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POLICY FORUM

Advancing biomarker development for chronic traumatic encephalopathy: Summary and recommendations from the 2025 Leon Thal Summit

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Abstract

The 2025 Leon Thal Summit convened an international panel of clinicians, neuroscientists, neuropathologists, and neuroimaging specialists to evaluate the current state of biomarker development for chronic traumatic encephalopathy (CTE) and to outline priorities for advancing translational research for this important area. Discussions integrated emerging findings from longitudinal cohorts, new molecular and neuroimaging approaches, expanding *post mortem* evidence, and evolving insights into exposure biology and genetic modifiers. Consensus themes emphasized the need for biomarkers that detect CTE-specific tau proteoforms, integration of existing imaging and fluid markers into traumatic encephalopathy syndrome research criteria, and refinement of multimodal magnetic resonance imaging and blood-based tools that capture early CTE pathology. The group underscored the importance of coordinated, longitudinal clinicopathological studies and collaborative research frameworks to validate candidate biomarkers and accelerate progress toward accurate diagnosis, disease monitoring, and therapeutic development for individuals at risk for or exhibiting signs of CTE.

KEYWORDS
biomarkers, chronic traumatic encephalopathy, neurodegeneration, neuroinflammation, repetitive head impacts, traumatic encephalopathy syndrome

1 | INTRODUCTION

Extensive exposure to repetitive head impacts (RHIs) is a risk factor for chronic traumatic encephalopathy (CTE) and other neurodegenerative disorders.[1] This degree of RHIs is found in contact or collision sports through substantial, repetitive direct blows to the head or in military service members via multiple blast exposures.[2] Despite being described almost 100 years ago, our understanding of the pathophysiologic processes and natural history of CTE is hampered by the lack of accurate tests or measures that can be applied during life to diagnose, monitor, or track the disease. There is general agreement that the discovery of biomarkers for CTE is a critical next step to advance our knowledge of this disease and provide the basis for prevention and treatment.

The 2025 Leon Thal Summit was focused on advancing biomarker development for CTE. The impetus for this topic arose in 2023 during the capstone meeting of the National Institutes of Health (NIH)-funded Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) study. That study used the National Institute of Neurological Disorders and Stroke (NINDS) consensus clinical criteria for traumatic encephalopathy syndrome (TES) to classify former college and professional American football players. However, as discussed below, these research criteria are based solely on clinical manifestations. The question of whether it was appropriate to add biomarkers to the consensus criteria was posed. Discussants concluded that it was premature to include biomarkers in clinical criteria at that time. Biomarkers are being developed at a rapid rate and with new findings emerging from analyses of cohorts from DIAGNOSE CTE and the Professional Athletes Brain Health Study (PABHS), as well as expanding neuropathological insights from *post mortem* changes, it seemed timely to readdress the current state of biomarkers in TES/CTE.

The Leon Thal Summits hosted by the Cleveland Clinic Lou Ruvo Center for Brain Health began in 2007 to honor Dr. Leon Thal, an early pioneer in the field of Alzheimer's disease (AD) therapeutics and a major figure in both the AD research and clinical communities. (Previously the Leon Thal Symposium for the Prevention of Dementia, which ran from 2007 to 2010, were a series of policy-oriented meetings led by Zaven Khachaturian, PhD, that significantly influenced the content of the National Alzheimer's Strategic Plan and the National Alzheimer Project Act of 2011.) The 2025 meeting brought together an international group of clinicians and researchers in CTE with the goal of reviewing what is currently known about potential biomarkers for CTE, identifying key gaps in knowledge, and providing recommendations on how to move the field forward. While identifying potential biomarkers that could aid in *ante mortem* diagnosis of CTE is an important need, the attendees were reminded to think broadly of other roles biomarkers might play in the clinical and research realm.

2 | METHODS

The progress-informed agenda of the meeting was structured to review and discuss each topic that is listed below and finished with a general session to generate the final recommendations. The goal was to summarize recent discoveries relevant to CTE and synthesize them into a next step research agenda. Each session consisted of a presentation that reviewed the current literature on the topic, followed by two breakout groups. Each group was advised to undertake a "SLOB" analysis (strengths, limitations, opportunities, and barriers), with one group focused on the role of current biomarkers for diagnosis, tracking disease progression, and understanding the natural history of exposure to RHI and the other group addressing what is needed to develop or identify novel CTE biomarkers for clinical and research purposes. The groups then came together for general discussion and recommendations.

