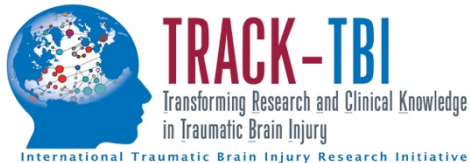


# TRACK-TBI: What Have We Learned and Where Are We Going

Geoffrey Manley, MD, PhD, on behalf of the  
TRACK-TBI and TED Investigators



# The Many Faces of Traumatic Brain Injury

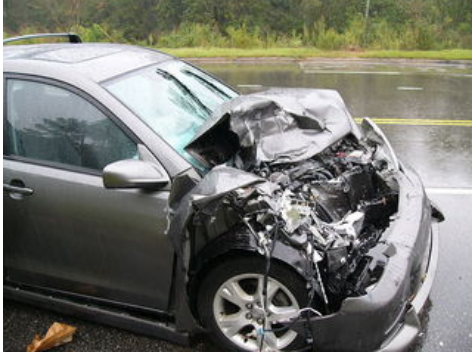


**400,000+  
TBI Diagnosed**



**1.6-3.8 million  
Per Year**

# The Many Faces of Traumatic Brain Injury



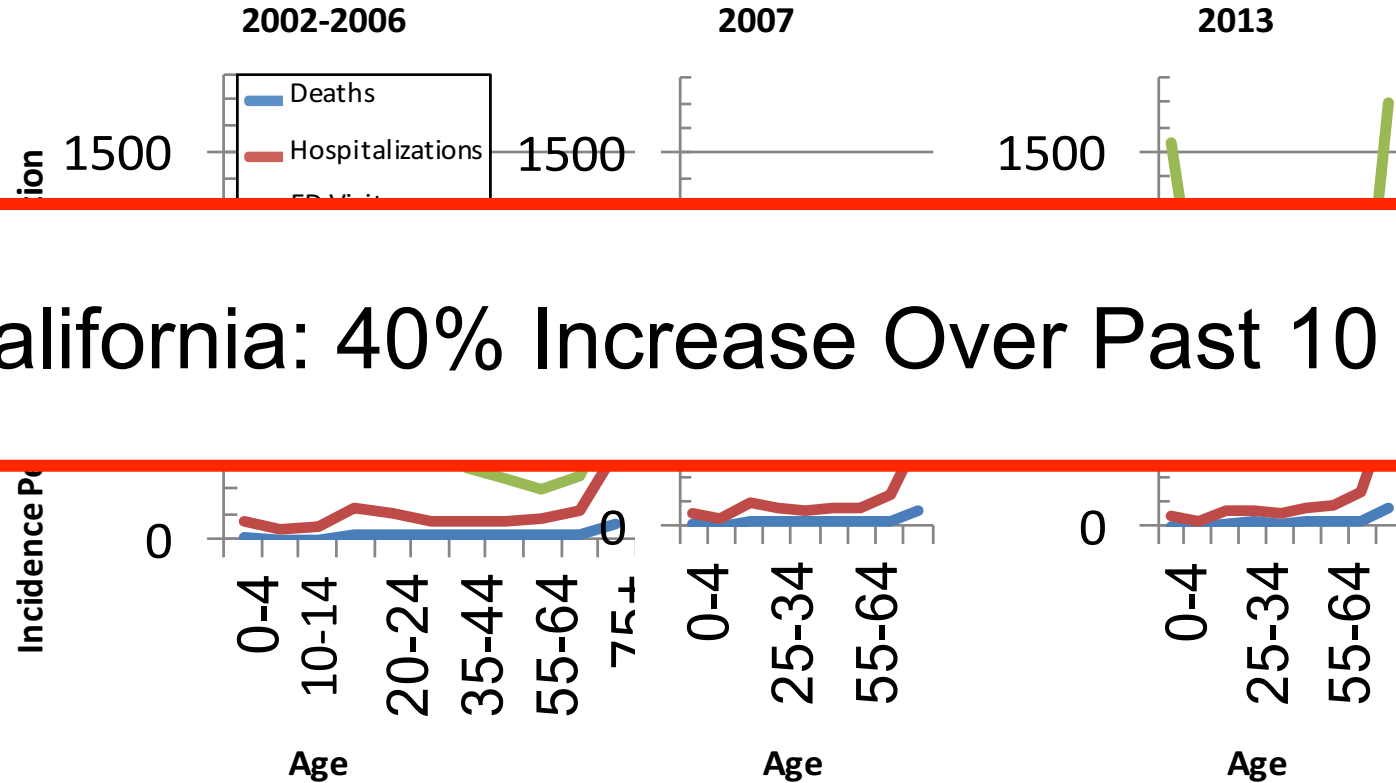
At least  
**4.8 million** seek  
medical care in the  
US each year

# The Many Faces of Traumatic Brain Injury





# Incidence of TBI is Increasing



California: 40% Increase Over Past 10 Years

*BMJ, 2018*

# Traumatic Brain Injury: 2019

Classification

**GCS**

(Glasgow Coma Scale)

**Mild**  
**Severe**  
**Concussion**



Outcome

**GOS**

(Glasgow Outcome Scale)

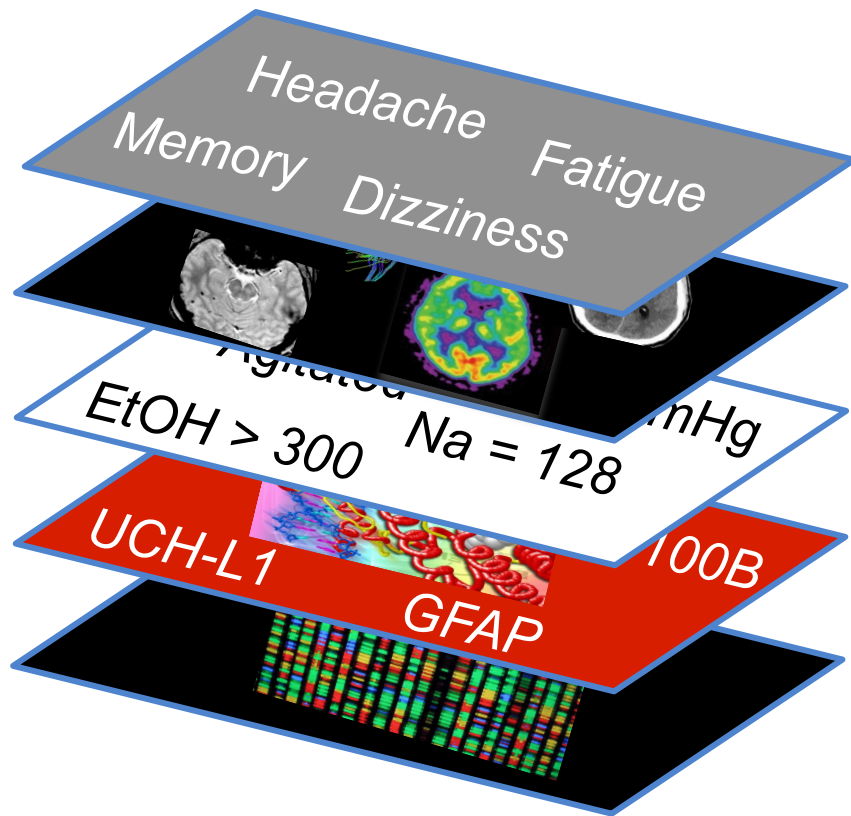
**PTSD**  
**Vegetative**  
**Death**  
**Depression**  
**Good Recovery**  
**Cognitive**

***A Complex and Heterogeneous Disease***

# A “Precision Medicine” Approach to TBI



**GCS**



**Symptoms**

**Imaging**

**Clinical Data**

**Proteome**

**Genome**



# TRACK-TBI

Transforming Research and Clinical Knowledge  
in Traumatic Brain Injury

International Traumatic Brain Injury Research Initiative

## Prospective Longitudinal Observational Study

- 3000 subjects, including **Controls**

*-Across the spectrum from concussion to coma*

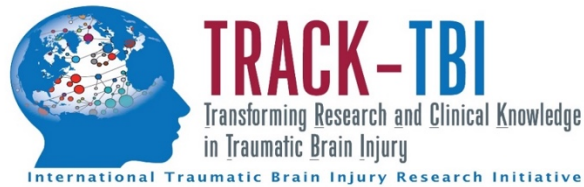
### Goals

- Improve TBI diagnosis and classification/taxonomy
- Improve TBI outcome assessment
- Identify the health and economic impact of Mild TBI
- Create an “Information Commons” to promote collaboration and acceleration of TBI research



# Clinical Sites

1. Baylor College of Medicine/  
TIRR Memorial Hermann
2. Denver Health Medical/  
Craig Rehabilitation
3. Emory University
4. Hennepin County Medical Center
5. Indiana University
6. Medical College of Wisconsin
7. Spaulding Rehabilitation Hospital/  
Massachusetts General Hospital
8. University of California, San  
Francisco
9. University of Cincinnati
10. University of Maryland
11. University of Miami
12. University of Pennsylvania
13. University of Pittsburgh
14. University of Utah Health Care
15. University of Washington
16. UT Austin-Seton
17. UT Health Houston
18. UT Southwestern
19. Virginia Commonwealth University



