Diagnosing CTE During Life:
Clinical Presentation and Potential Fluid and Neuroimaging Biomarkers

6th Annual Boston University CTE Conference

October 27, 2022

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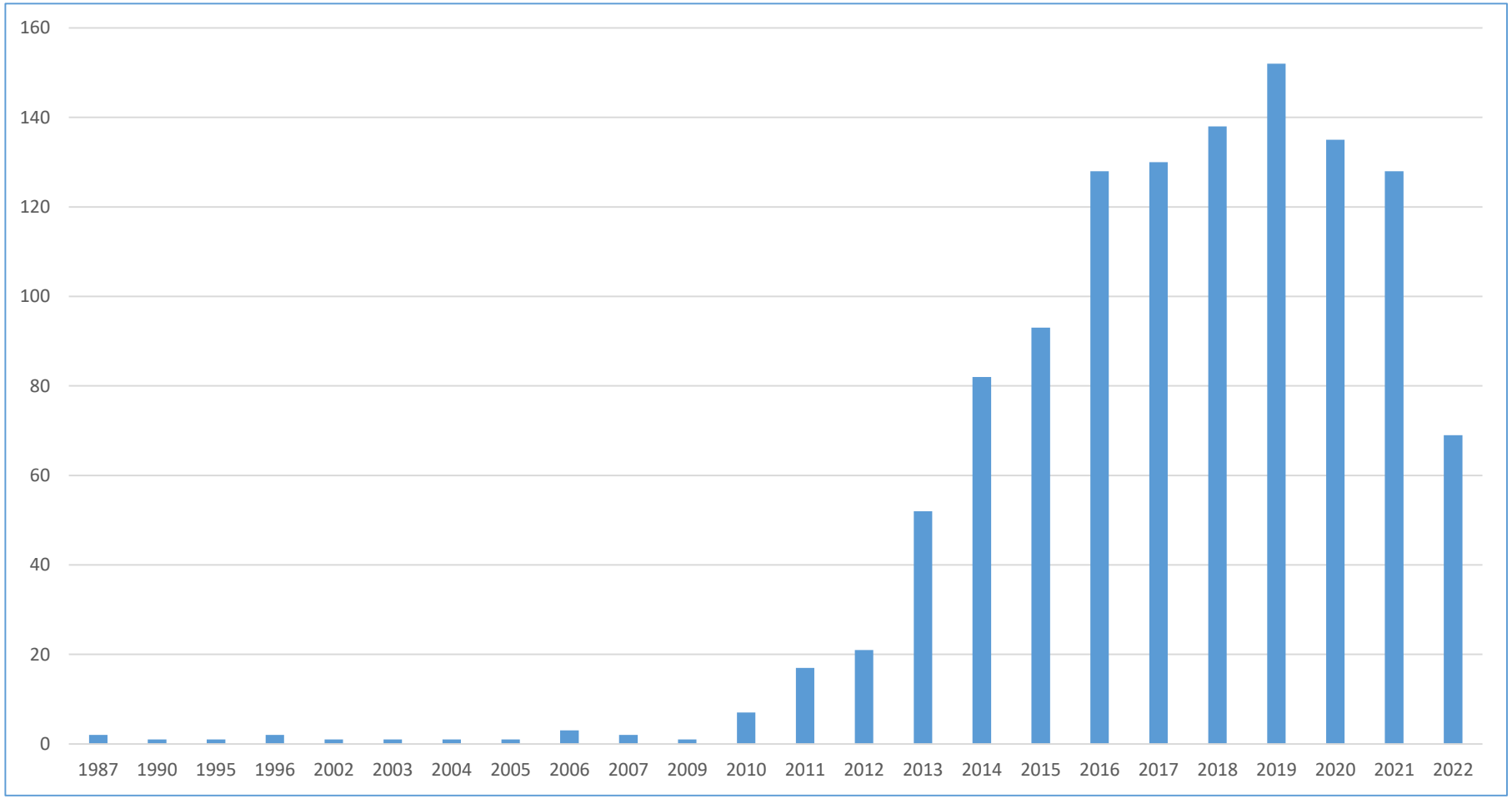
Disclosures

- Previous consultant for Biogen, Eli Lilly, Lundbeck
- King Devick Technologies (Board of Directors)
- Psychological Assessment Resources, Inc. (Royalties for Published Tests)
- Grant Funding:
  - National Institute of Neurological Disorders and Stroke
  - National Institute on Aging
  - Concussion Legacy Foundation

Number of Publications in PubMed with “Chronic Traumatic Encephalopathy” as Keyword

Total = 1168 (83% not from BU)



Important Unanswered Questions and Knowledge Gaps

- Is CTE common?
- What are the specific risk and resilience factors?
  - Head impact exposure (source, frequency, intensity, type, duration, age)
  - Genetics
  - Vascular
  - Racial/Sociocultural
  - Lifestyle
- What (if any) are the clinical features caused by CTE p-tau neuropathology?
- What (if any) are the clinical features caused by non-CTE neuropathology?
- How can we treat or prevent CTE?
- Critical Next Step: **Diagnose CTE During Life**

Can We Diagnose CTE During Life?

- Short answer: No….
- Longer answer: We are getting closer…
- What is needed?
  - Description of the clinical features and course
  - Development, validation, and refinement of diagnostic criteria for the clinical syndrome associated with CTE
  - Development and validation of sensitive and specific fluid and neuroimaging biomarkers of underlying CTE pathology

Early Description of Clinical Syndrome in Professional Boxers

- "Punch Drunk"
  - Martland, *JAMA,* 1928
    - *"cuckoo," "goofy," "slug-nutty"*
    - *"Finally, marked mental deterioration may set in necessitating commitment to an asylum"*
- "Dementia Pugilistica"
  - Millspaugh, 1937

Early Description of Clinical Syndrome in Professional Boxers

- "C*hronic traumatic encephalopathy*" first used by Bowman and Blau in 1940
  - 28-year-old professional boxer experiencing cognitive, behavioral, and mood symptoms.
  - Presented with short-term memory problems, depression, irritability, "childish" behavior, and paranoia, none of which improved over the course of 18 months

Early Description of Clinical Syndrome in Professional Boxers

- Critchley also used the term “chronic traumatic encephalopathy” in 1949 to diagnose a group of sailors, all former boxers, who presented with a similar profile
- Critchley (1957) further described the course of the condition:
  - *Of great interest, pathological as well as practical, is the fact that this traumatic encephalopathy is a progressive condition. Once established it not only does not permit of reversibility, but it ordinarily advances steadily. This is the case even though the boxer has retired from the ring and repeated cranial traumata are at an end. Neurologists have visualized this state of chronic traumatic encephalopathy as being based upon multiple minor cerebral contusions, possibly with initial pinpoint haemorrhages later replaced by a gliosis, cortical atrophy, and internal hydrocephalus.*

Clinical Syndrome Described in American **Football** Players as Early as the 1930s

- 1933 case report by the *Homeopathic Medical Society of the State of Pennsylvania*
  - Young football player who "did things suggesting the behavior of psychopathic personality" like "forging checks"
  - Described the "condition we sometimes find in pugilists…pummeled about the head."
- In 1937, former Columbia University football player, Frank Scully, interviewed his former teammates
  - 7 had varying degrees of "dementia, vagrancy, and motor deficiencies."
  - He believed the condition seen in boxers could be "multiplied many times if applied to football."


PUNCH-DRUNK FOOTBALL STARS!

Former Player Makes Sensational Accusations Against the National Sport

Charges Gridiron Ruins Men's Minds and Bodies

Why do half-backs become half-wits?
What is the scientific explanation for stumble-bums and stumble-backs?
What startling thing happened to 7 members of a great championship team, including a famous All-American quarterback?
Why do so many former players contract tuberculosis?
Find the answers in an amazing Liberty article:

"STUMBLE-BACKS—
Does Football Make Players Stupid?"
by Frank Scully

Scully knows football as a sports writer and a player. But today he is sorry that he was the man who restored football to Columbia after the war. In his startling article he cites numerous case histories to prove his damaging charges against football. Every player—every fan—MUST read "Stumble-backs" in the current issue of

Liberty 5c

Out today—on sale everywhere

"SPENCER TRACY CONQUERS HIMSELF" also in this issue

Chronology of Diagnostic Terminology for the Clinical Syndrome of Chronic Traumatic Encephalopathy

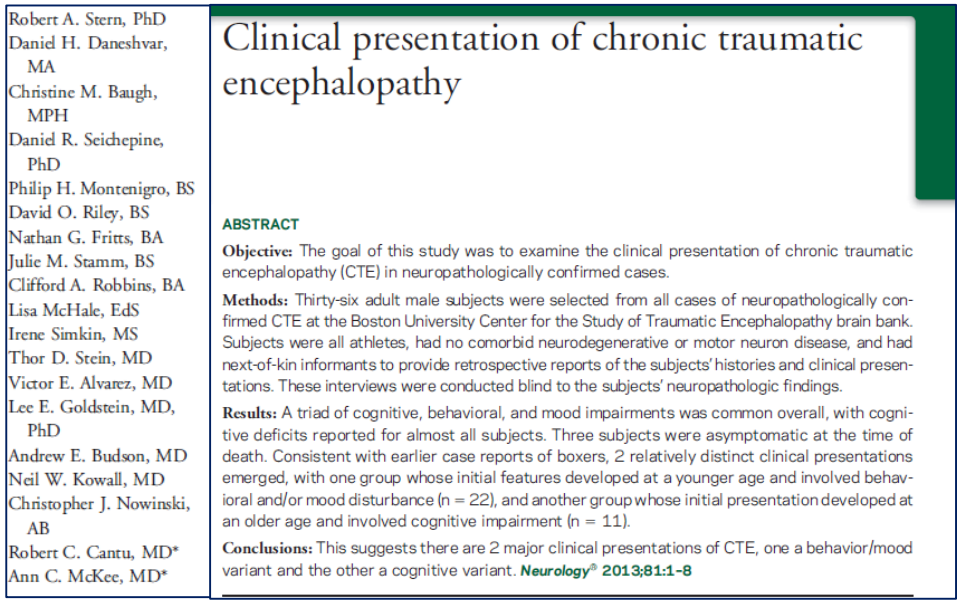
Term	Author	Year
Punch Drunk	Martland	1928
Traumatic Encephalopathy	Osnato	1929
Traumatic Encephalopathy of Pugilists	Parker	1934
Dementia Pugilistica	Millspaugh	1937
Chronic Traumatic Encephalopathy	Bowman and Blau	1940
Cumulative Encephalopathy of the Boxer	La Cava	1952
Chronic Progressive Traumatic Encephalopathy	Critchley	1957
Psychopathic Deterioration of Pugilists	Courville	1962
Chronic Boxer's Encephalopathy	Serel and Jaros	1962
Traumatic Boxer's Encephalopathy	Mawdsley and Ferguson	1963
Traumatic Encephalopathy	Victoroff	2013

Diagnosis of CTE During Life: Step 1

- Beyond “Punch Drunk” etc.
  - No neuropathological diagnosis
- Describe the clinical features associated with neuropathologically confirmed CTE

Clinical Features Associated with CTE?

- Based on retrospective reports of next-of-kin of deceased individuals
- Features are diverse and nonspecific



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Clinical presentation of chronic traumatic encephalopathy

ABSTRACT

Objective: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

Methods: Thirty-six adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank. Subjects were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had next-of-kin informants to provide retrospective reports of the subjects' histories and clinical presentations. These interviews were conducted blind to the subjects' neuropathologic findings.

Results: A triad of cognitive, behavioral, and mood impairments was common overall, with cognitive deficits reported for almost all subjects. Three subjects were asymptomatic at the time of death. Consistent with earlier case reports of boxers, 2 relatively distinct clinical presentations emerged, with one group whose initial features developed at a younger age and involved behavioral and/or mood disturbance (n = 22), and another group whose initial presentation developed at an older age and involved cognitive impairment (n = 11).

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavior/mood variant and the other a cognitive variant. *Neurology*® 2013;81:1–8

Montenigro *et al. Alzheimer's Research & Therapy* 2014, 6:68
http://alzres.com/content/6/8/68

alzheimer's research&therapy

REVIEW

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

Philip H Montenigro[1], Christine M Baugh[2], Daniel H Daneshvar[3], Jesse Mez[4], Andrew E Budson[4,5], Rhoda Au[2,6], Douglas I Katz[2,7], Robert C Cantu[8,9] and Robert A Stern[1,4,2,8*]

Clinical Features Associated with CTE

- **Changes in Emotional and Behavioral Control**
  - Rage
  - Short Fuse
  - Impulsivity
  - Emotional Lability
  - Not the social disinhibition of Behavioral Variant Frontotemporal Dementia (FTDbv)

➢ *This "Neurobehavioral Dysregulation" often occurs earlier in life, i.e., ages 30's-50's*

Clinical Features Associated with CTE

- **Changes in Cognitive Functioning**
  - Poor Short-Term (Episodic) Memory
    - cannot make new memories, rapid forgetting, repeating stories
  - Executive Dysfunction
    - poor judgment and decision-making, impaired organizational and planning skills, poor multi-tasking, cognitive disinhibition (*act first, think second*)
  - Other areas of cognitive functioning can also be impaired

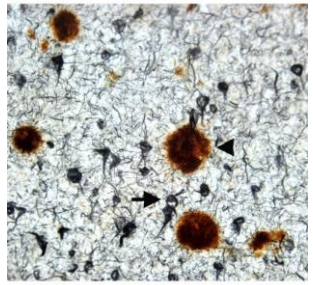
➢ *Cognitive Changes often begin later in life, i.e., ages 50's-70's*

- **Dementia**
  - Dementia = cognitive impairment significant enough to impact daily functioning (e.g., instrumental activities of living), independence
  - Dementia is not an illness or a disease; it is a clinical syndrome that is eventually seen in most/all neurodegenerative diseases

Other Neurodegenerative Diseases that Eventually Lead to Clinical Dementia

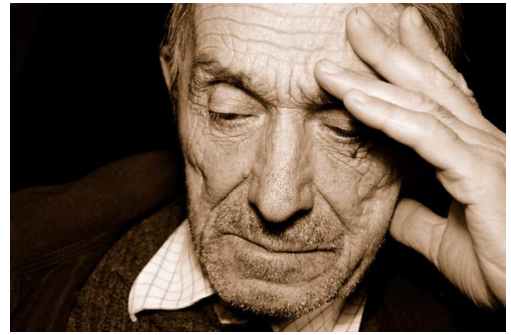
- Alzheimer's Disease (60-80% of all dementia)
- Cerebrovascular Disease (5-10%)
- Lewy Body Disease (5-10%)
- Frontotemporal Lobar Degeneration (5-10%)
- Parkinson's Disease
- Progressive Supranuclear Palsy (PSP)
- Corticobasal Degeneration (CBD)
- Prion Disease (e.g., Creutzfeldt-Jakob disease)
- Cerebral Amyloid Angiopathy
- Huntington Disease

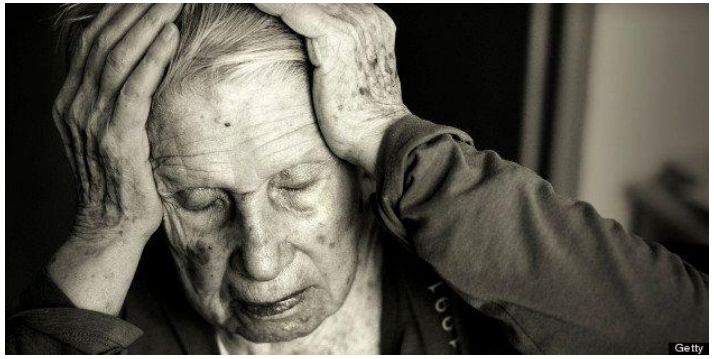
Specific Neurodegenerative Diseases are Diagnosed through a Postmortem Neuropathological Examination



Each Neurodegenerative Disease has an Associated Clinical Syndrome of Dementia, as well as "Prodromal" Syndromes

(e.g., Mild Cognitive Impairment, Mild Behavioral Impairment)



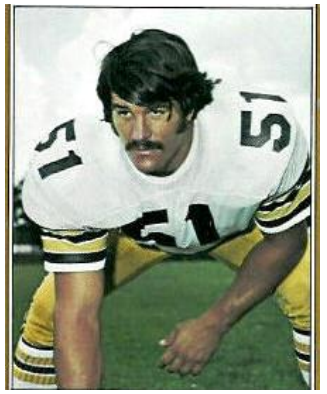


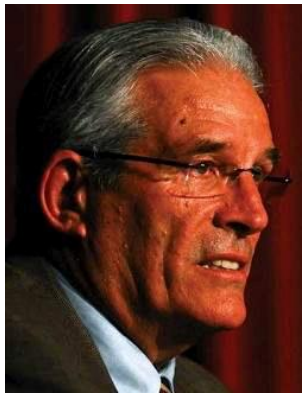
CTE and Dementia

- CTE can eventually cause dementia, but that does NOT mean that CTE causes “Alzheimer’s disease”
- Repetitive head impact exposure can cause CTE which can then eventually cause dementia, but that does NOT mean that RHI causes *Alzheimer’s disease*
- CTE dementia can easily be misdiagnosed as Alzheimer’s disease dementia

