Chronic traumatic encephalopathy: Emerging Concepts

Ann C. McKee M.D.
Professor of Neurology and Pathology  VA Boston Healthcare System
Boston University School of Medicine
Director of the CTE Center
Boston University Alzheimer’s Disease Center
What is Chronic Traumatic Encephalopathy?

“Punch Drunk”
“Dementia Pugilistica”
1928

First reported by Harrison Martland in 1928 in boxers

_Punch drunk._ JAMA 91:1103–1107, 1928

“nearly one half of the fighters who have stayed in the game long enough”

“Chronic Traumatic Encephalopathy“

Critchley M (1949) _Punch-drunk syndromes: the chronic traumatic encephalopathy of boxers_.
_In: Hommage à Clovis Vincent_. Paris.
Clinical symptoms typically present years - decades after the trauma, but not always.

**Diverse clinical symptoms:**
Emotional liability, slowness of thought & speech, memory problems and dementia.

Other symptoms: mood swings, irritability, violent behavior, depression & paranoia.

**Common motor features:** tremor & dysarthria

*(Critchley M. Medical aspects of boxing, particularly from a neurological standpoint. Br Med J 1957; 1: 357)*
The aftermath of boxing

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE

From the Department of Neuropathology, Runwell Hospital, Wickford, Essex

SYNOPSIS The brains of 15 retired boxers have been studied and the lives of the men concerned have been investigated in retrospect. A characteristic pattern of cerebral change has been identified which appears not only to be a result of the boxing but also to underlie many features of the punch-drunk syndrome.
Chronic Traumatic Encephalopathy 2005

**OBJECTIVE:** We present the results of the autopsy of a retired professional football player that revealed neuropathological changes consistent with long-term repetitive concussive brain injury. This case draws attention to the need for further studies in the cohort of retired National Football League players to elucidate the neuropathological sequelae of repeated mild traumatic brain injury in professional football.

**Mike Webster**

U Wisconsin 1974

Death at 52 years
Behavioinal and mood disorders
Cognitive loss
Parkinsonism

*Omalu et al. 2005, 2006*
Chronic Traumatic Encephalopathy (CTE) is a progressive tauopathy that occurs after repetitive head injury. In 2009, there were 51 cases reported in the world's literature. Among these, 3 cases were reported at the BU/VA Boston. Of these, 39 cases (76%) were boxers, and 5 cases (10%) were American football players.
<table>
<thead>
<tr>
<th>Sport</th>
<th>WORLD 2009</th>
<th>BU 2009</th>
<th>BU 2015</th>
</tr>
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<tbody>
<tr>
<td>Boxing</td>
<td>37</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>American Football</td>
<td>4</td>
<td>1</td>
<td>103</td>
</tr>
<tr>
<td>Ice Hockey</td>
<td>0</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Wrestling</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Rugby</td>
<td>0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Military Veterans*</td>
<td>0</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Soccer</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Other: physical abuse, poorly controlled epilepsy, head banging</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>48</strong></td>
<td><strong>3</strong></td>
<td><strong>133</strong></td>
</tr>
</tbody>
</table>

*McKee et al 2009; McKee et al 2010; McKee et al 2013, McKee et al 2014*
Clinical Presentations of CTE

36 athletes with neuropathological CTE:

<table>
<thead>
<tr>
<th>Behavioral and/or mood</th>
<th>Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age at onset</td>
<td>Older age at onset</td>
</tr>
<tr>
<td>(m 35 yrs)</td>
<td>(m 59 yrs)</td>
</tr>
<tr>
<td></td>
<td>Indistinguishable from AD</td>
</tr>
</tbody>
</table>

Most subjects (86%) who present with behavioral/mood symptoms progress to have cognitive symptoms (m age death: 51 yrs)

Behavioral or mood symptoms less likely to develop (46%) in subjects who present initially as cognitive impairment (m age death: 69 yrs)

Stern et al. Neurology 2013
Systematic review of the clinical features in 83 confirmed CTE cases:

An additional subtype, the “mixed subtype” was identified

Mixed subtype cases presented with a combination of behavioral, mood and cognitive features without dementia

68% cases were found to have a progressive clinical course

Younger subjects were found to have a higher degree of stability

Montenigro et al. Alzheimers Res Ther 2014
Most common clinical features
(>70% of CTE cases)

