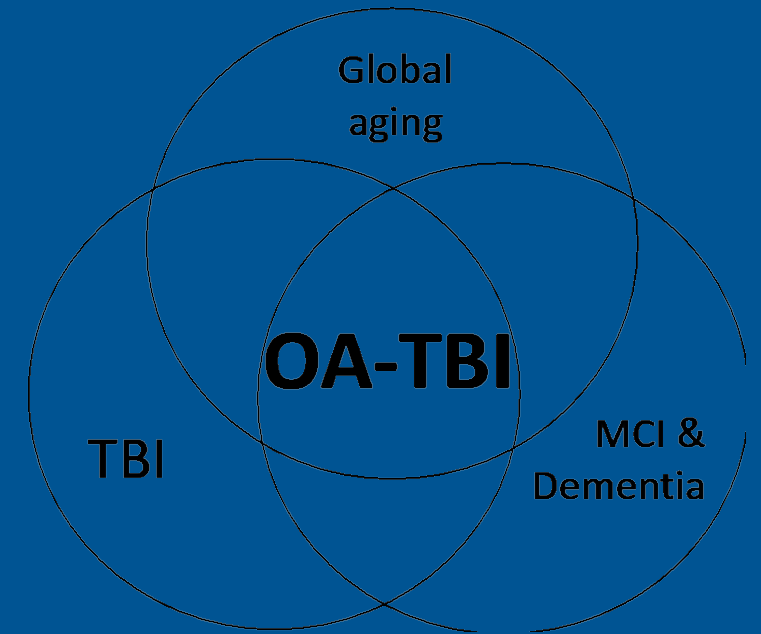


Session 2: Acute TBI Care for Older Adults

Trajectories of Function in the First Year Post-Injury

Raquel C. Gardner, MD
Director of Clinical Research
Sagol Neuroscience Center
Sheba Medical Center
Ramat Gan, Israel

*Formerly,
Associate Professor In Residence
UCSF Memory and Aging Center, SF, CA, USA
Staff Neurologist, Memory Clinic, SFVAMC*



TBI in older adults is shockingly common



Original Investigation | Neurology

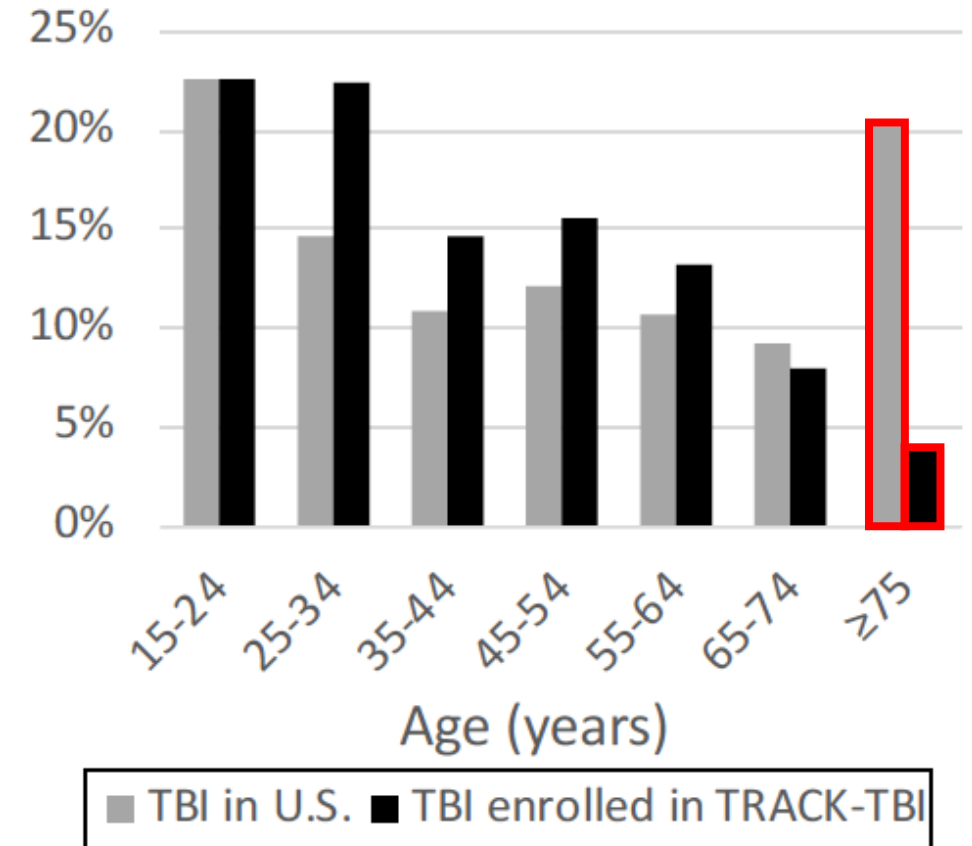
Incidence of Traumatic Brain Injury in a Longitudinal Cohort of Older Adults

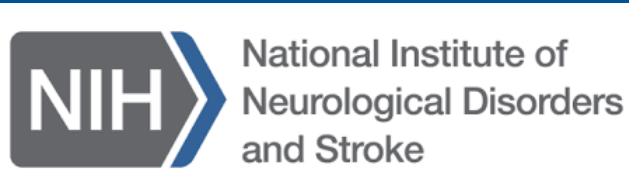
Erica Kornblith, PhD; L. Grisell Diaz-Ramirez, MS; Kristine Yaffe, MD; W. John Boscardin, PhD; Raquel C. Gardner, MD

- N=9,239 community-dwelling age 65y+ respondents to the nationally representative Health and Retirement Survey study
- Linked to Medicare claims data
- 18 years of data (2000-2018)
- 1 in 8 community-dwelling older adults received a TBI diagnosis.