CTE in an Older Patient Can Mimic *Alzheimer's Disease Dementia*

J.D. - 66 yo Former NFL Center





- **Exposure History**
  - 17 years of American football
  - Age of first exposure: 10
  - 6 years in the NFL as a Center
  - Approx. 50 concussions, 1 with brief LOC, no hospitalizations
- **Clinical Course**
  - Mid 50s: mild memory impairment, but continued to work
  - Age 64: retired, outbursts, apathy, depression, and anxiety
  - Mid 60s: progression of memory impairment, more outbursts, problems with navigation, word finding difficulty, paraphasic errors, gait instability, masked facies, mild impairment in iADLs, **dementia diagnosis**
- **Cause of Death**
  - myocardial infarction
- **Neuropathological Diagnosis**
  - CTE Stage IV and NO Evidence of AD or other pathology

Football does NOT lead to “Alzheimer’s disease”

but…

RHI Exposure from Football can eventually lead to cognitive impairment and “dementia” due to CTE

BUT…

Not everyone with a history of RHI Exposure from Football and who has cognitive impairment and dementia has CTE pathology, or if CTE pathology is present, there may be other primary or comorbid pathologies contributing to the clinical features (Dr. Asken)

CTE and Progression of Clinical Features

what we think we know

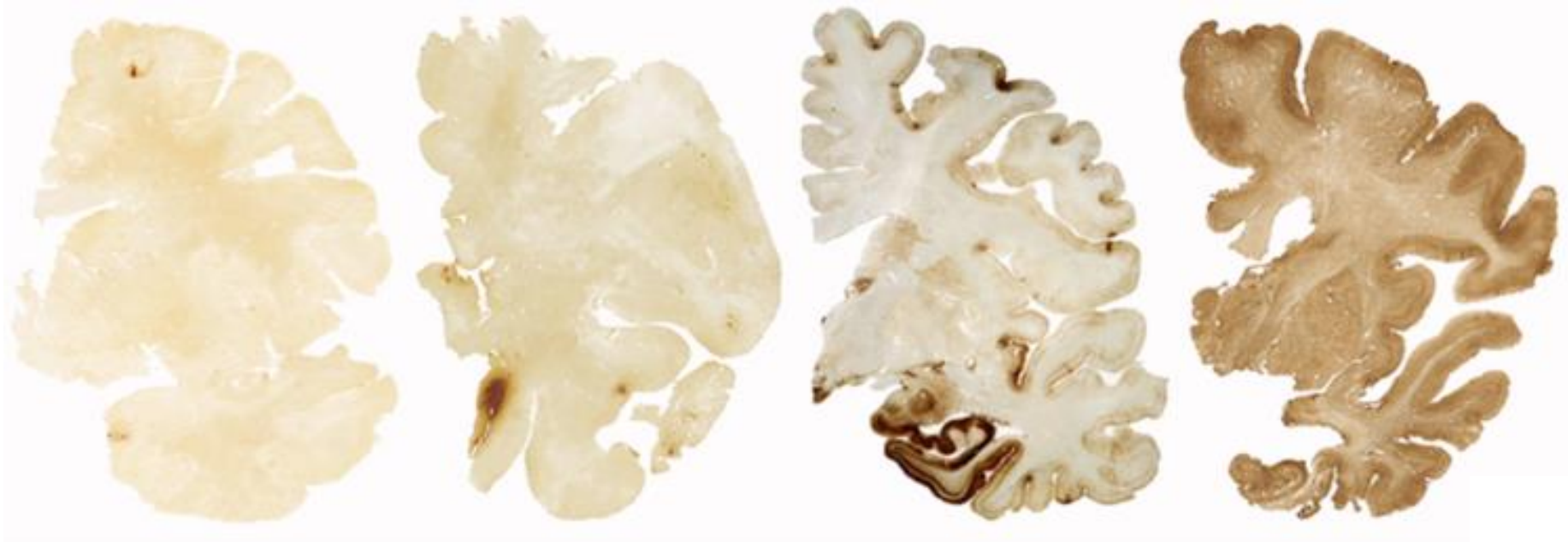
Asymptomatic "Preclinical"

Emotional and Behavioral Changes

Memory and Executive Function Decline

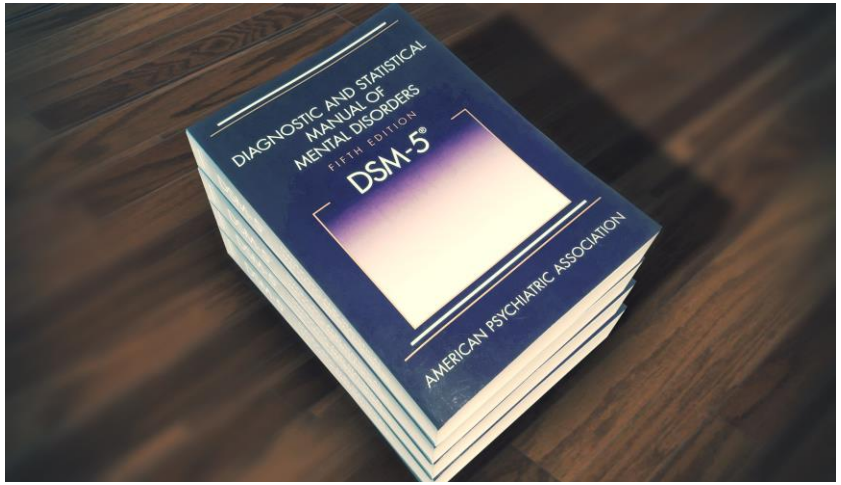
Dementia

Mild ***Moderate*** ***Severe***



Diagnosis of CTE During Life: Step 2

- Develop **Diagnostic Criteria** for the clinical manifestations of CTE neuropathology



Four Initially Proposed Diagnostic Criteria Schemata for the Clinical Presentation of CTE

Comparison and contrast of proposed clinical diagnostic criteria for chronic traumatic encephalopathy

	Jordan (2013)	Victoroff (2013)	Montenigro et al. (2014)	Reams et al. (2016)
Disease/ disorder	Chronic traumatic encephalopathy (CTE)	Traumatic encephalopathy (TE)	Traumatic encephalopathy syndrome (TES) + CTE	TES
Modifiers	Definite, probable. possible, improbable	Clinically probable, possible; acute, delayed onset	Behavioral/mood variant, cognitive variant, mixed variant, dementia; with motor features; CTE possible, probable, unlikely	Probable, possible, unlikely TES
Exposure to head trauma	Not specified	Exposure to one or more head injuries, including TBI, concussions, or subconcussive impacts, with or without loss of consciousness	History of multiple head impacts, including concussions, subconcussive injuries, or multiple moderate to severe TBIs	History of head trauma. Must be repetitive in nature for diagnosis of probable TES
Requisite symptom duration	Not specified	Two years following impact	Minimum of 12 months	Greater than 2 years
Onset of symptoms	Typically later in life after a period of latency	Acute: no period of latency following impact; delayed: decline following period of recovery	Interval greater than 2 years between symptom onset and exposure acts as a supportive feature	Delayed symptom onset required for diagnosis of probable TES
Clinical features	**Behavioral and psychiatric features** Aggression and/or agitation, apathy, impulsivity, depression, delusions (such as paranoia), suicidality **Cognitive features** Impaired attention and concentration, memory problems, executive dysfunction, dementia, visuospatial difficulties, language impairment **Motor features** Dysarthria, spasticity, ataxia, parkinsonism, gait disturbance, motor neuron disease (possibly)	**Symptoms** Headache, speech changes, tremor, deterioration in stance or gait, falls, cognitive decline, mood changes, anxiety, paranoia, personality change, alcohol abuse dependence or sensitivity, anger. or aggression **Neurologic signs** Nystagmus, dysarthria, reduced facial expression, hypertonia or rigidity, hyperreflexia, hemiparesis, tremor, limb ataxia, disorders of gait or stance **Neurobehavioral signs** Memory loss, other cognitive impairment, mood disturbance, thought disorder, pathologic personality traits, anger or aggression	**Core clinical features** Difficulties in cognition, including impairment of episodic memory, executive function and/or attention; behavioral dysregulation, including explosivity, physically and/or verbally violent behavior; mood disturbance, including feeling overly sad, depressed and/or hopeless **Supportive features** Impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs, documented decline, delayed onset	**Required features** Self-report or observer report of cognitive dysfunction, confirmed with objective cognitive decline documented by results of formal neuropsychologic testing **Supportive features** Emotional dysregulation, behavioral change, and motor disturbances
Clinical course	Not specified	Apparently persistent, progressive, improving	Stable, progressive, unknown/ inconsistent course	Progressive course required

2014 - Proposed Research Diagnostic Criteria for *"Traumatic Encephalopathy Syndrome"*

Montenigro *et al. Alzheimer's Research & Therapy* 2014, **6**:68
http://alzres.com/content/6/8/68

REVIEW

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

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2019 - First National Institute of Neurological Disorders and Stroke (NINDS) Consensus Workshop to Define the Diagnostic Criteria for Traumatic Encephalopathy Syndrome

Monday, April 15, 2019 Phoenix, Arizona

Attendees at the First NINDS Consensus Workshop to Define the Diagnostic Criteria for Traumatic Encephalopathy Syndrome (TES)

DIAGNOSE CTE Research Project

NINDS Observers	Invited External Voting Panelists	Investigators: Voting Panelists	Investigators: Non-Voting Observers
Walter Koroshetz, MD	David Brody, MD, PhD	Charles Adler, MD, PhD	Jeffrey Cummings, MD
Debra Babcock, MD, PhD	Kristen Dams-O'Connor, PhD	Michael Alosco, PhD	David Knopman, MD
Patrick Bellgowan, PhD	Barry Jordan, MD	Laura Balcer, MD	Eric Reiman, MD
	Tom McAllister, MD	William Barr, PhD	Yorghos Tripodis, PhD
	Ron Petersen, MD, PhD	Sara Banks, PhD	
	Ross Zafonte, DO	Charles Bernick, MD	
		Robert Cantu, MD	
		Dave Dodick, MD	
		Yonas Geda, MD	
		Doug Katz, MD	
		Jesse Mez, MD	
		Elaine Peskind, MD	
		Robert Stern, PhD	
		Jennifer Wethe, PhD	

- 20 expert panelists from 11 academic centers, representing multiple disciplines, interests and expertise
  - Neuropsychology, neurology, psychiatry, physical medicine and rehabilitation, neurosurgery
  - Experts in dementia, TBI, rehabilitation, sports medicine, behavioral neurology/neuropsychiatry…
  - Investigators from the DIAGNOSE-CTE investigator group and outside investigators
- 7 Observers, including NINDS Director and Program Officials

Goals set at Consensus Workshop

1. To develop evidence informed, expert consensus diagnostic criteria for Traumatic Encephalopathy Syndrome (TES), the clinical disorder associated with neuropathologically diagnosed Chronic Traumatic Encephalopathy (CTE).
2. To improve upon previously proposed research diagnostic criteria for TES by *maintaining adequate sensitivity* and *increasing the specificity* for underlying CTE pathology, defined by the NINDS/NIBIB consensus criteria.
3. To develop a criteria structure amenable to future updates, without the need for complete reorganization.

Modified Delphi Process to Achieve Consensus

- Overseen by Doug Katz, MD

- Panelists agreed to the following:
  - Maximum of four rounds of anonymous voting and revising
  - ≥80% agreement required for consensus
- Informed by literature review, available evidence for clinicopathological correlation
- Began with existing 2014 provisional criteria

2021 study of the ability of 2014 TES criteria to predict CTE pathology

Received: 12 October 2020 | Revised: 19 January 2021 | Accepted: 5 March 2021

DOI: 10.1002/alz.12338

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THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Validity of the 2014 traumatic encephalopathy syndrome criteria for CTE pathology

Jesse Mez[1,2] | Michael L. Alosco[1,2] | Daniel H. Daneshvar[1,3] | Nicole Saltiel[1,2,4,5] | Zachary Baucom[1,6] | Bobak Abdolmohammadi[1,2] | Madeline Uretsky[1,2] | Raymond Nicks[1,2,4,5] | Brett M. Martin[1,7] | Joseph N. Palmisano[1,7] | Christopher J. Nowinski[1,8] | Philip Montenigro[9] | Todd M. Solomon[10] | Ian Mahar[1,2] | Jonathan D. Cherry[1,4,5,11] | Victor E. Alvarez[1,4,5] | Brigid Dwyer[2,12] | Lee E. Goldstein[1,11,13,14] | Douglas I. Katz[2,12] | Robert C. Cantu[1,8,15,16] | Neil W. Kowall[1,2,4] | Yorghos Tripodis[1,6] | Bertrand R. Huber[1,2,4,5] | Thor D. Stein[1,4,5,11] | Robert A. Stern[1,2,15,17] | Ann C. McKee[1,2,4,5,11]

Abstract

Introduction: Validity of the 2014 traumatic encephalopathy syndrome (TES) criteria, proposed to diagnose chronic traumatic encephalopathy (CTE) in life, has not been assessed.

Methods: A total of 336 consecutive brain donors exposed to repetitive head impacts from contact sports, military service, and/or physical violence were included. Blinded to clinical information, neuropathologists applied National Institute on Neurological Disorders and Stroke/National Institute of Biomedical Imaging and Bioengineering CTE criteria. Blinded to neuropathological information, clinicians interviewed informants and reviewed medical records. An expert panel adjudicated TES diagnoses.

Results: A total of 309 donors were diagnosed with TES; 244 donors had CTE pathology. TES criteria demonstrated sensitivity and specificity of 0.97 and 0.21, respectively. Cognitive (odds ratio [OR] = 3.6; 95% confidence interval [CI]: 1.2–5.1), but not mood/behavior or motor symptoms, were significantly associated with CTE pathology. Having Alzheimer's disease (AD) pathology was significantly associated with reduced TES accuracy (OR = 0.27; 95% CI: 0.12–0.59).

Discussion: TES criteria provided good evidence to rule out, but limited evidence to rule in, CTE pathology. Requiring cognitive symptoms in revised criteria and using AD biomarkers may improve CTE pathology prediction.

Modified Delphi Process: Four Rounds of Voting and Revising and Voting and Revising…Almost Two Years Later:

National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

Douglas I. Katz, MD, Charles Bernick, MD, David W. Dodick, MD, Jesse Mez, MD, Megan L. Mariani, BS, Charles H. Adler, MD, PhD, Michael L. Alosco, PhD, Laura J. Balcer, MD, Sarah J. Banks, PhD, William B. Barr, PhD, David L. Brody, MD, PhD, Robert C. Cantu, MD, Kristen Dams-O'Connor, PhD, Yonas E. Geda, MD, Barry D. Jordan, MD, Thomas W. McAllister, MD, Elaine R. Peskind, MD, Ronald C. Petersen, MD, PhD, Jennifer V. Wethe, PhD, Ross D. Zafonte, DO, Éimear M. Foley, MS, Debra J. Babcock, MD, PhD, Walter J. Koroshetz, MD, Yorghos Tripodis, PhD, Ann C. McKee, MD, Martha E. Shenton, PhD, Jeffrey L. Cummings, MD, Eric M. Reiman, MD, and Robert A. Stern, PhD

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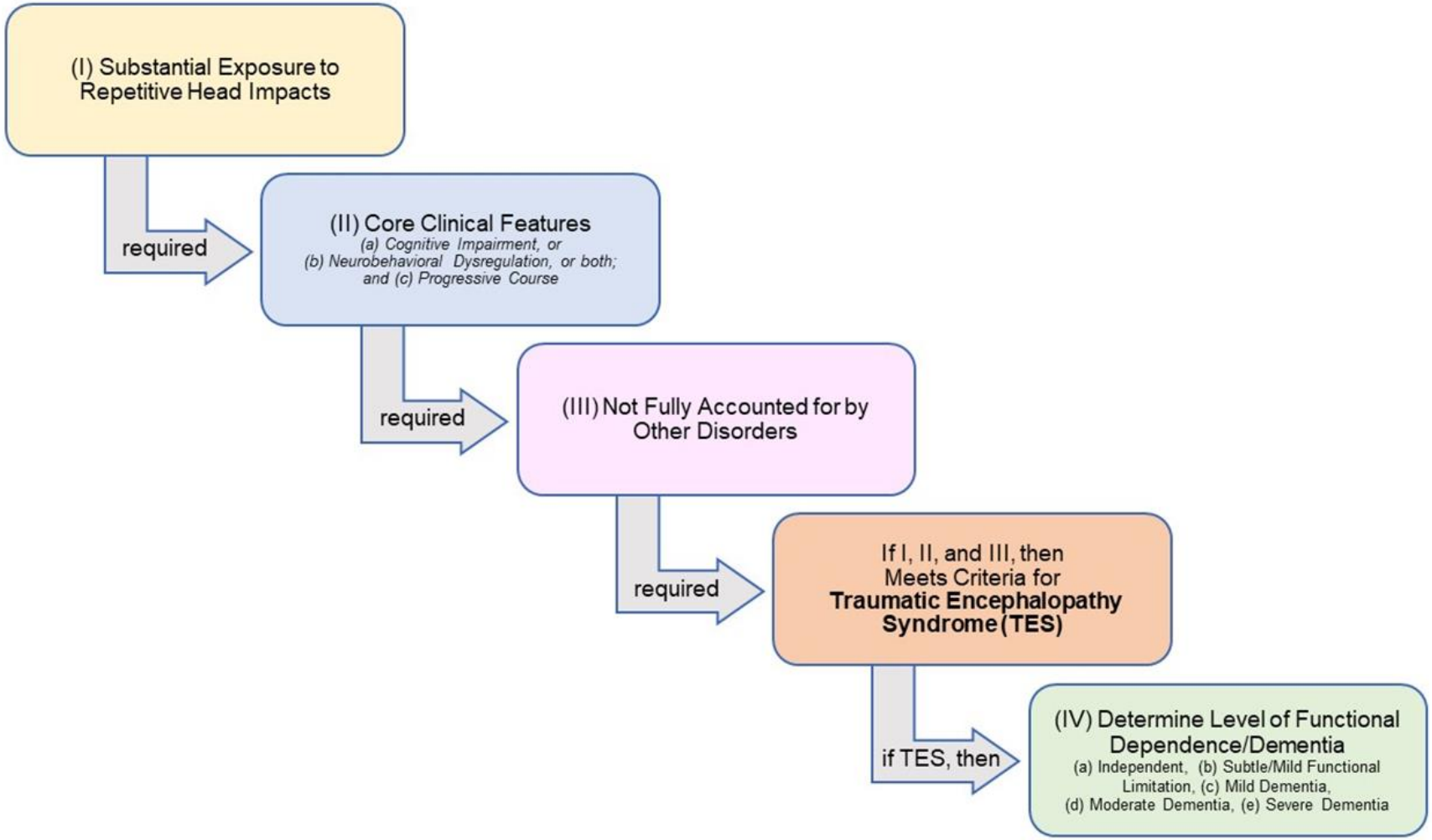
Neurology® 2021;96:848-863. doi:10.1212/WNL.0000000000011850