**The Top Trauma Centers in the Country**

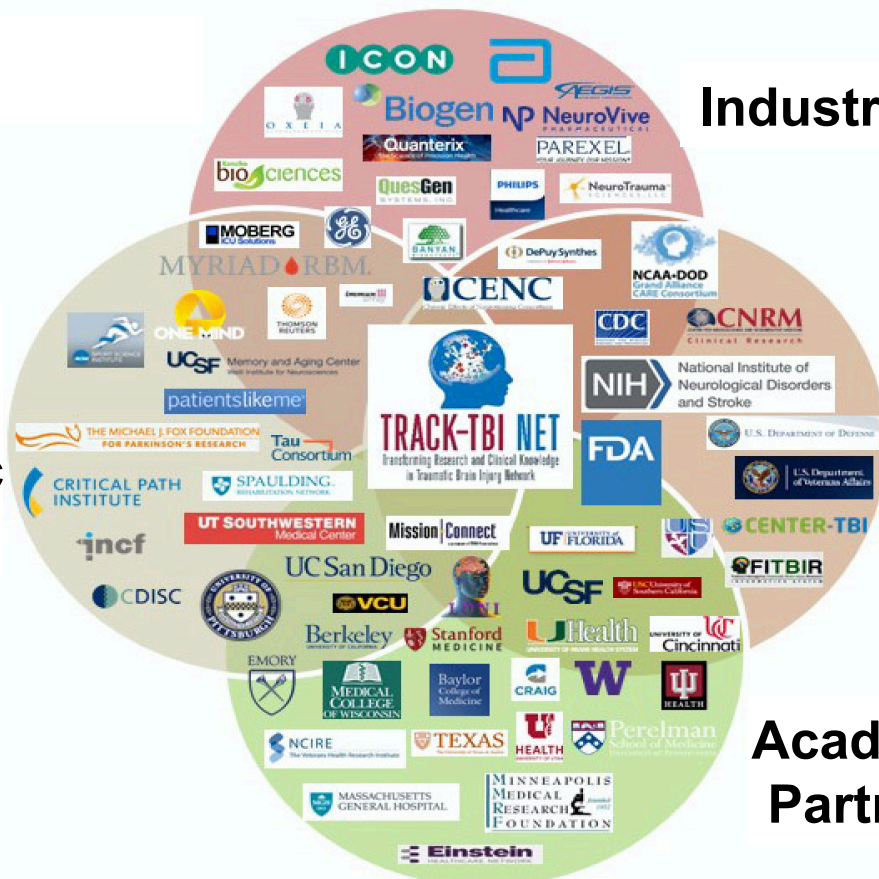
# TRACK-TBI Team



*Evolving from Competitors to Collaborators*

# Public-Private Partnership

Not for Profit  
and  
Philanthropic  
Partners



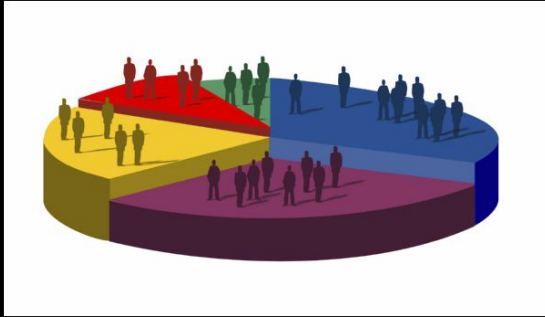
Industry Partners

Government  
Partners

Academic  
Partners



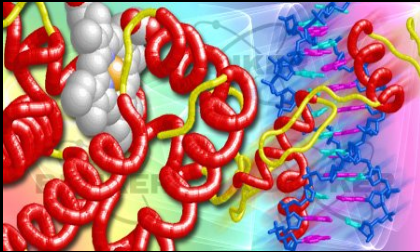
# TRACK-TBI: a Precision Medicine Approach



Demographics/Clinical



Genetics



Blood-Based (GFAP)



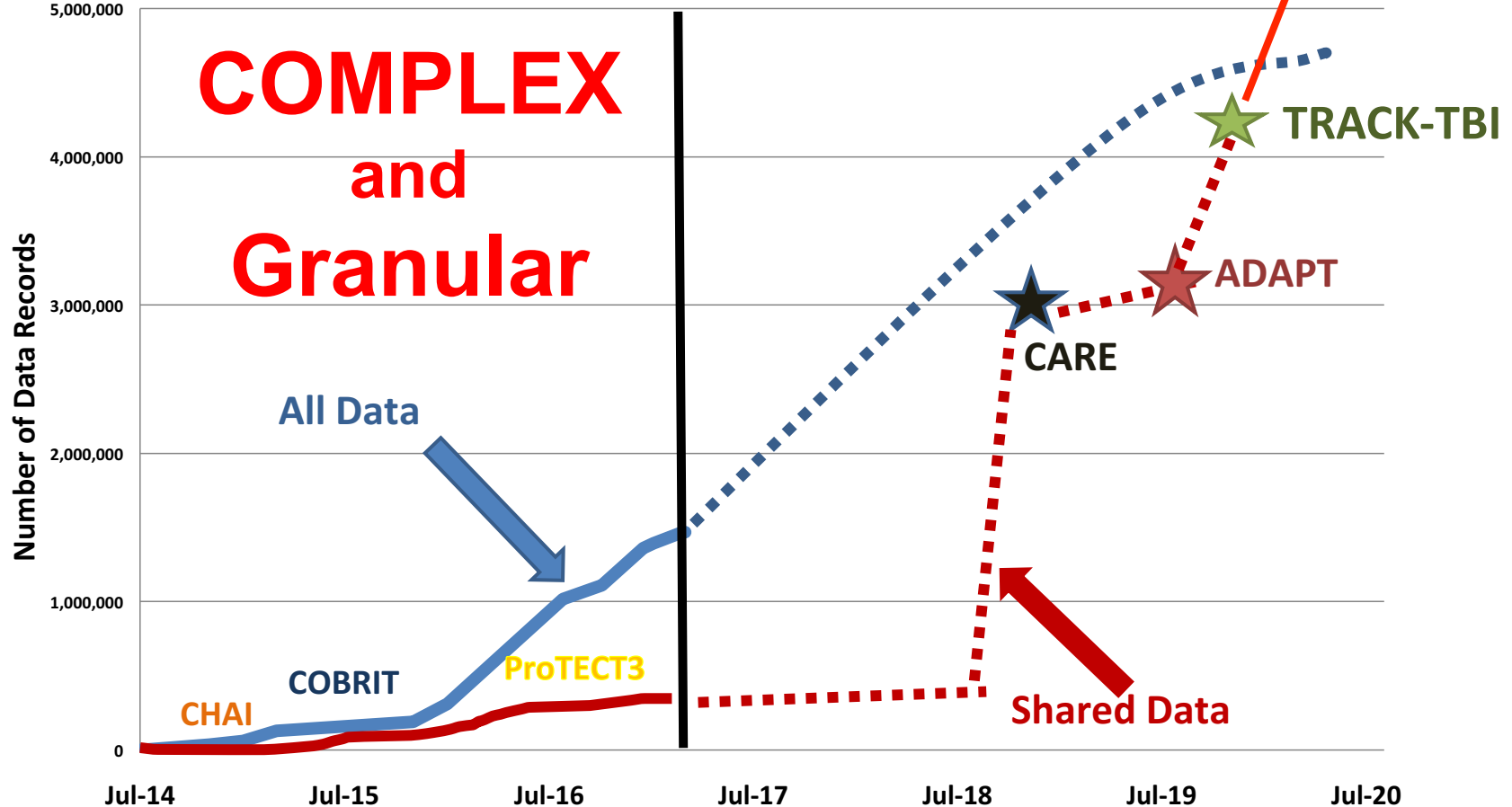
Imaging



Outcomes



## Data Projections with Current Studies



# Recovery After Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers

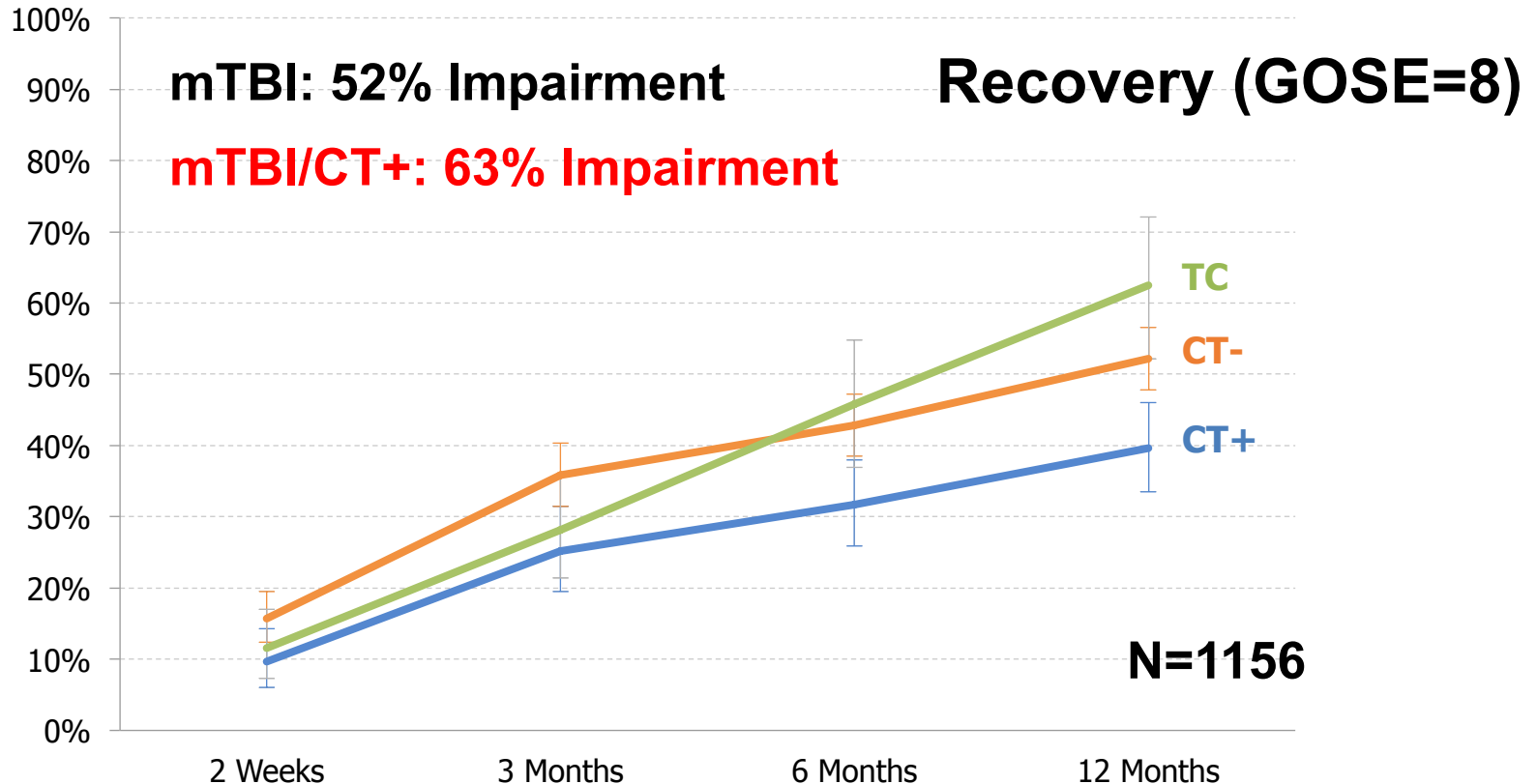
## A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study

