

Gaps and opportunities related to the clinical detection of Limbic-predominant Age-related TDP-43
Encephalopathy (LATE).

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Executive Summary

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List of Abbreviations

ABeta: Amyloid Beta
AD: Alzheimer's disease
ADL: Activities of daily living
ADNC: Alzheimer's Disease Neuropathological Change
ADRD: Alzheimer's Disease Related Dementias
ALS: Amyotrophic lateral sclerosis
AMD: Age-related macular degeneration
COPD: Chronic obstructive pulmonary disease
CSF: Cerebrospinal fluid
CTF: C-terminal fragment
DaTscan: Dopamine transporter scan
DAT: Dementia of the Alzheimer's Type
DLB: Dementia with Lewy bodies
DM: Diabetes mellitus
ERT: Estrogen replacement therapy
FDG: Fluorodeoxyglucose
FTD: Frontotemporal dementia
FTLD: Frontotemporal lobar degeneration
GWAS: Genome-wide association studies
HIPAA: Health Insurance Portability and Accountability Act
HS: Hippocampal sclerosis
IADL: Instrumental activities of daily living
LATE: Limbic-Predominant Age-Related TDP-43 Encephalopathy
LATE-NC: Limbic-Predominant Age-Related TDP-43 Encephalopathy Neuropathologic Changes
MCI: Mild cognitive impairment
MIBG: Iodine-123 metaiodobenzylguanidine
MMSE: Mini Mental State Exam
MOCA: Montreal Cognitive Assessment
MRI: Magnetic resonance imaging
NC: Neuropathologic changes
NIA-AA: National Institute on Aging and the Alzheimer's Association
PART: Primary age related tauopathy
PET: Positron emission tomography
TIA: Transient ischemic attack
TDP or TDP-43: Transactive response DNA-binding protein of 43 kDa (kilodaltons)
VCID: Vascular contributions to cognitive impairment and dementia

Gaps and Opportunities Related to Clinical Detection of LATE

Introduction

[Limbic-predominant Age-related TDP-43 Encephalopathy \(LATE\)](#) is a brain disorder that mimics the clinical features of Alzheimer's disease (AD).¹ Like AD, LATE is very common in older individuals and has a large public health impact. In contrast to AD, relatively little research has focused on LATE. This knowledge gap sparked a [workshop on LATE in 2018](#) (with a consensus paper published in 2019¹), the inclusion of a session on LATE at the [Alzheimer's Disease-Related Dementias \(ADRD\) Summits in 2019](#) and [2022](#), and the follow-up [open meeting LATE 2022](#), where panelists discussed the state of the research since the initial deliberations in 2018 and identified future directions.

Despite prior progress, there remains an unmet need to identify clinical and biomarker features of LATE. This will be an increasing problem as the oldest-old population ages, and as AD biomarkers and anti-amyloid beta (ABeta) therapies become more commonplace. Physicians will have diagnostic uncertainty in patients with predominantly amnesic syndrome and negative amyloid biomarkers. Moreover, patients with LATE and biomarker positivity for amyloid might differentially respond to anti-ABeta therapies. In May 2023, a 2-day hybrid workshop was convened with the goal of determining whether the science has evolved to the point where there is enough information to define a clinical syndrome that is associated with the neuropathological changes seen with LATE (LATE-NC: Limbic-predominant Age-related TDP-43 Encephalopathy Neuropathologic Changes), and whether there is sufficient confidence in the available research to categorize or diagnose individuals with LATE both in research settings and in the clinic. The workshop featured 15 talks on day one covering the current state of the science on neuropathological, clinical, epidemiological, and genetic predictors of LATE, and day two consisted of 5.5 hours of panel discussion on the path forward for identifying gaps, developing a clinical definition, and integrating clinical observations and biomarkers for diagnosing LATE and studying LATE in clinical trials.