Stepwise Process for Utilizing the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome



Stepwise Process for Utilizing the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

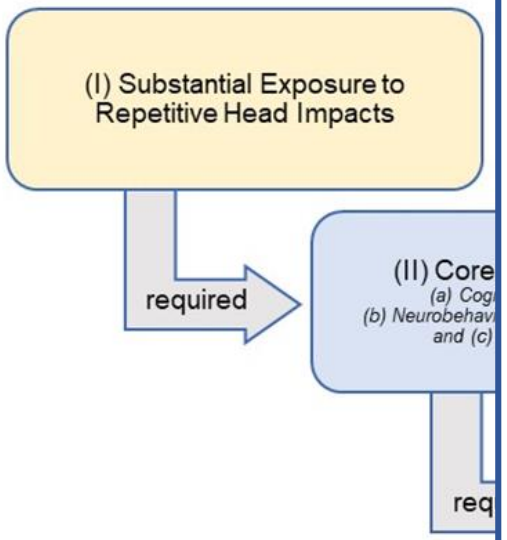
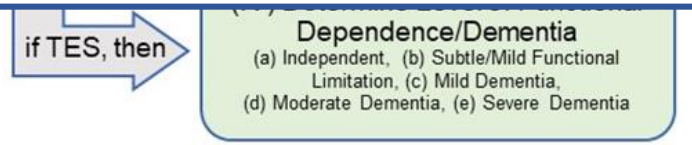


Table 1 Primary Diagnostic Criteria for TES: I. Substantial Exposure to Repetitive Head Impacts

History of substantial exposure to repetitive impacts to the head is required. These impacts may or may not have been associated with clinical symptoms or signs of concussion or TBI. Individuals should be screened for multiple possible sources of exposure over a lifetime. Examples of sources of substantial exposure to RHIs include the following:
Involvement in high-exposure contact or collision sports such as (but not limited to) boxing, American (tackle) football, ice hockey, soccer, rugby, professional wrestling, mixed martial arts, and some other sports with high risk of exposure to RHIs (e.g., motocross and bull riding).
For American football, a minimum of 5 y of organized play is required. This minimum should include ≥2 y at the high school level or beyond. [The inclusion of level of play (i.e., high school) is based on clinical judgment, with limited evidence]. Nearly all of the participants in a published study establishing the 5-y threshold played at least high school level football[1]
Exposure risk thresholds for other contact or collision sports, or combinations of contact/collision sports, have not yet been established but should be a substantial number of years (e.g., ≥ 5 y) at a level of play involving routine RHIs.
Military service involving RHIs, including (but not limited to) combat exposure to multiple blast and other explosions, noncombat exposure to explosions (including breacher training—blasting and forced opening of locked doors), or multiple blows to the head over an extended period of time (e.g., pugil stick training—repeated blows with a padded military training weapon).
Exposure risk thresholds for military service have not yet been established.
Other sources involving multiple head impacts over an extended period of time, including (but not limited to) domestic violence (or intimate partner violence), head banging, and vocational activities such as breaching locked doors and other barriers by first responders.
Exposure risk thresholds for other sources have not yet been established.
Abbreviations: RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome.



Stepwise Process for Utilizing the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

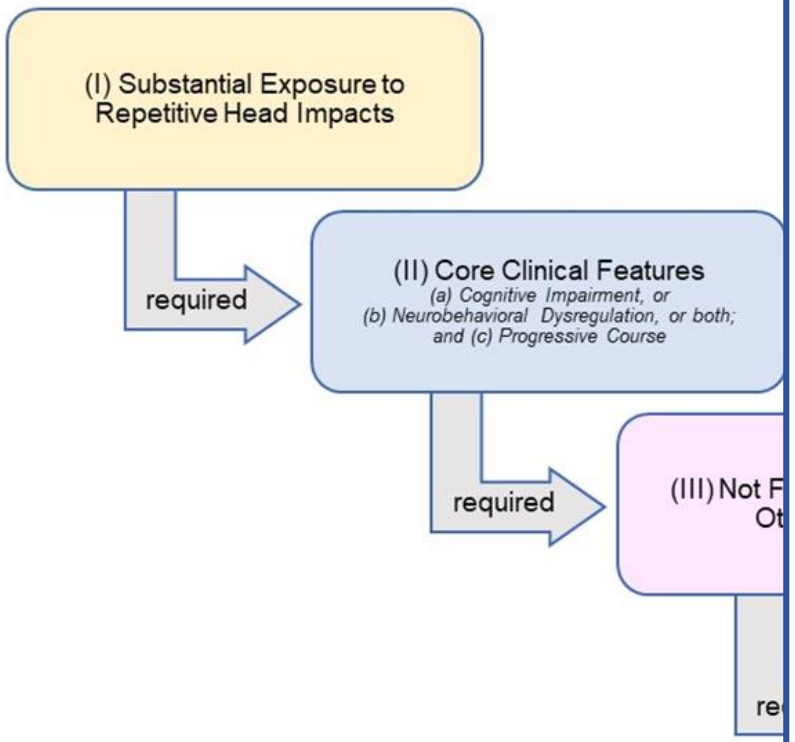


Table 2 Primary Diagnostic Criteria for TES: II. Core Clinical Features

Cognitive impairment or neurobehavioral dysregulation, or both, is required to meet TES criteria. A progressive course is also required to meet TES criteria.
Cognitive impairment (all 4 are required)
As reported by self or informant, or by clinician's report.
Representing a significant decline from baseline functioning. The determination of baseline level of functioning may be challenging and require clinical judgment in cases where decline may have begun during the period of RHI exposure.
With deficits in episodic memory and/or executive functioning (additional domains may be impaired in addition to these).
Substantiated by impaired performance on formal neuropsychological testing (if available), as defined by performance at a level of at least 1.5 SDs below appropriate norms, accounting for the individual's estimated premorbid functioning. If formal neuropsychological testing is not available, there should be substantial evidence of impairment below expected norms and/or a person's estimated baseline in episodic memory and/or executive functioning on a standardized mental status examination (e.g., MoCA and MMSE) by a clinician experienced in the evaluation of cognition.
Neurobehavioral dysregulation (all 3 are required)
As reported by self or informant, or by clinician's report.
Representing a significant change from baseline functioning. The determination of baseline level of functioning may require clinical judgment in cases where change may have begun during the period of RHI exposure.
With symptoms and/or observed behaviors representing poor regulation or control of emotions and/or behavior, including (but not limited to) explosiveness, impulsivity, rage, violent outbursts, having a short fuse (exceeding what might be described as periodic episodes of minor irritability), or emotional lability (often reported as mood swings), preferably substantiated by standardized measures that demonstrate clinical impairment in these domains. In most cases, standardized measures of neurobehavioral dysregulation will not be available, but there should be substantial evidence of change from a person's baseline. These symptoms and/or observed behaviors do not appear to represent a transient response to life events, e.g., divorce, death of loved one, and financial problems.
Progressive course
There is evidence of progressive worsening of these clinical features over a period of at least 1 y in the absence of continued exposure to RHIs or TBI. The evidence should be supported by serial standardized testing (if available) or clear history supporting a change in functioning over time (e.g., clinician reports, job performance evaluations, or self- or informant report).

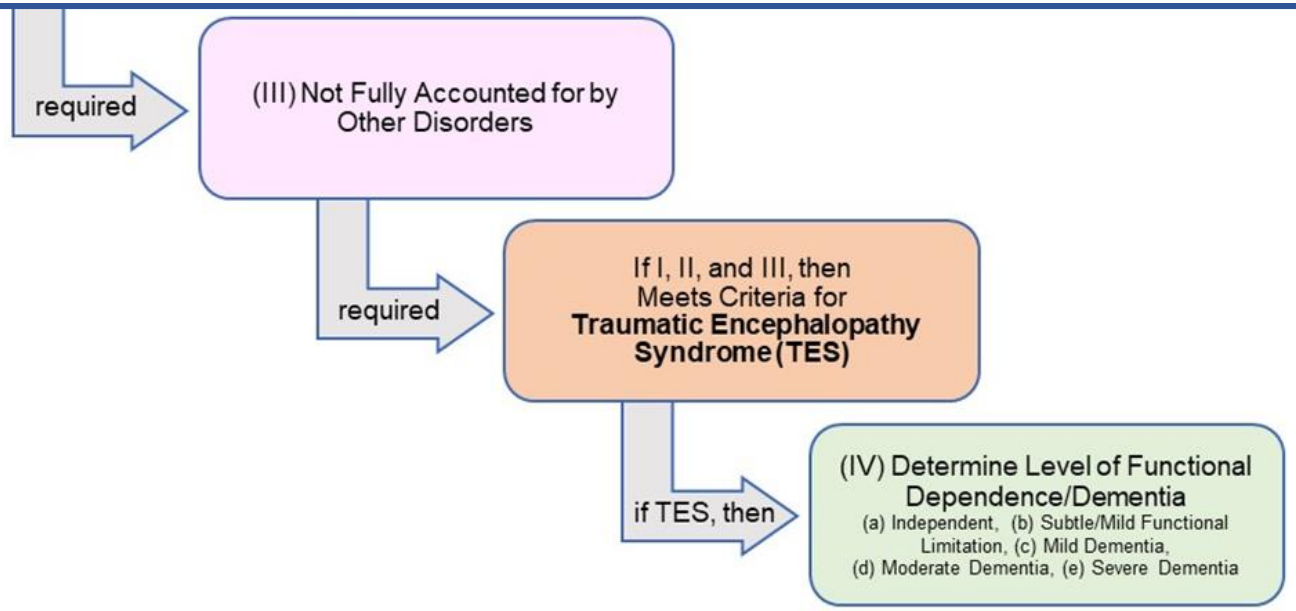
Abbreviations: RHI = repetitive head impact; TBI = traumatic brain injury; TES = traumatic encephalopathy syndrome.

Stepwise Process for Utilizing the NINDS Consensus Diagnostic Cri

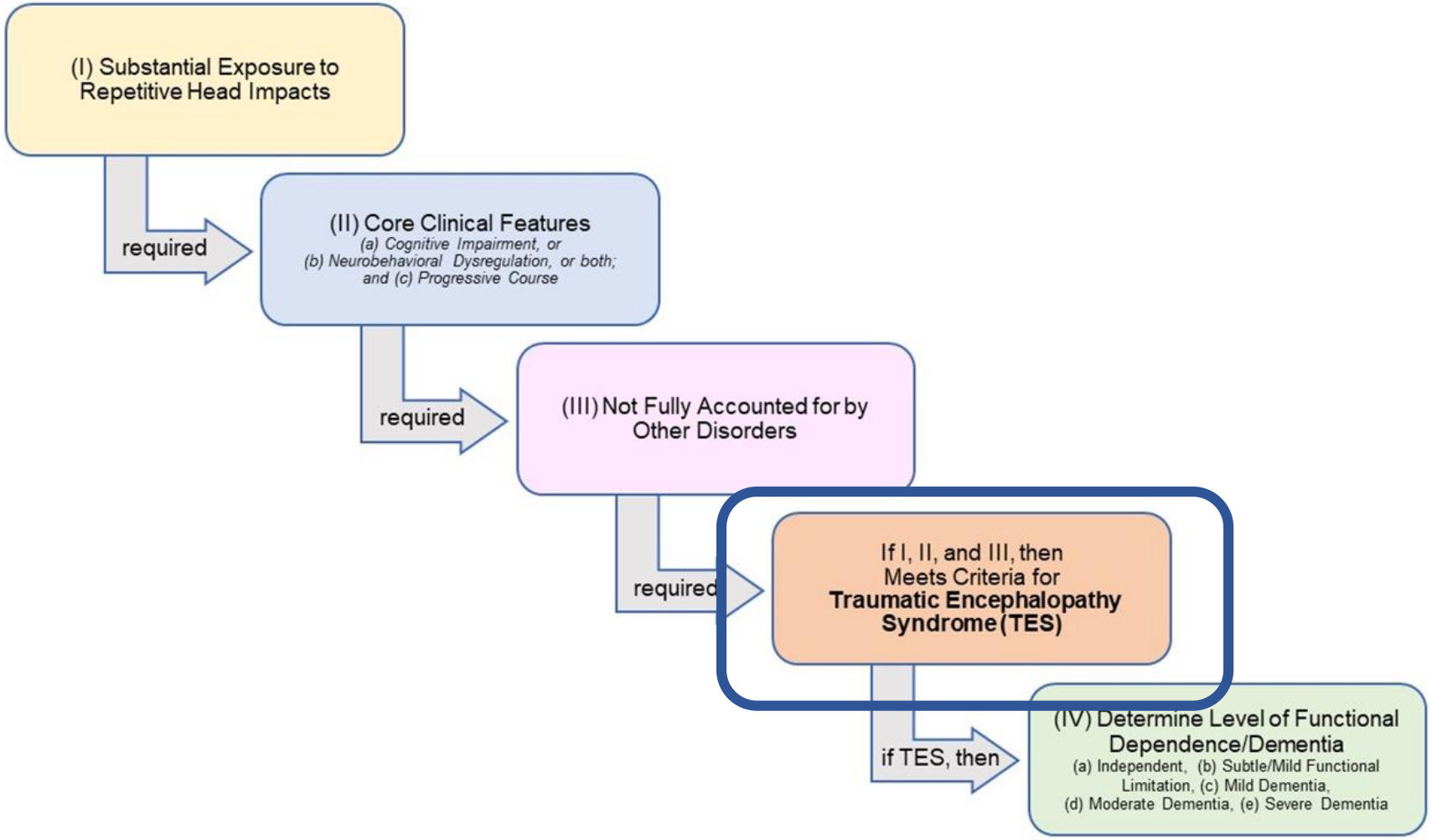
Table 3 Primary Diagnostic Criteria for TES: III. Not Fully Accounted for by Other Disorders

The pattern of the cognitive deficits is not fully accounted for by other preexisting, established, or acquired nondegenerative nervous system, medical, or psychiatric disorders and conditions.
The core clinical feature of neurobehavioral dysregulation, if present, is not fully accounted for by other preexisting, established, or acquired nondegenerative nervous system, medical, or psychiatric disorders and conditions.
Comorbid diagnosis of another neurodegenerative disease does not exclude a TES diagnosis. However, TES may be excluded if, based on clinical judgment, the clinical features and any available biomarkers are fully accounted for by another neurodegenerative disorder.
Comorbid diagnosis of substance use disorder, PTSD, mood or anxiety disorders, or a combination of these can be present and do not exclude a TES diagnosis, unless they are determined to account for all core clinical features.

Abbreviations: PTSD = posttraumatic stress disorder; TES = traumatic encephalopathy syndrome.



