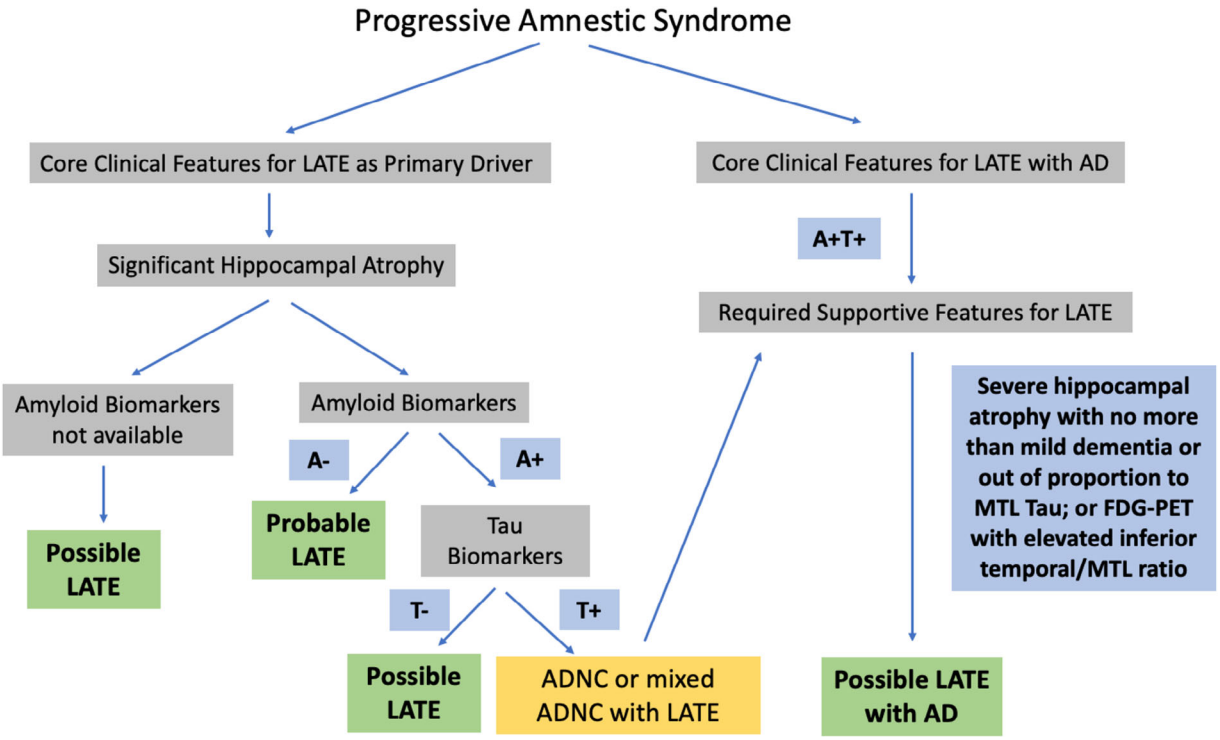

FIGURE 1 Flow for decisions about diagnosis of of LATE. A- , amyloid negative biomarker; A+ , amyloid positive biomarker; T- , tau negative biomarker; T+, tau positive biomarker; LATE.

TABLE 1 LATE as the primary diagnosis.

I. Core clinical syndrome[a] (1 and 2 required)	**Probable LATE**	**Possible LATE**
1. Primary amnestic syndrome with temporo-limbic memory loss.		
2. Other cognitive domains largely spared until much later in the course.		
3. May have mild semantic memory impairment.		
4. Indolent course with predominant amnestic syndrome present for at least 2 years.		
5. Age generally >75 years old.		
II. Required imaging		
Significant hippocampal atrophy (out of proportion to global atrophy)		
III. Required supportive features for probable LATE		
A negative test of one of the following to rule out amyloid beta (Aβ):		
a. Amyloid PET		
b. CSF A$\beta_{42/40}$		
c. CSF p-tau$_{181}$/Aβ_{42} or t-tau/Aβ_{42}		
IV. Required additional measures if amyloid positive		**Possible LATE**
If amyloid positive based on III, a negative measure of one of the following tau biomarkers is required:		
a. MTL tau PET (preferred measure)		
b. CSF p-tau$_{181}$		

Abbreviations: Aβ, amyloid beta; CSF, cerebrospinal fluid; MTL, medial temporal lobe; p-tau, phospho-tau.
[a]Core clinical syndrome differs from typical AD, which is generally defined as an amnestic, multi-domain syndrome, but the overlap is significant making a purely clinical diagnosis challenging. Overlap with limbic-predominant AD is even greater.

