

Components of TES Diagnosis	Method of Ascertainment	Operationalization
Primary Diagnostic Criteria		
(I) Substantial Exposure to Repetitive Head Impacts	Review of all available medical and research records, comprehensive neurological interviews and exams, and publicly available online records for participation in high exposure collision sports, military service, or other sources of repetitive head impacts. Qualifying collision sports included American football, ice hockey, soccer, rugby, wrestling, mixed martial arts, or other high risk activities. Military service must have documentation of repetitive head impacts through blast exposure or training activities (e.g., breachers, boxing).	≥ 5 years of American football or equivalent level of exposure from individual or combined activities as determined by investigator consensus. Participants with documented exposure to American football without explicit mention of duration were included based on investigator determination of cumulative exposure (e.g., documentation of an additional high risk activity) but assigned a maximum “Suggestive of CTE” level of diagnostic certainty.
(II) Core Clinical Features		
(IIa) Cognitive Impairment	Neurological examination and formal comprehensive neuropsychological testing including the domains of memory and executive functioning. A composite memory score was calculated based on average standardized performance of 3 test scores: a) CVLT – Short Form total immediate recall, b) CVLT – Short Form delayed recall, c) Benson figure delayed recall. A composite executive functioning score was calculated based on average standardized performance of 5 test scores: a) modified trail making test, b) lexical fluency, c) digit span backwards, d) Stroop Inhibition, e) design fluency.	Investigator consensus based on review of records that 1) the participant and/or informant reported cognitive changes, which 2) represented significant decline from prior functioning, <i>and</i> 3) included deficits in at least memory and/or executive functioning. Objective neuropsychological testing revealed composite memory <i>or</i> executive functioning performance was ≥ 1.5 SD below the mean of a large, clinically normal (CDR=0) older adult sample at any time point, <i>or</i> a decline of ≥ 1.5 SD from an earlier objective evaluation in either domain.

<p>(IIb) Neurobehavioral regulation</p>	<p>Neurological examination (including comprehensive history and clinical interview with participant and/or informant)</p>	<p>Investigator consensus based on review of records that 1) the participant and/or informant reported neurobehavioral changes, which 2) represented a significant change from prior functioning, <i>and</i> 3) included behaviors like poor emotional regulation (explosiveness, impulsivity, rage, violent outbursts, “short fuse,” “mood swings”) that do not appear to be transient responses to life events.</p>
<p>(IIc) Progressive Course</p>	<p>Neurological examination and/or formal comprehensive neuropsychological testing.</p>	<p>Investigator consensus based on review of records that 1) there was evidence of worsening of clinical features over a period of at least 1 year without continued head impact/TBI exposure supported by either a) serial neuropsychological testing <i>or</i> b) clear historical evidence per clinician, participant, or informant)</p>
<p>(III) Not Fully Accounted for by Other Disorders</p>	<p>Neurological examination and formal comprehensive neuropsychological testing.</p>	<p>Investigator consensus based on review of records that the pattern of cognitive and neurobehavioral deficits was not fully accounted for by other preexisting, established, or non-degenerative nervous system, medical, or psychiatric condition. This criterion was applied liberally given ongoing ambiguity regarding CTE-specific symptoms and inability to confidently determine that alternate neuropathologies might <i>fully</i> account for all observed symptoms in patients with substantial prior head trauma exposure.</p>

(IV) Level of Functional Independence	Neurological examination and Clinical Dementia Rating (CDR) scale	<p>“Independent”: reported independence in all instrumental and basic activities of daily living <i>and</i> global CDR = 0.</p> <p>“Subtle/Mild Functional Limitation”: reported slight challenges but with mostly maintained independence in completing some instrumental activities of daily living <i>and</i> maintained independence with basic activities of daily living <i>and</i> global CDR = 0.5.</p> <p>“Mild” to “Severe” Dementia: <i>minimum</i> of definite impairment with instrumental activities of daily living <i>and</i> requiring cues for basic activities of daily living <i>and</i> global CDR ≥ 1.</p>
<i>Supportive Features</i>		
Delayed Onset	Neurological examination	Investigator consensus based on review of records establishing a period (years) of stable functioning after repetitive head impact exposure ends without evidence that symptoms represent ongoing effects of a prior traumatic brain injury or other preexisting condition
Motor Signs	Neurological examination	Investigator consensus based on review of records indicating positive findings of parkinsonism (bradykinesia, rigidity, rest tremor, parkinsonian gait disorder), other motor signs (dysarthria, ataxia, imbalance with frequent falls), and/or motor neuron disease (weakness, dysphagia, lower motor neuron signs, upper motor neuron

		signs, diagnosis of amyotrophic lateral sclerosis).
Psychiatric Features (distinct from Neurobehavioral Dysregulation features)	Neurological examination and/or standardized assessments (when available), including but not limited to the Geriatric Depression Scale, Beck Depression Inventory, Geriatric Anxiety Scale, Beck Anxiety Inventory, Apathy Evaluation Scale, or Neuropsychiatric Inventory	Investigator consensus based on review of records indicating evidence of persistent anxiety, apathy, depression, and/or paranoia based on participant or informant report, history of treatment/diagnosis, clinical observation, or self-report questionnaires exceeding established cutoffs for clinically significant symptoms

Supplemental Table 1: Methods of ascertainment and operationalization of specific criterion from the 2021 research framework for traumatic encephalopathy syndrome (TES; Katz et al.).