Breakout and general discussions were designed to encourage diverse perspectives. The recommendations included in this report reflect areas of broad consensus among participants. We present a summary of the material reviewed by the presenters and conclusions of the group discussions. Recommendations that received general agreement among the group are summarized at the end of this report.

3 | TES

Sponsored by the NINDS, the first consensus diagnostic criteria for TES (CDC-TES) were published in 2021 and intended for research use.[3] The criteria for a TES diagnosis follow a stepwise process: (1) substantial exposure to RHIs; (2) a core clinical feature of neurobehavioral dysregulation and/or cognitive impairment; (3) a progressive course of symptoms; and (4) no other neurologic, psychiatric, or medical conditions that can fully account for the symptoms. Based on the presence of other clinical features, a level of certainty for CTE can be assigned. The CDC-TES has not yet been validated against *post mortem* findings and the diagnosis of CTE currently remains at pathologic diagnosis.

The addition of biomarkers to the current CDC-TES could potentially bridge the gap between clinical manifestations and pathophysiological changes in the brain. They could improve sensitivity and specificity, help monitor progression of the disease, and ultimately offer an opportunity for preclinical diagnosis. There was consensus that biomarkers that are now readily available could potentially be added to the TES criteria on an exploratory basis with two potential purposes: (1) to exclude other pathologies (such as AD) that could account for the presentation, or coexist with CTE pathology, and (2) improve the levels of certainty of CTE pathology (see Figure 1).

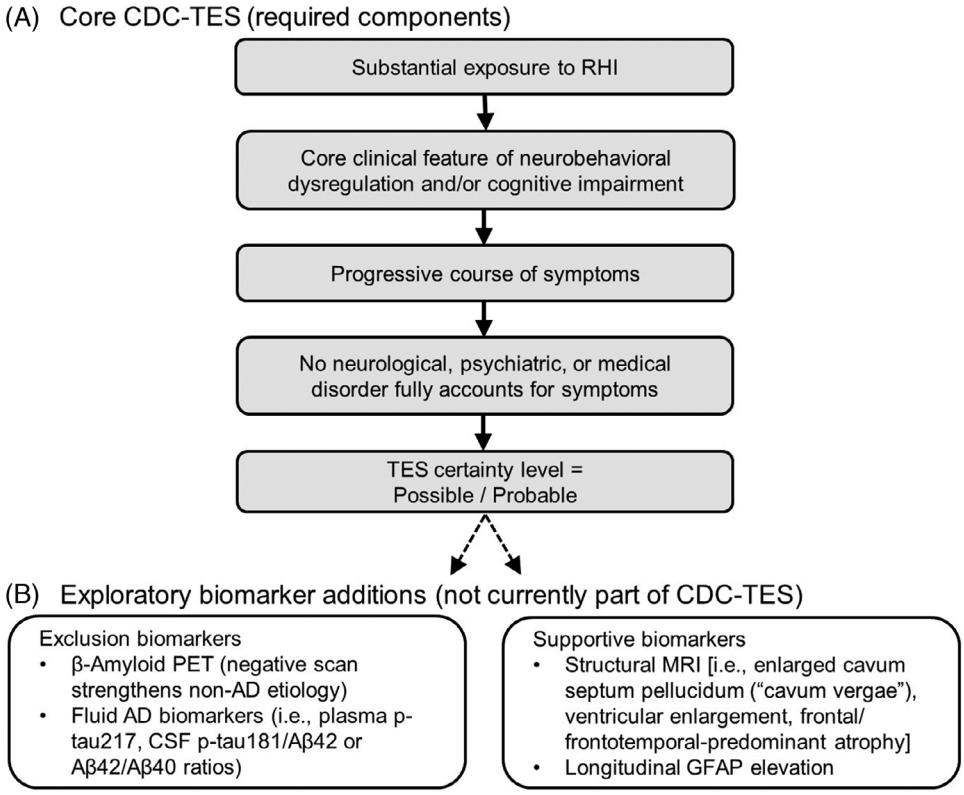

FIGURE 1 Description of the current core CDC-TES criteria and potential exploratory biomarker additions to include as exploratory exclusive and/or inclusive criteria. Aβ, amyloid beta; AD, Alzheimer's disease; CDC-TES, consensus diagnostic criteria-traumatic encephalopathy syndrome; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein MRI, magnetic resonance imaging; PET, positron emission tomography; p-tau, phosphorylated tau; RHI, repeated head injury.