features, the higher the likelihood of LATE-NC rather than ADNC. In other words, these cases tend to have an unusually slow course with regard to both rate of decline and development of impairment in additional cognitive domains in comparison to typical AD. Finally, LATE-NC becomes progressively more common with advanced age, particularly in individuals in their 80s and 90s.[2] Although a strict cutoff cannot be established, LATE-NC is understood to be uncommon in individuals younger than age 75 (particularly in its "pure" form, i.e., lacking no more than low levels of AD pathology (i.e. low ADNC).[2,11,21–23]

Although all the features described for the clinical syndrome are consistent with a LATE diagnosis, the first two features in Table 1 are required to consider LATE. Principally, the patient must have a pro-

gressive amnestic presentation that largely spares other domains of cognition. Strict cutoffs are not applied here, akin to the requirement of clinical judgment in prior criteria for MCI[24,25] and AD,[26,27] but more severe impairment of memory relative to other domains increases the likelihood of underlying LATE-NC.

2.1.2 | Required supportive imaging for a diagnosis of probable or possible LATE

A diagnosis of probable or possible LATE requires the presence of significant hippocampal atrophy (Figure 2A-C), which is often out of proportion to the expected atrophy in typical AD for a given level of memory impairment or disease severity.[18,28,29] Consistent with other clinical and research criteria for the AD continuum,[24,27,30] we do not provide strict cutoffs. That said, these patients will often have a Scheltens' medial temporal atrophy (MTA) scale score of 3 or 4, which is clearly discrepant from global brain atrophy.[31] Patients with LATE-NC often have hippocampal atrophy in the bottom quartile of the distribution of those with ADNC without LATE.[28] Such imaging features may be used as rough guidelines in clinical practice. An additional frequently notable feature is significant widening of the collateral sulcus and concomitant thinning of adjacent cortical structures, which is often less severe in the context of ADNC alone (Figure 2D).

Although there may be cases of early LATE-NC with less significant hippocampal atrophy, which might reduce the sensitivity of this requirement, the presence of such atrophy increases the specificity relative to other potential sources of memory decline. Thus, its presence with the above-defined core clinical syndrome is required for a clinical diagnosis of *possible or probable* LATE. In addition, although genetic associations with ADNC and LATE-NC have been identified, genetic testing cannot robustly differentiate these conditions and, thus, genetic markers are not currently included as supportive features.

2.1.3 | Possible LATE

In the absence of supportive features for probable LATE (noted below), the core clinical symptoms with hippocampal atrophy are sufficient evidence for only possible LATE, as the ability to clearly differentiate these cases from AD, particularly more limbic predominant AD cases,[32,33] is limited. This approach is largely akin to the prior clinical criteria for *possible* AD in which an alternative etiology is potentially present.[26] Additional supportive features described below allow for a diagnosis of *probable* LATE (Figure 1).

2.1.4 | Probable LATE

Additional required supportive features

In addition to the core clinical syndrome and hippocampal atrophy, greater certainty in the underlying etiology of the clinical syndrome may be achieved with biomarker studies that rule out ADNC. Indeed, the primary differential diagnosis for the described amnestic syndrome is AD versus LATE. Thus, as there are no current biofluid or neuroimaging biomarkers sensitive to the molecular pathology of LATE-NC, namely, TDP-43 (or other biomarkers strongly linked to TDP-43 pathology), the approach taken here to solidify a diagnosis of probable LATE is to rule out the presence of underlying AD pathology. There are currently a number of biomarkers that either directly or indirectly support the presence of the molecular pathology of AD.[34] Although these have not been widely integrated into most clinical practices outside of research-oriented clinics, they will likely become widely implemented with the regulatory approval and insurance coverage of anti-amyloid immunotherapies.[35] As such, it is likely that many patients with the described clinical syndrome will undergo such assessment in clinical practice in the near future.

Because the presence of amyloid beta (Aβ) plaques is a defining, early feature of ADNC, preceding clinical symptoms,[30,36] biomarkers that are sensitive to their presence can effectively rule-out AD as a contributor to cognitive symptoms. Recently, revised clinical criteria for AD have been proposed that build off the 2018 National Institute on Aging–Alzheimer's Association (NIA-AA) research framework.[30] Using the language of that proposal (https://aaic.alz.org/diagnostic-criteria.asp), "Core 1 biomarkers," or biomarkers that define the initial stage of AD through linkage to the presence or absence of Aβ, are required to determine the presence of probable LATE. These include amyloid PET and cerebrospinal fluid (CSF) $A\beta_{42/40}$, as well as the ratios of phosphorylated tau $(p\text{-}tau)_{181}/A\beta_{42}$ and total tau (t-tau)/ $A\beta_{42}$. A negative result for any of these measures effectively rules out ADNC and, thus, supports a diagnosis of LATE-NC in the clinical context described earlier.