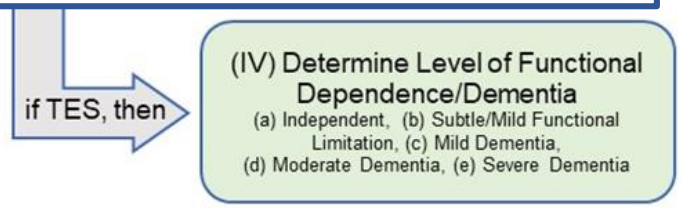
Stepwise Process for Utilizing the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome



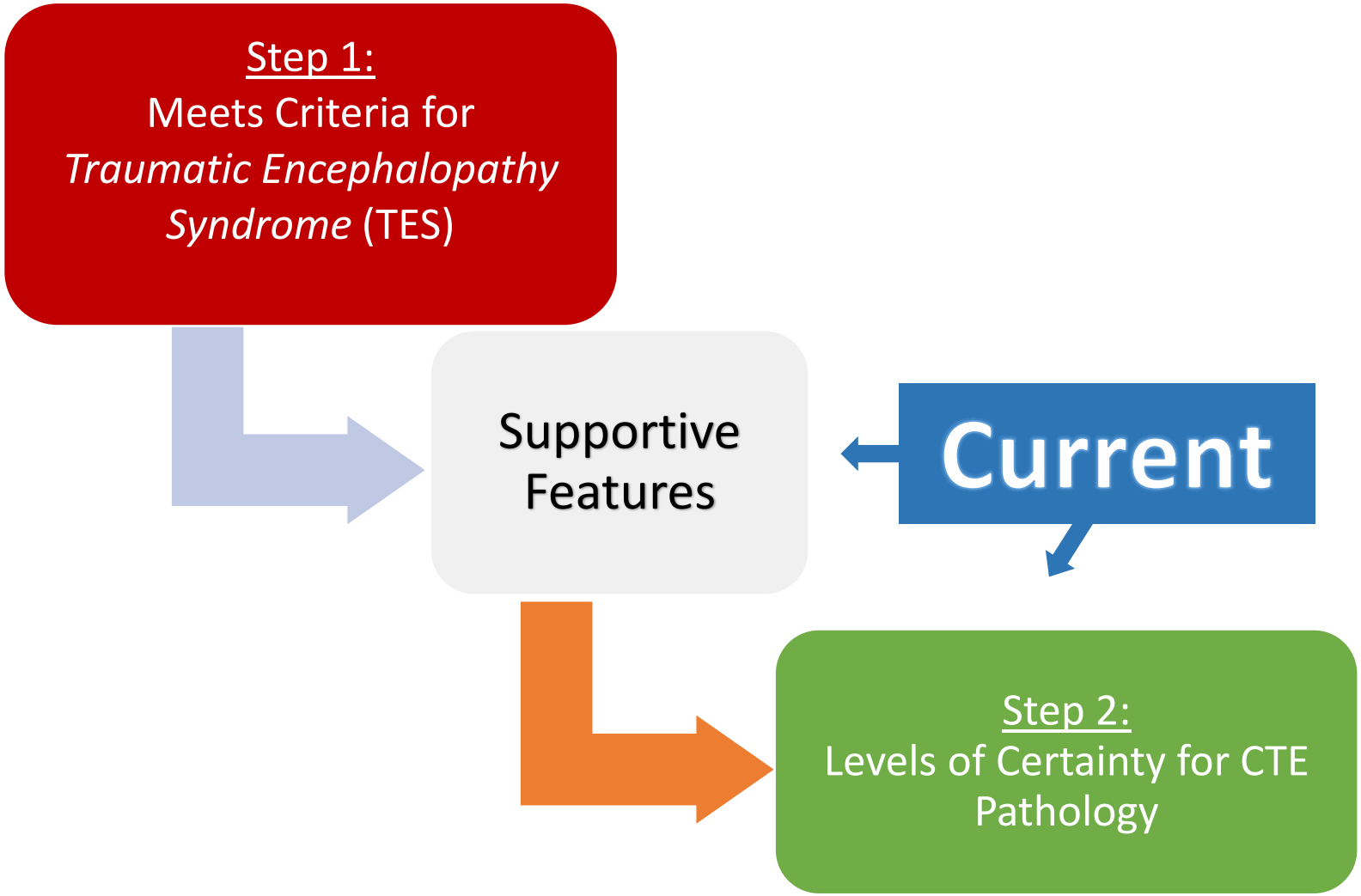
Stepwise Process for Utilizing the NINDS Consensus Diagnostic

Table 4 Primary Diagnostic Criteria for TES: IV. Level of Functional Dependence/Dementia

The level of functional dependence should be based on the impact of cognitive impairment and/or neurobehavioral dysregulation and not on physical limitations or medical illness. Information is obtained from self-report, informant, and/or clinical records. Functional dependence levels (other than independent) should represent a change from previous baseline functioning.
Independent Independent at usual level in job, household responsibilities, or family, social, and community roles. Able to engage in hobbies and intellectual activities at usual levels; fully independent instrumental and basic activities of daily living (ADLs).
Subtle/mild functional limitation Slightly reduced performance in job, household responsibilities, or family, social and community roles; slight problems in hobbies and intellectual interests reported; mostly independent but may be more challenged in some instrumental ADLs (e.g., managing money [e.g., paying bills and completing taxes], cleaning and maintaining the house, preparing meals, shopping for groceries and necessities, transportation within the community [e.g., driving and using public transportation], medication management, using the telephone [mobile or landline]) and fully independent in basic ADLs (personal hygiene and grooming [e.g., brushing/combing/styling hair], toilet hygiene [e.g., getting to the toilet, cleaning oneself, and getting back up], bathing/showering, dressing, self-feeding, and functional mobility [e.g., ability to walk, get in and out of bed, and get into and out of a chair]).
Mild dementia Definite impairment of instrumental ADLs; may be engaged in some home, family, social, and community activities; more difficult activities abandoned; needs cues for some basic ADLs.
Moderate dementia Not independent but can be taken to some functions outside the home; only simple chores preserved; very restricted interests; needs assistance with basic ADLs.
Severe dementia Cannot participate in functions outside the home; no significant function in home; impaired basic ADLs; not independent with self-care; frequently incontinent.



Two-Step Research Diagnostic Approach



Supportive Features Used to Determine Provisional *Levels of Certainty for CTE Pathology*

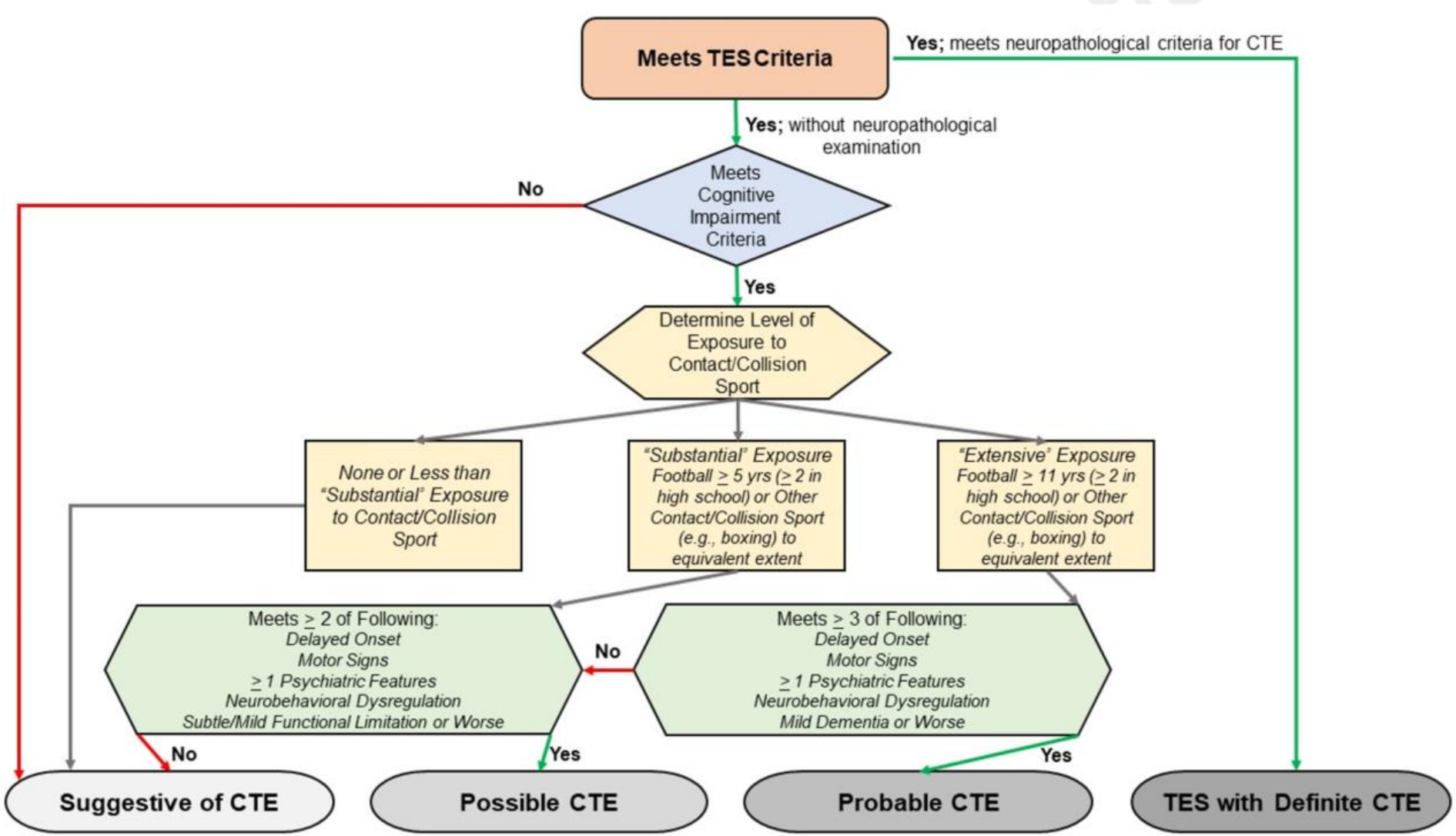
Depression, Anxiety, Apathy, Suicidality are NOT Core Clinical Features of TES

Table 5 Supportive Features Used in Determining Provisional Levels of Certainty for CTE Pathology

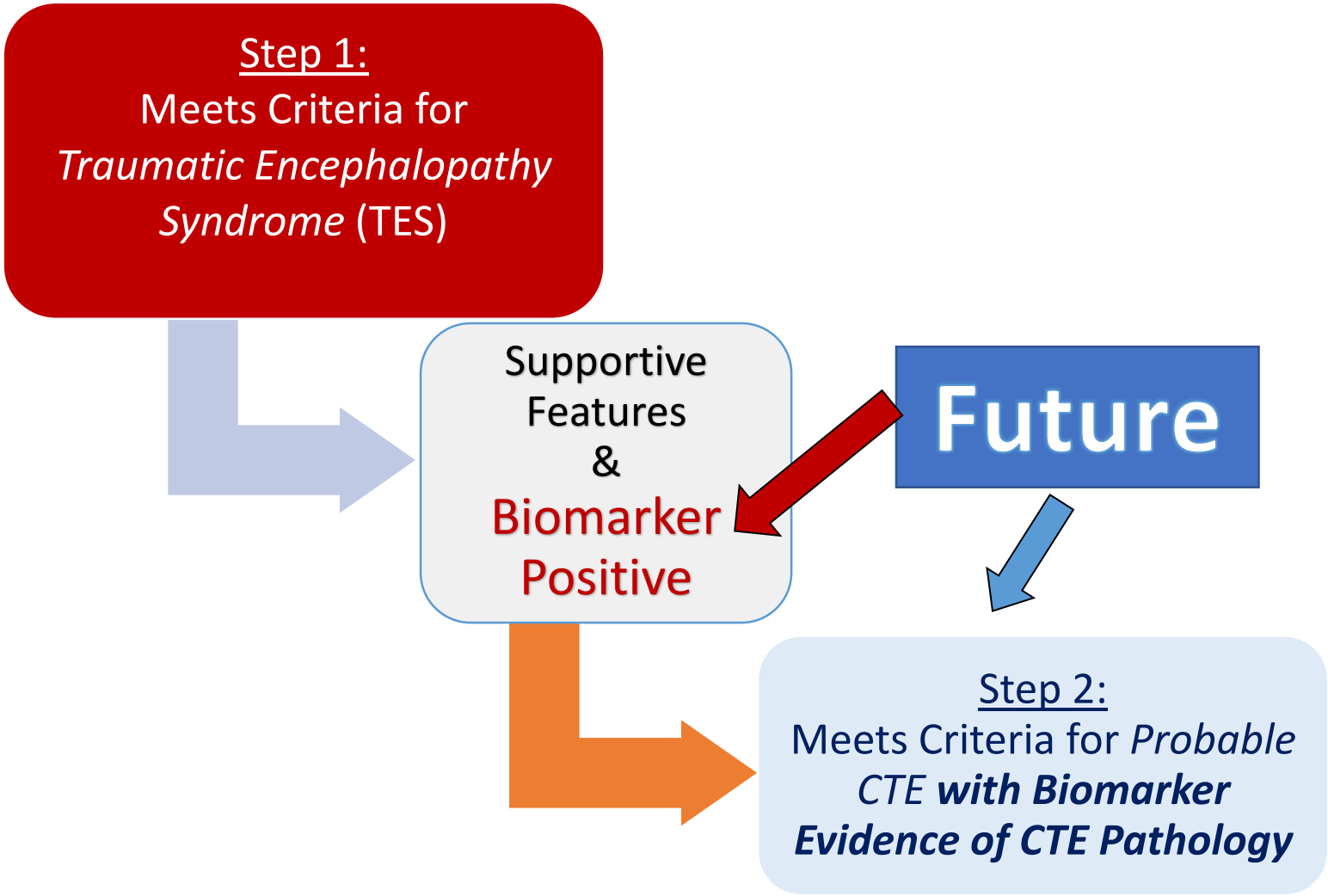
The following 3 supportive features are used in determining the provisional levels of certainty for chronic traumatic encephalopathy (CTE) pathology (table 6). These features are frequently present in individuals with underlying CTE pathology, but have insufficient predictive value to qualify as core clinical features.

Delayed onset
Core clinical features begin following a clearly established period of stable functioning after the RHI exposure ends. (A minimum time period of stability before onset and progression of symptoms has not been established but should be substantial [i.e., years] to suggest a history consistent with a degenerative disorder rather than problems associated with TBI or other preexisting conditions.)
Motor signs
Parkinsonism: bradykinesia, rigidity, rest tremor, and parkinsonian gait disorder; these motor signs should not be more consistent with the clinical features of nonparkinsonian neurologic conditions or primary orthopedic problems.
Other motor signs: dysarthria, ataxia, and imbalance; these motor signs should not be more consistent with the clinical features of other neurologic conditions or primary orthopedic problems.
Motor neuron disease: *Weakness, dysphagia, other lower motor neuron signs (fasciculations and muscle atrophy), and other upper motor neuron signs (spasticity, hyperreflexia, extensor plantar response, and spastic dysarthria); a diagnosis of amyotrophic lateral sclerosis (ALS) would meet this criterion but is not necessary.
Psychiatric features
These supportive psychiatric features have not been accounted for by neurobehavioral dysregulation described in the core clinical features. They may occur individually or in combination, should represent a clear change from baseline, and should be persistent (i.e., months to years) or progressive. These features can be based on self- or informant report, a history of treatment, or clinician's report. The supportive psychiatric features include the following:
Anxiety: pervasive worries, excessive fears, agitation, or obsessive or compulsive behavior (or both); a formal diagnosis of anxiety disorder would meet this criterion but is not necessary. If available, scores on an established, validated anxiety scale should indicate a moderate level of anxiety or higher.
Apathy: loss of interest in usual activities and loss of motivation or drive. If available, scores on an established, validated apathy scale should indicate a moderate level of apathy or higher.
Depression: feeling overly sad, dysphoric, or hopeless, with or without a history of suicidal thoughts or attempts; a formal diagnosis of major depressive disorder or persistent depressive disorder would meet this criterion but is not necessary. These symptoms should not be a time-limited reaction to an event (e.g., death of family member, illness, and trauma). If available, scores on an established, validated depression scale should indicate a moderate level of depression or higher.
Paranoia: delusional beliefs of suspicion, persecution, or unwarranted jealousy; a formal diagnosis of a psychotic disorder would meet this criterion but is not necessary. If available, scores on an established, validated paranoia scale should indicate a moderate level of paranoia or higher.

