



InTBIR

International Initiative for
Traumatic Brain Injury Research

“Working together to improve outcomes and lessen the global burden of TBI”

International Initiative for Traumatic Brain Injury Research (InTBIR) General Assembly and Scientific Meeting

Saturday 16th July 2022

11:00-17:30 CEST

The Ritz Carlton Hotel, Berlin

Connect to wifi:
RITZ_CONFERENCE
Password: ritz2022

Presentations will begin at 11:15 CEST

**We are grateful to the
European Brain Injury Consortium (EBIC)
for supporting this
InTBIR General Assembly Meeting**





The story so far.....

David Menon
University of Cambridge
Joint Coordinator - InTBIR

Meeting with EU Director General (Research)

22nd October 2009, Brussels



"The Brussels Pilgrims"



NNS 2010 SYMPOSIUM LAS VEGAS JUNE 14-17, 2010

Joint EC/NIH workshop
Brain Injury Research

- urgent need for validation of effective treatments
- best achieved through international collaboration
- estimated budget of 100 million

► International collaboration



Annual Meeting 17-21 February 2011 • Washington, DC



[Start](#) | [Speaker Index](#)

Transatlantic Synergies To Promote Effective Traumatic Brain Injury Research

Saturday, February 19, 2011: 8:00 AM-9:30 AM
146A (Washington Convention Center)

A Vision for the benefits of international traumatic brain injury research

Ruxandra D. ...
Director

"Health" Director
DG Research
European Commission

AAAS 2011
Washington DC, 19 February 2011

A to Z | Sitemap | Search | About this site | Contact | Legal notice | English (en)

RESEARCH & INNOVATION
Health

European Commission > Research & Innovation > Health > Medical Research > Brain Research

The International Initiative for Traumatic Brain Injury Research (InTBIR)

Brussels meeting October 2011(EU, NIH, CIHR)

- Total funding : > \$50 million (EU: €30 million)
- Planned data collection in 10-15,000 patients
- Study start: Autumn 2013
- Recruitment start: Autumn 2014

Focus:

- Advanced disease characterisation/classification (Precision Medicine)
- Comparative effectiveness research (Stratified/Personalized Medicine)



Hotel Metropole, Brussels, Belgium
October 18 – 21, 2011

InTBIR

International Initiative for TBI Research

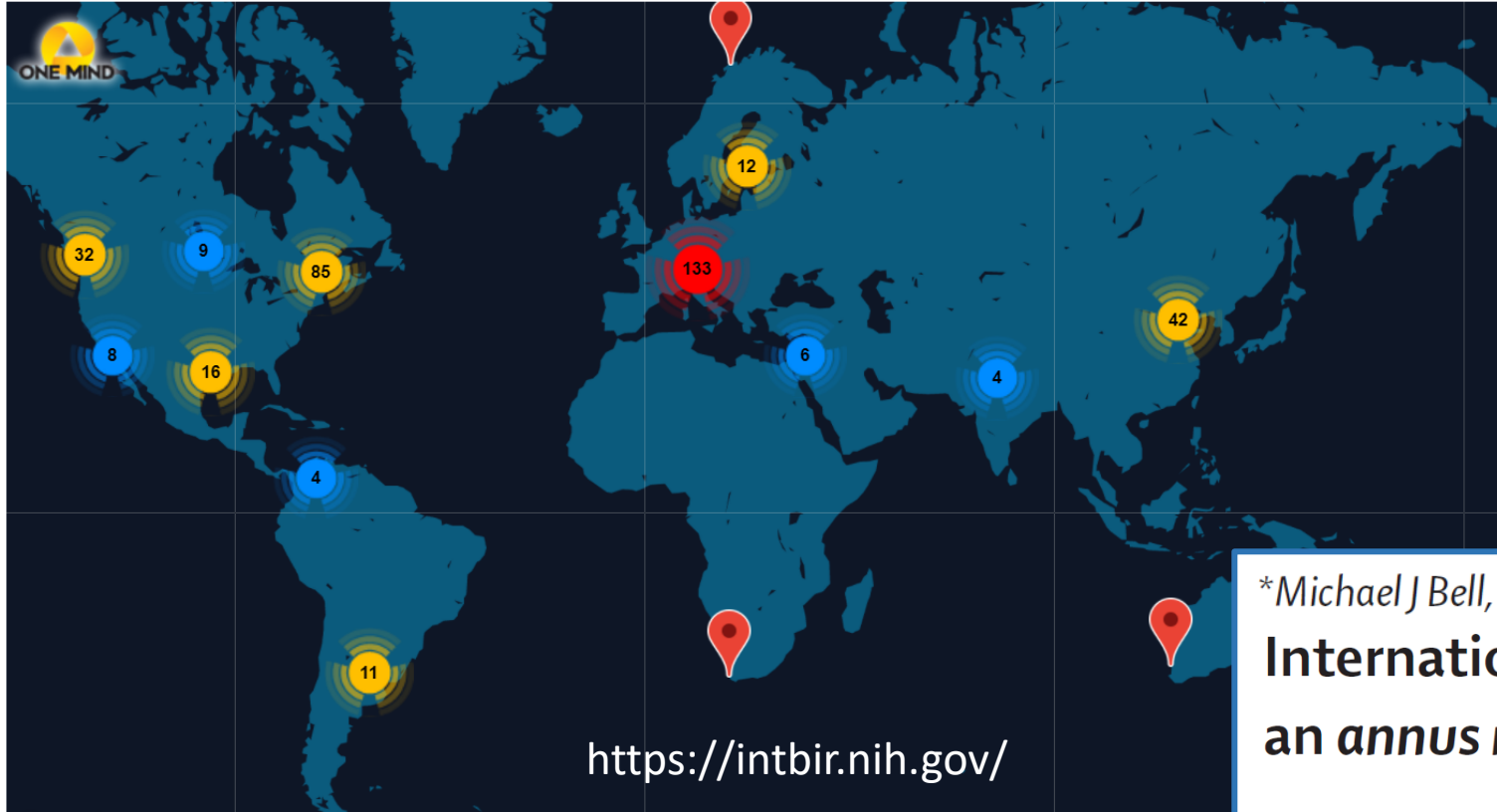
JOURNAL OF NEUROTRAUMA 30:1211–1222 (July 15, 2013)
© Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2013.2896

Original Articles

Toward an International Initiative for Traumatic Brain Injury Research

Patrizia Tosetti,¹ Ramona R. Hicks,² Elizabeth Theriault,³ Anthony Phillips,³ Walter Koroshetz,²
and Ruxandra Draghia-Akli,¹ and the Workshop Participants

☒ All (370)	Website ☒ 5P (9)	Website ☒ Creactive (72)	Website ☒ GNRG (16)
Website ☒ ADAPT (49)	Website ☒ 15-Yr Study (1)	Website ☒ CENTER-TBI (68)	Website ☒ CENTER-TBI Affiliate (47)
Website ☒ TRACK-TBI (20)	Website ☒ TEAM-TBI (1)	Website ☒ Ped-CDE (7)	Website ☒ Neurocare (1)
Website ☒ Hemotion (19)	Website ☒ Safe to Play (1)	Website ☒ PlayGame (1)	Website ☒ TBI-Prognosis (17)
Website ☒ CTRC (41)			



<https://intbir.nih.gov/>

A global consortium of **research funding agencies**

Over 20 studies, in 350 centres, recruited ~50,000 patients, with varying granularity of data

(all TBI severities and all ages)

Has helped to put TBI on the international health policy and research funding agenda

Helped to drive a *mirum decennium* (miraculous decade) in TBI research

Evolved into current phase of InTBIR as an **investigator led organisation**

*Michael J Bell, Patrick M Kochanek

**International traumatic brain injury research:
an *annus mirabilis*?**

Lancet Neurology 2019; 18: 904

Key messages

Apply existing knowledge to improve prevention and clinical care

Develop a common benchmarking

Advance knowledge research

- Support research through better data
- Develop and use common constructs
- Use **comparative** research to randomised trials
- Promote research on traumatic brain injury and spinal cord injury
- Increase **global collaborations** and establish national and international biorepositories and databases



THE LANCET Neurology

November, 2017

www.thelancet.com/neurology

Traumatic brain injury: integrated approaches to prevention, clinical care, and research



Traumatic brain injury is a public health challenge of vast, but insufficiently recognised, proportions. Concerted efforts are urgently needed to address deficiencies in prevention, care, and research."

A Commission by The Lancet Neurology

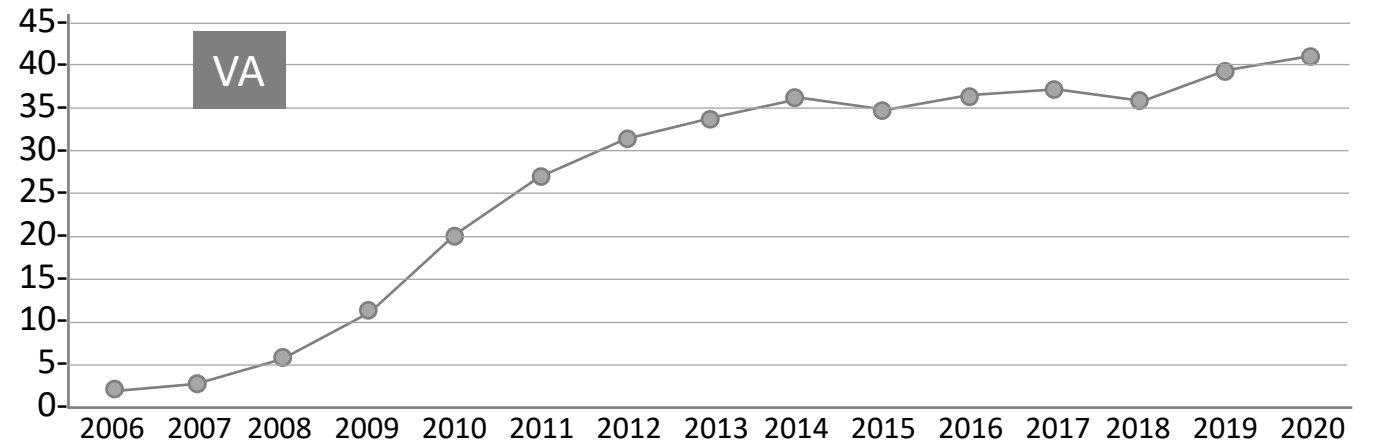
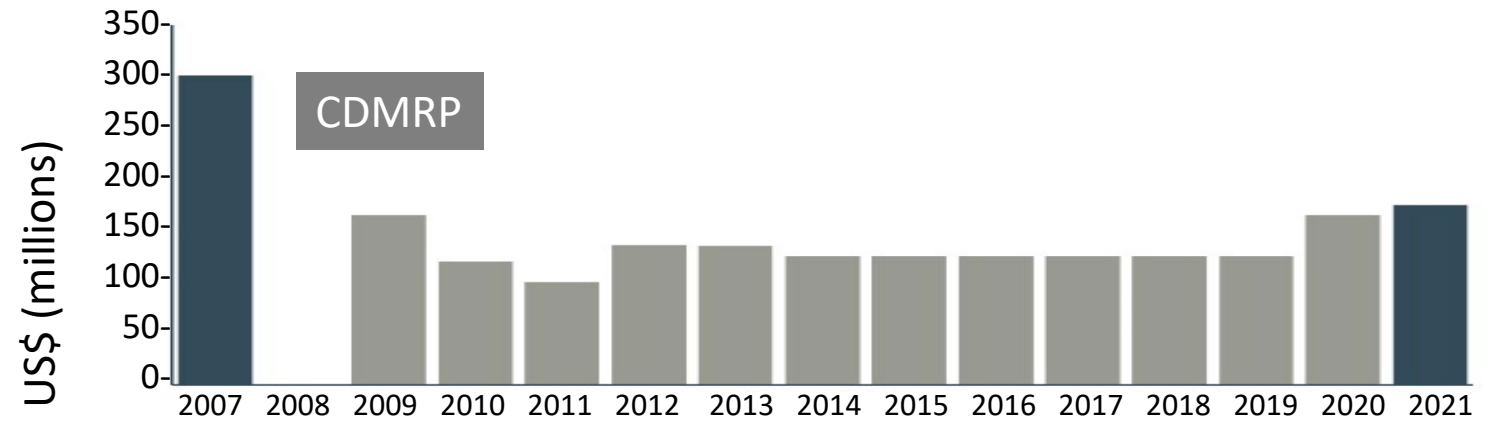
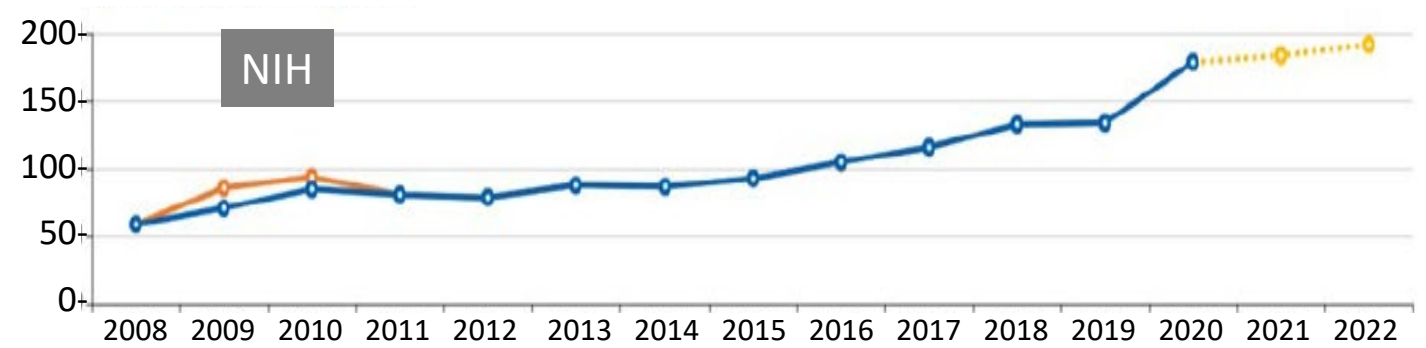
Maas, Menon, et al.

www.thelancet.com/commissions/traumatic-brain-injury

*Michael J Bell, Patrick M Kochanek

International traumatic brain injury research: an *annus mirabilis*?

Lancet Neurology 2019; 18: 904



Key messages

Apply existing knowledge to improve prevention and clinical care

Develop a common language for epidemiology and benchmarking care

Advance knowledge, clinical care and research

- Support research through better data
- Develop and validate constructs that quantify quality
- Use **comparative effectiveness research** as an adjunct to randomised trials to identify best practice
- Promote research on links between traumatic brain injury and increased **risk of later neurological disease**
- Increase **global collaborations** and establish national and international biorepositories and databases

Five year update planned release September/October 2022;
to also coincide with Lancet Neurology's 20th Birthday
Informed review of literature in last 5 years with ~400 references

Maas, Menon, et al.

www.thelancet.com/commissions/traumatic-brain-injury





Nemo solus satis sapit

InTBIR 2.0



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InTBIR

Working together to improve outcomes
and lessen the global burden of traumatic brain injury

InTBIR is a coalition of scientists and other stakeholders to foster
coordinated and collaborative TBI research.



Who we are



Our Mission



Resources



Join InTBIR

<https://intbir.incf.org>



Goals of InTBIR for next 2 years
Aims for this meeting
How will we define success

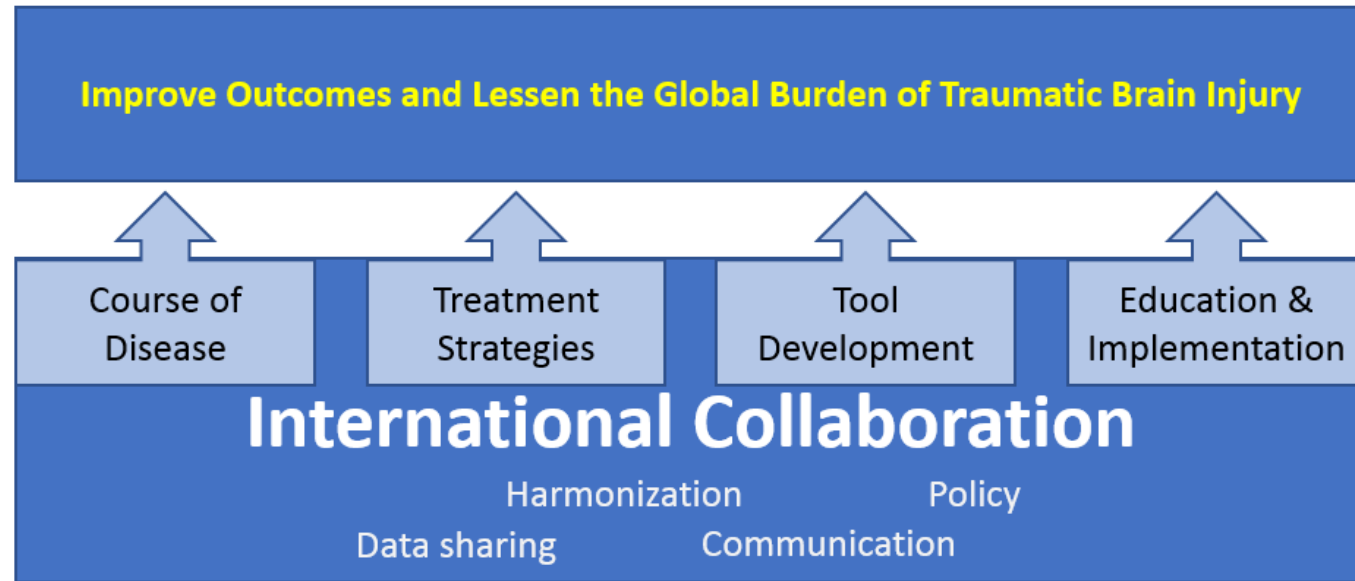


Ramon Diaz-Arrastia, MD, PhD
Joint Coordinator - InTBIR
University of Pennsylvania
Philadelphia, PA USA



Mission:

“Working together to improve outcomes and lessen the global burden of traumatic brain injury”



1. Exploit collective data gathered through multiple studies by various groups, utilizing rigorous data management, curation, harmonization, and careful statistical analysis, including federated analyses and new approaches including machine learning;
2. Validation of molecular, imaging, and physiologic biomarkers that identify targets for novel therapies and confirm target engagement;
3. Streamline and facilitate observational and interventional clinical trials aimed at improving outcome through the TBI spectrum, from concussion to coma, and from the time of injury to lifelong outcomes.



Goals for next 2 years

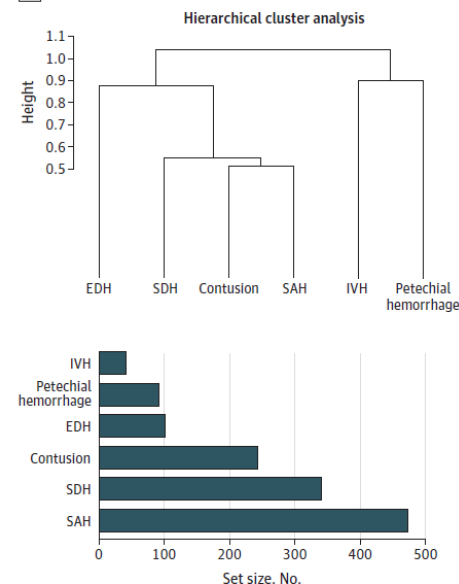
1. Continue to exploit datasets from recently completed studies (InTBIR 1.0)

- CENTER-TBI
- TRACK-TBI
- CanTBI

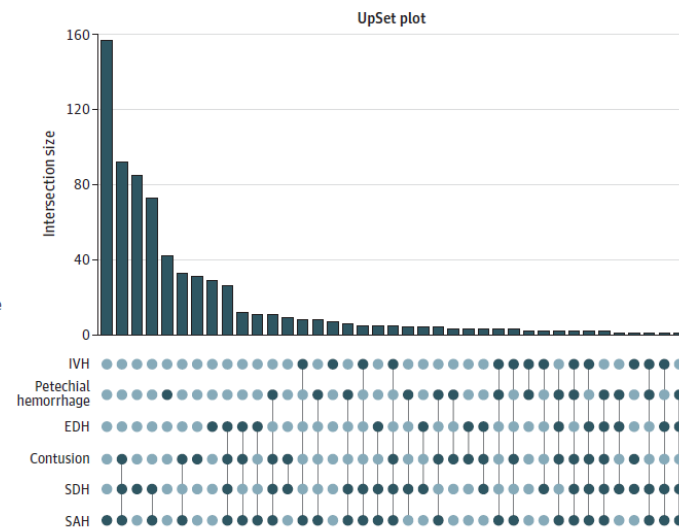
2. Focus on federated analyses that fully exploit the large sample size

- Example: Yuh et al *JAMA Neurology* 2021—CT CDEs
- Opportunities for federated MRI analyses
- Opportunities for federated analyses of blood biomarkers
- Others

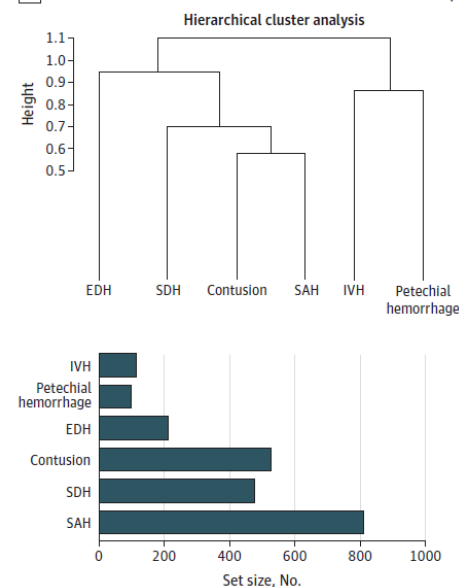
A TRACK-TBI distribution and co-occurrences of CT intracranial pathology in mTBI



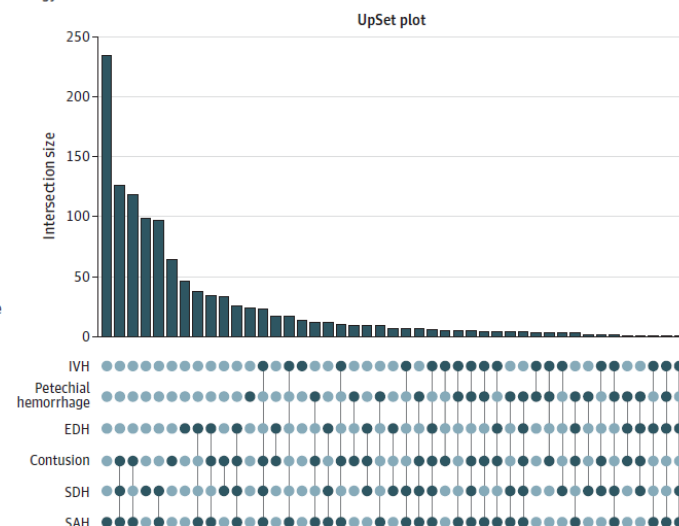
TRACK-TBI



B CENTER-TBI distribution and co-occurrences of CT intracranial pathology in mTBI



CENTER-TBI





Goals for next 2 years

3. Will need joint grant submissions to fully exploit what is available
 - “TRACK-TBI and CENTER-TBI: Federating for TBI Power and Precision.” (TRACER-TBI)
 - Submitted to NINDS March 15, 2022
 - “Analytical characterization and validation of blood-biomarkers for monitoring TBI evolution” (InTBIR Biomarker Validation)
 - Submitted to NINDS June 22, 2022
 - There are other proposals in process of submission/review without InTBIR “Brand”
 - How will InTBIR “Brand” facilitate funding?



Goals for next 2 years

4. Expand InTBIR beyond initial focus in Europe and North America
 - Australia (AUS-TBI; ANZIC)
 - China
 - India
 - Latin America
 - Africa
 - Build upon what already exists
 - Prof. Peter Hutchison's NIHR Global Neurotrauma Research Group
 - Prof. Randy Chesnut Latin American Brain Injury Consortium (LATBIC)
 - Particular opportunities for Comparative Effectiveness Research and Implementation Science



Goals for next 2 years

5. Expand Genetic Association in Neurotrauma (GAIN) Consortium
 - Other phenotypes (i.e. Psychiatric outcomes; PTSD)
 - Endophenotypes
 - Biomarkers
 - CT hematoma expansion
6. Create an International TBI Clinical Trials Network
 - TRACK-TBI NET in US to do DoD-funded trials, initially on repurposed drugs
 - Multiple potential industry partners will need to be convinced of capacity of neurotrauma field to conduct Phase 2 and Phase 3 trials
7. **Other ideas to come out of this meeting**



Aims for this Meeting

1. Get to know each other

- Particularly the next generation of leaders in TBI research

2. Brainstorm on:

- How we can maximally leverage the experience from InTBIR 1.0 studies over the past 10 years
- How InTBIR “Brand” can facilitate future grant proposals
- How best to collaborate with industry partners for diagnostic, therapeutic, and device development
- How InTBIR website can be maximally beneficial to TBI research community



How to Define Success

1. Metrics of intra- and international data sharing (e.g., number of data elements or subject-level data downloaded internationally, data access requests, etc).
2. Utilization of tools developed by InTBIR.
3. New multinational funded projects.
4. Alignment of pre-clinical research to most up-to-date findings from human studies to improve chances of successful translation
5. Multi-national clinical trials (including in Lower and Middle-income Countries)
6. Knowledge dissemination, including publications, guidelines development and updates, and policy recommendations to governmental and organizational groups that have influence on implementation of new findings.

InTBIR 2022 Updates: Biomarker Working Group

Ramon Diaz-Arrastia, MD, PhD

Professor of Neurology, University of Pennsylvania, USA

Stefania Mondello, MD, MPH, PhD

Professor, University of Messina, Italy

Kevin Wang, PhD

Professor, Morehouse University School of Medicine, USA

Cheryl Wellington, PhD

Professor, Pathology and Laboratory Medicine, University of British Columbia, Canada

Jamie Hutchison, MD

Professor, University of Toronto, Hospital for Sick Children, Toronto, Canada

Ava Puccio, RN, PhD

Assoc. Prof. Neurological Surgery, University of Pittsburgh, USA

Andras Buki, MD

Professor of Neurological Surgery, Orebro University, Sweden

Kimbra Kenney, MD

Professor of Neurology, Uniformed Services University, USA

Endre Creitzer, MD, PhD

Asst. Professor, University of Pecs, Hungary

David Okonkwo, MD, PhD

Professor of Neurosurgery, University of Pittsburgh, USA

Geoff Manley, MD, PhD

Professor of Neurosurgery, University of California, San Francisco, USA



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Biospecimen Holdings

Transforming Research And Clinical Knowledge in TBI (TRACK-TBI),
Collaborative European NeuroTrauma Effectiveness Research in TBI CENTER-TBI,
A Canadian biobank and database for Traumatic Brain Injury (CanTBI)
and Control Biorepository Specimens On-Hand

Study ID	Participants	Specimens					
		Buffy Coat	CSF	Plasma	Serum	Whole Blood	Total
TRACK-II	2,903	2,801		30,660	30,712	7,261	71,434
TRACK-II Ortho Controls	353	341		3,248	3,268	813	7,670
TRACK Healthy Controls	200	198		771	859	61	1,889
TRACK Friend Controls	289	275		1,642	1,973	470	4,360
TRACK CSF	115		1,778				1,778
CENTER-TBI	3,803				32,636		32,636
CanTBI	455	774	650	7,078	12,339		20,841
CanTBI and previous Pediatric Ortho Controls	200	Samples will be divided into aliquots					
CALIPER Healthy Control children	13,000	Aliquots will be provided as needed					13,000
Canadian Health Measures Survey aged 3 to 79 years	5,100			5,100			5,100
Total	26,418	4,389	2,428	48,499	81,787	8,605	158,708



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coordinated and collaborative TBI research.



Who we are



Our Mission



Resources



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<https://intbir.incf.org>



Lancet Neurology, 2012

The changing landscape of traumatic brain injury research

Editorial

Lancet Neurology, 2013

A rally for traumatic brain injury research

The Lancet Neurology Commission

Lancet Neurology, 2017

Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research



Andrew I R Maas*, David K Menon*, P David Adelson, Nada Andelic, Michael J Bell, Antonio Belli, Peter Bragge, Alexandra Brazinova, András Büki, Randall M Chesnut, Giuseppe Citerio, Mark Coburn, D Jamie Cooper, A Tamara Crowder, Endre Czeiter, Marek Czosnyka, Ramon Diaz-Arrastia, Jens P Dreier, Ann-Christine Duhaime, Ari Ercole, Thomas A van Essen, Valery L Feigin, Guoyi Gao, Joseph Giacino, Laura E Gonzalez-Lara, Russell L Gruen, Deepak Gupta, Jed A Hartings, Sean Hill, Ji-yao Jiang, Naomi Ketharanathan, Erwin J O Kompanje, Linda Lanyon, Steven Laureys, Fiona Lecky, Harvey Levin, Hester F Lingsma, Marc Maegele, Marek Majdan, Geoffrey Manley, Jill Marsteller, Luciana Mascia, Charles McFadyen, Stefania Mondello, Virginia Newcombe, Aarno Palotie, Paul M Parizel, Wilco Peul, James Piercy, Suzanne Polinder, Louis Puybasset, Todd E Rasmussen, Rolf Rossaint, Peter Smielewski, Jeannette Söderberg, Simon J Stanworth, Murray B Stein, Nicole von Steinbüchel, William Stewart, Ewout W Steyerberg, Nino Stocchetti, Anneliese Synnot, Braden Te Ao, Olli Tenovu, Alice Theadom, Dick Tibboel, Walter Videtta, Kevin K W Wang, W Huw Williams, Lindsay Wilson, Kristine Yaffe, for the INTBIR Participants and Investigators†‡

Genetic Associations in Neurotrauma (GAIN) Initiative

First genome- and transcriptome-wide association studies (GWAS, TWAS) of genetic effects on outcome in TBI. The study population consisted of:

- 5268 patients from prospective European and US studies,
- Enrolled within 24 h of TBI, and need for a CT scan

Articles

A genome-wide association study of outcome from traumatic brain injury



www.thelancet.com Vol 77 Month March, 2022

Mart Kals,^{a,b,1} Kevin Kunzmann,^{c,e} Ljilja Parodi,^{d,e,f,1} Farid Radmanesh,^g Lindsay Willson,^h Soef Izzy,^g Christopher D. Anderson,^{e,f,g} Ava M. Puccio,ⁱ David O. Okonkwo,^j Nancy Temkin,^j Ewout W. Steyerberg,^{k,l} Murray B. Stein,^m Geoff T. Manley,ⁿ Andrew LR. Maas,^o Sylvia Richardson,^e Ramon Diaz-Arrastia,^p Aarno Palotie,^{a,d,f} Samuli Ripatti,^{a,c,q} Jonathan Rosand,^{d,e,f,s} and David K. Menon^{t,u,v}, on behalf of The Genetic Associations In Neurotrauma (GAIN) Consortium (with contribution from the CENTER-TBI, TRACK-TBI, CABI, MGB, and TBIcare studies)

^aInstitute for Molecular Medicine Finland (FIMM), HiLIFE, University of Helsinki, Helsinki, Finland

^bEstonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia

^cMRC Biostatistics Unit, Cambridge Institute of Public Health, University of Cambridge, Cambridge, United Kingdom

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^gDepartment of Neurology, Brigham and Women's Hospital, Boston, MA, USA

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eBioMedicine 2022;77:
103933
Published online xxx
<https://doi.org/10.1016/j.ebiom.2022.103933>



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Although no significance was found in various loci to TBI outcome, promising loci.
Of note: APOE-4 did not remain significant after adjusting for multiple comparisons.

Highlights for future TBI studies:

- Collect key injury covariates and good quality outcome data
- Harmonizable common data elements
- Bank DNA, and obtain consent for subsequent collaborative analyses

Locus	Lead variant	Chr	Position (Hg38)	Alleles (EA/OA)	MR-MEGA	
					EAF	p-value
COL3A1	rs2390015	1	86101570	C/A	0.467	1.09×10^{-6}
BHLHE40*	rs2163909	3	5044114	A/G	0.441	1.51×10^{-6}
FHT	rs113548485	3	59415748	T/C	0.081	2.47×10^{-6}
EF4G1*	rs56148883	3	184333858	A/G	0.082	9.56×10^{-6}
BLOC1S5-TXNDC5	rs1150893	6	7967713	T/C	0.531	7.69×10^{-6}
PSD3	rs57832455	8	18484815	G/C	0.585	2.71×10^{-6}
MBL2*	rs11008134	10	52778399	A/C	0.138	4.14×10^{-6}
PIGH*	rs2319844	14	67598317	T/C	0.809	1.42×10^{-6}

Table 3: Loci attaining sub-genome-wide significance ($p < 10^{-5}$) in association with TBI outcome in trans-ethnic meta-regression ($n = 5268$).
Chr: chromosome; EA: effect allele; OA: other allele; EAF: effect allele frequency.
* New loci compared to European ancestry meta-analysis (Table 1).





InTBIR Session June 29, 2022

Implementing TBI Biomarkers in a Real-World Clinical Setting (InTBIR Work Group)

	Dr. Stefania Mondello Full Professor University of Messina	Session Chair
	Dr. Ava Puccio Assistant Professor University Of Pittsburgh	Session Co-Chair
	Dr. Ramon Diaz-Arrastia Professor University Of Pennsylvania	FNIH Developing Reference Standard 🕒 11:30 - 11:50
	Prof. Jamie Hutchison The Hospital For Sick Children	The Clinical Application of Blood Biomarkers in Infants, Children and Adolescents With Concussion and TBI 🕒 11:50 - 12:10
	Dr. Kimbra Kenney Professor/Service Chief Research Operations USUHS & WRNMMC	Biomarkers of Long-Term TBI Outcomes 🕒 12:10 - 12:30
	Dr. Cheryl Wellington Professor University Of British Columbia	Ethical, Legal and Social Implications of Implementing TBI Biomarkers Into Standard of Care 🕒 12:30 - 12:50

Industry interest in TBI Biomarkers

- Large pharmaceutical and diagnostic companies
 - Abbott
 - Roche
 - Quest
- Established biomarker companies
 - Quanterix
 - MesoScale Discoveries
 - BioMerieux
 - Biotechne
- Biotech startups
 - Banyan
 - Gryphon
 - BrainBox

Abbott gains FDA clearance for rapid concussion test

JANUARY 11, 2021 BY [SEAN WHOOLEY](#) - [LEAVE A COMMENT](#)

Abbott (NYSE:ABT) announced today that it received FDA 51o(k) clearance for its rapid handheld traumatic brain injury (TBI) blood test.



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Leading TBI Biomarkers

Biomarker	Cellular structure	Temporal Profile after TBI	Available assay platforms
Ubiquitin C-terminal Hydrolase L1 (UCH-L1)	Neuronal cell body	Peak ~6 hours	Abbott (i-STAT, Alinity) Quanterix
Glial Fibrillary Acidic Protein (GFAP)	Astrocytes	Peak ~24 hours	Abbott (i-STAT, Alinity) Quanterix MSD Roche Biotechne Ella
Neurofilament Light Chain (NFL)	Axons	Peak ~20 days	Quanterix MSD Biotechne Ella Quest (LC/MS)
Phospho-neurofilament heavy chain (p-NfH)	Axons	Unknown	Quanterix
Total Tau	Neurons, glial cells	Peak ~5 days	Quanterix MSD
Phospho-Tau 181 (pTau-181)	Neurons, glial cells	Unknown	Quanterix MSD
Phospho-Tau 231 (pTau-231)	Neurons, glial cells	Peak ~5 days	Quanterix MSD

‘Research Use Only’ to In-vitro Diagnostic

- **GFAP and UCH-L1 shown to be diagnostic in TBI**
 - Compared to +CT scans and + MRI scans
 - Better than S-100B
 - **GFAP diagnostic out to 2 weeks**

JOURNAL OF NEUROTRAUMA XX: 1–8 (XXXX 00, 2020)
© Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2020.7140

Original Article

**Point-of-Care Platform Blood Biomarker Testing
of Glial Fibrillary Acidic Protein versus S100 Calcium-Binding
Protein B for Prediction of Traumatic Brain Injuries:
A Transforming Research and Clinical Knowledge
in Traumatic Brain Injury Study**

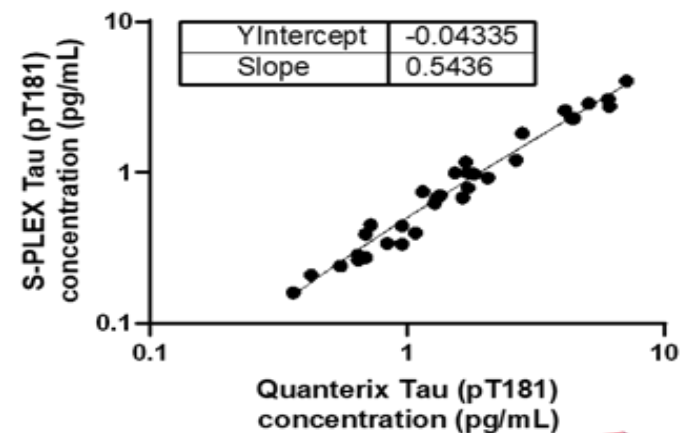
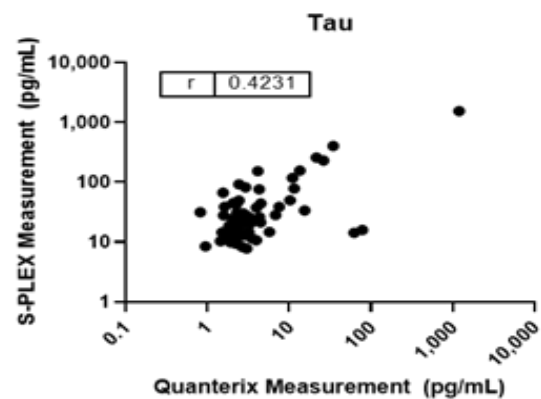
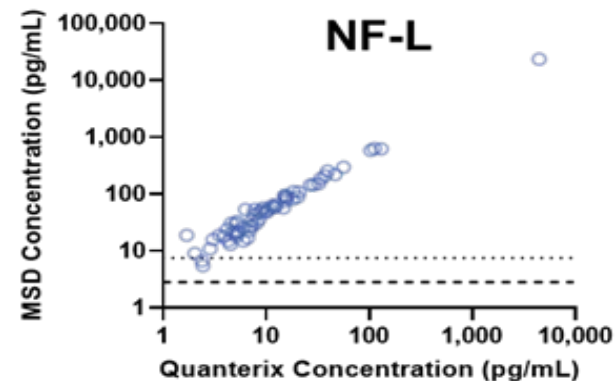
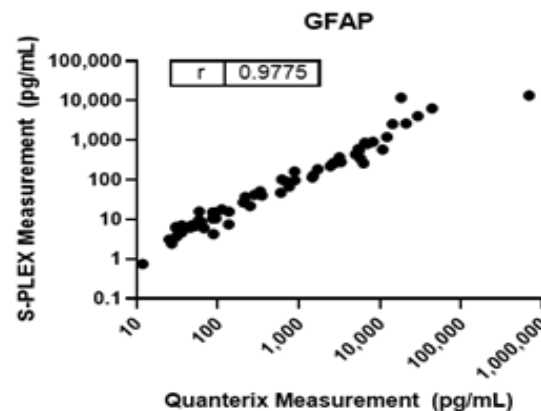
David O. Okonkwo,¹ Ross C. Puffer,^{1,2} Ava M. Puccio,¹ Esther L. Yuh,^{3–5} John K. Yue,^{4–6}
Ramon Diaz-Arrastia,⁷ Frederick K. Korley,⁸ Kevin K. W. Wang,⁹ Xiaoying Sun,¹⁰ Sabrina R. Taylor,^{4–6}
Pratik Mukherjee,^{3–5} Amy J. Markowitz,^{4–6} Sonia Jain,¹⁰ and Geoffrey T. Manley^{4–6},
and the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Investigators*



‘Research Use Only’ to In-vitro Diagnostic

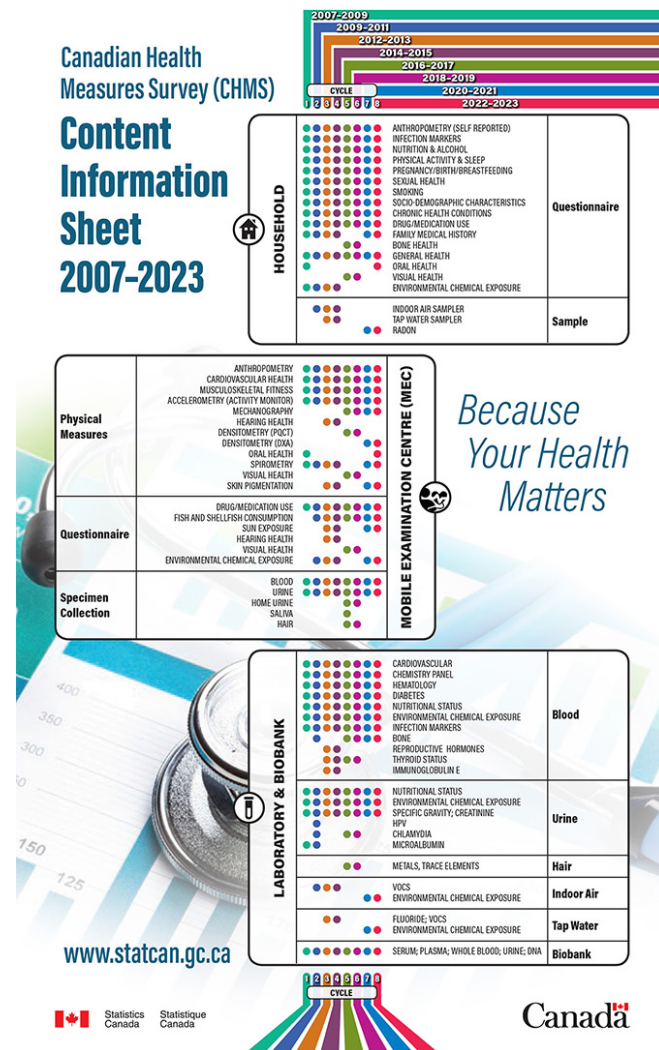
- From *Research Use Only* to *In-vitro Diagnostic*
- Additional Contexts-of-Use for TBI Biomarkers
- Needs:
 - Reference Materials
 - Reference Intervals
 - Cross-calibration across platforms
 - Assessment of robustness of each assay
- Pathways to regulatory acceptance

Need for internationally-validated calibrators



Reference Intervals

Define normal and clinical population-based normative data



The Canadian Health Measures Survey (CHMS), led by Statistics Canada, is a cross sectional epidemiological study of Canadians with Cycles every 2 years of 22,000 Canadians age 3-79. Of these, 5200 undergo an extensive health evaluation including specimen collection.



Statistics
Canada

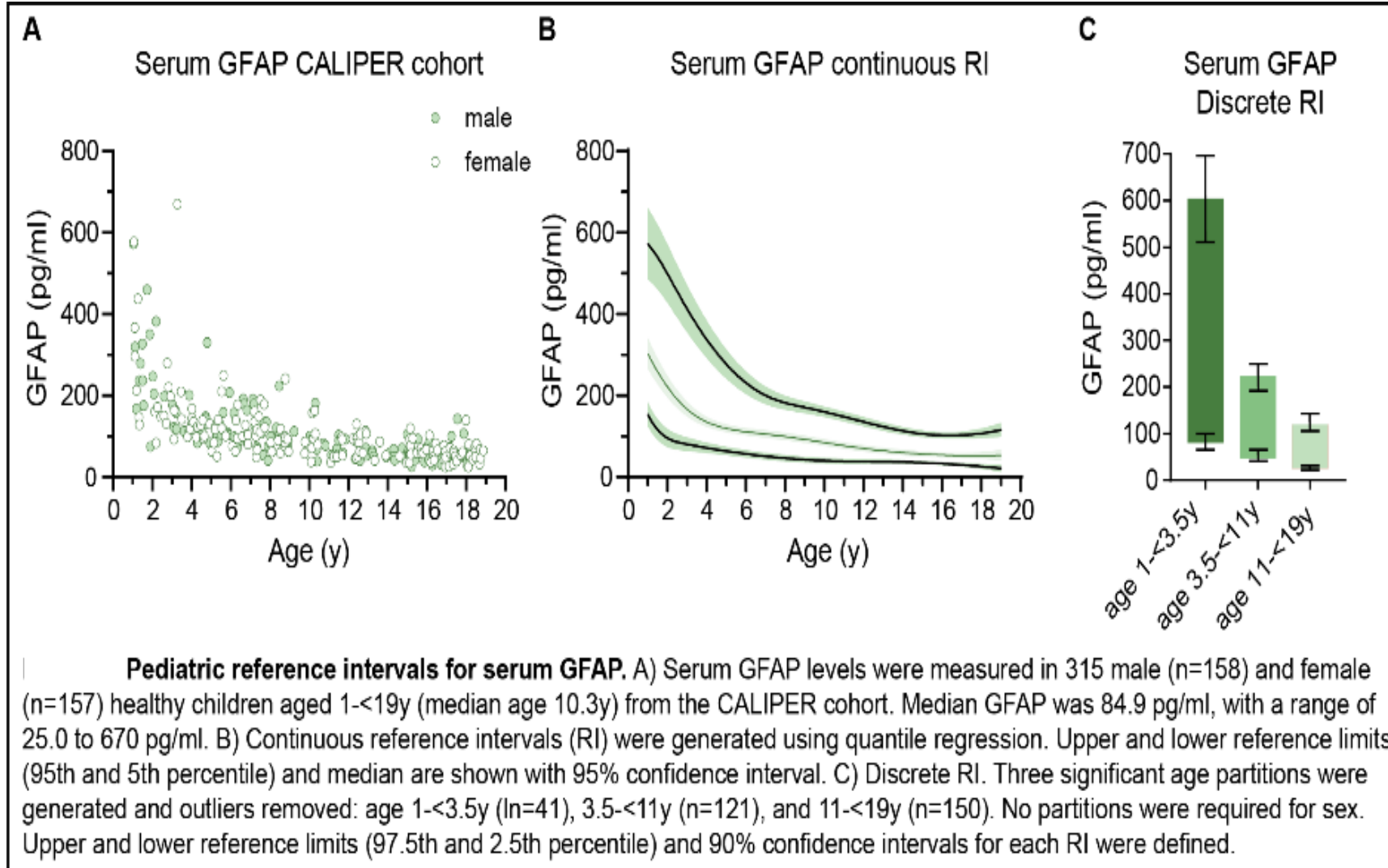
Statistique
Canada

Dr. Wellington (UBC) granted access to ~5200 plasma specimens from the CHMS across the age span.



Reference Intervals

Prof. Cheryl Wellington, Univ. British Columbia



Robustness

Set up a well-curated central depository and a data/sample management system

Develop standardized procedures (SOPs) and well defined Quality Assurance Criteria for sample handling, processing, and shipping

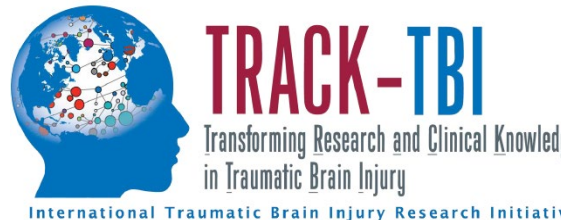


TRACK-TBI Biorepository UPMC



CENTER-TBI Biorepository
Pecs Univ.

- Information management System (BSI)
- Experience with biosample
 - Receiving and inventory management
 - Shipping to Analytical sites



Manual of Procedures

TRACK-TBI Biorepository

5 May 2016



CENTER-TBI

Collaborative European NeuroTrauma Effectiveness Research in TBI
A 2020 vision: Generating knowledge for improving TBI outcomes

**Standard Operating Procedures for
sample handling**

version: **1.0** (17.10.2014)



Robustness

- Tolerance of biomarker assays to variations in pre-analytical processing
 - Time of collection (circadian and post-prandial effects)
 - Time from collection to processing
 - Processing temperature and centrifugation speed
 - Effects of hemolysis and lipemia
 - Storage temperature
 - Effect of freeze-thaw cycles

Funding Opportunities

U01: PAR-21-056 Analytical Validation of Candidate Biomarkers for Neurological Disorders'

Submitted to NIH in June:

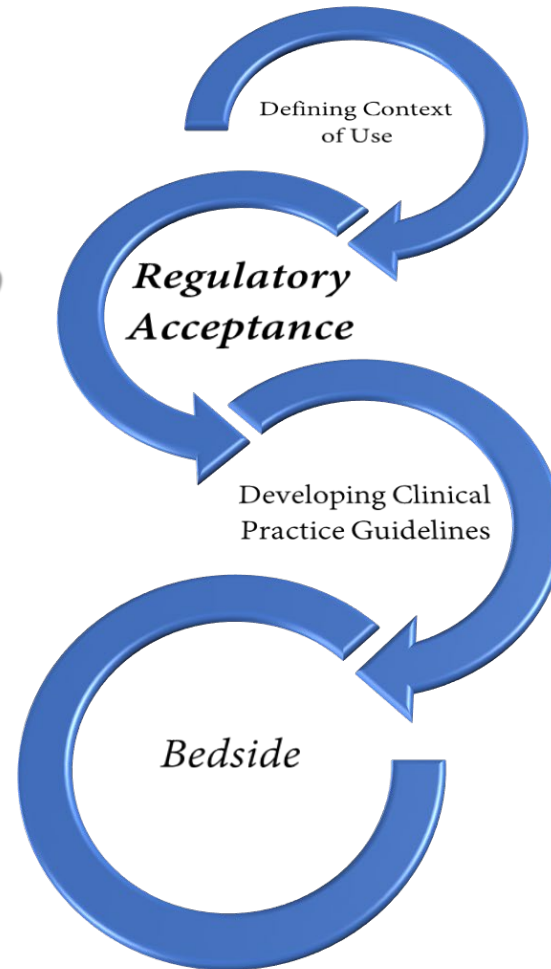
'Analytical characterization and validation of key biomarkers for neuromonitoring of patients with traumatic brain injury'

- Multi PI Proposal
 - Ava Puccio, RN, PhD: Contact PI, Project Coordination—U of Pittsburgh
 - Ramon Diaz-Arrastia, MD, PhD—U of Pennsylvania
 - Kevin Wang, PhD—Morehouse University
 - Cheryl Wellington, PhD—University of British Columbia
 - Jamie Hutchison, MD—Toronto, Hospital of Sick Kids
 - Stefania Mondello, MD-U of Messina

Pathways to Regulatory Acceptance

Promote regulatory acceptance and international adoption of TBI biomarkers

Bringing TBI Biomarkers to the People



The consortium will exploit its expertise in achieving regulatory acceptance of specified biomarkers, by timely and effectively interacting with regulatory agencies (EMA, FDA, Health Canada) which will be essential for the biomarker qualification submissions to the regulatory authorities, and thus for achieving the expected impact of bringing TBI biomarkers in the clinic.