A couple of important caveats should be noted. First, in the proposed criteria of the AA workgroup, plasma measures are included in these Core 1 AD biomarkers. We have chosen not to include plasma biomarkers formally in these criteria given the dynamic nature of their development and continued need for validation. That said, these measures are very likely to play an important role in clinical practice soon and will serve the role of ruling out AD in this context. In particular, plasma measures of $A\beta_{42/40}$, $p\text{-}tau_{181}$, and $p\text{-}tau_{217}$ are all relatively sensitive to early AD pathophysiology; indeed, $p\text{-}tau_{217}$ may be a particularly early marker of ADNC.[37–39] Thus, we expect that further validation and implementation of plasma markers will be able to be incorporated into these criteria in the near future.

Second, we acknowledge that other conditions, in the absence of ADNC, may also be in the differential diagnosis for the clinical syndrome described here, such as primary age-related tauopathy (PART) or vascular cognitive impairment and dementia (VCID). However, we would not expect the degree of hippocampal atrophy described here typically in these cases. Furthermore, VCID would be expected to be associated with other clinical and imaging features consistent with this entity. Nonetheless, these alternative are, in part, the motivation behind a "probable" designation applied here.

Third, a "positive" Aβ result alone does not rule out that LATE-NC is the primary pathologic driver of the patient's symptoms. Much