Flow Diagram for Determining Provisional Levels of Certainty for CTE Pathology



Two-Step Clinical Diagnostic Approach

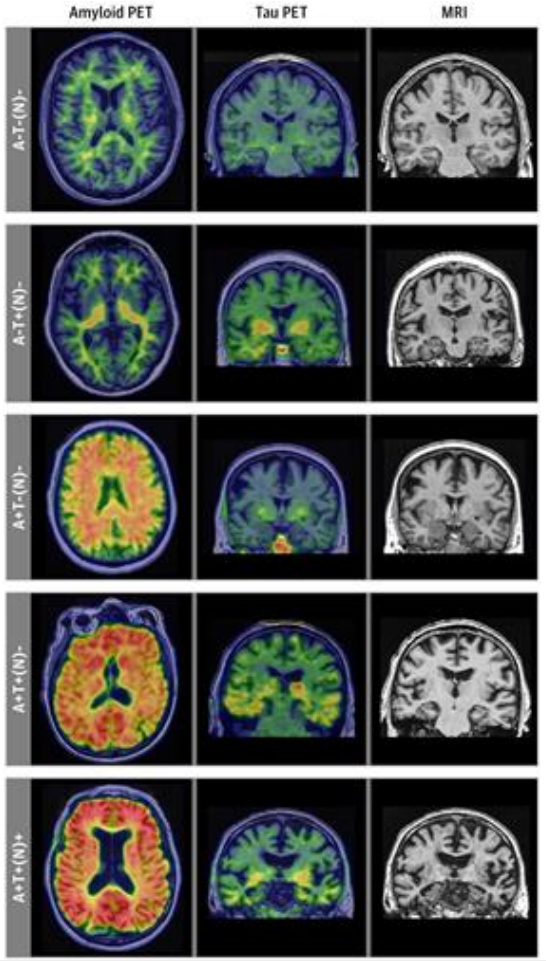


Diagnosis of CTE During Life: Step 3

- Develop Sensitive and Specific Biomarkers for CTE Pathology

Biomarkers for CTE: Similar to Alzheimer's Disease AT(N) Framework

- Jack et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535–62.
  - Division of the underlying disease (i.e., Alzheimer's disease) from the clinical syndromes associated with the disease (i.e., MCI, dementia)
  - Based on premise that defining AD purely by its clinical presentation is artificial and that, with advances in biomarker development and accuracy, the shift has been to view AD as a clinico-pathophysiological entity
- **A** = Aggregated b-amyloid or associated pathophysiology
  - CSF Ab 42, or 42/40 ratio
  - Amyloid PET
- **T** = Aggregated tau (neurofibrillary tangles) or associated pathophysiology
  - CSF p-tau 181
  - Tau PET
- **(N)** = Neurodegeneration/ neuronal injury
  - Anatomic MRI
  - FDG PET
  - CSF total tau
- Since these initial publications, tremendous advances have been made in **plasma** (and CSF) biomarkers of b-amyloid, p-tau, and measures of neurodegeneration and inflammation



From: **Associations of Amyloid, Tau, and Neurodegeneration Biomarker Profiles With Rates of Memory Decline Among Individuals Without Dementia**

JAMA. 2019;321(23):2316-2325. doi:10.1001/jama.2019.7437

Biomarkers for CTE: Similar to Alzheimer's Disease AT(N) Framework

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  - Plasma Ab or 42/40 ratio
  - Amyloid PET
- **T** = Aggregated tau (neurofibrillary tangles) or associated pathophysiology
  - CSF p-tau 181, 217, 231, others
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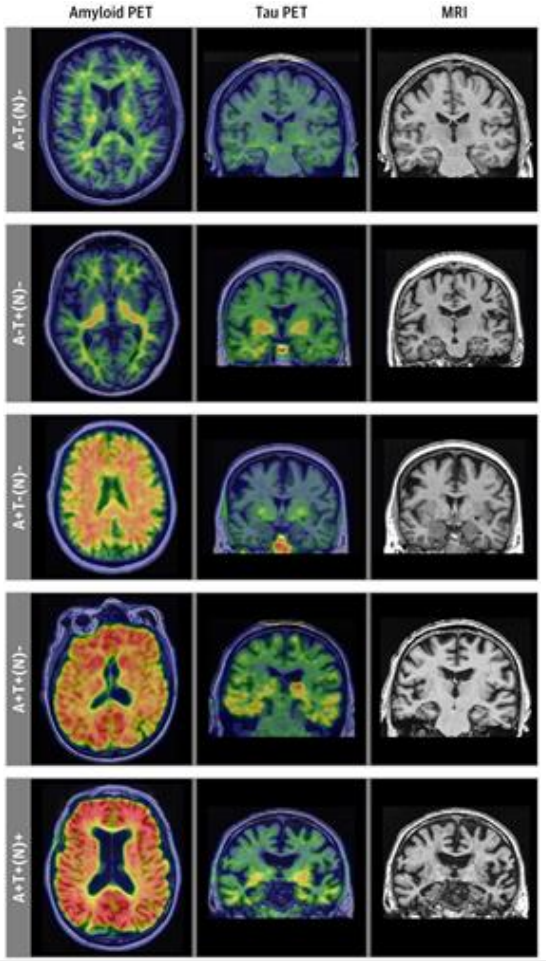
  - FDG PET
  - CSF total tau, NfL
  - Plasma total tau, NfL, GFAP,



From: **Associations of Amyloid, Tau, and Neurodegeneration Biomarker Profiles With Rates of Memory Decline Among Individuals Without Dementia**

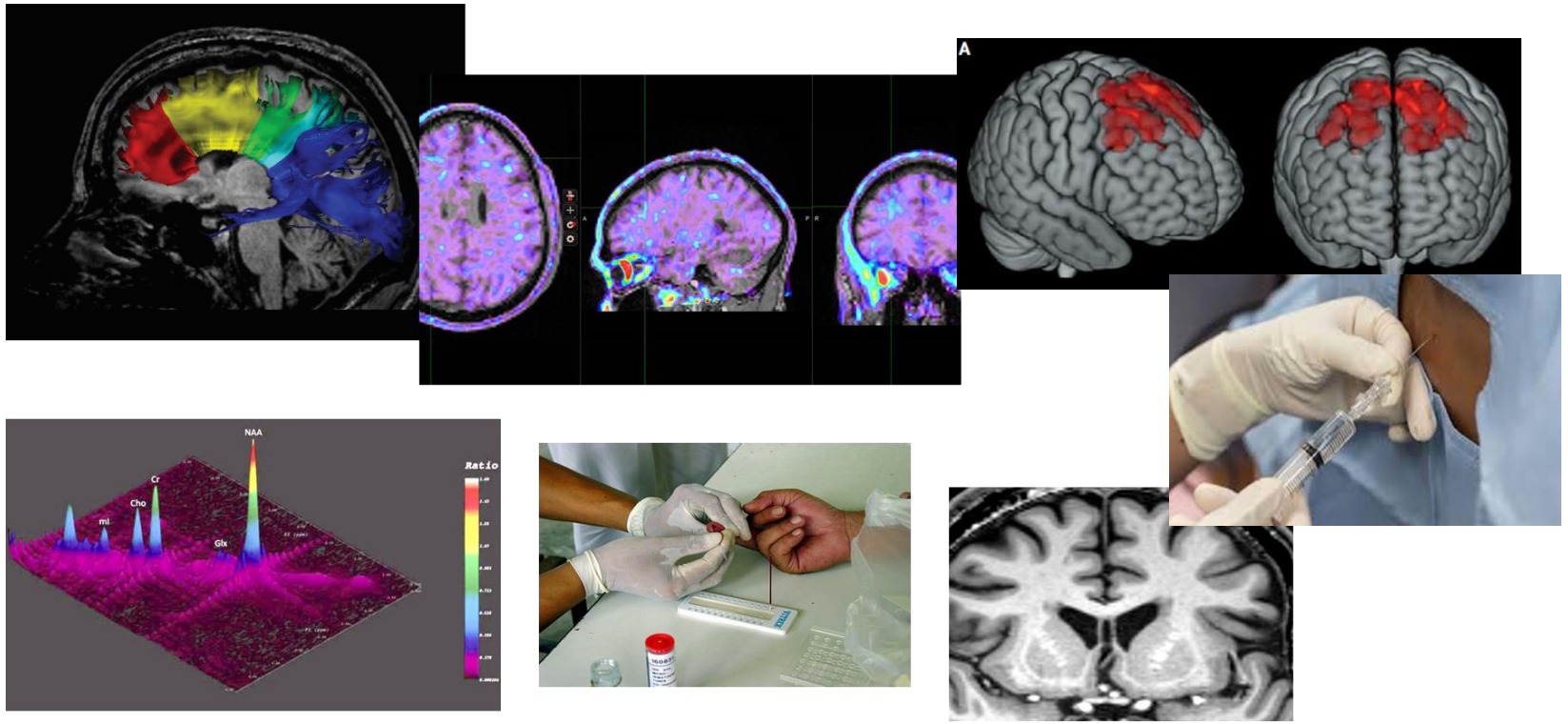
JAMA. 2019;321(23):2316-2325. doi:10.1001/jama.2019.7437

Biomarkers for CTE: T(N) (WM, Other?) Framework

- **T** = Aggregated tau (neurofibrillary tangles) – early perivascular at depths of cerebral sulci with later spread; changes in isomers from early (4R) to late (3R)
  - CSF p-tau 181, 217, 231, others
  - Plasma p-tau 181, 217, 231, others
  - Tau PET
- **(N)** = Neurodegeneration/ neuronal injury
  - Anatomic MRI
  - CSF total tau, NfL
  - Plasma total tau, NfL, GFAP
- **?WM** = Stay tuned (Dr. Alosco)

Potential CTE Biomarkers

- Several *preliminary* studies have examined various potential fluid and neuroimaging biomarkers of CTE, in living participants at high risk for CTE (e.g., former American football players), and in deceased individuals with neuropathologically-confirmed CTE diagnosis



DETECT

Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests

2011-2016

Goal:

To Examine Potential Biomarkers to Diagnose CTE During Life

Principle Investigator: Robert A. Stern

NIH R01 Grants R01NS078337 and R56NS078337

funded by:

National Institute of Neurologic Diseases and Stroke
National Institute of Aging
National Institute of Childhood Health and Development

DETECT Study - Subjects

- ~100 former NFL players (CTE High Risk)
  - ages 40-69
  - positions with highest exposure to RHI
  - currently symptomatic
- 30+ controls (CTE No Risk)
  - same age
  - no brain trauma exposure
  - asymptomatic

DETECT Study Publications

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Potential Fluid Biomarkers for CTE

- **Non-Specific**
  - CSF
    - total tau
    - NfL
    - GFAP
    - sTREM2
  - Plasma
    - total tau
    - exosomal total tau
    - NfL
    - GFAP
  - CSF and Plasma measures of:
    - cytokines, chemokines, vascular injury, angiogenesis, TH17

- **Specific to CTE?**
  - CSF
    - p-tau 217
    - p-tau 231
    - p-tau 181
    - p-tau other epitopes?
  - Plasma
    - p-tau 217
    - p-tau 231
    - p-tau 181
    - p-tau other epitopes?
  - Proteomic Profiling of CSF and/or Plasma

Potential Neuroimaging Biomarkers for CTE

- **Non-Specific**
  - Structural MRI
    - Cavum Septum Pellucidum
    - Volumetrics and Cortical Thickness
    - FLAIR
    - DTI
  - Functional MRI
    - resting state fMRI
  - MRS
  - FDG PET
  - Amyloid PET (negative)

- **Specific to CTE?**
  - Tau PET
    - flortaucipir?
    - Others, newer generation
    - Different radiotracers for different stages of disease (4R, 3R/4R, 3R)

PET Scans for Abnormal Tau in Alzheimer's Disease and Other Tauopathies

- PET tracers that bind to specific p-tau *species* is a major area of research in Alzheimer's disease, PSP, FTD, and other *tauopathies*
- Flortaucipir (T807, AV1451) PET tracer designed to detect abnormal tau in Alzheimer's disease (3R/4R Tau)
- Big Question: Is Flortaucipir appropriate for CTE tau?
  - FDA says NO; for now, only for Alzheimer's disease

The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2019;380:1716-25

ORIGINAL ARTICLE

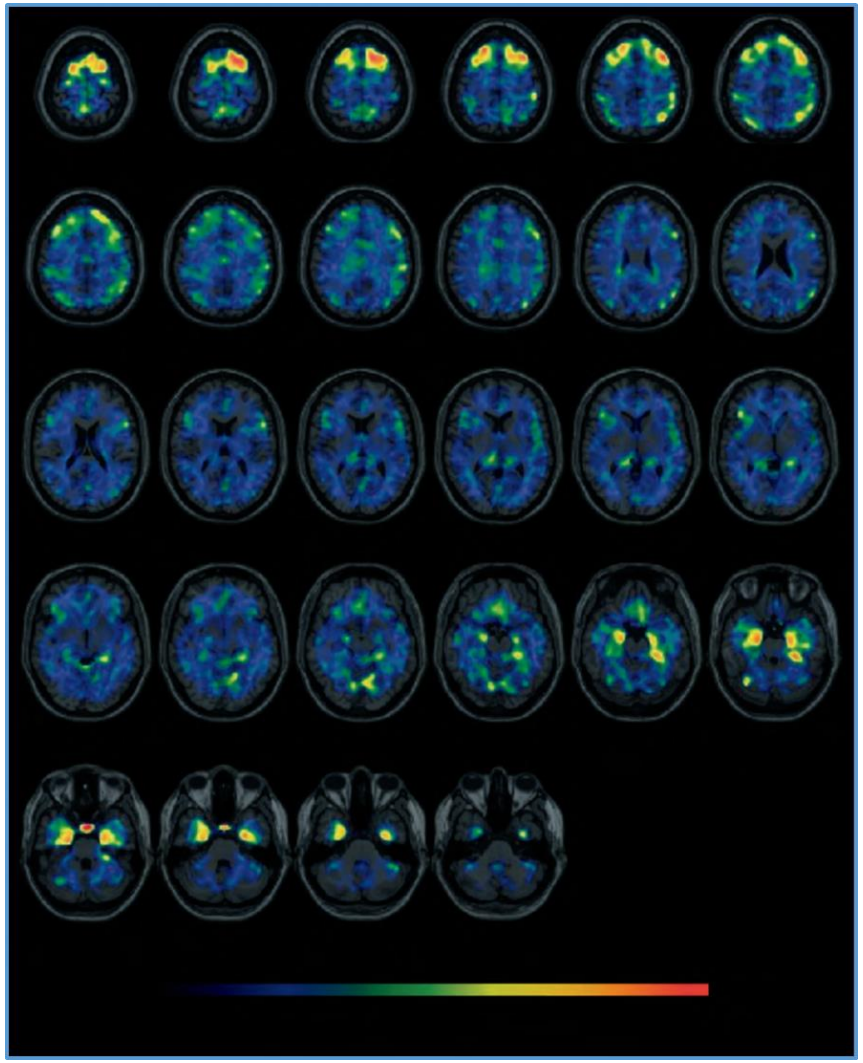
Tau Positron-Emission Tomography in Former National Football League Players

Robert A. Stern, Ph.D., Charles H. Adler, M.D., Ph.D., Kewei Chen, Ph.D., Michael Navitsky, M.S., Ji Luo, M.S., David W. Dodick, M.D., Michael L. Alosco, Ph.D., Yorghos Tripodis, Ph.D., Dhruman D. Goradia, Ph.D., Brett Martin, M.S., Diego Mastroeni, Ph.D., Nathan G. Fritts, B.A., Johnny Jarnagin, B.A., Michael D. Devous, Sr., Ph.D., Mark A. Mintun, M.D., Michael J. Pontecorvo, Ph.D., Martha E. Shenton, Ph.D., and Eric M. Reiman, M.D.

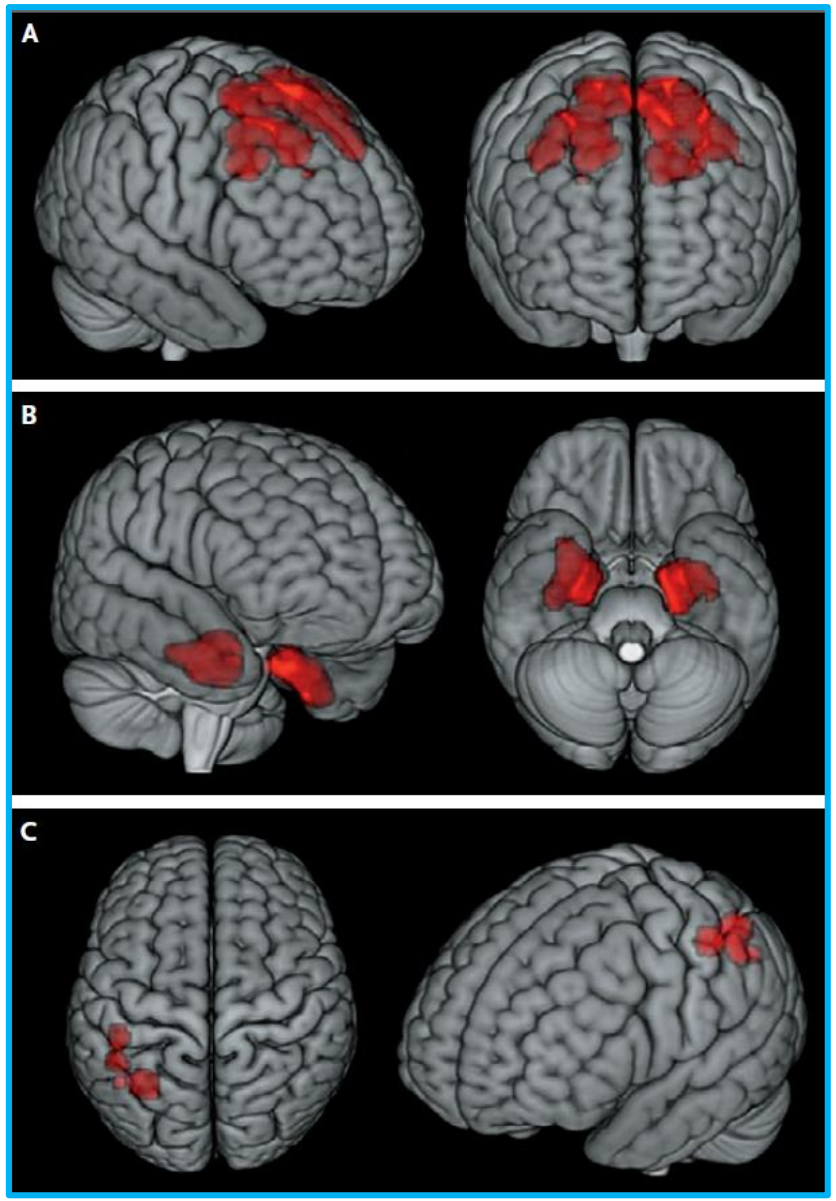
- **Participants**
- 26 symptomatic former NFL players
  - 40-69 years, > 2 yrs in NFL, > 12 yrs total tackle football, and self-reported complaints of cognitive, behavioral, and mood symptoms reported at telephone screening
- 31 asymptomatic controls
  - male, 40-69 years, no cognitive symptoms, and no history of traumatic brain injury