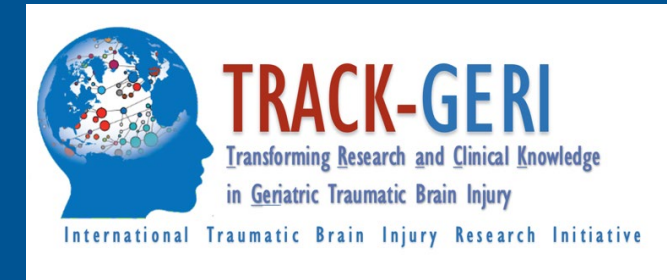
Barrier to Progress in Older Adult TBI (oaTBI)

- oaTBI = TBI super-imposed on aging, frailty, comorbidities, polypharmacy, & neuro-degeneration.
- To avoid complexity, prior state-of-the-art studies excluded OAs with multi-morbidity or cognitive impairment.
- We are left with minimal evidence to guide care of real-world oaTBI.





Transforming Research & Clinical Knowledge in Geriatric TBI “TRACK-GERI” 5-year 2-site Study (2019-2023, currently in 1-year NCE)



Aim 1: Assemble a cohort of N=270 patients age ≥ 65 y presenting to the ED ≤ 72 h after TBI who underwent CT and N=90 demographically similar controls. Collect baseline, 2-week, 3mo, 6mo, and 12mo neurobehavioral outcomes, blood, and brain donation.



Aim 2: Develop and validate optimized geriatric TBI predictors and longitudinal outcome assessments & characterize natural history.



Aim 3: Identify age-appropriate diagnostic & prognostic blood-based TBI biomarkers.



Raquel Gardner



Esther Yuh



Geoff Manley

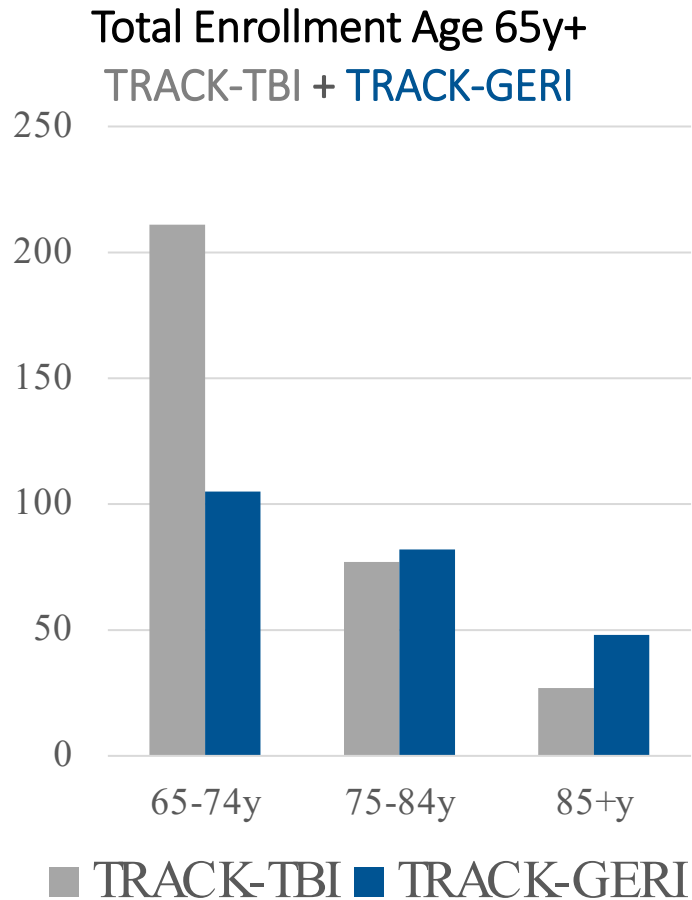


Ava Puccio

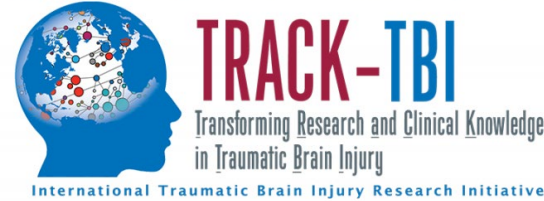
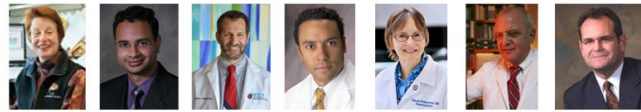


David Okonkwo

TRACK-TBI vs. TRACK-GERI



2-site TRACK-GERI
surpassed 75y+ enrollment vs.
18-site TRACK-TBI



N=270/270 TBI dyads
N=83/90 control dyads

- TRACK-TBI = Prospective 18-site study, enrolled 3,000 patients of **all ages** presenting to Level 1 Trauma Center **within 24h** of acute TBI; **excluded pre-injury cognitive impairment, multi-morbidity**
- TRACK-GERI = Prospective 2-site study, enrolling patients **age 65y+** presenting to Level 1 Trauma Centers **within 72h** of acute TBI; **did not exclude for ANY pre-injury health condition**

Guiding Principle of TRACK-GERI: Instead of excluding heterogeneity, measure it.