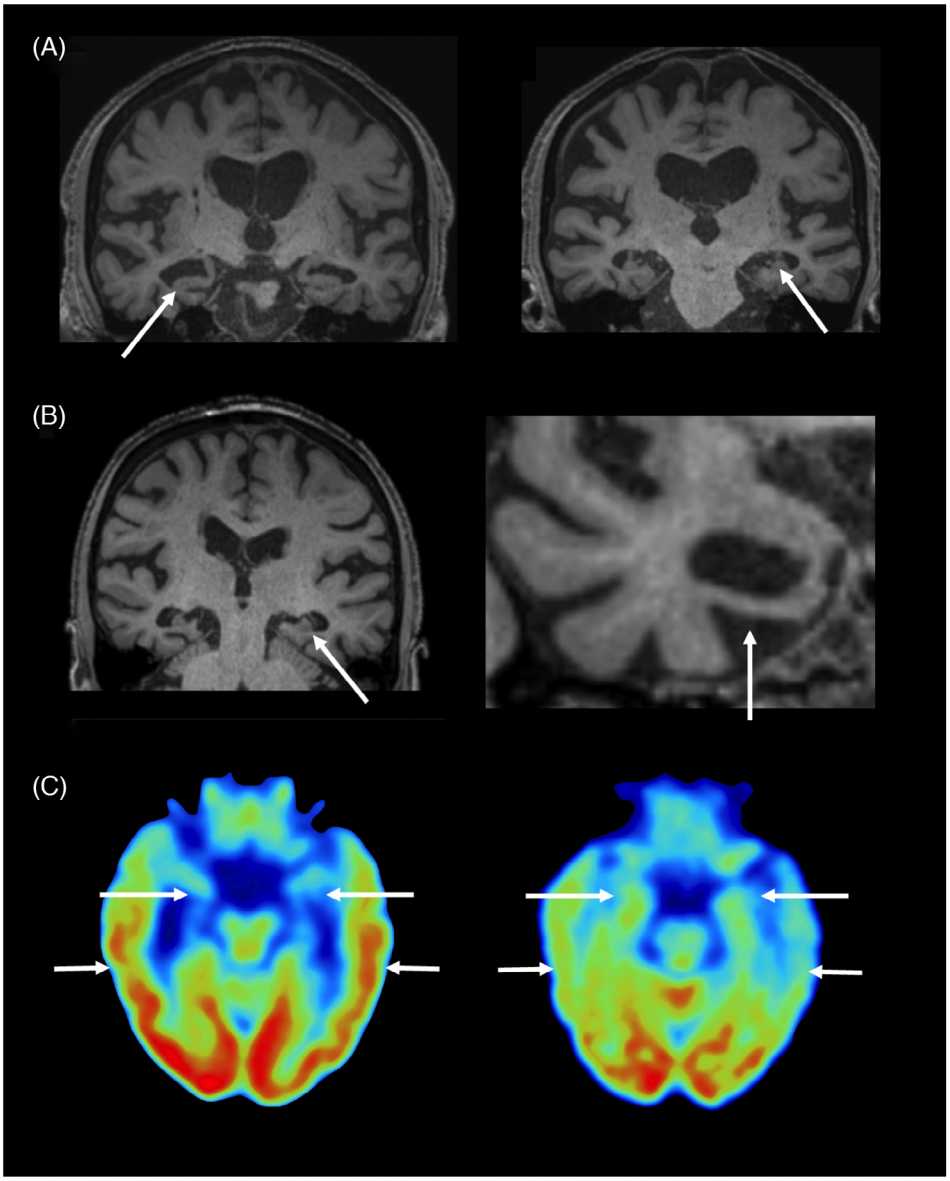

FIGURE 2 (A) MRI scans of a ≈90-year-old man with more than 8 years of a slowly progressive amnestic syndrome with more mild decline in category fluency. He had a negative amyloid PET scan and MRI with severe atrophy of the (left) head and (right) body of the hippocampus (see arrows). Autopsy revealed Stage 3 limbic-predominant, age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), hippocampal sclerosis, and low Alzheimer's Disease neuropathologic change (ADNC; A1, B2, C0). (B) MRI scan of an 86-year-old with a – to 3-year isolated progressive amnestic syndrome and a negative amyloid PET scan, who would qualify as "Probable LATE" based on proposed criteria. Coronal slices demonstrate (left) severe hippocampal atrophy and (right) severe cortical thinning in entorhinal cortex (arrow) with widening of the collateral sulcus. (C) FDG-PET pattern of hypometabolism in LATE-NC with arrows pointing to severe hypometabolism of the medial temporal lobe (MTL) and relative sparing of the inferolateral temporal cortex (left). This can be contrasted with the FDG-PET pattern of hypometabolism in typical ADNC (right), with more mild MTL hypometabolism and more significant hypometabolism in the inferolateral temporal cortex.

work has supported the notion that neurofibrillary tangle pathology is a more direct pathway of neurodegeneration in the ADNC continuum relative to Aβ plaques.[40,41] In turn, neurodegeneration and synaptic loss are more closely aligned with cognitive symptoms. Thus, the absence of significant tau pathology in the setting of the amnestic profile and high level of hippocampal atrophy described here would make it unlikely that AD is the primary driver of this structural and clinical phenotype regardless of Aβ amyloid status. Thus, if a Core 1 biomarker is positive, we advocate for obtaining a biomarker to assess tau load or stage, which is congruent with the "Core 2 biomarker" designation of the proposed AD criteria. Tau PET, or less ideally p-tau$_{181}$, best serves this role currently, but developing plasma and CSF markers more directly linked to tau load, such as p-tau-T205, MTBR-243, and C-terminal tau fragments, may also be of considerable use in this context in the future.[42–44] In the presence of a negative tau PET scan, including in the medial temporal lobe (MTL), or negative CSF p-tau$_{181}$, it is unlikely that ADNC is the primary driver of the clinical syndrome described, as in isolation these amyloid positive, tau

negative (A+T−) individuals tend to display much less tendency to progress over time and is a more frequent presentation of preclinical AD.[45,46]

In this context, it is also important to consider that the most commonly studied tau PET tracers do appear to have some degree of non-specific binding in areas of neurodegeneration due to non-ADNC pathology, including TDP-43.[47,48] However, binding levels tend to be much lower than that associated with tau-based neurofibrillary tangles and are generally not commensurate with the degree of atrophy. CSF p-tau$_{181}$ "positivity" may precede the detection of measurable MTL tau via PET, possibly increasing the specificity of a negative result.[49] Alternatively, these measures also may have limited sensitivity to earlier Braak stages (≤ Braak 4). With those points in mind, additional work will be required to determine appropriate PET or fluid biomarker thresholds for the determination that a case is "tau negative" in this context. Given these uncertainties, particularly with regard to the sensitivity of these measures, we feel that if a Core 1 biomarker is positive, but measures of tau load are negative (e.g., tau PET), we would consider these cases as only *possible* LATE. If tau positive, consideration of LATE-NC with mixed ADNC should be considered as described below.

2.1.5 | Additional supportive features for both possible and probable LATE

These features do not currently impact the diagnostic criteria for possible or probable LATE (Table 2) but may offer increased diagnostic certainty in routine clinical practice and research. Fluorodeoxyglucose (FDG) PET can provide supportive information for both "ruling out" AD and potentially "ruling-in" LATE. A pattern of posterior parietal and temporal hypometabolism, including the posterior cingulate, is a relatively specific and sensitive biomarker for ADNC.[50] Similar to the logic above, because brain hypometabolism is a downstream neurodegenerative marker of AD pathophysiology, it reflects the likely presence of neurofibrillary tangle pathology. Thus, the absence of this pattern suggests that AD may be less likely to be driving the amnestic clinical syndrome. That said, in an early amnestic MCI case due to AD, temporoparietal/cingulate hypometabolism may be subtle or not yet present.

TABLE 2 Supportive features.