<table>
<thead>
<tr>
<th>COGNITIVE</th>
<th>BEHAVIORAL</th>
<th>MOOD</th>
<th>MOTOR</th>
</tr>
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<tbody>
<tr>
<td>Memory</td>
<td>Physical violence</td>
<td>Depression</td>
<td>Ataxia</td>
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<tr>
<td>Executive dysfunction</td>
<td>Verbal violence</td>
<td>Hopelessness</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>Impaired attention</td>
<td>Explosivity</td>
<td>Suicidality</td>
<td>Gait impairment</td>
</tr>
<tr>
<td>Dementia</td>
<td>Loss of control</td>
<td>Anxiety</td>
<td>Tremor</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Short fuse</td>
<td>Irritability</td>
<td>Masked facies</td>
</tr>
<tr>
<td></td>
<td>Impulsivity</td>
<td>Apathy</td>
<td>Rigidity</td>
</tr>
<tr>
<td></td>
<td>Paranoia</td>
<td>Loss of interest</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rage</td>
<td>Fearfulness</td>
<td></td>
</tr>
</tbody>
</table>

Montenigro et al. Alzheimers Res Ther 2014
Pathology of CTE

- **Brain Atrophy**
- **Aggregation of Abnormal Proteins**
- **Axonal injury & loss**
- **Neuroinflammation**
Cavum septum pellucidum
Abnormalities of posterior septum pellucidum
Gross Characteristics:  Cerebral Atrophy

Severe II and III ventricular dilatation
severely fenestrated posterior septum pellucidum
pallor of the substantia nigra
CTE
Hyperphosphorylated tau protein (p-tau)
CTE

hypothalamus

thalamus

p tau
Staining

Substantia Nigra

Locus coeruleus

Medulla

CTE

p tau

Medulla
Hallmarks of CTE Pathology
PHF-tau neuronal & glial pathology

CTE

1. Focal epicenters at depth of sulci
2. Perivascular
Why is tau protein deposited in those brain regions?

Depth of sulcus and perivascular area are regions of physical stress concentration.
Figure 6.57  Coronal frontal section of the brain from the victim of a homicidal beating with a hammer that shattered the frontal skull, illustrating a peculiar pattern of contusions that

Leestma, Forensic Pathology, 2008, second edition
3 repeat (3R) and 4 repeat (4R) tau are present in CTE.
Distinctions between AD and CTE TAU pathology

Aβ is always present (100%) as neuritic plaques

Aβ is sometimes present (43%) as diffuse plaques; never in early stage disease

McKee et al, Brain 2013
# Neuropathological Dx: CTE Athletes

<table>
<thead>
<tr>
<th></th>
<th>Boxing</th>
<th>Football</th>
<th>Hockey</th>
<th>Soccer</th>
<th>Rugby</th>
<th>MLB</th>
<th>WWE</th>
<th>MMA</th>
<th>Total</th>
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<tr>
<td>#CTE</td>
<td>Pro</td>
<td>Am</td>
<td>NFL</td>
<td>CFL</td>
<td>SP</td>
<td>Coll</td>
<td>HS</td>
<td>NHL</td>
<td>Am</td>
</tr>
<tr>
<td>#evaluated</td>
<td>Pro</td>
<td>Am</td>
<td>NFL</td>
<td>CFL</td>
<td>SP</td>
<td>Coll</td>
<td>HS</td>
<td>NHL</td>
<td>Am</td>
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<tr>
<td></td>
<td>11</td>
<td>1</td>
<td>77</td>
<td>4</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>4</td>
<td>1</td>
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<tr>
<td></td>
<td>11</td>
<td>2</td>
<td>80</td>
<td>4</td>
<td>3</td>
<td>23</td>
<td>19</td>
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<tr>
<td></td>
<td>96%</td>
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</tbody>
</table>

*McKee et al. 2009; McKee et al, 2010; McKee et al 2013a, McKee et al. 2013b*
128 cases of CTE

CTE with comorbid neuropathology

- No comorbidity
- CTE + MND
- CTE + AD
- CTE + LBD
- CTE + FTLD

- n = 84 (63%)
- n = 13 (10%)
- n = 12 (9%)
- n = 10 (8%)
- n = 6 (5%)
<table>
<thead>
<tr>
<th>Stages of Tau Pathology</th>
<th>Age at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>mean age: 28.3 ± 13 years</td>
</tr>
<tr>
<td>Stage II</td>
<td>mean age: 44.3 ± 16 years</td>
</tr>
<tr>
<td>Stage III</td>
<td>mean age: 56.0 ± 14 years</td>
</tr>
<tr>
<td>Stage IV</td>
<td>mean age: 77.4 ± 12 years</td>
</tr>
</tbody>
</table>

For American football players: number years played, years since retirement, and age at death significantly correlated with pathological stage of CTE

