



The incidence of post-traumatic epilepsy after TBI: a TRACK-TBI study

18TH ANNUAL NEURO-TRAUMA SYMPOSIUM

Monday, December 2, 2019

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Traumatic Brain Injury: 2019

A Complex and Heterogeneous Disease

Clinical Assessment

GCS

(Glasgow Coma Scale)

Mild Severe
Concussion

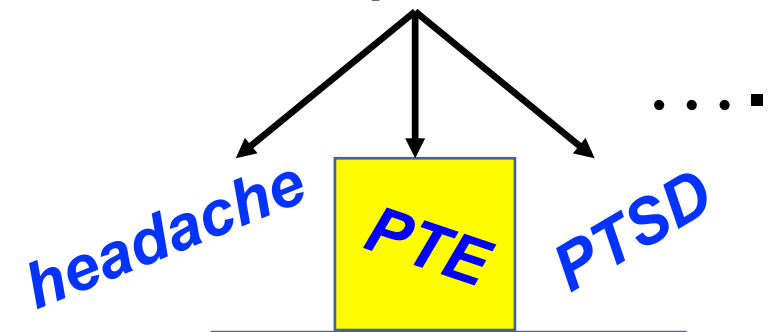
Outcome

GOS

(Glasgow Outcome Scale)

Death Vegetative
Good Recovery

Sequelae



1. Incidence
2. Risk-Factors
3. Outcome

Post-traumatic Epilepsy: Outcome

	Year 5	
	LPTS	Non-LPTS
DRS score ^b	3.0 ± 2.8	1.8 ± 2.2
FIM Cognitive subscale score ^c	29.7 ± 5.2	31.7 ± 3.7
FIM Motor subscale score	83.7 ± 12.5	87.9 ± 5.0
FIM Total score	114.1 ± 15.7	118.1 ± 8.0
SRS score		
Independent	29/56 (52%)	46/75 (61%)
Unsupervised overnight	18/56 (32%)	26/75 (35%)
Supervised overnight	9/56 (16%)	3/75 (4%)
Illegal drug use	16/79 (20%)	10/82 (12%)
Arrests ^d	5/80 (6%)	5/84 (6%)
Attempted suicide ^d	2/73 (3%)	2/79 (3%)
Psychiatric hospitalization ^d	3/73 (4%)	2/80 (3%)
Satisfaction with sexual activity ^d	23/29 (79%)	25/30 (83%)
SWLS score ^e	17.4 ± 8.2	22.9 ± 7.6

Bushnik, et al (2012), J Head Tr. Rehab¹

Why is it important to diagnose and treat PTE?

- Patients with TBI and PTE perform worse across several performance and clinical metrics:
 - Independence
 - Cognitive Assessments
 - Illegal drug use
 - Satisfaction with life
- Patients with PTE are significantly more disabled, less independent, and prone to higher rates of mental illness (depressions, addiction, etc)
- **Bottom-Line:** Preventing PTE will improve outcomes following TBI.

How likely is PTE after TBI?

