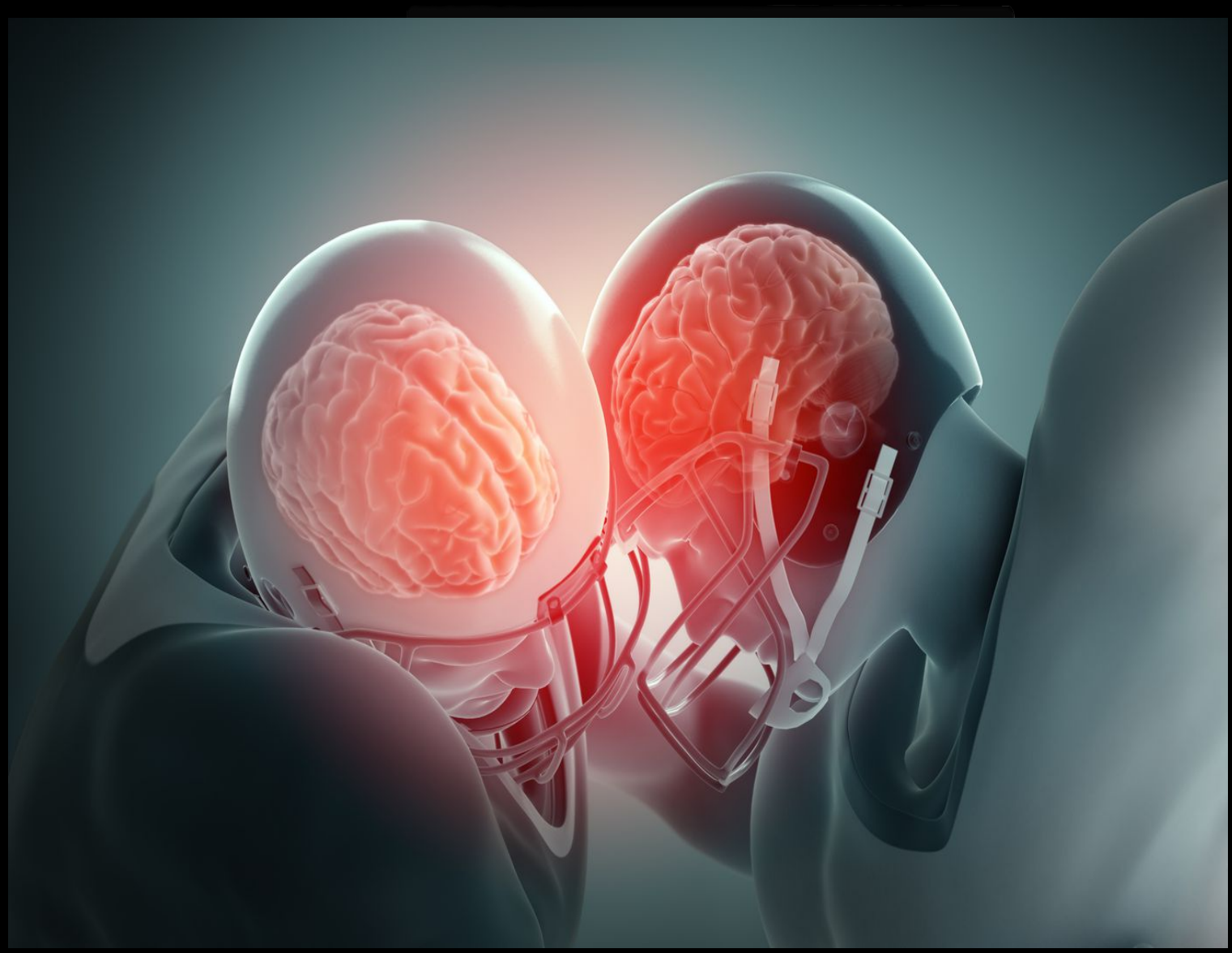
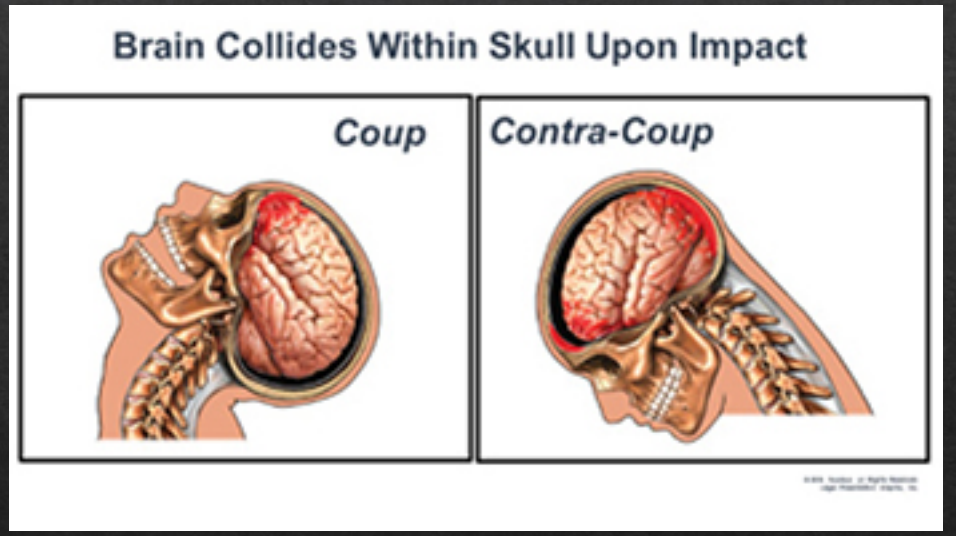
CHRONIC TRAUMATIC ENCEPHALOPATHY