InTBIR

Neuroimaging Working Group

Mission Statement:

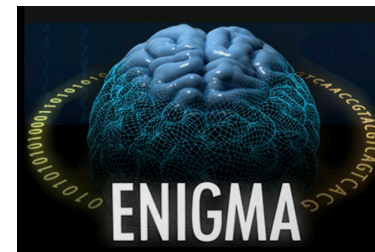
A concerted effort from experts in the field to define a framework for how different neuroimaging modalities, including CT, MRI, and PET will be leveraged to provide complementary information to help understand the effects of trauma on the brain and how they can inform differing prognoses and therapy requirements to enable precision medicine.

The Neuroimaging Working group will collate and coordinate the standardization of protocols required for MRI, PET, or CT, parameter optimization, and standardized analysis pipelines and preclinical-clinical translation



CONNECT-TBI

THE COLLABORATIVE NEUROPATHOLOGY NETWORK CHARACTERIZING OUTCOMES OF TBI



CTRC



TRACK-TBI



TBI
Endpoints
Development

TED

Aim 1

Seek to build on existing work done in the first generation of InTBIR studies, and also in other large international collaborations.

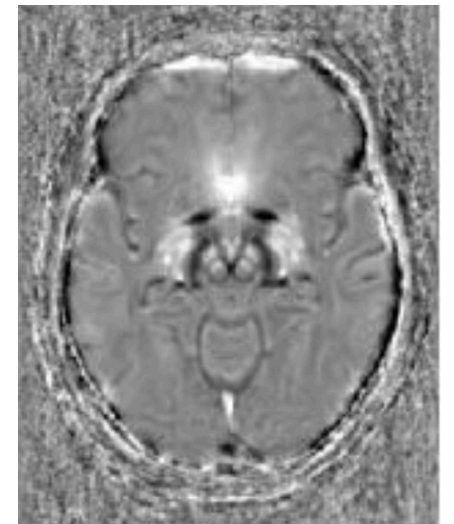
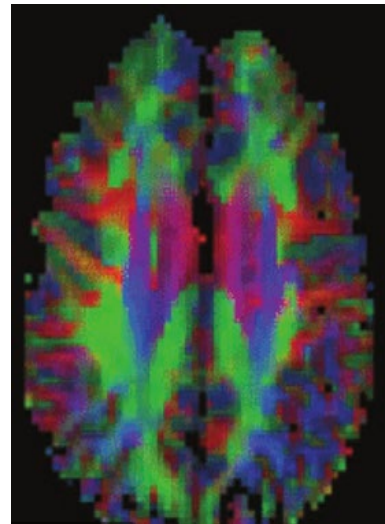
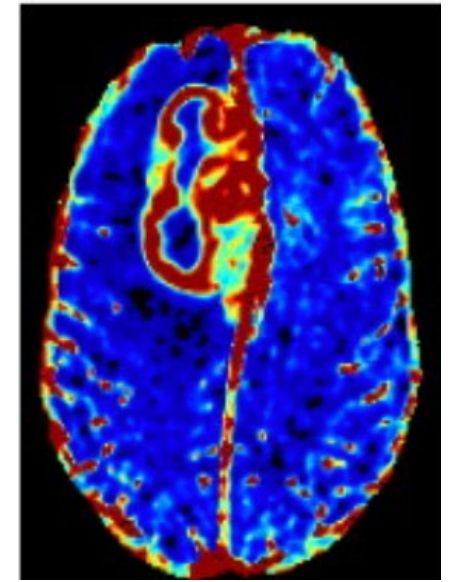
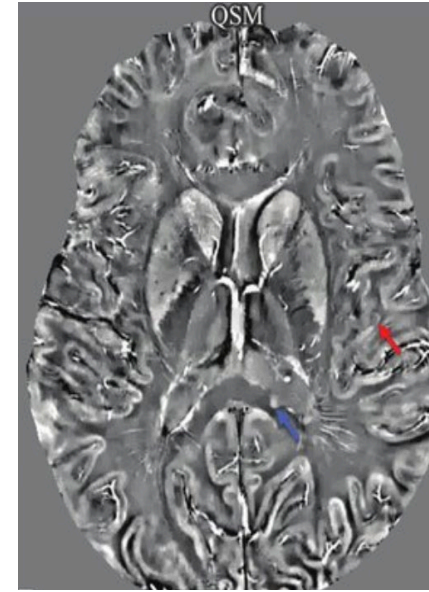
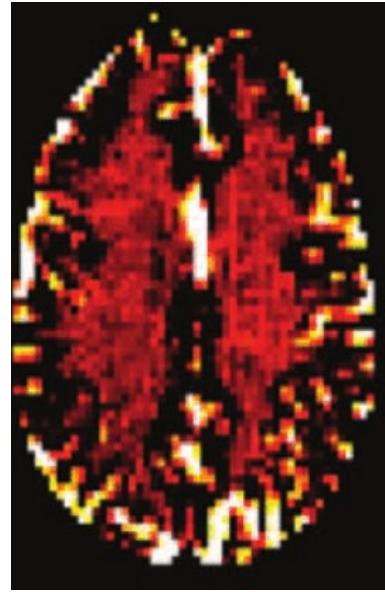


Aim 2

Establish best practices
for data acquisition
globally that will
maximize data sharing
and support
multidisciplinary
initiatives for
neuroimaging of TBI

**Toward Precision and Reproducibility of Diffusion Tensor
Imaging: A Multicenter Diffusion Phantom and Traveling
Volunteer Study**

 E.M. Palacios,  A.J. Martin,  M.A. Boss,  F. Ezekiel,  Y.S. Chang,  E.L. Yuh,  M.J. Vassar,  D.M. Schnyer,  C.L. MacDonald,
 K.L. Crawford,  A. Irimia,  A.W. Toga,  P. Mukherjee, and the TRACK-TBI Investigators



Aim 3

Provide a platform where data analysis and processing pipelines are made readily available, or sharable through collaboration.

Recommendations

- Use of CDE based radiological reporting
- Explore quantitative metrics for all modalities
- Increasing use of AI based analysis

PNAS **Expert-level detection of acute intracranial hemorrhage on head computed tomography using deep learning**

Weicheng Kuo^a, Christian Häne^a, Pratik Mukherjee^b, Jitendra Malik^{a,1}, and Esther L. Yuh^{b,1}

^aElectrical Engineering and Computer Sciences, University of California, Berkeley, CA 94720; and ^bDepartment of Radiology and Biomedical Imaging, University of California, San Francisco, CA 94107

Automatic Quantification of Computed Tomography Features in Acute Traumatic Brain Injury

JOURNAL OF NEUROTRAUMA 36:1794–1803

Saurabh Jain,¹ Thijs Vande Vyvere,^{1,2} Vasilis Terzopoulos,¹ Diana Maria Sima,¹ Eloy Roura,¹ Andrew Maas,³ Guido Wilms,^{1,4} and Jan Verheyden¹

Multiclass semantic segmentation and quantification of traumatic brain injury lesions on head CT using deep learning: an algorithm development and multicentre validation study

Miguel Monteiro*, Virginia F J Newcombe*, Francois Mathieu, Krishma Adatia, Konstantinos Kamnitsas, Enzo Ferrante, Tilak Das, Daniel Whitehouse, Daniel Rueckert, David K Menon†, Ben Glocker†

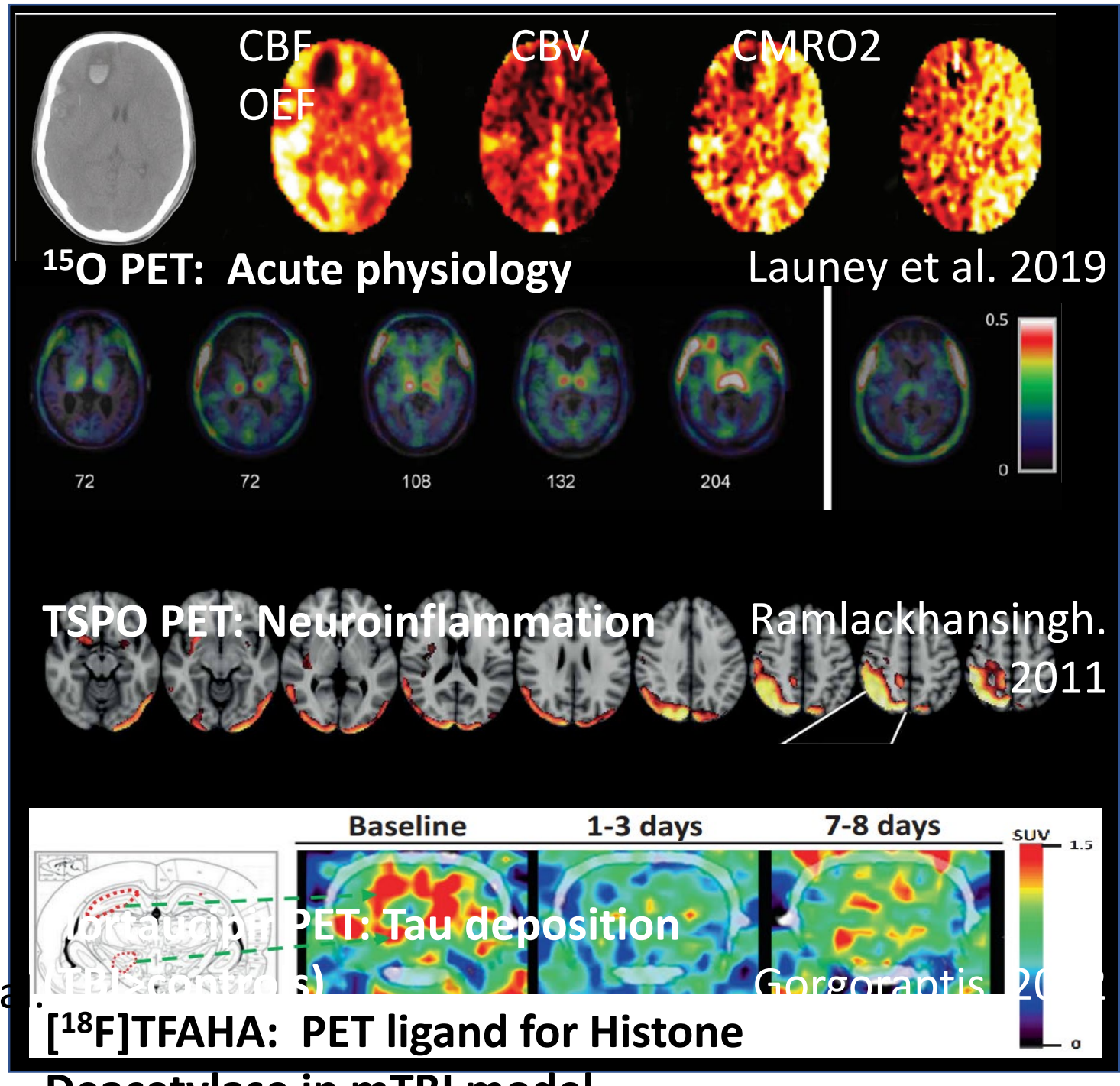


Lancet Digital Health 2020;
2: e314–22



Aim 4

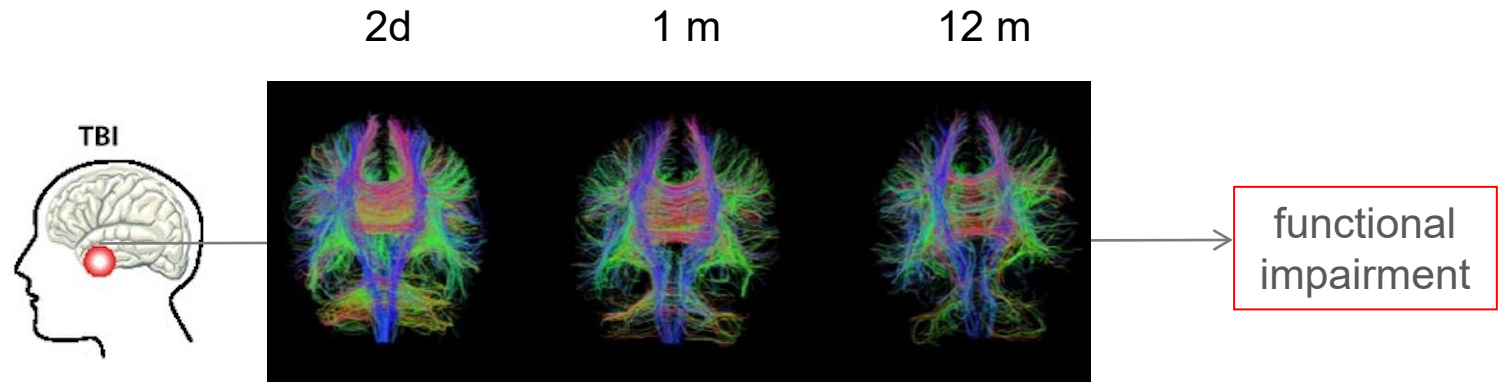
Leverage cutting-edge technical and methodological innovations in the field to encompass a full range of imaging modalities.



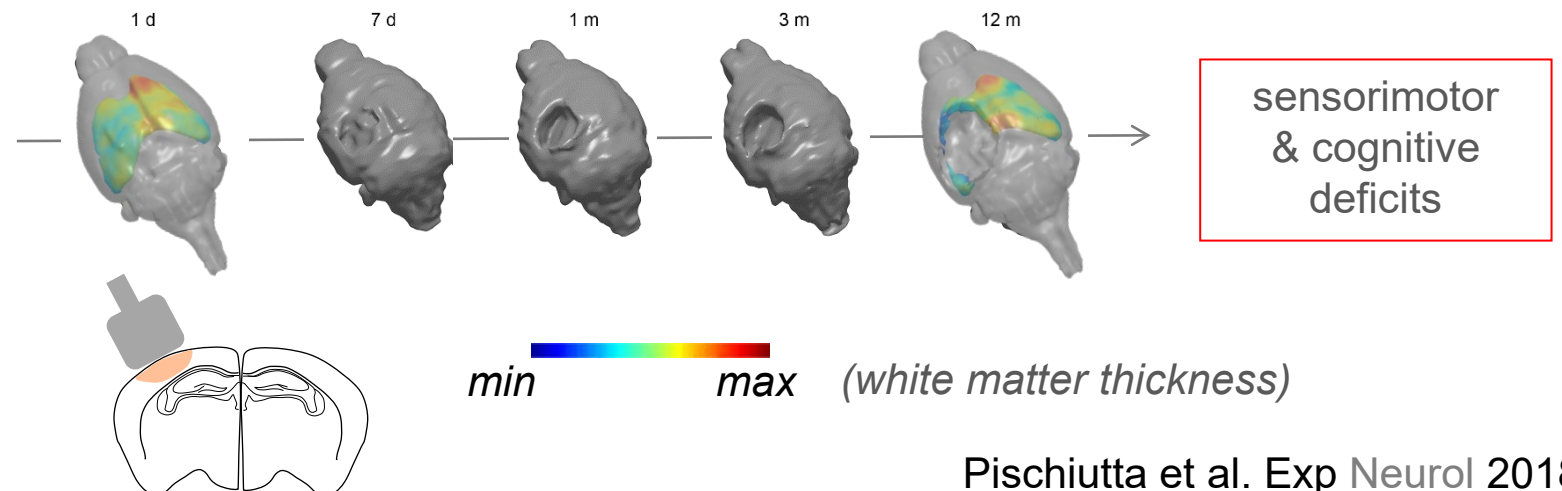
Clinical relevance of animal models: progressive white matter degeneration

Aim 5

Provide a platform
to translate
neuroimaging
between pre-
clinical models and
human disease



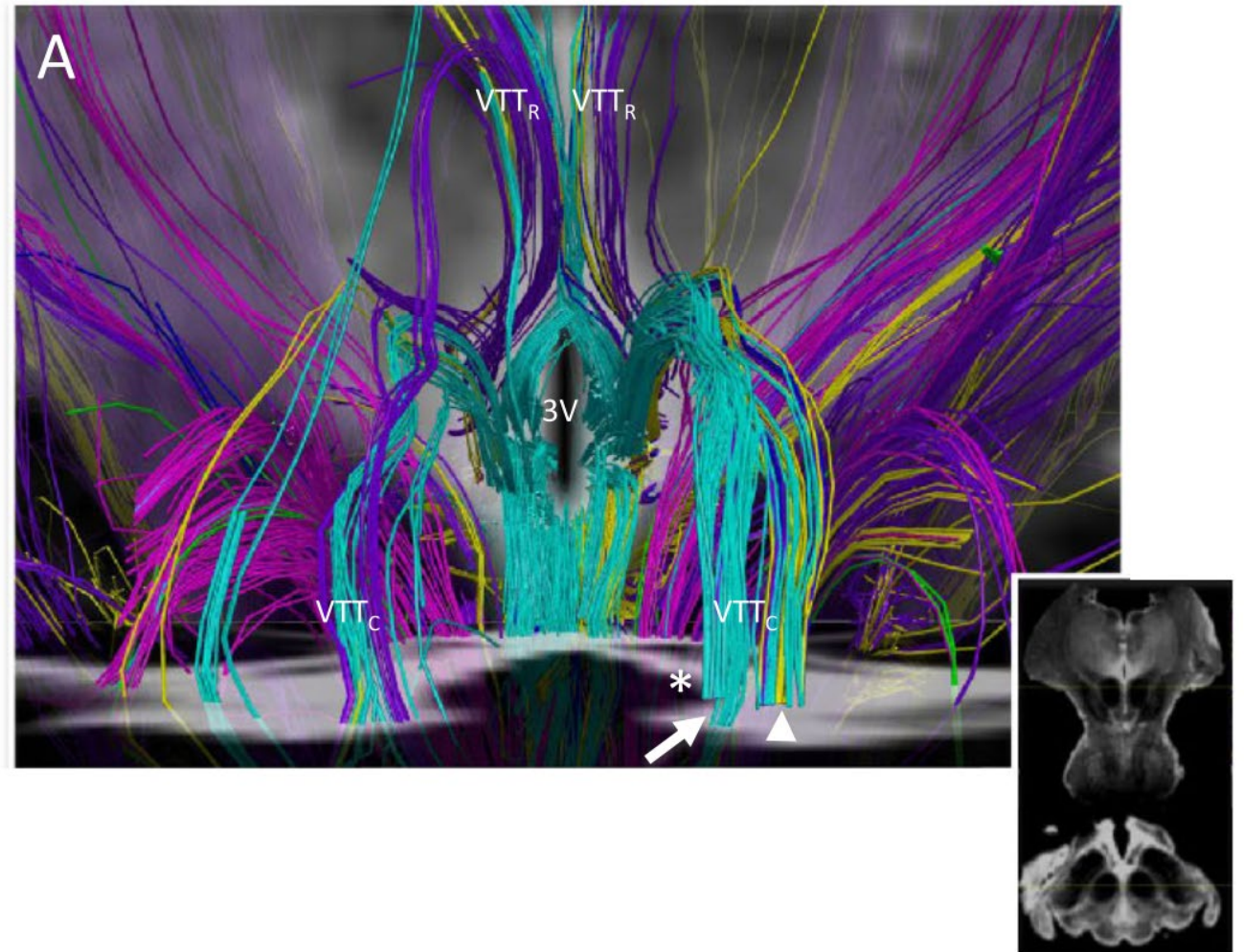
Newcombe et al., Neurorehab Neural Repair 2016



min max (white matter thickness)

Aim 6

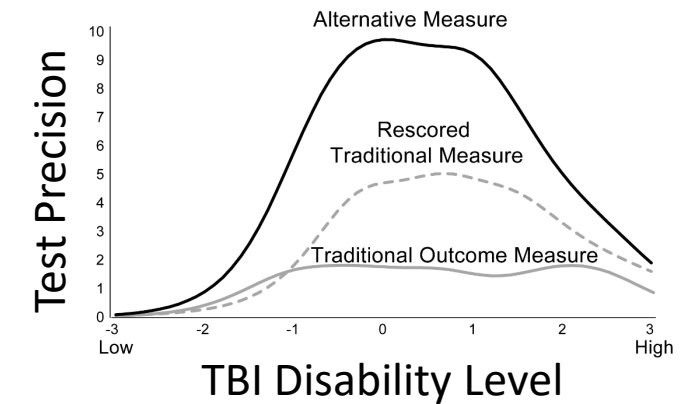
Seek correlations with
post-mortem imaging
to understand clinical
status and validate
findings in antemortem
imaging



Take home messages - Aims

1. Facilitate and support, with partners, access to integrated platforms where data can be used globally to inform TBI diagnosis and prognosis
2. To foster harmonization of combined and federated analysis methods across all neuroimaging studies in traumatic brain injury.
3. Foster international collaborations to develop innovative initiatives of neuroimaging research for traumatic brain injury
4. Create a rational framework for translational research between preclinical and human data; and ante-mortem and post-mortem human imaging
5. Facilitate a framework for precision medicine by integrating multimodality data across multiple disciplines

GOS	
1 = Dead	Unfavorable
2 = Vegetative state	
3 = Severe disability	
4 = Moderate disability	Favorable
5 = Good recovery	



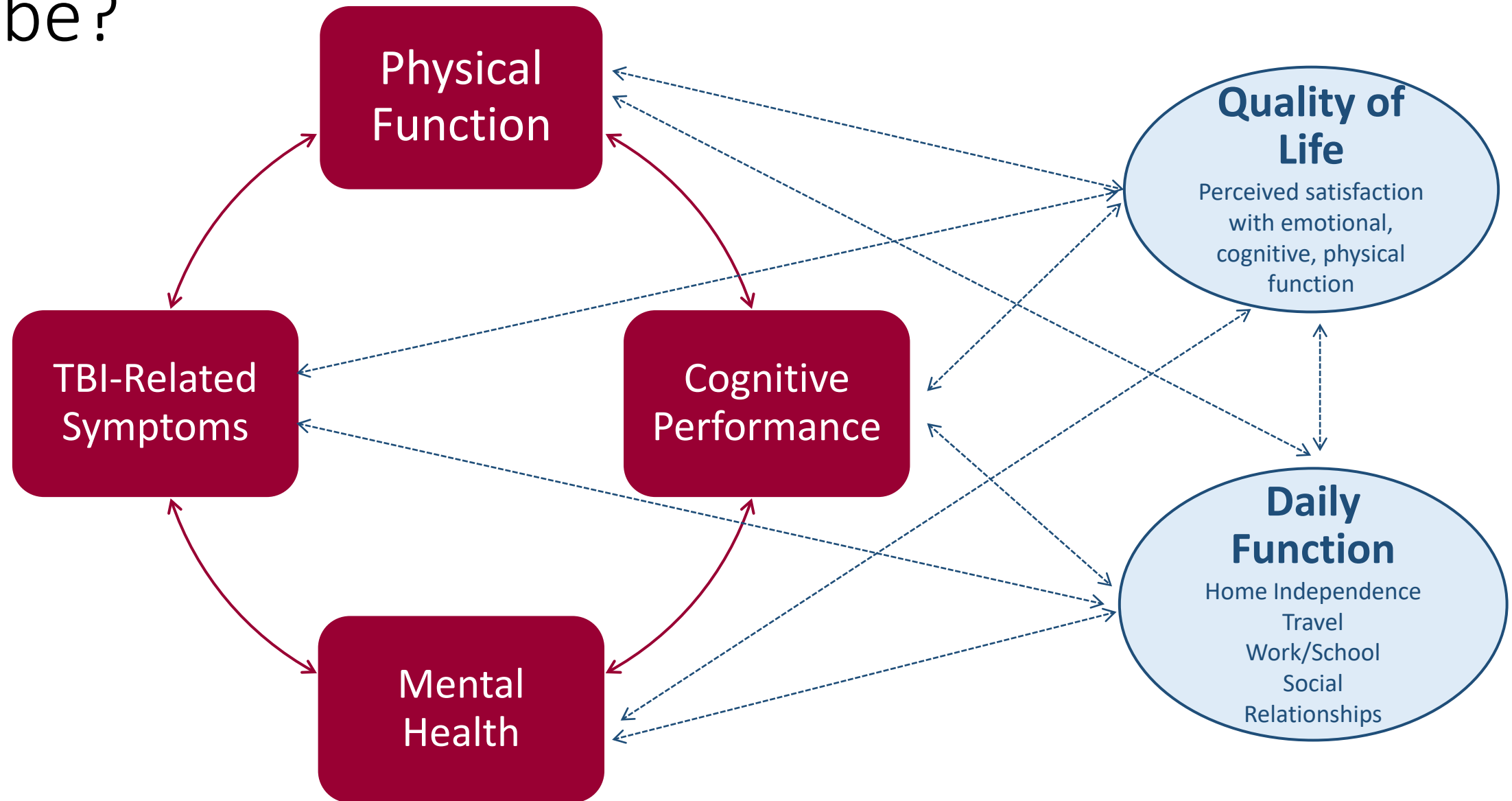
Measuring Clinical Outcomes of TBI: Let's Move the Needle



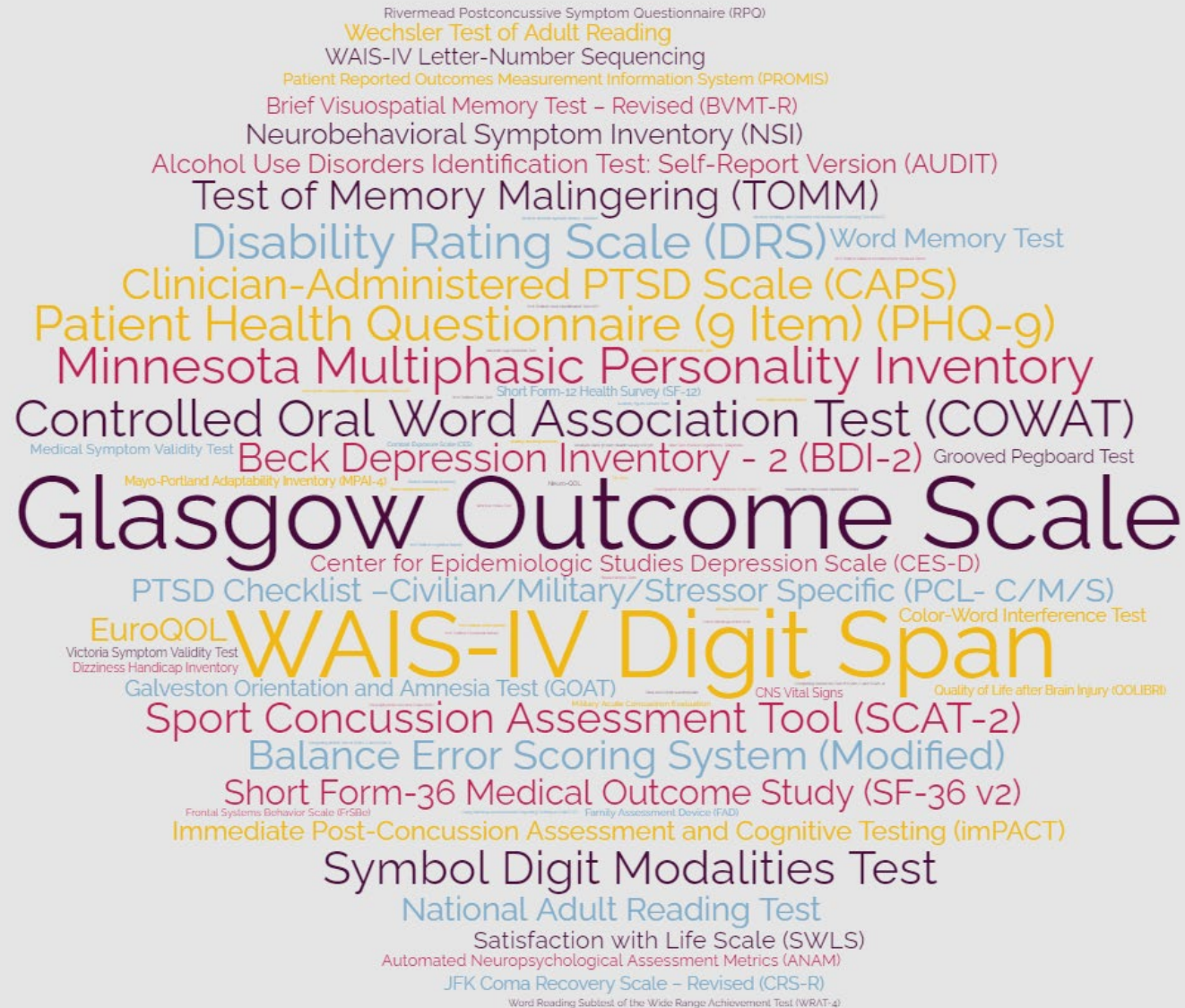
Lin Nelson, PhD, ABPP
Associate Professor
Clinical Neuropsychologist
Departments of Neurosurgery and Neurology



Assessing clinical outcomes of TBI: How hard could it be?



TBI CDE Outcomes by # Google Scholar Hits*



TBI Common Data Elements (CDE) (2010 v1, 2012 v2)

- **168 outcomes** stratified by Importance, TBI Subpopulation

Sport-Related Concussion (SRC) CDE (2018)

- **110 outcomes** stratified by Importance, Time since injury

Example – Adult, Acute/Hospitalized

- 1 Core measure – GOSE
- 6 Basic measures – BSI-18, RAVLT, WAIS-IV PSI, TMT, Cog-FIM, Motor-FIM
- 76 Supplemental

well over 13 hours of assessments to choose from

*Excludes 53 assessments that are only in the SRC CDE

Efficiency

Comprehensiveness

Specific endpoints

Broad/global outcomes

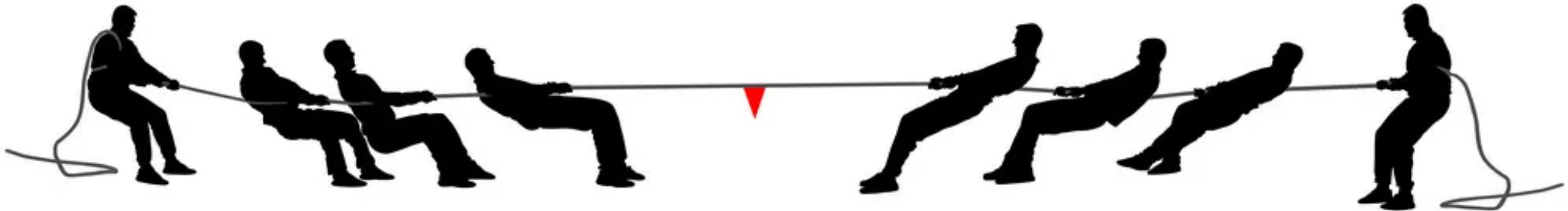
vs.

Tailor test battery to study

Use legacy battery to enable harmonization

History/convention

New (better?) instruments



Most popular doesn't mean best

GOS

1 = Dead

2 = Vegetative state

3 = Severe disability

4 = Moderate disability

5 = Good recovery

Unfavorable

Favorable

Clinical Neuro-Protection Trials in Severe Traumatic Brain Injury: Lessons from Previous Studies

JOURNAL OF NEUROTRAUMA
Volume 19, Number 5, 2002
© Mary Ann Liebert, Inc.

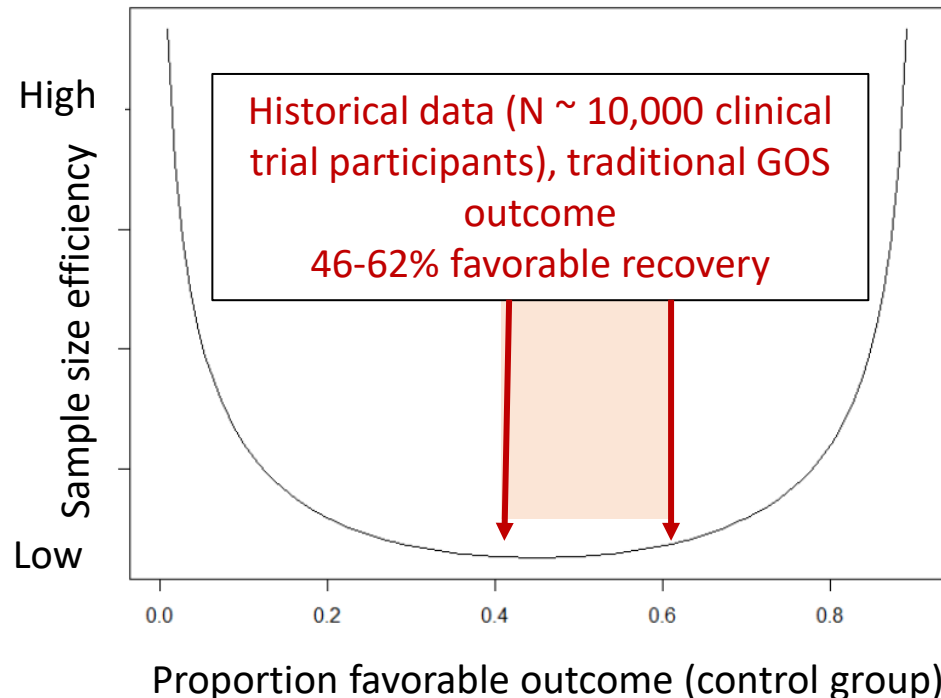
Clinical Trials in Head Injury

Clinical Trials in Traumatic Brain Injury

What Can We Learn from Previous Studies?

EGON M. R. DOPPENBERG,^a SUNG C. CHOI,^b
AND ROSS BULLOCK

GOS dichotomized in most trials at a level that minimizes sample size efficiency



IEL,^{2,†} and THE
ING[‡]; Beth Ans
lock,^{7,*} Sung C.
Dalton Dietrich

IMPACT Recommendations for Improving the Design and Analysis of Clinical Trials in Moderate to Severe Traumatic Brain Injury

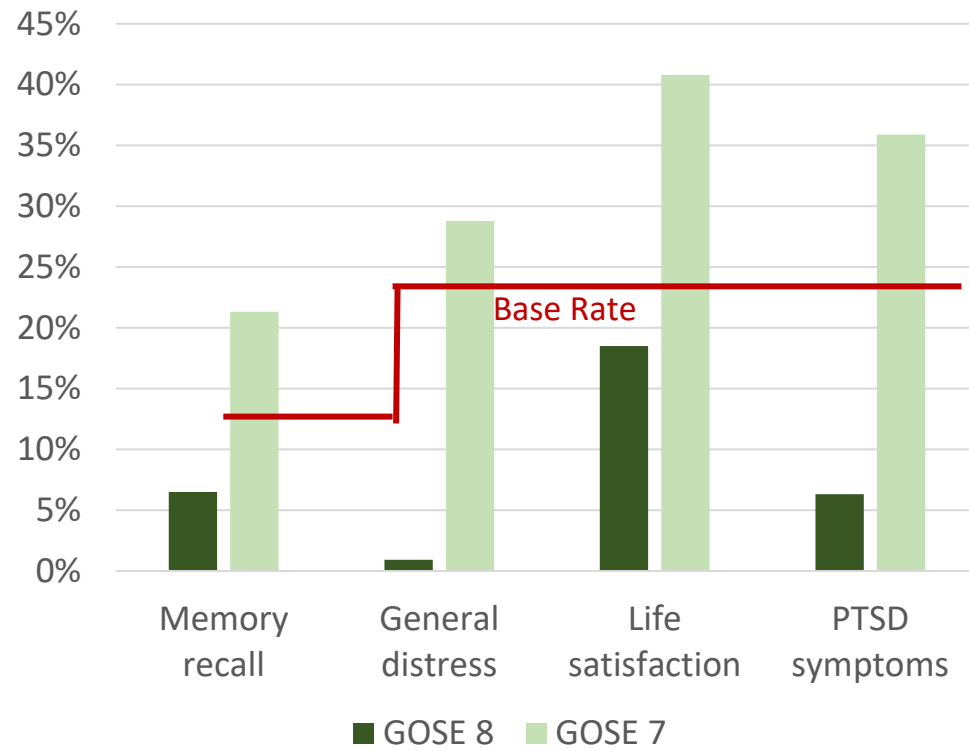
Andrew I. R. Maas,^{*} Ewout W. Steyerberg,[†] Anthony Marmarou,[§] Gillian S. McHugh,[¶]
Hester F. Lingsma,[†] Isabella Butcher,[¶] Juan Lu,[§] James Weir,[¶] Bob Roozenbeek,^{*,†} and
Gordon D. Murray[¶]

Early Issues With The GOS

- Unstandardized
- Limitations in reliability, precision
- Usage as a clinical trial endpoints (e.g., dichotomizing) further reduced its precision and efficiency

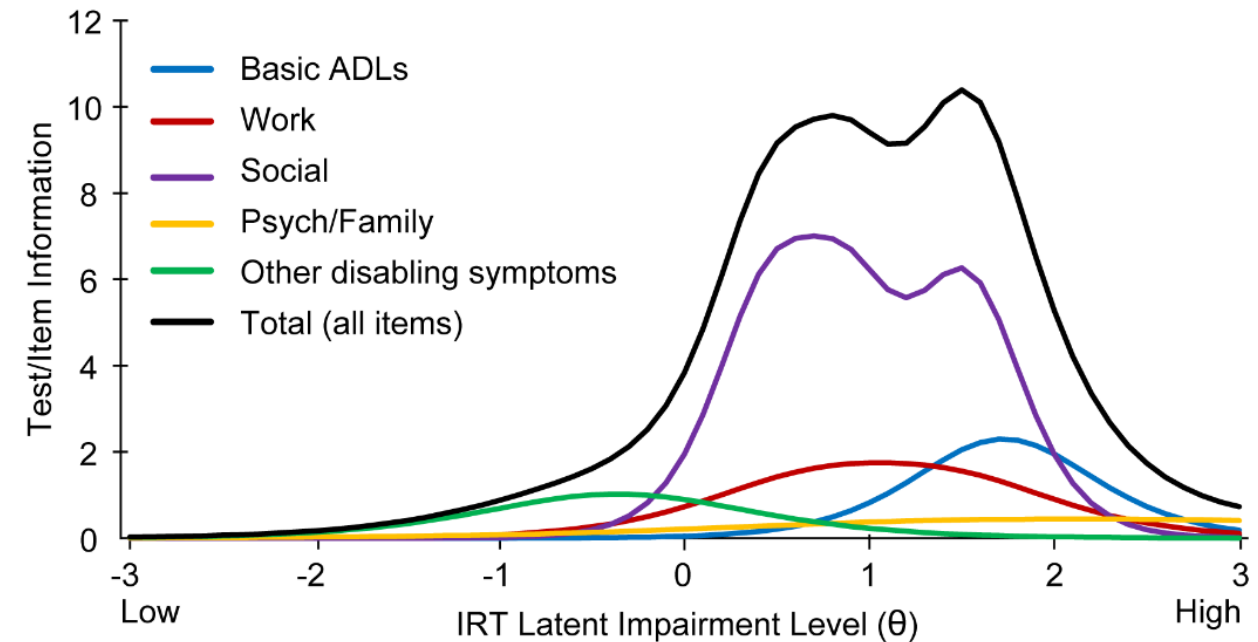
A recent history of advances in methods for assessing TBI-related disability

Common Practice to Combine GOSE 7 and 8 Conflates Important Individual Differences



Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, & the TRACK-TBI Investigators (2017; *J Neurotrauma*, 34)

GOSE Mainly Assesses Moderate-Severe Disability; Interview Questions Have Variable Relevance

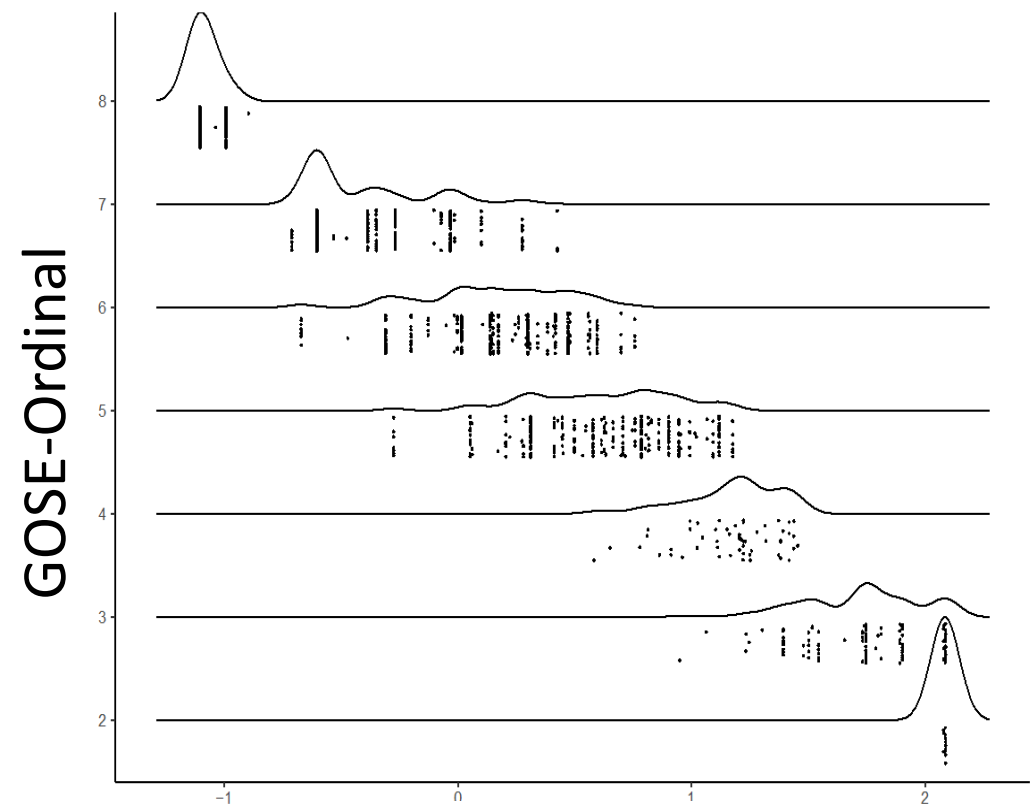


Ranson, Magnus, Temkin, Dikmen, Giacino, Okonkwo, Valadka, Manley, Nelson, & the TRACK-TBI Investigators (2019 *J Neurotrauma*, 36)

A recent history of advances in methods for assessing TBI-related disability

Rescoring the GOSE using item response theory (IRT) expands the score range, improving precision

Scatterplot of Traditional GOSE (1-8) Scores and Novel GOSE-IRT Scores



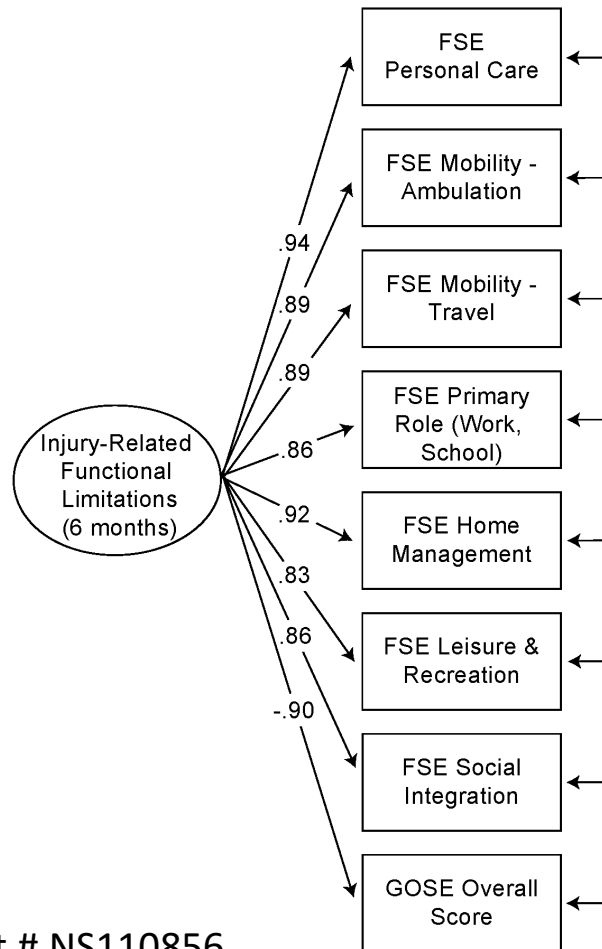
GOSE-IRT Strengthens Correlations with Criterion Measures

Pearson correlations between GOSE-IRT and criterion measures, stratified by ordinal GOSE score

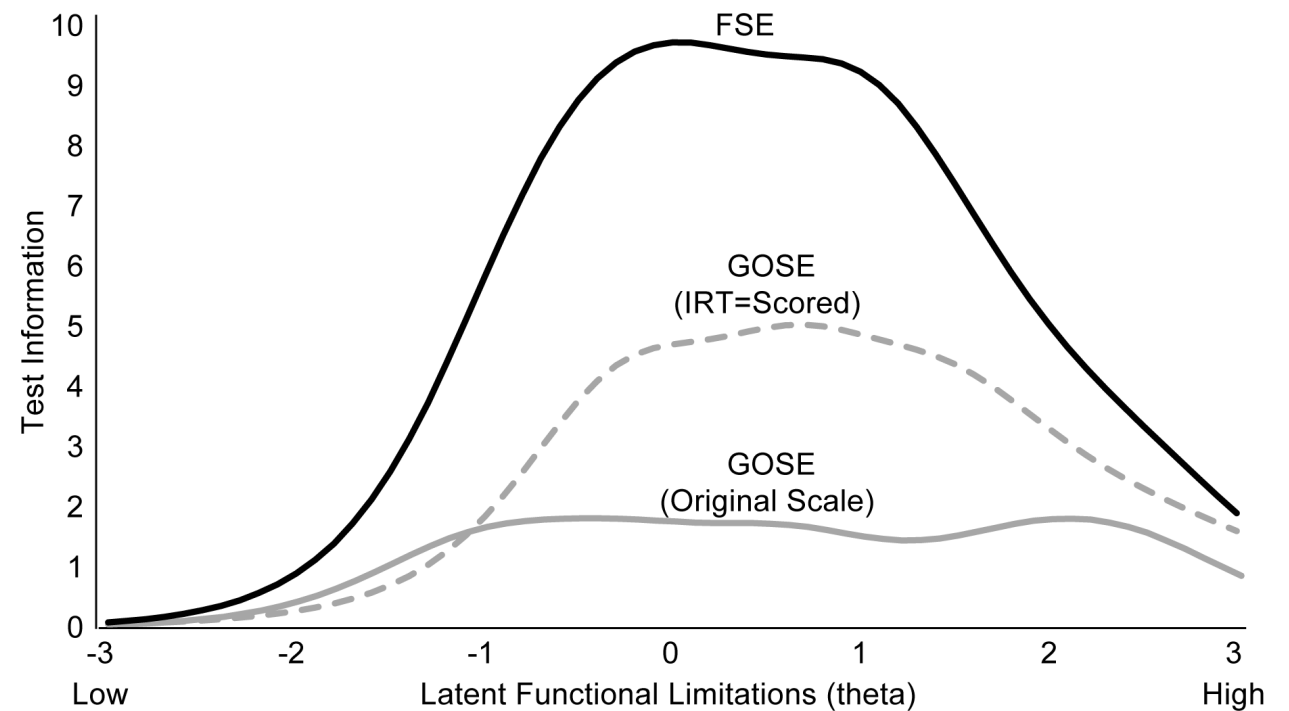
Ordinal GOSE Score Group	RPQ	BSI-18 GSI	QOLIBRI-OS
3	.47*	.57*	-.72***
4	.53**	.56***	-.50**
5	.38***	.33***	-.46***
6	.36***	.34***	-.34***
7	.16**	.23***	-.25***
8	.10	.00	-.08
Combined	.63***	.51***	-.61***

A recent history of advances in methods for assessing TBI-related disability

**Functional Status Examination (FSE) and GOSE
Measure the Same Thing**

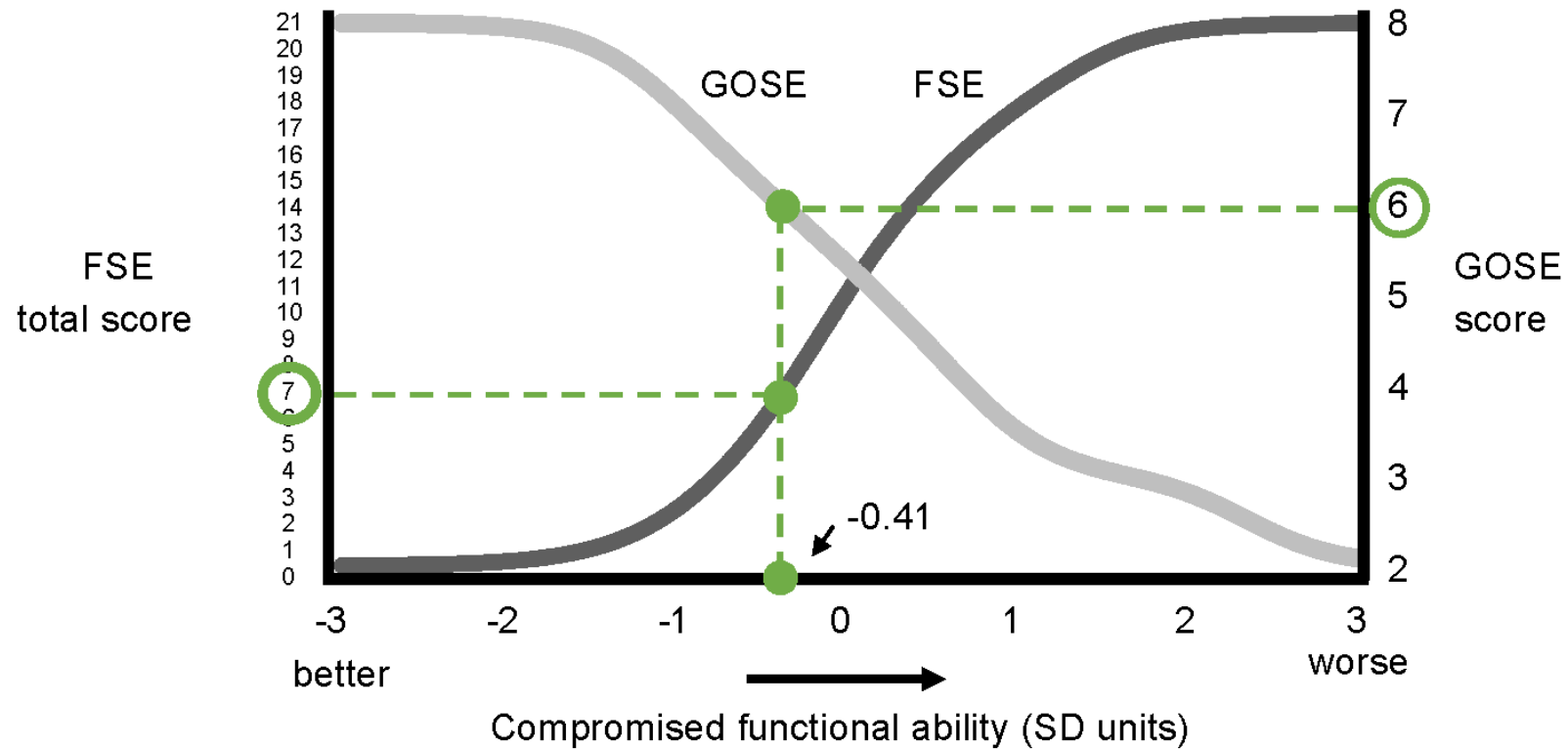


FSE is More Precise than the GOSE



A recent history of advances in methods for assessing TBI-related disability

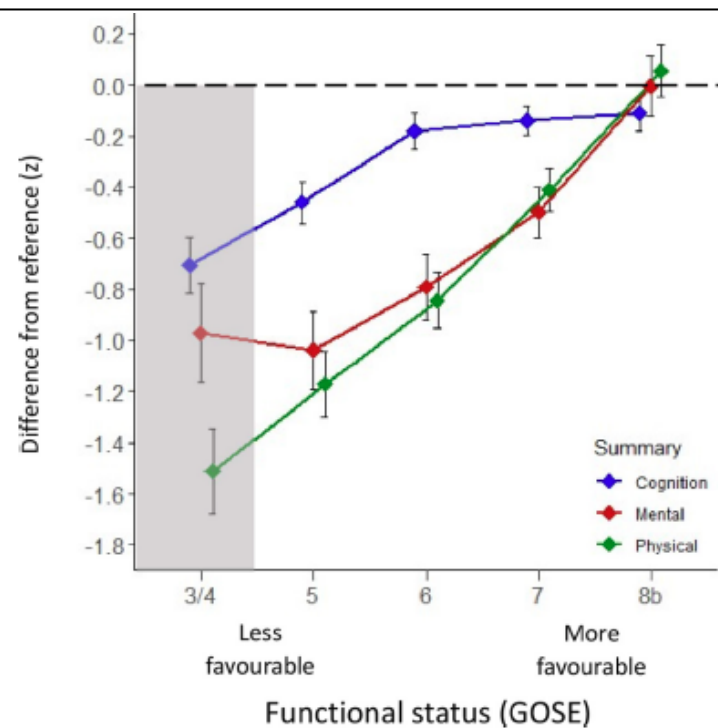
Using IRT to Link Alternative Measures



A Manual for the Glasgow Outcome Scale-Extended Interview



Lindsay Wilson,¹ Kim Boase,² Lindsay D. Nelson,³ Nancy R. Temkin,² Joseph T. Giacino,⁴
 Amy J. Markowitz,⁵ Andrew Maas,⁶ David K. Menon,⁷ Graham Teasdale,⁸ and Geoffrey T. Manley⁵



Original research

Understanding the relationship between cognitive performance and function in daily life after traumatic brain injury

Lindsay Wilson ,¹ Lindsay Horton,¹ Kevin Kunzmann,² Barbara J Sahakian,³
 Virginia FJ Newcombe ,⁴ Emmanuel A Stamatakis,⁴ Nicole von Steinbuechel,⁵
 Katrin Cunitz,⁵ Amra Covic,⁵ Andrew Maas,⁶ Dominique Van Praag,⁷ David Menon,⁴
 The CENTER-TBI participants and investigators



InTBIR
International Initiative for
Traumatic Brain Injury Research

Outcomes Working Group

Goals

- Serve as a resource for stakeholders
- Collaboratively design and conduct high-quality studies

Potential topics

- Develop multidimensional models of clinical outcome
- Validate assessments across languages, TBI subpopulations, assessment circumstances, etc.
- Link scores from competing instruments
- Develop practical tools and best practice guidelines
- Increase accessibility of outcomes for diverse participants
- Develop, norm, and validate new outcomes

Join us @ info@intbir.org

Reach out to me: linelson@mcw.edu

Share your feedback @

Outcomes Needs Assessment



<https://tinyurl.com/InTBIROutcomes>

LINKAGE WITH PRE- CLINICAL RESEARCH

Cheryl Wellington, Elisa
Zanier, Doug Smith
July 16, 2022

Fundamental and Translational Working Group

The newly established InTBIR Fundamental and Translational Working Group recognizes the importance of cellular and animal model systems to undertake studies difficult or impossible to conduct solely through clinical research.