Lindsay D. Nelson, PhD; Nancy R. Temkin, PhD; Sureyya Dikmen, PhD; Jason Barber, MS; Joseph T. Giacino, PhD; Esther Yuh, MD, PhD; Harvey S. Levin, PhD; Michael A. McCrea, PhD; Murray B. Stein, MD, MPH; Pratik Mukherjee, MD, PhD; David O. Okonkwo, MD, PhD; Ramon Diaz-Arrastia, MD, PhD; Geoffrey T. Manley, MD, PhD; and the TRACK-TBI Investigators

**Nelson, et al, June 2019**

**63% of GCS 13-15 with a + CT Findings are Impaired at 12 months**

# Is “Mild” TBI Mild?



# Specific Symptoms Endorsed at 12 months

Specific Symptoms Endorsed	mTBI	Ortho	Risk Ratio (95% CI)
	% Endorsed (95% CI)		
Headache	36% (33, 39)	9% (5, 16)	<b>3.41</b> (1.88, 6.17)
Dizziness	26% (23, 29)	9% (5, 16)	<b>2.47</b> (1.36, 4.49)
Nausea	10% (8, 13)	5% (2, 11)	1.44 (0.69, 3.03)
Noise sensitivity	28% (25, 31)	11% (6, 18)	<b>2.40</b> (1.36, 4.24)
Sleep disturbances	36% (33, 40)	26% (18, 35)	1.37 (0.97, 1.95)
Fatigue	41% (37, 44)	22% (15, 31)	<b>1.67</b> (1.16, 2.41)
Irritability/anger	33% (30, 37)	9% (5, 16)	<b>3.50</b> (1.87, 6.57)
Depression/tearfulness	26% (23, 29)	11% (6, 18)	<b>2.24</b> (1.27, 3.96)
Frustration/impatience	35% (31, 38)	11% (6, 18)	<b>2.95</b> (1.68, 5.18)
Forgetfulness/poor memory	47% (43, 50)	11% (6, 18)	<b>4.04</b> (2.31, 7.07)
Poor concentration	37% (34, 40)	11% (6, 18)	<b>3.20</b> (1.82, 5.61)
Taking longer to think	41% (38, 45)	9% (5, 16)	<b>4.33</b> (2.31, 8.11)
Blurred vision	20% (17, 23)	4% (1, 9)	<b>4.69</b> (1.78, 12.36)
Light sensitivity	20% (17, 23)	7% (3, 13)	<b>2.63</b> (1.27, 5.44)
Double vision	9% (7, 11)	1% (0, 4)	<b>8.14</b> (1.14, 57.98)
Restlessness	25% (22, 28)	12% (7, 20)	<b>1.82</b> (1.08, 3.06)



# Translating Research Innovation into Public Health Solutions



Original Investigation | Emergency Medicine

## Assessment of Follow-up Care After Emergency Department Presentation for Mild Traumatic Brain Injury and Concussion Results From the TRACK-TBI Study

Seth A. Seabury, PhD; Étienne Gaudette, PhD; Dana P. Goldman, PhD; Amy J. Markowitz, JD; Jordan Brooks, BA; Michael A. McCrea, PhD; David O. Okonkwo, MD, PhD; Geoffrey T. Manley, MD, PhD; and the TRACK-TBI Investigators

- **Major gaps in follow up and treatment**
- **Substantial number of patients with undiagnosed depression, anxiety, and other symptoms**