DEFINITION

- Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative syndrome that is caused by single, episodic, or repetitive blunt force impacts to the head and transfer of acceleration-deceleration forces to the brain.
- It is a unique disorder occurring as a latent consequence of cumulative repetitive head impacts (RHIs), including concussion and subconcussion.
- First demonstrated by Martland in 1928, who characterized boxers as displaying *“punch-drunk syndrome”* from repeated blows to the head.
- Later on, this phenomenon was named as ”*dementia pugilistica”* and is now well known as CTE.

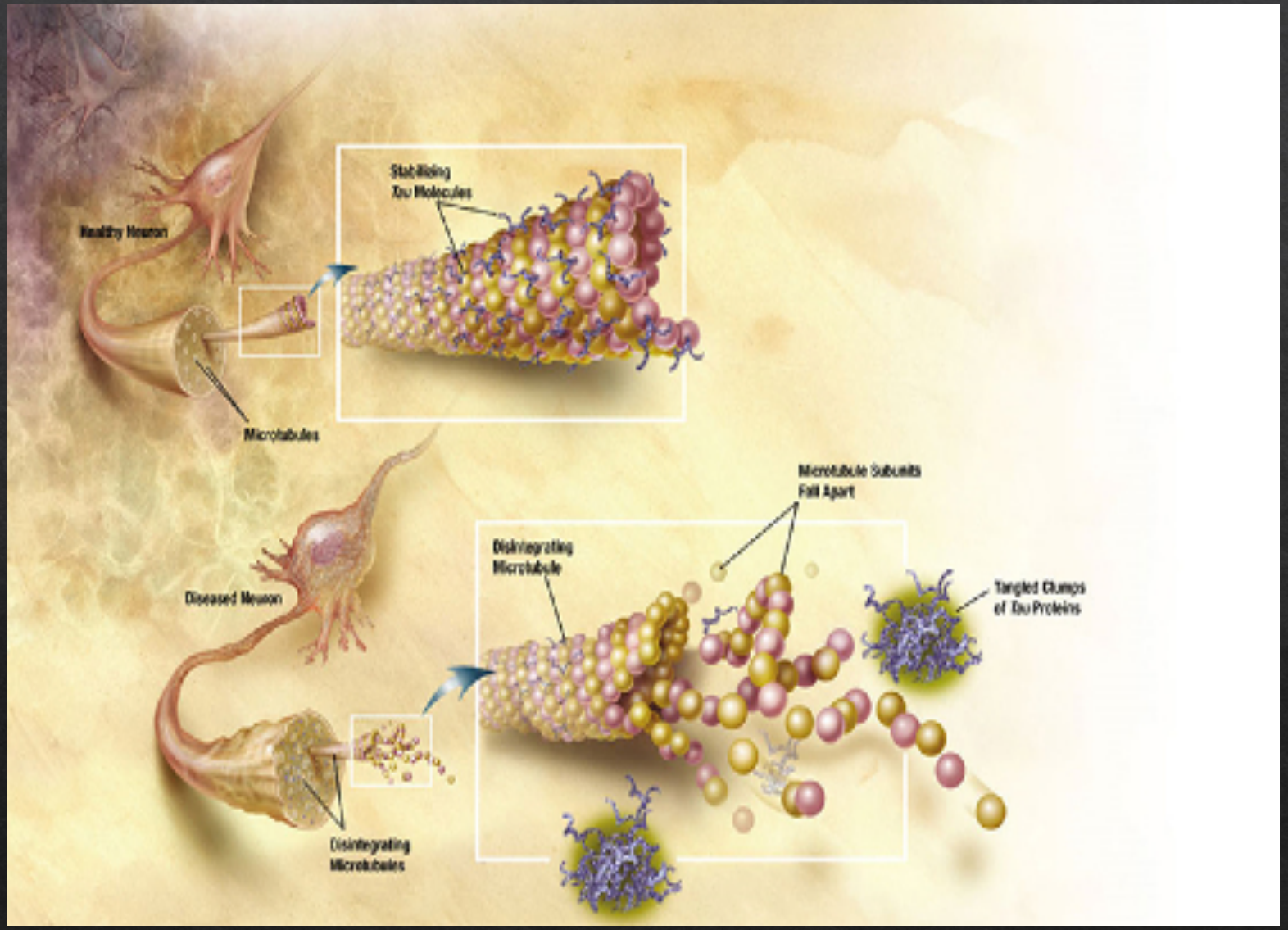


RISK FACTORS

- Repetitive head trauma sustained during activities like:
  - Contact sports – boxing, football, ice hockey, rugby, etc.
  - Military - due to exposure to biomechanical loading of kinetic energy and forces.