The ability to reliably generate cells or brain tissues injured under controlled experimental conditions allows mechanisms and potential therapeutic targets to be identified.

This Working Group aims to strengthen connections among clinical, fundamental and translational scientists to improve the relevance of model systems and increase our understanding of TBI pathophysiology.

Objective 1: Targeted Modeling

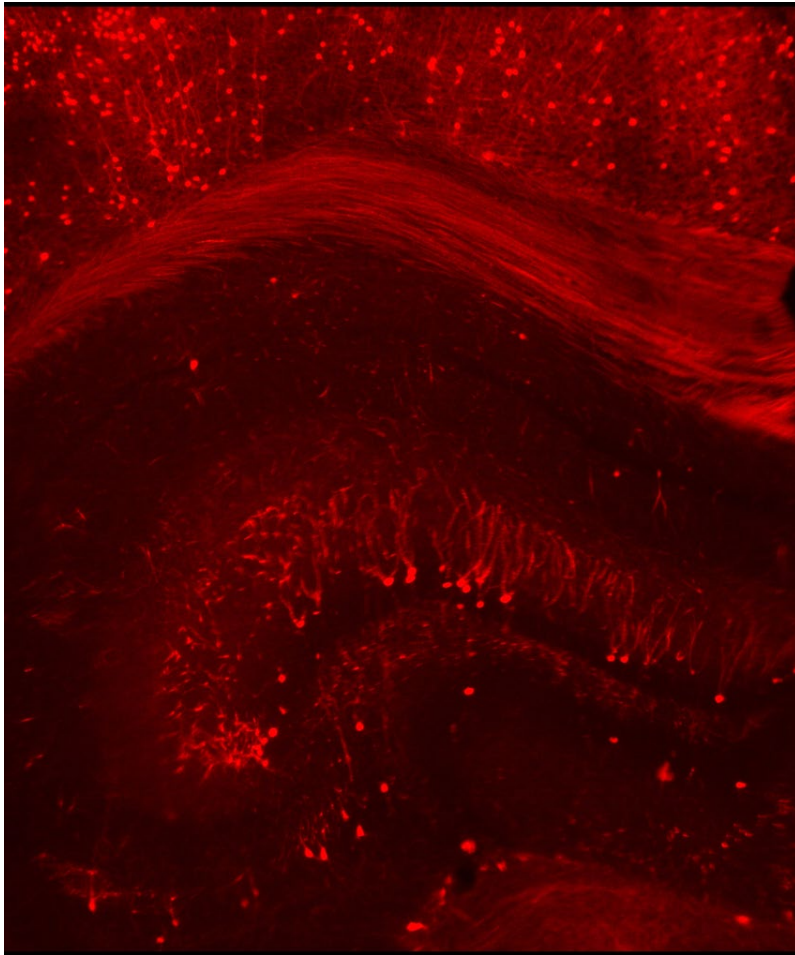
Move away from uninformative arbitrary “mild, moderate, severe” descriptors in animal models and emphasize characterizing specific pathologies such as vascular, axonal, inflammation.

Encourage research that uses more than one model that targets specific pathologies

Therapeutic trials should target specific pathologies with a priori consideration of target engagement and efficacy measures

Leverage new technologies to overcome limitations in traditional neuropathological analyses, i.e. whole brain analyses

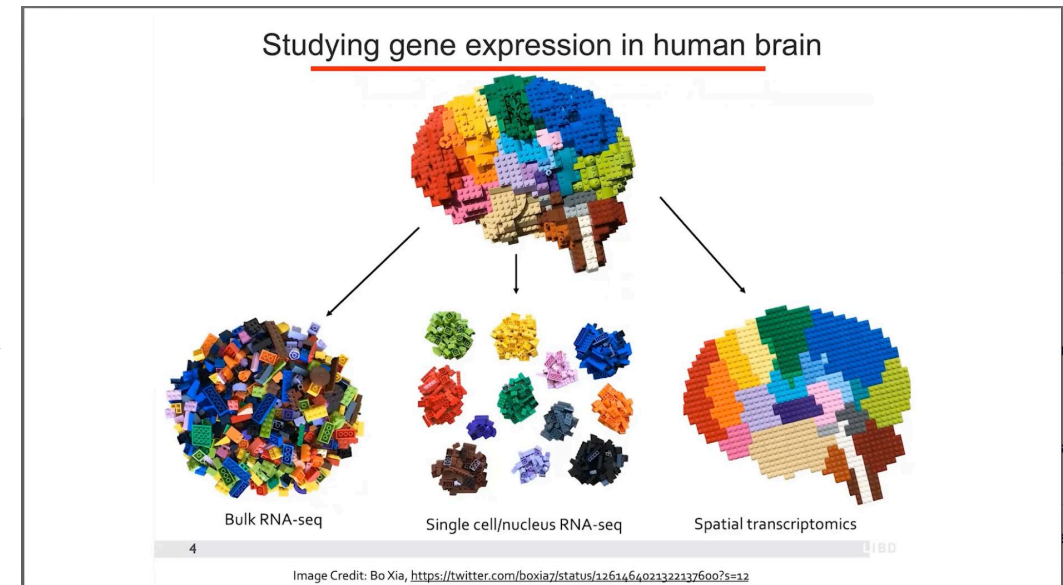
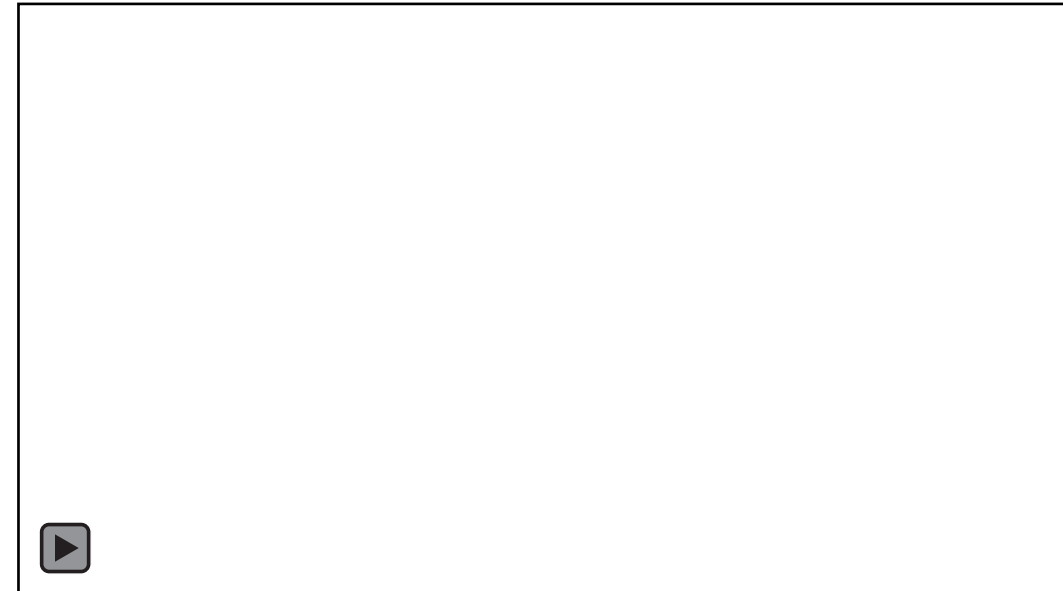
Whole brain 3D mapping of experimental TBI pathologies



Neuronal activity maps
using c-fos TRAP mice

+
●
Vascular
pathology maps
using fluorescent
markers

Spatial
transcriptomic
maps using 10X
Visium



+

•

○

Objective 2: Biomarkers

Emphasize imaging, fluid, and
molecular biomarkers with
translational relevance

Translational Fluid Biomarkers

Quanterix NfL assay works well in mice
We developed a GFAP assay for mice
on the MesoScale Discovery platform
These (and other) biomarkers may be
potential calibrators across models

Button et al. *Alzheimer's Research & Therapy* (2021) 13:58
<https://doi.org/10.1186/s13195-021-00793-9>

Alzheimer's
Research & Therapy

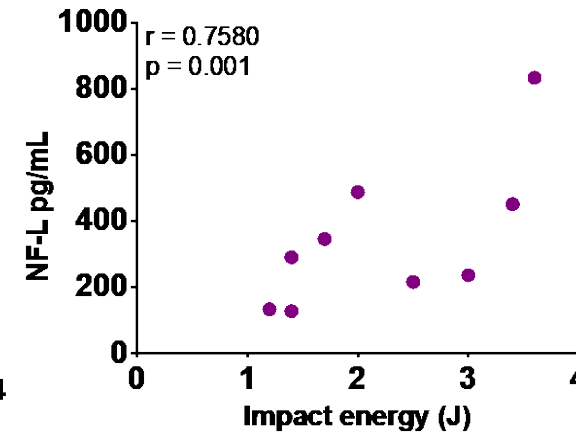
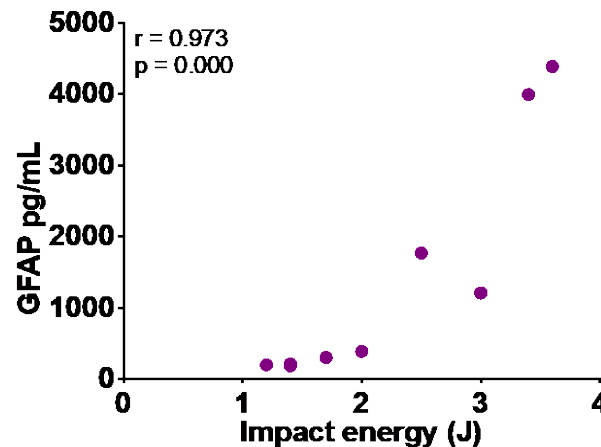
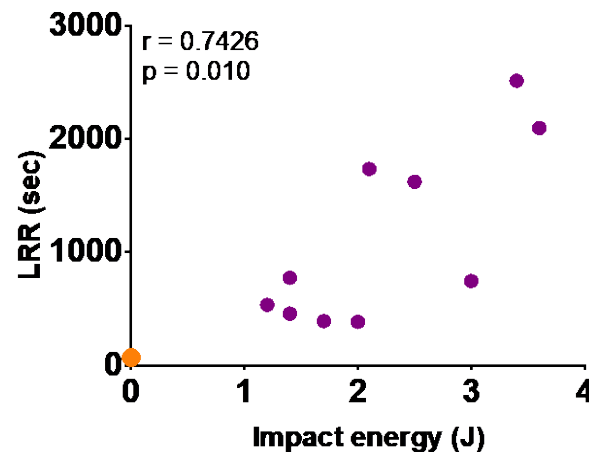
RESEARCH

Open Access



Development of a novel, sensitive
translational immunoassay to detect
plasma glial fibrillary acidic protein (GFAP)
after murine traumatic brain injury

Emily B. Button^{1,2}, Wai Hang Cheng^{1,2}, Carlos Barron^{1,2}, Honor Cheung^{1,2}, Asma Bashir^{1,2}, Jennifer Cooper^{1,2},
Jasmine Gill^{1,2}, Sophie Stukas^{1,2}, David C. Baron^{1,2}, Jerome Robert^{1,2}, Elyn M. Rowe^{1,2}, Peter A. Cripton^{3,4} and
Cheryl L. Wellington^{1,2,3,4*}



Setting priorities

This working group encourages bidirectional interactions and corroboration across clinical and basic studies, to agree upon research priorities for which animal models are an ethically appropriate and feasible choice

This working group aims to build a platform / network to facilitate improved rigor in the design of preclinical intervention trials

We welcome discussion on these efforts within InTBIR 2.0

Species Differences

Do we understand enough about anatomical, physiological and molecular differences between humans and mice, rats, pigs?

Encourage research that builds a database of molecular similarities for targets of specific pathologies, i.e. inflammatory pathways

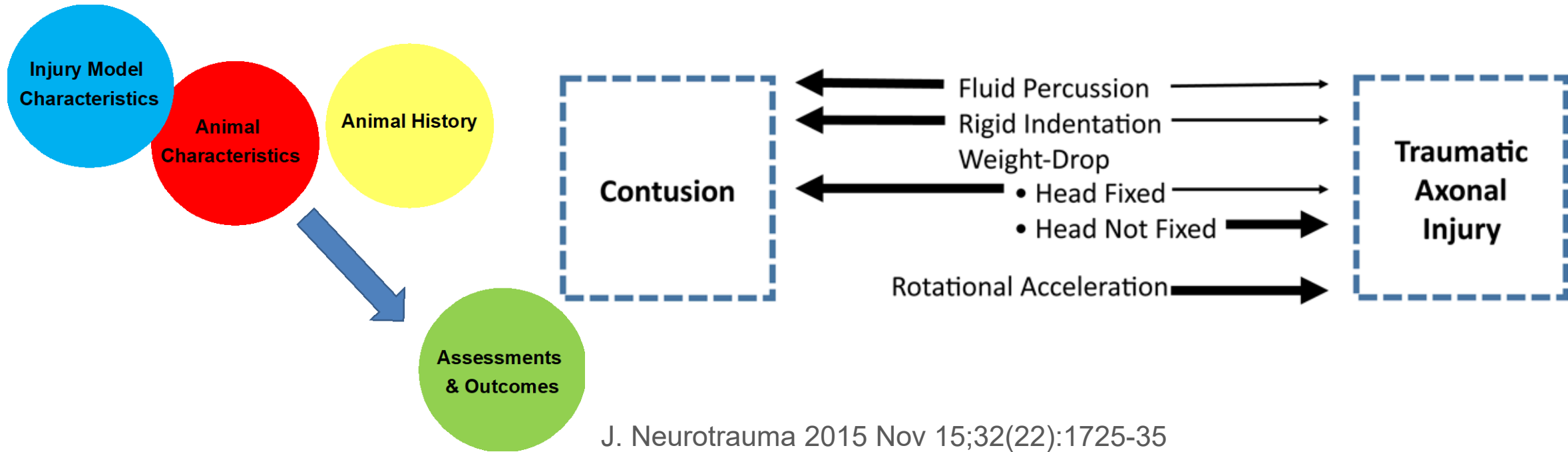
We welcome discussion on how to better calibrate across models

Study Design

It will be important to keep nomenclature accurate, i.e. use of “tauopathy” or “chronic traumatic encephalopathy”

Common data elements (CDEs) can be useful, but are challenging to mandate

Pre-clinical CDE domains



Pre-Clinical Traumatic Brain Injury Common Data Elements:
Toward a Common Language Across Laboratories

Douglas H. Smith, Ramona R. Hicks, Victoria E/ Johnson, Debra Bergstrom, Diana M. Cummings
Linda J. Noble, David Hovda, Michael Whalen, Stephen T. Ahlers, Michelle LaPlaca, Frank C. Tortella
Ann-Christine Duhaime and C. Edward Dixon

Recommendation 1

Similar to work in the Alzheimer Disease and Related Dementia space, encourage mechanisms of support to calibrate outcome measures to match underlying pathophysiology.

Early priorities will be:

- Identify what calibrators to use
- Identify support to establish an experimental biobank/repository and reporting via open science pathways

Recommendation 2

Identify methods to incentivise interactions for both clinicians/trialists and experimentalists.

Encourage literature reviews that cover human and animal model results. Encourage collaborative clinical-experimental responses to new RFAs.

CONNECT-TBI and other networks (Canadian Traumatic Brain Injury Research Consortium, Canadian Concussion Network, NFL Scientific Advisory Board, European Neurotrauma Organization) may be helpful in building translational awareness.



Linkage with post-mortem studies

Willie Stewart, NHS GGC/ University of Glasgow
Doug Smith, University of Pennsylvania

July 2022



CONNECT-TBI

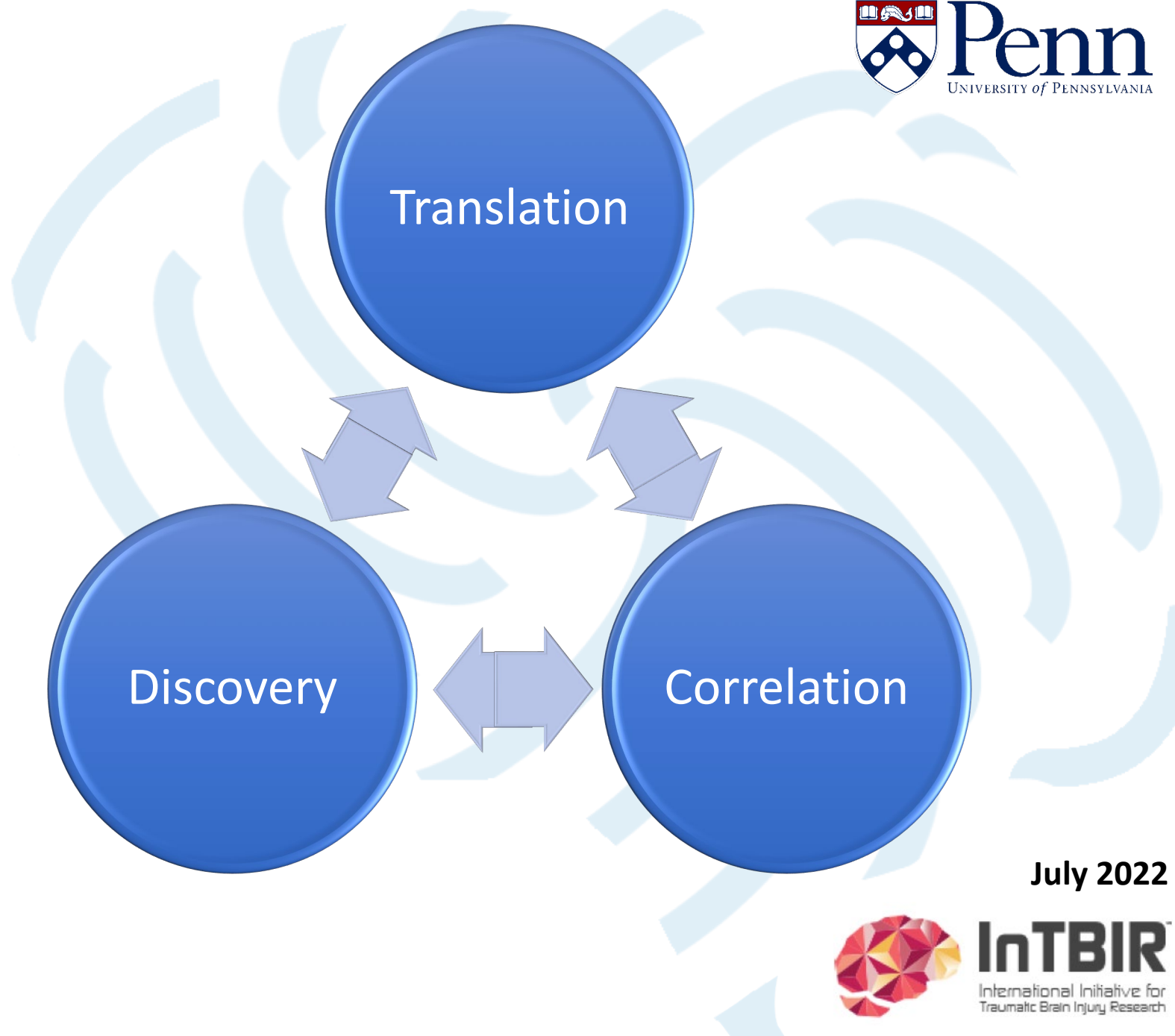
THE COLLABORATIVE NEUROPATHOLOGY NETWORK
CHARACTERIZING OUTCOMES OF TBI



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Linkage with post-mortem studies



July 2022



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THE COLLABORATIVE NEUROPATHOLOGY NETWORK
CHARACTERIZING OUTCOMES OF TBI

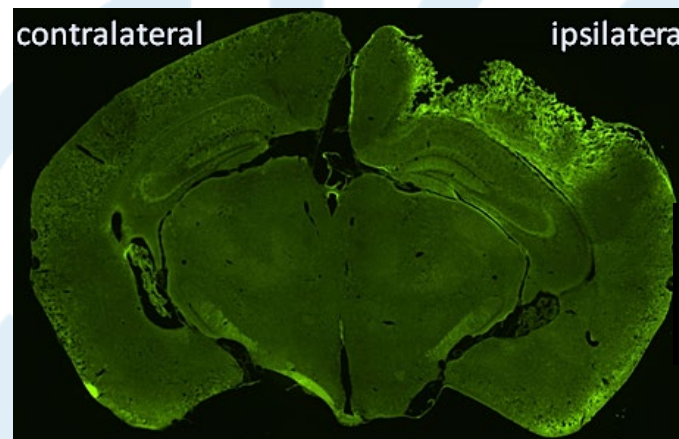
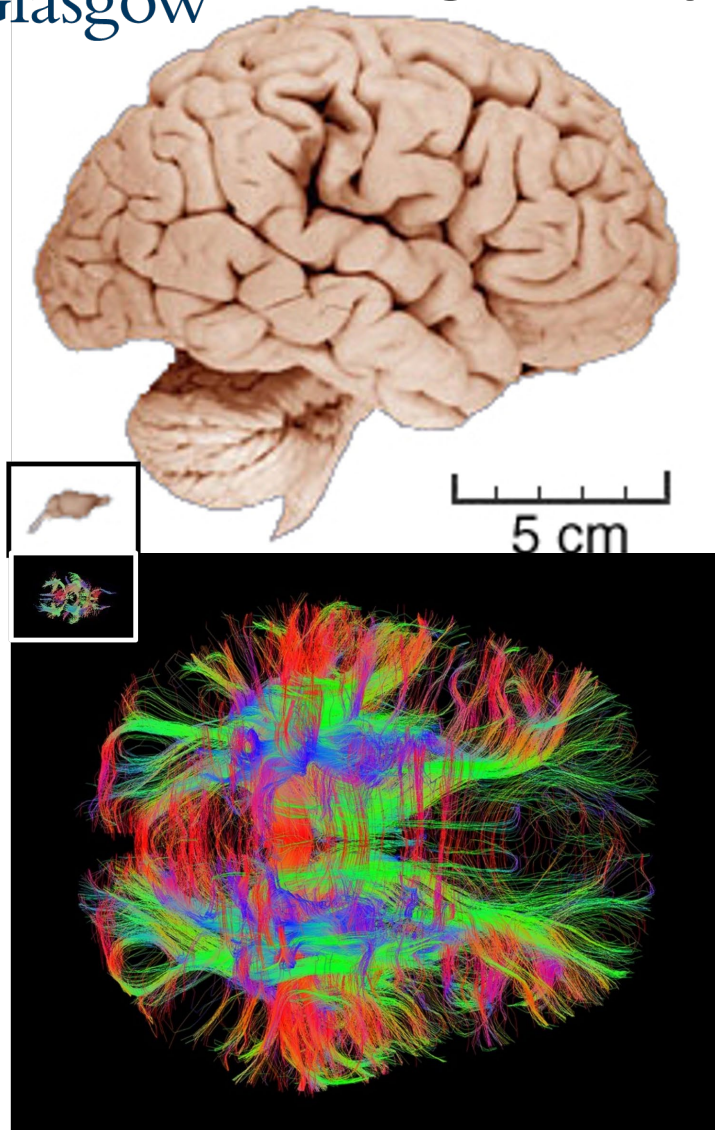


InTBIR

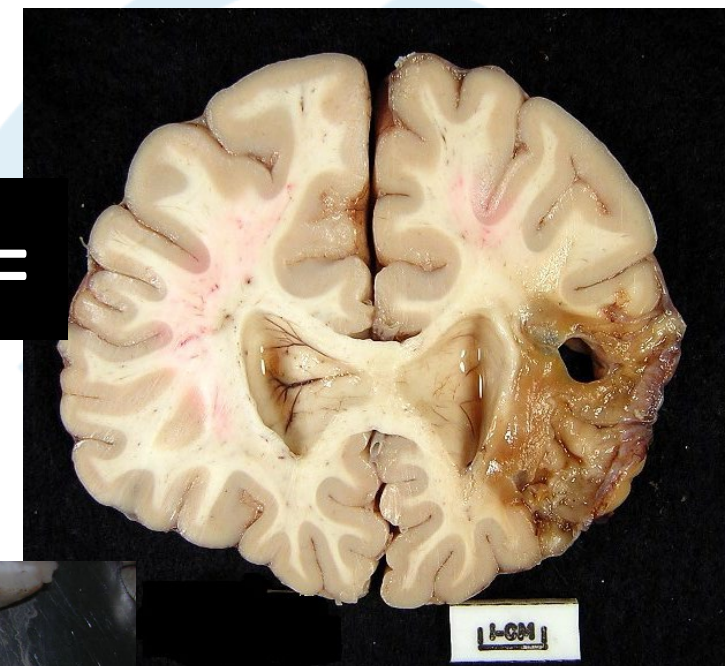
International Initiative for
Traumatic Brain Injury Research



Linkage with post-mortem studies: **translation**



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July 2022



CONNECT-TBI

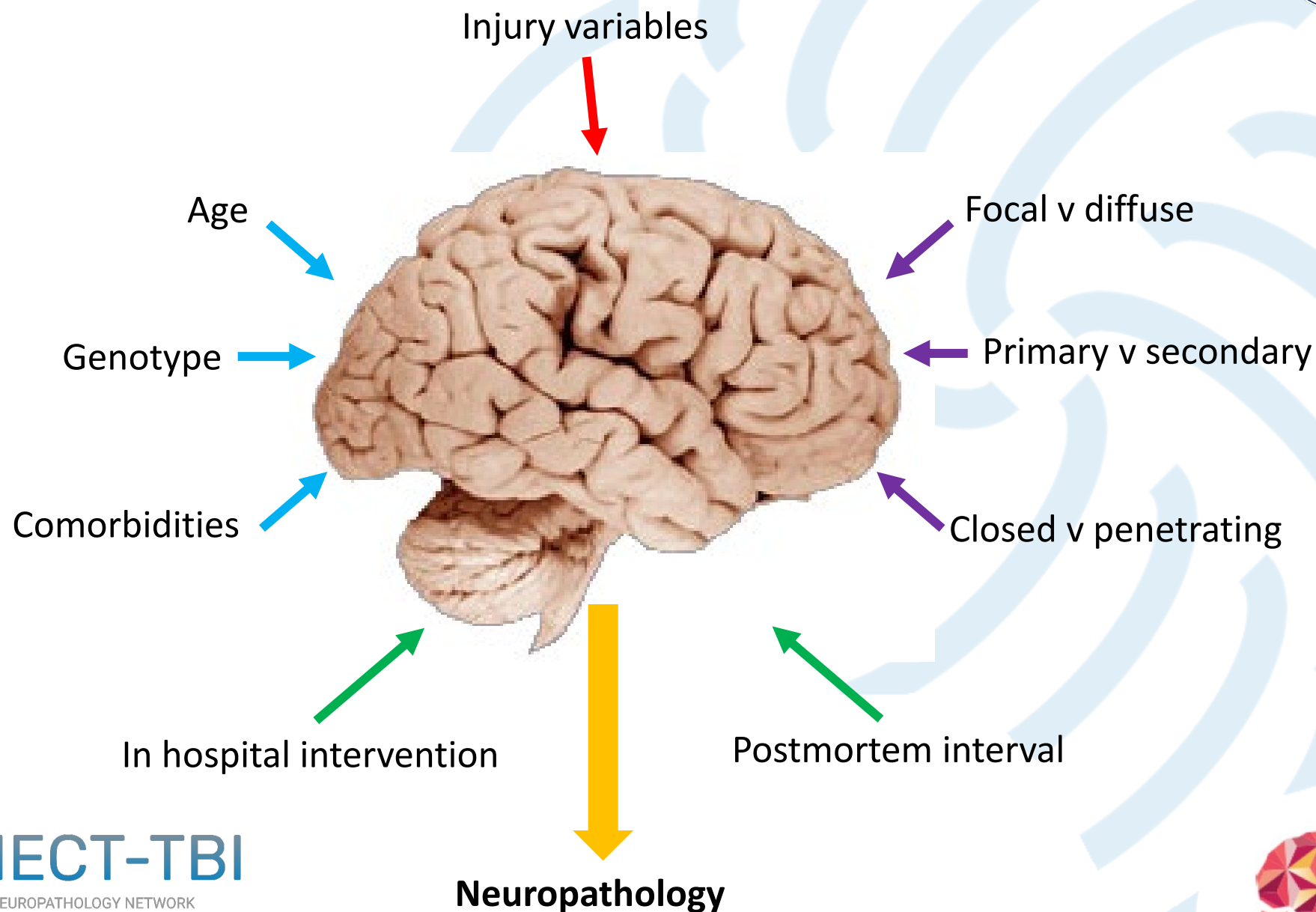
THE COLLABORATIVE NEUROPATHOLOGY NETWORK
CHARACTERIZING OUTCOMES OF TBI



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Linkage with post-mortem studies: **translation**



July 2022

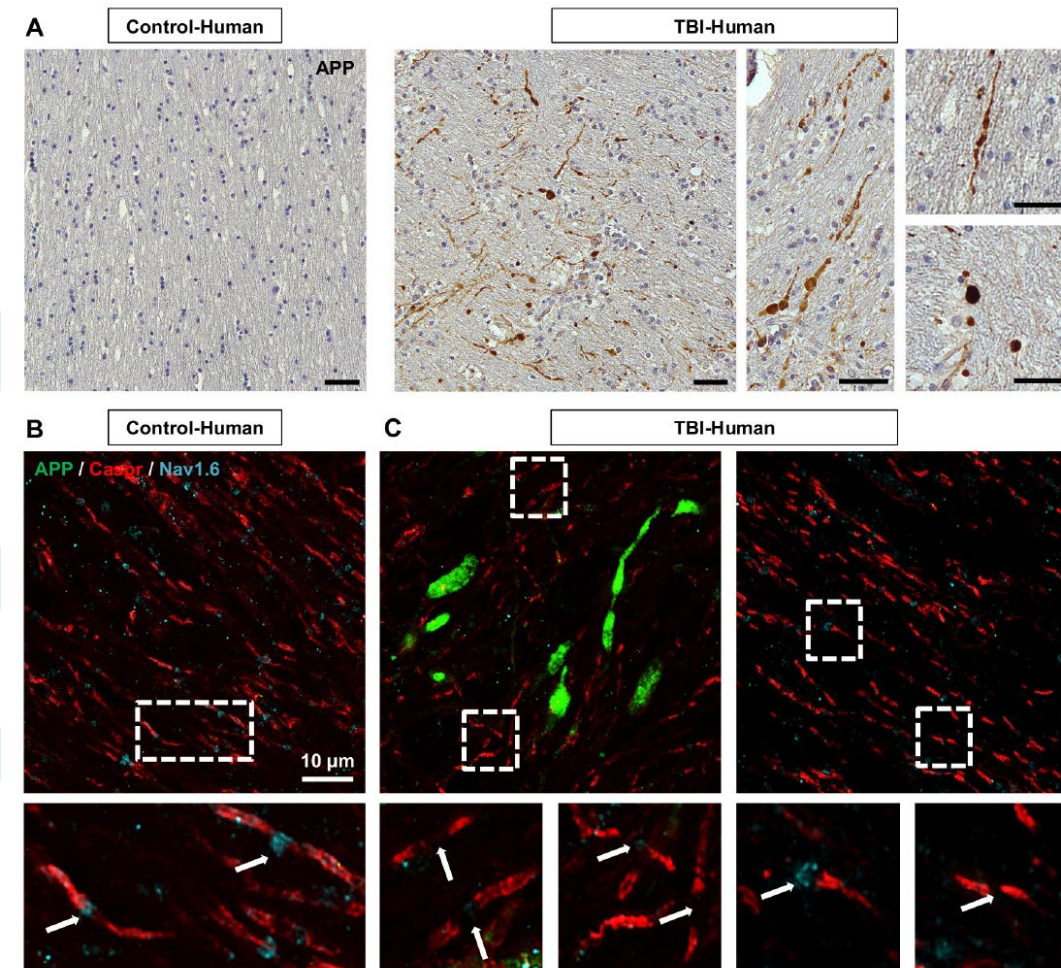
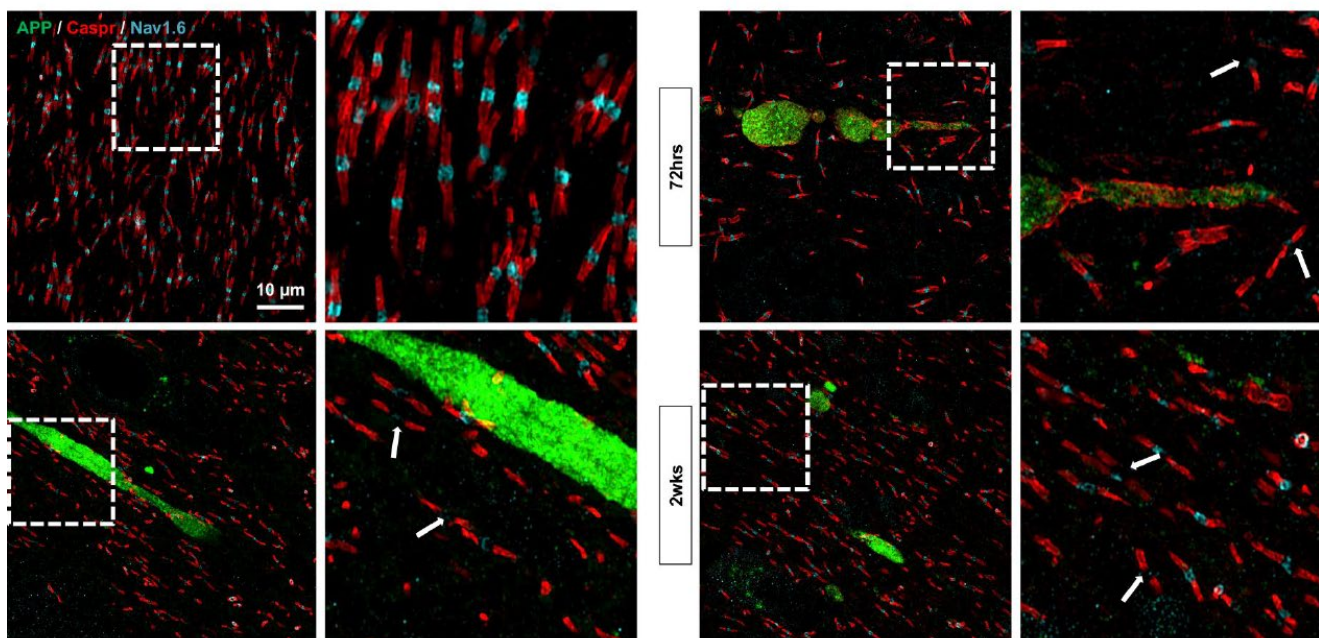


Linkage with post-mortem studies: **translation**



Concussion leads to widespread axonal sodium channel loss and disruption of the node
of Ranvier

Authors: Hailong Song¹, Przemyslaw P. McEwan¹, Kamar Ameen-Ali², Alexandra Tomasevich¹,
Claire Kennedy-Dietrich², Alexander Palma¹, Edgardo J. Arroyo¹, Jean-Pierre Dolle¹, Victoria E.
Johnson¹, William Stewart^{2,3}, Douglas H. Smith^{1,*}.



July 2022



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CHARACTERIZING OUTCOMES OF TBI



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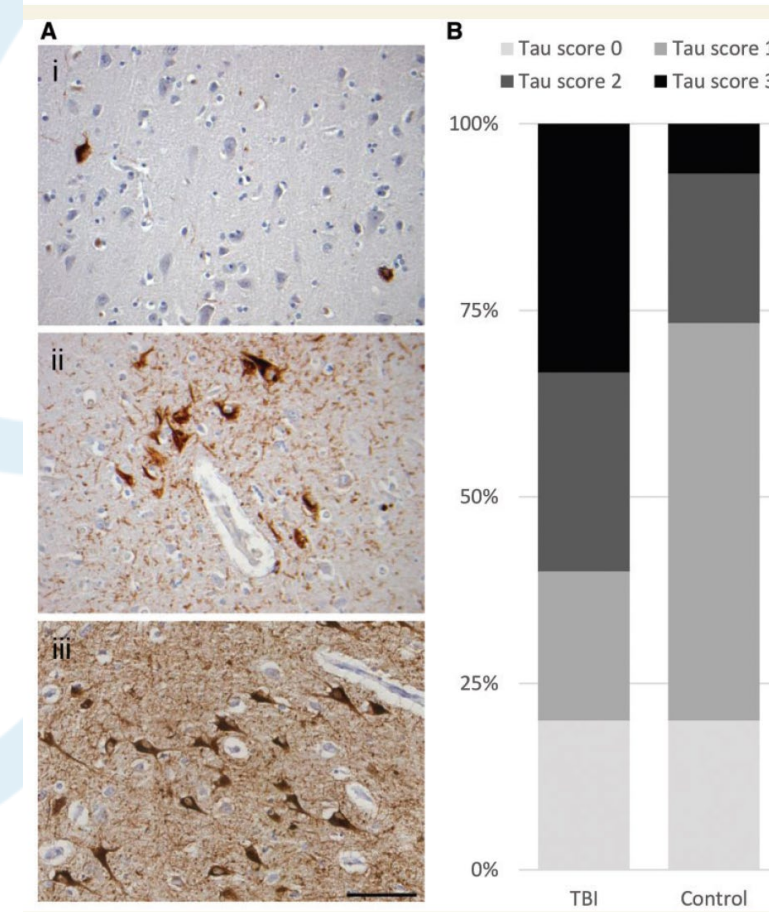
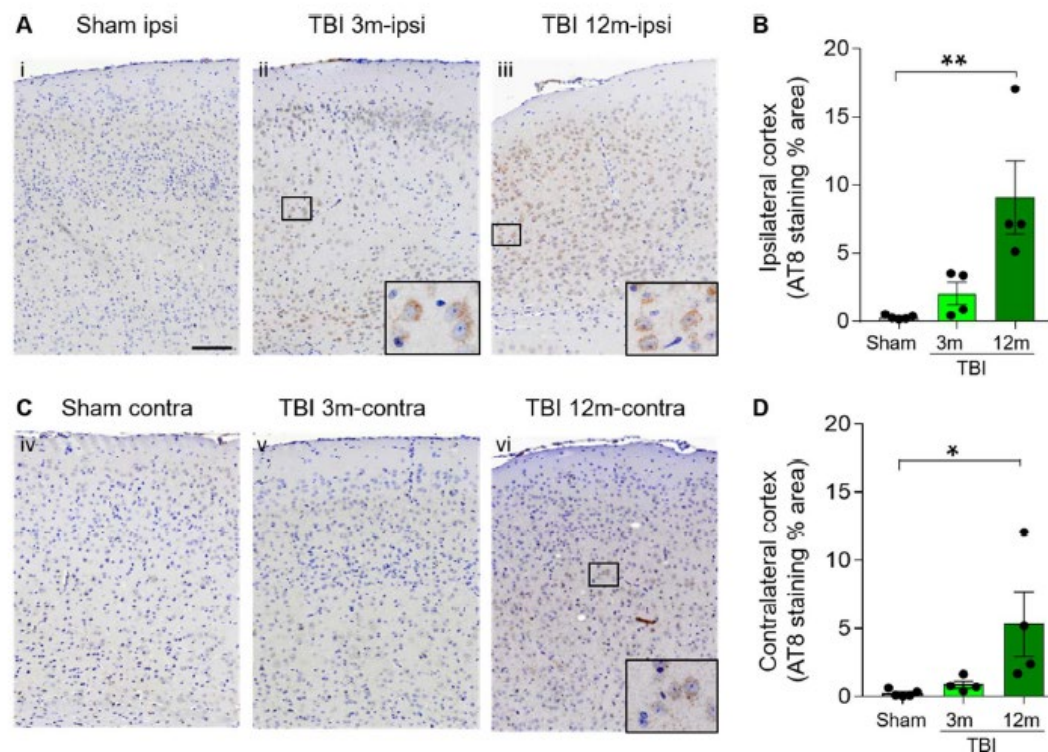


Linkage with post-mortem studies: translation



Induction of a transmissible tau pathology by traumatic brain injury

Elisa R. Zanier,¹ Ilaria Bertani,¹ Eliana Sammali,^{1,2} Francesca Pischiutta,¹ Maria Antonietta Chiaravalloti,¹ Gloria Vegliante,¹ Antonio Masone,¹ Alessandro Corbelli,³ Douglas H. Smith,⁴ David K. Menon,⁵ Nino Stocchetti,^{6,7} Fabio Fiordaliso,³ Maria-Grazia De Simoni,¹ William Stewart^{8,9} and Roberto Chiesa¹



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University
of Glasgow



Penn
UNIVERSITY of PENNSYLVANIA

Linkage with post-mortem studies: **discovery**

Multifactorial Inflammation and white matter degeneration Acute persist for years after single traumatic brain injury

Kun

David Victoria E. Johnson,¹ Janice
Douglas H. Smith¹

RESEARCH

Open Access



Tau G. M. Teasdale

Detection of astrocytic tau pathology
facilitates recognition of chronic traumatic
encephalopathy neuropathologic change

C. Smith¹ Department of
Glasgow, ²Public
Medical School
David S. Prineas^{8,9,10,11,12}, Douglas H. Smith¹⁷, Douglas J. Wiebe², William Stewart^{1,18} and CONNECT-TBI

The neuropathology of
brain injury

Colin Smith^{1,2}, Stephen M Gentleman¹,
Griffin⁴, David I Graham², and James A

J. HUME A.
T.A. GENNA.
*Department of
University of Glas
Neurosurgery, Unive

Disruption Is an Early Event That May Persist
After Traumatic Brain Injury in Humans

Victoria E. Johnson, MBChB, PhD, Adam M.H. Young, MBChB,
Douglas H. Smith, MD, and William Stewart, MBChB, PhD, FRCPATH

ELLAN*
Statistics,
Department of
Philadelphia, USA



CONNECT
THE COLLABORATIVE
CHARACTERIZING OUTCOMES OF TBI

July 2022



InTBIR
International Initiative for
Traumatic Brain Injury Research

Research

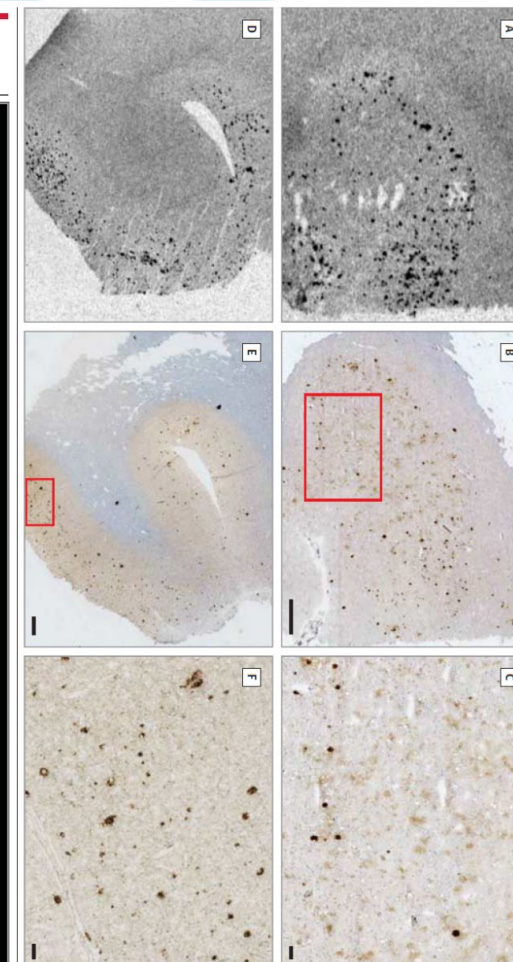
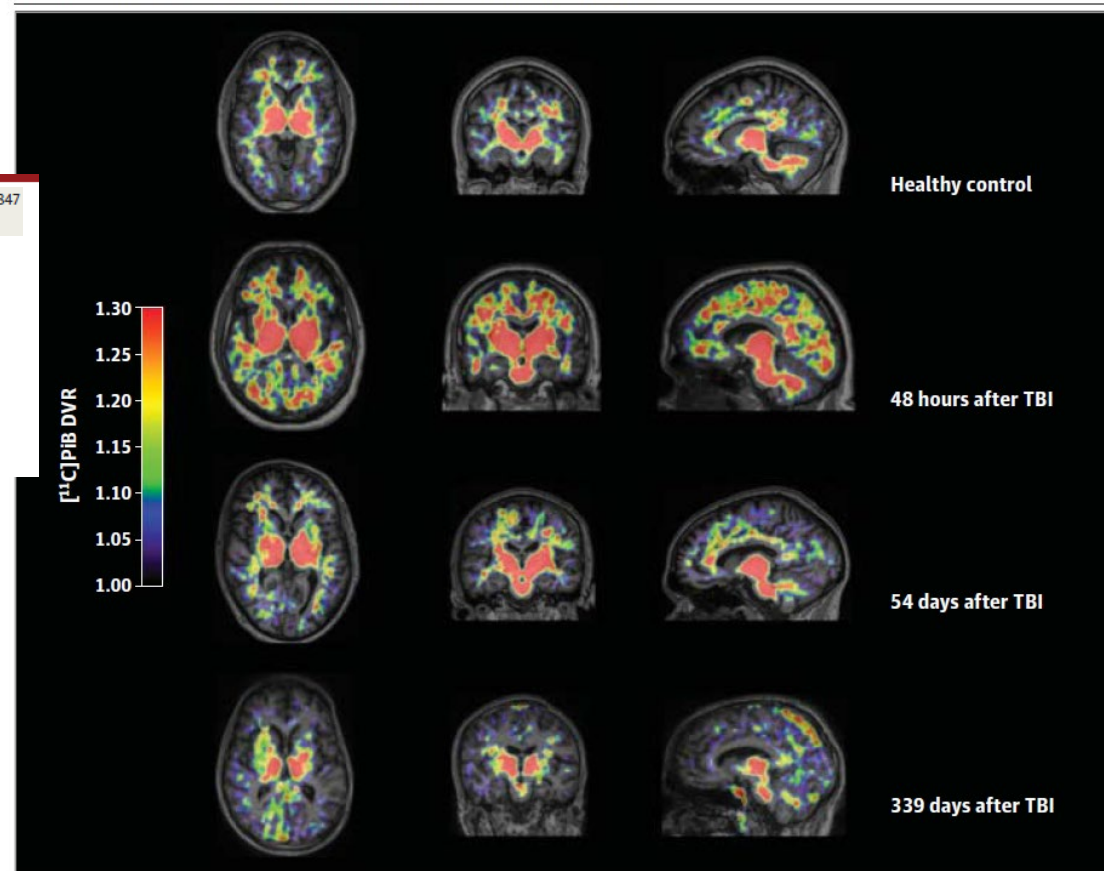
Original Investigation

Amyloid Imaging With Carbon 11-Labeled Pittsburgh Compound B for Traumatic Brain Injury

Young T. Hong, PhD; Tonny Veenith, FRCA; Deborah Dewar, PhD; Joanne G. Outtrim, MSc; Vaithianadan Mani, FRCA; Claire Williams, FRCA; Sally Pimlott, PhD; Peter J. A. Hutchinson, FRCS, PhD; Adriana Tavares, PhD; Roberto Canales, PhD; Chester A. Mathis, PhD; William E. Klunk, MD, PhD; Franklin I. Aigbirhio, DPhil; Jonathan P. Coles, FRCA, PhD; Jean-Claude Baron, ScD, FMedSci; John D. Pickard, FMedSci; Tim D. Fryer, PhD; William Stewart, FRCPath, PhD; David K. Menon, PhD, FMedSci

JAMA Neurol. doi:10.1001/jamaneurol.2013.4847
Published online November 11, 2013.