Requires close collaboration between clinical research experts in:

- TBI
- Dementia/geriatrics



Traumatic Brain Injury

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3
---------------------------------	---	-----	---	---	---

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home	
				Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Emerging Pearls from TRACK-GERI

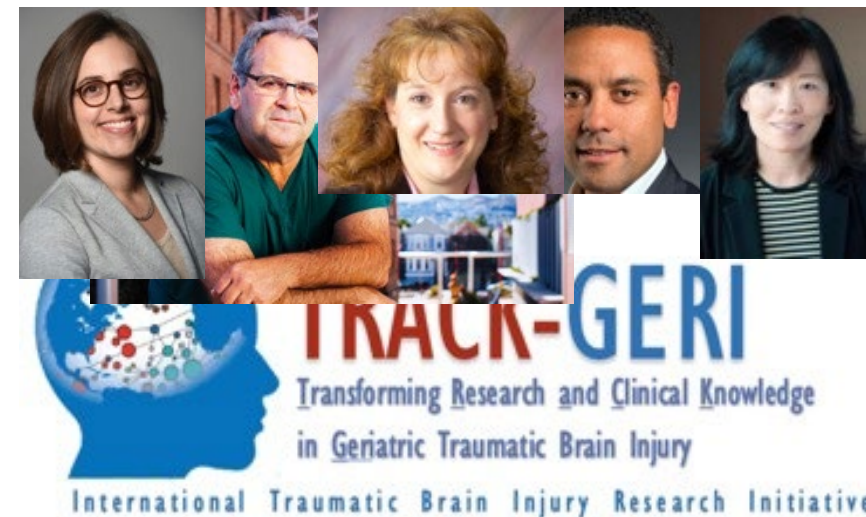
Baseline Features first N=246

- current age range: 65-100 years
- data curation ongoing
- follow-up of enrolled cohort ongoing
- data → FITBIR & available on request

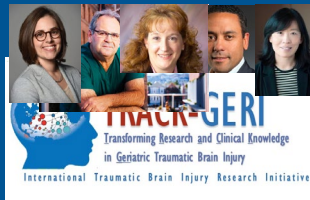
Collaborations welcome!

raquel.gardner@gardnerlab.health

	65-74y N=107	75-84y N=89	85y+ N=50
Age, years, mean	70y	79y	89y
Female	44%	50%	46%
White	78%	81%	86%
Veteran	11%	20%	36%
Employed	27%	9%	2%
Anticoagulant drug	16%	25%	34%
Anti-platelet drug	23%	34%	22%
Edu, years, mean	15	14	14
Hypertension	60%	61%	72%
Hyperlipidemia	33%	46%	44%
Diabetes	20%	32%	25%
Depression	30%	17%	4%
5+ comorbidities	34%	48%	42%
Glasgow Coma Scale			
15 ("normal")	65%	62%	70%
14 (confused)	24%	24%	18%
13	6%	2%	4%
<13 (more severe)	2%	10%	6%
Any LOC/PTA/AOC	68%	64%	50%
CT+ for acute trauma	67%	66%	56%
Mechanism: Fall	62%	75%	94%
ED Disposition			
ED discharge	22%	19%	16%
Ward admit	48%	51%	48%
ICU admit	30%	30%	36%