Day 1

Opening Remarks

TDP-43 (Transactive response DNA-binding protein of 43 kDa) is a protein involved in gene regulation in brain and other tissues.² Errors resulting in misfolded and phosphorylated TDP-43 are implicated in Amyotrophic lateral sclerosis (ALS) and (Frontotemporal lobar degeneration) FTL, which are relatively rare conditions.³⁻⁴ However, recent work shows that misfolded and phosphorylated TDP-43 protein is relatively common in older individuals, with up to a quarter of older individuals showing significant LATE-NC at autopsy.⁵

AD neuropathologic change (ADNC) is defined by the stereotypical pattern and progression of amyloid plaques and tau neurofibrillary tangles. Like ADNC LATE-NC has a stereotypical

pattern and progression of TDP-43 pathology across the brain, with or without concomitant hippocampal sclerosis. Clinical symptoms are typically apparent in life only in cases with pathologic diagnosis of LATE-NC Stage 2 or 3 (not Stage 1 where TDP-43 is only present in the amygdala), whereas AD typically requires intermediate or high ADNC to produce clinically apparent cognitive change.⁶⁻⁷ Therefore, lower pathologic levels of both ADNC (low ADNC) and LATE-NC (stage 1) are not associated with significant cognitive impairment. It is important to note that biomarkers for AD also correlate well with intermediate or high AD pathology.

Following the initial classification of LATE in 2019,¹ subsequent clinical and biomarker studies have improved our ability to recognize patients with “pure” LATE (Stage 2/3 LATE-NC). Individuals with pure LATE are generally of older age, show episodic memory impairment with varying degrees of semantic memory impairments, and thus may appear to show similar symptoms as those seen in “pure” AD (intermediate or high ADNC), albeit with a slower progression and less visuospatial impairment.^{6,8}

Many older people have AD pathology, and thus LATE commonly occurs in the same brains concurrent with AD pathology.⁶ With the emergence of medications targeting AD, it will be important to determine what the impact of LATE co-pathology will be on patient outcomes with these therapies. Importantly, as amyloid measures are obtained in patients as part of assessment of appropriate use for such therapies, many people will be found to be amyloid-negative and will be much more likely to have LATE as the driver of their symptoms. Thus, physicians will be confronted with the need to classify these patients in their practices.

While there is some debate about nomenclature of LATE, there is broad agreement that TDP-43 commonly accumulates in limbic regions in late-life aging and as a co-pathology with AD. Considerable work supports the relationship of higher levels of TDP-43 in these regions, which is found post-mortem, to alterations in cognition, brain structure, and function.^{1,6} The workshop participants described clinical correlates of these changes to allow for research on LATE to progress and to enhance clinicians’ ability to understand and prognosticate the course of brain aging in older people.

To move forward, issues around identified gaps in research on LATE need to be addressed. Some notable gaps discussed included the lack of a specific biomarker for TDP-43, the need to validate the clinical classification of LATE with and without AD, challenges in implementing interventional studies of LATE, the need for ethnic, racial and socioeconomic diversity in studies of LATE, and clinical and pathologic boundary issues of LATE/LATE-NC with other diseases, such as Frontotemporal dementia (FTD)/FTLD-TDP.

The burden of AD and amnestic dementia is increasing globally.⁹ In “real world” clinical medicine, amnestic dementias are commonly synonymous with AD, partly because of lack

of access and knowledge about AD biomarkers, less well-developed measures for non-AD conditions, as well as shortcomings of in vivo biomarkers. However, AD only accounts for some, not all, amnesic dementias. LATE has largely been unrecognized as a factor among amnesic dementias. Currently, most clinicians recognize AD, vascular contributions to cognitive impairment and dementia (VCID), dementia with Lewy bodies (DLB), and multiple-etiology dementias (or mixed dementia), although the latter is still primarily restricted to academic medicine settings. In patients with suspected dementia, clinicians will also search for other potential causes to rule out dementia, such as vitamin B12 deficiency, thyroid dysfunction, and structural brain lesions.¹⁰

At the meeting, multiple investigators described pathologic and clinical studies, in which pathological, clinical, and demographic factors associated with LATE could help contextualize LATE in the spectrum of amnesic dementias and Alzheimer's Disease Related Dementias (ADRD).