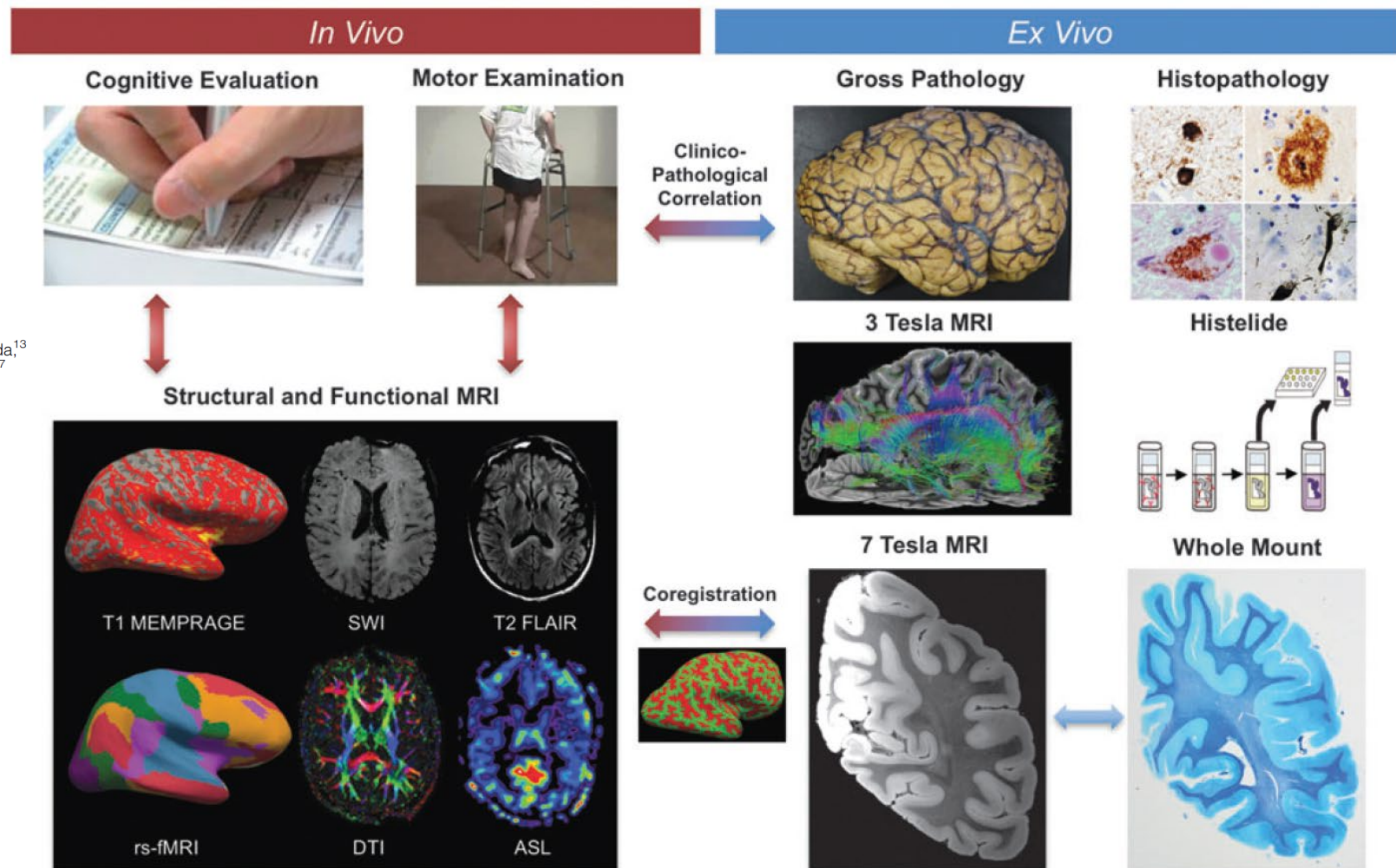
Figure 1. Carbon 11-Labeled Pittsburgh Compound B (^{11}C PIB) Distribution Volume Ratio (DVR) Maps From a Control and 3 Patients With Traumatic Brain Injury (TBI)



July 2022

Multimodal Characterization of the Late Effects of Traumatic Brain Injury: A Methodological Overview of the Late Effects of Traumatic Brain Injury Project

Brian L. Edlow,^{1,2} C. Dirk Keene,³ Daniel P. Perl,^{4,5} Diego Iacono,⁴⁻⁷ Rebecca D. Folkerth,^{8,9} William Stewart,¹⁰ Christine L. Mac Donald,¹¹ Jean Augustinack,² Ramon Diaz-Arrastia,¹² Camilo Estrada,¹³ Elissa Flannery,¹⁴ Wayne A. Gordon,¹⁴ Thomas J. Grabowski,^{15,16} Kelly Hansen,¹³ Jeanne Hoffman,¹⁷ Christopher Kroenke,¹⁸ Eric B. Larson,¹³ Patricia Lee,^{4,7} Azma Mareyam,² Jennifer A. McNab,¹⁹ Jeanne McPhee,¹⁴ Allison L. Moreau,² Anne Renz,¹³ Katie Rose Richmire,¹³ Allison Stevens,² Cheuk Y. Tang,²⁰ Lee S. Tirrell,² Emily H. Trittschuh,^{21,22} Andre van der Kouwe,² Ani Varjabedian,² Lawrence L. Wald,² Ona Wu,² Anastasia Yendiki,² Liza Young,¹⁶ Lilla Zöllei,² Bruce Fischl,² Paul K. Crane,²³ and Kristen Dams-O'Connor^{14,24}



July 2022



National Institute of
Neurological Disorders
and Stroke

Imaging the Future of In vivo Neuropathological Diagnosis through Postmortem Analyses

July 13–14, 2022 | 1:00pm – 5:00pm



July 2022

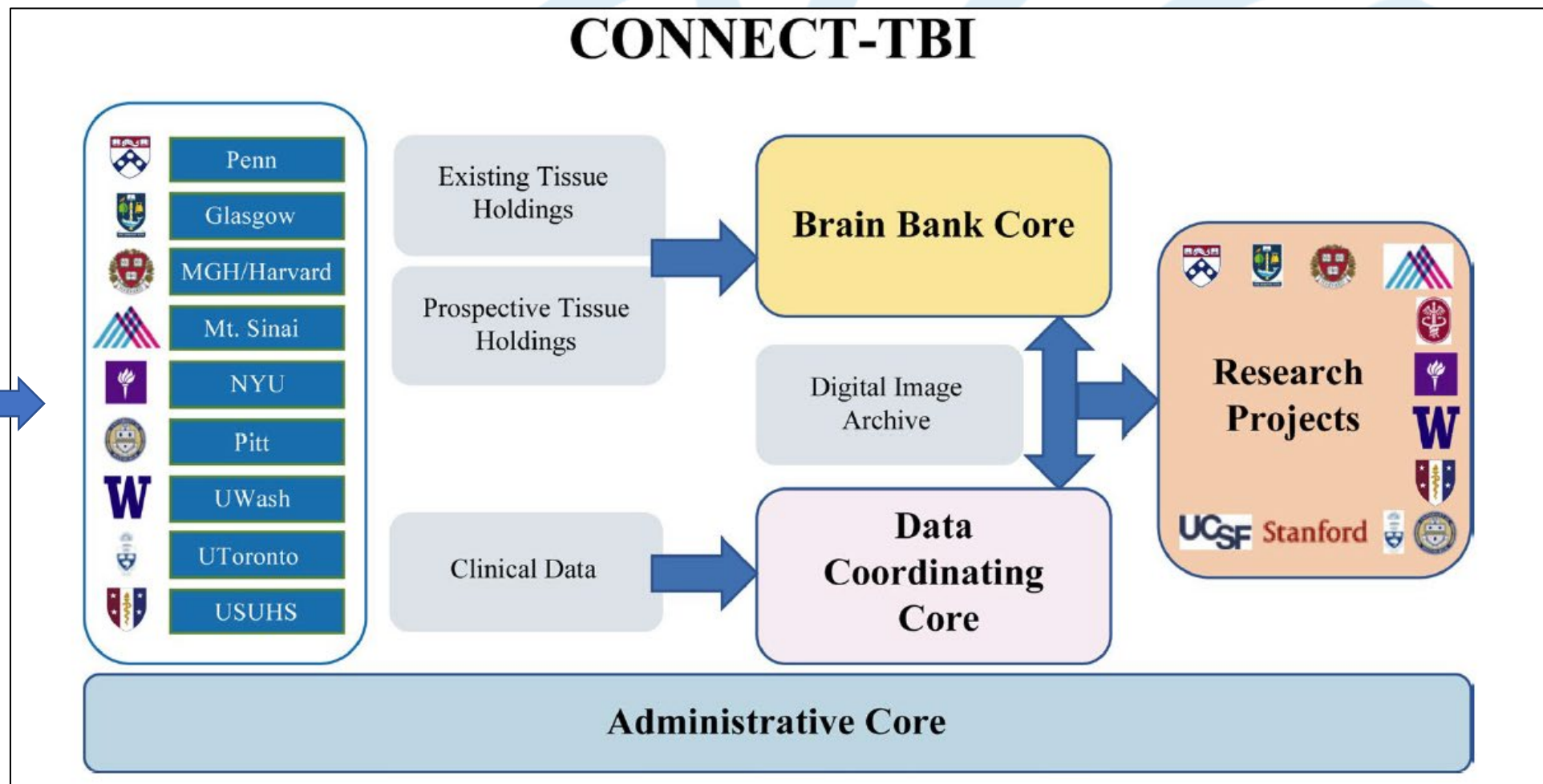


CONNECT-TBI

THE COLLABORATIVE NEUROPATHOLOGY NETWORK
CHARACTERIZING OUTCOMES OF TBI



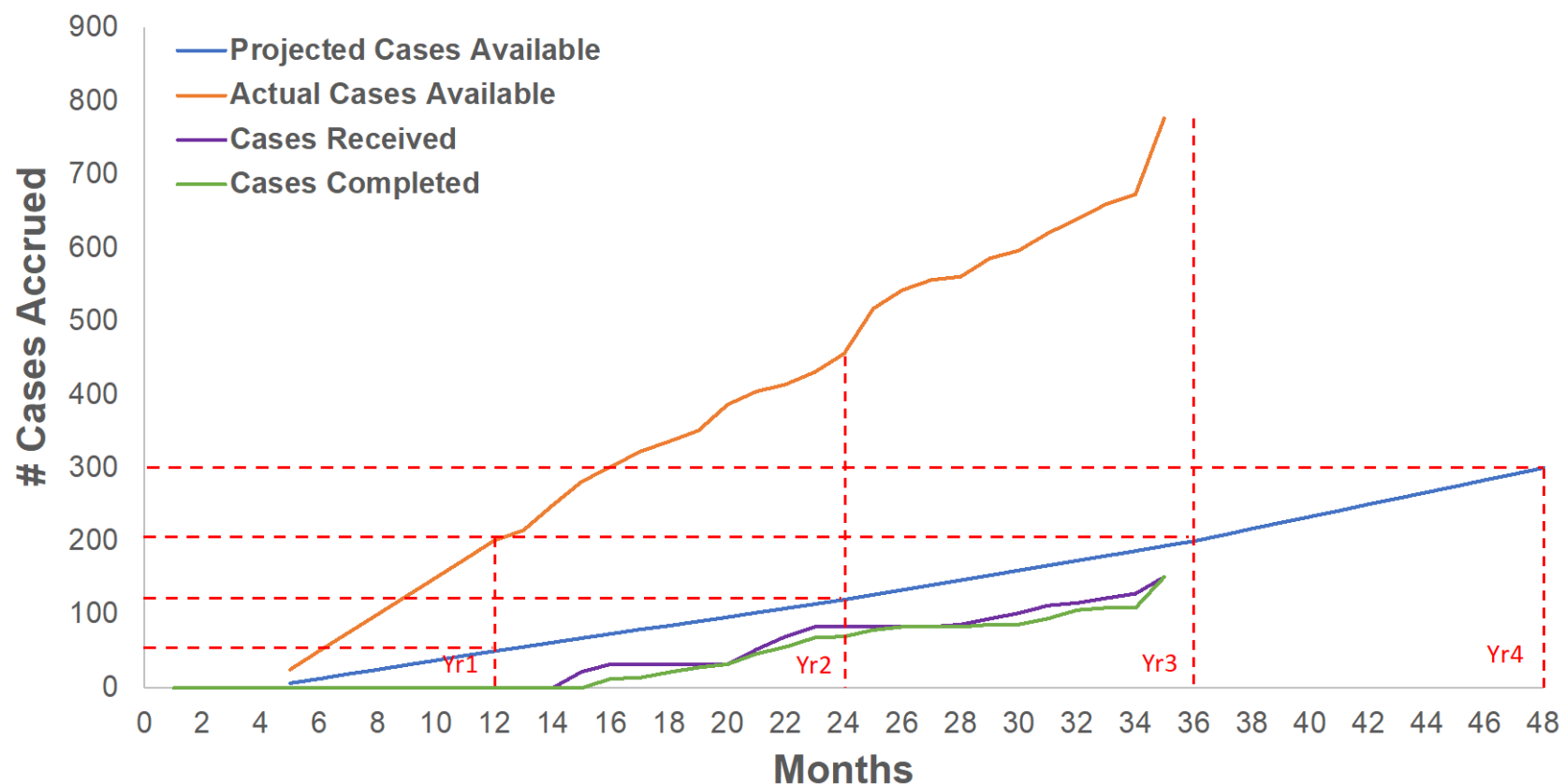
InTBIR
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July 2022



CONNECT-TBI Case Accrual



July 2022



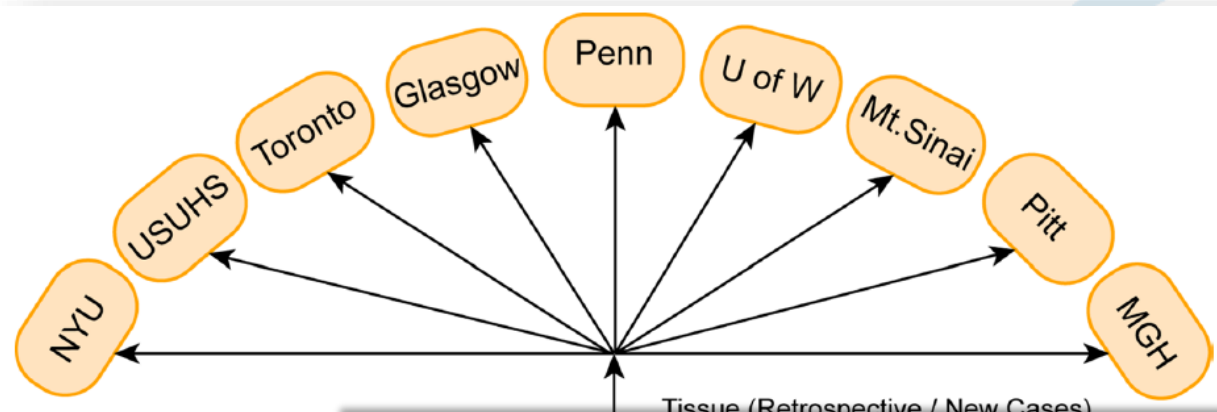
CONNECT-TBI

THE COLLABORATIVE NEUROPATHOLOGY NETWORK
CHARACTERIZING OUTCOMES OF TBI

<http://connect-tbi.med.upenn.edu/>



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International Initiative for
Traumatic Brain Injury Research



CONNECT-TBI

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CHARACTERIZING OUTCOMES OF TBI

Tissue Access Application Form

- 1) Pilot study of the role of spleen tyrosine kinase in pathobiology of repetitive mild TBI; Fiona Crawford (Roskamp Institute)
- 2) TDP-43 proteinopathy in traumatic brain injury related neurodegeneration (TReND): CONNECT-TBI Study; William Stewart, Hailong Song (Glasgow/UPenn)
- 3) Single Nucleus Transcriptomics in Chronic TBI; Principal Investigator: Victoria Johnson (UPenn)
- 4) Sodium channel changes after concussion and TBI; Principal Investigator: Hailong Song (UPenn)
- 5) Correlating Glycomics and Glycoproteomics Biomarker Signatures of traumatic brain injury and Alzheimer's disease; Stefania Mondello and Yehia Mechref (UMessina Italy, Texas Tech)
- 6) Effects of SARS-CoV-2 on human brain; Hailong Song (UPenn)
- 7) Defining Hypo N-Glycosylation following TBI; Douglas Adres (UKentucky)
- 8) Investigating the role of neuronal pentraxins in TBI-related neurodegeneration; Willie Stewart/Samuel Jones (UGlasgow)

Date of next review: TBD

Author: William Stewart

Authorized by: Douglas H. Smith, William Stewart

July 2022



CONNECT-TBI

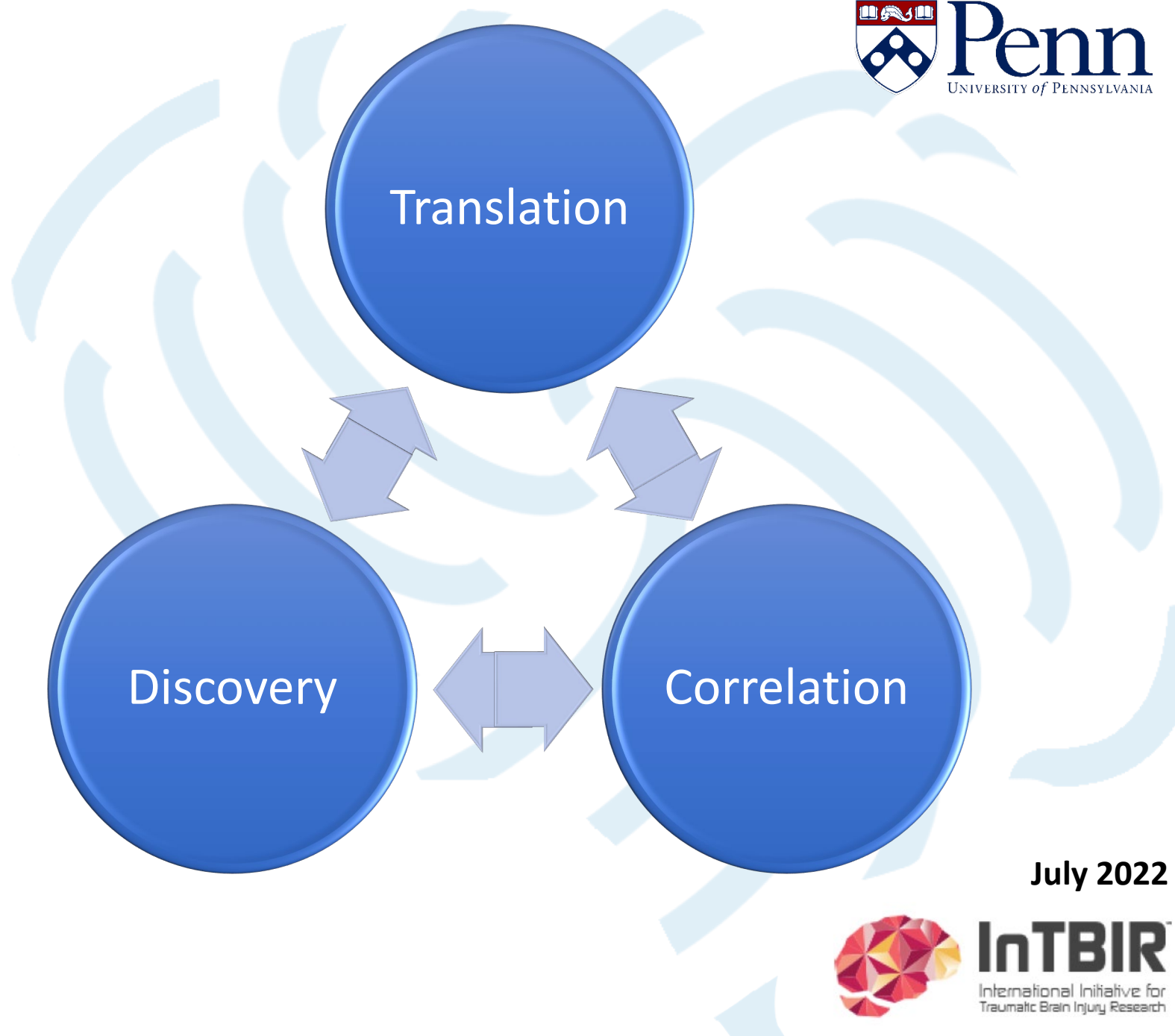
THE COLLABORATIVE NEUROPATHOLOGY NETWORK
CHARACTERIZING OUTCOMES OF TBI

<http://connect-tbi.med.upenn.edu/>



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Linkage with post-mortem studies



July 2022

Questions?



InTBIR

International Initiative for
Traumatic Brain Injury Research



Project introduction and overview

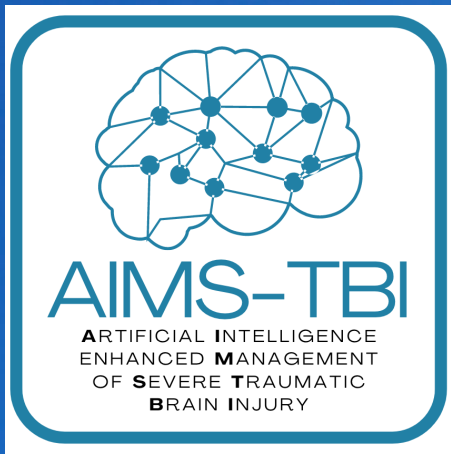
Dr. Robert McNamara (FCICM), ICU Specialist, Royal Perth Hospital
Director of ICU Research
PhD Candidate, Curtin University School of Medicine
Project Lead for AIMS-TBI

Acknowledgment of Country

The AIMS-TBI project acknowledges the Wadjuk people as the Traditional Custodians of the land upon which the project operates. We would like to pay respect to their Elders past, present and emerging and extend that respect to other Aboriginal people present.

Conflict of Interest Statement

Dr. McNamara and Mr. Meka have a patent pending for technologies developed in the AIMS-TBI project.



AIMS-TBI Objective

"Bring Data Science to the bedside"

Use Artificial Intelligence technology to enhance the clinical management of TBI patients

'Blue Sky' research

Human Research Ethics Committee approval - March 2020

Approval to access to "all digital data generated during the treatment of a TBI patient"

- Data Capture
- Data Streaming
- Cleaning & Pre-processing
- Security systems
- Hardware Engineering
- Supercomputing
- Machine learning
- Deep Learning
- Cloud computing
- Compression systems
- User Interface Systems
- Time Series Database

Acknowledgements



Supervisors: Lindy **FITZGERALD**, Andrew **UDY**, Daniel **FATOVICH** & Luke **HASELER**

AIMS-TBI team: Rinaldo **BELLOMO**, James **ANSTEY**, Toby **JEFFCOTE** & Shiv **MEKA**

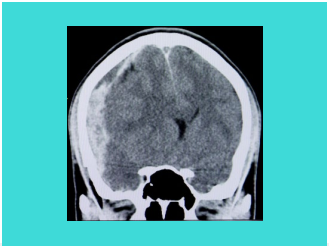
Consumer Advisors: Nakia **CHAPMAN**, Sandra **BLACKHAM**, Heather **ERICKSON** & Shelda **DEBOWSKI**

Unit Research Coordinators





DATA SOURCE PATIENT INCLUSION CRITERIA



TRAUMATIC BRAIN INJURY

Requiring ICU admission

+



ICP MONITORING

ICP or EVD

+



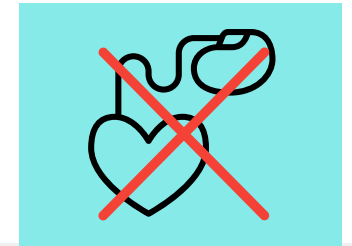
DATA CAPTURE

ICU monitor

Hospital Databases

Smart watch

+



NATIVE CARDIAC SIGNALS

Pacemaker-dependent and/or

Cardiac transplant recipients

excluded

DATA PIPELINE



Data capture

• Wave data (Live or HDF5)

- 500 Hz: ECG
- 250 Hz: ICP, ABP, CPP
- 1 Hz: T, SpO₂, ETCO₂, HR

• Image data

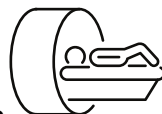
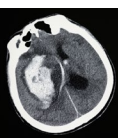
- MRI/CT *

• Text/tabular data

- Demographics, Disposition, outcomes, Clinical information system*

• Interfaces

- ICU monitor
 - ICM+
 - Raspberry Pi
- Fitbit / Apple Watch*
- Hospital networks*



Cleaning & pre-processing

• Spectral

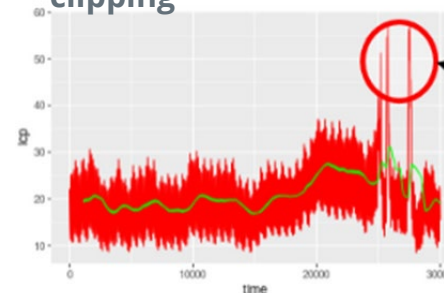
- Fast Fourier Transformation, Wavelet

• Machine and/or Deep Learning

- Compression, Outlier removal, median filter, waveform clipping

• Traditional Outlier removal

- Median filter, Waveform clipping



Processing

• Time-series forecasts

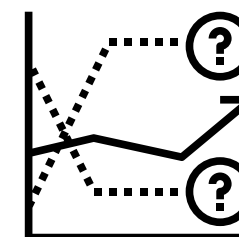
- ARIMA, Prophet

• Machine Learning

- Random forest, Gaussian Processes, etc., +/- Boosting and Bagging

• Deep Learning

- Convolutional networks, Memory-based methods, Transformers, etc.



Analysis & Reporting

• Live analysis

- Svelte UI
- PowerBI visuals

• Platform to securely share data and predictions

- SMS
- Web-based
- MS Teams



"*" = under development

AIMS-TBI Web Interface and Analysis

InTBIR meeting July 2022

Royal Perth

45 Total patients
14.89 ICP Mean
3.21 ICP Burden(23)
3.68 ICP Burden (22)
83.65 Data quality
14.70 First hour average

Royal Melbourne

52 Total patients
11.79 ICP Mean
1.89 ICP Burden(23)
2.18 ICP Burden (22)
82.91 Data quality
11.25 First hour average

Alfred

13 Total patients
11.81 ICP Mean
3.40 ICP Burden (23)
3.75 ICP Burden (22)
87.46 Data quality
13.22 First hour average



ICU Admission Date and Time
13/04/2019 11/08/2021

Gender at Birth
☐ (Blank)
☐ Female
☐ Male

AIMS
alpha v1.0

TBI monitoring demo to assess
scalability, speed, and security.

Heart beat
Key management
Live signals
Uploader (Beta)
Analytics
Settings

Cumulative Stats Patients



RPH
Monitored Days: 274.98
Monitored Patients: 61
Mean ICP burden: 3.38
Mean ICP purity: 84.71
First hour ICP average: 14.59

RMH
Monitored Days: 265.27
Monitored Patients: 53
Mean ICP burden: 2.18
Mean ICP purity: 83.12
First hour ICP average: 11.25

ALFRED
Monitored Days: 214.99
Monitored Patients: 54
Mean ICP burden: 3.7
Mean ICP purity: 88.04
First hour ICP average: 12.61



AIMS-TBI Hybrid Cloud

- **Pawsey Supercomputing Centre (PSC)**

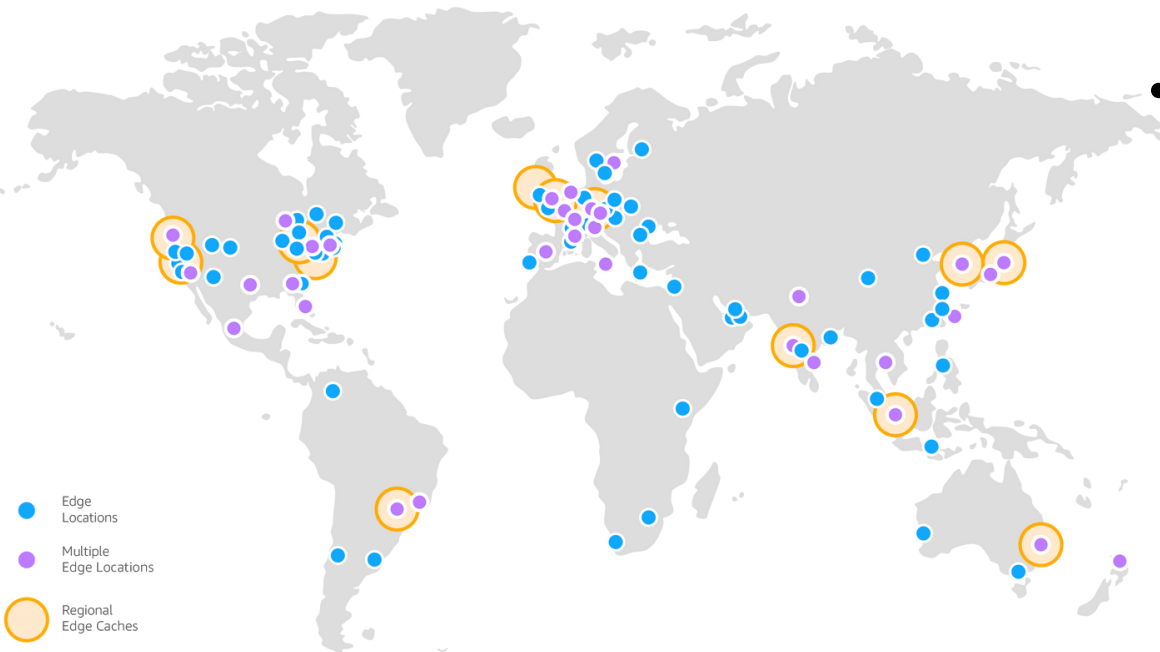
- 6 Petascale machines
- **1 Exascale machine**
 - 1.1×10^{18} FLOPS (ML/DL optimized)
 - 1 Quantum computer (under development)
- Algorithm training + calibration
- ~10 Petabytes storage allocated

**Computational power +
Accessibility**



- **Amazon Web Services (AWS)**

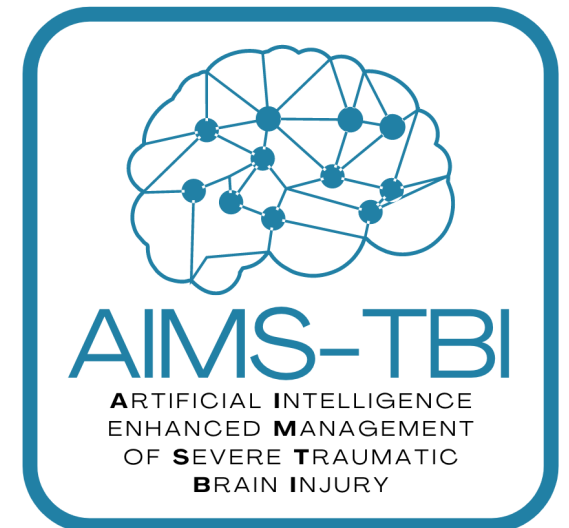
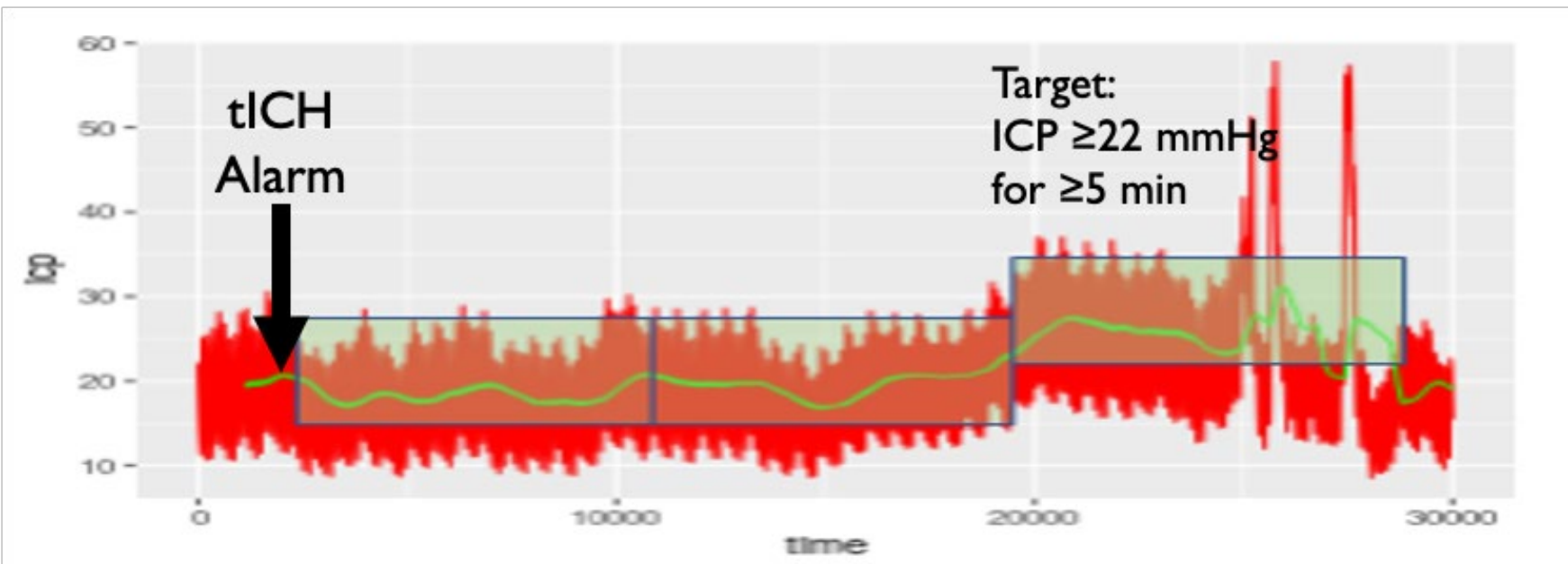
- Allows **co-location** to any AWS node globally
- AIMS data streamed to & **processed at the nearest AWS node**
- **Scalable:** 1 to 500,000+ algorithms operating simultaneously



Clinical Algorithms

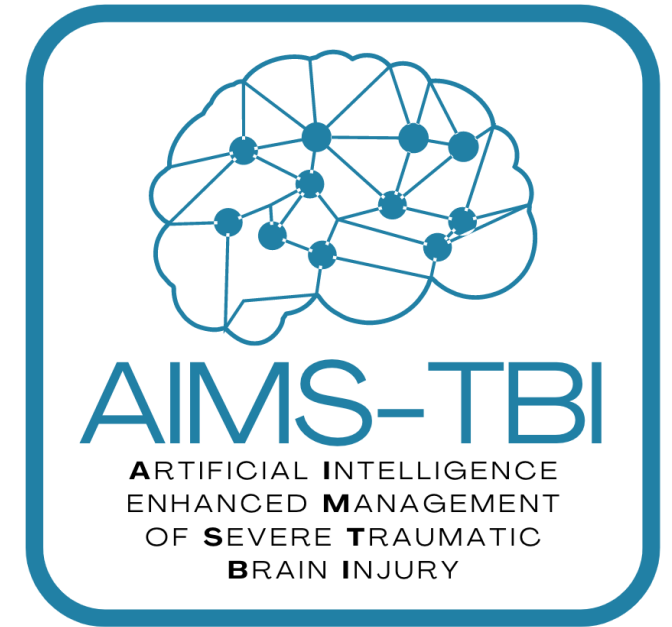
- tIH prediction algorithms
 - First class of clinically relevant algorithms developed in project
 - Machine and Deep Learning approaches
- Target: Mean ICP ≥ 22 mmHg for ≥ 5 minutes
- Horizon: 30 minutes
- Observational Testing ongoing (07/22)

PATIENT	BURDEN	ALERTS	ICH	OVERALL
 Anthony K.	30	PER SJ HYD VC	32	



Summary

- The AIMS-TBI project is developing systems to bring the benefits of Artificial Intelligence to the ICU bedside... and to research
- Clinical Deep Learning Cloud
 - Scalable & Deployable nationally, regionally and/or globally
 - Platform for Research
 - AI algorithm development and/or real time operation
 - Investigation of pre-emptive tIH management (hopefully)
 - Clinical Trial support
- Long & interesting road ahead...



Thank you for Listening

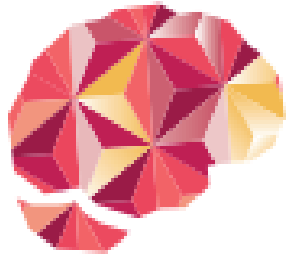
Royal Perth	45 Total patients	14.89 ICP Mean	3.21 ICP Burden(23)	3.68 ICP Burden(22)	83.65 Data quality	14.70 First hour average
Royal Melbourne	52 Total patients	11.79 ICP Mean	1.89 ICP Burden(23)	2.18 ICP Burden(22)	82.91 Data quality	11.25 First hour average
Alfred	13 Total patients	11.81 ICP Mean	3.40 ICP Burden(23)	3.75 ICP Burden(22)	87.46 Data quality	13.22 First hour average

Questions?

Dr. Robert McNamara
Royal Perth Hospital
e: robert.mcnamara@health.wa.gov.au

If interested in collaborating and/or learning more, please contact me





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International Initiative for
Traumatic Brain Injury Research

“Utility of biomarkers and MR imaging in TBI”

Dr Virginia Newcombe

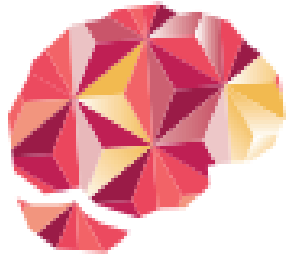
This presentation has been removed from the slide deck because it contained unpublished material. If you would like further information, please contact the presenter at vfjn2@cam.ac.uk.

Questions?



InTBIR

International Initiative for
Traumatic Brain Injury Research



InTBIR

International Initiative for
Traumatic Brain Injury Research

Lunch

International Initiative for
Traumatic Brain Injury Research (InTBIR)
General Assembly and Scientific Meeting

Connect to wifi:
RITZ_CONFERENCE
Password: ritz2022

Presentations will resume at 13:35 CEST

Observational and Comparative Effectiveness Studies Working Group

David Okonkwo, MD, PhD
University of Pittsburgh
Philadelphia, PA USA

Lindy Fitzgerald, PhD
Curtin University
Perth, WA AUS



Observational and Comparative Effectiveness Studies Working Group Members So Far...

David Okonkwo
Lindy Fitzgerald
Carolyn Emery
Ramon Diaz-Arrastia
William Stewart
Stuart Hoffman
Elisa Zanier
Roberto Latini
Xiang Mao
Joanne Fleming
Andrea Schneider
Nsini Umoh (NIH/NINDS)
Michael McCrea

Andrew Udy
Wu Xiang
Isabelle Gagnon
Guido Bertolini
David Menon
Vicki Anderson
Judith Bellapart
Hester Lingsma
Stephen Broglio
Laura Ngwenya
Jussi Posti
Andrew Maas



INTS2022
BERLIN





Vicki Anderson
Theme Director Clinical Sciences
Murdoch Children's Research
Institute, AUS



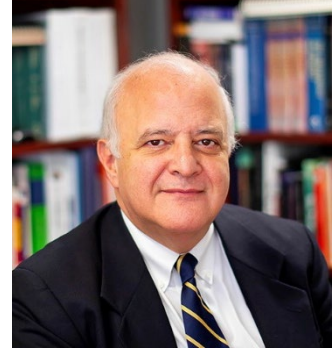
Guido Bertolini
Istituto di Ricerche Farmacologiche
Mario Negri IRCCS



Judith Bellapart
Senior Intensive Care Specialist
Royal Brisbane and Women's
Hospital, QLD AUS



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Associate Dean, Graduate Affairs
Director, Michigan Concussion Center
University of Michigan, School of
Kinesiology



Ramon Diaz-Arrastia
Department of Neurology
University of Pennsylvania



Melinda Fitzgerald
John Curtin Distinguished Professor
ADVCR Curtin University, WA AUS



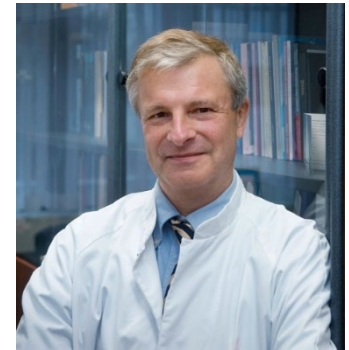
Isabelle Gagnon
School of Physical and Occupational
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Erasmus MC



David Menon
Head of Division of Anaesthesia
Cambridge Neuroscience
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U Cincinnati Director,
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David Okonkwo
Professor of Neurological Surgery,
Director Neurotrauma Clinical Trials
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Consultant Neurocenter,
Turku University Hospital, Finland



Andrea Schneider
Department of Neurology, U Penn
Perelman School of Medicine



Willie Stewart
Consultant Neuropathologist
Honorary Professor (UoG)



Andrew Udy
Deputy Director (Research),
Dept. Int Care & Hyperbaric Med,
The Alfred, VIC AUS



Nsini Umoh
Program Director, Division of
Neuroscience, NIH



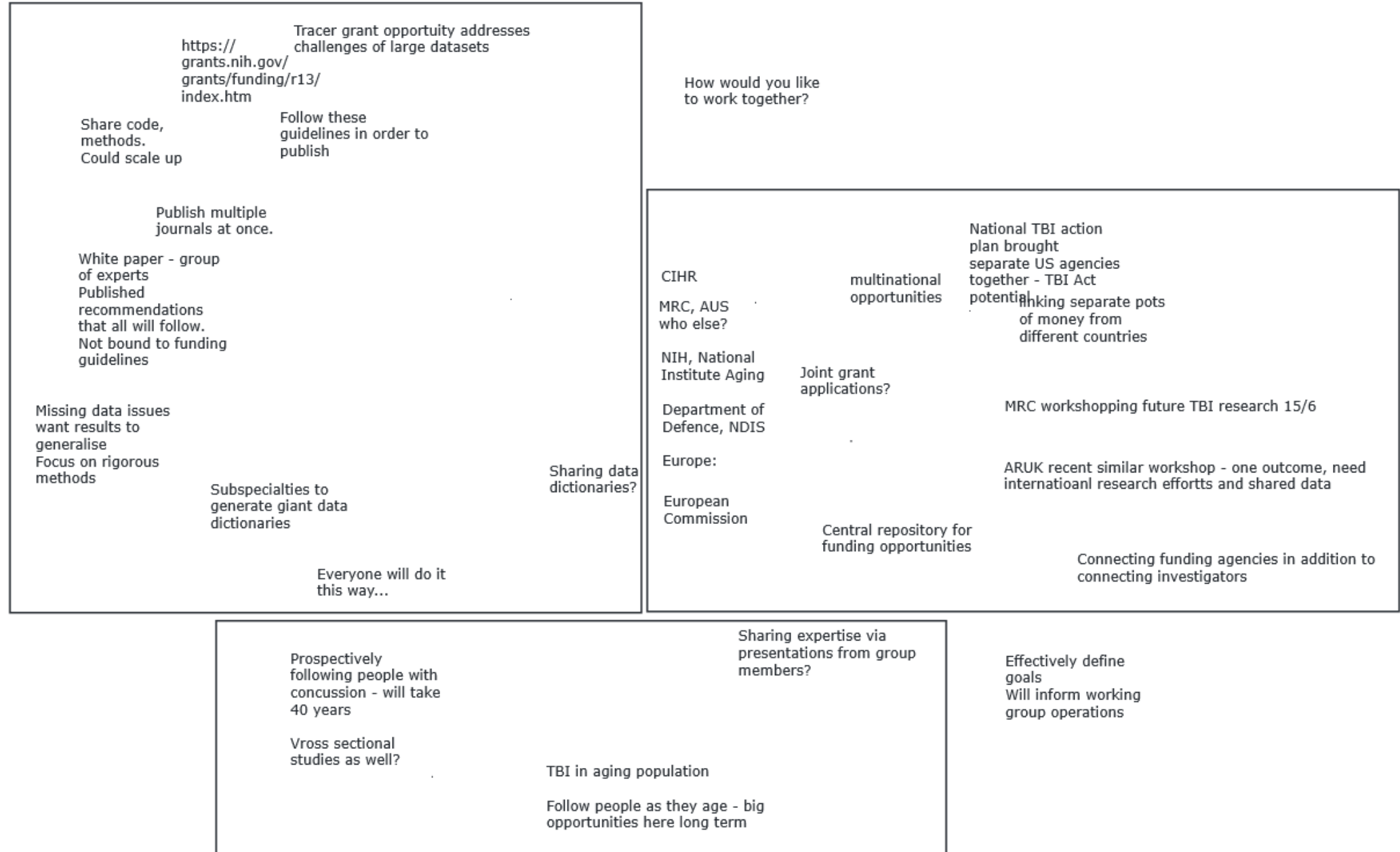
Elisa Zanier
Head at Mario Negri Institute
for Pharmacological Research

Observational and Comparative Effectiveness Studies Working Group: what the working group aims to achieve

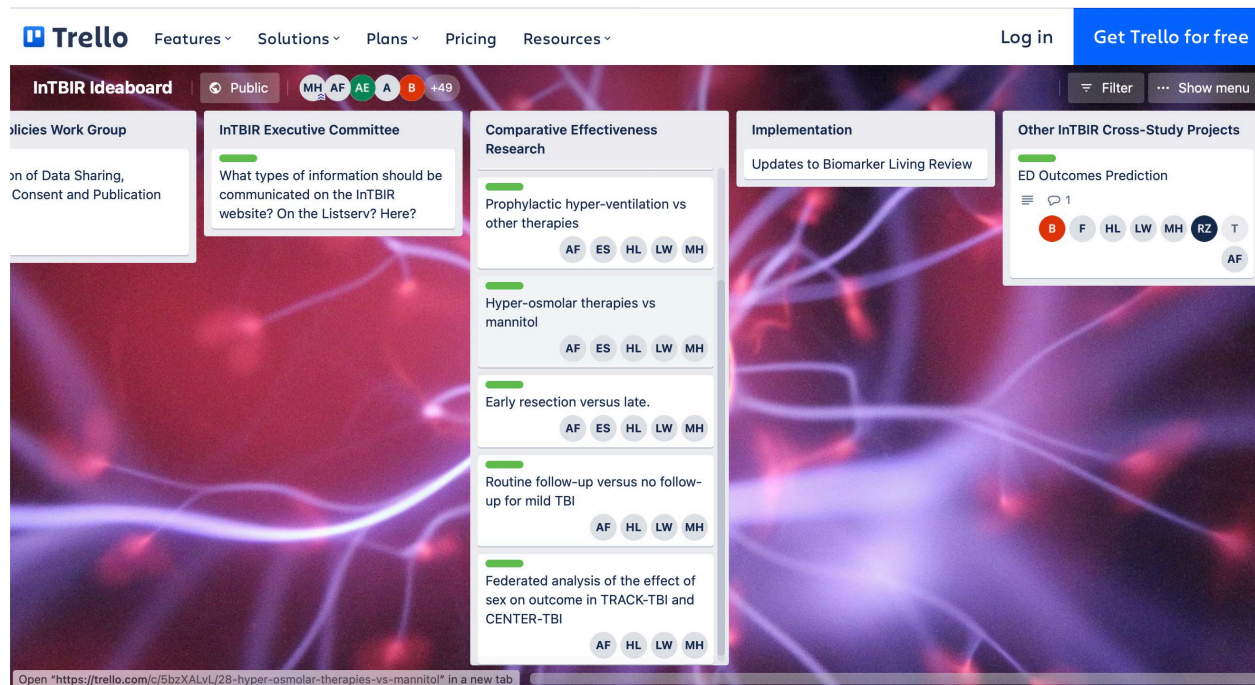
Observational registries and studies have underscored several important research efforts and advances in recent years in traumatic brain injury and will continue to be key research strategies. The Observational and Comparative Effectiveness Studies working group will act as a focal point and source of expertise for global researchers developing and utilising large scale data assets for traumatic brain injury research.