  3 or more concussions increase the likelihood of prolonged cognitive symptoms .
- Genetic Risk factors like :
  - Apolipoprotein E-ε4 allele – controversial association but, in previous studies, has been associated with – worse neurological outcomes, delayed recovery from neurotrauma, and greater cognitive deficits.

PATHOGENESIS AND NEUROBIOLOGY



Normal tau protein is predominantly axonal microtubule-binding protein that promotes microtubule assembly and stability.

Repetitive brain trauma leads to CTE through tau oligomerization following axonal deformation and microtubular destabilization.

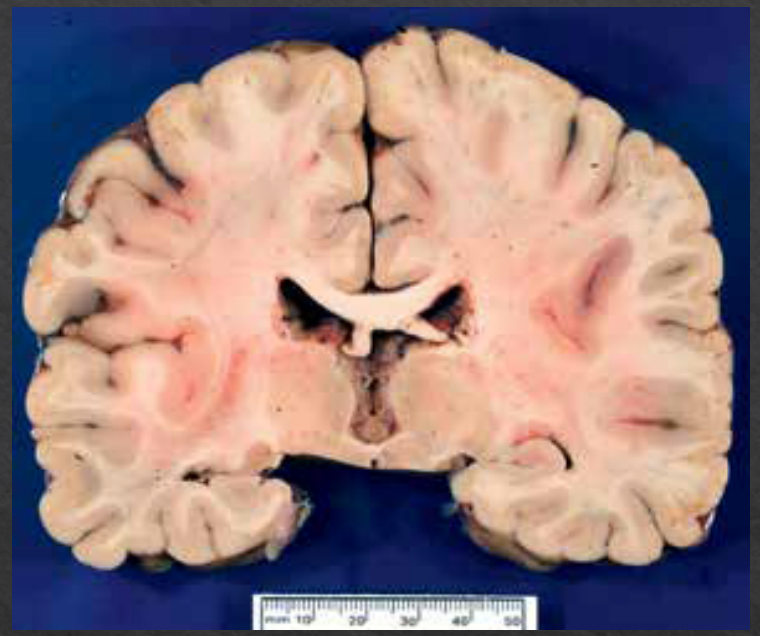
tau oligomers hyperphosphorylate & develop into paired helical and straight filamentous neurofibrillary tangles, which interfere with white matter tracts in the brain and cause signaling and communication abnormalities through denervation injury.