When considering the various neuropathological pathways involved in age-related dementia risk, about a third of the risk is associated with vascular pathology, and the remainder is associated with neurodegenerative diseases both within and outside of the "amyloid" pathway, including the hippocampal sclerosis (HS)/TDP (LATE) pathway (~20%), the ABeta/tau (AD) pathway (~40%), and, to a lesser degree, the Lewy body pathway (~10%).¹¹ Among the "oldest-old" (nonagenarians and centenarians), some data suggest that the attributable risk of LATE is greater than AD.¹² A pathologic diagnosis of AD (intermediate or high ADNC) and LATE-NC are associated independently with cognitive impairment and can occur on their own or as co-pathologies.¹³ Patients with pure AD show a faster decline in cognitive function relative to those with pure LATE. Unfortunately, mixed AD and LATE pathology is very common and associated with the most rapid cognitive and functional decline compared to those people with pure AD or pure LATE.¹⁴

In the case of LATE, much like other dementias, determination of clinical disease should be considered probabilistic until post-mortem confirmation. In the cases of AD, VCID, and LBD, there are some generally accepted biomarkers that can be measured, usually through imaging and clinical symptoms to facilitate a probable etiologic diagnosis. With the emergence of molecular markers for AD, this condition can be defined based on biomarkers as suggested by the 2018 National Institute on Aging and the Alzheimer's Association (NIA-AA) research framework.¹⁵ With LATE, however, there are no current clinical definitions or accepted biomarkers to support a probable diagnosis.

TDP-43 pathology in LATE is temporal lobe predominant and, unlike FTLTDP, is not associated with severe frontal cortical atrophy, neuronal loss, gliosis, or spongiform change.¹⁶ Clinically, individuals may display profound episodic amnesia in the absence of FTD-type behavioral or language dysfunction. The syndrome is noted as being very common and is associated typically with onset at older age (80s and 90s).⁵ TDP-43

pathology, i.e., LATE-NC, appears to be a major pathology in amnesic dementias and could explain a large component of amnesic dementia and cognitive decline.¹⁷ While some progress has been made in classification and terminology, there are still unresolved issues related to nomenclature of LATE and the relationship between clinical syndromes and diagnosis. TDP-43 proteinopathy is associated with dozens of different conditions and is not specific to LATE. Thus, TDP-43 and TDP-43 proteinopathies are analogous to tau and tauopathies. Importantly, and again similar to tau pathology in AD, there does appear to be a common pattern in the staging and distribution of TDP-43 pathology in association with LATE. LATE-NC, as measured by phospho-TDP-43 pathology, can be divided into three stereotypic stages whereby changes are first seen in the (1) amygdala region, followed by (2) the hippocampal region, and finally (3) the middle frontal gyrus.^{1,18} The distribution of TDP-43 in FTLD-TDP and LATE-NC differ; for instance, FTLD-TDP has significantly more cortical TDP-43 pathology, especially frontal pathology. Further, current research suggests that most age-related hippocampal sclerosis (HS; significant neuronal death in the hippocampus) is a subset of LATE-NC.¹⁹

Despite increasing pathologic and scientific recognition of LATE, there has been little to no recognition in most clinical settings. There is a critical need, therefore, to increase awareness (to both the public and clinicians) and to further examine the role of LATE in amnesic disorders.

Throughout the course of the workshop, the panel discussed the neuropsychological and clinical characteristics of LATE, current knowledge of the identification of biomarkers and the use of imaging to determine LATE, the known genetic predictors and risk factors for developing LATE, considerations around developing clinical trials to better study and understand LATE and the need to raise awareness of LATE. The workgroup intends to publish a white paper detailing the deliberations of this workshop, and the present executive summary describes the main topics covered in the workshop.

Neuropsychology, Clinical Characteristics Subcommittee

LATE is associated with increased risk of dementia²⁰ and preferentially affects episodic memory,²¹ although over time, as the disease progresses, other cognitive domains are also impacted. There are similar cognitive profiles between LATE and AD, however, the effects on non-memory abilities, specifically perceptual speed, working memory, and perceptual orientation, occur later for LATE in comparison to AD.²¹ The one exception may be semantic memory which occurs more proximal to memory decline.²¹ A diagnostic challenge, which may be insurmountable in the absence of biomarkers, will be to clinically distinguish LATE from AD using only standard psychometric measures. However, there may be non-standard assessments of cognition that will prove helpful. Further, with longer follow-up, a slower course may also suggest LATE.