- **Clinical Measures**
  - All participants were administered the MMSE
  - Former NFL players also administered a series of neuropsychological tests and neuropsychiatric measures
- **Imaging**
  - Each participant had flortaucipir (FTP) tau PET, florbetapir amyloid PET, and T1-weighted volumetric brain MRI

Results – Flortaucipir Tau PET

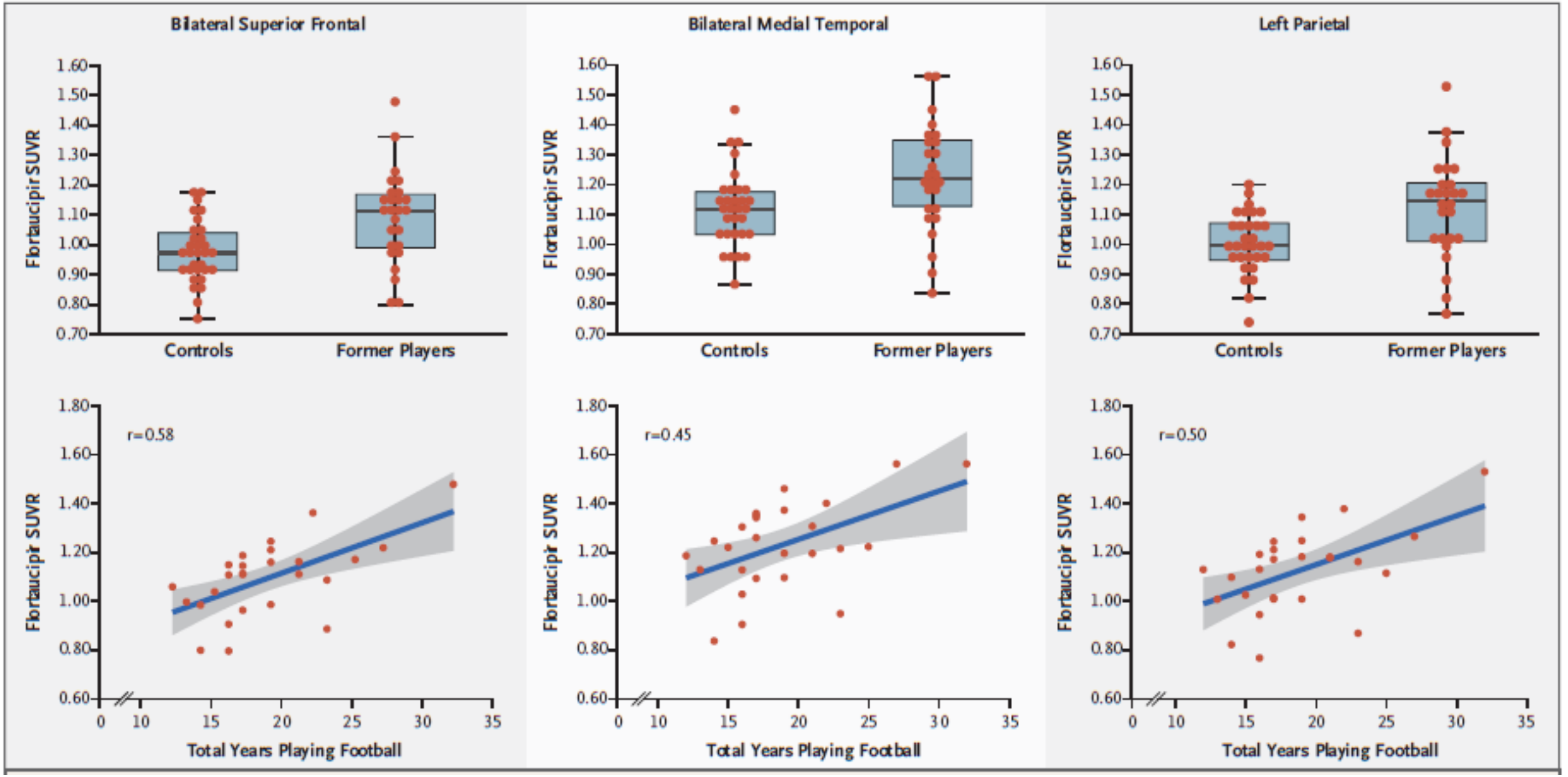


Statistical Parametric Maps of Flortaucipir Positron-Emission Tomography (PET). The maps show voxels with higher regional cerebellar gray-matter flortaucipir standard uptake value ratios (SUVRs) among former National Football League (NFL) players than among controls ($P<0.005$, uncorrected for multiple regional comparisons).



Results

Three-Dimensional Stereotactic Surface Projection Maps of Flortaucipir PET.
Higher flortaucipir SUVRs in the former-player group than in the control group were found in the bilateral superior frontal (Panel A), bilateral medial temporal (Panel B), and left parietal (Panel C) regions of the brain. The regions shown in red in these surface projection images correspond to the statistical parametric maps after restriction of the map to those clusters of at least 100 contiguous voxels associated with higher regional cerebellar gray-matter flortaucipir SUVRs in the former-player group than in the control group ($P<0.005$, uncorrected for multiple regional comparisons).


Bilateral Superior Frontal
Bilateral Medial Temporal
Left Parietal
Flortaucipir SUVR
1.60
1.50
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
Controls
Former Players
r=0.58
r=0.45
r=0.50
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0
10
15
20
25
30
35
Total Years Playing Football

Results – Clinical Associations?

- **Clinical Measures**: There were NO significant relationships between flortaucipir Tau PET levels and the clinical measures of memory, executive functioning, or mood/behavior
- Possible explanations:
  - Insufficient power due to small sample size and the patchy, focal distribution of tau deposition observed in postmortem studies of CTE
  - Exclusion of asymptomatic former NFL players from the study may have reduced the ability to detect a relationship between flortaucipir uptake and clinical features of CTE
  - Flortaucipir may not be that specific to CTE p-tau
  - Tau pathology alone may not be associated with the neuropsychiatric symptoms and cognitive impairment described in former American football players, boxers, and others with a history of extensive repetitive head impact exposure

CTE Clinical Diagnosis: Are we there yet?

- No…we are closer, but not there yet
- Some of the many questions:
- What clinical features are specifically related to p-tau pathology?
  - Initial sulcal depth p-tau deposition
  - Later medial temporal involvement
  - p-tau-related neurodegeneration
- Is the *cognitive* impairment from tauopathy?
- Is the *neurobehavioral dysregulation* from white matter degeneration?

CTE Clinical Diagnosis: Are we there yet?

- **Are some of the clinical features due to non-p-tau CTE-related and/or unrelated pathology**
  - Inflammatory responses
  - Chronic or progressive changes from single moderate-severe TBI
  - White matter damage (arteriosclerosis vs rarefaction)
  - Comorbid AD, other neurodegenerative diseases, proteinopathies
    - TDP-43
    - beta amyloid
    - cerebral amyloid angiopathy
    - alpha synuclein

CTE Clinical Diagnosis: Are we there yet?

- Are the clinical features associated with other factors:
  - Idiopathic psychiatric disorders
  - Sleep disorders
  - Chronic pain
  - Racial and associated inequities in social/cultural determinants of health
- Are all clinical features progressive?
- Can a *negative* amyloid PET be a "biomarker" for CTE (i.e., in a cognitively impaired individual with substantial RHI exposure who does not meet Dx criteria for other disorders)?
- Do current tau PET radiotracers actually detect CTE p-tau isoforms?
- Do current plasma and CSF p-tau analytes detect CTE p-tau epitopes?

Current Research

- Several studies currently underway to better understand the long-term effects of RHI, the clinical course of CTE, and potential biomarkers, including (but not limited to):
  - Professional Fighters Brain Health Study at the Cleveland Clinic Lou Ruvo Center
  - Concussion Assessment, Research, and Education (CARE) Consortium funded by the National Collegiate Athletic Association and the U.S. Department of Defense
  - Focused Imaging for the Neurodegenerative Disease-Chronic Traumatic Encephalopathy (FIND-CTE) at BU (Alosco) and UCSF (Rabinovici)
  - And…

DIAGNOSE CTE
Research Project

Diagnostics, **I**maging, **A**nd **G**enetics **N**etwork
for the **O**bjective **S**tudy and **E**valuation
of **C**hronic **T**raumatic **E**ncephalopathy (CTE)

$17 Million grant funded by the
National Institute of Neurological Disorders & Stroke
(U01NS093334; "Chronic Traumatic Encephalopathy:
Detection, Diagnosis, Course, and Risk Factors")

7+ Year Multicenter Study (2015-2022+)

Robert A. Stern, Ph.D., Principal Investigator (Contact)

Boston University Chobanian & Avedisian School of Medicine

NFL health officials confronted NIH about researcher selection

ESPN

Steve Fainaru and Mark Fainaru-Wada Jan 21, 2016

Three of the NFL's top health and safety officers confronted the National Institutes of Health last June after the NIH selected a Boston University researcher to lead a major study on football and brain disease, Outside the Lines has learned.

The new information contradicts denials by the NFL and a foundation it partners with that the league had any involvement or input in the fate of a $16 million study to find methods to diagnose -- in living patients -- chronic traumatic encephalopathy, a brain disease found in dozens of deceased NFL

The Washington Post

Redskins/NFL

NFL tried to influence 'unrestricted' research gift, Congressional report says

Rep. Frank Pallone said the NFL's actions regarding an NIH grant 'fit a longstanding pattern of attempts to influence the scientific understanding of degenerative diseases and sports-related head trauma' (Julio Cortez/AP)

By Rick Maese May 23

While the NFL pledged money, held news conferences and issued media releases about its commitment to player health, safety and concussion research, the league also was engaged in a campaign to steer money away from a prominent Boston University researcher and attempted to redirect it to members of its own committee on brain injuries, according to a scathing Congressional report.

The 91-page report issued Monday by the Democratic members of the House Energy and Commerce Committee, led by ranking member Rep. Frank Pallone Jr. (D-N.J.), charged league officials with trying to influence a major U.S. government research study on football and brain disease after agreeing to an unconditional donation to fund research. The report found the NFL's actions "fit a long-standing pattern of attempts to influence the scientific understanding of the consequences of repeated head trauma."

"The NFL attempted to use its 'unrestricted gift' as leverage to steer funding away from one of its critics," the report stated.

The National Institutes of Health stood by its selection of Robert Stern and a group of researchers from Boston University. The NFL ultimately did not fund the $16 million study; the costs were instead absorbed by taxpayers, according to the report.

U.S. House of Representatives
Committee on Energy and Commerce
Ranking Member Frank Pallone, Jr.
Democratic Staff Report

The National Football League's Attempt to Influence Funding Decisions at the National Institutes of Health

May 2016

PRO FOOTBALL

$16 Million for Brain Research, but $0 from N.F.L.

By KEN BELSON DEC. 22, 2015

The New York Times

Dr. Robert Stern, a professor at Boston University's School of Medicine, said he was optimistic that a project would lead to answers about chronic traumatic encephalopathy. Marcus Yam for The New York Times

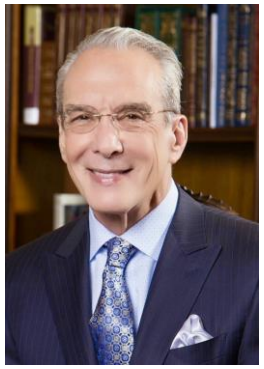
Researchers at several universities and research institutes were awarded almost $16 million Tuesday to find a way to diagnose, while victims are alive, chronic traumatic encephalopathy, a degenerative brain disease linked to repeated head hits in contact sports.

The National Institutes of Health and the National Institute of Neurological Disorders and Stroke issued the seven-year grant as part of a long-term study of brain disease in former N.F.L. and college football players, many of

Co-Principal Investigators

DIAGNOSE CTE Research Project

Jeffrey L. Cummings, M.D., Sc.D.



Joy Chambers-Grundy Professor of Brain Science, Vice Chair for Research, and Director of the Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV)

Dr. Cummings is the recipient of numerous prestigious awards, including the Henderson Award of the American Geriatrics Society (2006), the Ronald and Nancy Reagan Research Award of the national Alzheimer's Association (2008), the Lifetime Achievement Award of the Society for Behavioral and Cognitive Neurology (2017), Distinguished Scientist Award of the American Association of Geriatric Psychiatry (2010), and the Bengt Winblad Lifetime Achievement Award from the national Alzheimer's Association. In 2019, the International Psychogeriatric Association awarded him with the Distinguished Service Award and he received the Alzheimer's Drug Discovery Foundation's Melvin R. Goodes Prize that honors an innovative researcher who has made a significant and lasting impact in the field.

Eric M. Reiman, M.D.

Executive Director, Banner Alzheimer's Institute
Professor of Psychiatry, University of Arizona
University Professor of Neuroscience, Arizona State University
Senior Scientist, Translational Genomics Research Institute (TGen)
Director, Arizona Alzheimer's Consortium

Dr. Reiman is an author of more than 500 publications, a principal investigator of seven current NIH grants, and a member of the National Advisory Council on Aging (NIA Council). He is a recipient of the Potamkin Prize for his pioneering contributions to the study of preclinical AD and the accelerated evaluation of AD prevention therapies.

Martha Shenton, Ph.D.

Professor of Psychiatry and Radiology, Harvard Medical School
Director, Psychiatry Neuroimaging Laboratory
Senior Scientist, Brigham and Women's Hospital
Health Scientist, VA Boston Healthcare System

Dr. Shenton has more than 500 publications and has received several career awards from the National Institute of Mental Health, including a K01 Mentored Award (1988-1993), two K02 Independent Investigator Awards (1994-1999, 1998-2004), and a K05 Senior Scientist Award (2004-2009). She has also been the recipient of the Joseph Zubin Memorial Fund Award for Research in Psychopathology, the William Silen Lifetime Achievement Award for Mentoring, and a Distinguished NARSAD Award.

External Advisory Board (EAB)

DIAGNOSE CTE Research Project

David Knopman, M.D., EAB Chair
Professor of Neurology
Mayo Clinic

Col. Dallas Hack, M.D., MPH (Ret.)
Brain Health Consultant

Brian Hainline, M.D.
Chief Medical Officer, National Collegiate Athletic Association

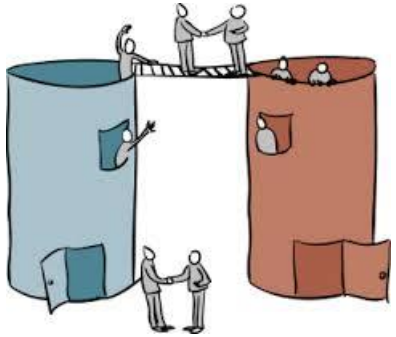
Mike Haynes
Member of the Pro Football Hall of Fame

Thomas McAllister, M.D.
Chair, Department of Psychiatry
Indiana University School of Medicine

Arthur Toga, M.D.
Provost Professor; Director of the Institute for Neuroimaging and Informatics (INI)
University of Southern California

Michael Weiner, M.D.
Professor of Medicine, Radiology, Psychiatry, and Neurology
University of California San Francisco

Breaking Down Silos



DIAGNOSE CTE Research Project

- **Interdisciplinary Science**
  - neurology, neuropsychology, psychiatry, neuroimaging, molecular medicine, neuropathology, exposure science, genetics, biochemistry, biostatistics, bioinformatics, engineering
- **Inter-Institution**
  - Banner Alzheimer's Institute
  - Boston University Schools of Medicine and Public Health
  - Brigham and Women's Hospital, Harvard Medical School
  - Cleveland Clinic Lou Ruvo Center for Brain Health
  - Invicro
  - Mayo Clinic Arizona
  - NYU School of Medicine
  - University of Gothenburg (Sweden)
  - University of Nevada, Las Vegas
  - University of Washington
  - VA Puget Sound
  - Washington University School of Medicine (CNDA)

Specific Aims

DIAGNOSE CTE Research Project

1. Collect and analyze neuroimaging and fluid biomarkers for the *in vivo* detection of CTE
2. Characterize the clinical presentation of CTE
3. Examine the progression of CTE over a three-year period
4. Refine and validate diagnostic criteria for the clinical diagnosis of CTE
5. Investigate genetic and head impact exposure risk factors for CTE
6. Share project data with researchers across the country and abroad

DIAGNOSE CTE
Research Project

Who is being studied?