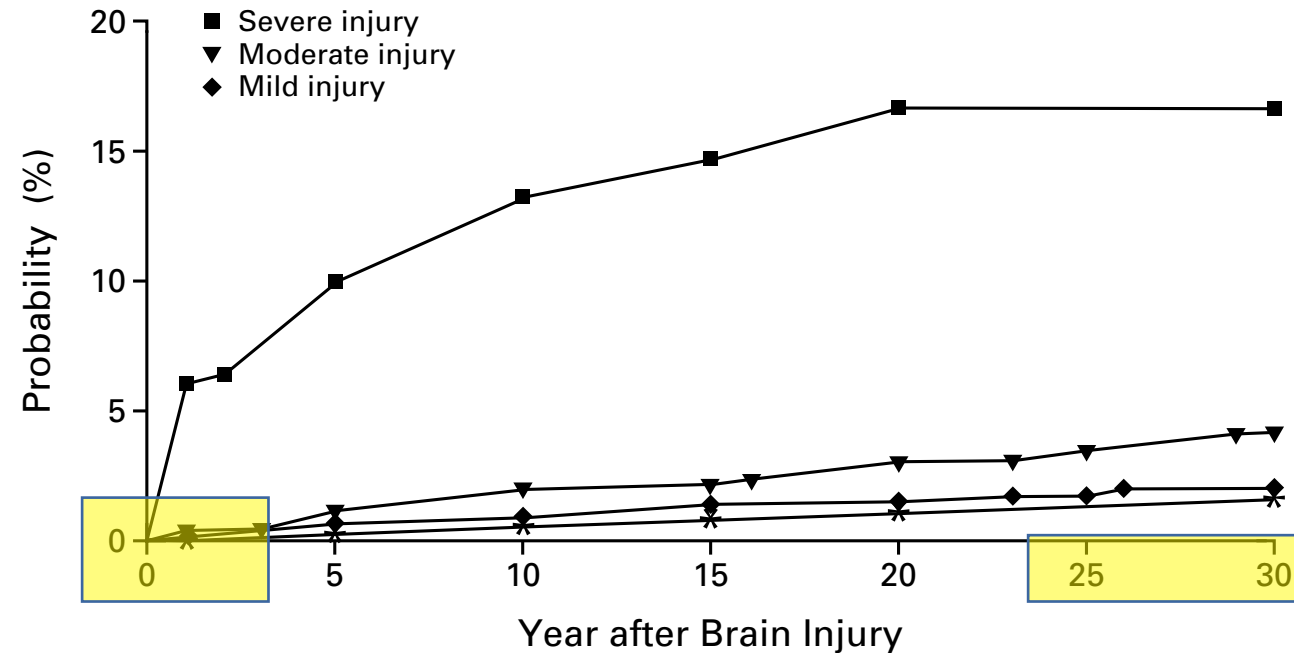
Post-traumatic Epilepsy: Incidence

Why is it important to know the incidence of PTE?

- 2.8 million TBI/yr in US
- 20% symptomatic epilepsy from trauma²
- Understanding the incidence, risk factors, and mechanisms for PTE has major public health implications

What do we know?

- Best incidence data over 20+ yrs old.
- **Relation between injury severity and PTE**
 - “mild TBI” incidence 0.7% at 5 years
- PTE incidence goes up linearly to 30 yrs
 - 2.1% at 30 years



Annegers, et al (1998), NEJM³

What is our approach?

Prospective longitudinal Precision Medicine Study

- 3000 subjects, including **Controls**

-Across the spectrum from concussion to coma

TRACK TBI Goals

1. Improve TBI diagnosis and classification/taxonomy →
2. Improve TBI outcome assessment →
3. Identify the health and economic impact of Mild TBI →
4. Create a “Information Commons” to promote collaboration and acceleration of TBI research →

PTE Study Goals

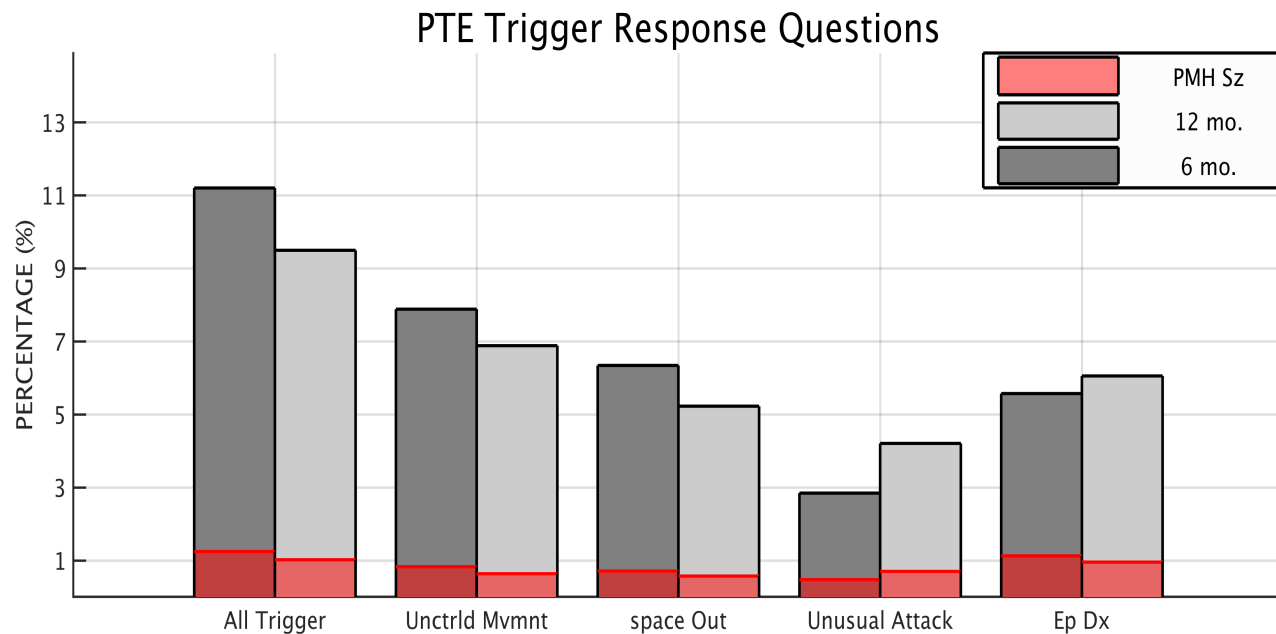
1. **Sequelae: who develops PTE?**
2. How does PTE affect outcome?
3. PTE as a cause of seizures.
4. Predictive models/risk calculators of developing PTE at time of injury.