Thus far, progress has been made in establishing the prevalence of LATE-NC and its attributable risk for clinical (“AD-type”) dementia.^{5,22} (In this case, attributable risk provides an estimate of overall risk in a population for clinical dementia that is caused by a particular subtype of pathology.) Data from the 90+ study suggest that LATE-NC is frequently associated with other neuropathologic changes related to dementia including AD, HS, LBD, and arteriosclerosis.²³ Like AD, age is a primary risk factor for LATE, and LATE (including cases that are “pure” or “mixed”) accounts for approximately 20% of dementia in individuals over 90 (in the 90+ cohort). Sex and education levels do not show a relationship.²³

There does not appear to be a difference between Black and White individuals, but many studies do not have diverse representation of race and ethnicity.²⁴ This is a gap in the current understanding of LATE in the general population, and the workgroup discussed the importance of enrolling a greater diversity of participants into LATE studies..

With respect to other health conditions in the 90+ cohort, no relationship was seen between LATE and hypercholesterolemia, heart disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), stroke/transient ischemic attack (TIA), seizure, age-related macular degeneration (AMD), glaucoma, rheumatologic disease, or thyroid disease.²³ Some data suggest that LATE-NC is lower in individuals with hypertension, congestive heart failure, and osteoarthritis, although the nature of this relationship is unclear.²³ Some data suggest that in women, long-term (15+ yrs) estrogen replacement therapy (ERT) or recent use of ERT was associated with lower risk of LATE-NC.²⁵ These findings will need to be replicated in other cohorts.

Biomarker and Imaging Subcommittee

Research to establish biomarkers specifically for TDP-43 in LATE and other diseases with TDP-43 is ongoing. Like the clinical measures described above, much work needs to be done to verify the reliability of pathological measures and biomarkers. Plasma biomarkers provide one potential method for identifying LATE in the clinical context.²⁶⁻²⁷ One study²⁸ found in a relatively small cohort that the level of TDP-43 protein in plasma astrocyte exosomes (small vesicles secreted from different cell types) was a useful biomarker to differentiate individuals with eventual autopsy-confirmed LATE.²⁹

Although plasma bioassays are in development, imaging modalities, both magnetic resonance imaging (MRI) and positron emission tomography (PET), are sensitive to changes associated with neurodegeneration, and are currently used to rule in or out other potential causes of cognitive impairment and cognitive decline.³⁰⁻³¹ MRI imaging shows changes in hippocampal atrophy and, as noted above, there is a stereotypic progression of LATE-NC which may mirror atrophy on MRI.³²⁻³³ Therefore, MRI has the potential to provide some degree of specificity in identifying LATE-NC.¹ Within the medial temporal lobe, some work has suggested that a more anterior to posterior gradient of atrophy may differentiate LATE from AD.³⁴ In general, hippocampal atrophy in LATE tends to be more severe than that

seen with pure AD, and this may provide clues as to whether an individual has LATE.³⁵ Moreover, within the spectrum of hippocampal atrophy associated with AD, those in the lowest quartile are clearly enriched in individuals with concomitant LATE.³⁶

To validate imaging approaches, researchers will need to evaluate people with suspected LATE using MRI and follow them through post-mortem examination to link imaging findings with histology. Additionally, use of ex-vivo MRI and histopathology allows for temporally more direct links that can then be translated into in vivo observations. The ultimate goal will be to build an atlas of MRI markers of LATE-NC using a large and diverse population of older (ideally community-based) adults. Given that there is much variation between individuals, imaging assessments over time in individuals with autopsy confirmation will likely be needed to establish presence and progression of LATE-NC.

