Towards evidence-based indvidual decision-making in TBI - the TBIcare project

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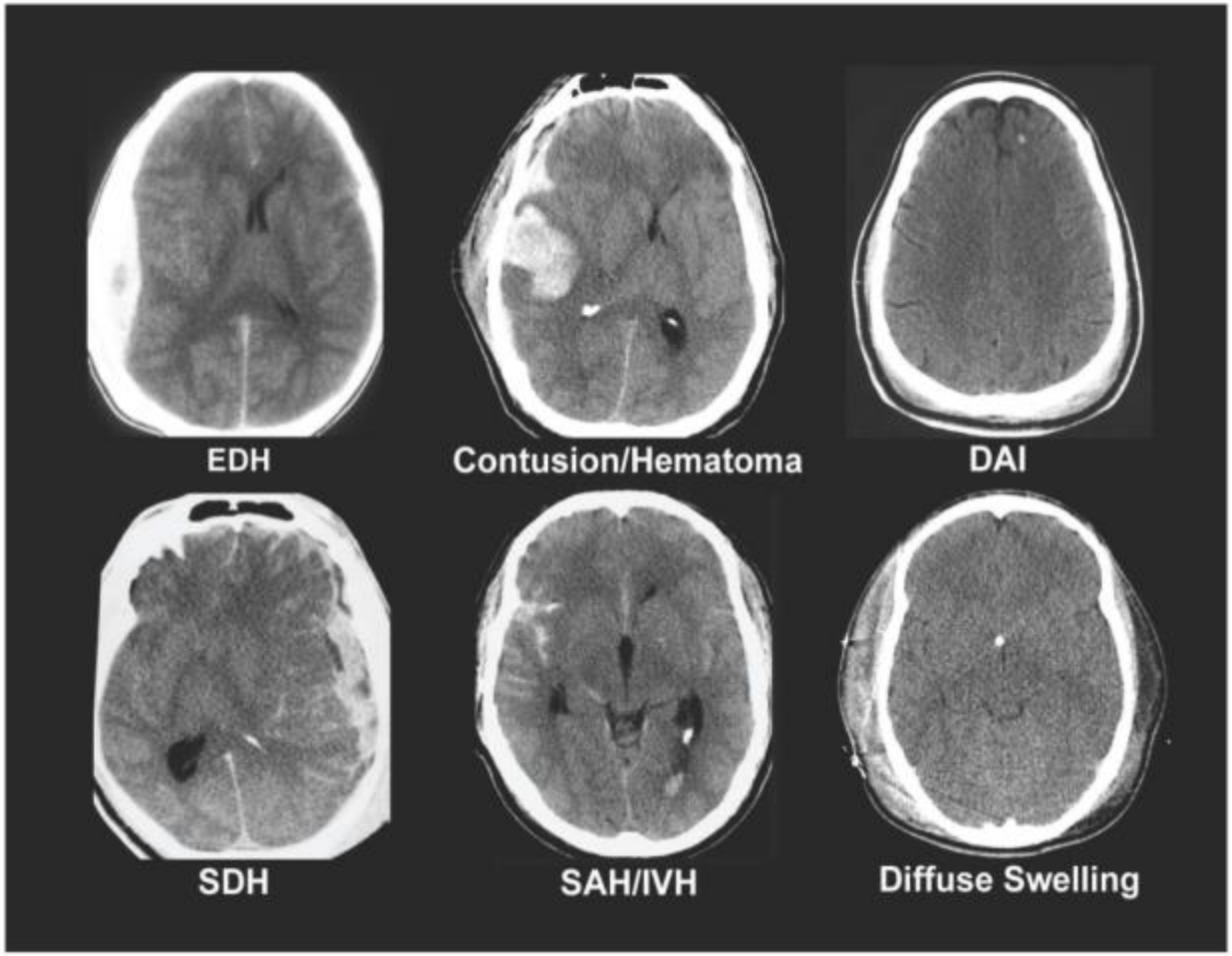
Background

- TBI has been called "our most complex disease, in our most complex organ"
- There are no two injuries that are alike, and the clinical course after the incident is influenced by a vast number of known and unknown factors

Great history of TBI-medicine… in failures

The crude spectrum of "severe TBI"