Methods: NINDS PTE screening questionnaire

- 2,698 TRACK TBI patients
- At **6-** and **12-**month follow up, patients given an epilepsy screening questionnaire
- Based on results of four “trigger” questions, patients were asked additional questions to verify PTE cases.
- Trigger questions based on NINDS PTE screening questionnaire

Have you had or has anyone ever told you that you had any of the following?	
55a.	Uncontrolled movements of part or all of your body such as twitching, jerking, shaking, or going limp, lasting about 5 minutes or less? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unknown
55b.	An unexplained change in mental state or level of awareness; or an episode of “spacing out” which you could not control, lasting about 5 minutes or less? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unknown
55c.	Any other type of repeated unusual attacks or convulsions lasting about 5 minutes or less? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unknown
56.	Has anyone ever told you that you have seizure(s) or epilepsy? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unknown
If 1 or more of questions 55a, 55b, 55c or 56 = yes then ask questions 57 – 62. If 55a – 56 are each = no then skip question 57 – 62 and go to question 63.	

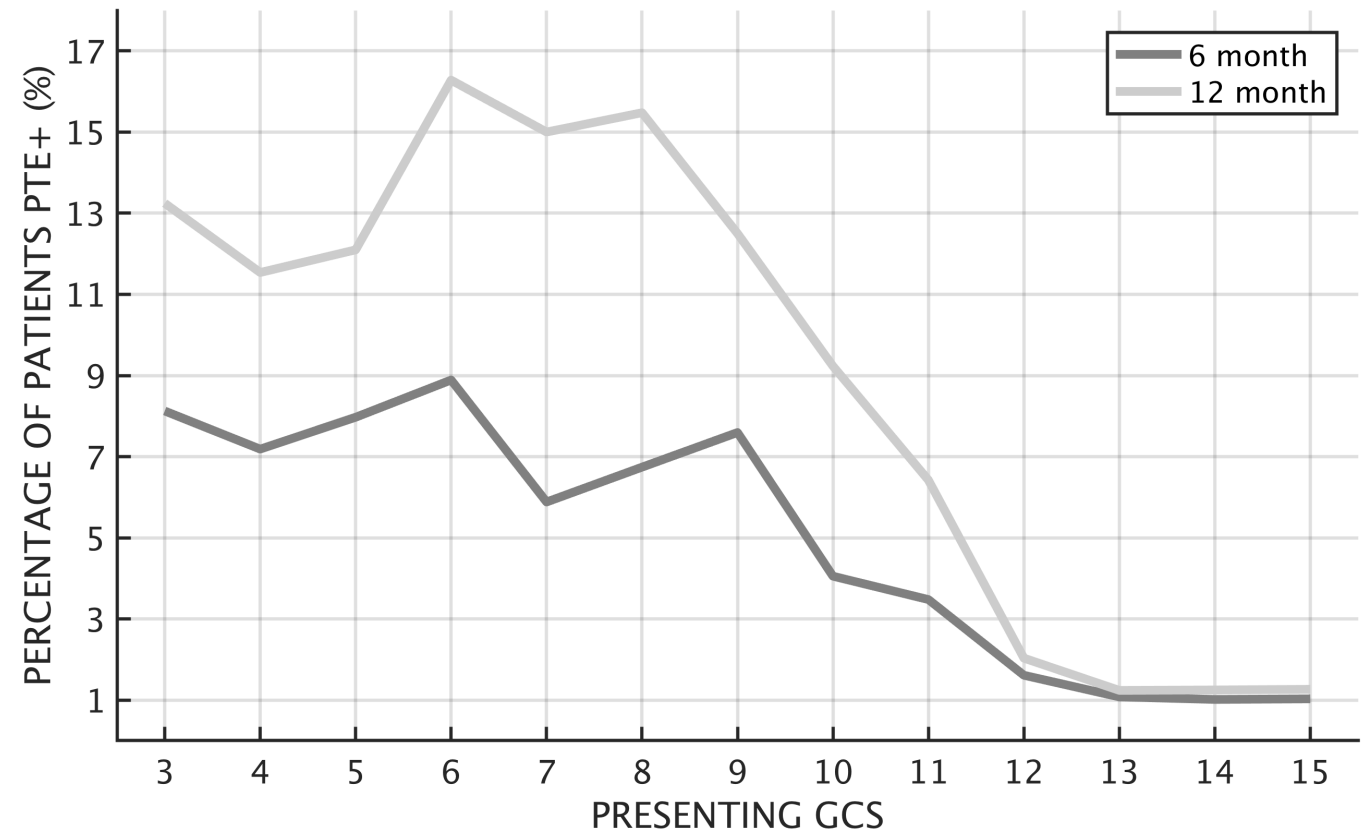
Results: Response to “triggers”



- Detecting heterogeneous pathology
 - concussion syndrome
 - nausea/vomiting, vertigo manifesting as “unusual attacks”
 - Sensitive not specific
- Increased incidence at 6 months
 - not expected based on Anneger’s data
 - possible increased vigilance
- Far above baseline epilepsy rate
 - also should the cohort of patients who seized and fell