The working group will promote and foster standards and expectations for data collection in TBI research. New research initiatives will be encouraged to incorporate common data elements, research methods, and ways to use, analyse and draw conclusions from data, so as to maximise opportunities, value and impact of internationally collaborative research. New and emerging analytic approaches will be incorporated, such as artificial intelligence and machine learning. The group will define the standards and expectations for global TBI research and foster global collaborative initiatives. The resultant large scale data assets can be used for comparative effectiveness research and to generate predictive models to improve clinical care and outcomes for people with traumatic brain injury.





Observational and Comparative Effectiveness Studies Working Group: initial thoughts and action plans



- Brainstorming of additional studies
 - Longer-term follow up for CENTER-TBI participants
 - Combination of existing large-scale datasets (ala TRACER)
- Form a work group to produce a guidance document on methodology in large scale TBI data collection
 - will be clearly distinguishable from other common data element initiatives currently underway



Working group

Study design and analysis

Prof. Hester Lingsma, Erasmus MC, Rotterdam, the Netherlands

Prof. Alexis Turgeon, Université Laval, Québec City, Canada

Design and analysis in TBI research

1990-2010:

Neutral RCTs, partly due to poorly dealing with heterogeneity of TBI

→ Methodological advances in RCT design and analysis (Maas et al. Advancing the care for traumatic brain injury: summary results from the IMPACT studies and perspectives on future research, Lancet Neurology 2013)

2010-2020:

Large observational studies to exploit heterogeneity using comparative effectiveness research

→ New methods in the field of TBI, such as instrumental variable analysis and propensity scores (e.g. van Essen et al. Surgery versus conservative treatment for traumatic acute subdural haematoma: a prospective, multicentre, observational, comparative effectiveness study. Lancet Neurology 2022)

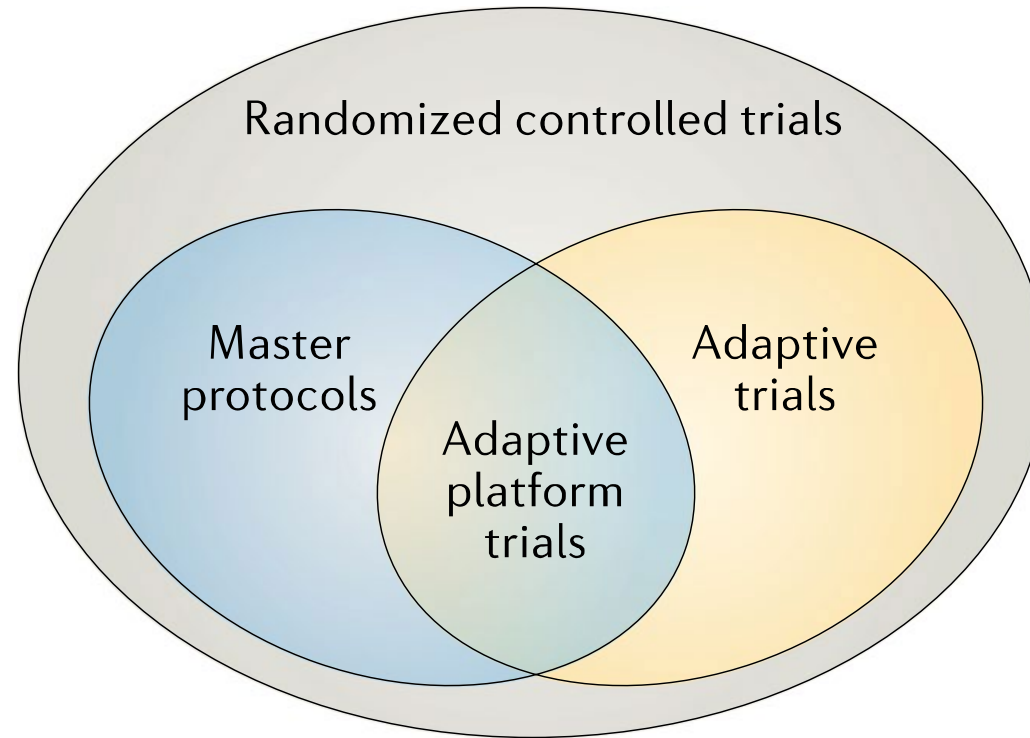
→ Standardized data collection (Common Data Elements), Standardized approaches to analysis (e.g. Ercole et al. Imputation strategies for missing baseline neurological assessment covariates after traumatic brain injury: A CENTER-TBI study, PLoS One 2021)

Design and analysis in TBI research

2020 - ...

- Use the right design for the right question:
E.g. Observational studies when there is no consensus on usual care, intervention, or population, to help inform if future RCT are needed
- Further develop and advocate standardized approaches to data-analysis in TBI
- Explore novel methods and designs and their applicability in TBI

Different new trial designs informed from recent research



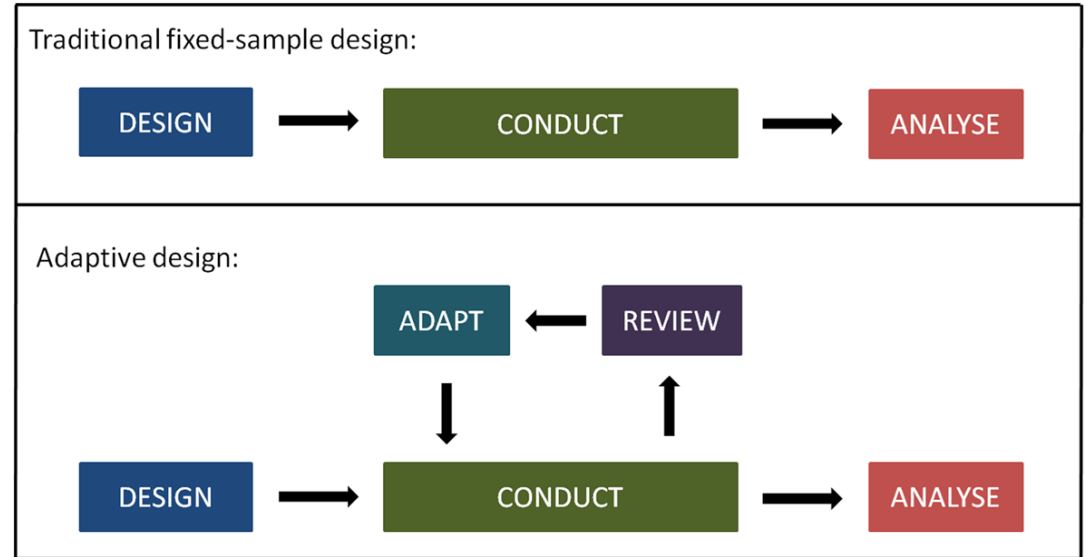
The Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. Nature Reviews Drug Discovery. 2019 Oct 1;18(10):797-808.

What is a Randomised Adaptive Platform Trial?

- Designed for conducting trials for a specific health care condition
- Common and shared platform trial including common data elements (common CRF and outcome measures)
- Designed to study several interventions simultaneously
- Most often using a pragmatic design

Fixed trial vs. adaptive trial design

- **Fixed trial designs:** Conventional clinical trials with fixed sample size and single analysis at the end of the trial
- **Adaptive trial designs:** A type of clinical trial design that allows for *pre-specified modifications* to the trial design based on interim data collected



Pallmann P et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC medicine. 2018 Dec;16(1):1-5.

Common types of adaptive trial designs

Adaptive trial designs	Adaptations
• Interim analyses for superiority and/or futility	• Sample size
• Sample size re-assessment	• Increases in the final sample size
• Response adaptive randomization	• Changes in allocation ratio
• Enrichment designs (not all-comers)	• Modified patient eligibility criteria

Analytical plan in an adaptive platform trial

- Periodic interim analyses
- Depends on recruitment (periodic scans)
- Response adaptive randomisation within a specific domain when several interventions are studied

Analytical plan in an adaptive platform trial – when bayesian statistics are used

- The sample size is not determined a priori but depends on the statistical thresholds:
 - $>XX\%$ posterior probability of superiority
 - $<X\%$ posterior probability for an odds ratio of X
- Analyses accounting for potential interactions between domains when suspected

Can we use example in other patient populations?

- Randomised, Embedded, Multifactorial, Adaptive Platform trial



www.remapcap.org

Designing a similar platform trial in TBI: opportunities and challenges

- Ready to go platform for testing interventions in TBI
- Avoid repeating the development of CRF/database
- Lower costs for conducting a trial
- Sites can chose to randomise or not in a specific domain/intervention
- Challenges
 - Long-term outcome (GOSe) may limit the response adaptive randomization
 - Ongoing costs related to the infrastructure (bayesian statistical models and analyses)
 - Change in paradigm for KUs in how to interpret the data

Our working group

- Establish state-of-the art in design and analysis of TBI studies
- Advocate and facilitate the use of these standards
- Develop and/or apply novel approaches, including adaptive trial design

Join us!

Towards an International TBI Clinical Trials Network

Peter Hutchinson
Alexis Turgeon

International initiative for Traumatic Brain Injury Research (InTBIR)
Berlin. July 16, 2022



What are the main issues in TBI research?

- Suboptimal global collaboration
- Work in silos
- Underproductive work and repetition of infrastructures

What could become inTBIR 2.0?

- A clinical collaborative research and trial network

Why a clinical collaborative trial network?

- To build collaboration amongst investigators and research groups engaged in investigator-initiated clinical research
- To advance the science and conduct clinical applied research through practice changing trials

What is a clinical trials network?

- An network infrastructure to develop research and projects in a collaborative environment
- Facilitate linkages, communication and knowledge translation across a specific research community
- Support research program in integrating global TBI research efforts

What models of acute care trials group do we have?



1989



1994



2006



2008



2016



What models of acute care trials group do we have?



- International Forum for Acute Care Trialists, is a global collaboration of acute care clinicians and researchers

What is a collaborative clinical trials group?

Investigator-led clinical research consortia: The Canadian Critical Care Trials Group

John C. Marshall, MD, FRCSC, Deborah J. Cook, MD, MSc, FRCPC, for the Canadian Critical Care Trials Group

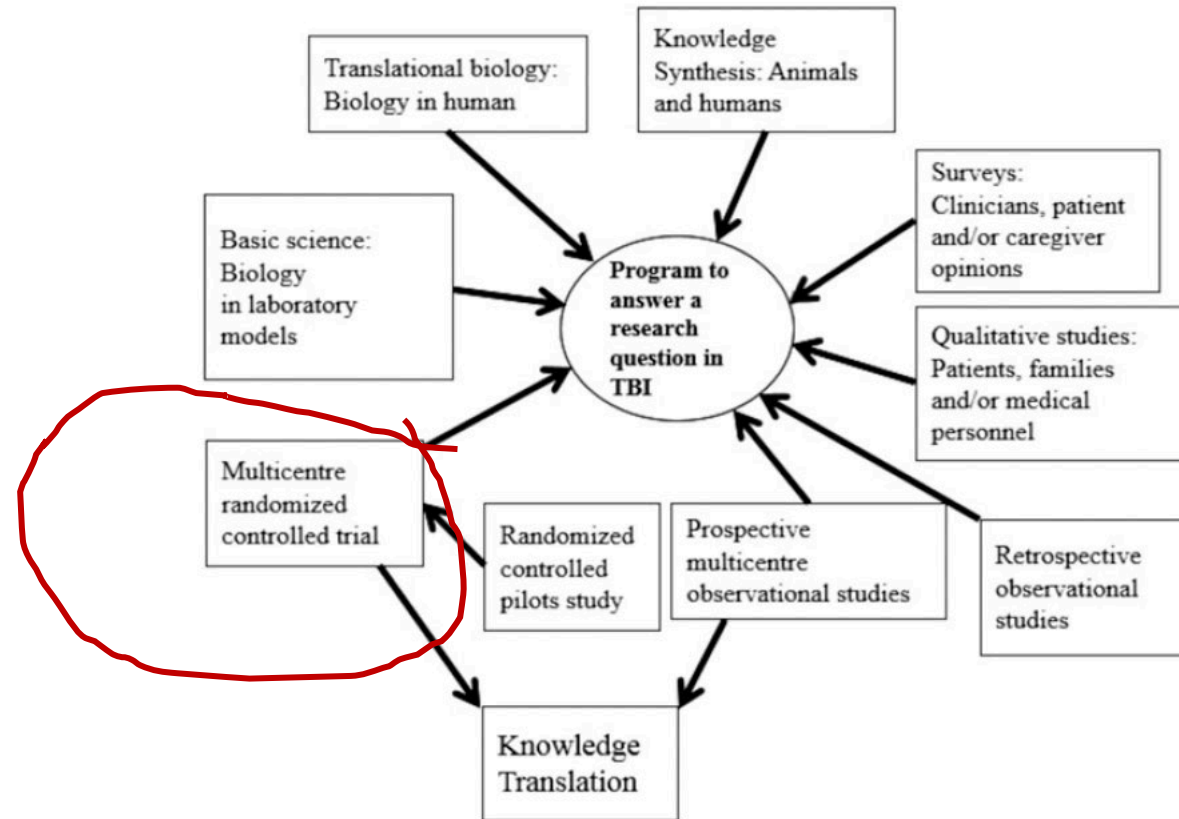
Crit Care Med 2009

The Canadian Traumatic Brain Injury Research Consortium: Epitomizing Collaborative Research in Canada

James S. Hutchison,^{1-4,*} Carolyn Emery,^{5,6} Isabelle Gagnon,^{7,8} Caroline Léger,⁹ Richard Riopelle,^{10,11}
Cheryl Wellington,^{1,2} Elisa Wilson,² and Alexis F. Turgeon^{9,13,*}
on behalf of the Canadian Traumatic Brain Injury Research Consortium

J Neurotrauma 2018

What is a collaborative clinical trials group?



What is a collaborative clinical trials group?

- Aims at being inclusive
- Investigator initiated and led research
- Several programs and initiatives
- Meetings to present new and ongoing research programs
- Develop multicentre research/trial in collaboration

What is NOT a collaborative clinical trials group?

- It is not a granting agency
 - Funding must be obtained by PIs and teams
- It is not a medical society
- It is not about one, two or three initiatives
- It is not a network providing access to sites but a network where research is discussed and collaborations are established

International Registry of Clinical Trials in TBI

Link to individual trial website

Protocol

Progress

Benefits:

1. Assist with recruitment
2. Duplication awareness
3. Potential for pooled analysis
4. Learning from each other



Clinical Trials Initiative

UK perspective



Commissioned trial funding – Health Technology Assessment

Trial delivery – Clinical Research Network

International collaboration – AUSNZ

British Neurosurgical Trainee Research Collaborative



Trainee research collaborative

Associate PI scheme

Publishing: collaborative publishing model



How can we improve?

Collaborative research environment

Clinical collaborative research and trial network

Specific trial infrastructure – trial platform

Neuroprotection

Single bullet

Align mechanistic study to clinical trials

Improved phase 1 and phase 2 design

Translate academic endeavour into change of practice
and policy implementation



Special Contexts

CHERYL WELLINGTON, RAQUEL GARDNER, ROGER ZEMEK

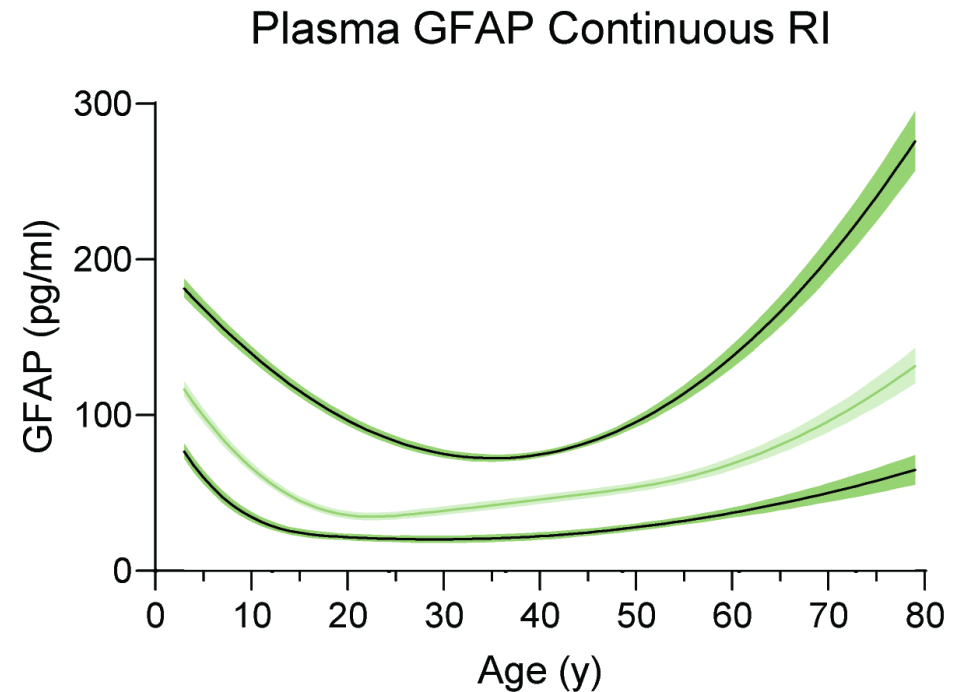
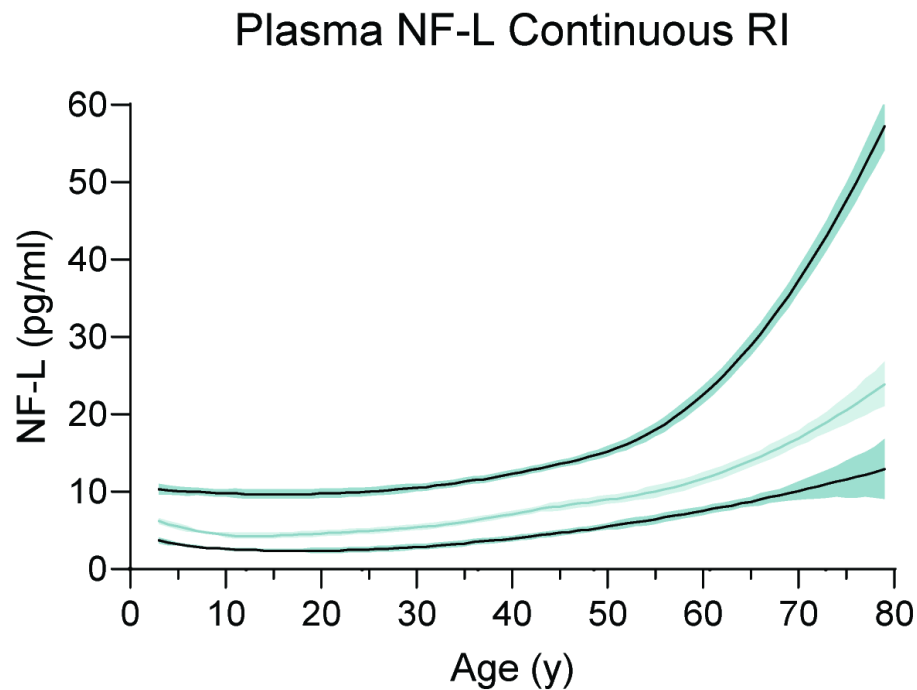
JULY 16, 2022

Working group objectives

- To encourage research that embraces the diversity of persons who are vulnerable to TBI, beyond sport, military and general community settings, i.e.
 - Children and elderly
 - Precariously-housed persons
 - Survivors of intimate partner violence
 - Persons of cultural and ethnic diversity
 - Low and middle income countries
- To encourage discussion of the ethical, legal and social implications (ELSI) of TBI research in special contexts
- To encourage inclusion of special contexts cohorts in TBI research studies

Children and Elderly

- Biomarker interpretation will need age-specific reference intervals



Current data is from the Canadian Health Measures Survey is not yet weighted and therefore these results do not yet fully represent the Canadian population

Non-accidental neurotrauma in pre-verbal children

- Abusive head trauma is one of the leading causes of death in children under 5, with babies <1 year of age at the highest risk
- The Government of Canada has released a Joint Statement on Traumatic Head Injury due to Child Maltreatment (THI-CM) <https://www.canada.ca/en/public-health/services/health-promotion/childhood-adolescence/publications/joint-statement-traumatic-head-injury-child-maltreatment.html>
- The PedsConcussion guidelines will include a new domain on THI-CM with Child and Youth Protection expertise



Nomenclature:

Canada: THI-CM

US: Abusive head trauma

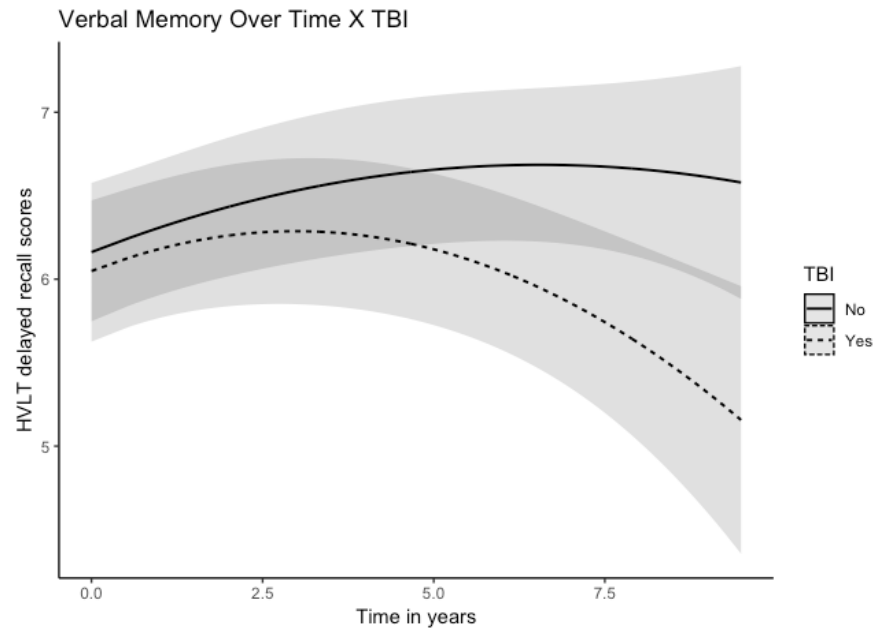
UK: Shaken Baby Syndrome

Vulnerably housed persons: The HOTEL Study

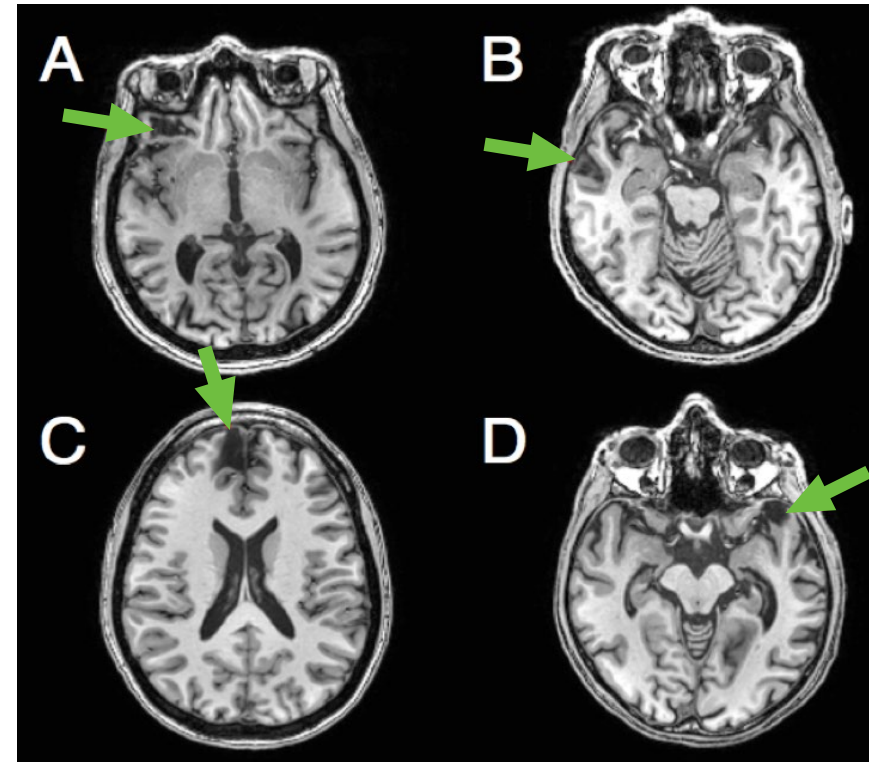
- 
- A photograph of a person with curly hair, wearing a white tank top and dark pants, sitting on a bed with white linens. They have their hands covering their face in a gesture of distress or despair. The background shows a window with light coming through.
- Longitudinal study initiated in 2010 to reveal multiple health concerns faced by >600 tenants in single-room occupancy (SRO) hotels in Vancouver's Downtown Eastside (DTES)
 - Monthly and yearly health assessments including multimodal MRI
 - 95% have substance dependence and ~67% use injected drugs
 - 50% have psychosis and 50% have a neurological disorder
 - 50% are women
 - Account for the majority of catchment hospital visits for neurologic, substance abuse and mental health concerns

TBI in HOTEL Participants

Cognitive: History of moderate-severe TBI is associated with rapid cognitive decline compared to HOTEL participants without TBI

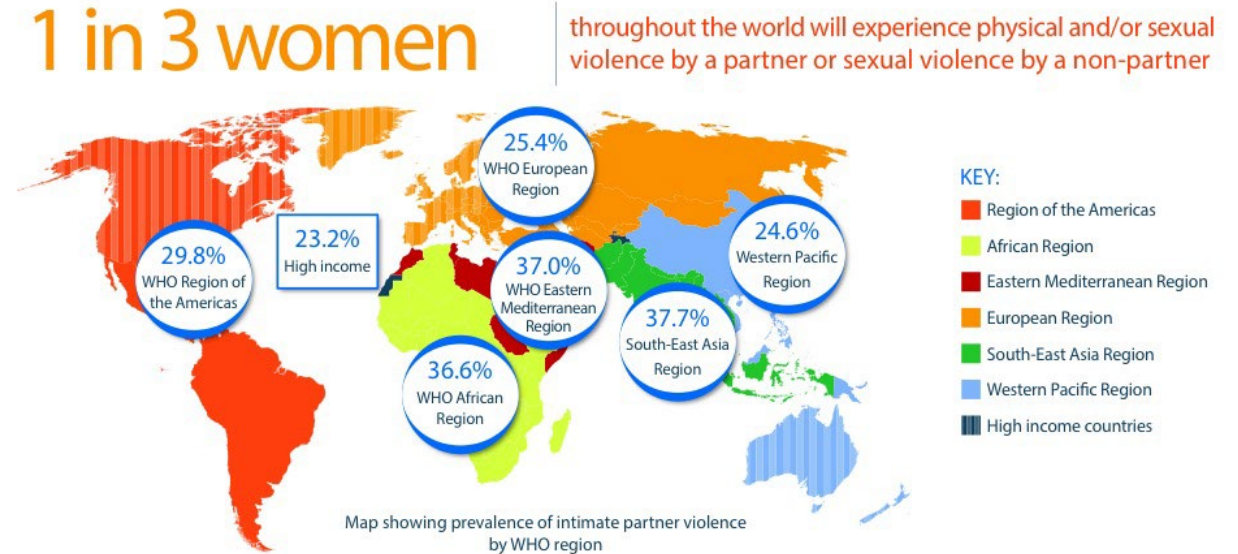


Neuroimaging: 8% of participants have evidence of trauma induced encephalomalacia, markedly higher than would be expected in the regular population



Brain Injury in Intimate Partner Violence

- IPV is widespread in all WHO countries studied
- ~230,000 Canadian women suffer a violent physical attack at the hands of an intimate partner each year
- The BC Royal Canadian Mounted Police receive >8,000 calls for IPV each year
- As only 1 in 5 IPV victimization are reported, the true incidence is likely much higher
- As many as 92% IPV victims report symptoms consistent with brain injury, induced by strangulation or impact
- Rate of IPV is 2-3x higher in Indigenous women and they experience more severe violence
- Many professionals who work in the gender-based violence, and other sectors are not educated in brain injury and lack tools to support survivors
- Many IPV survivors do not know they may have experienced brain injury



Survivors of Abuse and Brain Injury Through Research (SOAR)

Majority of participants have experienced at least 1 episode of IPV-TBI

Strangulation associated with more severe IPV-TBI

Number of symptoms greater than that observed in acute sport-related concussion

Reductions in cognitive-motor function associated with severity of IPV-BI

Effects of IPV-BI intersect with comorbidities (i.e., PTSD, depression, anxiety, etc)

BRAIN INJURY
<https://doi.org/10.1080/02699052.2019.1658129>



Characterizing symptoms of traumatic brain injury in survivors of intimate partner violence

Jonathan D. Smirl^a, K. Elisabeth Jones^a, Paige Copeland^a, Omeeth Khatri^b, Edward H. Taylor^c, and Paul Van Donkelaar^a on behalf of the Canadian Traumatic brain injury Research Consortium (CTRC)

Journal of Neurotrauma
XX: 1–8 (XXXX 00, 2021)
Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2021.0042

Journal of
Neurotrauma

ORIGINAL ARTICLE

CLINICAL STUDIES

Characterization of Cognitive-Motor Function in Women Who Have Experienced Intimate Partner Violence-Related Brain Injury

Naomi Maldonado-Rodriguez,^{1,*} Clara Val Crocker,^{1,*} Edward Taylor,² K. Elisabeth Jones,¹ Krystal Rothlander,¹ Jon Smirl,³ Colin Wallace,¹ and Paul van Donkelaar¹; on behalf of the Canadian Traumatic Brain Injury Research Consortium

Ethico-legal considerations of screening for brain injury in women who have experienced IPV



- Background:
 - Family law has a history of discriminatory treatment of women
 - Most judges will prioritize inclusion of both parents in ongoing care of children
- Methods: Semi-structured interviews based on hypothetical scenarios explored the impact of IPV-BI on parenting disputes with n=12 family law lawyers
- Results: A positive BI may:
 1. Influence the defense of the accused abuser by counsel
 2. Influence the aid status of the woman as well as pose barriers to obtaining IPV-informed legal counsel
 3. Set a legal precedent for decision-making
 4. Adversely bias perceptions of the parenting ability of women compared to men

Summary

- Research on TBI in special contexts is in its infancy
- InTBIR is poised to play a leadership role in consulting with persons with expertise in vulnerable populations
- A less nihilistic approach to TBI in special contexts is a worthy goal



Examples of expertise needed

(and who were consulted for this presentation)

- **Amanda McCormick**, Associate Professor, School of Criminology and Criminal Justice, University of the Fraser Valley
- **Judy Illes**, UBC Distinguished Scholar and Professor of Neuroethics, Professor of Neurology, University of British Columbia
- **Karen Mason**, Co-founder and director of community practice for SOAR (Supporting Survivors of Abuse and Brain Injury through Research), former Executive Director of Kelowna Women's Shelter



Acknowledgments

Amanda McCormick

Judy Illes

Paul van Donkelaar

Karen Mason

William Panenka

InTBIR Working Groups:

Roger Zemek

Raquel Gardner

Ramon Diaz-Arrastia





Global Health

Peter Hutchinson
NIHR Global Health
Research Group on Neurotrauma

Global discrepancy in TBI outcome

11000 trauma deaths per year

Quality of care and outcomes of TBI vary throughout the world

Lancet Neurology Commission on TBI

IMPACT studies

3.3 times difference in odds of unfavourable outcome between centres
at the extremes of the outcome range (2.5th vs 97.5th percentiles)

CRASH trial (includes LMICs)

6.6 times difference

Casemix, management, and mortality of patients receiving emergency neurosurgery for traumatic brain injury in the Global Neurotrauma Outcomes Study: a prospective observational cohort study

*David Clark, Alexis Joannides, Amos Olufemi Adeleye, Abdul Hafid Bajamal, Tom Bashford, Hagos Biluts, Karol Budohoski, Ari Ercole, Rocío Fernández-Méndez, Anthony Figaji, Deepak Kumar Gupta, Roger Härtl, Corrado Iaccarino, Tariq Khan, Tsegazeab Laeke, Andrés Rubiano, Hamisi K Shabani, Kachinga Sichizya, Manoj Tewari, Abenezer Tirsit, Myat Thu, Manjul Tripathi, Rikin Trivedi, Bhagavatula Indira Devi, Franco Servadei, David Menon, Angelos Kolias, Peter Hutchinson, on behalf of the Global Neurotrauma Outcomes Study collaborative**

Interpretation Patients receiving emergency neurosurgery for TBI differed considerably in their admission characteristics and management across human development settings. Level of human development was associated with mortality. Substantial opportunities to improve care globally were identified, including reducing delays to surgery. Between-hospital variation in mortality suggests changes at an institutional level could influence outcome and comparative effectiveness research could identify best practices.

Lancet Neurol 2022; 21: 438–49

Published Online

March 16, 2022

[https://doi.org/10.1016/](https://doi.org/10.1016/S1474-4422(22)00037-0)

S1474-4422(22)00037-0



Overall mortality was 18% (299 of 1635)

Adjustment for casemix, the odds of mortality relative to the very high HDI tier

greater in the medium HDI tier (2.84, 1.55–5.2)

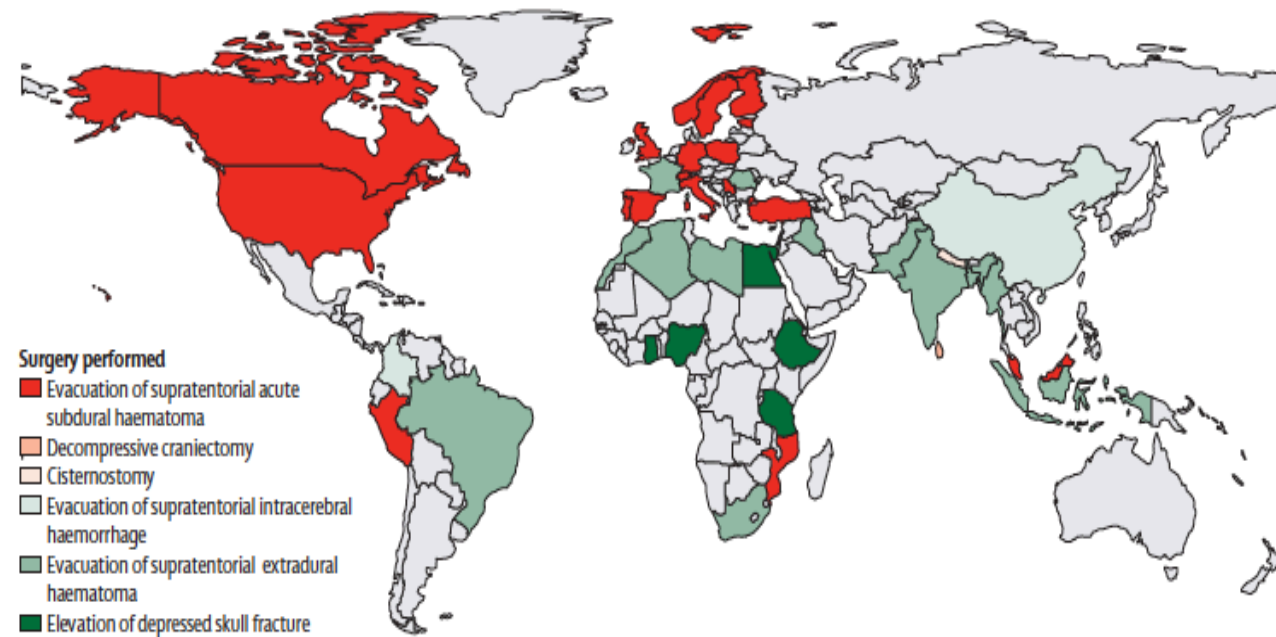
greater in the high HDI tier (2.26, 1.23–4.15)

less in the low HDI tier (1.66, 0.61–4.46)

Significant between-hospital variation in mortality (median OR 2.04, 95% CI 1.17–2.49)



E Most common surgical procedure



Median time from injury to surgery was 13 h (IQR 6–32)



Access to care

Patients in countries with medium and low levels of human development temporal delays to surgery, lack of access to CT scanning, intensive care and ICP monitoring.

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

DECEMBER 27, 2012

VOL. 367 NO. 26

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

Randall M. Chesnut, M.D., Nancy Temkin, Ph.D., Nancy Carney, Ph.D., Sureyya Dikmen, Ph.D., Carlos Rondina, M.D.,
Walter Videtta, M.D., Gustavo Petroni, M.D., Silvia Lujan, M.D., Jim Pridgeon, M.H.A., Jason Barber, M.S.,
Joan Machamer, M.A., Kelley Chaddock, B.A., Juanita M. Celix, M.D., Marianna Cherner, Ph.D., and Terence Hendrix, B.A.,
for the Global Neurotrauma Research Group*

BEST-TRIP
Only 45% patients
transported to the
first hospital by
ambulance



CENTER TBI 89.6% of patients received emergency care at scene of incident in Europe

v

only 5.8% in India

LMIC: when to perform a CT head scan

- Depends on access!
- Depends on funding
- Many places limited to one scan per patient

ICU care

Lack of ICU beds often results in severe TBI being managed in the emergency department or wards with less monitoring, physiological support, and medical attention.

ICU beds are generally allocated on a first-come, first-served basis in the absence of triage support.

The most critical limitations to care are not lack of advanced technology, but the availability of ICU beds, ventilators, monitors.

Rehabilitation



In Europe, 16.3 % were discharged from hospital to a rehabilitation facility versus 0.4% in India

MAP 6: EARLY
INPATIENT REHAB.
FOR HI PTS. ABLE
TO OBEY
COMMANDS/CO-
OPERATE
(REHABILITATION
CATEGORY 40)

Global institutional and Governmental initiatives

Road traffic safety

WHO Decade for Action on Road Safety in 2021

Aims to reduce traffic related deaths and injuries by at least 50% by 2030

Implemented following the adoption of resolution A/RES/74/299 "Improving global road safety" by the UN General Assembly

FIA (Federation Internationale de l'Automobile) Action for Road safety

Launched in support of the UN Decade of Action for Road Safety

4 key priorities: Advocacy at the highest levels, action by clubs on the ground, involvement of the motor sport community and campaigns & partnerships.

The National Highways Authority India (NHAI)

Seeking bids for providing free emergency clinical care for automotive incidents occurring on highways connecting Delhi-Mumbai-Chennai, Chennai-Kolkata, Kolkata-Agra, Agra-Delhi Corridors (the "Golden Quadrilateral").

The World Bank Road Safety Project in Bangladesh

Pilot comprehensive road safety measures, including improved engineering designs, signing and marking, pedestrian facilities, speed enforcement, and emergency care on two major highways in Bangladesh

**Investigator-
led initiatives
Improving
care provision
and
stimulating
research**

- The NIH/Fogarty-International-Research-Institute funded Global Neurotrauma Research Group Focus is on Spanish speaking countries in Central and South America, with a central aim to build capacity and implement/test protocols for TBI management in LMICs

- NIHR Global Health Research Group on Neurotrauma

- The overarching mission is to improve global neurotrauma care.

- Four main themes are identified:

 - Mapping TBI Care,

 - Understanding TBI care,

 - Innovation in TBI

 - Measuring & nurturing research capacity.

- 57 countries are involved in the collaboration.



NIHR Global Health Research Group on Neurotrauma



Theme 1

Global Neurotrauma Outcomes Study (GNOS)

Global Epidemiology and Outcomes in TBI (GEO-TBI)

Detailed hospital based registry for TBI management:
(Zam-Cam)

Global Prevention Of Neurotrauma-Road Traffic Collisions
(GPONT-RTC)

Global Health
Research Group
on Neurotrauma



GEO-TBI



Global Epidemiology and Outcomes in
Traumatic Brain Injury

An international registry to support care and research excellence in traumatic brain injury

Aims

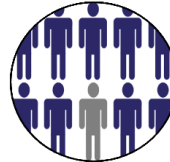
Global collaboration



ASSEMBLE

Provide robust
epidemiological data and
enable research collaboration

Care challenges



BENCHMARK

Enable clinical auditing
programmes to improve
neurotrauma treatment

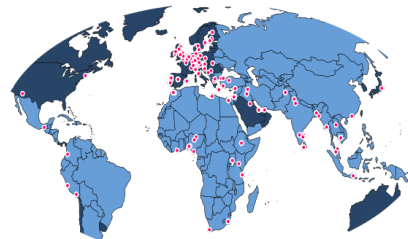
Local utility



EMPOWER

Provide infrastructure for
high-quality data collection
and archiving

Registry dataset and inclusion criteria were developed based on international consensus



Any centre treating TBI is eligible to join!

Inclusion criteria

Neurosurgical admission with TBI
ICU admission with TBI
Operation due to TBI

Concise dataset

Baseline, admission, imaging,
treatment and outcome data points

Benchmarking against a global
standard is enabled via the
online ORION platform

The platform encourages
straight-forward data sharing
and research collaboration

Data ownership and means of
use remain with the
participating centres



e-mail geotbi@orion.net



<https://www.neurotrauma.world>



UNIVERSITY OF
CAMBRIDGE

A Systems Improvement Approach to TBI (ASIA-TBI)

Using a systems engineering approach to understand TBI care in Yangon General Hospital, Myanmar

Qualitative approach using narrative analysis

Aim is to derive systems maps based on the experience of clinicians, patients, families, and other stakeholders, and then use these redesign the TBI service



Cambridge
Global Health Partnerships



Where is the Partnership for a Global Problem?

People

Who are the stakeholders?

What are their needs?

Systems

Who / what are the elements?

What are the interactions?

What is the model?



Open access

Original research

BMJ Open Systems approach to improving traumatic brain injury care in Myanmar: a mixed-methods study from lived experience to discrete event simulation

Katharina Kohler ^{1,2} Phyu Phyu Nwe Myint,³ Sein Wynn,⁴ Alexander Komashie,^{5,6} Robyn Winters,⁷ Myat Thu,⁴ Mu Mu Naing,⁸ Thinn Hlaing,⁹ Rowan Burnstein,^{7,10} Zaw Wai Soe,¹¹ John Clarkson,¹² David Menon ¹, Peter John Hutchinson ^{2,3} Tom Bashford ^{2,12}



Innovation in traumatic brain injury care

Technology, clinical practice, & data collection

- develop innovative technologies & practices to improve neurotrauma care
- targeting system optimisation
- surgical intervention
- long-term outcome data collection
- rehabilitation (family)



Detection of haematoma



Follow up / outcome assessments

Miss S Pollard
1 Chapel Hill
Heswall
BOURNEMOUTH
BH1 1AA



Traumatic brain injury research capacity

Capacity, output, and training

- map current research capacity and output
- create network of institutions engaged in international clinical trials
- develop appropriate formal research skills training

Academic outputs



- 14 partner institutions across the world
- Local, national and international research projects
- Projects range from public health to clinical trials
- >30 supported LMIC PIs & research fellows
- >50 peer-reviewed publications
- >40 national and international presentations

www.neurotrauma.world/outputs

- Advocating at international, national and local levels
- International guidelines drawn up and disseminated
- Informing national policy in partner countries
- Engaged in service redesign at multiple sites
- Engaged in training and clinical mentorship
- Formal programme of research capacity building
- Strong medical student engagement



www.neurotrauma.world

Conclusion

- The issues of improving prevention, advancing care, and stimulating research in LMIC settings are huge
- Current efforts should be strengthened, and new efforts developed.
- Reverse translation
- Policy implementation





NeuroTrauma 2024

31 August – 5 September 2024



NeuroTrauma 2024
CAMBRIDGE • UNITED KINGDOM

Questions?



InTBIR

International Initiative for
Traumatic Brain Injury Research



InTBIR

International Initiative for
Traumatic Brain Injury Research

“Temporal Profile of blood Tau, pTau
Biomarker levels in rodent and
human TBI might be different”

Dr Kevin Wang

This presentation has been removed from the slide deck because it contained unpublished material. If you would like further information, please contact the presenter at

kawangwang17@gmail.com.