McKee et al, 2013, Brain
**McKee et al.’s (2013) CTE Tau Staging**

**STAGE I**
- Isolated perivascular epicenters
- Predilection for depths of sulci
- Neocortex: superior, dorsolateral and inferior frontal
- Locus coeruleus (66% of cases)

**STAGE II**
- Multiple epicenters
  - in frontal, temporal cortex, and parietal neocortices
- Diencephalon

**STAGE III**
- Widespread neocortical involvement
- Hippocampus
- Entorhinal cortex
- Amygdala
- Nucleus basalis of Meynert

**STAGE IV**
- Thalamus
- Basal ganglia
- Brain stem
- Cerebellum

**Braak et al.’s (2011) Aging/AD Tau Staging**

**STAGE a-c**
- Locus coeruleus
- Upper raphe nuclei
- Magnocellular nuclei

**STAGE 1a, 1b, I-II**
- Transentorhinal cortex
- Entorhinal cortex

**STAGE III-IV**
- Hippocampus
- Amygdala
- Basal temporal
- Insular
- Basal frontal

**STAGE V-VI**
- Widespread neocortical involvement
- Sparing of cerebellum
Eric Pelly: 18 yo high school football & rugby player
Death 10 days after 4\textsuperscript{th} concussion

Stage I CTE
Death 10 days after 4th concussion

Stage I CTE

18 year old high school football and rugby player

Stage I CTE

P-Tau
Stage II CTE

Owen Thomas
21 year old
U Penn football player
Death from suicide
Derek Boogaard
28 year old
NHL player
Death from overdose oxycontin and alcohol
25 yo college football player

• 16 year exposure to football, 3 years division I college FB Linebacker and special teams

• Several severe concussions during college with persistent vision changes, memory problems, confusion, difficulty sleeping and debilitating headaches.

• Quit football after 3 yrs. Continued to experience episodic memory loss, disorientation, difficulty with attention and concentration and word finding, progressively worsened over the last 18-24 months of his life.

• Also experienced depression, bouts of impulsivity and severe anger.

• He died at age 25 following a staph infection.
Stage II CTE
25 yo College Football Player

PHF-tau
Stage II CTE: 25 yo College Football Player

P-tau (AT8)
Joseph Chernach
25 year old
Former HS football player, pole vaulter, wrestler
Death from suicide

Stage II CTE
Dave Duerson

Death at age 50 years

Football since at age 8 - 11-year NFL career

Post-NFL, successful businessman
Active in NFLPA; Benefits Board
Business and financial difficulties began in 2007

Personal difficulties in 2007
Increasingly out of control:
- Short fuse, hot temper, physically and verbally abusive
- Long-standing complaint of headaches since retirement NFL
- Worsening short-term memory, word-finding and vision difficulties

Self-inflicted gunshot wound, texted family to donate brain to NFL brain bank
Stage III CTE
Stage III CTE

Diffuse axonopathy

TDP-43 Deposition

SMI-31
52 year old former NFL player  
24 years football, 14 in NFL  
memory problems occurred intermittently in college and NFL  
at end of his NFL career, memory loss, depression, short fuse,  
angry outbursts, gambling, drinking excessively, irresponsible behaviors  
Death from myocardial infarction
Stage III CTE

Mosi Tatupu
Began playing rugby at age 13, played 6 years of U21 rugby, and 10 years of senior rugby as flanker and breakaway (18 years).

Age 54: Cognitive problems, memory loss, attention difficulties, executive dysfunction, followed by depression and anxiety, worsening explosivity and impulsivity.

Age 65: physically and verbally abusive, with paranoia, disinhibition and severe dementia

Died at age 77 from myocardial infarction
77 yo Australian Rugby Player

Brain weight: 1030 grams
Barry “Tizza” Taylor
Stage IV CTE

P-tau

pTDP-43
Brain Trauma Extends Reach Into Soccer

Researchers Find Bellini, Star for Brazil, Had Brain Disease C.T.E.

By SAM BORDEN  SEPTEMBER 23, 2014

Bellini, right, as Brazil's captain in the 1958 World Cup. He died in March and was found to have had chronic traumatic encephalopathy. Associated Press
3 professional athletes (2 former NFL players, 1 former boxer) had a progressive motor neuron disease that looked clinically like ALS, but pathologically had CTE with florid TDP-43 + inclusions throughout the central nervous system including motor neurons of brain and spinal cord.
Did ALS or concussions kill Lou Gehrig?

Maybe Lou Gehrig Didn't Die of Lou Gehrig's Disease

By ALICE PARK  Tuesday, Aug. 17, 2010
3,400 NFL players who played between 1959 and 1988. By 2007, 334 of them had died at an average age of 54.