Additional supportive neuroimaging features
1. FDG-PET without the stereotypical posterior temporoparietal hypometabolism seen in AD or anterior temporal/frontoinsular pattern seen in temporal variant FTLD.
2. FDG-PET with elevated inferior temporal/MTL ratio and absence of other degenerative patterns.
3. Structural MTL changes suggestive of LATE (severe atrophy particularly hippocampal head and anterior ERC/PRC; elevated inferior temporal/MTL ratio).

Abbreviations: AD, Alzheimer's Disease; ERC, entorhinal cortex; FDG-PET, flurodeoxyglucose PET; FTLD, frontotemporal lobar degeneration; LATE, limbic-predominant, age-associated TDP-43 encephalopathy; MTL, medial temporal lobe; PRC, perirhinal cortex.

In addition, an FDG-PET pattern of hypometabolism in the MTL and orbitofrontal cortex with relatively preserved inferior temporal cortex is the most well-established neurodegenerative biomarker for LATE-NC (Figure 2E). A quantitative measure calculated as the ratio of inferior to medial temporal metabolism (IMT), has been shown to be elevated in autopsy-confirmed cases with LATE-NC with relatively high sensitivity and specificity.[51–53] This ratio over a frontal supraorbital measure (FSO), decreased in LATE-NC, may offer additional accuracy in classification. Because qualitative description and quantitative measurement of this pattern is not yet commonly considered in interpretative reports of FDG-PET in clinical practice, even in specialty centers, we do not include it as one of the primary required imaging features to support a probable LATE diagnosis. Moreover, it is unclear to what degree this pattern would support LATE as the primary driver of symptoms without concomitantly ruling out the presence of AD, which we prioritize as the critical supportive feature in this context. That said, we advocate assessing for the presence of this pattern when FDG-PET is obtained, and, in combination with a lack of an AD pattern, it enhances the confidence in a LATE-NC diagnosis. Indeed, this FDG-PET pattern displayed promise in prior work supporting the differentiation of LATE-NC from ADNC in autopsy-confirmed cases.[18,53] Further research is needed to determine how well this FDGPET pattern suggestive of LATE-NC can be differentiated from the anterior temporal and frontoinsular hypometabolic pattern present in temporal lobe predominant forms of frontotemporal lobar degeneration (FTLD)-TDP-43.

A similar ratio has been described for structural magnetic resonance imaging (MRI), which is somewhat less accurate than FDG-PET in LATE-NC classification, but may also be used to support the diagnosis.[52,54] TDP-43 deposition and its associated atrophy also tend to display a greater anterior-to-posterior gradient along the long axis of the hippocampus, whereas AD has a more uniform pattern of atrophy.[55,56] Thus this gradient is supportive of a diagnosis of LATE.[55,56] Quantitative assessment using a ratio of the anterior hippocampus with parahippocampal gyrus volume appears sensitive to TDP-43 pathology, even in the context of ADNC, but requires additional validation.[57]

2.2 | Clinical criteria for possible LATE in persons with ADNC

The conditions of AD and LATE are difficult to disentangle for at least four practical reasons. (1) There is considerable overlap in the pathologic involvement of TDP-43 and neurofibrillary tangle deposition in LATE-NC and ADNC, respectively, within limbic structures (i.e., amygdala, entorhinal cortex, and hippocampus).[58] (2) In connection with this temporo-limbic anatomic distribution of pathology, temporo-limbic memory loss is a common early feature of both diseases.[59] (3) LATE-NC is commonly observed together with ADNC (among 85-year-olds, about 50% of severe ADNC cases have comorbid LATE-NC, in comparison to LATE-NC being present in about 25% of brains that lack ADNC) and associated with a faster rate of cognitive decline.[8,9,60]

(4) The apolipoprotein E (*APOE*) ε4 allele appears to be a risk factor for both ADNC and LATE-NC.[61–63]

The interconnections between AD and LATE have implications for new therapeutics specifically targeting AD pathophysiology and the potential for differential effectiveness of these therapies in persons with concomitant ADNC and LATE-NC. Nonetheless, we recognize that LATE also co-occurs with other non-AD pathologies, such as Lewy bodies and vascular changes associated with Lewy body dementia (DLB) and VCID, respectively, and that their diagnostic criteria may also be applicable in specific cases of LATE with additional relevant features. Thus, a progressive amnestic presentation with significant hippocampal atrophy in persons meeting clinical, radiographic, and biomarker definitions of DLB and VCID, increases the probability of comorbid LATE-NC with these conditions.

Detecting the presence of LATE-NC in the clinic among patients with comorbid ADNC presents a significant challenge in the absence of a TDP-43 specific in vivo clinical biomarker given the overlapping features of both conditions. The degree to which such mixed pathology modulates responsiveness to disease-modifying anti-amyloid immunotherapies is unclear and a critical gap for weighing risks with potential benefits. Even a probabilistic classification of individuals with mixed ADNC and LATE-NC classified during life can provide an enriched population to help address these essential questions with real potential consequences for patients.