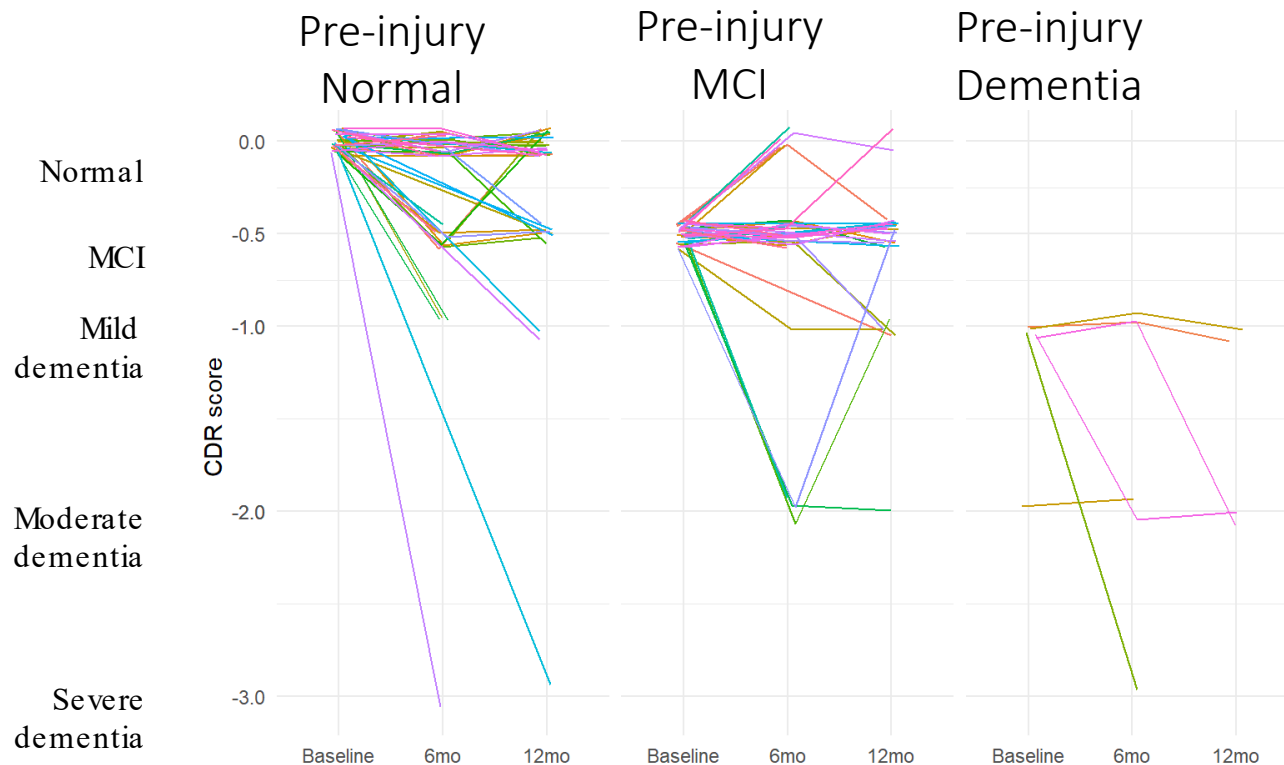


Pre- and Post- injury cognitive status

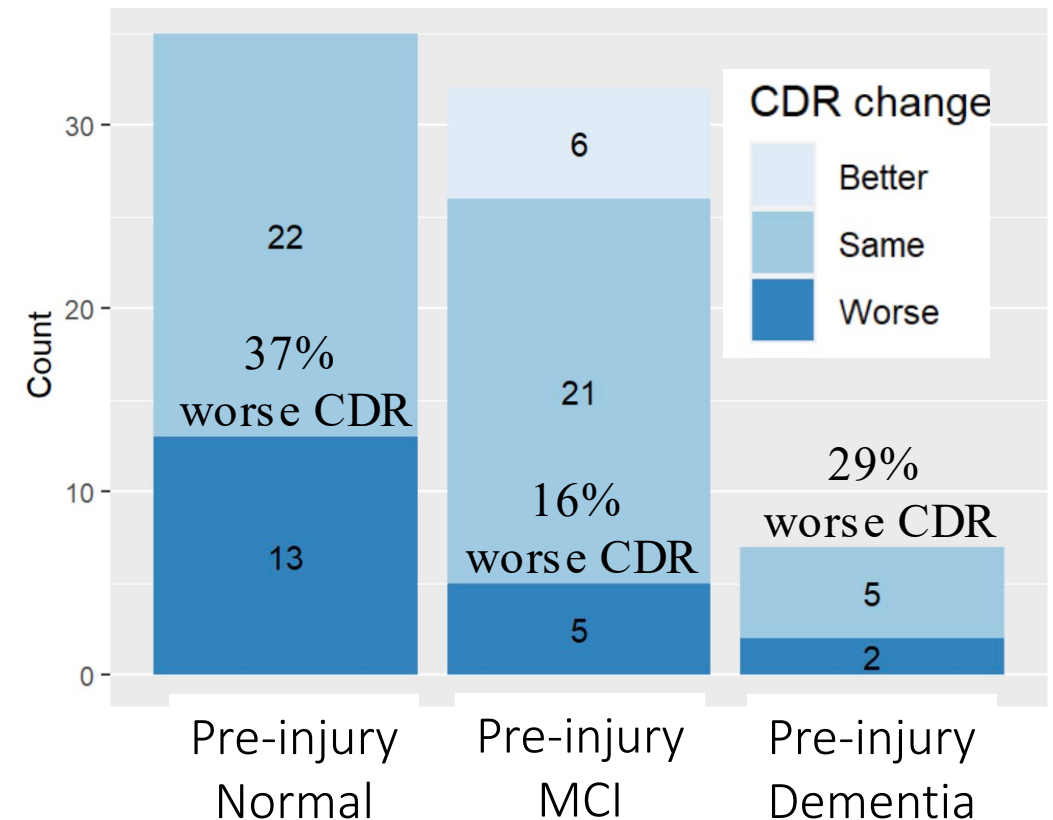


- Nearly **half have pre-injury cognitive impairment** per CDR Global score:
 - 33% Mild Cognitive Impairment (MCI)
 - 14% Dementia

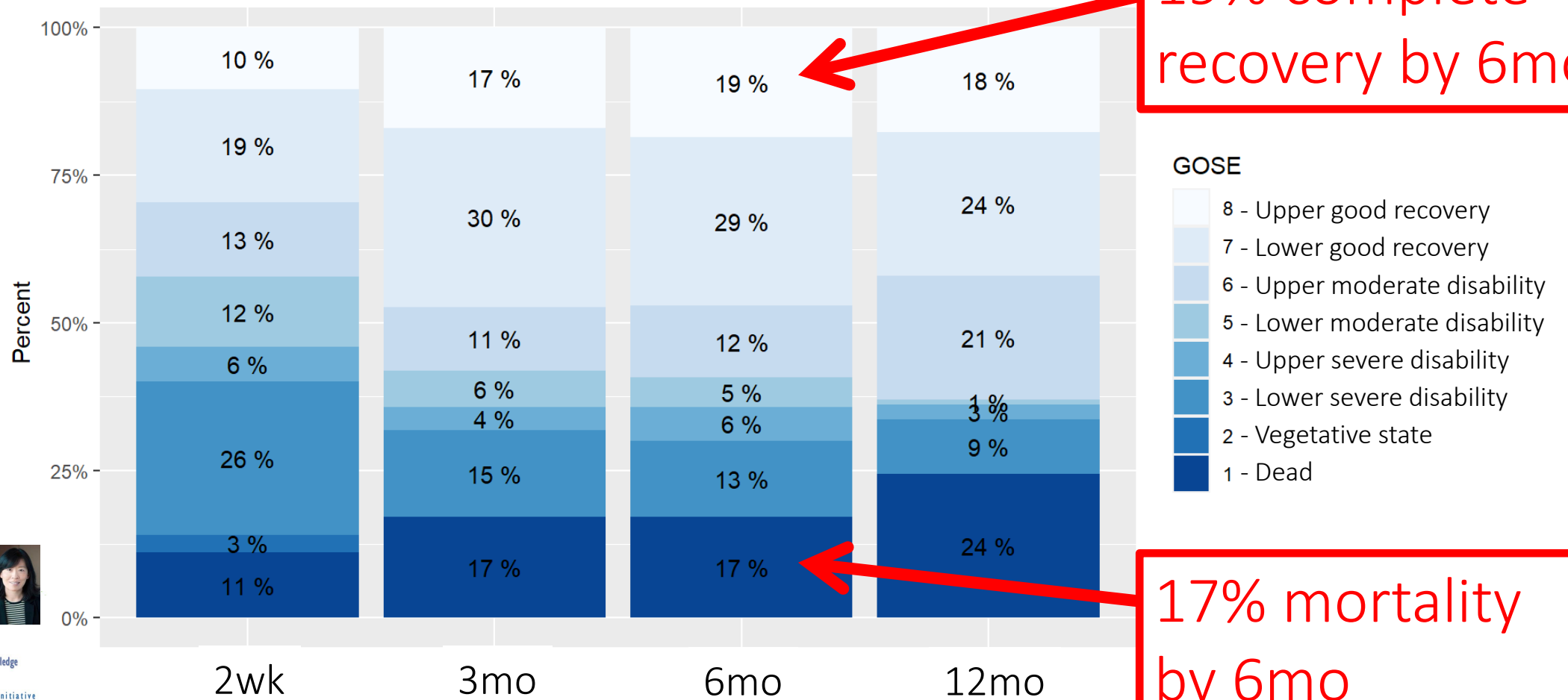
Clinical Dementia Rating (CDR) 12-Mo Trajectories