Players who spent > 5 seasons in the NFL were 3 X more likely to die of a neurodegenerative disease, including PD, AD, and ALS than the general population.

Deaths related to:
- Dementia/AD: 3.86 X higher
- ALS: 4.31 X higher
Ron Perryman

42 year old former college football player

- Football since age 8
- 7-8 concussions high school football, 3-4 concussion college, fractured vertebrae in neck (C3-C4)
- Age 37, developed weakness of left arm.
- Age 38 diagnosed ALS
- Age 40, wife noticed he was forgetful, inattentive, difficulty concentrating, disinhibited, short fuse

- Death at age 42
Stage II-III CTE with MND
Patrick Grange

• Began playing soccer at 3 years old
• Started heading the ball at 5 years
• Played soccer throughout grade school, middle school, high school, college, 2 1/2 years of semi-professional soccer
• Age 27, diagnosed with ALS.
• Death at age 29
29 yo soccer player: Stage II CTE + MND

Perivascular p-tau in frontal, parietal and temporal cortex

McKee et al, Acta Neuropathol 2014
<table>
<thead>
<tr>
<th>N</th>
<th>Sport</th>
<th>Onset</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Soccer</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>2*</td>
<td>Army Boxing, Gulf War</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>3*</td>
<td>College football</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>4*</td>
<td>High school football, police officer</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>College football</td>
<td>32</td>
<td>44</td>
</tr>
<tr>
<td>6*</td>
<td>College football</td>
<td>32</td>
<td>49</td>
</tr>
<tr>
<td>7*</td>
<td>College football</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>NFL</td>
<td>40</td>
<td>67</td>
</tr>
<tr>
<td>9*</td>
<td>College football</td>
<td>40</td>
<td>52</td>
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<td>10*</td>
<td>College football</td>
<td>42</td>
<td>52</td>
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<tr>
<td>11*</td>
<td>NFL</td>
<td>47</td>
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<tr>
<td>12•</td>
<td>Pro Boxing</td>
<td>52</td>
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<tr>
<td>13</td>
<td>NFL</td>
<td>57</td>
<td>67</td>
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<td>14•</td>
<td>NFL</td>
<td>64</td>
<td>66</td>
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<td>Pro Boxing</td>
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<td>69</td>
</tr>
<tr>
<td>16•</td>
<td>Pro Boxing</td>
<td>66</td>
<td>67</td>
</tr>
</tbody>
</table>
Chronic traumatic encephalopathy and amyotrophic lateral sclerosis

Kevin F. Bieniek¹,², Thor D. Stein³,⁴,⁵,⁶, Daryl R. Jones¹, Victor E. Alvarez⁵, Brian T. Fry⁵, Amelia Johnston⁷, Pamela DeSaro⁷, Karen Overstreet⁷, Kevin B. Boylan⁷, Dennis W. Dickson¹ and Ann C. McKee³,⁴,⁵,⁶

Departments of Neuroscience ¹ and Neurology ⁷, Mayo Clinic, Jacksonville, FL, USA ² Mayo Graduate School, Mayo Clinic, Rochester, MN, USA ³ Veterans Affairs Boston Healthcare System, Boston, MA, USA, Departments of Pathology and Medicine ⁴, Neurology ⁵, and Alzheimer Disease Center ⁶, Boston University School of Medicine, Boston, MA, USA

• The frequency of CTE pathology in two ALS-recruited cohorts was approximately 5%
NFL players diagnosed with ALS

Steve Smith, age 50
Kevin Turner, age 45
O.J. Brigance, age 45
Steve Gleason, age 37
Tim Shaw, age 30
CTE: where are we now?

• CTE can only be diagnosed at autopsy; however, promising efforts to develop neuroimaging, CSF & blood biomarkers are underway.

• Future therapeutic efforts in mTBI will need to address management of acute mTBI as well as identification and monitoring of the long-term progressive neurodegeneration that follows.

• Currently, prevention of trauma and continued public education regarding proper detection and management of acute mTBI are our best strategies to lessen to reduce the development of CTE.
CTE:
What are the unresolved questions?

- Incidence and prevalence of CTE
- Unclear relationship to concussion and subconcussion
- Diagnosis of CTE during life
  - Blood, CSF, saliva assays
  - Neuroimaging: DTI, SWI, PET tau, TDP43 and inflammatory ligands
- Validated animal models: to understand the pathogenetic mechanisms
- Genetic risk factors, other environmental risk factors
- Treatment, comprehensive care, rehabilitation strategies
Validation of neuropathological criteria for CTE:

Ann McKee, M.D., Nigel Cairns, Ph.D., John Crary, M.D., Rebecca Folkerth, MD, C. Dirk Keene, M.D., Thomas Montine, M.D., Ph.D., Daniel Perl, M.D., Thor Stein M.D., Ph.D., William Stewart, M.D., Jean Paul Vonsattel, M.D., Dennis Dickson, M.D.