DIAGNOSE CTE Research Project

- Males between 45-74 years old
- Three groups based on history of exposure to repetitive head impacts
  - **120 Former NFL Players**
    - No Symptoms
    - Mild Symptoms
    - Dementia
  - **60 Former College Football Players** (no other contact sports)
    - No Symptoms
    - Mild Symptoms
    - Dementia
  - **60 Unexposed "Controls"** (no contact sports, TBI, mTBI, Military)
    - No Symptoms at telephone screening

DIAGNOSE CTE
Research Project

Performance Evaluation Sites

Arizona **Mayo Clinic-Scottsdale** Site PI: Charles H. Adler, MD, PhD PET scans at Banner Alzheimer's Institute, Phoenix	**Boston** **Boston University** **Chobanian & Avedisian School of Medicine** Site PI: Robert A. Stern, PhD MRI's at Brigham and Women's Hospital
Las Vegas **Cleveland Clinic Lou Ruvo Center for Brain Health** Site PI: Charles Bernick, MD	**New York** **New York University Langone Medical Center** Site PI: Laura Balcer, MD, MSCE

DIAGNOSE CTE Research Project

Baseline Evaluation

Clinical Examinations

- History
  - *Football and other RHI Exposure; concussion/TBI*
  - *Medical, Neurological, Psychiatric, Substance*
  - *Family Hx*
- Neurological
- Motor
- Neurocognitive
  - *Subjective Report*
  - *Neuropsychological Tests*
- Neuropsychiatric
  - *Interview*
  - *Standardized Self-Report Measures*
- Study Partner Questionnaires
  - *Neurocognitive*
  - *Neuropsychiatric*
  - *Functional Dependence*

Biofluids & Neuroimaging

- Biofluids
  - *Lumbar Puncture: CSF*
  - *Venipuncture: Plasma, Serum, Whole Blood*
  - *Saliva Collection*
  - *All biofluids processed, aliquoted, banked -70°*
- Neuroimaging
  - *MRI: Volumetrics, DTI, rs-fMRI, MRS*
  - *Amyloid PET (florbetapir)*
  - *Tau PET (flortaucipir)*

Multidisciplinary Diagnostic Consensus Conferences

- Twice monthly video conferences
- 15 clinicians
  - *neurologists, psychiatrists, neuropsychologists, neurosurgeon*
- Video conferences
  - *Case presentation*
  - *Real-time REDCap voting*
  - *Discussion*
  - *Consensus Diagnosis*
- NINDS Consensus Diagnostic Criteria
  - *Traumatic Encephalopathy Syndrome*
  - *Level of Certainty for CTE Pathology*

DIAGNOSE CTE Research Project

Baseline Evaluation

Clinical Examinations

- History
  - *Football and other RHI Exposure; concussion/TBI*
  - *M[illegible]*
  - *P[illegible]*
  - *F[illegible]*
- Neuro[illegible]
- Moto[illegible]
- Neurocognitive
  - *Subjective Report*
  - *Neuropsychological Tests*
- Neuropsychiatric
  - *Interview*
  - *Standardized Self-Report Measures*
- Study Partner Questionnaires
  - *Neurocognitive*
  - *Neuropsychiatric*
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Biofluids & Neuroimaging

- Biofluids
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  - *Consensus Diagnosis*
- NINDS Consensus Diagnostic Criteria
  - *Traumatic Encephalopathy Syndrome*
  - *Level of Certainty for CTE Pathology*

Baseline Examinations Completed February 26, 2020 !!!!!!!!!!

DIAGNOSE CTE Research Project

Planned 3-yr Follow-Up Evaluation

Clinical Examinations

- History
  - *Football and other RHI Exposure; concussion/TBI*
  - *Medical, Neurological, Psychiatric, Substance*
  - *Family Hx*
- Neurological
- Motor
- Neurocognitive
  - *Subjective Report*
  - *Neuropsychological Tests*
- Neuropsychiatric
  - *Interview*
  - *Standardized Self-Report Measures*
- Study Partner Questionnaires
  - *Neurocognitive*
  - *Neuropsychiatric*
  - *Functional Dependence*

Biofluids & Neuroimaging

- Biofluids
  - *Lumbar Puncture: CSF*
  - *Venipuncture: Plasma, Serum, Whole Blood*
  - *Saliva Collection*
  - *All biofluids processed, aliquoted, banked -70°*
- Neuroimaging
  - *MRI: Volumetrics, DTI, rs-fMRI, MRS*
  - *Tau PET (flortaucipir)*

Multidisciplinary Diagnostic Consensus Conferences

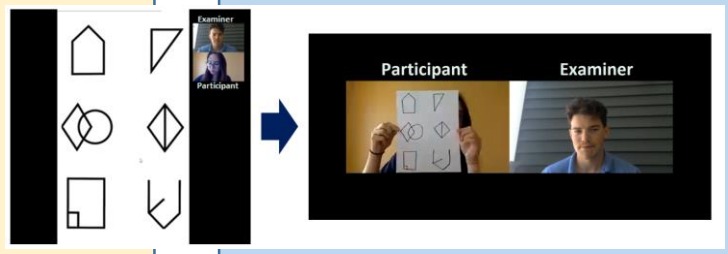
- Twice monthly video conferences
- 15 clinicians
  - *neurologists, psychiatrists, neuropsychologists, neurosurgeon*
- Video conferences
  - *Case presentation*
  - *Real-time REDCap voting*
  - *Discussion*
  - *Consensus Diagnosis*
- NINDS Consensus Diagnostic Criteria
  - *Traumatic Encephalopathy Syndrome*
  - *Level of Certainty for CTE Pathology*

DIAGNOSE CTE
Research Project

New 4-yr Remote Follow-Up Evaluation

Clinical Examinations

- History - Updates
- Neurological/Motor Modified – Single Neurologist (Movement Disorder) done over Zoom
- Neurocognitive
  - *Subjective Report*
  - *Neuropsychological Tests*
    - *Telephone – T-Cog*
    - *Video – Zoom*
    - *Online - CANTAB*
- Neuropsychiatric
  - *Interview*
  - *Standardized Self-Report Measures*
- Study Partner Questionnaires
  - *Neurocognitive*
  - *Neuropsychiatric*
  - *Functional Dependence*



Biofluids & Neuroimaging

- Biofluids
  - *In-Home Venipuncture: Plasma, Serum, Whole Blood*
  - *Processed locally and aliquots shipped (dry ice) to project freezers at VA Puget Sound*

Multidisciplinary Diagnostic Consensus Conferences

- Twice monthly video conferences
- 15 clinicians
  - *neurologists, psychiatrists, neuropsychologists, neurosurgeon*
- Video conferences
  - *Case presentation*
  - *Real-time REDCap voting*
  - *Discussion*
  - *Consensus Diagnosis*
- NINDS Consensus Diagnostic Criteria
  - *Traumatic Encephalopathy Syndrome*
  - *Level of Certainty for CTE Pathology*

DIAGNOSE CTE
Research Project

Alosco et al. Alzheimer's Research & Therapy (2021) 13:136
https://doi.org/10.1186/s13195-021-00872-x

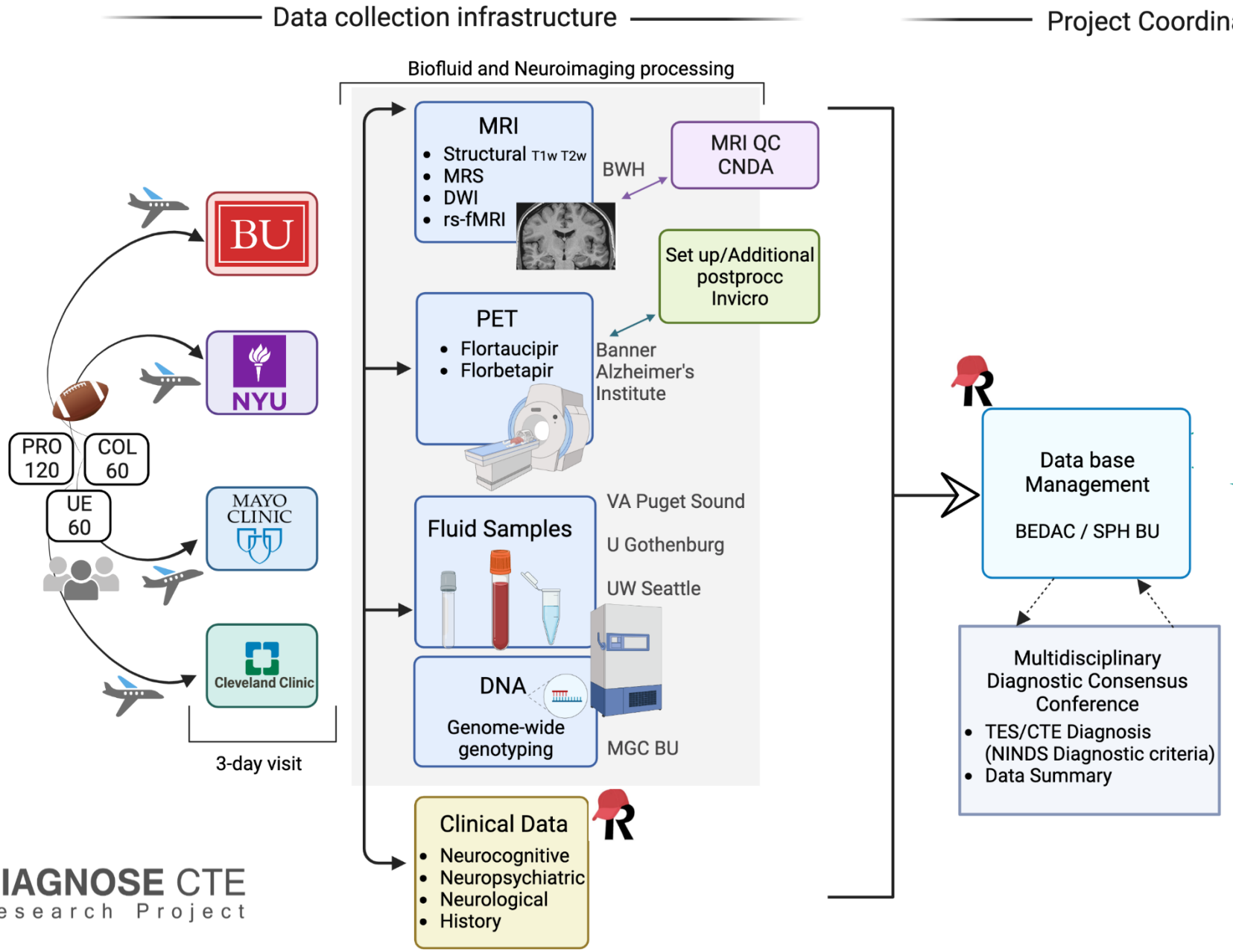
Alzheimer's
Research & Therapy

RESEARCH Open Access

Developing methods to detect and diagnose chronic traumatic encephalopathy during life: rationale, design, and methodology for the DIAGNOSE CTE Research Project

Michael L. Alosco[1], Megan L. Mariani[2], Charles H. Adler[3], Laura J. Balcer[4], Charles Bernick[5,29], Rhoda Au[6,30,31], Sarah J. Banks[7], William B. Barr[8], Sylvain Bouix[9], Robert C. Cantu[10], Michael J. Coleman[11], David W. Dodick[3], Lindsay A. Farrer[12], Yonas E. Geda[13], Douglas I. Katz[14,32], Inga K. Koerte[9,33], Neil W. Kowall[10,34], Alexander P. Lin[15], Daniel S. Marcus[16], Kenneth L. Marek[17], Michael D. McClean[18], Ann C. McKee[1,34], Jesse Mez[19], Joseph N. Palmisano[20], Elaine R. Peskind[21], Yorghos Tripodis[22], Robert W. Turner II[23], Jennifer V. Wethe[24], Jeffrey L. Cummings[25], Eric M. Reiman[26], Martha E. Shenton[27], Robert A. Stern[28*] for the DIAGNOSE CTE Research Project Investigators

Baseline Data Pipeline



DIAGNOSE CTE
Research Project

Baseline Data!

- Demographics
- Medical History
- Athletic, Military, and TBI History
- Pain and Headache
- Sleep
- Neurological and Motor Examination
- Neurocognitive Measures
- Neuropsychiatric Measures
- Magnetic Resonance Imaging (MRI)
- Florbetapir (Amyloid) Positron Emission Tomography (PET)
- Flortaucipir (Tau) PET
- Genetics
- CSF Biomarkers
- Blood Biomarkers

  Saliva Biomarkers
- Traumatic Encephalopathy Syndrome (TES)

Medical History

- Demographics
- Medical History
  - Family History
  - Neurological History
  - Sleep Related Disorders
  - Psychiatric History
  - Substance Abuse History
  - Vascular Disease and Risk Factors
  - Exercise History
  - Orthopedic History
  - Other Medical History
  - Subject Medications
- Athletic, Military, and TBI History
- Pain and Headache
- Sleep

Athletic, Military, and TBI History

- **Demographics**
- **Medical History**
- **Athletic, Military, and TBI History**
  - **Football and Other Athletic History**

    This includes the subject's football history, including the following for youth, high school, college, semi-professional and professional participation: age start, age stop, years, seasons, positions. Additionally, this includes the subject's history of participation in hockey, boxing and other organized sports.

    Click to Download Data Dictionary File
  - **Military History**

    This includes the subject's military history, including: branch, age, participation in combatant or breacher training, combat exposure, military TBI.

    Click to Download Data Dictionary File
  - **Traumatic Brain Injury History**

    This includes the subject's lifetime history of TBI via the structured Ohio State University (OSU) Traumatic Brain Injury (TBI) Identification survey. Additionally, the subject's reported number of concussions, age at concussions, history of post-concussion syndrome, and history of hospitalizations from head injury.

    Click to Download Data Dictionary File
- **Pain and Headache**
- **Sleep**

Neurocognitive Measures - Domains

- Demographics
- Medical History
- Athletic, Military, and TBI History
- Pain and Headache
- Sleep
- Neurological and Motor Examination
- Neurocognitive Measures
  - Primary Neurocognitive Measures
  - Montreal Cognitive Assessment (MoCA)
  - Subjective Cognitive Impairment
  - Estimated Premorbid Intelligence
  - Effort and Symptom Validity
  - Attention and Executive Function
  - Learning and Memory
  - Visuospatial Ability
  - Language
  - Olfaction
  - Dementia Severity - Functional Dependence
  - Neuropsychological Test Factor Scores
- Neuropsychiatric Measures
- Magnetic Resonance Imaging (MRI)
- Florbetapir (Amyloid) Positron Emission Tomography (PET)
- Flortaucipir (Tau) PET

Neurocognitive Measures

- Neurological and Motor Examination
- Neurocognitive Measures
  - Primary Neurocognitive Measures
  - Montreal Cognitive Assessment (MoCA)
  - Subjective Cognitive Impairment
  - Estimated Premorbid Intelligence
  - Effort and Symptom Validity
  - Attention and Executive Function
  - Learning and Memory
    - Brief Visuospatial Memory Test - Revised (BVMT - R)

      The Brief Visuospatial Memory Test-Revised (BVMT-R) assesses visuospatial memory. The subject views a stimulus page for three learning trials and is asked to draw as many figures as possible in their correct location. A delayed recall trial and recognition trial is administered after a 25 minute delay.

      Click to Download Data Dictionary File
    - Craft Story 21

      The Craft Story 21 Recall is part of the NACC UDS Neuropsychological Battery. It assesses the ability to recall a short story after a short and long delay, providing scores for both verbatim and phrase recall at both conditions.

      Click to Download Data Dictionary File
    - NAB List Learning

      The Neuropsychological Assessment Battery (NAB) List Learning test assesses learning of verbal information (12-word list) across 3 trials, short and long delayed recall, and delayed recognition.

      Click to Download Data Dictionary File
  - Visuospatial Ability
  - Language
  - Olfaction

Neuropsychiatric Measures - Domains

- Demographics
- Medical History
- Athletic, Military, and TBI History
- Pain and Headache
- Sleep
- Neurological and Motor Examination
- Neurocognitive Measures
- Neuropsychiatric Measures
  - Primary Neuropsychiatric Measures
  - Study Specific Mood and Behavior Questionnaires
  - Behavior Standardized Measures
  - Mood and Affect Standardized Measures
  - Quality of Life
  - PTSD
  - Suicidality
- Magnetic Resonance Imaging (MRI)
- Florbetapir (Amyloid) Positron Emission Tomography (PET)
- Flortaucipir (Tau) PET
- Genetics
- CSF Biomarkers
- Blood Biomarkers

Saliva Biomarkers

- Traumatic Encephalopathy Syndrome (TES)

Neuropsychiatric Measures

Neuropsychiatric Measures

Primary Neuropsychiatric Measures

Study Specific Mood and Behavior Questionnaires

Behavior Standardized Measures

BRIEF - A Behavioral Regulation Index (BRI) - Subject

The Behavior Rating Inventory of Executive Function (BRIEF-A) Behavioral Regulation Index (BRI) - Subject is a self-report measure to assess the participant's perception of their ability to regulate their behavior and emotional responses.

Click to Download Data Dictionary File

BRIEF - A Behavioral Regulation Index (BRI) - Study Partner

The Study Partner Behavior Rating Inventory of Executive Function (BRIEF - A) Behavioral Regulation Index (BRI) - Study Partner is an informant-report measure to assess the infomant's perception of the participant's ability to regulate their behavior and emotional responses.

Click to Download Data Dictionary File

Buss-Durkee Hostility Inventory (BDHI)

The Buss-Durkee Hostility Inventory (BDHI) is a self-report questionnaire used to assess aggression, anger and hostility.

Click to Download Data Dictionary File

Barratt Impulsiveness Scale (BIS)

The Barratt Impulsiveness Scale (BIS) is a self-report questionnaire used to assess impulsiveness.

Click to Download Data Dictionary File

Brown-Goodwin Lifetime History of Aggression (BGLHA)

The Brown-Goodwin Lifetime History of Aggression (BGLHA) is a structured interview regarding history of anger and aggressive behavior from childhood, adolescences, and adulthood.

Click to Download Data Dictionary File

State-Trait Anger Expression Inventory 2 (STAXI 2)

The State-Trait Anger Expression Inventory (STAXI 2) is a self-report questionnaire used to assess the experience, expression and control of anger. It measures anger as an emotional state (State Anger) and dispostion to experience angry feelings as a personality trait (Trait Anger).