Penn Medicine

Long-term Outcomes after TBI: Leveraging Data from Existing Epidemiologic Studies

Andrea Schneider, MD, PhD

Assistant Professor

Department of Neurology, Division of Neurocritical Care

Department of Biostatistics, Epidemiology, and Informatics

Perelman School of Medicine at the University of Pennsylvania

July 16, 2022

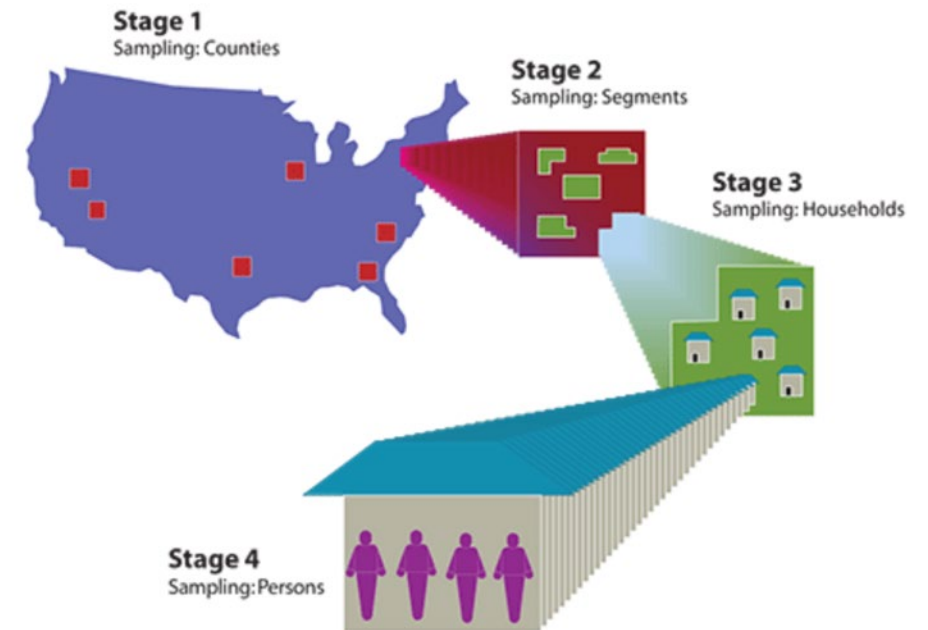


Long-term Outcomes After TBI

- ▶ How do we study long-term outcomes after TBI when very few studies designed to study TBI from the time of injury have long-term follow-up (i.e., 20-30+ years)?
- ▶ How do we obtain nationally representative estimates of the burden of TBI and its outcomes?
- ▶ How do we study the impact of TBI among community-dwelling individuals?
- ▶ **Leverage data from ongoing, deeply phenotyped epidemiologic studies**
 - National Health and Nutrition Examination Survey (NHANES)
 - Atherosclerosis Risk in Communities (ARIC) Study
 - Many other existing epidemiologic studies with opportunities to study TBI

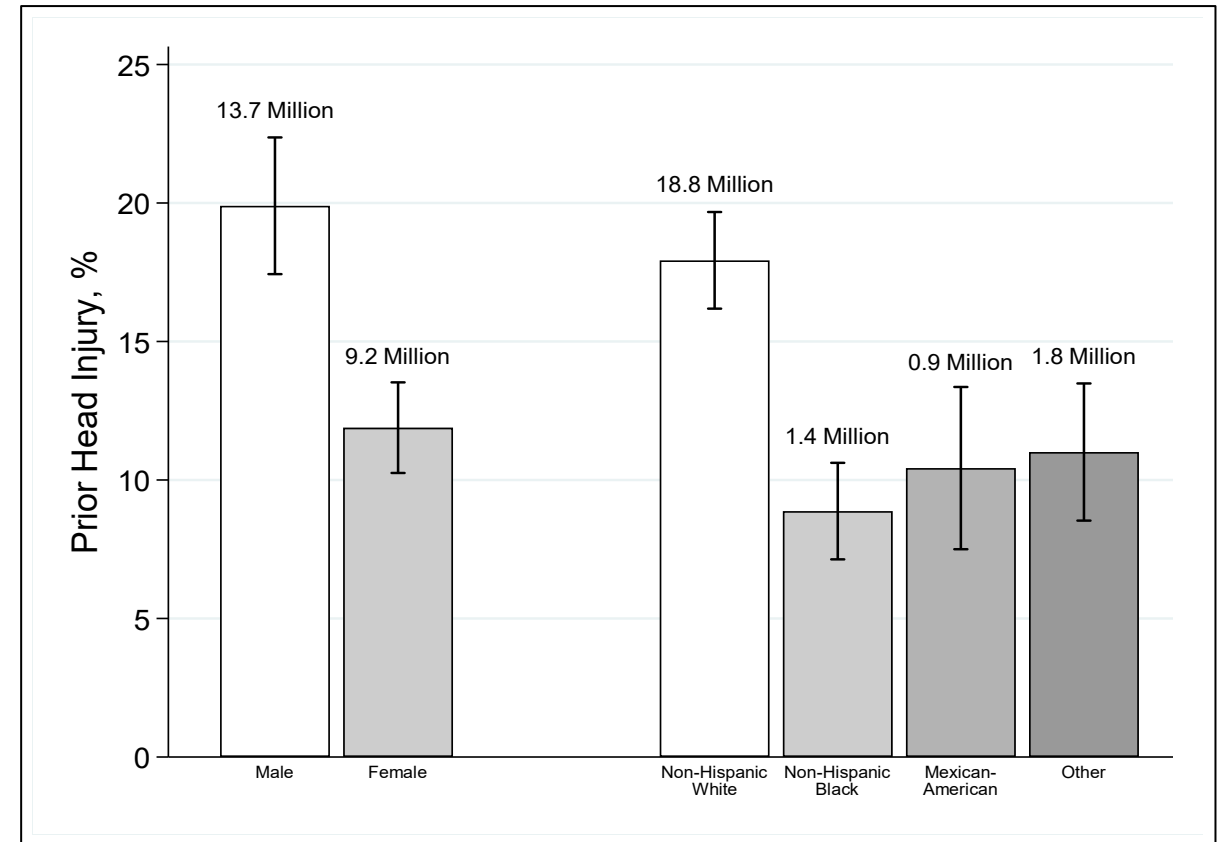
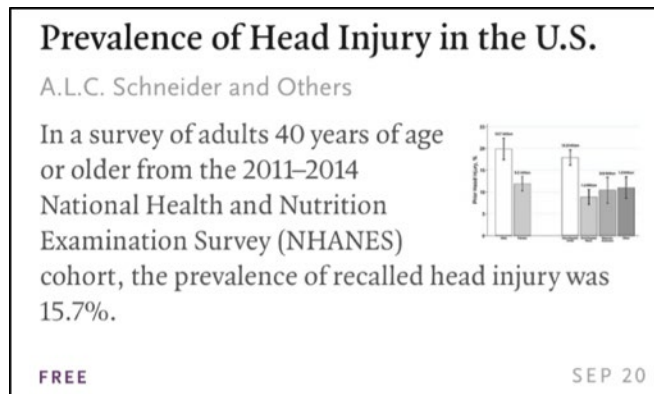
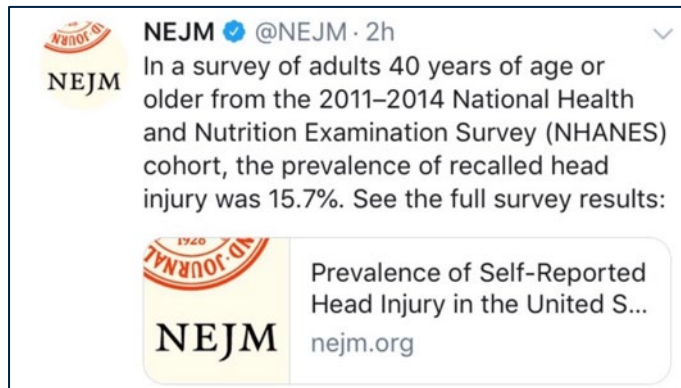
National Health and Nutrition Examination Survey (NHANES)

- ▶ NHANES is series of cross-sectional surveys conducted yearly (starting in 1999) by the National Center for Health Statistics of the Centers for Disease Control and Prevention
- ▶ Participants are selected using a stratified multi-stage probability sampling design of the noninstitutionalized civilian U.S. population
- ▶ Survey weights to account for the complex NHANES sampling design make the estimates reported nationally representative of this general U.S. population
- ▶ Head injury was assessed among individuals aged 40 years or older during the 2011-2012 and 2013-2014 survey cycles using the question, “Have you ever had a loss of consciousness because of a head injury?”



Prevalence of Prior Head Injury in the United States

- ▶ The overall prevalence of prior head injury with loss of consciousness was 15.7%, which corresponds to 22.9 million affected U.S. adults aged 40 years or older

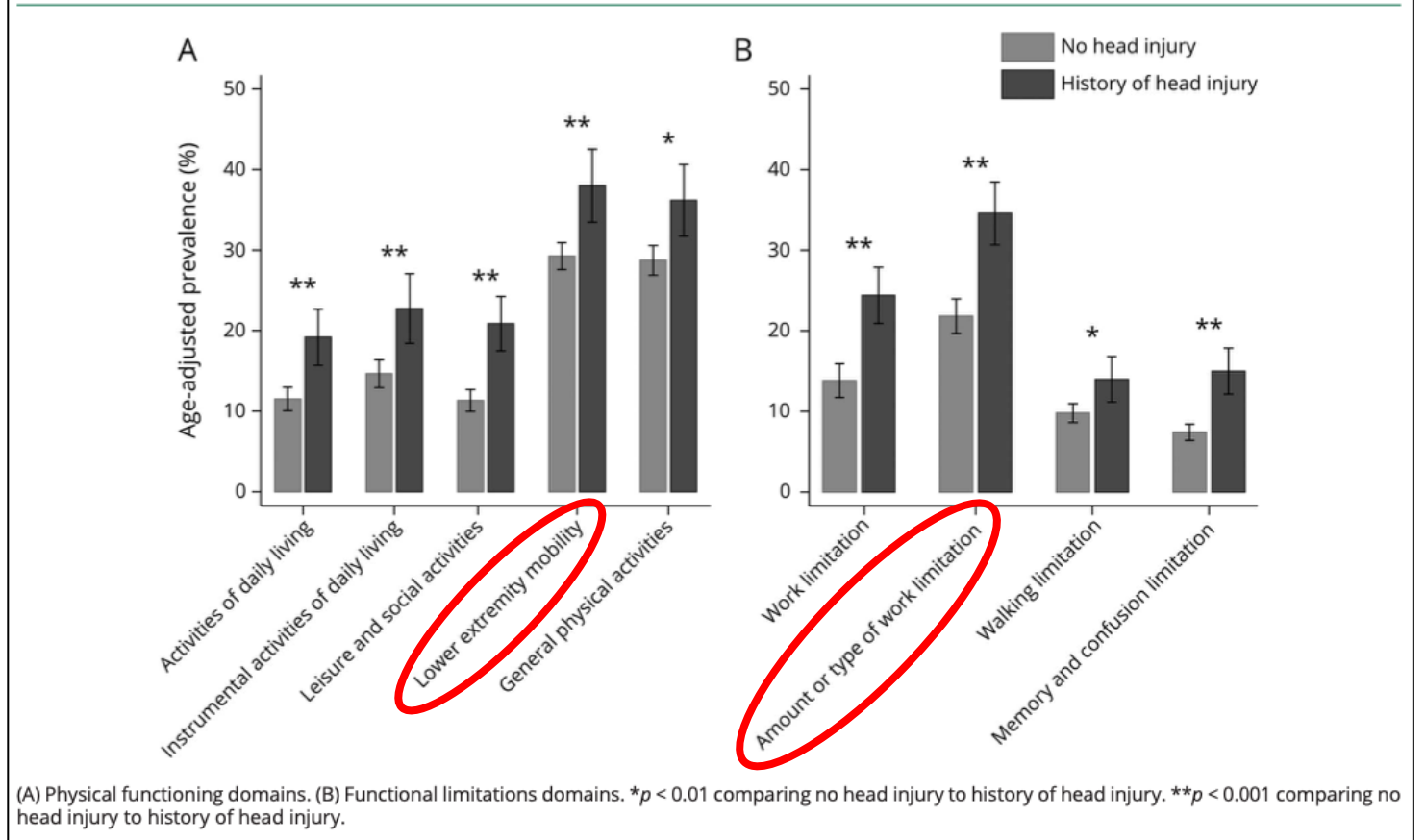


Prevalence of Disability Associated with Prior Head Injury

- Individuals with a history of head injury had higher prevalence of disability in at least 1 domain of functioning compared to individuals without head injury (47.4% versus 38.6%, $p < 0.001$).



Figure 2 Age-Adjusted Prevalence (95% confidence interval) of Disability by History of Head Injury With Loss of Consciousness



Atherosclerosis Risk in Communities (ARIC) Study



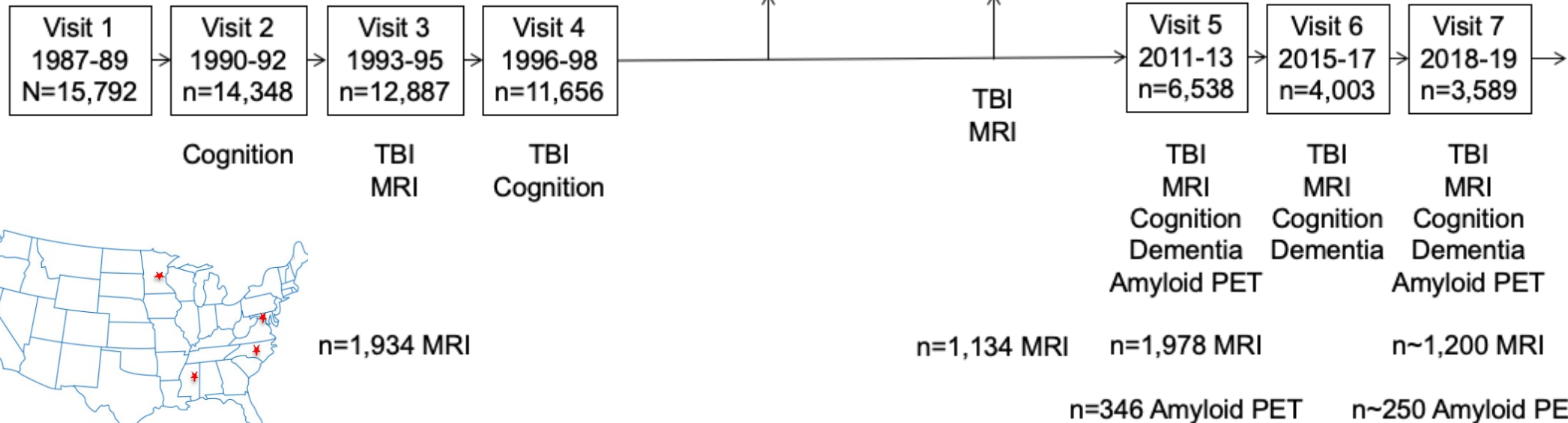
Hospitalization, and Centers for Medicare/Medicaid Surveillance – ICD-9/10 Codes for TBI

Continuous Death, Stroke, Coronary Heart Disease, Heart Failure, Dementia Adjudication

Annual and Semi-Annual Telephone Follow-up Calls

On-going community-based prospective cohort of 15,792 middle-aged adults (aged 45-65 at baseline) from 4 U.S. communities

- Very low loss to follow-up over 30 years: ~1-2%
- Death over 30-years: ~55%



ARIC Study TBI / Head Injury Definition



Visit-Based Self-Report Questions

ARIC Visit 3 (1993-1995) 1. Have you ever had a head injury which led you to see a physician or seek hospital care? 2. How many times has this happened? 3. How many of these head injuries resulted in your losing consciousness, no matter how briefly? 4. In what year was your head injury for which you sought medical care?
ARIC Visit 4 (1996-1998) 1. Have you ever had a major head injury? That is, one that resulted in your losing consciousness, no matter how briefly, or that led you to see a physician or seek hospital care? 2. How many times has this happened? 3. How many head injuries resulted in your losing consciousness, no matter how briefly? 4. In what year was your head injury for which you lost consciousness sought medical care?
ARIC Brain MRI Visit (2004-2006)* 1. Have you ever had a head injury that resulted in loss of consciousness (knocked out)? 2. How many times? 3. In what year or how old were you when this first occurred? 4. In what year or how old were you when this last occurred?
ARIC Visit 5 (2011-2013)* 1. Have you ever had a head injury that resulted in loss of consciousness? 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? 3. Have you had a head injury that resulted in long-term problems or dysfunction?
ARIC Visit 6 (2016-2017) 1. Have you ever had a head injury that resulted in loss of consciousness? 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? 3. Have you had a head injury that resulted in long-term problems or dysfunction?
ARIC Visit 7 (2018-2019) 1. Have you ever had a head injury that resulted in loss of consciousness? 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? 3. Have you had a head injury that resulted in long-term problems or dysfunction?

*Questions asked in a subgroup of ARIC participants selected for brain magnetic resonance imaging scans.

Continuously Collected ICD-9/10 Codes

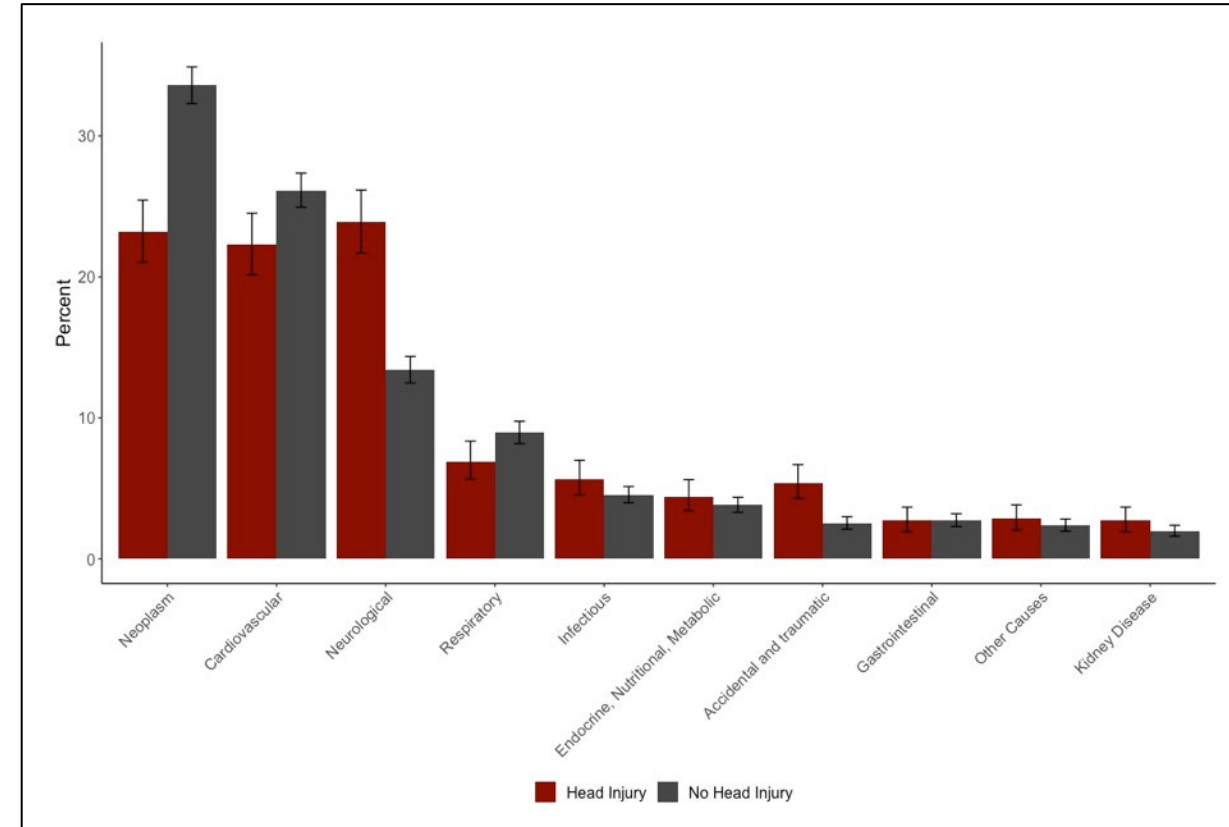
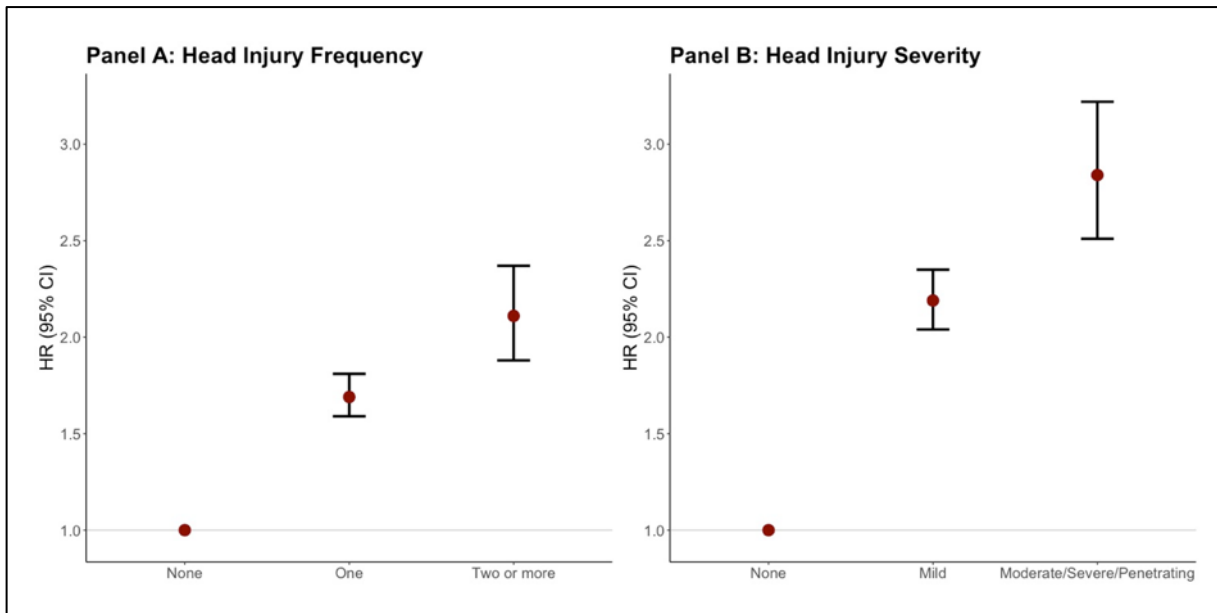
ICD-9 Codes	
800.xx	Fracture of vault of skull
801.xx	Fracture of base of skull
803.xx	Other and unqualified skull fractures
804.xx	Multiple fractures involving skull or face with other bones
850.xx	Concussion
851.xx	Cerebral laceration and contusion
852.xx	Subarachnoid, subdural, and extradural hemorrhage following injury
853.xx	Other and unspecified intracranial hemorrhage following injury
854.xx	Intracranial injury of other and unspecified nature
959.01	Head injury, unspecified
ICD-10 Codes	
S02.0	Fracture of vault of skull
S02.1X	Fracture of base of skull
S02.8	Fractures of other unspecified skull and facial bones
S02.91	Unspecified fracture of skull
S04.02	Injury of optic chiasm
S04.03X	Injury of optic tract and pathways
S04.04X	Injury of visual cortex
S06.X	Intracranial injuries, concussion, traumatic cerebral edema, diffuse and focal traumatic brain injury, traumatic epidural, subdural, and subarachnoid hemorrhage
S07.1	Crushing injury of skull

Head Injury and Mortality

- ▶ Prospective cohort study of 12,204 ARIC participants (19% with head injury)
- ▶ Head injury was associated with 2 times increased risk of mortality over a median of 28 years



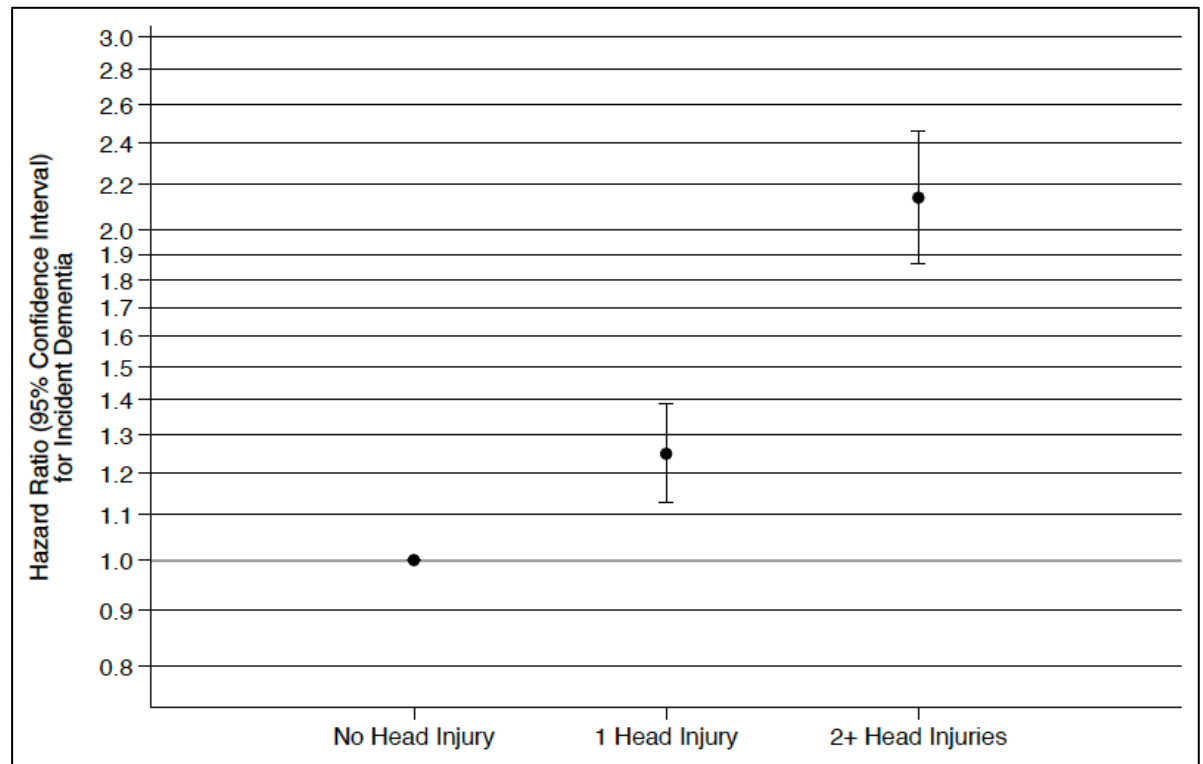
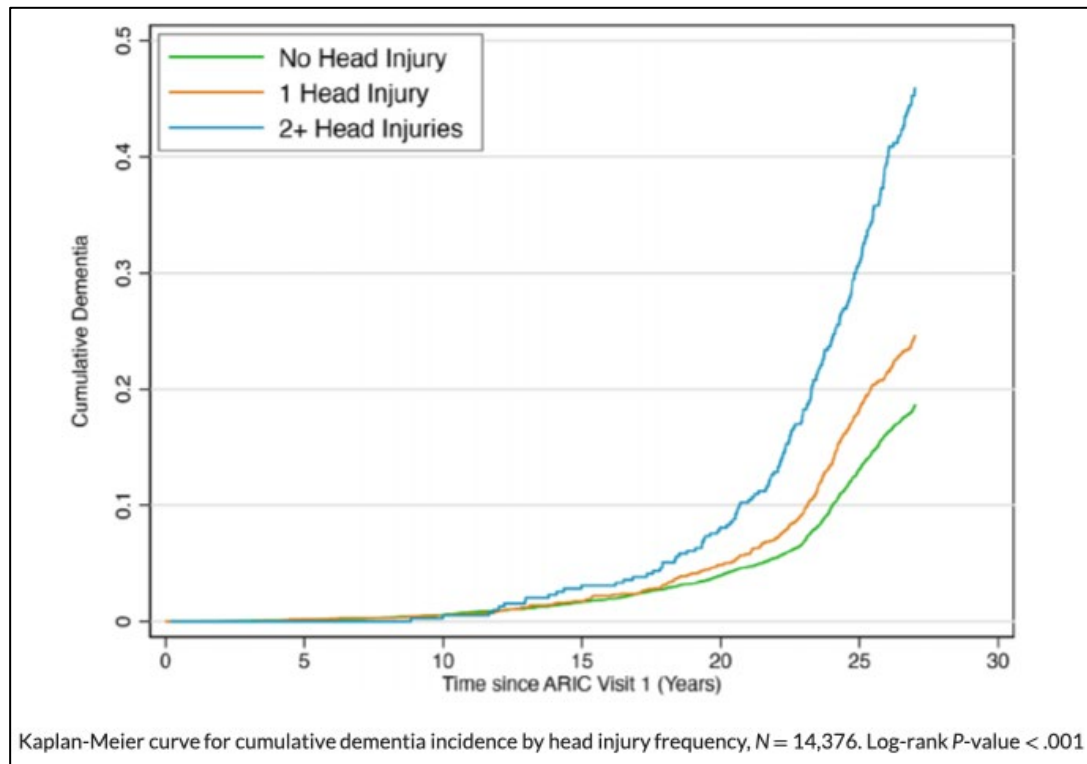
Holly Elser, MD, PhD



Head Injury and Dementia Risk



- ▶ Head injury was associated with a 1.44 times (95% CI: 1.32-1.57) increased dementia risk over a median of 25 years of follow-up among 14,376 white and black ARIC study participants (24% with head injury)



Head Injury and 20-Year Cognitive Decline



	20-year Z-Score Decline (95% CI)	Difference in Z-Score (95% CI)	Percent Additional Decline (95% CI)
Global			
No Head Injury	-0.88 (-0.91, -0.84)	Reference	Reference
Head Injury	-1.01 (-1.07, -0.95)	-0.13 (-0.19, -0.08)	14.8% (9.5%, 20.9%)
Delayed Word Recall			
No Head Injury	-1.08 (-1.14, -1.03)	Reference	Reference
Head Injury	-1.23 (-1.31, -1.15)	-0.15 (-0.23, -0.06)	13.9% (6.8%, 20.2%)
Digit Symbol Substitution			
No Head Injury	-0.76 (-0.79, -0.73)	Reference	Reference
Head Injury	-0.82 (-0.86, -0.78)	-0.06 (-0.10, -0.02)	9.2% (4.1%, 12.7%)
Word Fluency			
No Head Injury	-0.21 (-0.24, -0.18)	Reference	Reference
Head Injury	-0.30 (-0.35, -0.25)	-0.09 (-0.13, -0.04)	42.9% (22.2%, 54.2%)

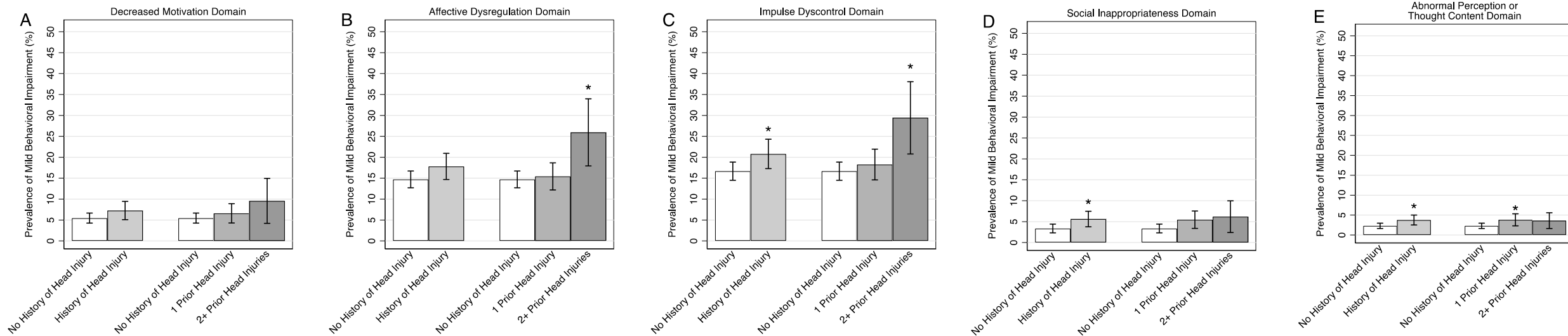
Head Injury and 20-Year Cognitive Decline



	20-year Z-Score Decline (95% CI)	Difference in Z-Score (95% CI)	Percent Additional Decline (95% CI)
Global			
No Head Injury	-0.88 (-0.91, -0.84)	Reference	Reference
Head Injury	-1.01 (-1.07, -0.95)	-0.13 (-0.19, -0.08)	14.8% (9.5%, 20.9%)
Delayed Word Recall			
No Head Injury	-1.08 (-1.14, -1.03)	Reference	Reference
Head Injury	-1.23 (-1.31, -1.15)	-0.15 (-0.23, -0.06)	13.9% (6.8%, 20.2%)
Digit Symbol Substitution			
No Head Injury	-0.76 (-0.79, -0.73)	Reference	Reference
Head Injury	-0.82 (-0.86, -0.78)	-0.06 (-0.10, -0.02)	9.2% (4.1%, 12.7%)
Word Fluency			
No Head Injury	-0.21 (-0.24, -0.18)	Reference	Reference
Head Injury	-0.30 (-0.35, -0.25)	-0.09 (-0.13, -0.04)	42.9% (22.2%, 54.2%)

Head Injury and Mild Behavioral Impairment

- ▶ Cross-sectional study of 2,534 participants attending ARIC Visit 5 in 2011-2013 (32% with prior head injury)
- ▶ Mild behavioral impairment domains assessed using the neuropsychiatric symptoms inventory



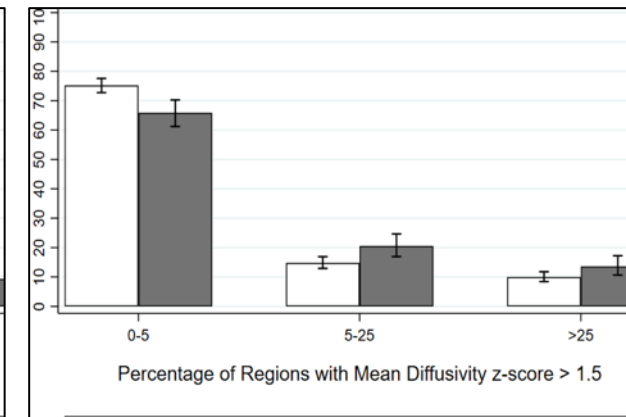
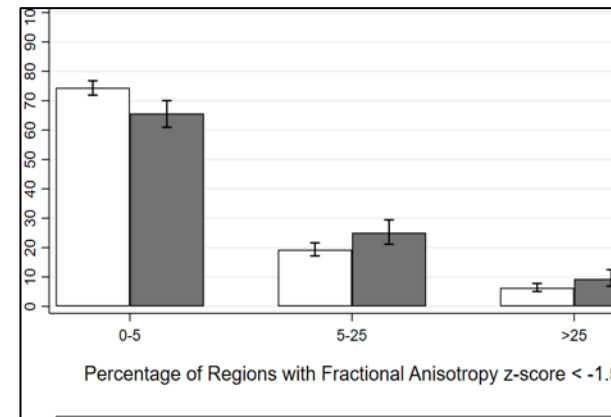
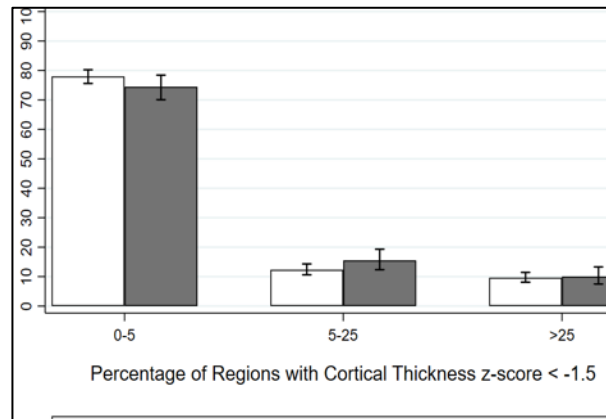
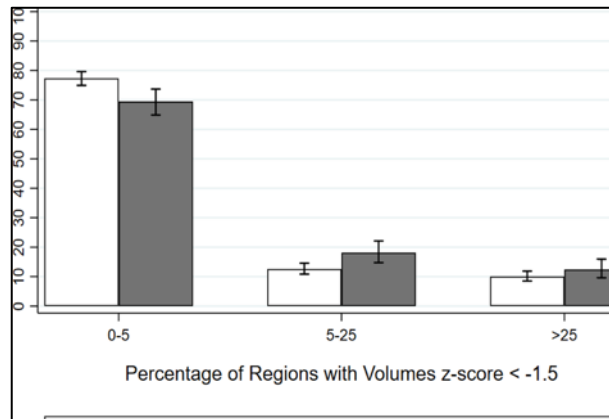
Head Injury and Long-Term Brain MRI Findings



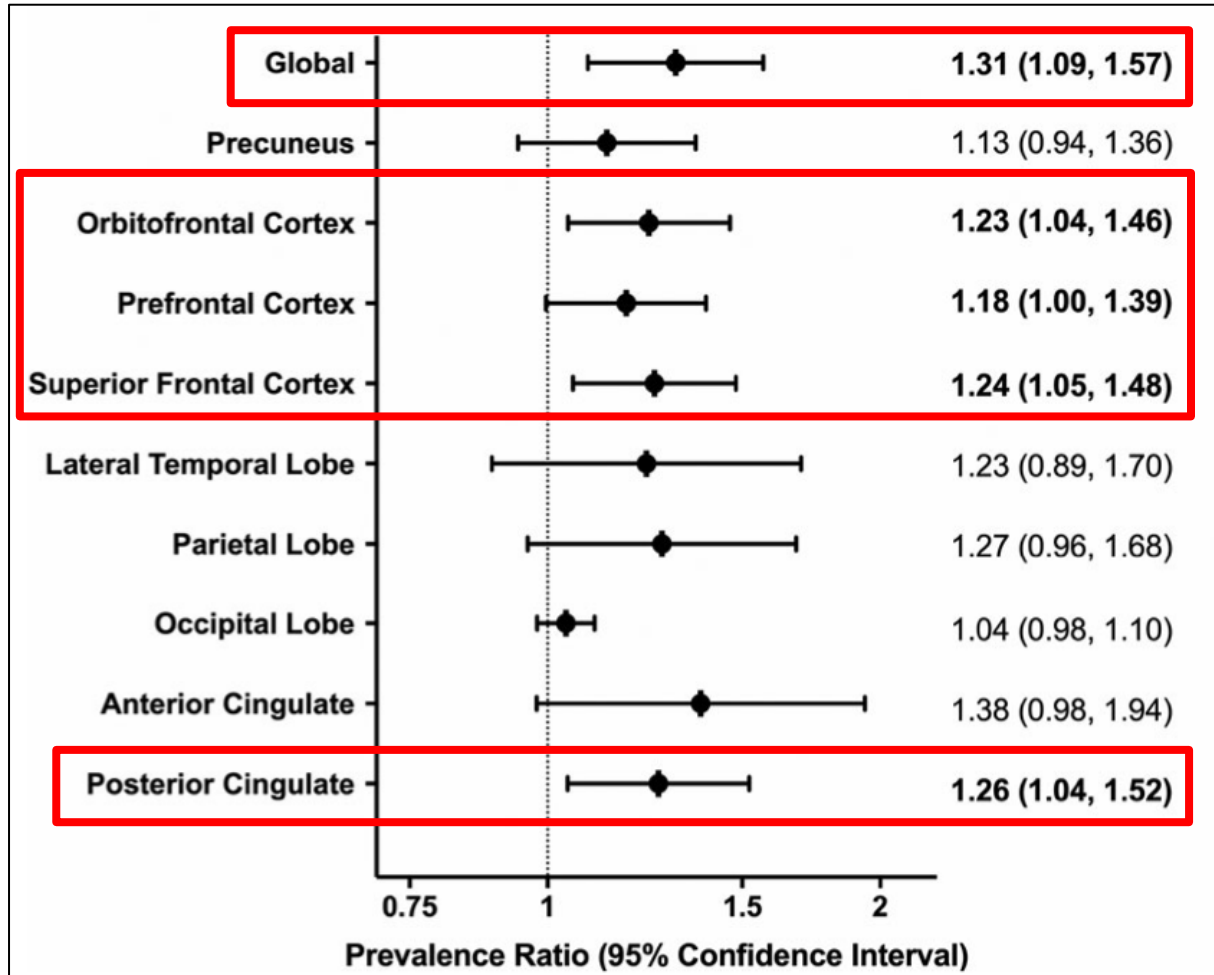
- Cross-sectional study of 1,642 participants attending ARIC Visit 5 in 2011-2013 who underwent a brain MRI scan (26% with head injury, scan occurring a median of 38 years after first head injury)



Alexa Walter, PhD



Head Injury and Brain Amyloid Deposition



- ▶ Cross-sectional analysis of 329 white and black ARIC Study participants (mean age 76 years) without dementia (81 with prior head injury)
 - ▶ Brain amyloid deposition assessed using Florbetapir (^{18}F) PET imaging
-
- ▶ Number of head injuries was also associated with elevated brain amyloid deposition in a dose-dependent manner globally, and in the orbitofrontal, prefrontal, and superior frontal cortex cortices.

Head Injury and Olfaction



- ▶ Cross-sectional study of 5,951 participants attending ARIC Visit 5 in 2011-2013 (28% with head injury)
- ▶ Subjective Olfaction: “Do you suffer from smell loss or a significantly decreased sense of smell?”
- ▶ Objective Olfaction: 12-item Sniffin’ Sticks Odor Identification Test

	No Head Injury OR (95% CI)	Head Injury OR (95% CI)	No Head Injury OR (95% CI)	1 Head Injury OR (95% CI)	2+ Head injuries OR (95% CI)
Subjective Olfactory Function					
Subjective Olfactory Dysfunction Versus No Subjective Olfactory Dysfunction	1 (Reference)	1.16 (1.01, 1.34)	1 (Reference)	1.11 (0.95, 1.29)	1.35 (1.06, 1.71)
Objective Olfactory Function					
Objective Hyposmia Versus Normosmia	1 (Reference)	1.11 (0.94, 1.30)	1 (Reference)	1.06 (0.89, 1.27)	1.27 (0.95, 1.71)
Objective Anosmia Versus Normosmia	1 (Reference)	1.15 (0.97, 1.38)	1 (Reference)	1.01 (0.83, 1.24)	1.72 (1.27, 2.32)

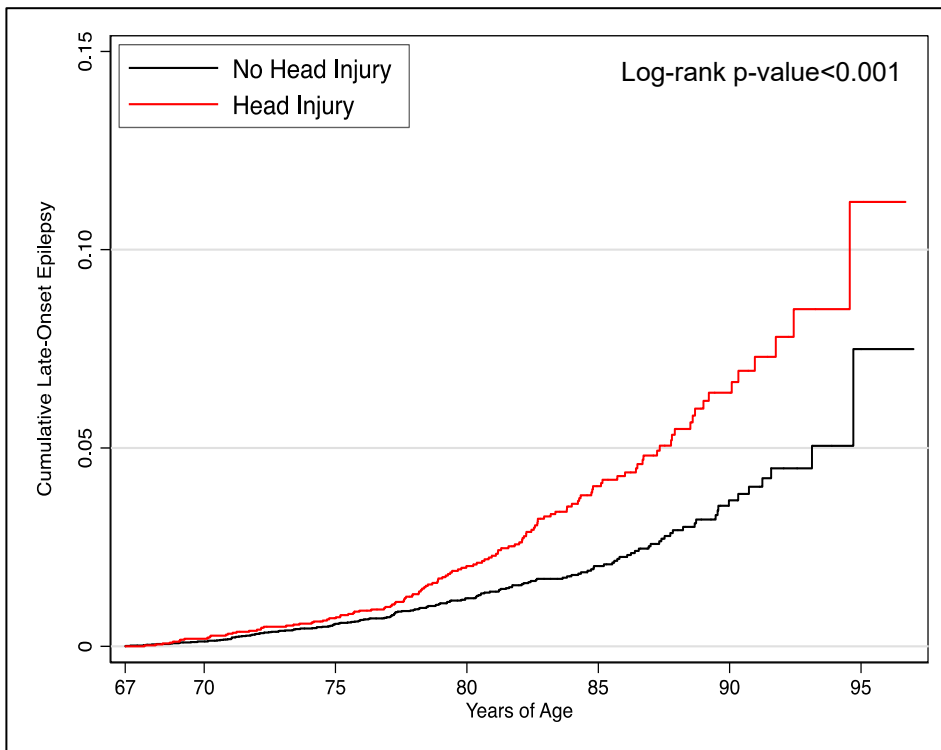
Model adjusted for age, sex, race, field center, education, military veteran status, smoking, alcohol consumption, diabetes, depression, and cognitive status.



Post-traumatic Epilepsy



- Among 8,878 participants (aged 67+ years, 55.1% women, 21.6% black, 30% with prior head injury), head injury was associated with a 1.88 times (95% CI 1.44-2.43) increased risk of epilepsy over a median of 11 years follow-up.



	Hazard Ratio (95% Confidence Interval)
Any head Injury	1.88 (1.44-2.43)
Number of head injuries	
0 head injuries	1 (Reference)
1 head injury	1.37 (1.01-1.88)
2+ head injuries	3.55 (2.52-5.02)
Head Injury Severity	
No head injuries	1 (Reference)
Mild head injury	1.63 (1.20-2.21)
Moderate/severe head injury	3.37 (2.17-5.25)

Head Injury and Physical Function and Frailty



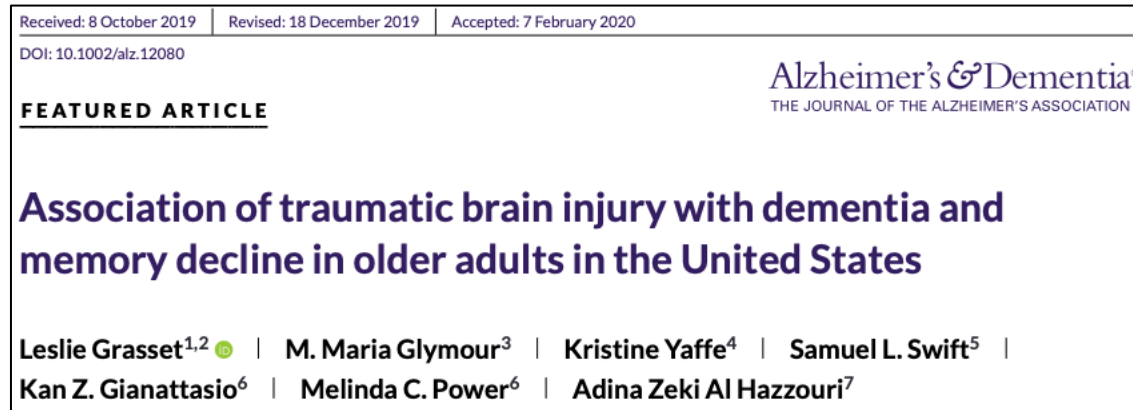
Katherine Hunzinger, PhD

- ▶ Cross-sectional analysis of 5,598 participants (27% with prior head injury) who attended ARIC Visit 5 in 2011-2013
- ▶ Physical function assessed using the Short Physical Performance Battery (SPPB)
- ▶ Frailty definition incorporates measures of weight loss, exhaustion, slow walking speed, low physical activity, and low grip strength

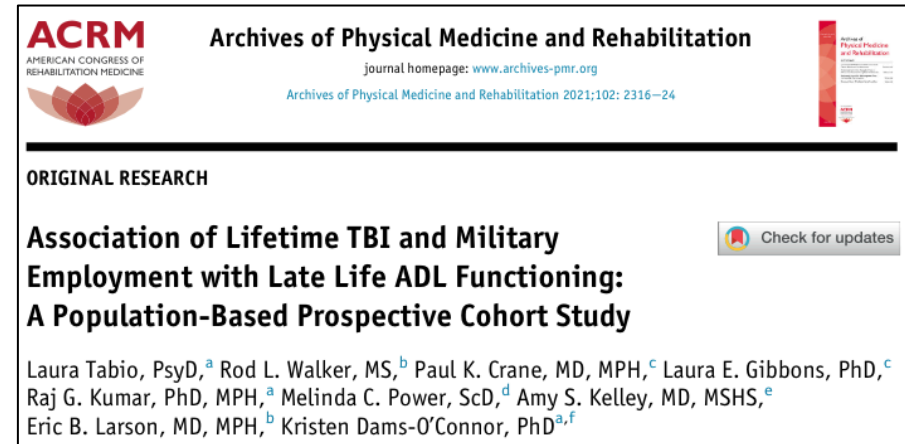
	No Head Injury (n=4,065)	Head Injury (n=1,533)
SPPB Chair Stand	1 (Reference)	1.03 (0.91, 1.17)
SPPB Balance	1 (Reference)	1.16 (1.00, 1.35)
SPPB Gait Speed	1 (Reference)	1.26 (1.02, 1.56)
SPPB Composite	1 (Reference)	1.32 (1.09, 1.59)



Examples of Other Existing Epidemiologic Studies with TBI Data



Health and Retirement Study (HRS)



Adult Changes in Thought (ACT) Study



1946 British Birth Cohort



Nurses' Health Study II Cohort

Conclusions

- ▶ Leveraging data from ongoing deeply phenotyped epidemiologic studies provides unique opportunities to provide nationally representative estimates of TBI burden, to study long-term outcomes of TBI, and to identify risk factors for TBI events
- ▶ However, these existing epidemiologic studies often do not have detailed information on TBI events
- ▶ Recent attention has been drawn to the importance of adding TBI assessment to ongoing epidemiologic studies, with a FY2022 NINDS Administrative Supplement focused on adding life-time TBI exposure to AD/ADRD cohorts
- ▶ Would advocate to make TBI an adjudicated event in epidemiologic studies, like what is done for cardiovascular disease and stroke events.
- ▶ There is valuable knowledge to be gained from the addition of valid and reliable TBI assessments in epidemiologic studies

Adding TBI Assessments to AD/ADRD Cohorts NOT-NS-22-022. These administrative supplements will provide funding to existing NINDS-funded AD/ADRD relevant cohort studies to support the inclusion/addition of NINDS Common Data Elements (CDEs) for life-time exposure to TBI (Ohio State University TBI Identification Form), other FITBIR CDE for life-time TBI exposure measures (e.g. FITBIR Injury History Form) or Brain Injury Screening Questionnaire (BISQ), and other relevant TBI-related NINDS CDEs to current clinical assessment batteries. Data will be available to better understand the prevalence of TBI history in these populations and could be hypothesis generating for studying the pathophysiology underlying TBI as a risk factor for AD/ADRDs. The deadline to submit applications has passed.

Acknowledgements

Collaborators

- ▶ Ramon Diaz-Arrastia, MD, PhD - University of Pennsylvania
- ▶ Danielle Sandsmark, MD, PhD - University of Pennsylvania
- ▶ James Gugger, MD, PhD - University of Pennsylvania
- ▶ Josef Coresh, MD, PhD - Johns Hopkins University
- ▶ Elizabeth Selvin, PhD, MPH - Johns Hopkins University
- ▶ Rebecca Gottesman, MD, PhD - NIH/NINDS
- ▶ Thomas Mosley, PhD - University of Mississippi
- ▶ Dan Wang, MS - Johns Hopkins University
- ▶ Alexa Walter, PhD - University of Pennsylvania
- ▶ Holly Elser, MD, PhD - University of Pennsylvania
- ▶ Katherine Hunzinger, PhD - University of Pennsylvania

Funding

- ▶ Andrea Schneider, MD, PhD: NIH Loan Repayment Program (2018-2022), DoD W81XWH-21-1-0590 (2021-2024), NIH/NINDS K23NS123340 (2022-2027), Penn University Research Foundation Award (Fall21-5221994427) (2022-2024)
- ▶ ARIC Study: NHLBI HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, HHSN268201100012C
- ▶ ARIC Neurocognitive Study: NINDS, NHLBI, NIA, NIDCD U01HL096812, U01HL096814, U01HL096899, U01HL096902, U01HL096917

Thank You!

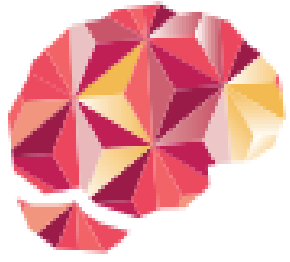
- ▶ Please reach out to me if you have any questions or are interested in collaboration!
- ▶ Email: Andrea.Schneider@pennmedicine.upenn.edu

Questions?