# TRACK-TBI

Transforming Research and Clinical Knowledge  
in Traumatic Brain Injury

International Traumatic Brain Injury Research Initiative

## Follow-up GCS 13-15

### 13 Study Sites

Washington

UCSF

UTSW

Baylor/UT Houston

Austin

Miami

Cincinnati

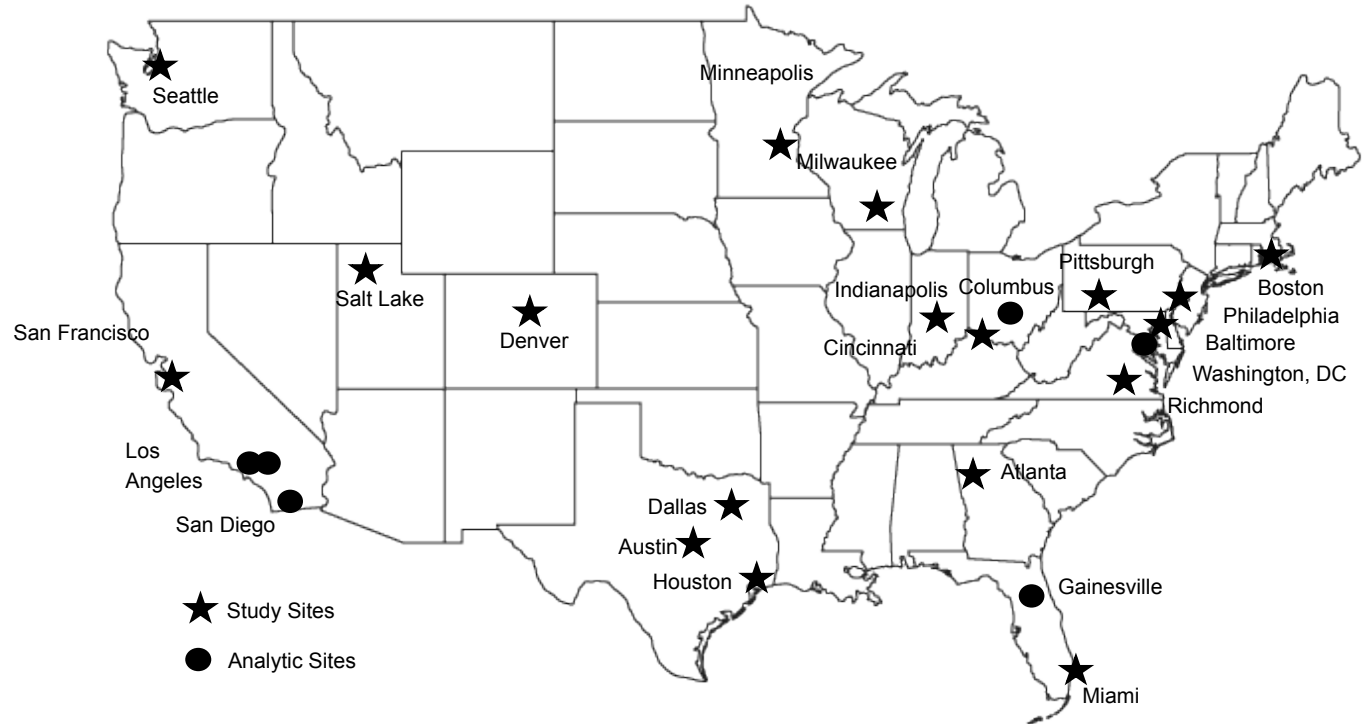
Penn

Pittsburgh

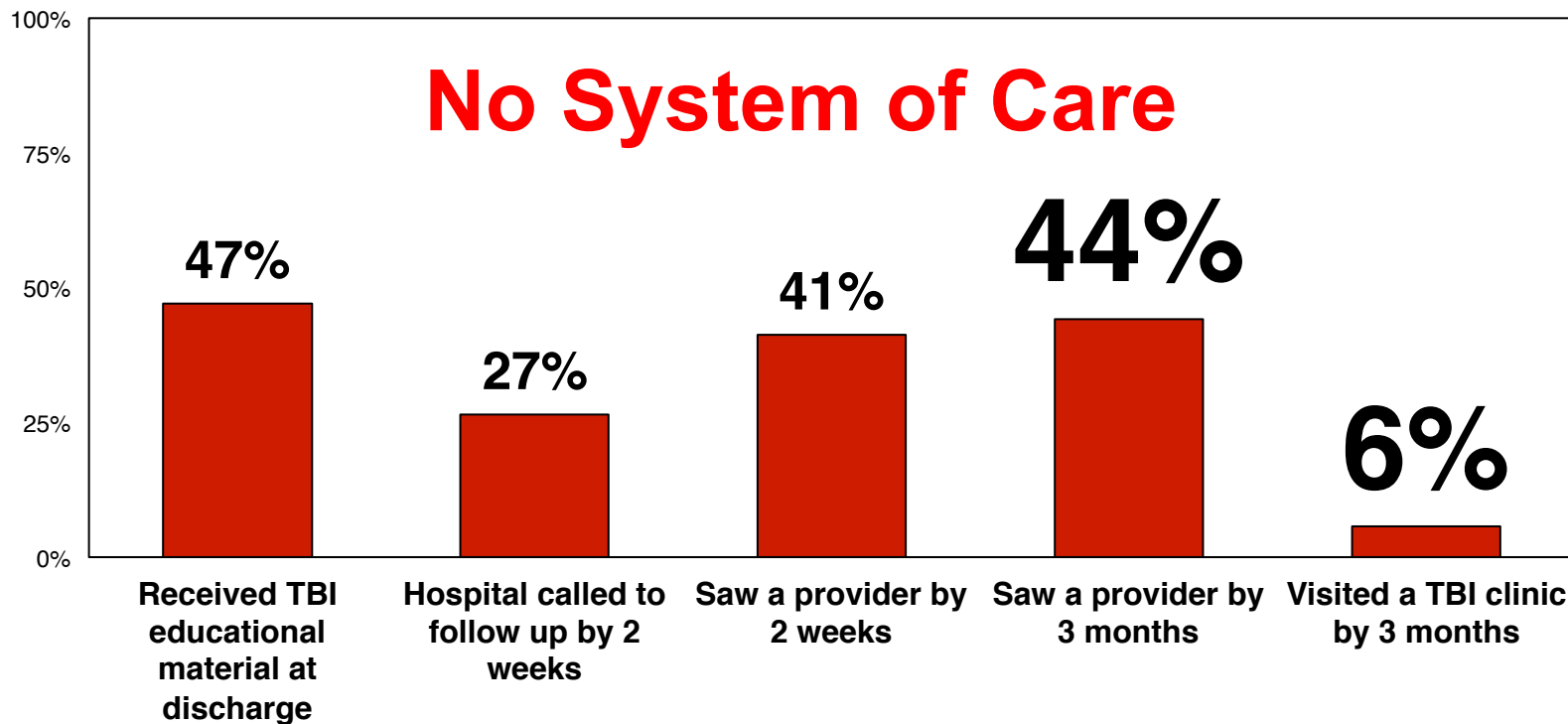
VCU

Maryland

Harvard



# Follow-Up Care After Discharge



# Translating Research Innovation into Public Health Solutions

## Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study

*John K Yue\*, Esther L Yuh\*, Frederick K Korley\*, Ethan A Winkler, Xiaoying Sun, Ross C Puffer, Hansen Deng, Winward Choy, Ankush Chandra, Sabrina R Taylor, Adam R Ferguson, J Russell Huie, Miri Rabinowitz, Ava M Puccio, Pratik Mukherjee, Mary J Vassar, Kevin K W Wang, Ramon Diaz-Arrastia, David O Okonkwo, Sonia Jain, Geoffrey T Manley, and the TRACK-TBI Investigators†*



# FROM BENCH TO BEDSIDE



## News & Events

Home > News & Events > Newsroom > Press Announcements

### FDA News Release

## FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults

*New quick testing option to help reduce need for CT scans, radiation exposure for patients*

[f SHARE](#) [t TWEET](#) [in LINKEDIN](#) [p PIN IT](#) [e EMAIL](#) [p PRINT](#)

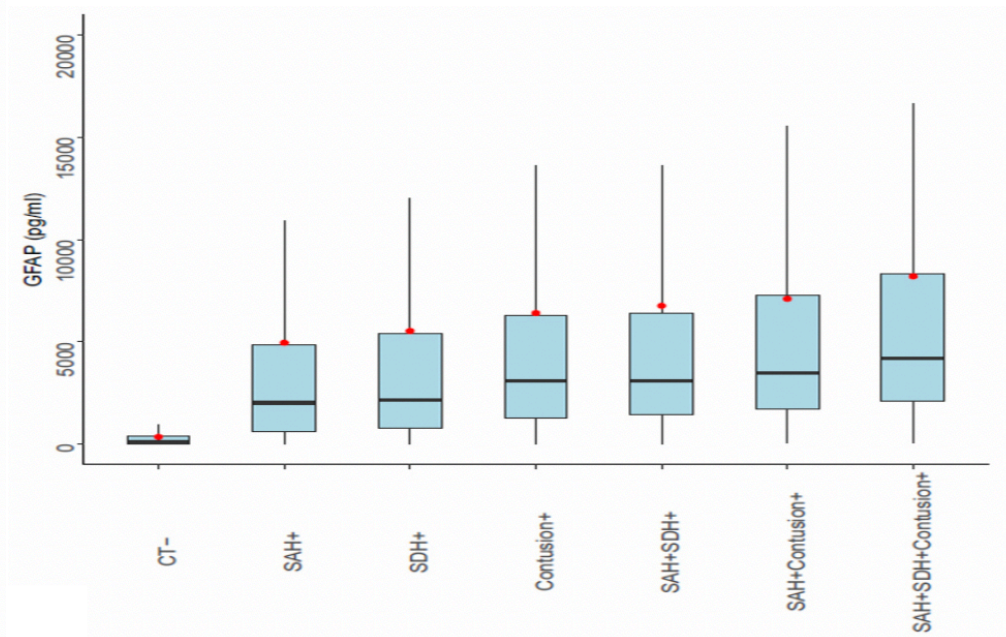
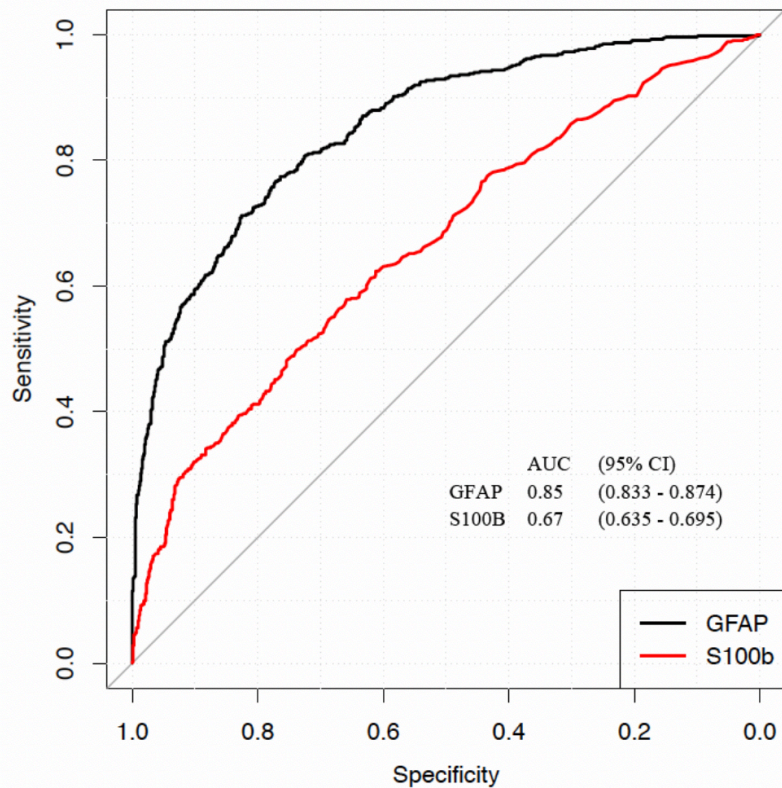
For Immediate  
Release

February 14, 2018



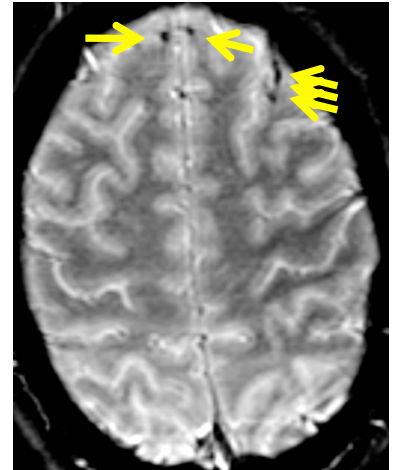
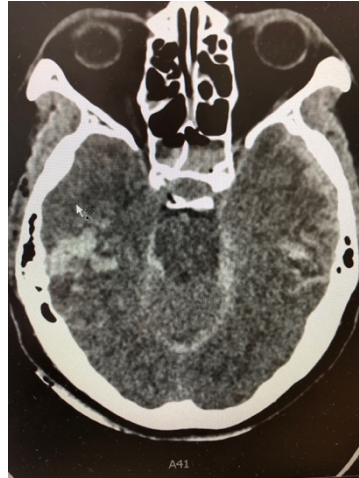
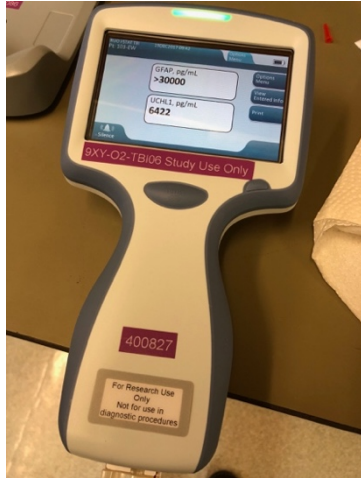
**RAPID CLINICAL TRANSLATION**