AD
PSP
CBD
PART
AGD
GPDC
Pathology of Concussion

Axonal injury: APP immunostain

Neuroinflammation: microgliosis and astrocytosis

PHF-tau deposition

• Axonal injury
• Neuroinflammation
• Microvascular disruption/ loss of BBB/ microhemorrhage
• Focal deposition of p-tau

Reversible or Progressive?
Does it depend on the amount of repeat injury?

McKee et al, Acta Neuropathol 2014
Diffusion Tensor Imaging

Suspected CTE

Healthy Control

M Shenton, R Stern et al BWH
A 71 year old NFL player, 10 years in the NFL presented with impaired short-term memory. Agitation, memory decline; mood was normal.

[18F]-Florbetapir PET imaging was negative.

[18F]-T807 PET imaging revealed [18F]-T807 retention in the substantial nigra, globus pallidus and hippocampus
CTE presenting as AD

Abnormal uptake in SN, globus pallidus, hippocampus – "off-target labeling"

"an effective method of diagnosing or ruling out CTE in a living brain"
Retinal pathology in CTE

VA Boston and BUSM, University of Washington, Emory University

A way to diagnose CTE during life?
Murine Blast Neurotrauma Shock Tube System
Neurotrauma Laboratory, Boston University School of Medicine

CTE-Linked Neuropathology — Adult C57BL/6 Mice
Two Weeks After Single Blast Exposure

The Role of Aβ in CTE

Thor Stein, MD, PhD VA Boston and BUSM

- Aβ deposition - as diffuse or neuritic plaques - 43% of CTE
- Aβ plaque deposition in CTE occurred at earlier age and an accelerated rate compared to a normal aging population (OR=11.1, p=0.025)
- Aβ plaques significantly associated with the presence of the APOE e4 allele (DP: Z=3.65, p<0.001; NP: Z=2.33, p=0.020).

- Controlling for age, Aβ plaques were significantly associated with:
  - increased CTE stage ( p=0.003)
  - co-morbid Lewy body disease (OR=6.77, p=0.009)
  - dementia (OR=4.50, p=0.007)
  - Parkinsonism (OR=14.32, p=0.019)
Molecular & Genetic Investigation
Tau in CTE

John Crary, MD, PhD
Mount Sinai

Molecular and Genetic Investigation of Tau in CTE
John Crary, PI
DOD ERMS# 13267017

Ann McKee, Co-I
Urgent need to help living athletes and other individuals who are concerned that they have CTE

Urgent need to determine the relationship between concussion and the development of long-term disabilities

Jim McMahon
Chicago Bears

Tony Dorsett
Dallas Cowboys

Brett Favre
Green Bay Packers

Ted Johnson
New England Patriots
VA Boston/ Boston University/ SLI
Chronic Traumatic Encephalopathy Program

**BU/VA CTE Program**

Victor Alvarez MD  
Alexandra Bourlas  
Christine Baugh  
Robert Cantu, MD FACS  
Kerry Cormier  
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Brian Frye  
Matthew Jacobs  
Lee Goldstein MD PhD  
Doug Katz, MD  
Patrick Kiernan  
Neil Kowall, MD  
Carol Kubilus  
Lisa McHale  
Jesse Mez, MD  
Phillip Montenigro  
Lauren Murphy  
Chris Nowinski  
David Riley  
Cliff Robbins  
David Salat, PhD

Hyo Soon-Lee MD  
Todd Solomen, PhD  
Thor Stein, MD, PhD  
Robert Stern PhD  
Prince Williams  
Rhoda Au, PhD  
Andrew Budson MD  
Ben Wolozin MD, PhD

All the families who participated in our research

**BU Goldstein Lab**

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Chad Tagge, PhD  
Juliet Montcaster, PhD  
Mark Wojnarowicz

**SLI**

Robert Cantu, MD FACS  
Chris Nowinski

**Other Institutions**

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Rebecca Folkerth, MD Brigham  
Garth Hall, PhD U Mass Lowell  
Keith Johnson, MGH  
Dirk Keene, MD U Wash  
Alexander Lin, PhD, BWH  
Irene Litvan, MD UC San Diego  
Thomas Montine, MD, PhD U Wash  
Daniel Perl, MD USHS  
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NOCSAE
SUPER BOWL