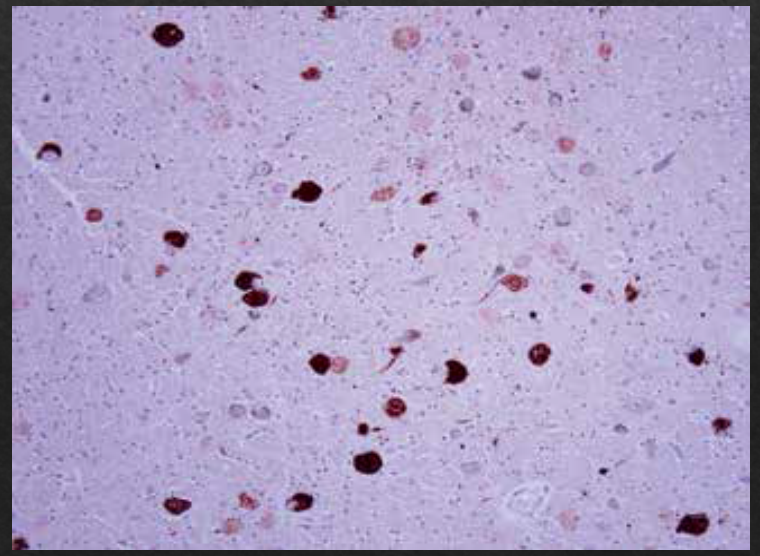
PATHOGENESIS

- Hyperphosphorylation of tau results in microtubule disassembly, impaired axonal transport, neuronal and synaptic dysfunction, and eventually neuronal death.
- It is thought that TBI induces the activation and accumulation of kinases, which hyperphosphorylate tau.
- Other proposed mechanisms include :
  - chronic neuroinflammation,
  - microglial activation,
  - glutamate-driven neuronal immunoexcitoxicity,
  - mitochondrial dysfunction and oxidative stress, and
  - calcium dysregulation

PATHOLOGY

- GROSS EXAMINATION - unremarkable without any focal or lobar necrosis, infarct, hemorrhage, or significant cortical atrophy.
- MICROCOPIC EXAMINATION – on IHC- presence of neurofibrillary tangles (NFTs) and neuritic threads (NTs) in all regions of the brain.
- Exhibit a distinctive *skip phenomenon* in the neocortex, whereby NFTs are haphazardly located, being present and absent in adjacent regions of the neocortex (laminae 2 and 3) within the same lobe of the brain.
- Distributed more in perivascular regions and in the depths of the sulci.
- Secondary amyloidopathy may accompany the primary tauopathy of CTE in about 20–30% of cases but is not a prerequisite or defining proteinopathy of CTE.





CLINICAL FEATURES

- CTE presents clinically after a prolonged latent period as a composite syndrome of mood disorders and behavioral and cognitive impairment, with or without sensorimotor impairment.
- Mean onset of symptom presentation was 42.8 years of age after initial exposure, but ranges from 25 to 76 years of age.
- Stern et al. report CTE to present in two distinct patterns:
  - Young-age onset with initial behavior/mood perturbations that manifest at around age 35. These include impulsivity, aggressiveness, violent tendencies, and progression to deficits in cognition.
  - Late-age onset with cognitive deterioration, which presents around age 60. This subset is characterized by deficits in executive function and attention memory.

Table 2. Reported symptoms and signs of CTE

A. Cognitive impairment
1. Loss of memory and memory disturbances
2. Deterioration in linguistic coherence and language impairment
3. Deterioration in professional competence, work performance and socioeconomic status
   i. Poor attainment of set goals
4. Impaired capacity to engage in complex intellectual reasoning and executive functioning
5. Impaired attention and concentration
6. Deterioration in capacity to manage money and personal bank accounts
7. Visuospatial impairment and difficulties

B. Behavioral impairment and mood disorders
1. Insomnia
   i. Deteriorating capacity to fall asleep and remain asleep for long
   ii. Waking up in the middle of the night and in the early morning, and not being able to fall back asleep
2. Paranoid ideations and delusions
3. Social phobias
4. Breakdown of intimate and family relationships
   i. Spousal separation and divorces
5. Disinhibition and loss of social etiquette
   i. Poor social judgment, social and sexual indiscretions and improprieties
   ii. Violent and criminal behaviors and tendencies
   iii. Socially disinhibited speech
   iv. Abuse of alcohol, prescription and illicit drugs
6. Increasing impulsivity
7. Increasing religiosity
8. Mood disorders
   i. Rampant fluctuations in mood, and mood swings
      1. Sudden highs and lows; happy and sullen
      2. Intermittent periods of high-energy levels, drives and enthusiasm; low energy levels, no drive and no enthusiasm
   ii. Exaggerated responses to minor life stressors and issues of daily living
      1. Bouts of explosive anger, worry, and agitation
   iii. Increasing irritability and aggression
   iv. Anxiety and agitation
   v. Major depression, suicidal thoughts and ideations, parasuicides and suicides
      1. Apathy and feelings of hopelessness