4 | PATHOLOGY OF CTE

The pathognomonic CTE lesion at the microscopic level consists of phosphorylated tau (p-tau) aggregates in neurons, with or without glial tau, at the depths of cortical sulci around small blood vessels.[4,5] While many tau post-translational modifications are shared with AD and AD-related disorders, unique structural differences of tau conformers in CTE have been demonstrated by cryo-electron microscopy.[6–8] This heterogeneity in tau aggregates between diseases was emphasized, particularly as it relates to the development of molecular imaging tracers and fluid biomarkers (discussed below). The conformation of these aggregates can take the form of paired helical or straight or twisted filaments.[9] These filaments may be comprised of 3-repeat (3R), 4-repeat (4R), or both 3R/4R-microtubule binding domains within the tau protein.[10] These proteoforms of tau are temporally dynamic in CTE (going from a predominantly 4R form in earlier stages to mixed 3R/4R later in the disease).[10,11] Elevated levels of p-tau202 have also been reported in CTE.[8] CTE proteomic studies are promising and may lead to more specific blood biomarkers or molecular imaging targets for in vivo identification of CTE pathology.

Multiple other comorbid pathologic proteins may co-occur with CTE, including phospho-transactive response DNA-binding protein 43 (TDP-43), amyloid beta (Aβ), and α-synuclein. Table 1 summarizes neuropathological comorbidities and reported frequencies, adapted from prior work.[12] Phospho-TDP-43–positive inclusions and dots in the medial temporal lobe are considered a supportive pathological feature of CTE and represent potential biomarker targets.[13–16]

TABLE 1 Neuropathological comorbidities and reported frequencies in CTE [12].

	Frequency[a]	Percent (%)	Mean sample age (years)
Amyotrophic lateral sclerosis[17]	11/166	6	67
Alzheimer's disease[17]	23/154	13	67
Aβ plaques			
Diffuse[14]	59/55	52	60
Neuritic[14]	41/73	36	60
Cerebral amyloid angiopathy[13]	72/179	29	60
Lewy body disease			
Any[15]	53/86	38	57
Neocortical[13]	13/238	5.2	60

Abbreviations: Aβ, amyloid beta; CTE, chronic traumatic encephalopathy.
Table adapted from Stein and Crary.[12]
[a]Frequencies are presented as counts with/without per sample population.

While not being a core component of CTE pathology, Aβ deposition has been observed in nearly 50% of pathologically confirmed CTE cases.[14] Amyloid in CTE more frequently occurs as diffuse rather than neuritic plaque and is often sparse or patchy. When present, it accumulates at a younger age and at a faster rate compared to a community-based autopsy series. Likewise, α-synuclein pathology is present in a subset of individuals with CTE and is considered a comorbidity rather than intrinsic to CTE.[17]

At a cellular level, glial tau pathology develops in the perivascular CTE lesions with aging. The high expression of nicotinamide adenine dinucleotide (NADH) quinone-dehydrogenase and L-ferritin at these sites raises the possibility that this glial reaction is driven by iron-induced oxidative stress, in turn leading to astrocyte and oligodendrocyte degeneration seen in CTE.[18]

Vascular injury and inflammation may be latent or prodromal features of CTE pathophysiology. Exposure to RHIs can result in axonal injury, inflammation, microvascular injury with impaired blood–brain barrier function, astrocytosis, and neuronal loss.[19] The effect on microvascular structure can be seen as increased vascular branching, along with an increase in vascular injury markers in CTE cases.[20] Astrocytic cellular phenotypes consistent with inflammation, angiogenesis, and reactivity are also associated with CTE; biomarkers that can identify these early changes and track progression may inform mechanisms and potential treatment targets in CTE.[21]