InTBIR

International Initiative for
Traumatic Brain Injury Research



InTBIR™

International Initiative for
Traumatic Brain Injury Research

Coffee

International Initiative for Traumatic Brain Injury Research (InTBIR) General Assembly and Scientific Meeting

Connect to wifi:

RITZ_CONFERENCE

Password: ritz2022

Presentations will resume at 15:15 CEST

Working group

Data science and harmonization

Prof. Hester Lingsma, Erasmus MC

Dr. Lindsay Nelson, Medical College of Wisconsin

Dr. Mathew Abrams, INCF

Why data harmonization?

Clear benefit of cross-study analysis:

- Increased precision
- Sufficient numbers for subgroup analysis, e.g. less common TBI subtypes
- Using heterogeneity
 - Learn about generalizability
 - Comparative effectiveness studies

Harmonization upfront

The IMPACT project

- Bringing together 11 datasets of clinical trials (n=8) and observational studies (n=3)
- Five years of at least 2 fte and 20.000 lines of code to harmonize 'Core' variables
- Incentive to Common Data Elements

Harmonization in theory.....

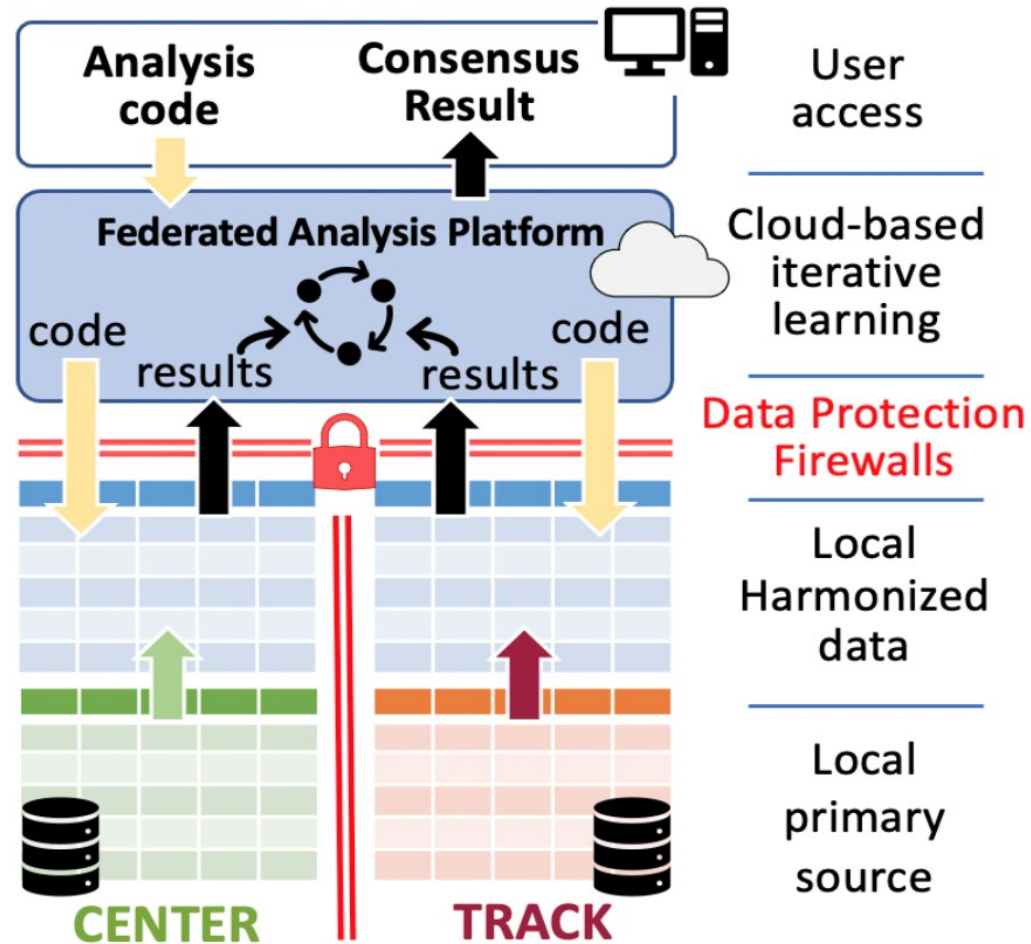
- Practice shows that in-depth knowledge of data is crucial
 - GOSE is interpreted differently in the EU (“all-cause” disability including extracranial injuries) and the US (TBI-specific disability)
- Just bringing ‘harmonized’ data together is not enough, and potentially even misleading
- **‘Deep harmonization’** to be certain that same label also means the same

If harmonized in practice.....

- Study level (meta analysis):
 - Easy
 - Not all advantages of combined data
 - Only more conventional analysis
- Patient level:
 - Allows really joint analysis
 - Complicated for sensitive health data in the current regulatory environment
 - Not compatible with efforts spend on collecting data

Bring the analyses to the data instead of the data to the analysis

Federated data analysis



TRACER-TBI (**TRACK**- TBI and **CENTER**-TBI)

Challenges in federated data analysis

- Tools exist for implementation of standard statistical analyses, but implementation of e.g. machine learning approaches requires further support
- Balancing FAIR data principles with the importance of inside knowledge of the data
 - Governance structures
 - Solutions to make access to data and analysis plans dynamic
- Data-sharing typically happens after a study
 - Mechanisms to fund maintenance of data, sharing and appropriate guidance to external researchers
 - Inclusion of an appropriate budget and planning in the original grant award

Our working group

“The Data Science and Harmonization working group will act as a source of expertise for global researchers working towards data harmonization and infrastructure interoperability for traumatic brain injury research”

Specific activities:

- Advocate harmonized data collection
- Establish the state-of-the-art in data harmonization and federated analysis in the field of TBI
- Harmonization and mapping CDEs between different IntBIR projects
- Development of platforms and tools to ease the burden of data sharing by the international community (INCF)

Join us!

h.lingsma@erasmusmc.nl, linelson@mcw.edu, mathew@incf.org

InTBIR Website

<https://www.intbir.incf.org>



Ramon Diaz-Arrastia, MD, PhD

University of Pennsylvania

Philadelphia, PA USA



InTBIR

InTBIR is a coalition of scientists and other stakeholders to foster coordinated and collaborative TBI research

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Who we are



Our Mission



Resources



Join InTBIR

Hosted by INCF

- International Neuroinformatics Coordinating Facility
- INCF Mission:
 - To develop, evaluate, and endorse standards and best practices that embrace the principles of Open, FAIR, and Citable neuroscience
 - Provide training on how standards and best practices facilitate reproducibility and enables the publishing of the entirety of research output, including data and code
- Composed of researchers, infrastructure providers, industry, and publishers from 18 countries, spanning 4 continents committed to the Mission

INCF National Nodes



INCF Member Countries

- Governing Countries (Actively Contribute)
 - Canada
 - Norway
 - Sweden
- Associate Nodes (no longer contribute). Collaborate but do not vote
 - Australia
 - Belgium
 - Czech Republic
 - Finland
 - France
 - Germany
 - India
 - Italy
 - Japan
 - Korea
 - Malaysia
 - Poland
 - The Netherlands
 - United Kingdom
 - United States

How can the InTBIR Website be most useful?

- List of members (facilitate networking)
- List of funded studies
- Clearinghouse for materials and resources
 - Protocols, SOPs, CRFs, CDEs
 - Imaging studies (CTs, MRIs, others)
 - Biological samples
- Warehouse for InTBIR work products
- Ideaboard
- **OTHER IDEAS?**



InTBIR™
International Initiative for
Traumatic Brain Injury Research

Policy Engagement

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



TRACK-TBI
Transforming Research and Clinical Knowledge
in Traumatic Brain Injury

International Traumatic Brain Injury Research Initiative



CENTER-TBI
Collaborative European NeuroTrauma Effectiveness Research in TBI
A 2020 vision: Generating knowledge for improving TBI outcomes



**TBI
Endpoints
Development**

A collaborative for advancing diagnosis and treatment of TBI

Traumatic brain injury: *progress and challenges* in prevention, clinical care, and research

THE LANCET
Neurology

2022

Neurotrauma researchers traditionally seek translation of their research results through publication, clinical guidelines, and industry collaborations. However, to effectively impact clinical care and outcome, interactions are also needed with **research funders, regulators, and policy makers, and partnership with patient organisations.**

Traumatic brain injury: integrated approaches to
improve prevention, clinical care, and research



"Traumatic brain injury is a public health challenge of vast, but insufficiently recognised, proportions. Concerted efforts are urgently needed to address deficiencies in prevention, care, and research."

**A Commissioned Issue
on TBI presented at the
European Parliament
on Nov 7th, 2017**

Examples of Regulatory and Policy Engagement

The UK All Party Parliamentary Group on Acquired Brain Injury (APPG ABI)

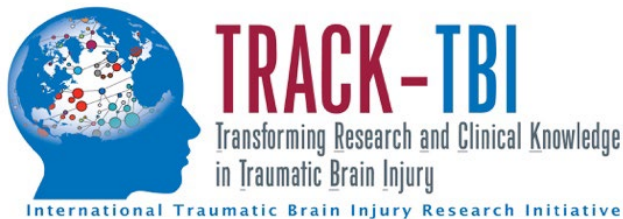
- Launched 2017 by non-partisan group of Members of Parliament
- Broad input facilitated by UK Acquired Brain Injury Forum
- 2018 launched “Time for Change”, addressed issues in neurorehabilitation, education, criminal justice system, sports-related concussion, and welfare benefits
- Informed parliamentary debates and development of government policy

Examples of Regulatory and Policy Engagement



Regulatory Pathways for Biomarkers in TBI

March 2016



TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI



TBI Endpoints Development Initiative

A collaborative for advancing diagnosis and treatment of TBI

FDA and Regulatory Expert Collaborations & Pathways

FDA Letter of Support to explore neuroimaging biomarkers (03/13/2017)

Seed Project advances to Qualification Stage of MDDT pathway

Rancho Biosciences imaging annotation tool and MDDT potentially deployed to future clinical trials

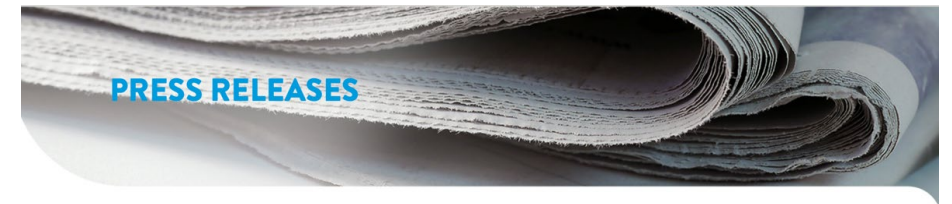
FDA Letter of Support to explore biofluid biomarkers (01/18/2018)

Regulatory progress in biofluid biomarker space: De Novo request granted by FDA to Banyan Biomarkers (02/14/2018)

Abbott Laboratories accepted into FDA Breakthrough Devices Program for the iSTAT[®] (March 2018)

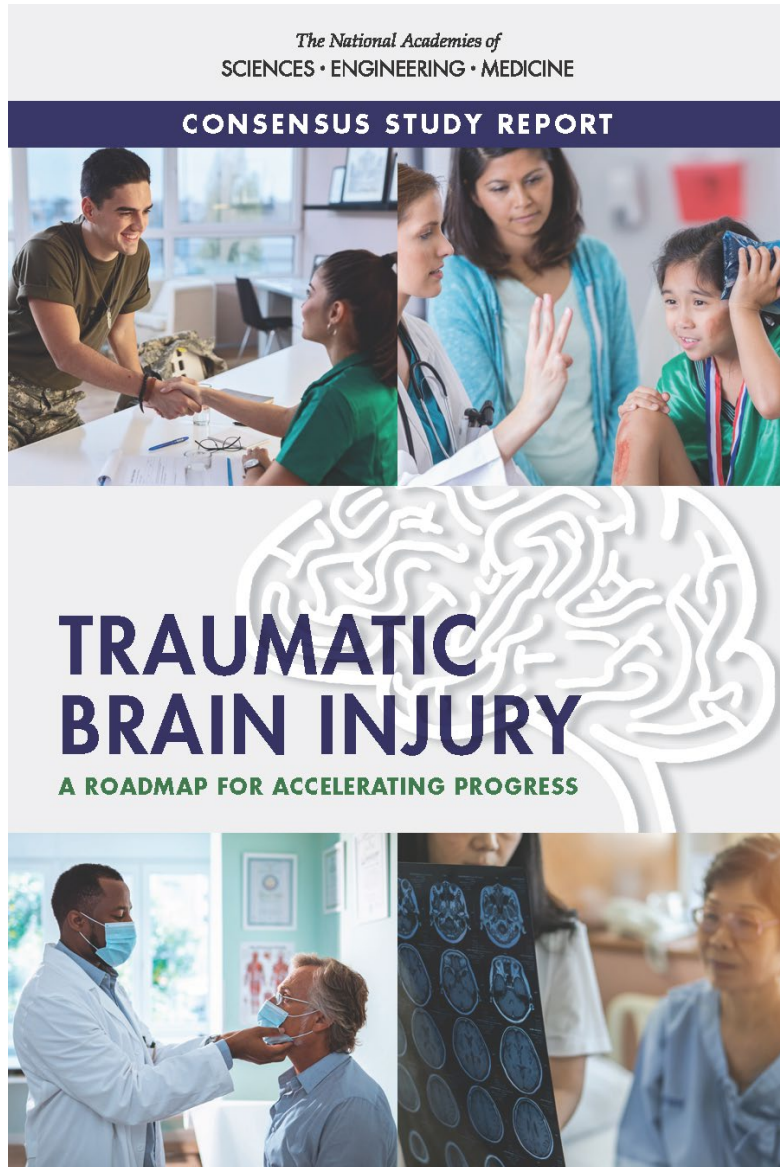


January, 2021



[BACK TO PRESS RELEASES](#)

ABBOTT RECEIVES FDA 510(K) CLEARANCE FOR THE FIRST RAPID HANDHELD BLOOD TEST FOR CONCUSSIONS



Traumatic Brain Injury: A Roadmap for Accelerating Progress

Committee on Accelerating Progress in Traumatic
Brain Injury Research and Care

*The National
Academies of*

SCIENCES
ENGINEERING
MEDICINE

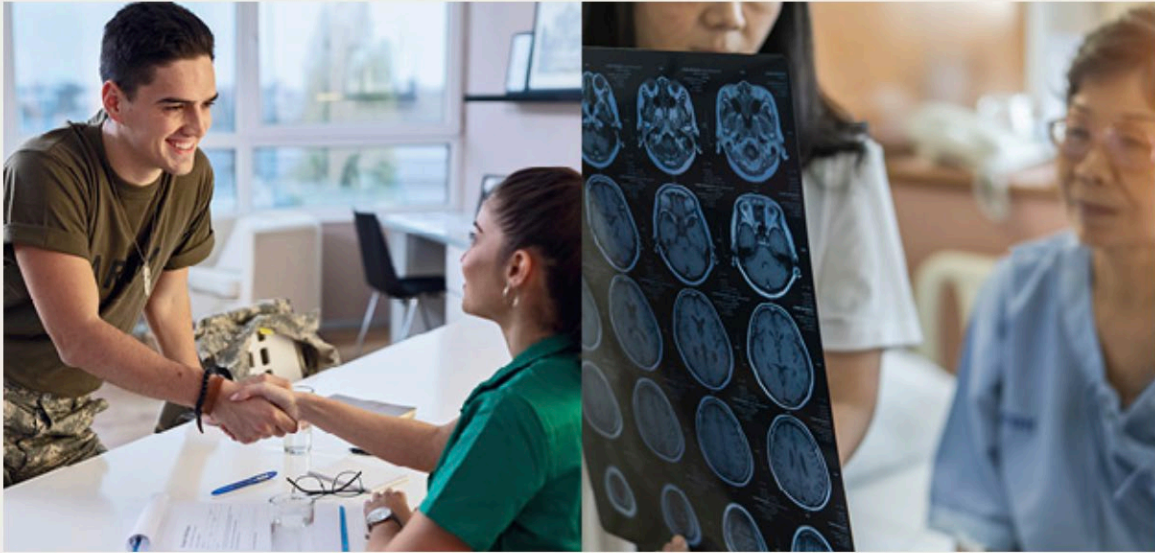
RECOMMENDATIONS

- 1** **Create** and implement an **updated classification system** for TBI.
- 2** **Integrate** **acute** and **long-term** person- and family-centered **management** of TBI.
- 3** **Reduce** unwarranted **variability** and **gaps** in administrative and clinical **care guidance** to assure high quality care for TBI.
- 4** **Enhance** **awareness** and **identification of TBI** by healthcare providers and the public.
- 5** **Establish** and reinforce local and regional **integrated care delivery systems** for TBI.
- 6** **Integrate** the TBI system of **care** with TBI **research** into a **learning system**.
- 7** **Improve** the quality and **expand** the range of **TBI studies** and **study designs**.
- 8** **Create** and **promulgate** a **national framework** and **plan** for improvement of TBI care.

*The National
Academies of*

SCIENCES
ENGINEERING
MEDICINE

Forum on Traumatic Brain Injury



Foster multi-disciplinary relationships and cross-sector collaboration across the diverse TBI stakeholder community

Inspire action to improve TBI research and care systems along the full continuum from prevention through acute care, rehabilitation, and return

Inform policy dialogues and priority setting to advance TBI research and care.

Questions?



InTBIR

International Initiative for
Traumatic Brain Injury Research

Fluid management in critically ill traumatic brain injury patients

STUDY PROPOSAL: A feasibility randomized clinical trial

Mathieu van der Jagt, MD
Associate professor
Dept Intensive Care Adults
Erasmus MC Rotterdam, The Netherlands
m.vanderjagt@erasmusmc.nl





Fluid balance and outcome in critically ill patients with traumatic brain injury (CENTER-TBI and OzENTER-TBI): a prospective, multicentre, comparative effectiveness study

*Eveline Janine Anna Wiegers, Hester Floor Lingsma, Jilske Antonia Huijben, David James Cooper, Giuseppe Citerio, Shirin Frisvold, Raimund Helbok, Andrew Ian Ramsay Maas, David Krishna Menon, Elizabeth Madeleine Moore, Nino Stocchetti, Diederik Willem Dippel, Ewout Willem Steyerberg, Mathieu van der Jagt, on behalf of the CENTER-TBI and OzENTER-TBI Collaboration Groups**

Lancet Neurol 2021; 20: 627–38

New answers, new questions!

- Was there residual confounding in spite of best efforts to adjust in center-level analyses?
- What is the best design for a clinical trial on fluid management in TBI?
- How to define control and intervention groups?
- Interaction of fluid strategy with CPP?
 - fluid versus vasopressors to optimise CPP?

Steering committee

- Dr. Antonio Messina, Dr. Chiara Robba
- Prof. Dr. Fabio Taccone, Dr. Mathieu van der Jagt
- Statistician: Prof. Dr. Hester Lingsma



OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

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Erasmus MC



Feasibility trial: Intervention

CONTROL	INTERVENTION
• Fluid management as per routine practice • No standard advanced or invasive HD monitoring	CCO-guided fluid management • <u>AIM</u>: fluid restriction guided by absent fluid responsiveness (FR-), as assessed with continuous CO monitoring • <i>Definition FR-: CO increase <5% upon mini-fluid challenge (= rapid 100-150ml bolus < 60-120s)*</i> • aFR: refrain from further fluid bolus; decrease maintenance fluids and re-assess FR every 4 hours

*Monnet et al. Ann Intensive Care 2022

Interventions

CONTROL	INTERVENTION
• Fluid management as per routine practice • No standard advanced or invasive HD monitoring	CCO-guided fluid management • <u>AIM</u>: fluid balance absent • <i>Overarching goal is to prevent fluid administration/bolus when CO increase is unlikely</i> • <i>FR increase < 5%</i> • <i>Challenge (= rapid FR increase < 60-120s)*</i> • <i>Prevent further fluid bolus; decrease maintenance fluids and re-assess FR every 4 hours</i>

*Monnet et al. Ann Intensive Care 2022

Management of **low CPP**

CONTROL	INTERVENTION
• As per routine practice; may use fluid bolus, vasopressor or combination	CCO-guided fluid management • FR-: start or increase vasopressor (no fluid bolus) • FR+: titrate with mini-fluid challenge(s) according to CO response

Inclusion criteria

- Adult TBI patients (>17 years) admitted to ICU
- Estimated ICU admission >72 hours
- Hemodynamically stable as judged by treating physician:
 - No active bleeding loss
 - Vasoactive drugs mainly for reversal of sedative-associated hypotension and CPP maintenance

(*excluding* septic shock or traumatic SIRS-associated shock; requiring active fluid loading next to maintenance fluids)

Exclusion criterion

- Spinal shock
- Extra cranial injury, as long as it results in HD unstable situation as judged by treating physician
- Massive transfusion (>10 PC within first 24 hours after admission to hospital)

Fluid balance calculation

- Difference between
- **fluid input** (all intravenous fluids including any crystalloid, hyperosmotic, or colloid fluids, blood products, enteral fluids, *IV pumps for drugs* and renal replacement therapy fluids) and
- (measurable) **fluid loss** (urine output, enteral losses, drain losses, and dialysis effluent from continuous renal replacement therapy)
- calculated daily mean per day per patient in the ICU
- *Insensible losses*: statistical adjustment with temperature and mechanical ventilation status as covariables for analyses

Outcomes

Primary: % patients with **mean daily fluid balance <500ml at ICU** (calculated up to day 7 after randomisation)

Secondary:

- Glasgow Outcome Scale Extended (GOSE) at 6 m
- mean daily CPP (+ lowest and highest)
- mean daily fluid balance/fluid input
- ICU mortality
- ICU complications (respiratory, cardiological, kidney)
- Need for vasopressors
- 28 days ventilator free days

Power calculation

Primary outcome: proportion of patients with mean daily fluid balance < 500 ml (%)

- 40% control arm
- 60% intervention arm
- sample size = 95

(N=97 when estimated FB difference = 250 ml; SD 0,64L)

Results will be used to determine feasibility for adequately powered MC trial

Points for discussion

- Level of equipoise on fluid management guided by (neutral) fluid balances (w/o CCO)
- Cut-off of 500ml Mean Daily ICU-FB for primary outcome
- Patient-level randomisation vs center-level



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Erasmus MC
Erasmus

BRAINapt

Adaptive Platform Trial in TBI

Alexis Turgeon

on behalf of the BRAINapt investigators

Disclosures

Grant funding:

- Canadian Institutes of Health Research, Canada Research Chair, Canada Foundation for Innovation, Fonds de la Recherche du Québec – Santé

Clinical trial roles:

- **HEMOTION** trial (Trial PI), **REMAP-CAP** platform trial (International Trial Steering Committee, Reporting & Analysis Committee, Immunoglobulin country lead (Canada)); **ATTACC** multiplatform trial (co-PI); **CAN-ADAPT** Canadian National Platform trial (Protocol Development Committee)
- Canadian Traumatic Brain Injury Research Consortium (**CTRC**) (co-Chair), Cochrane Canada Francophone (Chair), Canadian Critical Care Trials Group (**CCCTG**), Perioperative Anesthesia Clinical Trials (**PACT**) Group

What is BRAINapt?

- International Multicenter Adaptive Platform Trial in TBI
- Designed to study different interventions within three specific families of domains: (i) drugs, (ii) devices, (iii) non-drug neither device related.
- Developed on the knowledge gained from the recent pandemic
 - REMAP-CAP multicenter platform trial
 - ATTACC-CAP

What are the benefits of a clinical trial platform?

- Allow the develop an infrastructure for several trials
- Allow to testing of more than one intervention simultaneously
- Allow to efficiently draw conclusions of superiority or futility once sufficient data have accrued
- Allow to add and test novel interventions
- Allow to evaluate potential interactions between interventions

What is BRAINapt?

- **Study Design and population**
 - BRAINapt will enroll critically ill adult patients with traumatic brain injury
 - Real-world pragmatic trial that follows the PRECIS-2 tool criteria
 - Designed using Bayesian statistics

What are the eligibility criteria in BRAINapt?

- **INCLUSION CRITERIA**

- Adult patients (≥ 18 years old)
- Acute moderate or severe acute TBI ($GCS \leq 12$)
- Admitted to an ICU

- **EXCLUSION CRITERIA**

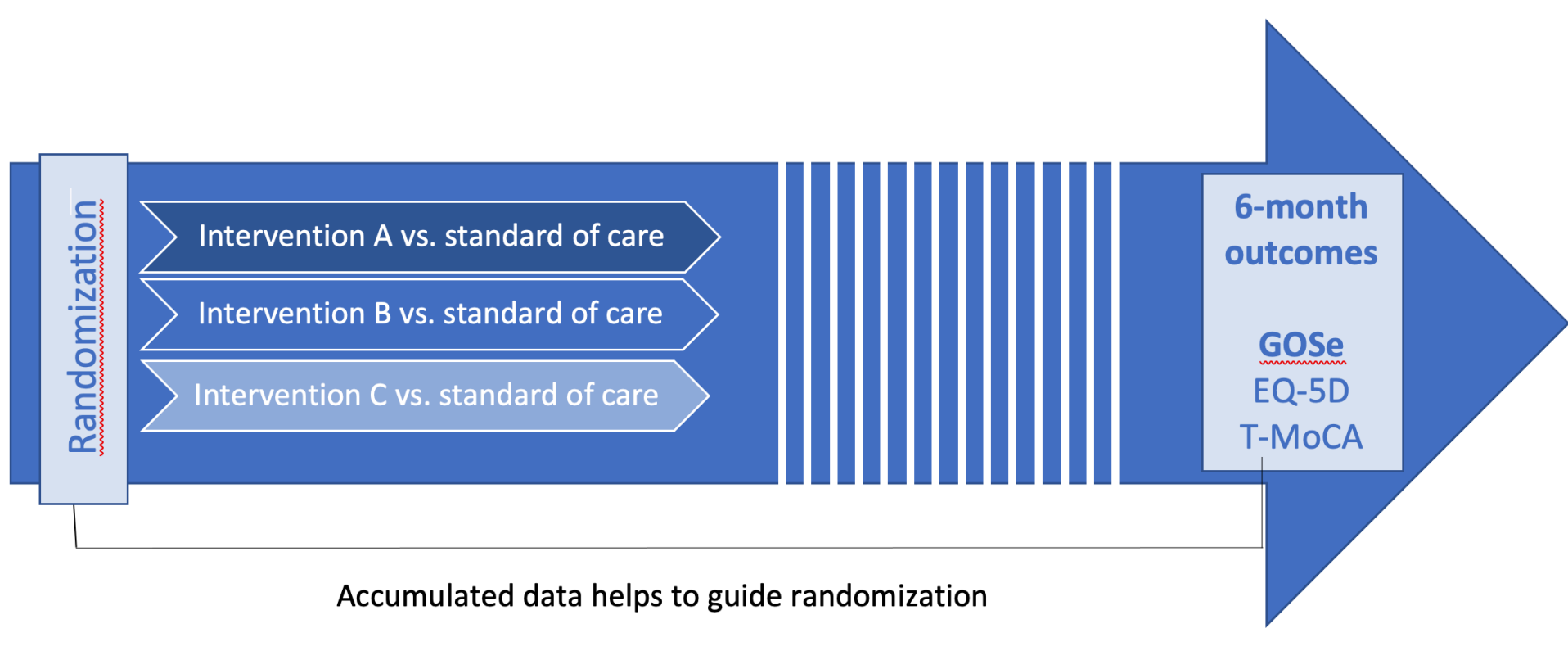
- Contraindication to the intervention on the basis of clinical risk (as per treating physician)
- A decision to withhold or withdraw life-sustaining therapies was made

- **ADDITIONAL ELIGIBILITY CRITERIA ADDED BASED ON THE INTERVENTION STUDIED**

What are the outcome measures?

- **PRIMARY OUTCOME:** Glasgow Outcome Scale extended (GOSe) at 6 months
- **SECONDARY OUTCOMES:** Quality of life (EQ-5D-5L) at 6 months, cognition (T-MoCA) at 6 months, mortality, organ support free days, ICU-free days, ventilator-free days, delirium.

What is BRAINapt?



What is the sample size ?

- Enrolment until pre-specified stopping thresholds are reached:
- **Superiority criteria** defined as $>97.5\%$ posterior probability of proportional OR >1
- **Futility criteria** defined as $<5\%$ posterior probability of proportional OR > 1.25 .
- A maximal sample size of 1500 patients will provide 92% power to detect an OR of 1.25 or 80% power for an OR of 1.2
 - Modeled on event rates from previous trials

First two interventions

- Two intervention in the drug domains
 - **Beta-blockers**
 - Beta-blockers are suggested to control paroxysmal sympathetic hyperactivity that was suggest that could have an impact on long term outcomes
 - **Anticonvulsants**
 - Anticonvulsant are used to prevent early seizures with unknow long term benefit
- These two interventions are currently used in a variable manner at the bedside with limited evidence.

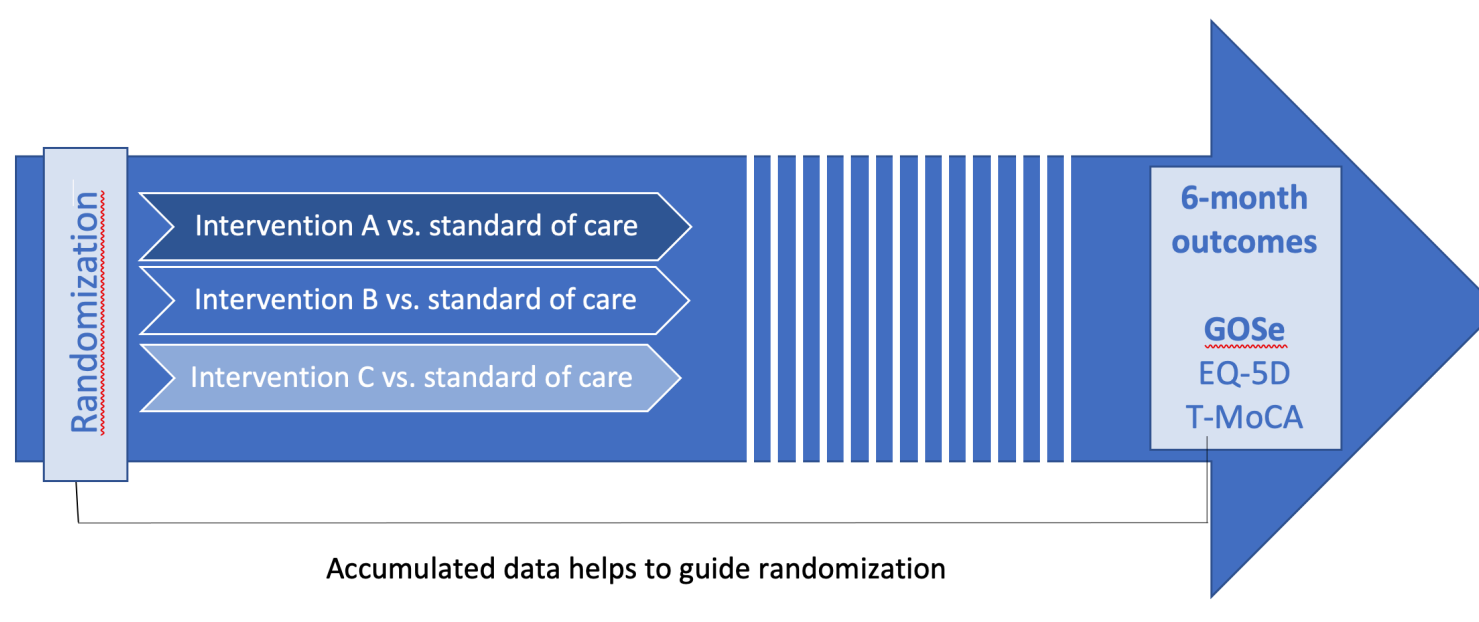
Pragmatic approach

- **Beta-blockers:** Patients will be randomized (1:1 ratio) to receive beta-blockers or no beta-blockers
- **Anticonvulsants:** Patients will be randomized (1:1 ratio) to receive prophylactic anticonvulsants or no anticonvulsants
- Administered up to ICU discharge, death or a decision to withdraw life-sustaining therapies is made
- Patients randomized to the control arm will not receive either drug

Pragmatic approach

- The choice of drug for each intervention will be according to local preferences/practice at each site
 - Lipophilic beta-blocker (most common are metoprolol, propranolol)
 - Any anticonvulsant (most common are phenytoin and levetiracetam)
- At least the minimal therapeutic dose recommended by the manufacturer

What is BRAINapt?



- Patients can be randomised in several interventions
- Interventions can be added over time
- Regions / sites can decide on which interventions they want to participate in

BRAINapt and feasibility

- This platform trial take advantage of the HEMOTION Trial infrastructure
- It builds on our experience with other platform trials (REMAP-CAP, ATTACC-CAP)
- CIHR funding to start

BRAINapt in the long-term

- The overarching goal is to establish a platform trial infrastructure for the TBI community to facilitate the conduction of trials in a timely manner and at lower costs
- We hope the community will join the concept and help developing new coordinating hubs

Questions?



InTBIR

International Initiative for
Traumatic Brain Injury Research



Future funding and developments

David Menon
Joint Coordinator - InTBIR

What should/can/will we use InTBIR for? (I)

- Inventory of ongoing, completed, or planned clinical research
 - Webpage/link for each partner study
- Platform for collaboration (at any stage of development of a project)
 - As an information dissemination resource – *“I have a study....”*
 - As an information collection resource – *“I’m looking to participate in...”*
 - Collaborations routed through specific workgroups – *but only if helpful*
- Access to existing datasets
 - InTBIR will act as a portal to collaboration – *each study maintains complete independence*
 - Summary of data content and sample availability for each study (*n ; severity, age, what data*)
 - Each study will have specific requirements for data access – *details on website*
 - Collaboration between PIs of individual datasets for study level or IPD meta-analysis

What should/can/will we use InTBIR for? (I)

- Source of data standards and research tools:
 - Access to CDEs and existing CRFs
 - Access to data collection tools – directly or via member studies (CENTER-TBI translations)
 - Analysis tools - facilities to deposit scripts etc.
- Interaction with funders
 - Communicate key research highlights to funders
 - Horizon scanning to inform funding calls
 - Funders interact with researchers through InTBIR to disseminate calls
 - Repository for publications from study partners (+ other open access papers of interest)
 - If resource available, regular digests of relevant available funding calls
- Access to methodological expertise and collaboration
 - Conventional analysis
 - Federated analysis

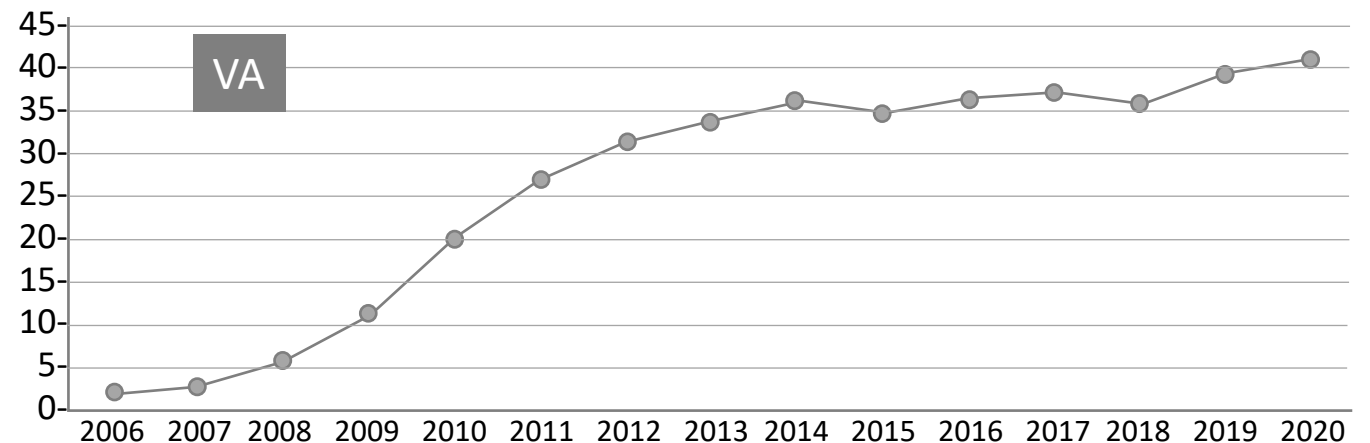
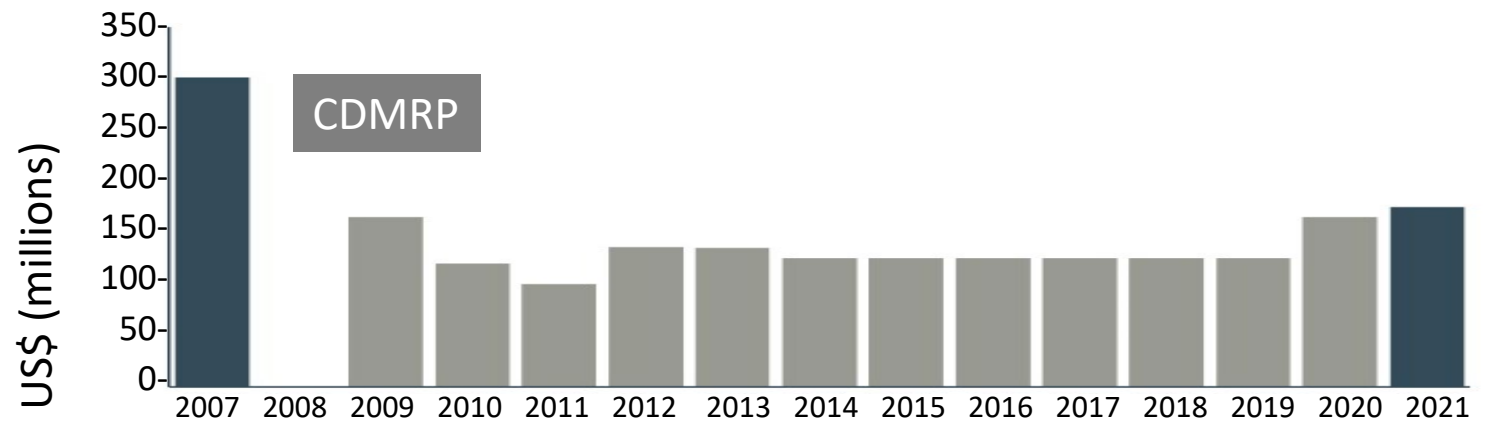
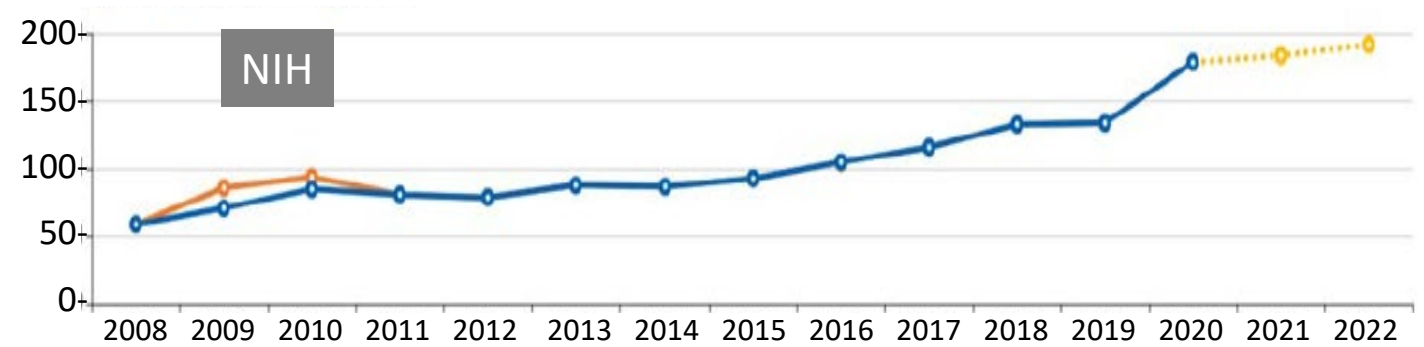
What do we need funding for

- Annual meetings (this meeting largely supported by EBIC)
- Website – hosted by INCF
 - Critical to our plans
 - Portal for interaction with member studies
 - Gateway to shared resources
- Support of network administration
 - Lean organisation – mostly online
 - Maintenance of membership
 - Linkage of collaborations
 - Support for Work Group meetings
- New research plans
 - TBI-related calls
 - More general calls - adapted TBI research (e.g. Data Sharing, precision medicine, healthy ageing)

NIH have provisionally agreed to host the next InTBIR Annual Meeting at Bethesda

Details are still being worked out, but the provisional plan is for:

- An ambitious program with support from NIH
- To include LMIC priorities
- Prioritised involvement of emerging researchers
- Scholarships to help attendance of junior researchers from LMICs
- Planning to start as soon as this meeting finished – suggestions welcome



European Union Funding

- **Direct calls through Research and Innovation funding**
- **Indirect funding through shared activities such as JPND and ERANET-NEURON**

FINAL CONFERENCE

[Home](#) / [Final Conference](#)



EUROPEAN BRAIN RESEARCH AREA FINAL CONFERENCE

11 October 2022
Brussels, Belgium



The EBRA project partners are delighted to invite you to the upcoming Final Conference, which will take place on 11 October 2022 in Brussels, Belgium.

Four years have already passed and plenty of work is to be presented this coming October, including the [EBRA Landscape Analysis](#), the [Shared European Brain Research Agenda](#) (SEBRA) as well as the work undertaken by the [six EBRA Clusters](#). The event will be an occasion to bring the wider brain research community and key players together, to discuss key aims of the project: the current state of brain research in Europe, increased patient engagement and public awareness, research infrastructures and data sharing and the future potentials and need for a brain health partnership going forward.

Collaboration and cooperation in the brain research area remain more important than ever and the EBRA Final Conference will be a major milestone to ensure unification and commitment to the future of brain research in Europe.

The conference will take place at the historical building of the [Les Ateliers des Tanneurs](#), in the centre of Brussels, located in Rue des Tanneurs 60A, 1000 Brussels.

[REGISTER HERE](#)

<https://www.ebra.eu/final-conference/>



The next collection date **will be 20 October 2022 at 12:00 noon (CET)**

EBRAINS is powering a new era in Brain Research

[Learn how scientists are using EBRAINS](#)

[Explore our services](#)

[What is EBRAINS](#)

[Read the latest news](#)

What is EBRAINS

A key enabler to advance brain science

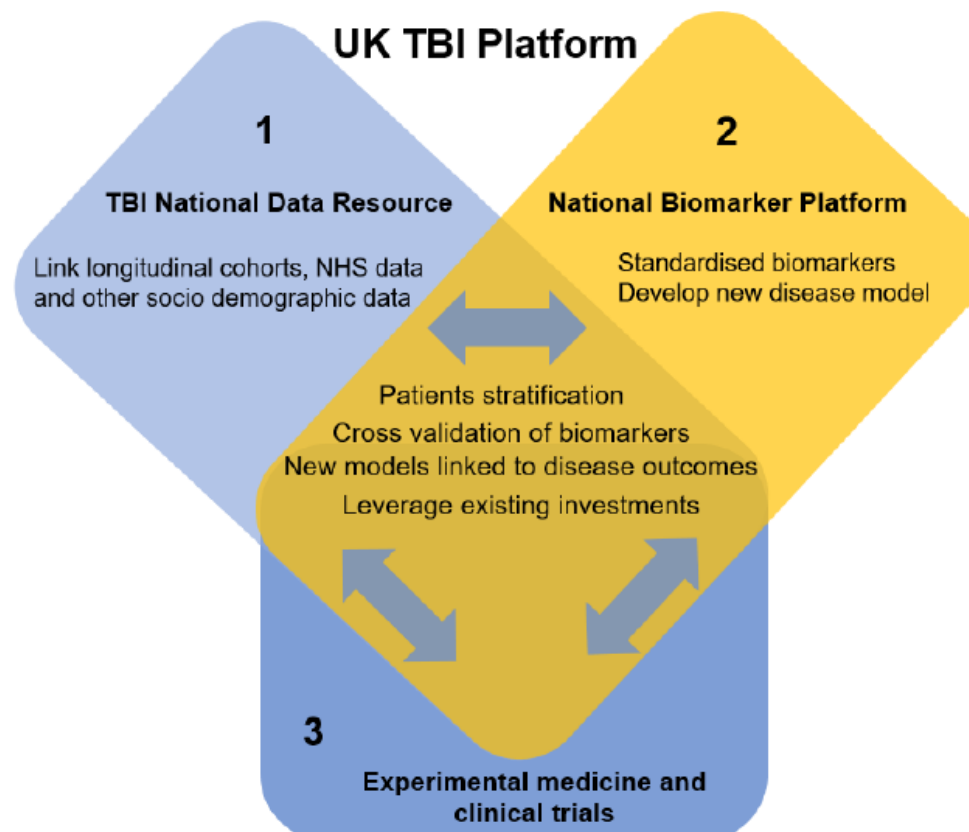
EBRAINS is a new digital research infrastructure, created by the EU-funded Human Brain Project, that gathers an extensive range of data and tools for brain-related research. EBRAINS will capitalize on the work performed by the Human Brain Project teams in digital neuroscience, brain medicine, and brain-inspired technology and will take it to the next level. Read more and discover EBRAINS in our introduction document.

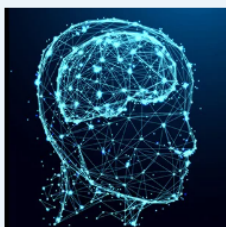
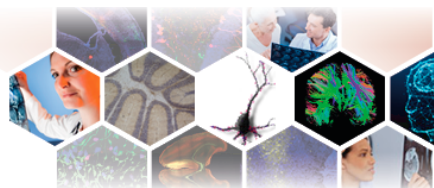


Medical
Research
Council

Workshop report

Traumatic Brain Injury across the life course: priorities, challenges, and opportunities





© Adobe Stock/pickup

Welcome to ERA-NET NEURON

Research into the diseases of the brain benefits from joint funding schemes by networks of funding agencies and ministries in Europe and beyond the European borders. The ERA-Net NEURON Cofund2 as a funding platform focused on neurological research communities.

[Read more](#)

Networking Calls

The success of biomedical research is often hampered by the lack of harmonization of procedures, experimental methodologies, and data management. For the translation and implementation of future research outcomes into clinical practice, as well as for shaping future research priorities, it is essential to **form synergies in the research community**, to overcome gaps and hurdles, to build overarching networks, and to generate harmonizing concepts and ideas. To address this **networking group calls** are launched under the umbrella of the ERA-NET NEURON.

Open Calls & Pre-Announcements

Pre-Announcement



2022 "Chronic Pain"

New Call Opening Soon: Transnational Networking Groups on Chronic Pain (expected to be launched on September 9th 2022)

Deadline: 8.11.2022 | 2pm Berlin Time

[Read more](#)

News

Apply until 25 July for the new Cajal hands-on course on neuroepigenetics in November in Berlin

[Read more](#) >

Save the date for the EBRA Final Conference: 2022 in Brussels, Belgium

[Read more](#) >

5 - 9 September 2022 | Conference in Berlin, Germany



Australian Government

Department of Health and Aged Care

[Home](#)

[Topics](#)

[Initiatives and programs](#)

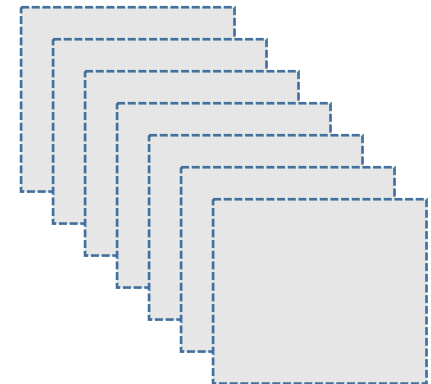
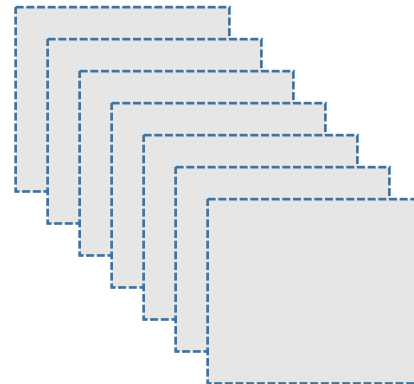
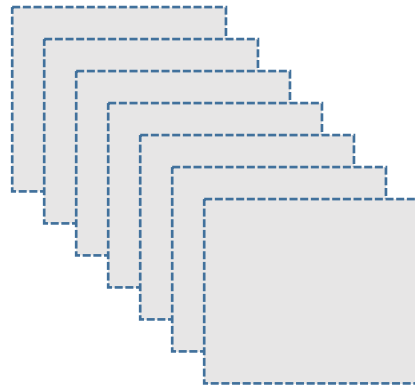
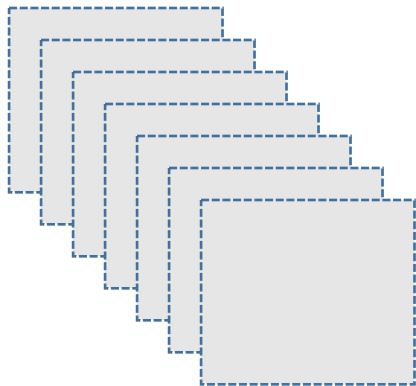
[Resources](#)

[Home](#) > [Initiatives and programs](#)

Traumatic Brain Injury Mission

The Traumatic Brain Injury Mission is investing \$50 million to improve patient recovery after brain injury. It will support projects that predict recovery outcomes, or identify the most effective care and treatments.