C. Physical symptoms and motor dysfunction
1. Headaches, generalized body aches and pain
2. Motor speech impairment (dysarthria)
3. Spasticity and parkinsonism including tremors
4. Gait impairment and motor incoordination (ataxia)
5. Muscle weakness, spasms, and pain, and other bulbar and spinal motor neuron symptoms

Posttraumatic epilepsy or seizure disorder is more a feature of PTE and not CTE.

DIAGNOSIS

- The definitive diagnosis of CTE rests on microscopic tissue examination with histochemical and immunohistochemical tissue analysis of whole brain on post mortem examination.
- McKee et al. proposed a 4-stage classification system for CTE based on the extent of lesions and disease severity

Stage	Criteria
I	1 or 2 focal perivascular CTE lesions in cerebral cortex at the depths of the sulci.
II	>3 CTE lesions in multiple cortical regions and superficial NFTs along the sulcal wall and gyral crests.
III	Multiple CTE lesions, widespread cortical NFTs, and NFTs in the medial temporal lobes.
IV	Multiple CTE lesions, widespread cortical NFTs, NFTs in the medial temporal lobes, widespread astrocytic p-tau pathology, neuronal loss, and gliosis.

Note: Aß amyloid plaques are entirely age-dependent and have no relationship to staging.
Adapted from (56) with permission.

- Emerging evidence has highlighted the use of 2-(1-{6-[(2-[F-18] fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) malononitrile-positron emission tomography ([F-18] FDDNP PET) and other neuroimaging techniques for a preliminary pre-mortem diagnosis.
- FDDNP-PET measures both tau tangle and amyloid plaque deposition.
- Another emerging imaging modality, magnetic resonance spectroscopy (MRS) is being considered as a “virtual biopsy” to diagnose CTE. Neurometabolites such as N-acetyl aspartate, choline, and glutamine/glutamate (NAA, Cho and Glx) are shown to have similar changes on MRS imaging to CTE pathological changes, although not specific.
- Recently, there has been a range of biomarkers approaching clinical validation (glial fibrillary acidic protein, S100B), and some are more emerging, such as microtubule-associated protein-2 (MAP-2) and brain-derived neurotrophic factor (BDNF).

CTE vs PTE

- POST TRAUMATIC ENCEPHALOPATHY (PTE) – in contrast to CTE, PTE is a nonprogressive clinicopathologic syndrome characterized by persistent sequelae induced by focal and or diffuse traumatic brain injury.
  - PTE spectrum includes but is not limited to, contusions and lacerations of the brain, secondary traumatic hypoxic-ischemic cerebral injury and hippocampal necrosis, traumatic intracranial hemorrhages, and secondary traumatic cerebral herniations and necrosis.
  - PTE injuries typically induce focal necrosis of brain tissue, cavitation, activation of microglia, and infiltration by histiocytes, resulting in gross scarring of the brain.
  - Post-traumatic epilepsy is a well-known subtype of PTE.
  - Changes are more likely to present with focal lateralizing neurological symptoms and signs.

PTE is non-progressive and is not a neurodegenerative disorder while CTE is a progressive and neurodegenerative disorder.

DIFFERENTIAL DIAGNOSIS

- Conditions that might mimick CTE include :
  - Alzheimer’s disease *(in contrast to CTE, NF tangles are seen in the deeper cortex laminae 5 and 6)*
  - Corticobasal degeneration
  - Amyotrophic Lateral Sclerosis
  - Frontotemporal dementia

TREATMENT

- Currently, there are no curative treatments for CTE.
- Symptomatic treatments are the mainstay.
- Future Prospects in Potential Therapeutics-
  - Salslate, a non-steroidal anti-inflammatory drug (NSAID), reduces p-300 mediated acetylation of tau resulting in improved cognition and reduced atrophy of brain regions such as the hippocampus.
  - Methylene Blue (MB), an inhibitor of tau aggregation, may thus be promising if findings are consistent in large-scale human clinical trials.

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