Gross pathological findings in CTE provide features can be detected and characterized with available imaging techniques. Common structural changes include generalized cerebral cortical atrophy, predominantly of the frontal lobes, often with localized thinning of the cerebral ribbon at the sulcal depths, concomitant enlargement of the frontal horns of the lateral ventricles and third ventricle, gross medial temporal atrophy, and atrophy of the fornix.[10] Cavum septum pellucidum; thalamic and hypothalamic atrophy, with a sharply concave medial thalamic contour (thalamic notch); mammillary body atrophy; thinning of the posterior corpus callosum; and pallor of the substantia nigra have also been observed among those with RHIs and possible CTE.[17]

Despite advances from *post mortem* studies, several critical gaps in knowledge remain, including:

1. The mechanisms linking RHIs to neurodegeneration remain unclear, particularly features promoting the transition from acute injury to chronic disease.
2. Overlapping features with other tauopathies make differentiation from CTE challenging.
3. The cross-sectional nature of autopsy studies does not inform longitudinal disease pathophysiology and biomarkers are needed to document disease progression.

5 | BIOMARKERS

Among potential biomarkers, two major types were emphasized: imaging and biofluids. These were considered to have the most available data and the greatest potential for near-term development as CTE biomarkers.

5.1 | Magnetic resonance imaging

The availability, affordability, and structural detail provided by magnetic resonance imaging (MRI) make it a desirable adjunctive tool in the evaluation of neurodegenerative conditions. Current research aims to identify a neuroimaging signature of CTE that distinguishes it from other effects of RHI, and from AD and related dementias. Several common structural changes seen *post mortem* in CTE have been evaluated via MRI.

Multiple studies across cohorts of professional fighters and former professional American football players have shown a higher prevalence of a cavum septum pellucidum (CSP) compared to individuals not exposed to high levels of RHI.[22–24] While often considered a marker of high RHI exposure, some studies have reported an association between increased CSP size, cognitive impairment, and increased exposure to rotational forces. Similarly, lower or declining brain volumes have been reported in regions linked to TES and CTE neuropathology spanning the amygdala, hippocampus, entorhinal cortex, parahippocampal gyrus, insula, temporal pole, superior frontal gyrus, thalamus, fornix, and mamillary bodies.[25,26]

Machine learning techniques using MRI data from cohorts of professional fighters and former American football players to develop a classifier that could differentiate those with and without TES are being developed. Other modalities such as shape analysis and sulcal morphology are potential measures to track CTE disease progression.[27,28] Development of methods to detect iron-related oxidative stress or early vascular damage may have potential in helping us understand pathogenetic processes in CTE.[20,21]

Key to advancing CTE research at this time are standardizing acquisition and preprocessing across sites; building multimodal panels (ventricular indices, CSP metrics, Papez circuit volumes, diffusion measures, shape/sulcal features) rather than relying on single markers; and deriving interpretable, threshold-based risk scores linked to TES probability. These aims underscore the need for prospective, longitudinal validation with test–retest reliability, cross-site generalizability, and correlations with clinical change.

5.2 | Positron emission tomography

There has been a hope that through molecular imaging, a tracer could be developed that would label the specific tau aggregates that occur in CTE and thus allow diagnostic specificity during life.[29] Barriers to achieving this goal include the sparse amount and geographical distribution of tau in early phases of the disease, the evolution of tau isoforms from 4R to 3R/4R as the disease progresses, and the lack of validated clinical criteria (resulting in the requirement of autopsy confirmation for CTE diagnosis).[30,31] Additional challenges in

incorporating tau positron emission tomography (PET) imaging include technical issues such as signal loss due to partial volume effects in certain regions and off-target binding of existing tau tracers.[29]

Initial studies of tau PET imaging in patients who are at risk of CTE used repurposed tau tracers that have been successful in AD, such as [^{18}F]flortaucipir, (also known as Tauvid), [^{18}F]MK-6240, and [^{18}F]fluoroethyl(methyl)amino-2-naphthyl}ethylidene)malononitrile (FDDNP).Overall, results indicate that small elevations in tracer uptake may occur in regions such as the superior frontal and medial temporal cortices, but these are not sufficient to reliably indicate CTE pathology at the individual patient level.[30] This aligns with autoradiographic studies showing absent or weak binding of these radiotracers to CTE tau, with stronger signals observed only in cases with a high tau burden at autopsy.[30,32]

Tau PET ligands that recognize a broader complement of tau forms than those occurring in AD have promise for study of CTE. However, there remains a need for tracers that can recognize 3R, 4R, and CTE-tau to diagnose CTE at an early stage. As a promising example, [^{18}F]OXD-2314 (also known as [^{18}F]STX-TP1) is a novel PET radiopharmaceutical that has high affinity to tau aggregates in several non-AD tauopathies,[33] and was recently advanced for first-in-human PET studies,[34] with imaging in patients with progressive nuclear palsy and people with suspected CTE presently underway. These data are not yet published, and preliminary results are expected upon completion of ongoing studies.