# GFAP vs S100b for Prediction of TBI on CT



**GCS 3 - 15**

# Imaging and Blood-Based Biomarkers



**The Potential to Transform our TBI Care**

# Biomarker-Driven TBI Care



## Median GFAP

**CT+ 949**

**CT- 108**

**CT-/MRI+ 417**

**CT-/MRI- 75**

**Ortho 13**

**10 pg/ml**

**Preliminary**

# Biomarker-Driven TBI Care



## Median GFAP

**CT+ 949**

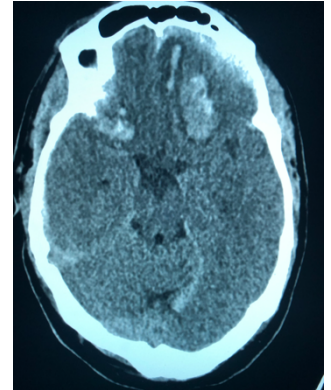
**CT- 108**

**CT-/MRI+ 417**

**CT-/MRI- 75**

**Ortho 13**

**1200 pg/ml**



**Preliminary**

# Biomarker-Driven TBI Care



## Median GFAP

**CT+ 949**

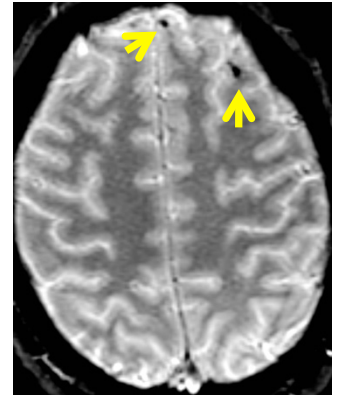
**CT- 108**

**CT-/MRI+ 417**

**CT-/MRI- 75**

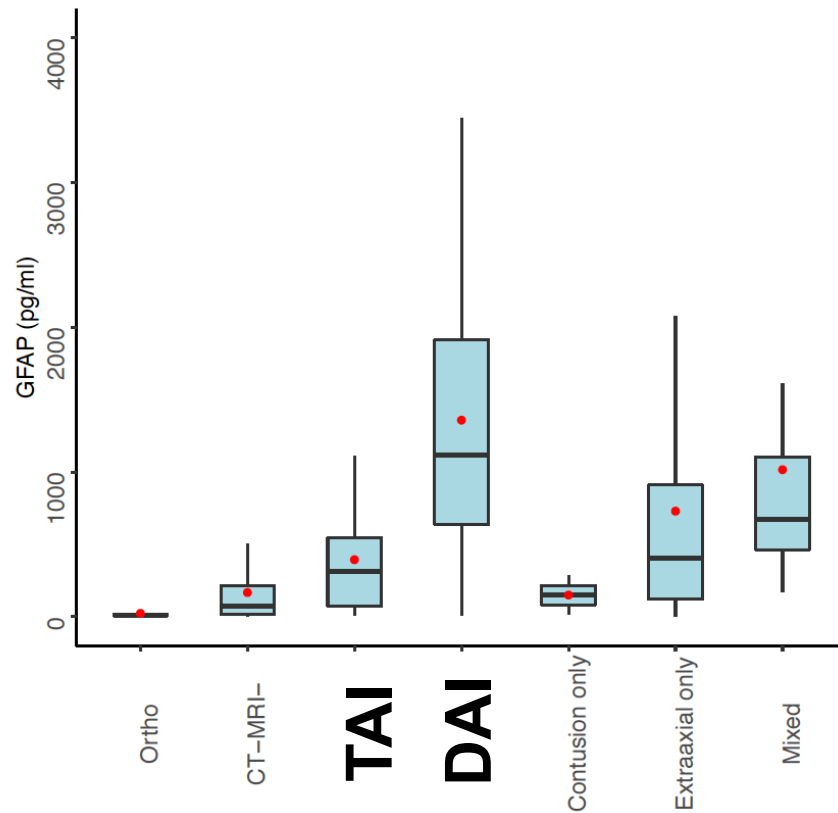
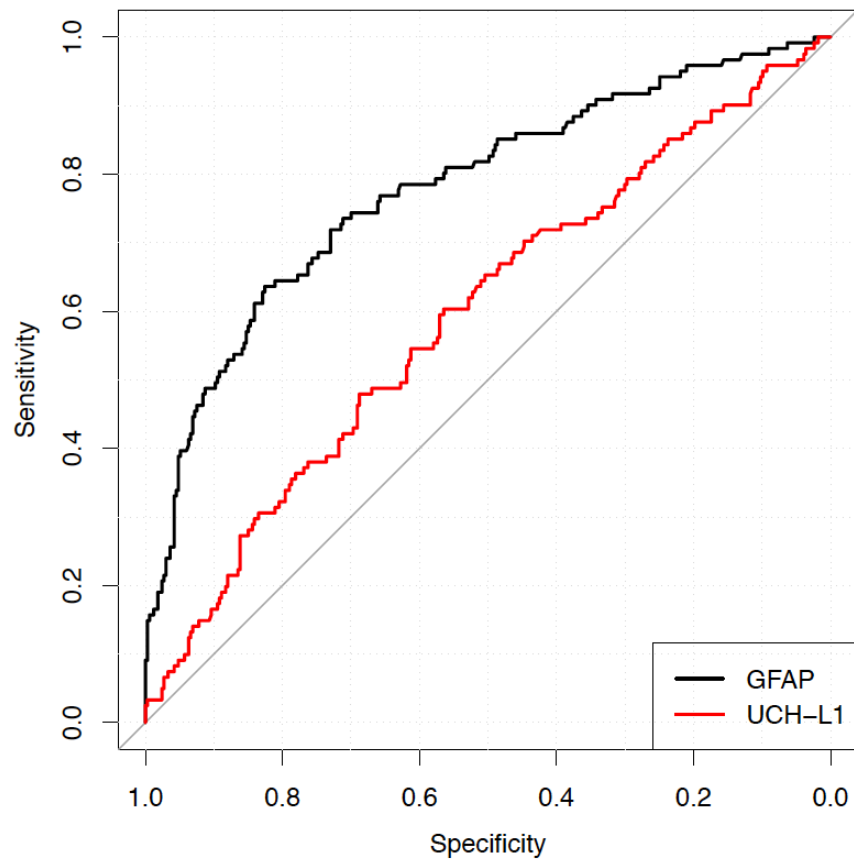
**Ortho 13**

**200 pg/ml**



**Preliminary**

# GFAP for Prediction of TBI on MRI





# Biomarker-Driven TBI Care



## Median GFAP

CT+ 949

CT- 108

CT-/MRI+ 417

CT-/MRI- 75

Ortho 13

50 pg/ml

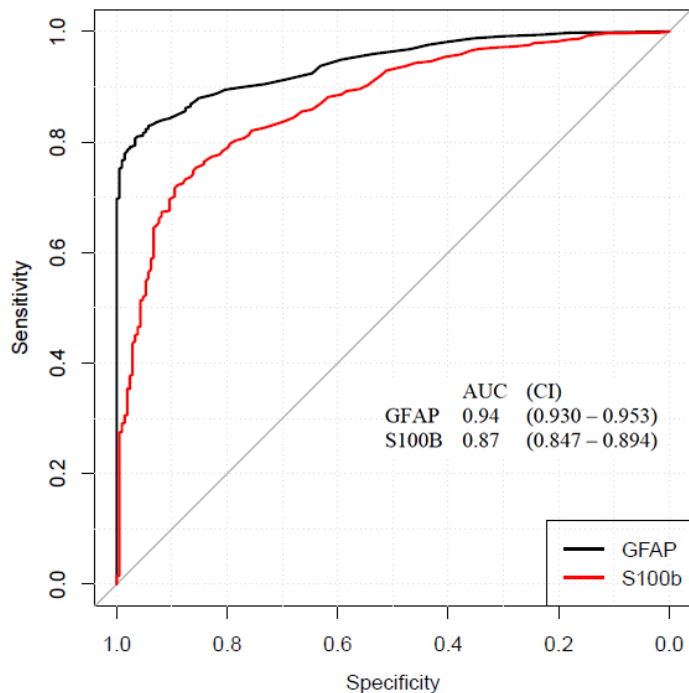
**TBI**

Preliminary



# GFAP for Aid in Diagnosis of TBI

- GFAP (plasma) cutoffs for TBI vs Healthy Controls



For aid in diagnosis of TBI, **POC GFAP** significantly outperformed core lab S100B

**GFAP AUC**

**0.94**

**95% CI**

**0.93-0.95**

**S100B AUC**

**0.87**

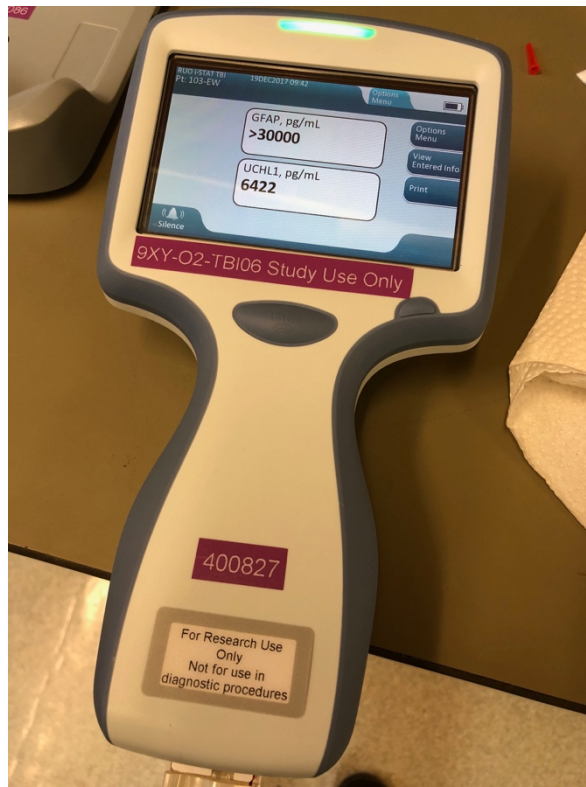
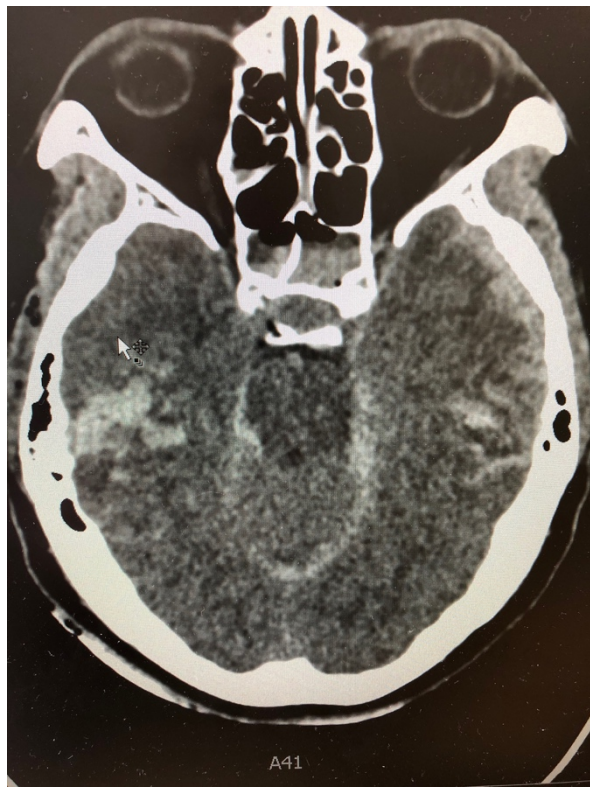
**95% CI 0.85-0.89**