CDR change at 6-mo by Pre-injury Cognitive Status

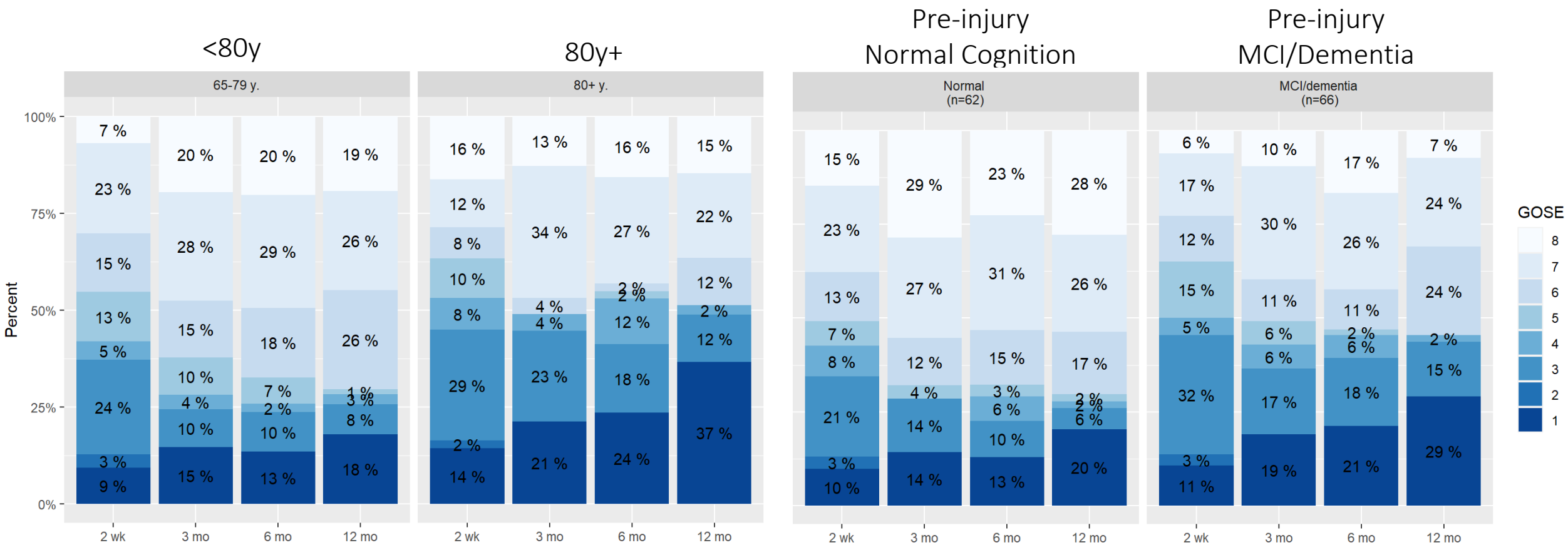


Functional Outcome: Glasgow Outcome Scale Extended (GOSE)





Functional Outcome (GOSE) by age & cognitive status



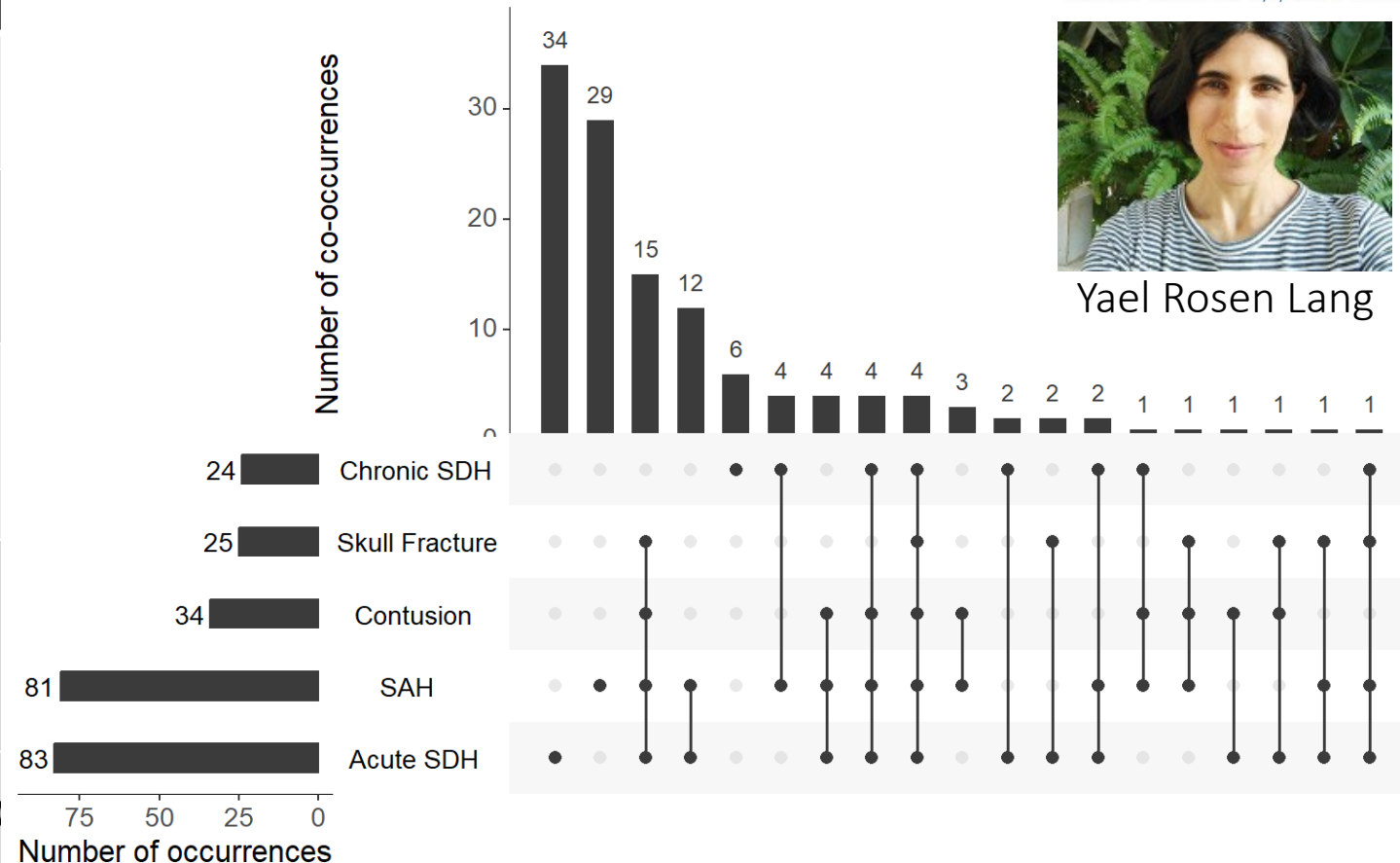
Likelihood of complete recovery (GOSE 8) may be more impacted by pre-injury cognitive status (28% vs 7%) than age (19% vs. 15%)