Beyond tau PET imaging, other potential uses of molecular imaging were discussed. PET amyloid imaging could be used to identify AD pathology and exclude patients with AD changes from cohorts being assessed for CTE;[35] the presence of a negative amyloid PET scan could be added to the TES clinical criteria as a feature to strengthen the likelihood of CTE.[36] However, the routine use of amyloid PET as an exclusionary criterion is constrained by cost, limited availability across clinical settings, insurance coverage variability, and restricted access outside of specialized centers. This may limit its feasibility for broad implementation in research and clinical practice. Given the evidence for inflammation and microglial activation after head impact, and the role inflammation may play in the development of CTE, the ability to image neuroinflammatory activity may allow better understanding of the pathogenetic mechanisms involved in CTE.[37,38] Research studies with translocator protein (TSPO) tracers as a putative marker of microglial activation found them to lack specificity and they are susceptible to technical issues like poor signal-to-noise ratios and genotype-driven differences in radiotracer affinity and limited blood–brain barrier penetration.[39] Future TSPO-like ligands may allow visualization of inflammatory changes with PET. Fluorodeoxyglucose PET, a marker of cerebral glucose metabolism, though more widely available, has been studied only in small RHI-exposed cohorts; while not diagnostic on its own, characteristic metabolic patterns may provide supportive evidence in establishing the level of certainty for CTE within the TES criteria.[40]

5.3 | Fluid biomarkers

The evolution of ultrasensitive assays and new analytical techniques has transformed the field of fluid biomarkers for neurodegenerative diseases. Biomarkers for AD have become useful for a variety of contextual uses including diagnosis; eligibility for trials; providing prognostic information; and serving as pathophysiological markers for tracking disease progression, monitoring therapeutic responses, or serving as end points for trials. Specific markers of disease (i.e., cerebrospinal fluid [CSF] Aβ42/40 or p-tau181/Aβ42 ratios for AD, blood p-tau217 for AD, CSF α-synuclein seeding assays for Parkinson's disease and Lewy body disease), along with proteins associated with non-specific processes such as glial fibrillary acidic protein (GFAP) reflecting astrogliosis or neurofilament light chain (NfL) indicating axonal injury, are valid and reliable and are now commercially available.[41]

There is no validated fluid biomarker for CTE. As with molecular imaging, AD fluid biomarkers have been evaluated in high-risk CTE cohorts and have been found to be largely uninformative beyond establishing the presence or absence of AD pathology. Importantly, plasma p-tau217, a robust marker of amyloid-associated AD tau pathology, does not appear to reflect the tau aggregates characteristic of CTE. In contrast, alternative phosphorylation sites within the proline-rich region of tau may be more relevant to CTE-related tau pathology; for instance, p-tau202 has been found to be elevated in the frontal cortex in a pathological series of CTE cases.[8] The strong relationship between plasma p-tau217 and amyloid PET suggests that plasma measures may be adequate to assess the presence of AD pathology in individuals being assessed for CTE.[42] In parallel, CSF α-synuclein seeding amplification assays (SAA), which demonstrate high sensitivity and specificity for Lewy body diseases, may serve an important complementary role by identifying co-existing or primary synucleinopathies, thereby aiding differential diagnosis, and may be integrated into future biologically informed CTE classification frameworks.[43,44]

Beyond disease-specific biomarkers, markers reflecting more general neuroglial injury processes have also been evaluated. Regarding other fluid biomarkers, higher levels of GFAP, which is a more general indicator of astrogliosis associated with inflammation, and in particular a longitudinal rise in GFAP, has been associated with both volumetric worsening on MRI and cognitive measures over time in a group of professional fighters at risk of CTE;[45] this finding has not yet been validated in other cohorts exposed to RHI. Work on other common co-pathologies, such as TDP-43 and α-synuclein, as well as other potential markers of neuroinflammation, are being advanced. From an implementation standpoint, capillary blood sampling ("blood spot") for p-tau217 and NfL shows strong correlation with plasma measures, potentially extending access to testing. However, interpretation is complicated by assay variability, comorbidities, and non-brain sources of analytes.[46]