Fluorodeoxyglucose (FDG)-PET is a promising method that elucidates changes in regional brain metabolism that can help differentiate neurodegenerative disorders.³⁷ LATE is characterized by a specific temporo-limbic pattern of hypometabolism that clearly differs from the typical temporo-parietal pattern in AD.³⁵ Current work shows that patients with amnesic dementia who exhibit a LATE-like FDG-PET pattern have lower AD biomarker levels and show specific clinical and genetic features consistent with LATE.³⁸

Integration of Neuropsychology and Biomarkers towards a Clinical Diagnosis of LATE

There was robust discussion around a proposed LATE clinical syndrome score. A draft proposed list of attributes and scoring was presented along with an example case of a woman with progressive amnesic dementia. The preliminary proposed LATE clinical syndrome criteria will be discussed in the Day 2 summary.

The illustrative case was an 83-year-old woman with gradually progressive difficulty with short term memory and was consistent with mild dementia originally deemed likely related to AD. Neurocognitive testing showed profound memory decrements but relatively normal performance in other cognitive domains outside of memory. She showed no or minimal evidence of amyloid and tau on PET and severe medial temporal atrophy on MRI. The profile of negative amyloid and tau measures, but with severe MTL neurodegeneration suggested non-ADNC etiology.¹⁵ Taken together, the patient's profile suggested probable LATE with HS. Postmortem examination revealed TDP-43 pathology with HS, and no significant ADNC.³⁷ While thus far more people who have been examined at autopsy have LATE in conjunction with AD or other pathologies (rather than pure LATE),¹ this case demonstrates the potential utility of applying current neurocognitive testing and imaging to make a probabilistic determination of pure LATE.

Genetic Predictors/Risk Factors Subcommittee

Genetic variants associated with altered risk for LATE-NC/HS have been identified and include the genes VOG 328D, I TP."CDEE; ."CRQG"Y Y QZ."MEP OD4, and VREP 3.³⁹⁻⁴⁰ Genetic

risk factors for mixed pathologies, such as LATE-NC + HS or LATE-NC + ADNC have not yet been studied in detail but there may be a signal for LATE-NC + ADNC in UQTNB.³⁹ There is some shared genetic risk between pathologies, but it is difficult to distinguish between vertical and horizontal pleiotropy such as VOGO328D/TP between LATE-NC, FTLD-TDP Type A, and HS, or CRQG between LATE-NC and ADNC. Prior studies highlight the importance of neuropathology, age, and ancestry, and it was noted that there are large differences seen in LATE-NC risk allele frequencies by ancestry (European vs. African ancestries).

There are distinct genetic drivers of TDP-43 proteinopathy and HS in LATE-NC.⁵ Pathologic associations include VOGO328D and ITP which influence TDP-43 pathology, whereas CDEE; is associated with HS pathology. The association between CDEE; and LATE-HS is of interest in particular as CDEE; is a “druggable” target with a current trial underway (NCT04120766) to assess the safety of nicorandil and its potential to modify changes in hippocampal volume in patients at risk for LATE+HS.⁴¹

Gene mutations relevant to amnesic (“Alzheimer’s-type”) dementia may influence symptoms via LATE-NC (e.g., YYQZ variants), rather than AD pathology.⁴² It was noted that APOE e4 is a highly impactful genetic risk factor of LATE-NC.⁴³⁻⁴⁴ However, the CRQGe4locus/LATE-NC association is not fully explained by AD pathology itself, suggesting pleiotropy. Additionally, lysosomal dysregulation may be a converging point of CRQGe4/A-beta and VOGO328d leading to LATE-NC.⁴⁵

The VOGO328D risk haplotype also is associated with LATE-NC and correlates with more TMEM106B pathology in brain.⁴⁶ Other work showed that VOGO328D is a risk factor for FTLD-TDP.⁴⁷ More TMEM106B protein pathology is seen in AD cases with LATE-NC in both the frontal cortex and hippocampus relative to patients with ADNC and no LATE-NC.⁴⁶ Presence of TMEM106B C-terminal fragments (CTFs) correlate strongly with age and the presence of VOGO328D risk haplotype, and risk haplotype was associated with more TMEM106B pathology.⁴⁸ TMEM106B CTFs are present as amyloid fibrils across neurodegenerative diseases and are particularly abundant in LATE-NC.⁴⁶ Of note, FTLD-TDP type A shares key genetic risk factors (ITP and VOGO328D) with LATE-NC, but not with other FTLD-TDP subtypes.¹⁸