Other potential stakeholders – engagement being explored

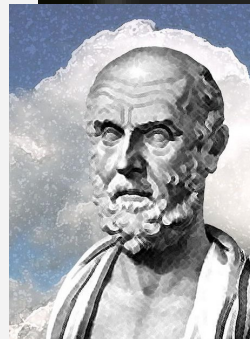


Once InTBIR is well established (2-3 years).....

- We anticipate that InTBIR will provide valuable resources and networking
- This will be useful to new studies – economies of scale may reduce costs
- Where InTBIR resources are of use for a fully funded large study
 - Make contact with InTBIR in advance
 - Potential help with funding application, and study design, conduct, analysis, dissemination
- Consider including small contribution towards InTBIR running costs in the grant

Take home messages

- InTBIR has been a substantial success
- InTBIR 2 aims to build on this as a consortium of collaborating researchers
- This requires funding for:
 - Meetings (2023 sorted out – exploring options for 2024 & 2025)
 - Core administrative functions – currently supported by EBIC & U Penn
 - Website maintenance and development
 - New research
- Some progress in each of these fields – other opportunities being explored
- Input from InTBIR members would be hugely valuable



The farther backward you can look,
the farther forward you can see.

— Winston Churchill —

AZ QUOTES



InTBIR meeting, Berlin, 16 July, 2022

Andrew I.R. Maas
University Hospital of Antwerp, Belgium

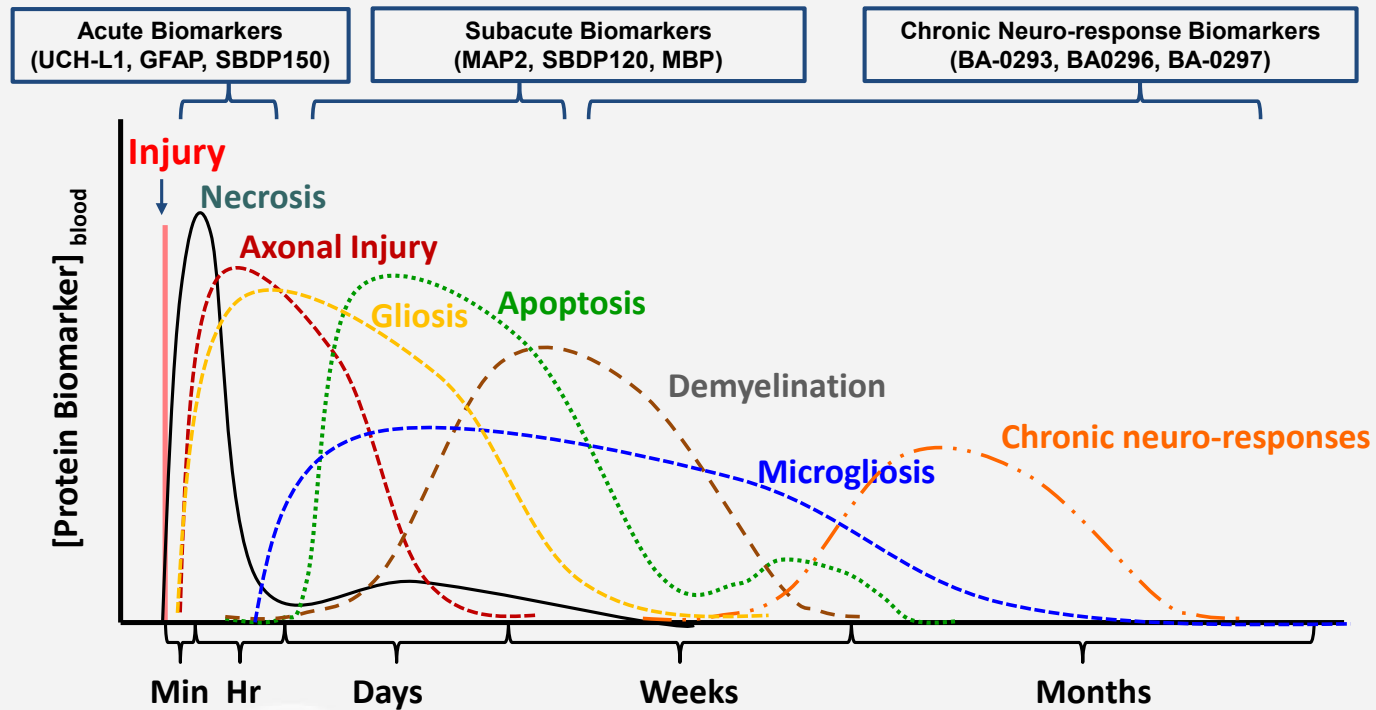


TOPICS

- “Old” evidence may still be informative
 - Biomarkers
 - Targeting brain oxygenation
- “New” concepts are often older idea’s dressed up
- How “Failures” can stimulate progress
- The strength of interactions, collaborations and networking



Traumatic Brain Injury Pathophysiology – A Continuum of Biomarkers



Mondello S, et al. 2013 Med Res Rev. 34(3):503-31



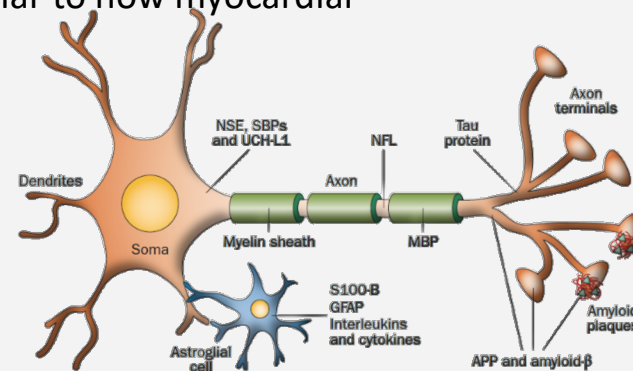
Triaging patients with mTBI for CT scanning

Clinical decision rules:

- New Orleans Criteria (NOC)
- Canadian CT head rule (CCHR)
- CHIP (CT in Head Injury)
- NICE Guideline for Head Injury
- Scandinavian Guidelines

Biomarkers in mild TBI: “Troponin for the Brain”

Biomarkers found in blood after patients have suffered a TBI could potentially be used in the ER to inform a diagnosis of TBI, similar to how myocardial infarct patients are diagnosed with troponin.



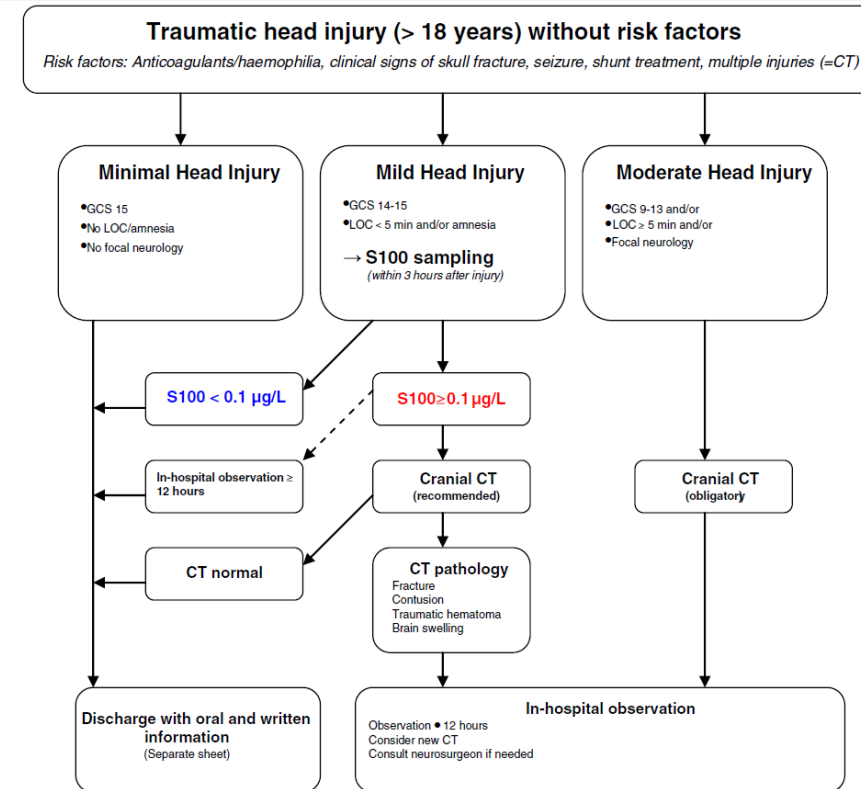
SCANDINAVIAN GUIDELINES

GUIDELINE

Open Access

Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update

Johan Undén^{1*}, Tor Ingebrigtsen² and Bertil Romner³, for the Scandinavian Neurotrauma Committee (SNC)



BMC Medicine 2013



THE DIAGNOSTIC VALUE OF BIOMARKERS IN MILD TBI

What is the evidence?

Is S100B the best choice?

- Affected by extracranial injuries
- Affected by sampling time

Do Biomarkers provide “added” value over CDRs?



Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study



Jeffrey J Bazzarian*, Peter Biberthaler*, Robert D Welch, Lawrence M Lewis, Pal Barzo, Viktoria Bogner-Flatz, P Gunnar Brodinson, Andras Buki, James Y Chen, Robert H Christenson, Dallas Hack, J Stephen Huff, Sandeep Johar, J Dedrick Jordan, Bernd A Leidel, Tobias Lindner, Elizabeth Ludington, David O Okonkwo, Joseph Ornato, W Frank Peacock, Kara Schmidt, Joseph A Tyndall, Arastoo Vossough, Andy S Jagoda

Summary

Background More than 50 million people worldwide sustain a traumatic brain injury (TBI) annually. Detection of intracranial injuries relies on head CT, which is overused and resource intensive. Blood-based brain biomarkers hold the potential to predict absence of intracranial injury and thus reduce unnecessary head CT scanning. We sought to validate a test combining ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), at predetermined cutoff values, to predict traumatic intracranial injuries on head CT scan acutely after TBI.

Methods This prospective, multicentre observational trial included adults (≥ 18 years) presenting to participating emergency departments with suspected, non-penetrating TBI and a Glasgow Coma Scale score of 9–15. Patients were eligible if they had undergone head CT as part of standard emergency care and blood collection within 12 h of injury. UCH-L1 and GFAP were measured in serum and analysed using prespecified cutoff values of 327 pg/mL and 22 pg/mL, respectively. UCH-L1 and GFAP assay results were combined into a single test result that was compared with head CT results. The primary study outcomes were the sensitivity and the negative predictive value (NPV) of the test result for the detection of traumatic intracranial injury on head CT.

Findings Between Dec 6, 2012, and March 20, 2014, 1977 patients were recruited, of whom 1959 had analysable data. 125 (6%) patients had CT-detected intracranial injuries and eight (<1%) had neurosurgically manageable injuries. 1288 (66%) patients had a positive UCH-L1 and GFAP test result and 671 (34%) had a negative test result. For detection of intracranial injury, the test had a sensitivity of 0.976 (95% CI 0.931–0.995) and an NPV of 0.996 (0.987–0.999). In three (<1%) of 1959 patients, the CT scan was positive when the test was negative.

Interpretation These results show the high sensitivity and NPV of the UCH-L1 and GFAP test. This supports its potential clinical role for ruling out the need for a CT scan among patients with TBI presenting at emergency departments in whom a head CT is felt to be clinically indicated. Future studies to determine the value added by this biomarker test to head CT clinical decision rules could be warranted.

Lancet Neurol 2018

Published Online

July 24, 2018

[http://dx.doi.org/10.1016/S1473-4422\(18\)30233-X](http://dx.doi.org/10.1016/S1473-4422(18)30233-X)

See Online/Comment

[http://dx.doi.org/10.1016/S1473-4422\(18\)30275-8](http://dx.doi.org/10.1016/S1473-4422(18)30275-8)

*Contributed equally

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Munich, Germany

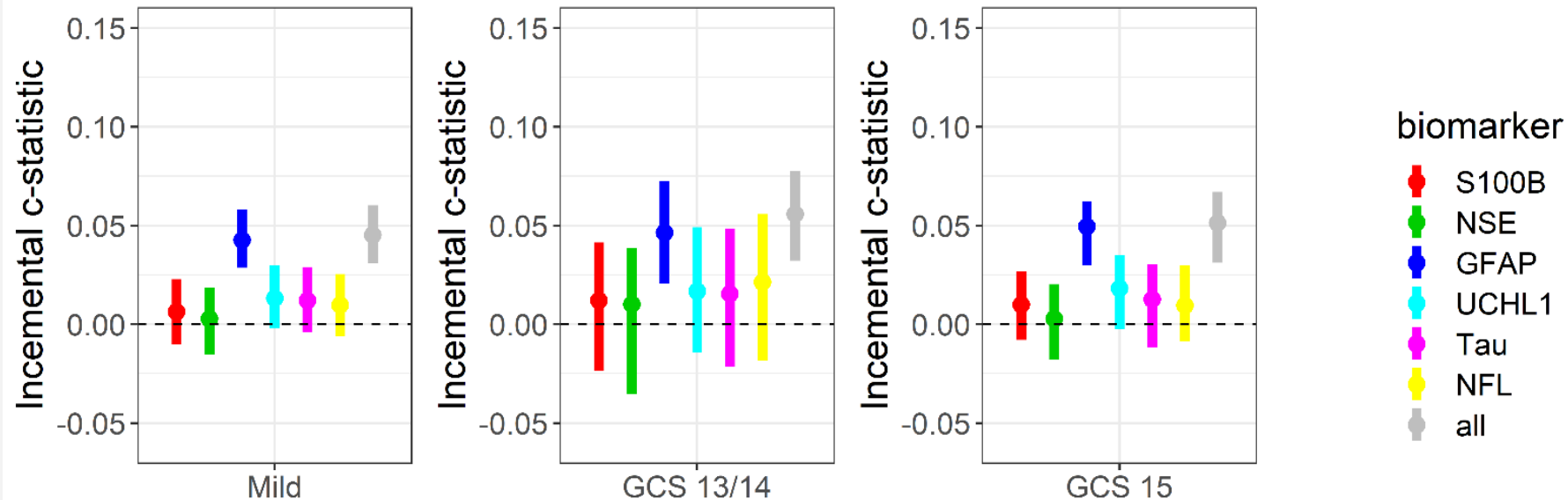
Open questions:

- Does the test offer “added value” over current practice?
- Are 2 biomarkers better than one?
- Are thresholds valid?

Bazzarian JJ, Biberthaler P, Welch RD, et al. Serum GFAP and UCH1-L1 in prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicenter observational study. Lancet Neurol 2018; published online July 24.



Incremental diagnostic value of biomarkers for triaging CT scanning in mTBI



Blood biomarkers on admission in acute traumatic brain injury: Relations to severity, CT findings and care path in the CENTER-TBI study

Endre Czeiter^{a,b,c,1,*}, Krisztina Amrein^{a,b,1}, Benjamin Y. Gravesteijn^{d,1}, Fiona Lecky^{e,f}, David K. Menon^g, Stefania Mondello^h, Virginia F.J. Newcombe^g, Sophie Richter^g, Ewout W. Steyerberg^{d,i}, Thijs Vande Vyver^{e,j,k}, Jan Verheyden^j, Haiyan Xu^l, Zhihui Yang^l, Andrew I.R. Maas^{m,1}, Kevin K.W. Wang^{l,n,1}, András Büki^{a,b,1}, CENTER-TBI Participants and Investigators²



Analysis of 2867 patients, of whom 1951 with mild TBI (GCS 13/14: 457; GCS 15: 1494)

All samples (serum) obtained within 24 hours of injury

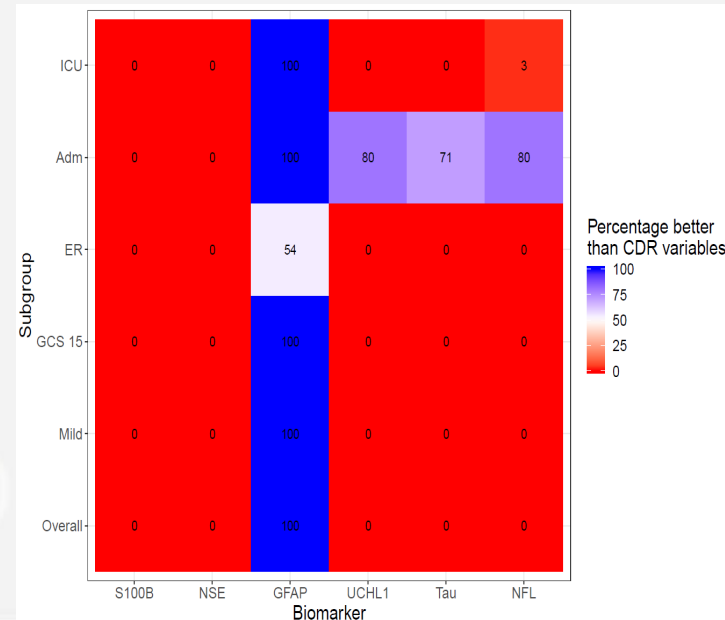
Ebiomedicine 2020



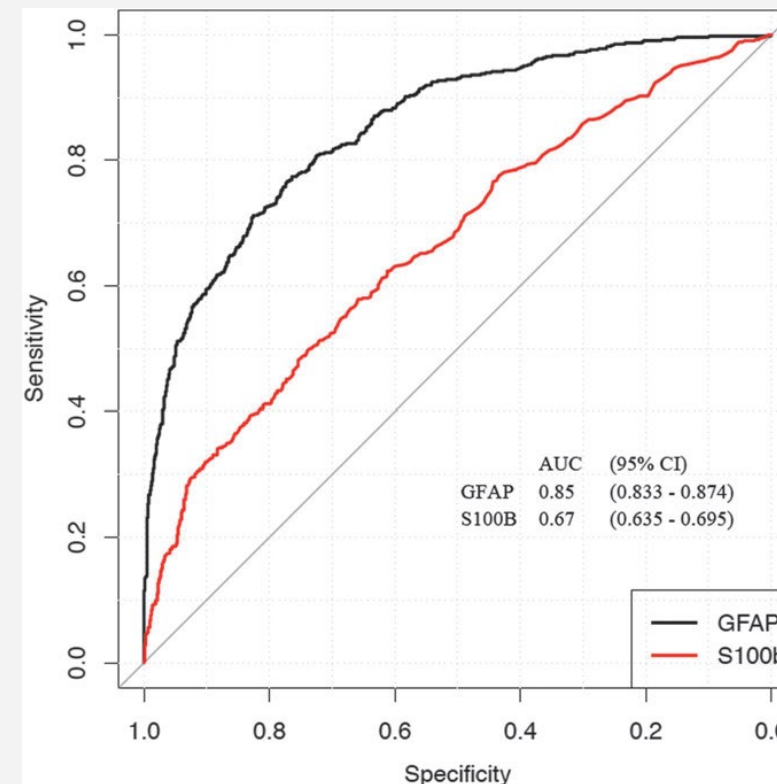
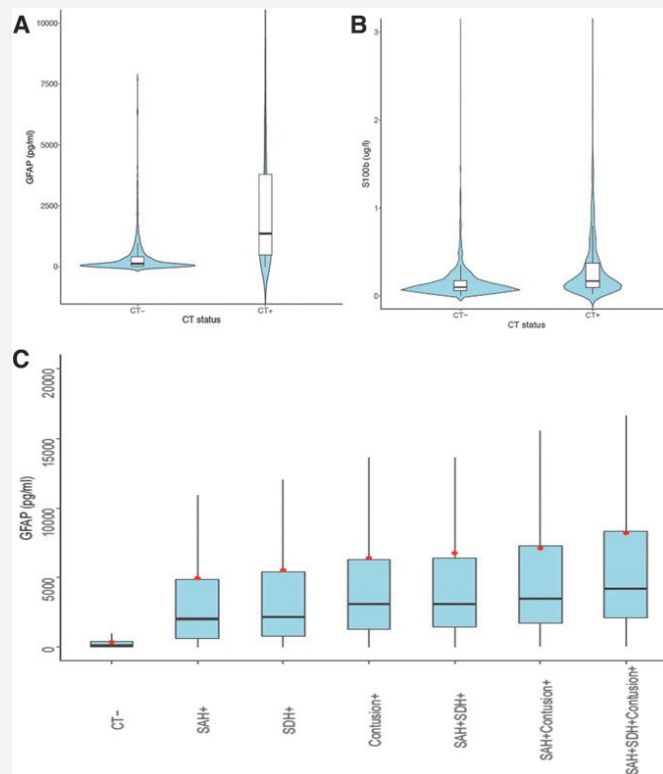
Biomarkers for triaging CT scanning in mTBI

The biomarker GFAP should be included in decision rules for triaging patients with mild TBI for CT scanning.

In patients with mild TBI, GFAP showed incremental diagnostic value: discrimination increased from 0.84 [95%CI: 0.83-0.86] to 0.89 [95%CI: 0.87-0.90] when GFAP was included



TRACK-TBI: GFAP PERFORMS BETTER THAN S100B IN PREDICTING CT ABNORMALITIES



1359 patients with TBI (GCS 3-15)
 GFAP: plasma, point-of-care
 S100B: serum

Okonkwo et al; J. Neurotrauma 202



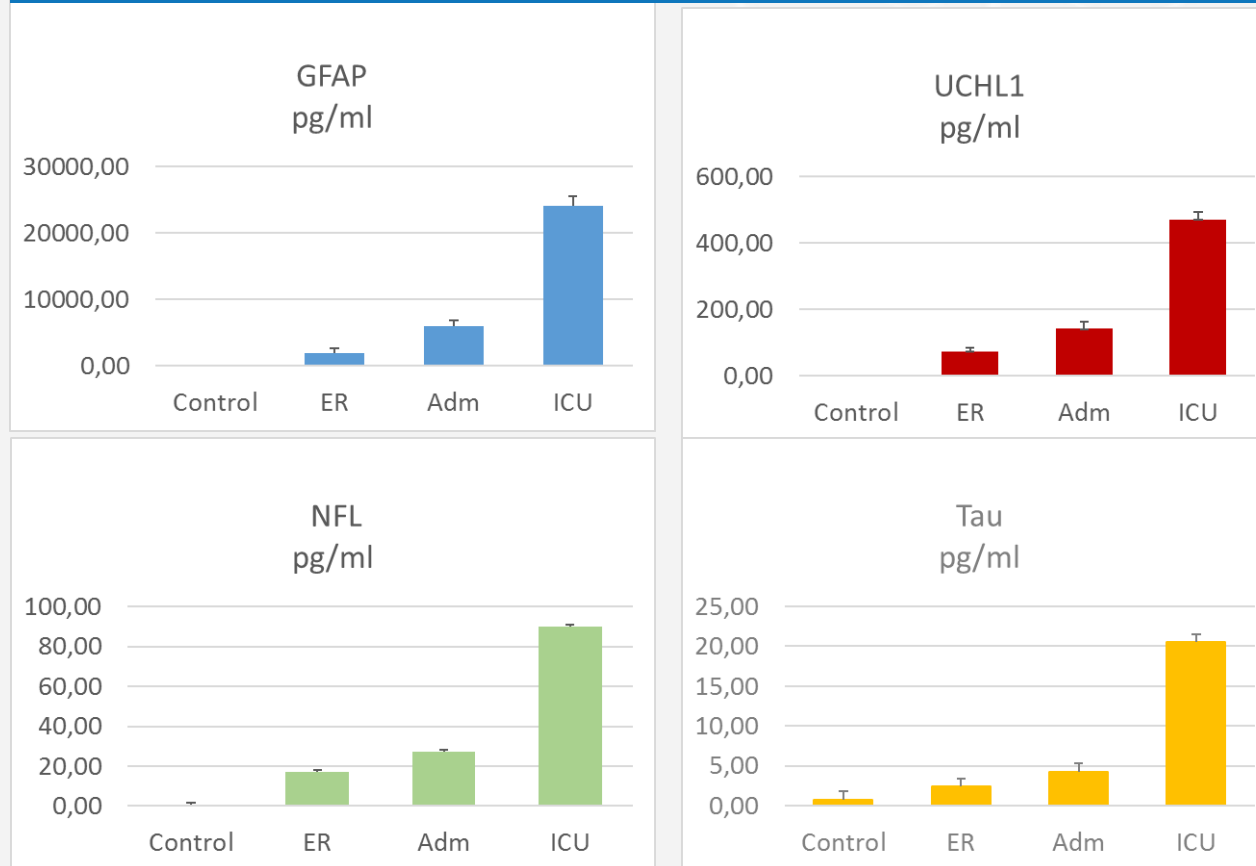
CONCLUSIONS ON DIAGNOSTIC VALUE OF BIOMARKERS

- GFAP performs better than S100B
- GFAP performs as well as all biomarkers combined
- No added value of combining GFAP with UCHL1
- GFAP outperforms CDRs
- GFAP can predict traumatic abnormalities on MR in patients with a normal CT

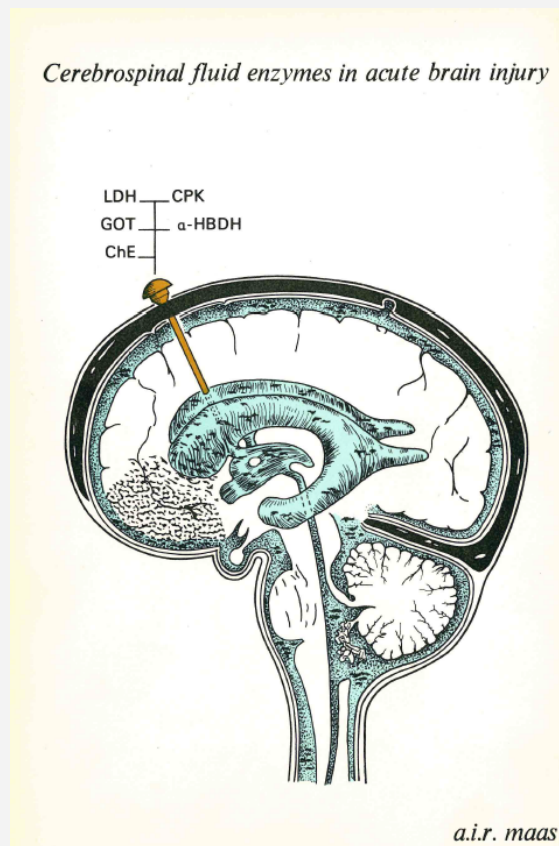


Relation to Injury Severity and Prognostic Value

CENTER-TBI: Biomarker levels differentiated by stratum



Cerebrospinal Fluid Enzymes in Acute Brain Injury



Promotoren:

Prof. Dr. S.A. De Lange

Prof. Dr. J.W.F. Beks

Co-referenten:

Dr. H.G. Van Eijk

Dr. D.L. Westbroek

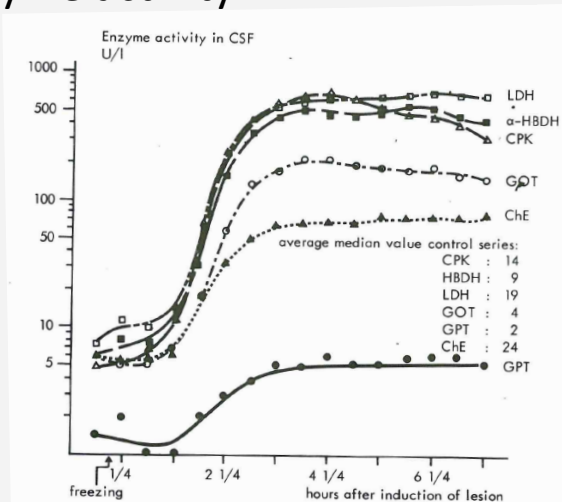
3/07/1977



CSF Enzymes: Pioneering Biomarkers

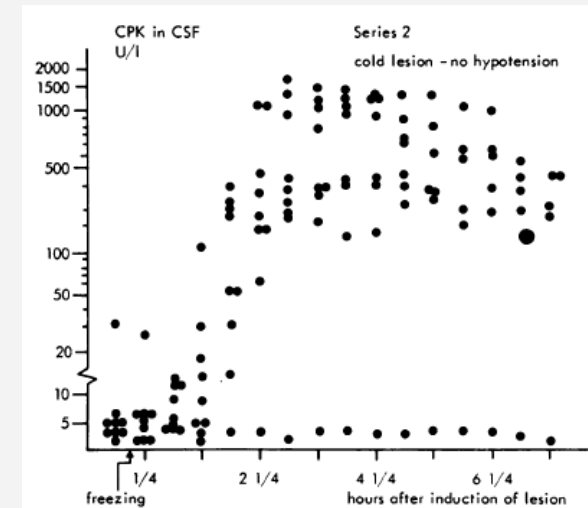
Main results:

- enzymes start to increase 1-2 hours after injury
- Isoenzyme studies confirmed brain origin
- Higher CSF enzyme levels in more severe injuries
- Induction of hypotension prevented enzyme increase
- No consistently significant changes in serum enzyme activity



Transport:

- Bulk flow, not diffusion
- Dependent on ABP



TARGETING CEREBRAL OXYGENATION

3 Phase 3 trials ongoing:

- BOOST-3 (US)
- OXY-TC (France)
- Bonanza (Australia)

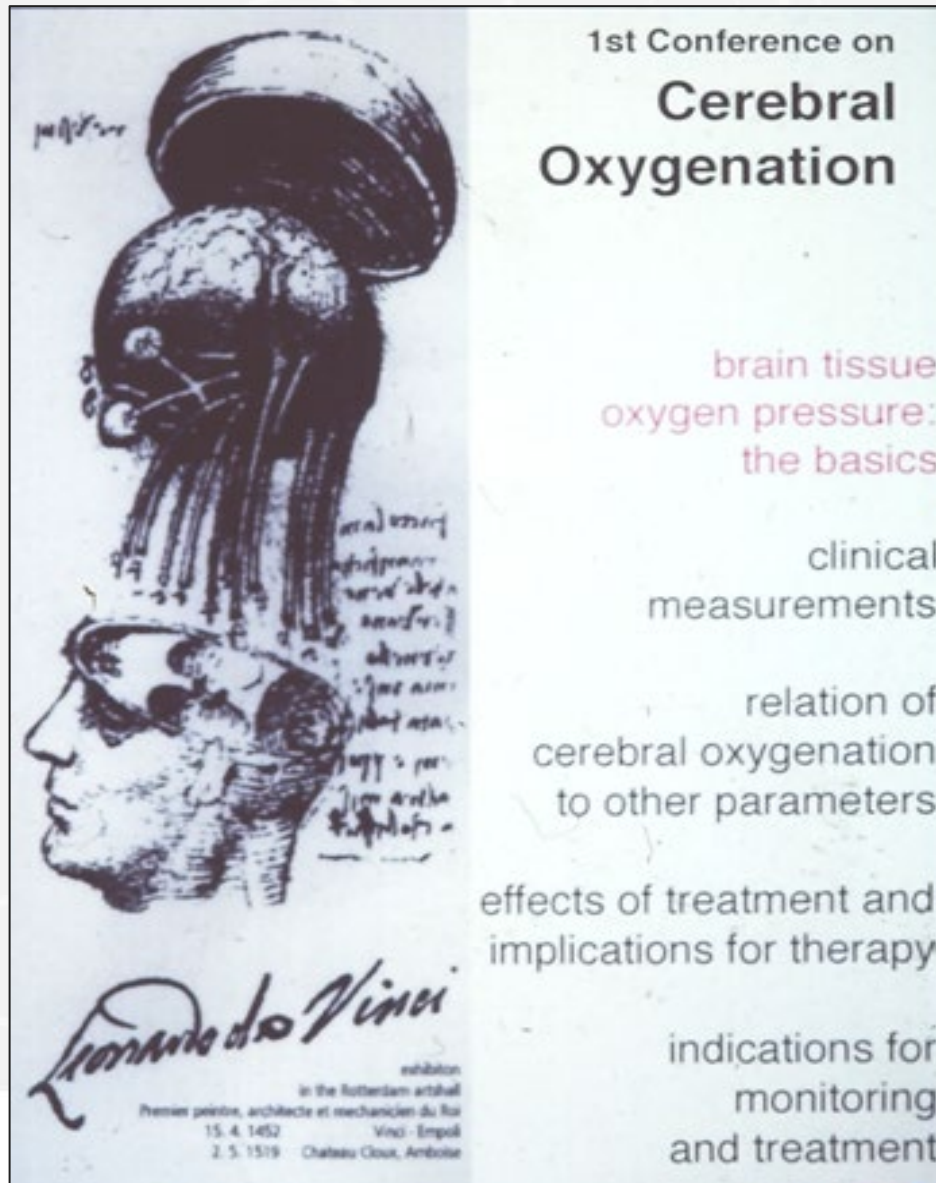
Interventions:

- Increase FiO₂
- Increase CPP
- Increase Hb

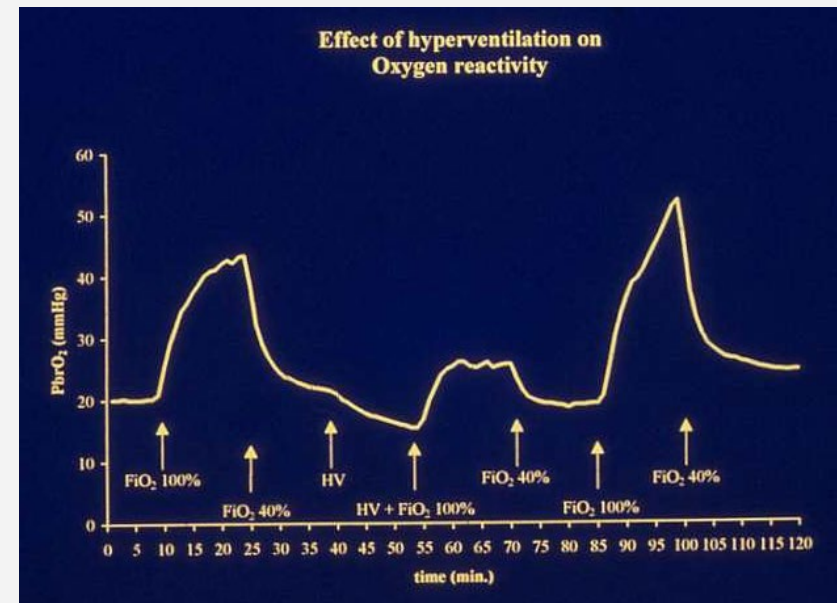
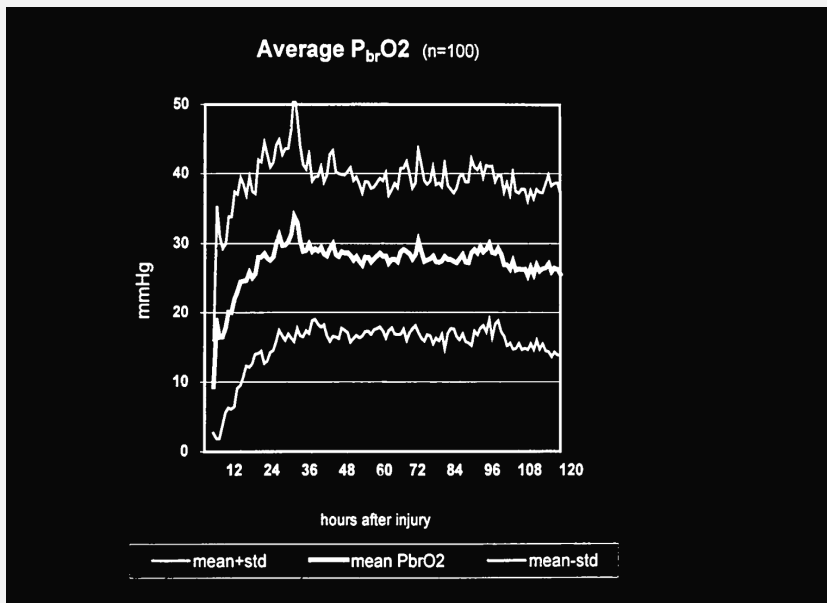
How many individual patients respond to these interventions, and what may be confounding variables?



Collaboration with Basic Scientists



Time Course of $P_{br}O_2$

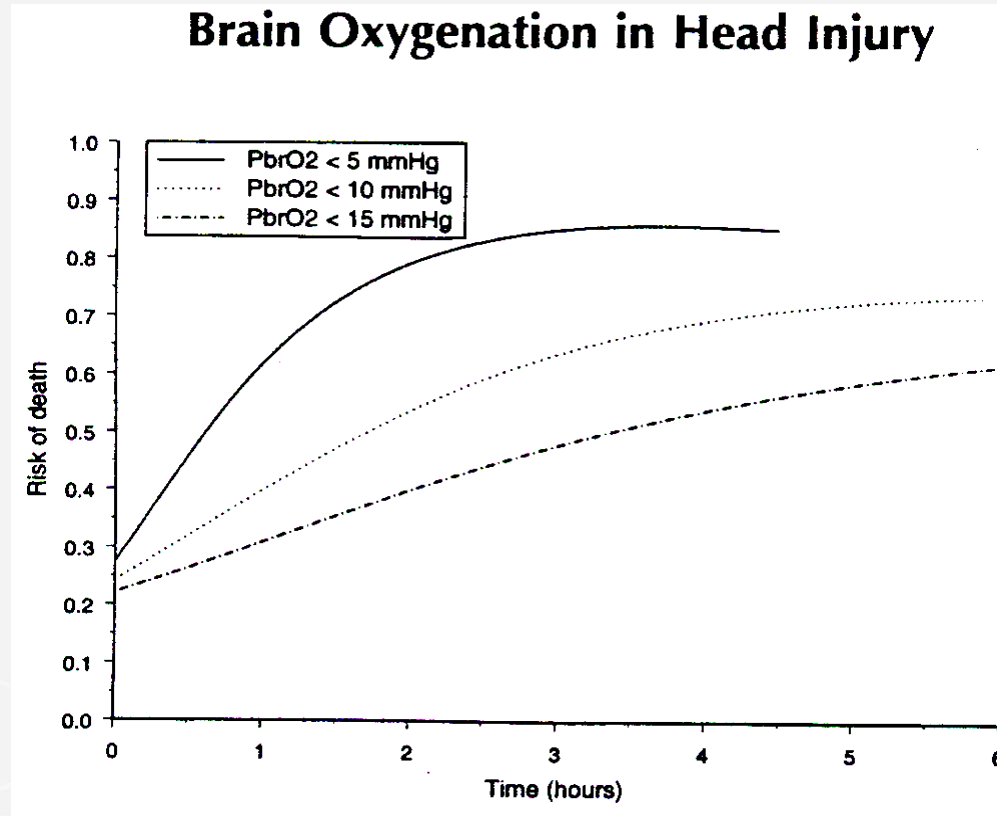


Additional focus on:

- prognosis
- oxygen reactivity
- CO_2 Reactivity
- Effect of $PaCO_2$ on Oxygen reactivity



Low Brain Tissue oxygen associated with increased risk of death



Odds for Mortality

LOW pbrO2 3.8 [1.6-8.4]

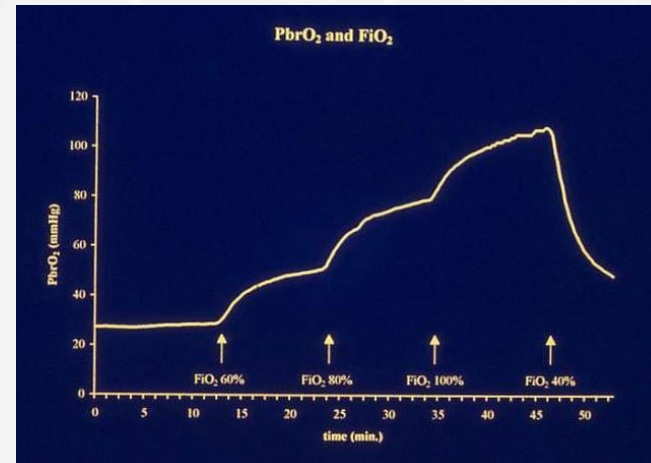
ADJUSTED FOR CLINICAL VARIABLES

-	AGE	3.7 [1.6-8.9]
-	GCS	3.6 [1.6-9.0]
-	PUPIL	4.0 [1.6-10]
-	MEI	3.7 [1.6-8.8]
-	ICP	4.1 [1.7-10]

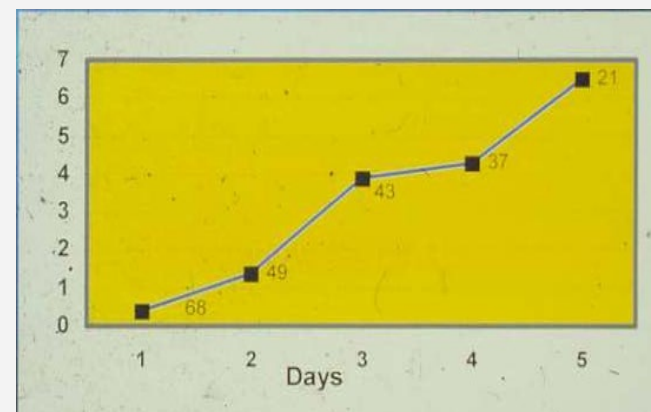


CHALLENGING THE SYSTEM

O2 REACTIVITY



CO2 REACTIVITY



INTERPRETING REACTIVITY TESTS

CO2 reactivity

- LOW REACTIVITY ON DAY 1
- (INCREASED) HYPERVENTILATION CAUSES SIGNIFICANT REDUCTION IN PbrO₂
- INCREASING REACTIVITY DAY 2-5 SUGGESTS INCREASING RISK OF HYPERVENTILATION TO COMPROMISE CEREBRAL OXYGENATION

O₂ reactivity

- LOW IN THE FIRST 24 HOURS AFTER INJURY
- HIGH VALUES RELATED TO POORER OUTCOME IN FIRST 24 HOURS

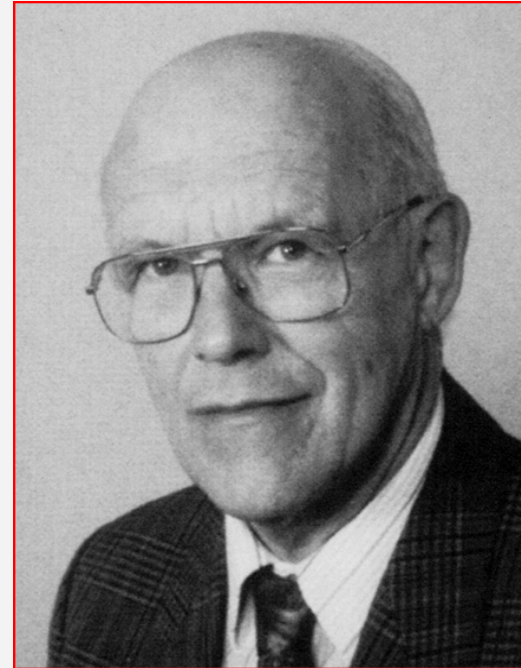


“New” concepts: older idea’s dressed up?

THE ART OF MEDICINE VERSUS EVIDENCE BASED TREATMENT



Samuel de Lange

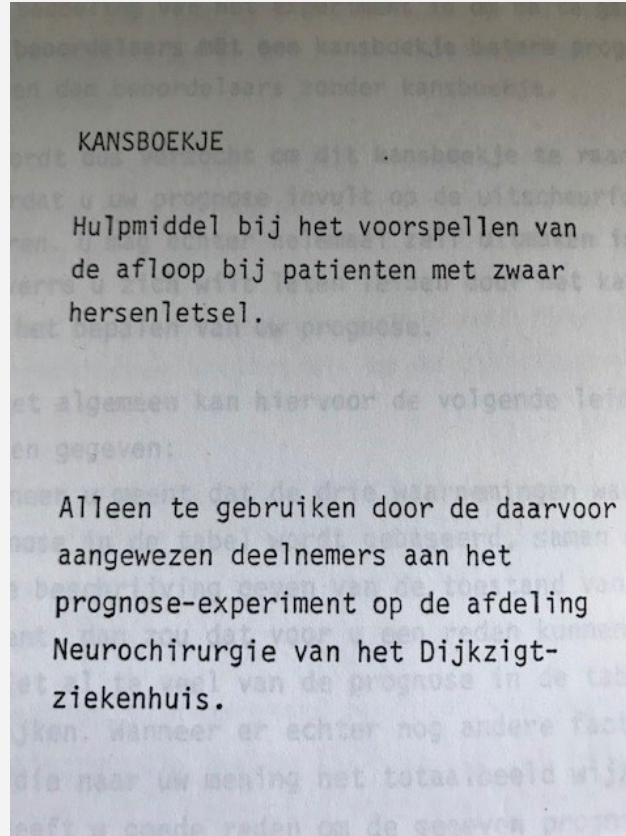


Reinder Braakman

PERSONALIZED MANAGEMENT VS POPULATION AVERAGES



DYNAMIC PREDICTION MODELLING



Predictors:

- Age
- GCS
- Pupils

Time of predictions:

24 hrs
2-3 Days
7 Days
14 days
28 Days



Collaborations in Europe



NEMO SOLUS SAPIT





Neuroprotection trials in TBI have failed often – and well!

Schumpeter

Fail often, fail well

Companies have a great deal to learn from failure—provided they manage it successfully

Apr 14th 2011 | from the print edition



Success and failure are not polar opposites: you often need to endure the second to enjoy the first. Failure can indeed be a better teacher than success. It can also be a sign of creativity.

He who follows another, sees nothing,
learns nothing, nay, seeks nothing

Sir William Osler

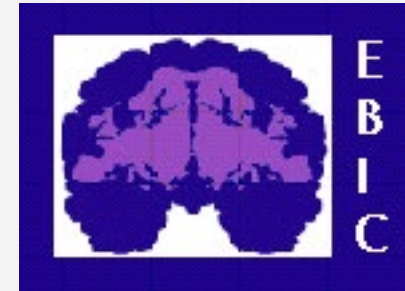


Collaboration with Statisticians

IMPACT

*International Mission for
Prognosis and Analysis of Clinical Trials in TBI*

**NIH funded project NS-042691
2003-2011**



Collaborative venture:

- University Hospital Antwerp
- Erasmus Medical Center Rotterdam
- Virginia Commonwealth University Richmond
- University of Edinburgh UK



Fail often in order to succeed sooner



The IMPACT Investigators

IMPACT I (2003-2006)

PI:

Andrew Maas

IMPACT II (2007-2011)

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Gordon Murray
Izzy Butcher
Gillian McHugh
Morag Leitch

RICHMOND:

Tony Marmarou
Sung Choi
Justin Austin
Juan Lu

ROTTERDAM:

Andrew Maas
Ewout Steyerberg
Nino Mushkudiani
Adrian Hernandez
Marja van Gemerden
Rodrigo Labouriau

EDINBURGH:

Gordon Murray
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The IMPACT Project

The problem:

Vast heterogeneity of TBI populations

No mechanistic or surrogate endpoints available (yet)

Database:

A culture medium for exploring concepts to improve clinical trials in TBI

Global aim:

To optimize the design and analysis of clinical trials in TBI, to increase the likelihood of demonstrating benefit of a truly effective new therapy or therapeutic agent.



The IMPACT Project

International Mission for Prognosis and Analysis of Clinical Trials in TBI

- Prognosis
- Trial design and analysis
- Common Data Elements

www.tbi-impact.org



The IMPACT Recommendations

- Inclusion criteria should be as broad as is compatible with the current understanding of the mechanisms of action of the intervention being evaluated. This will maximize recruitment rates and enhance the generalizability of the results
- The statistical analysis should incorporate prespecified covariate adjustment to mitigate the effects of the heterogeneity
- The statistical analysis should use an ordinal approach, based on either sliding dichotomy or proportional odds methodology





Creating Opportunities



"The Brussels Pilgrims"



InTBIR

International Initiative for TBI Research

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Original Articles

Toward an International Initiative for Traumatic Brain Injury Research

Patrizia Tosetti,¹ Ramona R. Hicks,² Elizabeth Theriault,³ Anthony Phillips,³ Walter Koroshetz,²
and Ruxandra Draghia-Akli,¹ and the Workshop Participants

European commission – NIH/NINDS – CIHR

The Lancet Neurology. Editorial: the changing landscape of
traumatic brain injury research. Lancet Neurol.;11(8):651.
2012.

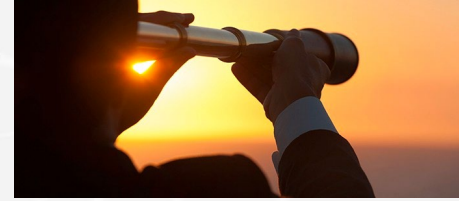


THE CONCEPTION OF CENTER-TBI





ING AHEAD



Collaboration – Network – Teamwork

- Identification of subgroups that may be more responsive to therapies (precision medicine approaches)
- Integration of basic pathophysiology into clinical algorithms
- Develop and refine multidimensional approaches to classification of initial severity and outcome
- Meta-analyses across studies (CENTER/TRACK and others)
- Focus on Mild TBI



THE ART OF MEDICINE

Some odd diagnostic pills to swallow.

Nature always hangs out a "little flag", which when SEEN & understood points to the diagnosis.

Diagnosis is the centre of the clinician's life, the "HINGE" on which all else turns.

When you hear hoof beats, think of HORSES, not ZEBRAS!

Tutorials in Differential Diagnosis

"It is not seeing MUCH but seeing WISELY that is valuable."

It is not seeing, now.
"He who follows another, sees nothing, learns nothing, nay,
seeks nothing." (Sir William Osler)

"Acquire the art of detachment, the virtue of method, & the quality of thoroughness, but above all the grace of humility." (Osler)

Experience is a good teacher, but her fees are very high! (Inge)

"We know accurately only when we know little; doubt-increases." (Goethe)