6 | GENETICS

It is recognized that not all individuals exposed to the same amount of RHI will develop CTE. In CTE, multiple risk or protective factors, including general medical comorbidities, lifestyle, psychosocial factors, and genetics, are involved in clinical outcomes. Genetic variation may modify exposure response and disease severity. Identifying genetic modifiers of susceptibility and progression can clarify pathophysiology and inform potential targets for disease-modifying therapies, though use for individual risk counseling remains premature.

Apolipoprotein E (*APOE*) genotype has a prominent role in AD and outcomes after head trauma. Studies suggest that the ε4 allele of *APOE* is associated with higher CTE pathologic stage and greater quantitative tau burden in certain cortical regions, particularly in older age groups.[47] Emerging data indicate that the influence of *APOE* extends beyond neuropathology to in vivo biomarkers. In living retired professional fighters, ε4 carriers show steeper longitudinal increases in plasma GFAP with greater lifetime fight exposure, consistent with heightened astroglial reactivity, while plasma p-tau231 shows no relationship to exposure, indicating these effects are independent of tau pathology.[48]

MAPT and *TMEM106B* may modify response to RHI.[49] A structural haplotype in the 17q21.31 region (H1b1g1) has been associated with higher cortical tau burden and dementia in CTE brain donors; each additional H1b1g1 allele confers an effect size comparable to ≈ 9.6 years of football play and is accompanied by upregulation of immune and inflammatory pathways.[50] This genetic association provides a potential biological mechanism for the neuroinflammatory phenotype of CTE modulating the glial reactivity observed in CTE.

Genetic research requires large sample size to overcome the burden of multiple testing. While there are > 1700 subjects in the Boston University Brain Bank, with ≈ 800 having CTE findings, collaboration and data pooling across brain banks and the inclusion of longitudinal, genotyped cohorts of living individuals at risk of CTE will be essential to validate these and future emerging gene × exposure effects. Such studies should incorporate *APOE* and 17q21.31 haplotypes, pre-specify exposure × genotype, and stratify tau outcomes by *MAPT* haplotype to clarify how inherited variation shapes progression and biomarker trajectories.

7 | TEMPORAL DYNAMICS OF BIOMARKER UTILITY ACROSS THE CTE DISEASE CONTINUUM

CTE is widely conceptualized as a progressive disorder that may evolve over decades, beginning with RHI exposure and potentially culminating in late-life neurodegeneration. An important theme of the summit discussion was that biomarker development must be aligned with the temporal evolution of the biology of the disease. Different biomarkers are likely to be most informative at distinct phases of the CTE continuum, ranging from active exposure to late neurodegenerative stages.

During periods of active or recent exposure to RHI, biomarkers are more likely to reflect acute or subacute injury processes, including axonal injury, blood–brain barrier disruption, neuroinflammation, and astroglial activation. Once exposure to RHI ceases and a neurodegenerative process begins, persistent neuroinflammatory changes, microvascular remodeling, and evolving astrocytic reactivity may predominate.[18,21] Biomarkers capable of detecting inflammatory signaling, vascular injury, or early tau proteoforms may therefore be most relevant in this window.

With disease progression, the accumulation and spatial spread of mixed 3R/4R tau aggregates, neuronal loss, and macroscopic atrophy become more prominent.[10,22,26,31] These changes may be detected by structural MRI markers and fluid biomarkers reflecting neurodegeneration and astroglial activation.[45,48] Co-pathologies including Aβ, TDP-43, and α-synuclein may emerge with aging, further influencing biomarker interpretation.[14–17]

Most biomarkers currently under investigation in CTE are thought to reflect intermediate or late-stage neurodegenerative changes rather than the earliest mechanistic events linking RHI to tau aggregation. Longitudinal studies spanning active exposure through post-exposure aging, with clinicopathological validation, will be essential to map biomarker trajectories onto stages of disease evolution and to determine which markers are best suited for risk stratification, early detection, progression monitoring, or clinical trials.