There are limitations to these observations. Most individuals in these studies are genetically similar to the European ancestry reference panel from the 1000 Genomes project.⁴⁰ This may result in outcomes that cannot be confidently projected onto other ethnoracial groups. For example, it is important to consider that the CRQGe4/LATE-NC association might be absent or weaker in individuals who are not of European ancestry.⁴⁹ The limited genome-wide association study (GWAS) sample size means low statistical power of these observations.⁴⁹⁻⁵⁰ It is possible to discover associated variants with current

sample sizes but there is a need for larger cohorts, including from individuals of non-European lineage.^{49,51}

Clinical Trials Subcommittee

Better understanding of LATE and LATE-NC leads to the question: Are we ready to utilize the concept of LATE in clinical trials? Current AD trials use amyloid and tau biomarkers to rule in AD. However, researchers cannot rule out LATE as a comorbidity without established biomarkers for TDP-43. This may affect treatment responses to anti-ABeta therapies. But it remains to be determined the degree to which biomarkers could be used for discriminating LATE from other conditions in the context of clinical trials. For example, current DLB trials may use alternate radioactive tracers as biomarkers, such as [123I]-MIGB myocardial scintigraphy and more commonly dopamine transporter scans (DaTscans), to aid in the diagnosis of DLB.⁵² Current FTD trials leverage genetic identification and congruent interventions. With increasing information, it may be possible to use genetics to identify participants and guide therapeutic approaches in people with suspected LATE, but this is currently not possible.

LATE is a potential confound in non-LATE targeted ADRD clinical trials. For example, the University of Kentucky ADRC ([P30AG072946](#)) database was screened for all participants who had come to autopsy after having engaged in clinical trials since 2005 (n=546). In this sample, approximately 30% of cases who had engaged in AD clinical trials had confounding LATE-NC, and 14-37% HS pathology (Jicha G., manuscript in preparation). Co-morbid or “pure” LATE-NC +/- HS should therefore be considered a major potential confounding factor in studies of anti-amyloid therapies.

The workgroup outlined some essential design considerations for developing clinical trials of LATE. Older participants are underrepresented in clinical trials, therefore, recruitment and retention of this population is critical to trial success and inclusion across the lifespan is [required](#) for NIH funded research.⁵³ There are a number of challenges to recruiting older participants, including challenges in obtaining informed consent (e.g., due to hearing or vision impairment), comorbid conditions impacting outcome assessment, polypharmacy, cost of medical management and compensation, and investigator preferences, among others.⁵⁴ Additionally, as alluded to above, the vast majority of people enrolled in AD trials are white, leading to substantial underrepresentation of other racial and ethnic groups.⁵⁵ With respect to data collection, there is a need for data on function, comorbidity, and social determinants of health in participants. Contingencies need to be in place for handling missing data due to difficulty answering questions, refusal to take or complete exams, and participant fatigue after long assessments. To mitigate issues in trial operations, input from personnel with expertise in geriatric medicine will be crucial in trial design and trial conduct. As LATE is seen most frequently in older individuals, care will need to be taken with deidentifying participant age and the Health Insurance Portability and Accountability

Act's (HIPAA) Safe Harbor rule. Additionally, it will be important to consider how safety issues, pharmacokinetics and pharmacodynamics may potentially differ from younger participants.

It may be possible to leverage existing infrastructure to support clinical trials for LATE. For example, biomarkers used for screening in existing AD trials—if participants do not screen amyloid positive, one could obtain an MRI scan to establish hippocampal atrophy. One of the major challenges to intervention studies of LATE is the heterogeneity, due in part to co-pathologies, which may reduce sample size and therefore decrease statistical power.⁵⁶ Observational studies are being leveraged to guide appropriate study design, statistical power, and robust effect sizes.⁵⁷ Well characterized, trial-ready cohorts would improve the speed and efficiency of future trials.^{8,57}

Day 2

Summation on the Clinical Detection of Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) with no or low AD