**p<0.001**

Cutoff	Sensitivity	Specificity	NPV	PPV
14.05	0.902 (0.884, 0.918)	0.775 (0.713, 0.828)	0.544 (0.502, 0.594)	0.963 (0.954, 0.972)
11.15	0.928 (0.913, 0.941)	0.646 (0.579, 0.708)	0.576 (0.524, 0.63)	0.945 (0.935, 0.955)
10.05	0.943 (0.932, 0.955)	0.632 (0.56, 0.694)	0.626 (0.573, 0.683)	0.944 (0.933, 0.953)
8.05	0.962 (0.952, 0.972)	0.536 (0.469, 0.603)	0.685 (0.623, 0.748)	0.932 (0.922, 0.941)
5.1	0.984 (0.977, 0.991)	0.402 (0.335, 0.474)	0.793 (0.717, 0.867)	0.915 (0.907, 0.925)

**This is not just for "Mild" TBI**





**>30,000 pg/ml**

# Biomarker-Driven TBI Care



## Median GFAP

CT+ 949

CT- 108

CT-/MRI+ 417

CT-/MRI- 75

Ortho 13

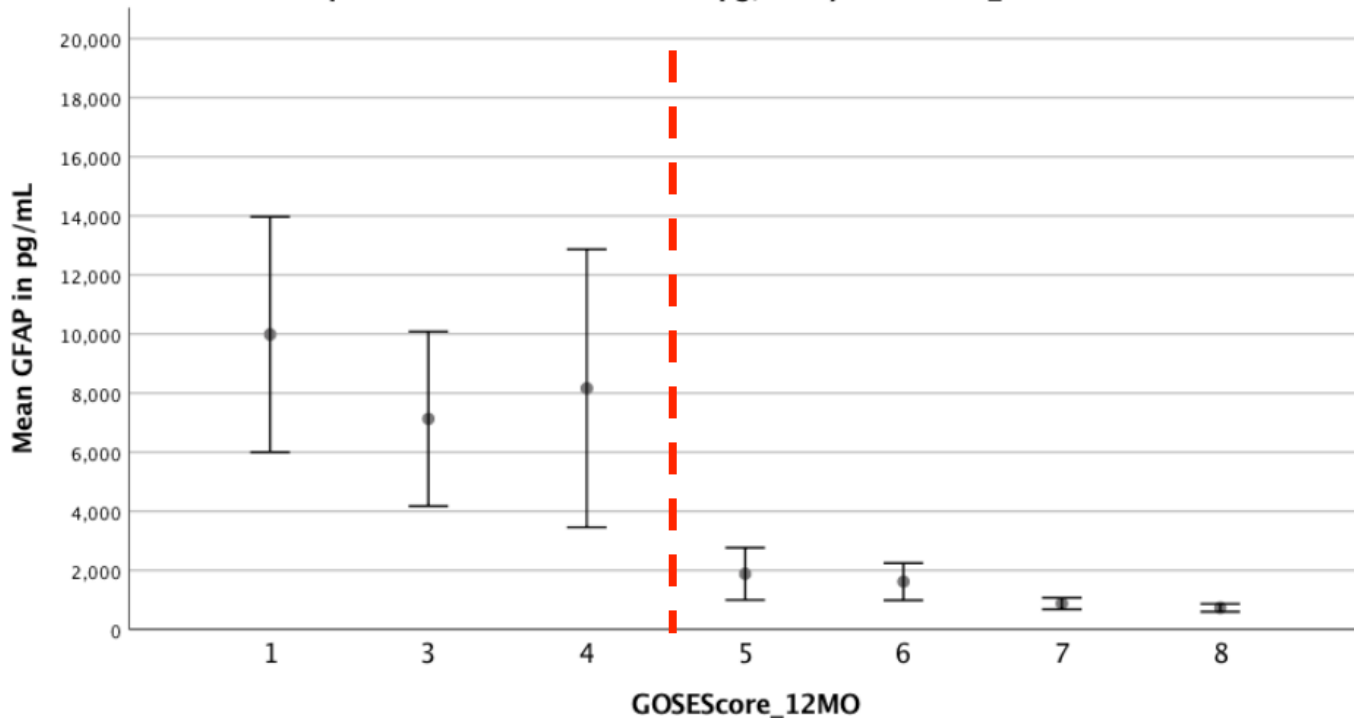
**>30,000 pg/ml**

**Preliminary**



# Outcome Prognosis: 12 Months

Simple Error Bar Mean of GFAP in pg/mL by GOSEScore\_12MO



Error Bars: 95% CI

## GOSE

**1 = Dead**

**2 = Vegetative**

**3 = Lower SD**

**4 = Upper SD**

**5 = Lower MD**

**6 = Upper MD**

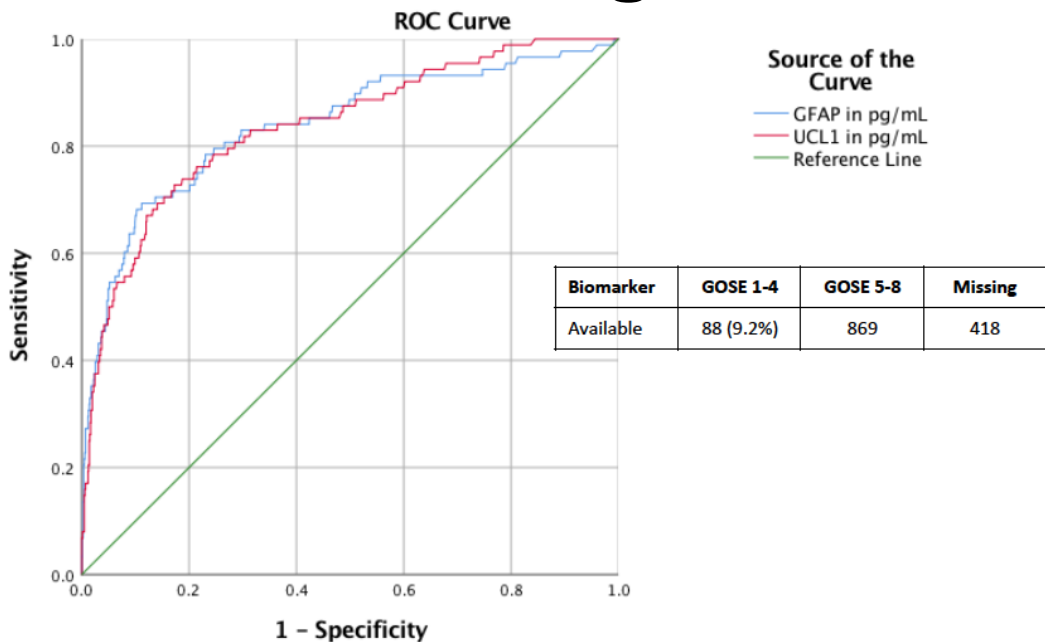
**7 = Lower GR**

**8 = Upper GR**





# Outcome Prognosis: 12 Months



Diagonal segments are produced by ties.