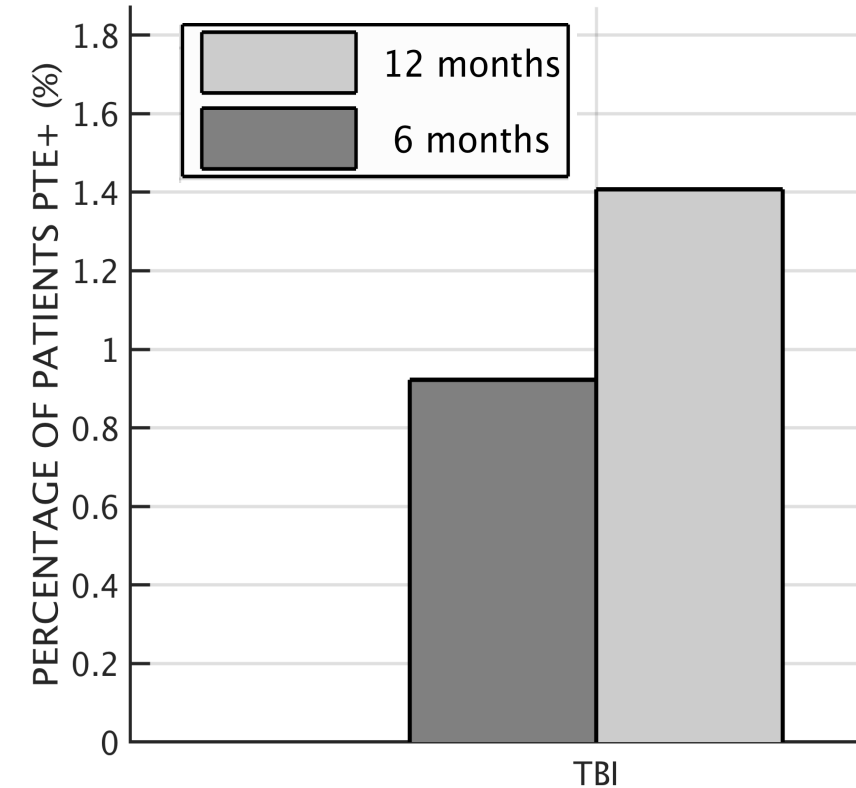
Results: PTE across TBI spectrum

- full incidence of PTE depends on the severity of presentation
- dramatic increase in PTE risk in GCS 3 - 8
- higher rate at 12 months indicates increasing seizure development
- GCS 13-15
 - non-trivial (~1%)
 - What is combined rate of PTE for GCS 13-15 cohort?



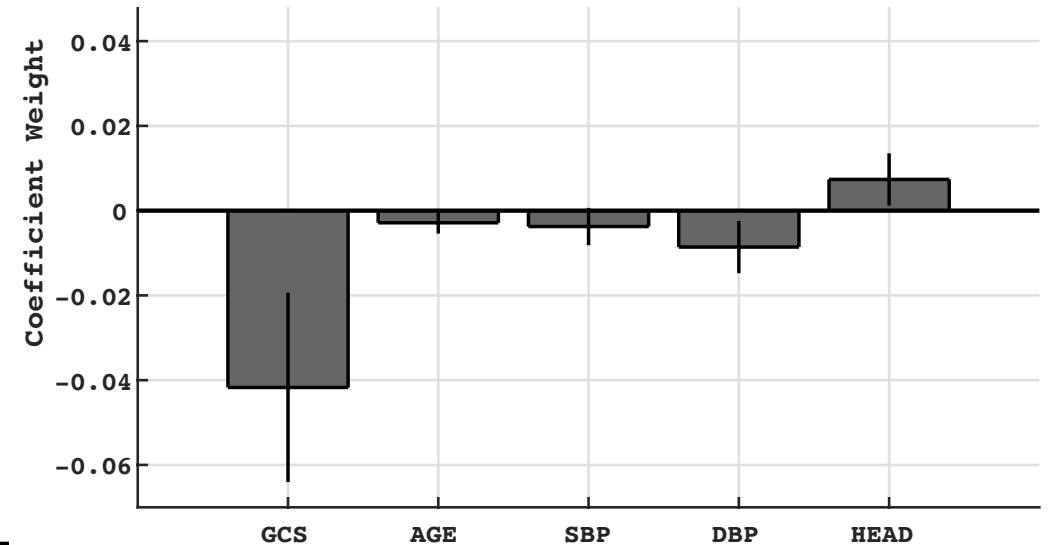
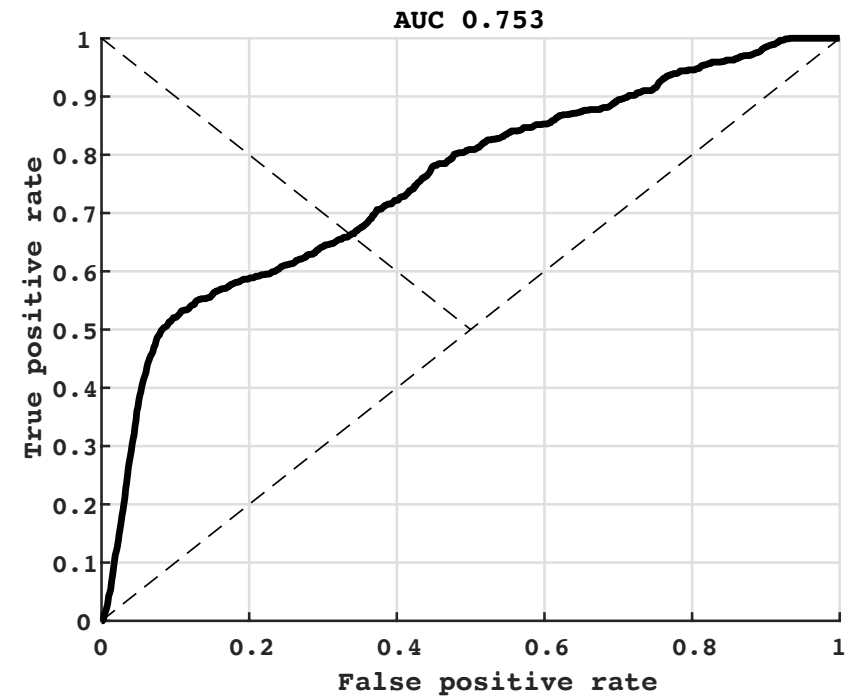
Results: PTE after TBI (GCS 13-15)