Outcome Prediction: Standard CT-based Mortality Prediction Models are Not Sensitive in Older Adults

Performance metric	Marshall's CT score	Rotterdam's score
AUC	0.77	0.73
95% CI	0.65-0.90	0.56-0.89
Sensitivity	59%	53%
Specificity	96%	100%

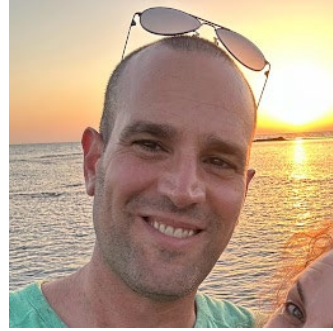
- Marshall's threshold (injury category II) as in IMPACT

CT Features



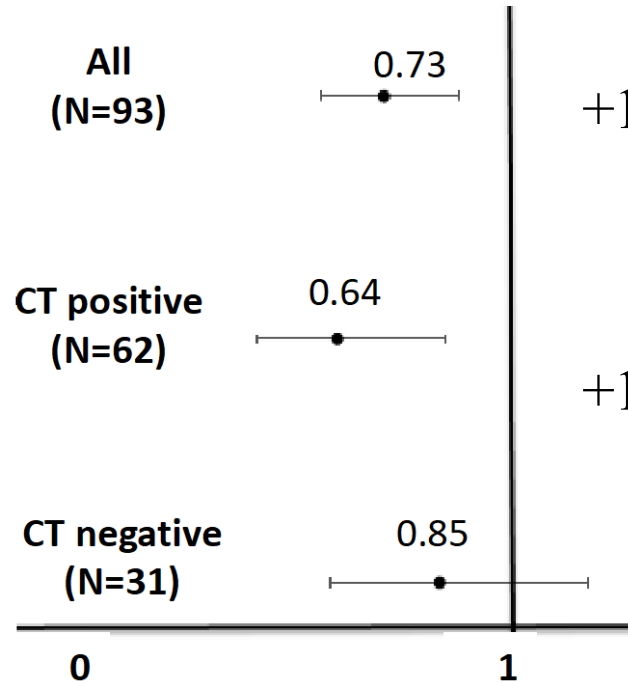
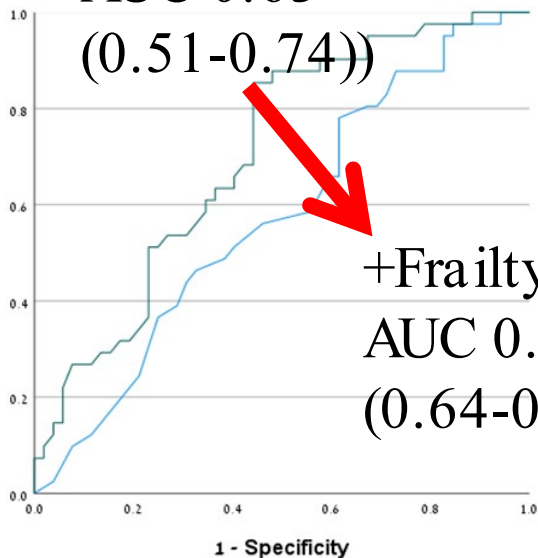
Outcome Prediction: Added value of frailty

- N=93 with baseline **Groningen Frailty Index (GFI)** and 6 month GOSE
- **54% frail (GFI $\geq$ 4) at baseline**
- 44% 6-mo GOSE 7-8 (“favorable outcome”)
- GFI is an independent predictor of favorable outcome in logit model adjusted for IMPACT Extended (age, GCS motor, pupil reactivity, hypoxia, hypotension, CT findings, glucose, hemoglobin)



Roy Tzemah-Shahar

Impact Extended
AUC 0.63
(0.51-0.74))