The criteria for diagnosing LATE in the setting of AD thus represents an effort to define such an enriched population and, at this time, can provide no more than a designation of *possible* LATE given the limitations of current biomarkers and lack of distinctive clinical features. Note that in this context we are referring specifically to individuals with biomarkers indicating the presence of both Aβ plaques and tau-based neurofibrillary tangles (positive Core 1 and 2 biomarkers), as opposed to Aβ plaques alone without significant tau in which LATE-NC could still be the primary disease driving etiology (see above). In other words, these individuals need to have "positive" (+) biomarkers for amyloid (A) *and* tau (T). The logic of requiring evidence of tau is that Aβ is unlikely to result in symptoms in the absence of significant neurofibrillary tangles, which are linked to neurodegeneration and impaired cognition. In the parlance of the newly proposed AD clinical criteria, these patients would be in at least the "early biological stage" of AD marked by at least evidence of MTL tau pathology. However, as noted above, non-specific binding in areas of neurodegeneration due to non-ADNC pathology may be present and some caution must be considered. Nonetheless, the assumption of the criteria (Table 3) is that AD has been established based on the presence of tau pathology or downstream neurodegeneration relatively specific to AD, such as an FDG-PET pattern of posterior temporal and parietal hypometabolism. Cortical atrophy patterns associated with AD are also suggestive, such as the "cortical signature of AD,"[64] but less specific in clinical practice. In this context, the criteria below may support possible LATE as a contributing factor, but further study is needed.

2.2.1 | Core clinical syndrome/features for possible LATE in persons with ADNC

The clinical syndrome of LATE with AD is difficult to distinguish from AD alone, which is most frequently an amnestic, multi-domain cognitive syndrome. When LATE co-occurs, there may be disproportionately greater memory loss relative to other domains. More quantitative thresholds for relative impairment of episodic memory, such as those measured by free recall, with non-memory domains, like processing speed, executive function, and visuospatial function, have not been established. However, this may be an avenue for future work to better establish thresholds for individuals more likely to have concomitant LATE and AD rather than purely relying on clinical judgment. These patients also will generally have a swifter and more severe clinical decline than typical AD.[5,8,60] Of course, in any individual this is difficult to establish given the heterogeneity of AD progression. Finally, additional non-cognitive clinical sequelae also are more common with concomitant ADNC and LATE-NC, but not distinguishing on their own.[10,60,65,66]

2.2.2 | Required supportive features for possible LATE in persons with ADNC

Additional biomarker driven features are required for possible LATE in persons with AD. We recommend using structural imaging focused on the hippocampus in relation to disease severity as assessed by cognitive status or tau accumulation.

Given the co-pathology of ADNC and LATE-NC in limbic structures, hippocampal atrophy beyond what is expected for clinical stage of AD is a supportive feature.[18,54] In other words, severe hippocampal atrophy in the setting of the mild cognitive impairment or mild dementia

TABLE 3 Possible LATE in persons with concomitant AD (i.e., with evidence of amyloid and tau).

Core clinical syndrome	**Possible LATE**
1. Progressive amnestic, multi-domain syndrome; memory loss may be particularly severe relative to other cognitive domains.	
2. Generally, more rapid course than typical AD alone.	
Required supportive features for Possible LATE (at least one of the following)	
1. Severe hippocampal atrophy in the setting of no more than mildly symptomatic dementia.	
2. MTL/hippocampal atrophy out of proportion to degree of tau pathologic burden measured by tau PET.	
3. FDG-PET with elevated inferior temporal/MTL ratio.	

Abbreviations: AD, Alzheimer's Disease; FDG-PET, fluorodeoxyglucose PET; LATE, limbic-predominant, age-associated TDP-43 encephalopathy; MTL, medial temporal lobe.

TABLE 4 Areas requiring further research.

- Development of TDP-43-specific biomarkers and their link to LATE-NC and other TDP-43 neurodegenerative conditions.
- Sharper delineations of probabilities for the presence of TDP-43 and non–TDP-43 pathologies based on proposed imaging biomarkers alone and in combination with clinical features in large, multi-site prospective cohorts.
- Determine more specific probabilities of LATE-NC based on the degree of hippocampal atrophy or FDG-PET pattern for a given load of tau pathology or AD stage for detection of ADNC with LATE-NC
- Visual versus quantitative assessments of MRI (e.g., hippocampal volume) and FDG-PET measures associated with LATE-NC.
- Assessment of more ethnically and socioeconomically diverse populations and cohorts.
- A better understanding of the implications of basic parameters such as sex and age on diagnostic probabilities.
- A fuller recognition of influence of genetic risk factors and their potential role in diagnosis.
- More insight into the degree to which different cognitive and non-cognitive clinical manifestations are present and their relative severity in mixed LATE-NC with ADNC (e.g., is there a threshold of memory loss to other domains that supports ADNC with or without LATE-NC?).
- Information about the potential for "upstream" β amyloidosis (and therapies that attenuate that amyloidosis) to influence LATE-NC.