**AUC**  
**GOSE 1-4 vs 5-8**

**GFAP = 0.84**

**UCH-L1 = 0.84**

## GOSE 1-4 (12-month)

Biomarker	AUC	SE	Sig.	95% CI Low	95% CI High
GFAP	0.839	0.026	0.000	0.788	0.890
UCH-L1	0.838	0.024	0.000	0.790	0.885

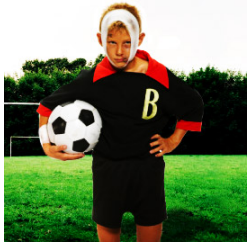
# Translating Research Innovation into Public Health Solutions

JAMA Psychiatry | [Original Investigation](#)

## Risk of Posttraumatic Stress Disorder and Major Depression in Civilian Patients After Mild Traumatic Brain Injury A TRACK-TBI Study

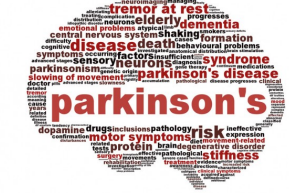
Murray B. Stein, MD, MPH; Sonia Jain, PhD; Joseph T. Giacino, PhD; Harvey Levin, PhD; Sureyya Dikmen, PhD; Lindsay D. Nelson, PhD; Mary J. Vassar, RN, MS; David O. Okonkwo, MD, PhD; Ramon Diaz-Arrastia, MD, PhD; Claudia S. Robertson, MD; Pratik Mukherjee, MD, PhD; Michael McCrea, PhD; Christine L. Mac Donald, PhD; John K. Yue, MD; Esther Yuh, MD, PhD; Xiaoying Sun, MS; Laura Campbell-Sills, PhD; Nancy Temkin, PhD; Geoffrey T. Manley, MD, PhD; and the TRACK-TBI Investigators

- **Patients with TBI were twice as likely to develop Major Depression and PTSD as compared to orthopedic injury controls**
- **Identification of risk factors**



# TRACK-TBI LONG

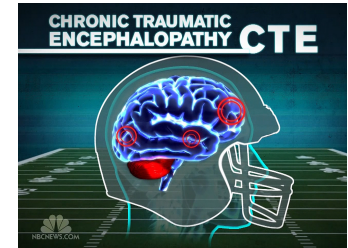
Transforming Research and Clinical Knowledge  
in Traumatic Brain Injury Longitudinal



## Traumatic Brain Injury



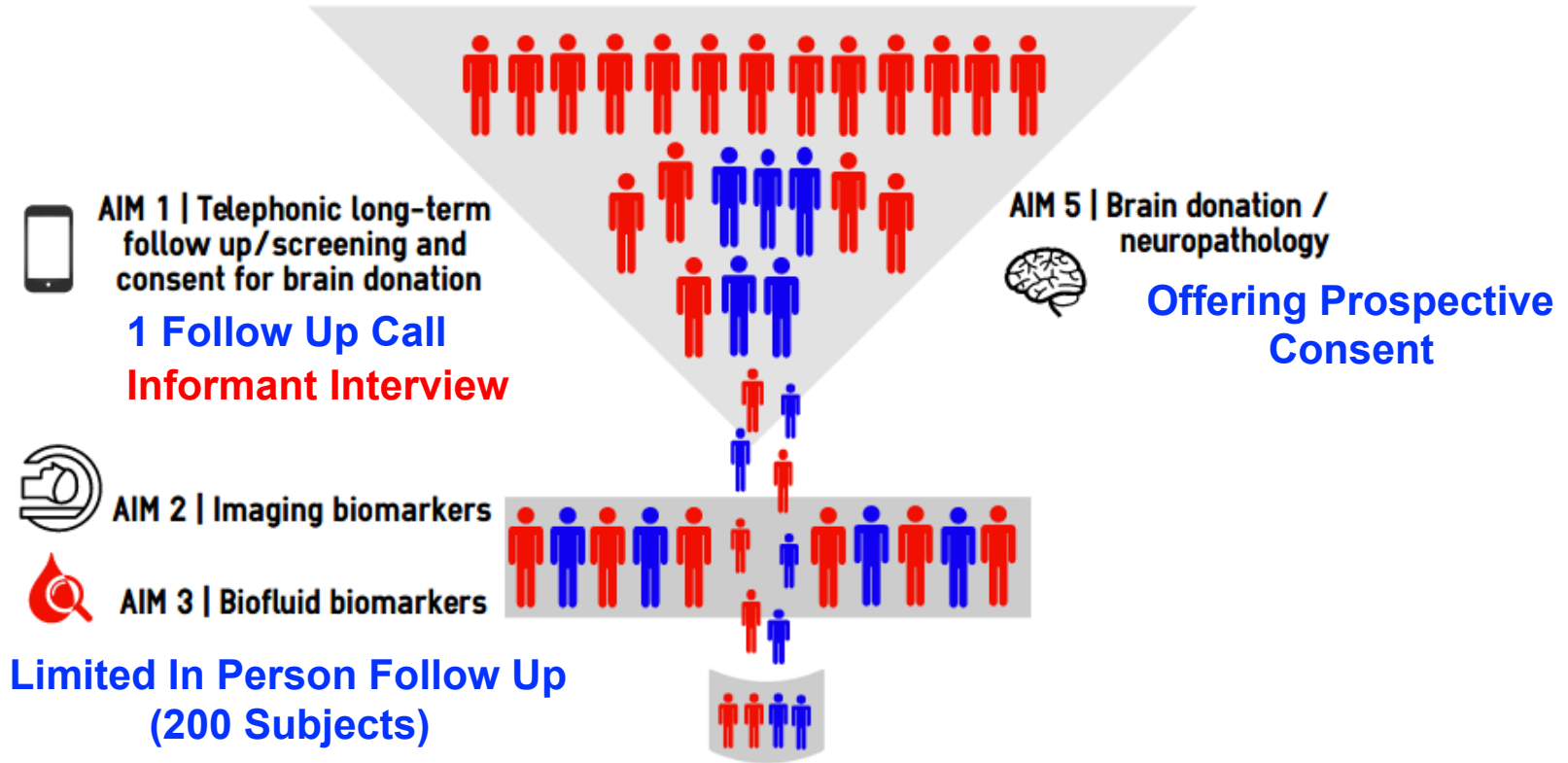
# GAP





# Overview of TRACK-TBI LONG Pilot

## N = 3300 TBI and Control Subjects



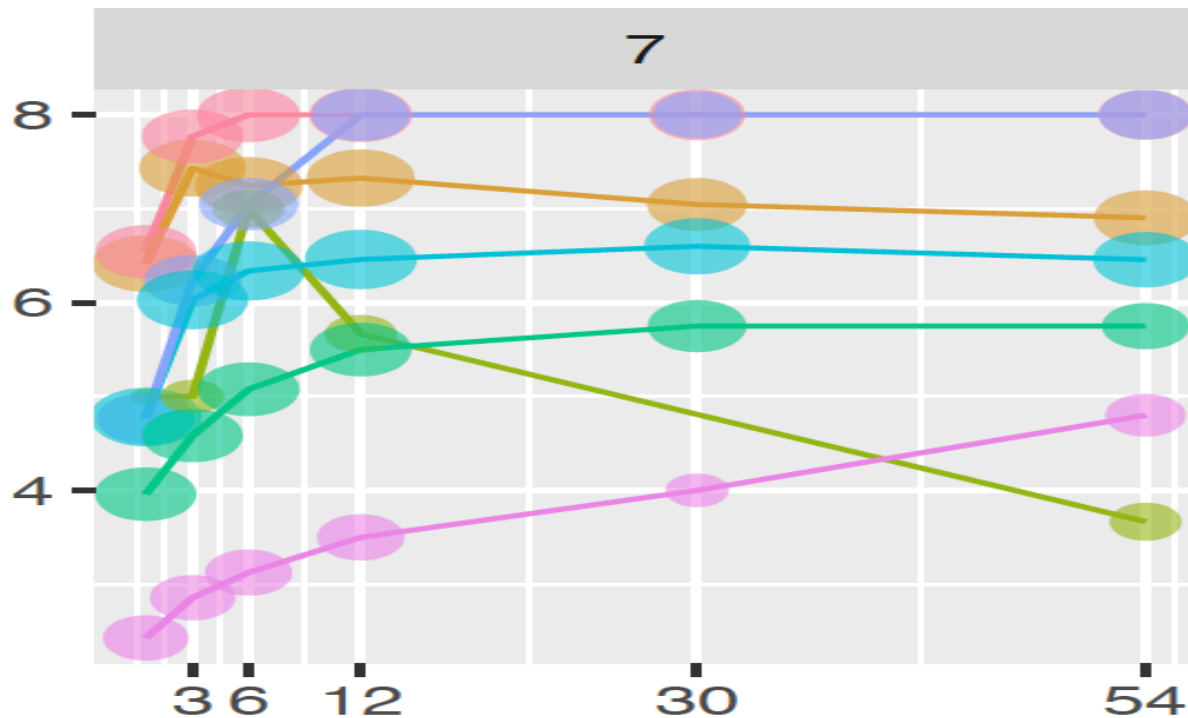
# TRACK-TBI LONG Enrollment and Targets by Site\*

LONG Sites	Enrolled	Total LONG Subjects Completed	Total LONG Informants Completed	LONG Subjects Completed in September	LONG target/month
BCM-TIRR-UTH	65	61	41	12	24-34
MGH	23	25	17	6	15-21
UCSF	67	60	29	7	21-29
U Miami	17	17	7	4	8-12
U Pittsburgh	151	144	90	22	21-30
UT Austin	93	93	58	16	12-17
UTSW	5	3	3	3	9-13
U Washington	62	55	15	3	11-16
VCU	17	17	8	7	12-17
UPenn	0	0	0	0	6-8
MCW	0	0	0	0	1-2
<b>Grand Total</b>	<b>500</b>	<b>475</b>	<b>268 (56%)</b>	<b>80</b>	<b>140-201</b>

**500 Enrolled**

**\* 11 Sites Activated**

# TRACK-TBI: GOSE Latent Trajectories



# TRACK-TBI LONG Assessments

	TBI	Control
<b>Patient Interview</b> (Long)		
9b. Worse difficulty of movement (incorporates 9a)	16/113 (14%)	2/15 (13%)
9c. Told might have Parkinson's/dementia	3/113 (3%)	0/15 (0%)
9d. Think might have Parkinson's/dementia	8/112 (7%)	0/15 (0%)
10a. Worse taking care of self (either level)	3/112 (3%)	0/15 (0%)
10b. Worse physical function	13/112 (12%)	2/15 (13%)
10c. Worse mental function	20/113 (18%)	1/15 (7%)
10d. Worse emotional function	13/113 (12%)	0/15 (0%)