+1 GFI $\rightarrow$ 27% decreased odds GOSE 7-8

Among those with positive CT,
+1 GFI $\rightarrow$ 36% decreased odds GOSE 7-8



Brain Autopsy Findings Align with Pre-injury CDR

	1 (Pilot 03-5018)	2 (GP-03-2063)	3 (GP-03-2081)	4 (GP-03-2078)
Age/Sex	65M	81M	96M	76F
Mechanism	Assault	Fall	Fall	MVA
GCS	15→3	3	14→3	14
CT	Fx, SDH, IPH, contusions, subfalcine herniation	SDH, shift, subfalcine + temporal herniation, IVH	Fx, SDH, IPH, shift	Fx, SAH, SDH, contusions, shift,
Time to death	3 days	1.5 days	2 days	8 months
Pre-Injury CDR	0 (normal)	1 (mild dementia)	3 (severe dementia)	1 (mild dementia)
Pathology	Thal 1, Braak <3, Cerad 0, LB 0, no CSVID	Thal 5, Braak 5, Cerad 3 severe CSVID	Thal 5, Braak 6, Cerad 3, no CSVID	Thal 3, Braak 3, Cerad 0, mod CSVID



Amber Nolan
Assist Prof.
Neuropathology
UW

Transforming Research & Clinical Knowledge in Veterans with Acute TBI

“TRACK-VA” 4-year Single-Site Study

Aim 1: Characterize baseline and 12-mo longitudinal clinical features using TBI Common Data Elements (CDEs) among Veterans age ≥ 65 y enrolled in the TRACK-TBI and TRACK-GERI studies with acute TBI.

Aim 2: Assemble a **new prospective cohort of Veterans age ≥ 65 y presenting to SFVA ED ≤ 72 h after TBI who received CT (“TRACK-VA”) and deeply phenotype clinical and biological features over 12-months using TBI CDEs. (N=70 TBI; N=30 controls)**

Aim 3: Characterize neuroimaging features of acute geriatric TBI in Veterans using TBI CDEs and **quantitative structural and functional MRI**

Aim 4: Determine accuracy of blood-based GFAP, P-tau, Abeta, and NFL for TBI diagnosis, prognosis of outcome, and disease-monitoring in older Veterans.

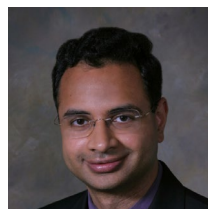
Over this 4-year project, it is estimated that the total number of TBIs sustained by older Veterans in the U.S. (est. N>520,000) will exceed the total number of TBIs sustained by active-duty service members in the past 24 years (N=505,896).



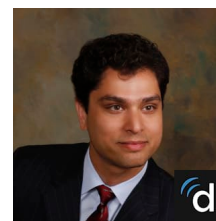
Kristine Yaffe



Geoff Manley



Pratik Mukherjee



Phiroz Tarapore



Erica Kornblith



Post-Traumatic Delirium Risk Factors & Outcomes: A TRACK-GERI Ancillary Study

- NIH Beeson 5-Year Career Development Award
- Will enroll N=170 adults age 65y+ with acute TBI at UCSF who will undergo comprehensive clinical evaluation with a TRACK-GERI type protocol + deep phenotyping of post-injury DELIRIUM.



Sara LaHue MD
Assist Prof of Neurology
UCSF
Visiting Scientist
Buck Institute
for Research on Aging



Top 3 Research METHODS Priorities for Older Adult TBI

1. Older Adult TBI Common Data Elements (CDEs)

Human CDEs	imaging 	blood NFL GFAP 	frailty grip survey 	digital mobility Axivity 	mobility falls SPPB 	cognition CDR tests 	neuro-pathology* 
Mouse CDEs		NFL GFAP 	grip 	CatWalk XT CW 	CW 	tests 	

2. Funders must treat pre-injury health status like gender or they risk funding studies that will not generalize to HALF of this population.

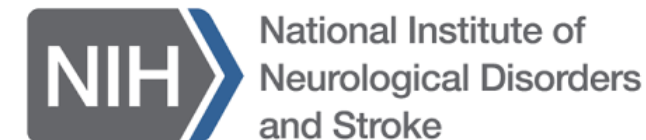
→ require consideration of high-priority pre-injury health factor(s): cognitive status, frailty, multi-morbidity, polypharmacy

→ actively discourage exclusion of specific sub-groups based on pre-injury health status.