- Seizure in less severe TBI (GCS 13-15) is 1.4% at 12 months
- Higher than the rate quoted in Anneger's et al (largest **retrospective** study to date, 0.7%)
- Indicates less clinically severe TBI confers an additional seizure risk even at 12 months



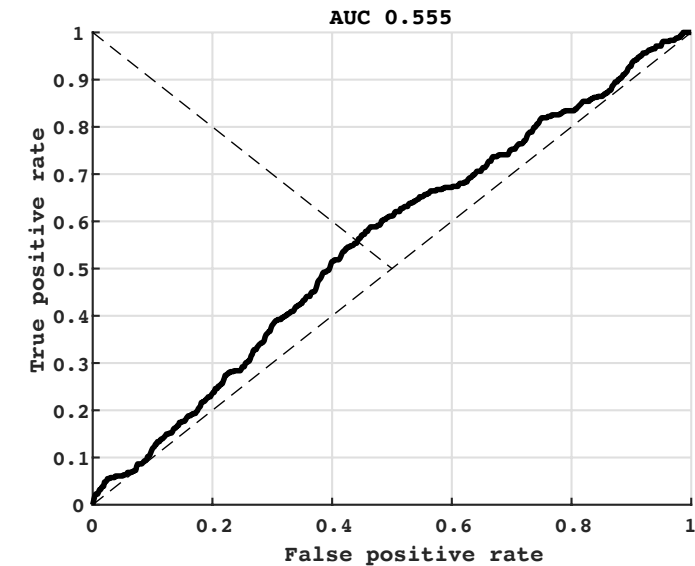
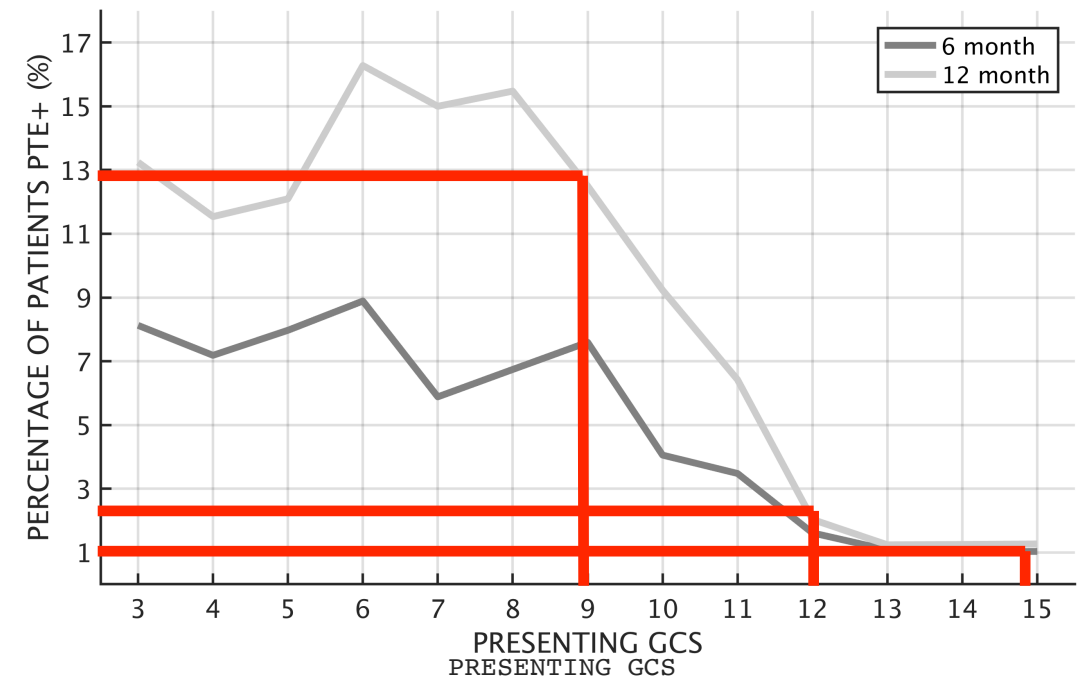
Prediction I