Click to Download Data Dictionary File

Neuropsychiatric Inventory Questionnaire (NPI-Q)

The Neuropsychiatric Inventory Questionnaire (NPI-Q) is the study partner's assessment of the participant's neuropsychiatric symptoms over the past month.

Click to Download Data Dictionary File

Mood and Affect Standardized Measures

Quality of Life

MRI - Overview

- Demographics
- Medical History
- Athletic, Military, and TBI History
- Pain and Headache
- Sleep
- Neurological and Motor Examination
- Neurocognitive Measures
- Neuropsychiatric Measures
- Magnetic Resonance Imaging (MRI)
  - FreeSurfer Morphometric Measures Version 7.1
  - FreeSurfer Morphometric Measures Version 6
  - Magnetic Resonance Spectroscopy (MRS)
  - Fluid Attenuation Inversion Recovery (FLAIR)
  - Diffusion Tensor Imaging (DTI)
- Florbetapir (Amyloid) Positron Emission Tomography (PET)
- Flortaucipir (Tau) PET
- Genetics
- CSF Biomarkers
- Blood Biomarkers

  Saliva Biomarkers
- Traumatic Encephalopathy Syndrome (TES)

PET (Amyloid and Tau)

- Magnetic Resonance Imaging (MRI)
- Florbetapir (Amyloid) Positron Emission Tomography (PET)
  - Primary Florbetapir (Amyloid) PET
  - Detailed Florbetapir (Amyloid) PET
- Flortaucipir (Tau) PET
  - Invicro Tau IQ
  - BAI Flortaucipir (Tau) PET Measures
    - BAI Tau SUVR - PET Unified Pipeline (PUP)
    - BAI Tau SUVR - PET Unified Pipeline (PUP) with RSF
    - BAI Tau SUVR - NEJM Three Region SUVR Replication
- Genetics
- CSF Biomarkers
- Blood Biomarkers
- Saliva Biomarkers
- Traumatic Encephalopathy Syndrome (TES)

Genetics, CSF and Blood Biomarkers

Genetics

ApoE Genotype

This includes the specific ApoE genotype (i.e., 2-2, 2-3, 2-4, 3-3, 3-4, 4-4) and ApoE carrier status (i.e., e4 non-carrier, e4 carrier) for each participant.

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CSF Biomarkers

University of Gothenburg (Sweden) CSF Assays

This includes the following CSF analytes: Abeta40, Abeta42, GFAP, P-tau181, P-tau231, P-tau217, T-tau, NfL, sTREM2, sPDGFRbeta. Missing values are due to either insufficient sample volume or values that are below the level of detection. The values that are below the level of detection have been imputed. For CSF P-tau217, please note that values below the lower limit of quantification (LLOQ) or undetectable values should not be used under normal circumstances for any analyses.

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Seattle CSF Assays

This includes 55 analytes from the following panels: cytokine (1 and 2), proinflammatory, chemokine (1 and 2), vascular injury, angiogenesis, and TH17. Missing values are due to either insufficient sample volume or values that are below the level of detection. The values that were below the level of detection were imputed.

Click to Download Data Dictionary File

Blood Biomarkers

University of Gothenburg (Sweden) Blood Assays

This includes the following blood analytes: Abeta40, Abeta42, GFAP, P-tau181, P-tau231,T-tau, NfL, sPDGFRbeta.Missing values are due to either insufficient sample volume or values that are below the level of detection. The values that are below the level of detection have been imputed. For plasma total tau, please note that values below the lower limit of quantification (LLOQ) should not be used under normal circumstances for any analyses.

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Seattle Blood Assays

This includes 55 analytes from the following panels: cytokine (1 and 2), proinflammatory, chemokine (1 and 2), vascular injury, angiogenesis, and TH17. Missing values are due to either insufficient sample volume or values that are below the level of detection. The values that were below the level of detection were imputed.

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DIAGNOSE CTE Research Project

First of Many Publications from Baseline Data (Dr. Alosco Talk…)

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DOI: 10.1002/alz.12779

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

White matter hyperintensities in former American football players

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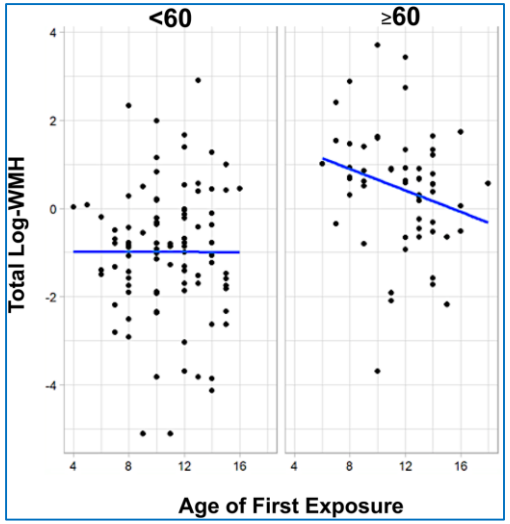
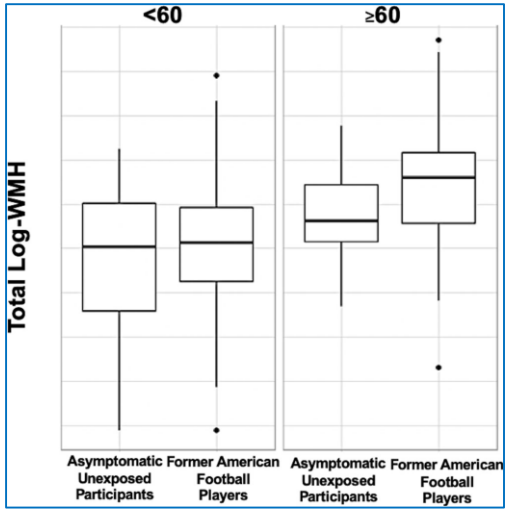




Highlights

- Older but not younger former football players had greater total, frontal, temporal, and parietal lobe white matter hyperintensities (WMH) compared to same-age asymptomatic unexposed men.
- Younger age of first exposure to football was associated with greater WMH in older but not younger former American football players.
- In former football players, greater WMH was associated with worse executive function and verbal memory.

DIAGNOSE CTE Research Project

2nd of Many Publications from Baseline Data (Dr. Reiman Talk…)

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-022-05963-x

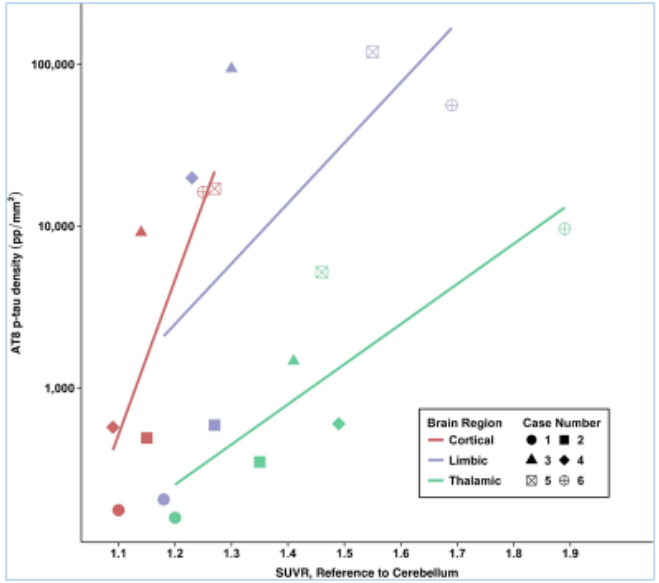
ORIGINAL ARTICLE

Check for updates

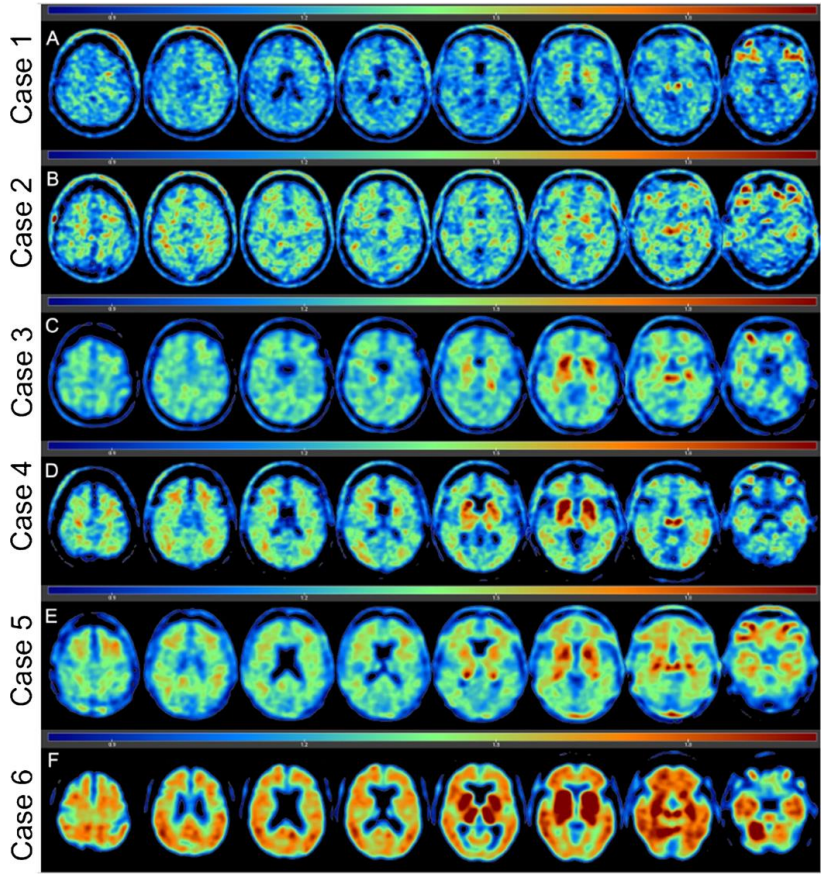
Associations between near end-of-life flortaucipir PET and postmortem CTE-related tau neuropathology in six former American football players

Michael L. Alosco[1] · Yi Su[2] · Thor D. Stein[1,3,4,5] · Hillary Protas[6] · Jonathan D. Cherry[1,3] · Charles H. Adler[7] · Laura J. Balcer[8] · Charles Bernick[9,10] · Surya Vamsi Pulukuri[1] · Bobak Abdolmohammadi[1] · Michael J. Coleman[11] · Joseph N. Palmisano[12] · Yorghos Tripodis[1,13] · Jesse Mez[1,4] · Gil D. Rabinovici[14] · Kenneth L. Marek[15] · Thomas G. Beach[16] · Keith A. Johnson[17,18,19,20] · Bertrand Russell Huber[1,3,5,21] · Inga Koerte[11,17,22,23,24] · Alexander P. Lin[11,25] · Sylvain Bouix[11] · Jeffrey L. Cummings[26] · Martha E. Shenton[3,11,20,27] · Eric M. Reiman[28] · Ann C. McKee[1,3,4,5] · Robert A. Stern[1,29] · for the DIAGNOSE C. T. E. Research Project

Received: 30 June 2022 / Accepted: 1 September 2022

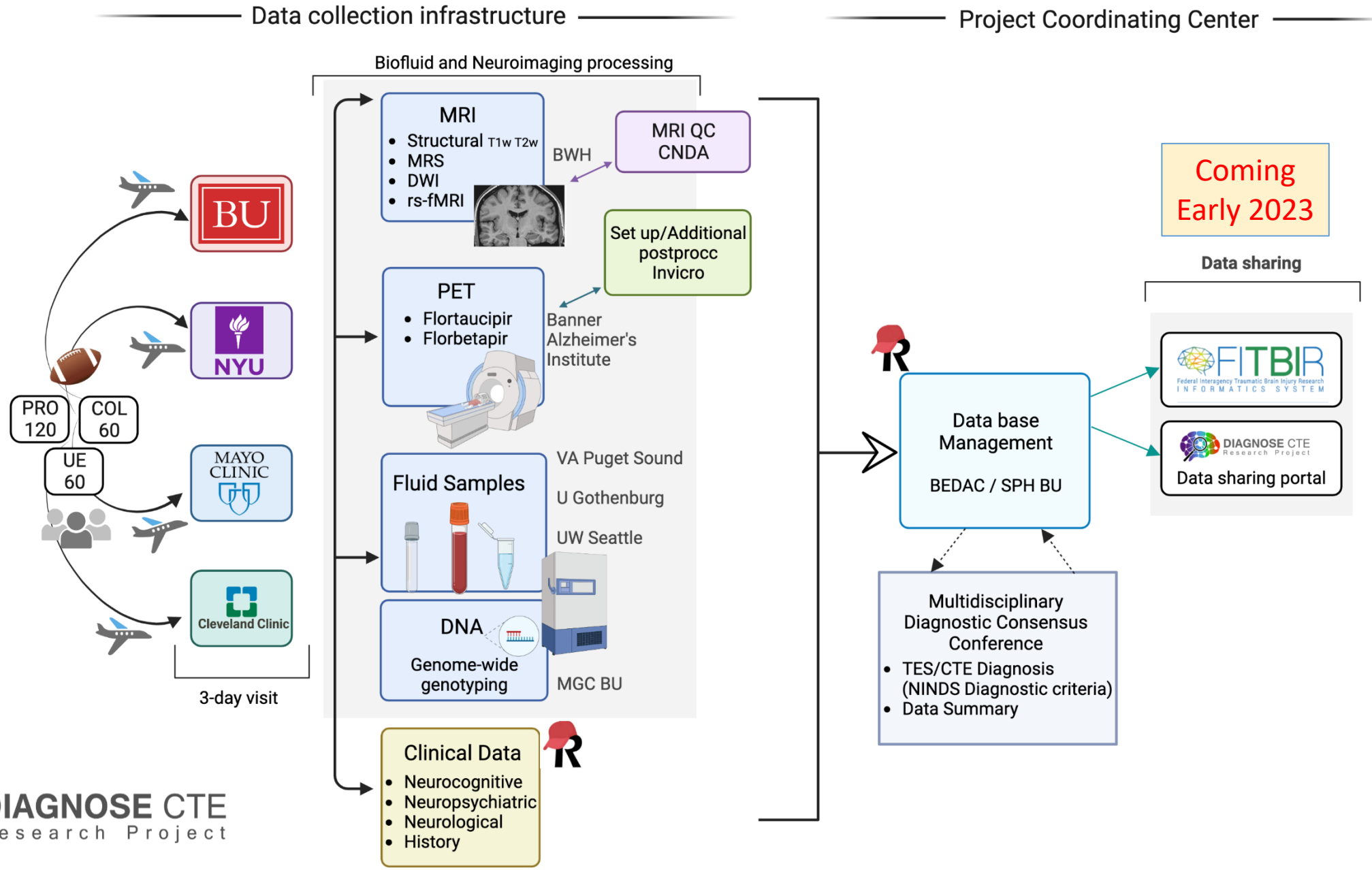


Associations between antemortem flortaucipir SUVRs and postmortem phosphorylated tau density. **Cortical composite** is the mean of the dorsolateral frontal cortex, orbital-frontal cortex, superior temporal cortex, and the inferior parietal cortex. **Limbic composite** is the mean of the entorhinal cortex, amygdala, and the hippocampus



Flortaucipir PET images of six deceased American football players. Five participants had dynamically acquired PET scans after 80 min post-injection for at least 20 min and one participant's flortaucipir scan ended at 90 min after injection. Voxel-wise SUVR values are represented relative to a cerebellar reference region and scaled for a range of 0–2.0. The flortaucipir PET images are of two former American football players without autopsy-confirmed CTE (a, b), three who had CTE stage III at autopsy (c–e), and one who had CTE stage IV at autopsy (f)

Baseline Data Pipeline



DIAGNOSE CTE Research Project

New Study

Risk for Later-Life Cognitive Impairment, Neurobehavioral Dysregulation, and Dementia in Former Soccer and American Football Players:

Head Impact & Trauma Surveillance Study

Funded by a grant from NINDS and NIA
2/1/2021 – 1/30/2026 - R01 NS119651 (PI: Stern)

BOSTON UNIVERSITY

BrainHealth REGISTRY

UCSF

HITSS
Head Impact & Trauma Surveillance Study
HITSS.org

- Fully online study (prescience: grant submitted February 5, 2020)
- In collaboration with the Brain Health Registry (BHR) at UCSF (Mike Weiner, MD, PI)
- Longitudinal (annual) neurocognitive, neuropsychiatric, and dementia assessment (including TES diagnosis) of female and male contact/collision sport (CCS) athletes across different sports, levels of play, and RHI exposure
- For the initial 5-year grant period, **4800 former soccer and football players** will be enrolled

Former Contact/Collision Sport Athletes:

- Total N=4800
- 1200 female soccer players
- 1200 male soccer players
- 2400 male football players
- Across all levels of play, i.e., up through youth, high school, college, or elite/professional
- Ages 40+
- Complete online BHR and new HITSS Module annually
- Study Partners (requested) complete BHR and new HITSS Module informant measures annually

Future Research

- Once we can diagnose CTE during life, we will be able to begin clinical trials for treatment
- And, if we can detect it early in the disease course, prior to symptoms, we can conduct clinical trials for disease modifying medications for delay or prevention of symptoms
- And, if we can understand the specific risk and resiliency factors for CTE, **prevention** strategies can be implemented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Research Project

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DIAGNOSE CTE
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