3. Multi-disciplinary teams including TBI experts and dementia/geriatrics experts.

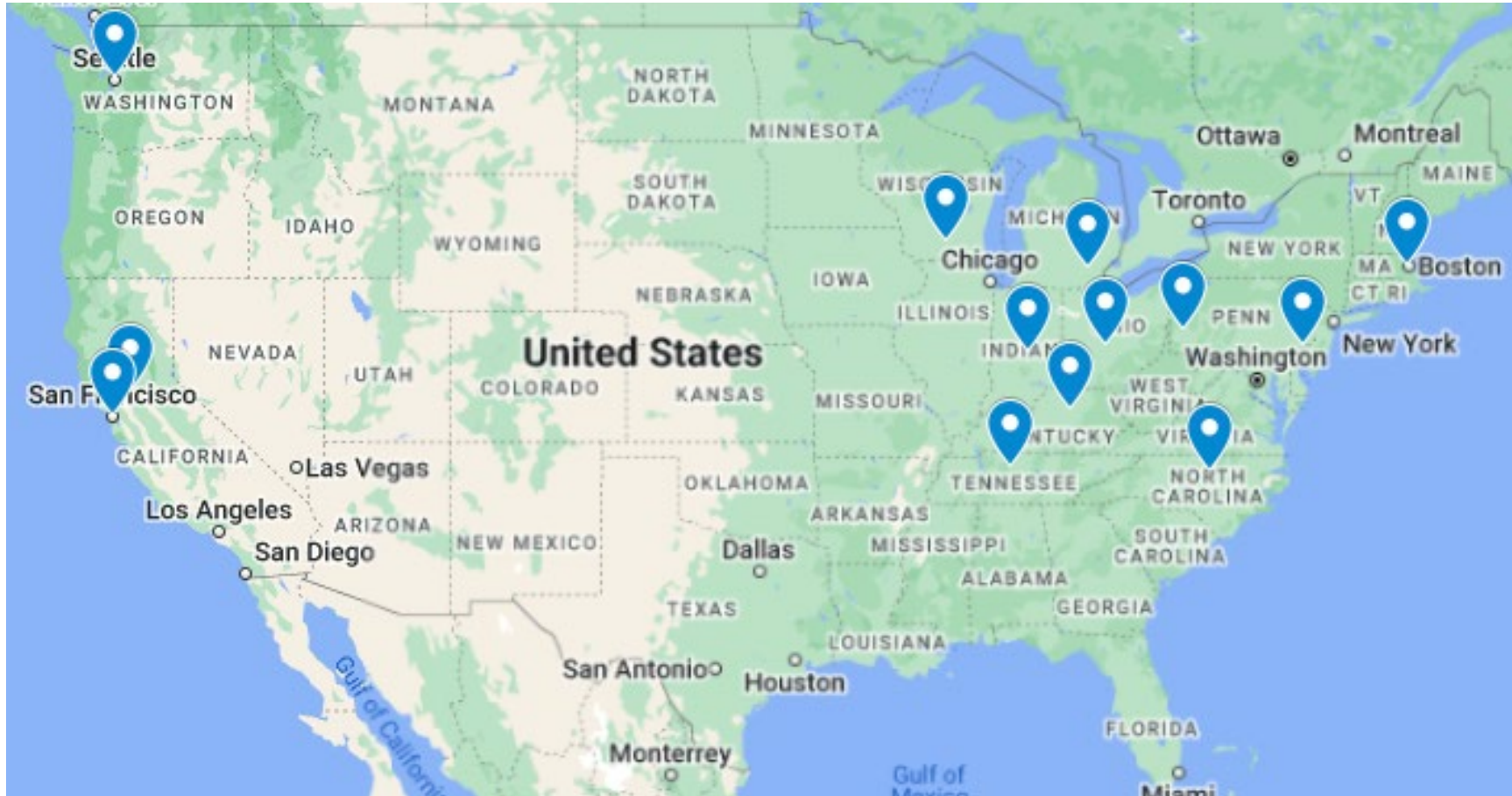
#1 TOP RESEARCH PRIORITY for Older Adult TBI: We need all hands on deck

- Large-scale multi-center prospective cohort study of all severity REAL-WORLD (e.g. no exclusions for pre-injury health) older adult TBI.
- Co-localized TBI clinical research teams + NIA-funded Alzheimer's Disease Research Centers / VA Centers of Excellence + Industry Partners.
 - TBI teams conduct state-of-the-art "CBIM" (clinical-blood-imaging-modifiers) TBI endophenotyping.
 - ADRC teams conduct post-acute phenotyping and longitudinal follow-up with state-of-the-art neurodegenerative disease biomarkers and clinical syndromic phenotyping.
- Studies must be designed to immediately:
 - Inform evidence-based clinical guidelines.
 - Inform design of high-impact clinical trials to advance precision medicine management.



Currently there are N=13 co-localized
TRACK-TBI + NIA-ADRC Sites
and more TRACK-TBI sites are being added all the time...

- UC Davis
- UCSF
- Indiana U
- U Kentucky
- Harvard
- U Michigan
- Duke
- UPMC
- Vanderbilt
- U Washington
- U Wisconsin
- Penn
- OHSU



Acknowledgments/Disclosures

Gardner Lab @ Sheba

Adi Gidali

Alisa Sheldon

Anton Peled

Avital Perry

Efrat

Noa Angel

Orit Lesman-Segev

Roy Tzemah-Shachar

Shlomit Pasternak

Yael Rozen Lang

Zohar Treisman

(Former Gardner Lab @ UCSF)

Michelle Diaz Nelson

Erica Kornblith

Sara LaHue

Domenico Lombardi

Katherine Kuang

Lisa Kritikos

UCSF/SFVAMC Center for

Population Brain Health

Kristine Yaffe

Deborah Barnes

Amy Byers

Erica Kornblith

UCSF Brain & Spinal

Injury Ctr

Geoff Manley

Adam Ferguson

Russell Huie

UCSF Neuroradiology

Esther Yuh

TRACK-TBI Network

Geoffrey T. Manley

Joseph Giacino

Lindsay Nelson

Ramon Diaz-Arrastia

UCSF Memory & Aging

Center

Bruce Miller

Joel Kramer

Kate Possin

Gil Rabinovici

Victor Valcour

UCSF Division of

Geriatrics

Kenneth Covinsky

John Boscardin

University of Michigan

Kenneth Langa

University of Pittsburgh

Ava Puccio

David Okonkwo

University of Florida

Kevin Wang

Firas Kobaissy

Data Sources

VA Nationwide Data

TRACK-TBI / TED Meta-dataset

TRACK-GERI

HCUP

Funding

NINDS

U.S. Dept. of Defense

American Federation for Aging Research

UCSF Weill Institute for Neurosciences

Global Brain Health Institute

UCSF Research Allocation Program

Veterans Health Administration

No current consulting/COIs.

Prior consulting for BrainBox Inc.



Inspiration from the most aged country on Earth...

To: Geoff Manley



Just flying back from Tokyo. I have spent the last 3 days immersed in geriatric TBI. As you know, Japan has the oldest population in the world.

What they are doing for OA TBI care is very educational. Evacuating SDH in 103 yo with local anesthesia and endoscopic surgery! Full return to cognitively intact baseline

Amazing.

How do they decide who to operate on

And who not to operate on

Frailty