stage of AD would be suggestive of coexisting possible LATE. Thresholds are, again, not well established, but a Scheltens' medial temporal atrophy (MTA) visual rating of 3 or 4, would be supportive at early clinical disease stages. Individuals in the bottom quartile of the hippocampal volume of the distribution of those with AD are disproportionately enriched in those who also have LATE-NC[28] compared to those who have less atrophy. Thus, a cutoff at this lower quartile could be used as a threshold for possible LATE. Note that at more severe clinical stages, the reliability of degree of hippocampal atrophy is likely limited. Other features of the pattern of atrophy, such as an anterior-to-posterior gradient of atrophy may be useful,[57] but need additional validation.

Another potential supportive feature is hippocampal atrophy out of proportion to medial temporal lobe neurofibrillary tau pathology as measured by tau PET. Again, clinical judgment is necessary in making this assessment and tau PET remains in very limited use in clinical practice (although this may change with the emergence of disease-modifying therapies). Isolated MTL tau in the setting of more severe hippocampal atrophy or tau tracer uptake peri-threshold in this region would constitute this discordance and suggest concomitant LATE-NC. Normative relationships between volume and tau could be established that would provide more quantitative thresholds in the future where "mismatch" between tau and neurodegeneration would suggest the presence of LATE.[46,67–69] Given the lack of spatial specificity and more direct relationship to neurofibrillary tangle load, current biofluid tau markers are of less utility in this regard.

As described, FDG-PET has been associated with a pattern that differentiates LATE-NC from ADNC. However, this pattern may be present to some extent in mixed cases. In particular, presence of an intermediate IMT ratio has been shown to suggest ADNC+LATE-NC mixed pathology.[18,51] Yet, this feature remains difficult to operationalize in practice presently.

2.3 | Areas for further research

The proposed criteria reflect expert opinion based on the existing clinicopathological literature that describes the phenotypic features of LATE-NC. Although all of the proposed features in these criteria have been associated with the presence of LATE-NC, large prospective studies followed to autopsy (or application to large clinicopathologic series) in more diverse populations will be needed to provide more precision in terms of the likelihood that specific measures support its presence. For example, in the absence of high or intermediate AD at autopsy (amyloid negative), significant hippocampal atrophy is disproportionately associated with LATE-NC, and in those with an amnestic AD-like dementia syndrome, LATE-NC has a greater influence on hippocampal variance than AD pathology.[28] Furthermore, other pathologies, including cerebrovascular disease and Lewy body pathology, appear to have much less significant modulating effects on the hippocampus. Nonetheless, specific probabilities based on hippocampal volume and amyloid status in clinical populations require more detailed study. Likewise, discrimination of LATE-NC with AD with use of FDG-PET has been demonstrated to have area under of the curve (AUC) values of ≈0.85, but largely come from relatively small cohorts.[18,52,53] Probabilities of the proposed imaging measures in mixed AD and LATE also require additional study, with small reports available at this point. Indeed, an area of significant need is additional autopsy data in samples with in vivo tau PET, which remain somewhat limited at this point even in studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), but will likely grow in the coming years with a variety of active efforts. Table 4 provides some additional areas of needed research for further refinement of these criteria.

3 | CONCLUSION

Provisional criteria are hereby provided for possible and probable LATE, either when LATE-NC is the presumed primary disease-driving diagnosis or when it is present in combination with ADNC. Although these criteria reflect the existent literature and expert opinion, they will almost certainly need to be refined over time. That said, we do believe that the present criteria will provide for identification of populations enriched with patients who have LATE-NC and, thus, will serve as an important initial step in selecting appropriate participants for clinical research studies. Of course, consideration will be needed in how best to communicate this diagnosis and its implications to the broader community in the future.

Ultimately, specific molecular biomarkers are required to provide a true biological definition of LATE in a manner analogous to AD.[30] Progress is being made, with emerging biofluid and PET imaging markers for TDP-43 on the horizon.[70–74] The clinical criteria provided here will facilitate that process by providing in vivo populations to test these

biomarkers, as well as to assist in staging and characterization of phenotypic variability. Furthermore, application of these criteria allows for clinical trials directed at LATE-NC to be pursued and may provide critical insights in mixed disease in the context of AD-specific therapies (e.g., anti-amyloid monoclonal antibodies) in clinical practice.