8 | SUMMARY AND RECOMMENDATIONS

Development of clinically applicable diagnostic tools and identification of safe and efficacious therapies are urgently needed to respond to the needs of the growing number of individuals with sports-related and military-based RHIs and CTE. *Ante mortem* diagnosis of CTE and a better understanding of the natural history and pathophysiology of the disease would be greatly benefited by new biomarkers specific to CTE. Therapies to prevent the transition from RHI to CTE as well as therapies to arrest, slow, or prevent the progression of CTE are needed. The 2025 Leon Thal Summit was focused on reviewing our current knowledge of potential biomarkers for CTE and generating ideas on how to advance a CTE-related scientific agenda. The following recommendations emerged:

1. Biomarkers specific to the CTE tau proteoform must be identified: Initial research with fluid and molecular imaging approaches leveraged methods developed to detect amyloid and AD-associated tau. There was general agreement that this strategy has not yielded sufficient specificity for CTE. Future efforts should prioritize development of biomarkers that recognize the unique proteoform of tau observed in CTE, acknowledging that this proteoform may evolve across disease stages. In the near term, tau-directed proteomic strategies and exploratory imaging ligands may refine candidate targets. Clinicopathologically validated assays capable of distinguishing CTE from other tauopathies are required to enable reliable *ante mortem* diagnosis.

2. Currently available biomarkers should be incorporated into the NINDS consensus research clinical criteria for TES on an exploratory basis: Biomarkers can be added and studied to determine whether they improve the level of certainty of CTE within the TES diagnostic criteria. Preliminary cohort evidence supports exploratory evaluation of structural MRI findings such as cavum septum pellucidum, AD-related biomarkers (amyloid PET, plasma p-tau217, CSF Aβ42/40 or p-tau181/Aβ42) to identify coexisting pathology, and longitudinally increasing GFAP as a marker of astroglial activation.
3. Biomarkers that are targeted to the pathophysiological processes that are involved in CTE should be developed and applied: Though specific tests to recognize CTE p-tau are a primary goal of biomarker research as mentioned in Recommendation 1, there are important roles for non-specific biomarkers that reflect the variety of pathogenetic pathways that likely occur in CTE and that could be the targets for therapies. These biomarkers not only advance understanding of disease mechanisms and natural history but may also serve as outcome measures in clinical trials. While markers such as GFAP and NfL are currently available, further efforts are needed to develop methods for detecting early neuropathological changes, including neuroinflammation, microvascular pathology, and co-pathologies such as TDP-43 in CTE.
4. Longitudinal, collaborative clinicopathological studies must be encouraged and supported:

    Development of specific imaging or fluid biomarkers for CTE requires neuropathological validation. Longitudinal biofluid sampling and brain imaging of cohorts at risk of CTE to better understand the natural history of the disease will assist in constructing plausible models of disease pathophysiology, biomarker identification, and therapy development. Given the small number of people with CTE in the general population compared to AD and the long latency between exposure and death, a unified field-wide effort with sustained funding is needed to increase research participation, including *ante mortem* biomarker assessment and brain donation. Creation of a Professional Interest Area within the Alzheimer's Association's International Society to Advance Alzheimer's Research and Treatment has begun and is an example of a way to link researchers with an interest in CTE and foster collaborations. A permanent research network, modeled after the Alzheimer's Disease Research Centers with uniform core datasets and site-specific projects, could accelerate biomarker discovery.

    Funding mechanisms to support this work may include targeted NIH initiatives (e.g., NINDS, National Institute on Aging), Department of Defense and Veterans Affairs programs addressing blast and repetitive head impact exposure, public–private partnerships, and collaborative industry-supported consortia. Coordinated, sustained investment will be essential to establish standardized longitudinal cohorts and ensure neuropathological validation.

Those who care for current and former elite athletes or military veterans exposed to RHI are limited in what they can advise these patients regarding CTE. The discovery of specific CTE biomarkers and the study of non-specific markers of the disease and other long-term effects of RHIs are the necessary steps to allow more specific diagnostic, prognostic, and therapeutic decision making to occur. Progress in these areas is required to conduct clinical trials and develop effective therapeutics to prevent or treat CTE.

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CONFLICT OF INTEREST STATEMENT

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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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