**N=113 TBI and 15 Ortho Controls**

# New Partnerships and Collaborations



U.S. DEPARTMENT OF  
**ENERGY**

**Artificial Intelligence  
Machine Learning  
High-Performance Computing**

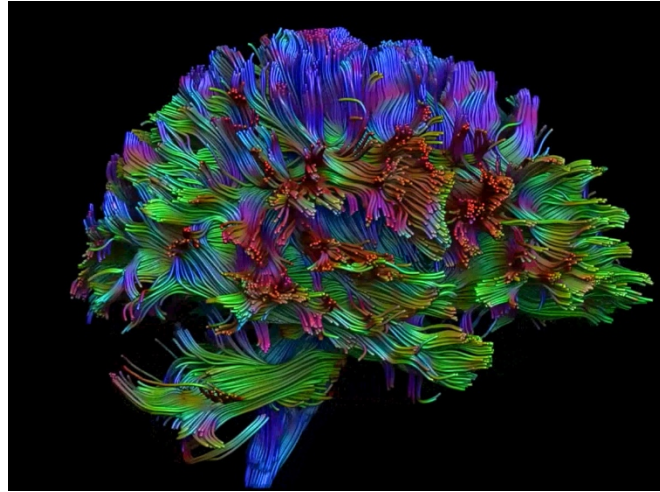


# Precision Imaging for TBI

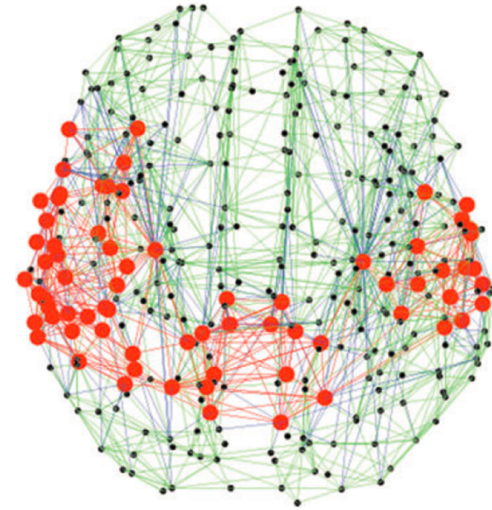


**Invisible  
Wounds**

*Uncertain Outcome*



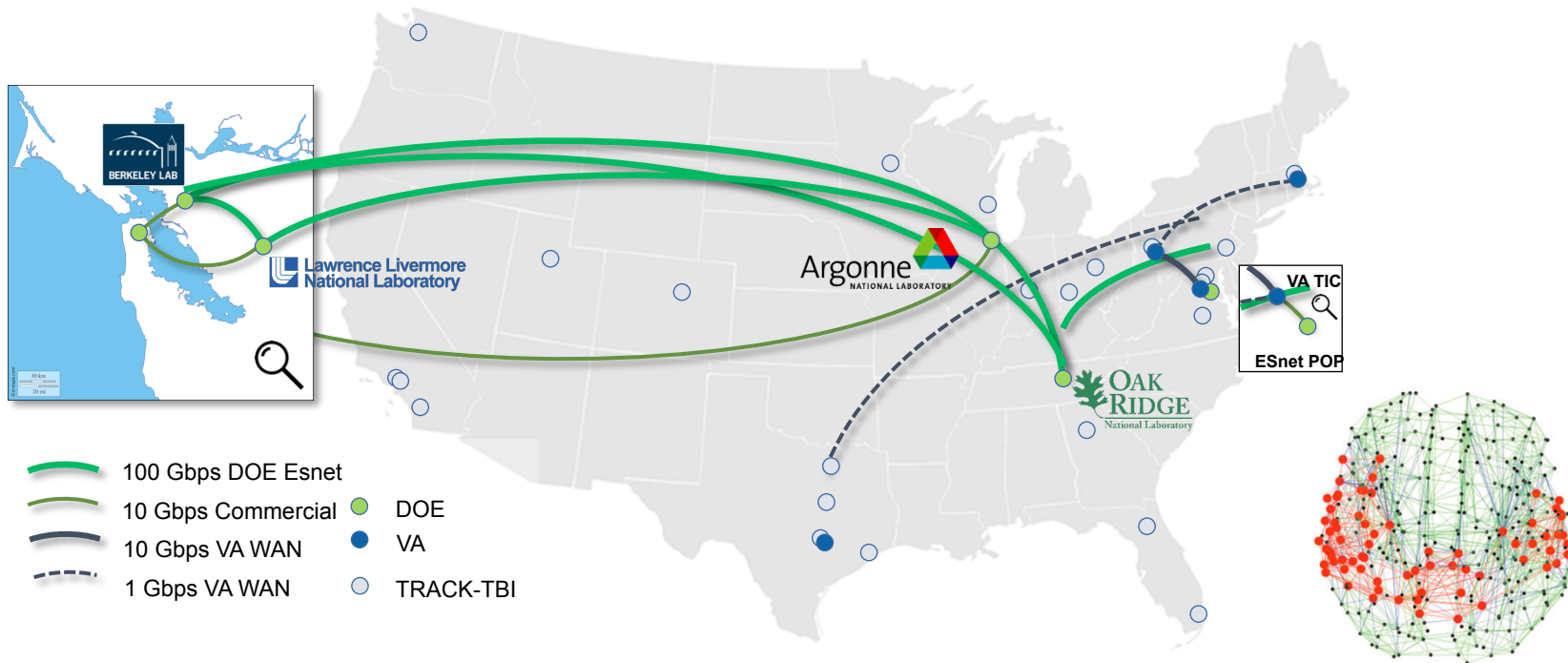
**MRI  
Tractography**



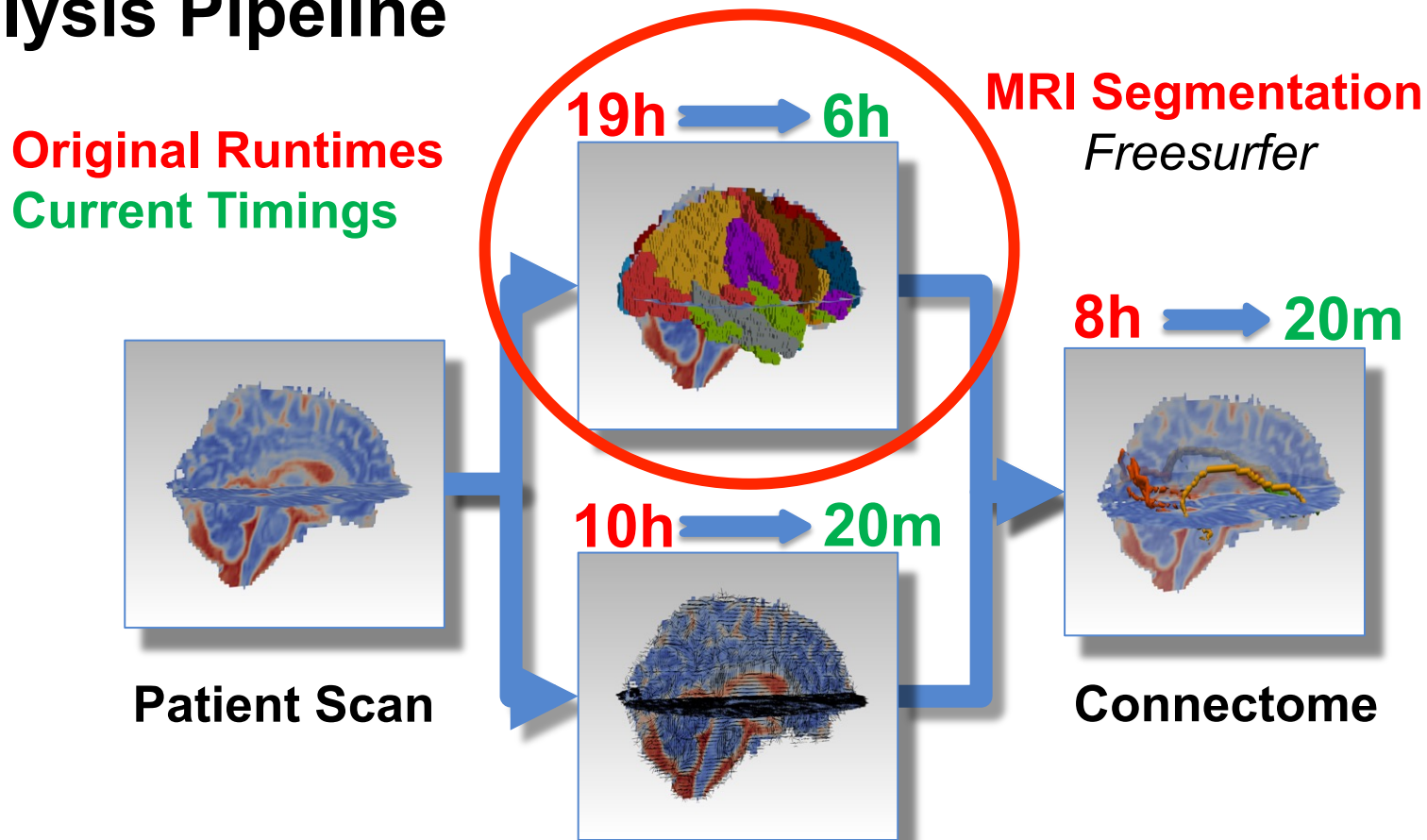
***Real-Time  
Connectome***



# Bringing DOE's Data Network to ZSFG



# Accelerating and Standardizing the Connectome Analysis Pipeline



# Deep Learning MRI Segmentation

- Segmentation is the bottleneck of the connectome pipeline
- Model trained on 1,000s of MRIs and anatomical atlases
- Faster processing to enable downstream diagnosis/prognosis



**Trained Deep learning model processes TRACK-TBI patient in ~1min**

# ZSFG TBI Program



**Clinical Care**



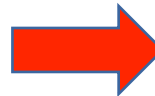
**Education**



**Research**



**Community**





**Thank You !**