- Ultimate goal is to predict who is at risk of PTE, and enter them into an aggressive seizure monitoring/treatment protocol
- One strategy is to use all clinical variables in a multivariate classifier, to maximize prediction accuracy.
 - Very good results
 - prediction > chance ($0.75 > 0.5$)
- When we look at the weights initial GCS is the most predictive variable
 - Caution: What is driving this effect?



Prediction II

- First results suggest GCS is best predictor
 - Double the risk of PTE at 12 months when $GCS < 12$
 - 10 x the risk for all $GCS \leq 8$
 - **Simple rule:** all patients with GCS 12 or less should be monitored closely with intensive PTE screening
- GCS 13-15: where prediction algorithms are needed the most
 - Large number of patients, few get PTE
 - More challenging to predict
 - $AUC = 0.555$ is still significantly > 0.5
 - Future classifiers should incorporate use of serum biomarkers, imaging, clinical data:
Precision medicine approach



Limitations

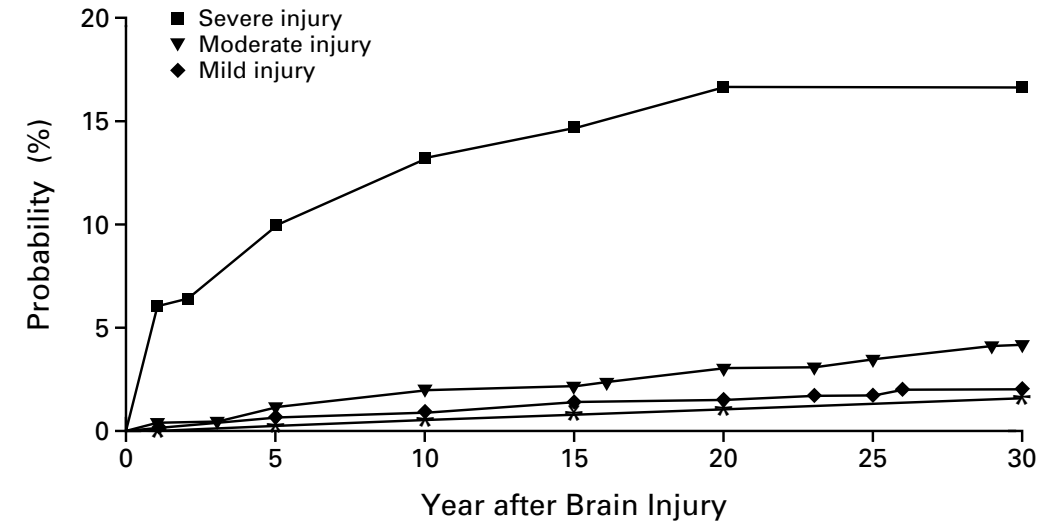
Three major limitations in this analysis

1. Follow-up

- Anneger's data suggest that there is a linear increase in PTE rate up to 30 years
- 12 month follow-up means we are misclassifying PTE patients

2. Diagnosis

- Epilepsy should be diagnosed by an epileptologist
- We need more accurate seizure work-up and assessments