Discussion during Day 2's session of the workshop, which included participants from each of the four subcommittees, focused on features that could be used to define probabilistic LATE Clinical Syndrome criteria. A preliminary list of possible core, clinical, imaging, and biomarker features were discussed in detail and are presented below (Table 1). While the conversation centered on distinguishing the syndrome of pure LATE, there was also discussion on the more difficult task of how certain features could be used to diagnose LATE in the setting of AD (e.g., Mixed AD/LATE), and several discussants noted that LATE is much less likely to be seen in a "pure" rather than "mixed" state. Some of the proposed supporting features are specifically related to the use of imaging and biomarkers in older people with amnesic memory loss, because as previously noted, LATE is most commonly seen in people over the age of 80. It was suggested that while it might be possible eventually to use some genetic markers to rule in or out LATE, such as identifying those with autosomal dominant progranulin (GRN) mutation in FTLD-TDP studies, the Genetics Subcommittee concluded that there was not enough current information that would be sufficient to enable the development and implementation of a polygenic risk score at this time.

Table 1: Preliminary List of Clinical Characteristics Supporting "pure" LATE

Core Features

Must present with an insidious and progressive amnesic predominant syndrome (some propose specific guidance of time)

Additional Clinical Features

1. Older age at symptom onset (some suggest specific age)
2. Mild clinical syndrome with largely preserved non-memory cognitive domains
3. Mild semantic impairment in the setting of a mild syndrome (some suggest specific types of semantic deficits such as salient historical information)

Supportive Biomarker/Imaging Features

1. Hippocampal atrophy out of proportion to syndrome severity determined by MRI
 - a. May be symmetric or asymmetric
 - b. Greater medial temporal relative to inferior temporal
2. Low likelihood of significant tau pathology
 - a. Negative amyloid-specific biomarkers – increases probability LATE is underlying pathology
(Note: Positive amyloid-specific biomarkers would not rule out LATE)
 - b. Negative tau measures
 - c. FDG PET without AD pattern (e.g., posterior temporal/parietal hypometabolism)
3. LATE-like pattern on FDG-PET

Exclusion Criteria

1. Exclusion criteria: If person presenting with behavioral phenomena consistent with DLB or consistent with FTD – should discount a primary diagnosis of LATE
2. Exclude autosomal dominant progranulin (GRN) mutation

AD: Alzheimer's Disease; FDG: fluorodeoxyglucose; FTD: Frontotemporal dementia; LATE: Limbic Predominant TDP-43 Encephalopathy; PET: Positron emission tomography

As the panel discussed the future development of clinical criteria for LATE, they noted the importance that the criteria should be feasible for clinicians with varying levels of access to PET or MRI imaging technology, and more specialized neuropsychological testing. Another larger challenge would be the diagnosis of LATE when LATE co-occurs with AD and potentially other conditions such as DLB or VCID. Importantly, many people have both AD and LATE, and the ability to assign levels of severity to each syndrome could help characterize individual cases, and eventually help determine overall prognosis and the likelihood of success or failure of a treatment. Although much remains unknown, it could be, for example, that people with some likelihood of LATE and some co-occurring likelihood of AD might not respond as well to anti-amyloid treatments as those with AD alone if only the AD is modulated by the therapy. Alternatively, one could imagine synergistic benefits for both pathologies. These are important gaps to understand for implementing treatments as effectively as possible.

The panel discussed additional gaps and opportunities related to LATE, including collaborations across fields and including researchers who focus on ALS, FTD, and other neurodegenerative diseases and processes. They emphasized the importance of capturing the heterogeneity within AD to allow better differentiation of patterns of AD that may be suggestive of different pathologies, the need for a disease-specific marker for LATE, the importance of brain donation, especially in diverse populations, and the need for educating care providers, people with cognitive impairment, and families about LATE and what LATE means relative to other possible neurological conditions.

Appendix A: Speakers and Subcommittee Members

Chairs

Peter T. Nelson, MD, PhD, University of Kentucky
Julie Schneider, MD, MS, Rush University
David A. Wolk, MD, University of Pennsylvania

Speakers and Moderators

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Appendix B: References

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