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CONFLICT OF INTEREST STATEMENT

H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche; and is a co-founder of Brain Biomarker Solutions (BBS) in Gothenburg AB, a part of the GU Ventures Incubator Program (outside submitted work). L.G.A. has provided consultation to Eli Lilly, Biogen, Genentech, General Electric (GE) Healthcare, Eisai, Roche Diagnostics, Siemens, Alnylam, Corium, Otsuka, Two Labs, Florida Department of Health, and the National Institutes of Health (NIH) Biobank; receives research support from the Alzheimer's Association, Roche Diagnostics, Avid Pharmaceuticals, and Life Molecular Imaging; and has received honoraria for participating in independent data safety monitoring boards (DMSB) and providing educational continuing medical education (CME) lectures and programs. R.P. has served as a consultant for Roche, Genentech, Eli Lilly, Eisai, and Nestle; receives royalties from Oxford University Press and UpToDate; and has participated in educational activities with Medscape. D.A.W. has served as a paid consultant to Eli Lilly, GE Healthcare, and Qynapse; serves on a data safety monitoring board for Functional Neuromodulation and GSK; and receives research support paid to his institution from Biogen. H.-S.Y. received honoraria from Genetech, Incorporated (Inc), unrelated to this study. D.J.I. served as unpaid member of the scientific advisory board for the Lewy Body Disorder Association (LBDA) and Denali Therapeutics. R.A.S. receives grant support from the Alzheimer's Association and GHR Foundation to her institution; grant support from Eisai and Eli Lilly to clinical trial sites; and she has served as a paid consultant for AbbVie, AC Immune, Acumen, Alector, Alnylam, Biohaven, Bristol Myers Squibb, Genentech, Jannsen, JOMDD, Nervgen, Neuroaly, Neurocentria, Oligomerix, Prothena, Renew, Roche, Shionogi, Vigil Neuroscience, Ionis, and Vaxxinity. R.M.E. is a full-time employee of the Alzheimer's Association. Rosa R. has a patent and receives royalties from "Detecting and Treating Dementia"; has served as a consultant to Arkuda Therapeutics; is on the scientific advisory board of the Alzheimer Fondation, France and the Kissick Family Foundation Grant Program; and is on the Medical Advisory Council for the Association for Frontotemporal Degeneration. Rema R. serves as an unpaid Alzheimer's Association San Diego/Imperial Chapter Board Chair. P.S. has grant support paid to his institution from Novo Nordisk, is a member of a DSMB for ImmunoBrain Checkpoint, is Chair of the World Dementia Council, and has shares in EQT AB. He is a full-time employee of EQT Life Sciences. E.C.M. has received consulting fees from Eli Lilly, Biogen Idec, Hoffmann-La Roche Ltd., Janssen, and Alector. G.E.M. has served on the diversity advisory board for Genentech and the scientific advisory board for University of Texas (UT) Health Science Center at Houston; she is also on the board of Fundaconciencia Inc. and APPREMED. B.C.D. has received consulting fees from Acadia, Alector, Arkuda, Biogen, Denali, Eisai, Genentech, Lilly, Merck, Takeda, and Wave LifeSciences; royalties from Oxford University Press and Cambridge University Press; and has served on the DSMB for Eli Lilly and Merck. T.J.H. holds stock in Vivid Genomics. P.A.D. is a paid employee of the Association for Frontotemporal Degeneration. C.U.O. has grant funding paid to his institution from Alector, Inc and Transposon Therapeutics. He

has served as a consultant for Acadia Pharmaceuticals, Reata Pharmaceuticals, Otsuka Pharmaceutical, Eli Lilly, Alexion Pharmaceuticals, Lykos Therapeutics, and Zevra Therapeutics. J.A.S. has served on the advisory board for the Framingham Heart Study, National Institute on Neurological Disorders and Stroke (NINDS) Discovery, and Foundation France Alzheimer's. K.D.R. received payments for presentations with MedBridge. C.M.C. serves in the DSMB for the US POnINTER study and two NIH clinical trials at the University of Kansas and University of California Los Angeles (UCLA). G.D.R. has received grant funding paid to his institution from Eli Lilly, Life Molecular Imaging, GE Healthcare, Genentch, and the Rainwater Charitable Foundation; he has received consulting fees from Eli Lilly, GE Healthcare, Roche, Genentech, and Alector; and is on a DSMB for Johnson & Johnson. R.C.P. receives grant funding to his institution from the GHR Foundation; royalties from Oxford University Press and UpToDate; and consulting fees from Roche, Genentech, Eli Lilly, Nestle, and Eisai. He is on a DSMB for Genentech and financial interests in Medscape. All other authors do not declare any conflicts of interest.

CONSENT STATEMENT

This study did not involve research using human subjects and, thus, consent was not necessary.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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