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Overview of TRACK-TBI LONG

N = 3300 TBI and Control Subjects



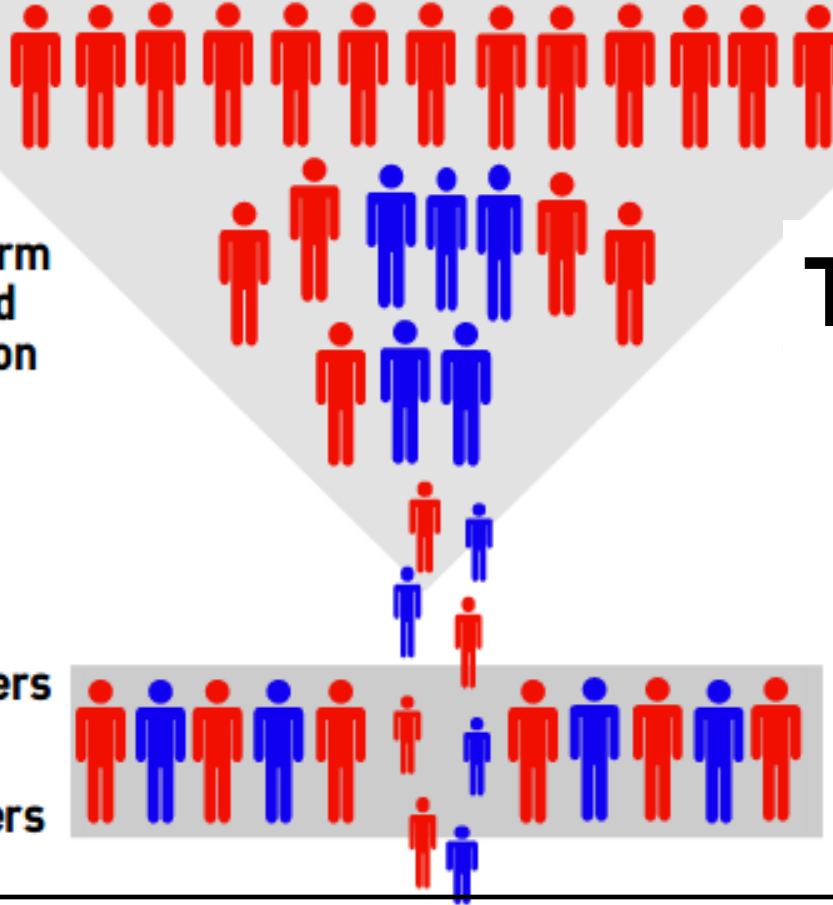
AIM 1 | Telephonic long-term follow up/screening and consent for brain donation



AIM 2 | Imaging biomarkers



AIM 3 | Biofluid biomarkers



TRACK-TBI EPI

- All subjects in TRACK-TBI
 - contacted via phone 5 years after index TBI
- Subjects with positive NINDS screen → evaluated in clinic
 - EEG/epileptologist evaluation
 - repeat psychological evaluation
 - MRI/blood biomarker evaluation

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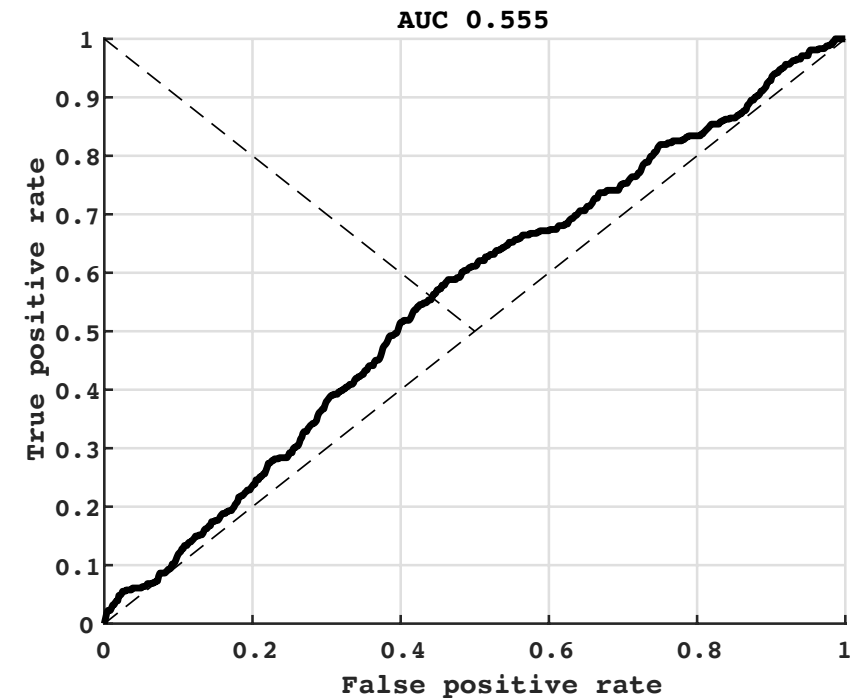
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3. Prediction models

- Ripe for predictive analytic approach
- Blood biomarkers, imaging, clinical, genome...



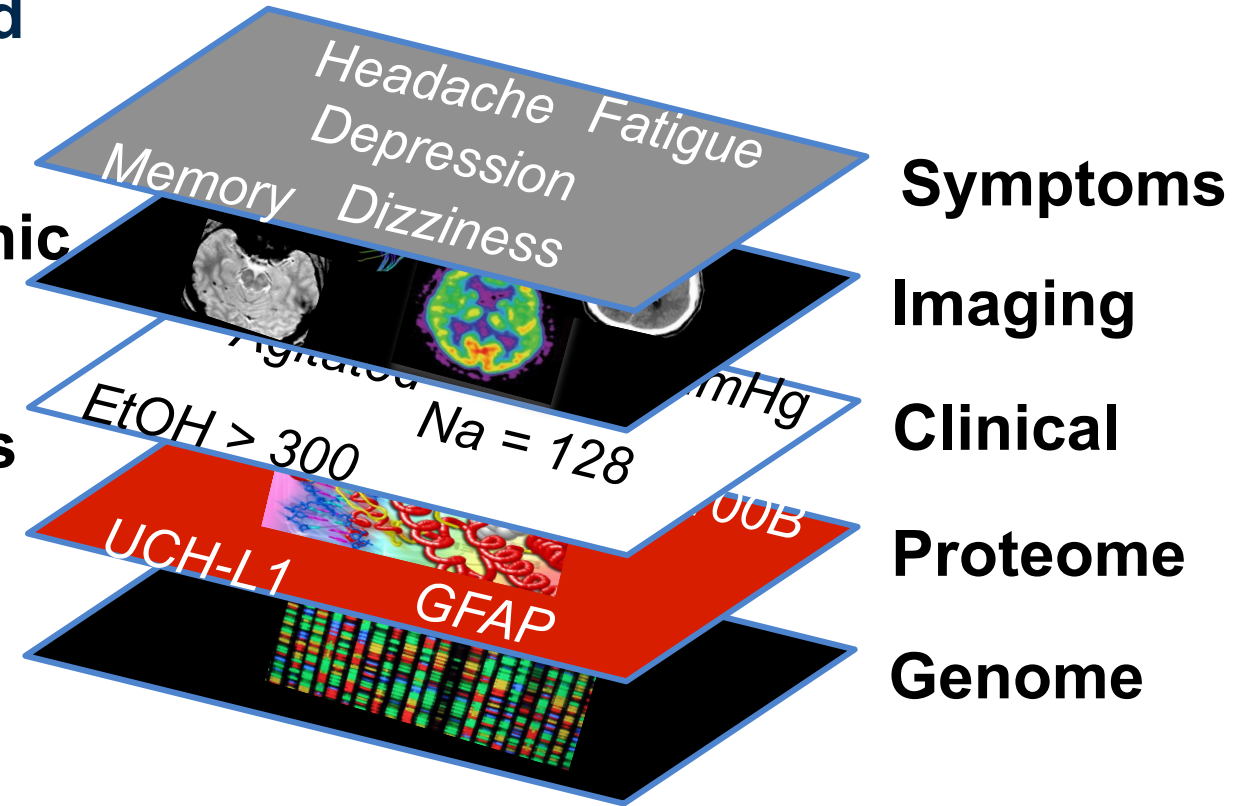
Conclusions and next steps

PTE is a common complication of TBI and cause of epilepsy

Development of effective anti-epileptogenic treatments will require a sophisticated understanding of the clinical, imaging, neurophysiologic, and molecular features of epileptogenicity resulting from TBI

A Precision Medicine approach to PTE

- Clinical risk factors
- Imaging and blood-based biomarkers
- Genetics



Thank you

Acknowledgements

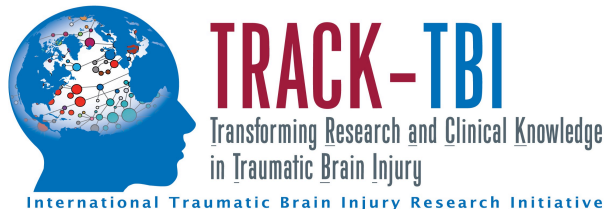
- Dr. Geoffrey Manley, Dr. Michael Huang, Dr. Phiroz Tarapore, Dr. Sanjay Dhall

TRACK-TBI Team, including

- Dr. Ramon Diaz-Arrastia
- Dr. Nancy Temkin
- Dr. Dan Lowenstein
- Brian Fabian
- Sabrina Taylor

SFGH BASIC Team, including

- Lawrence Chyall, MS, RN
- Julia Thompson Gallego, MS, ACNP-BC
- Daniel McGuire, MS, ACNP-BC
- Amy Winkelman, MSN, ACNP-BC
- Twyila Lay, MS, ACNP-BC
- Among others!



TBI
Endpoints
Development

A Collaborative for Advancing Diagnosis and Treatment of TBI

UCSF Weill Institute for
Neurosciences | Department of
Neurological
Surgery

References

1. Bushnik T, Englander J, Wright J, Kolakowsky-Hayner SA: Traumatic Brain Injury With and Without Late Posttraumatic Seizures: What Are the Impacts in the Post–Acute Phase: A NIDRR Traumatic Brain Injury Model Systems Study. **J Head Trauma Rehabil.** 27 (6): E36-E44
2. Lowenstein DH: Epilepsy after head injury: An overview. **Epilepsia** 50:4–9, 2009
3. Annegers JF, Hauser WA, Coan SP, Rocca WA: A Population-Based Study of Seizures after Traumatic Brain Injuries. **N Engl J Med** 338:20–24, 1998