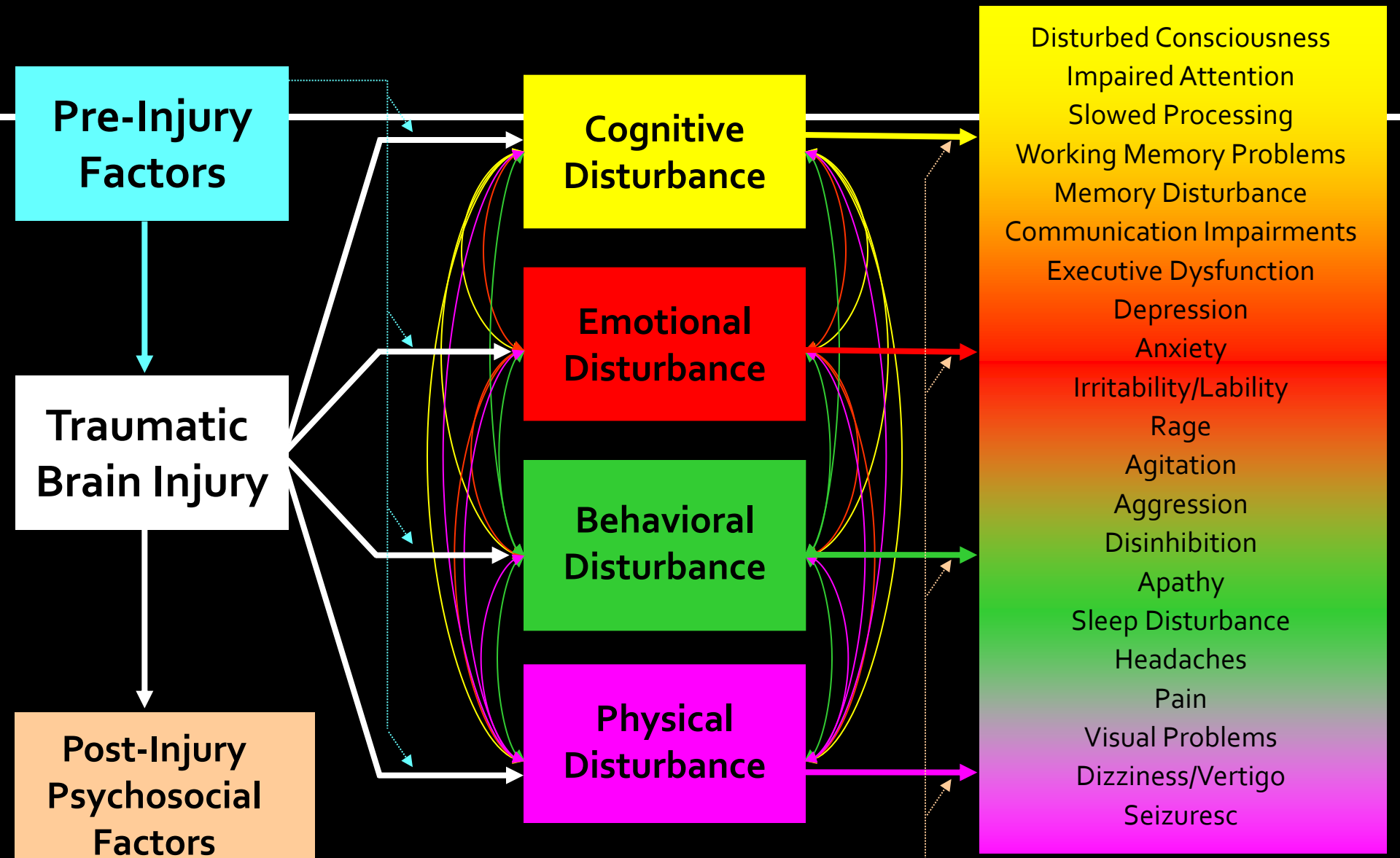


Complexity in practice…

- Gross pathology may include axonal injury, oedema, contusions, epidural haematoma, subdural haematoma and tSAH alone or in various combinations
  = 2^6 = 64 different types of injuries
  – simply by gross pathology

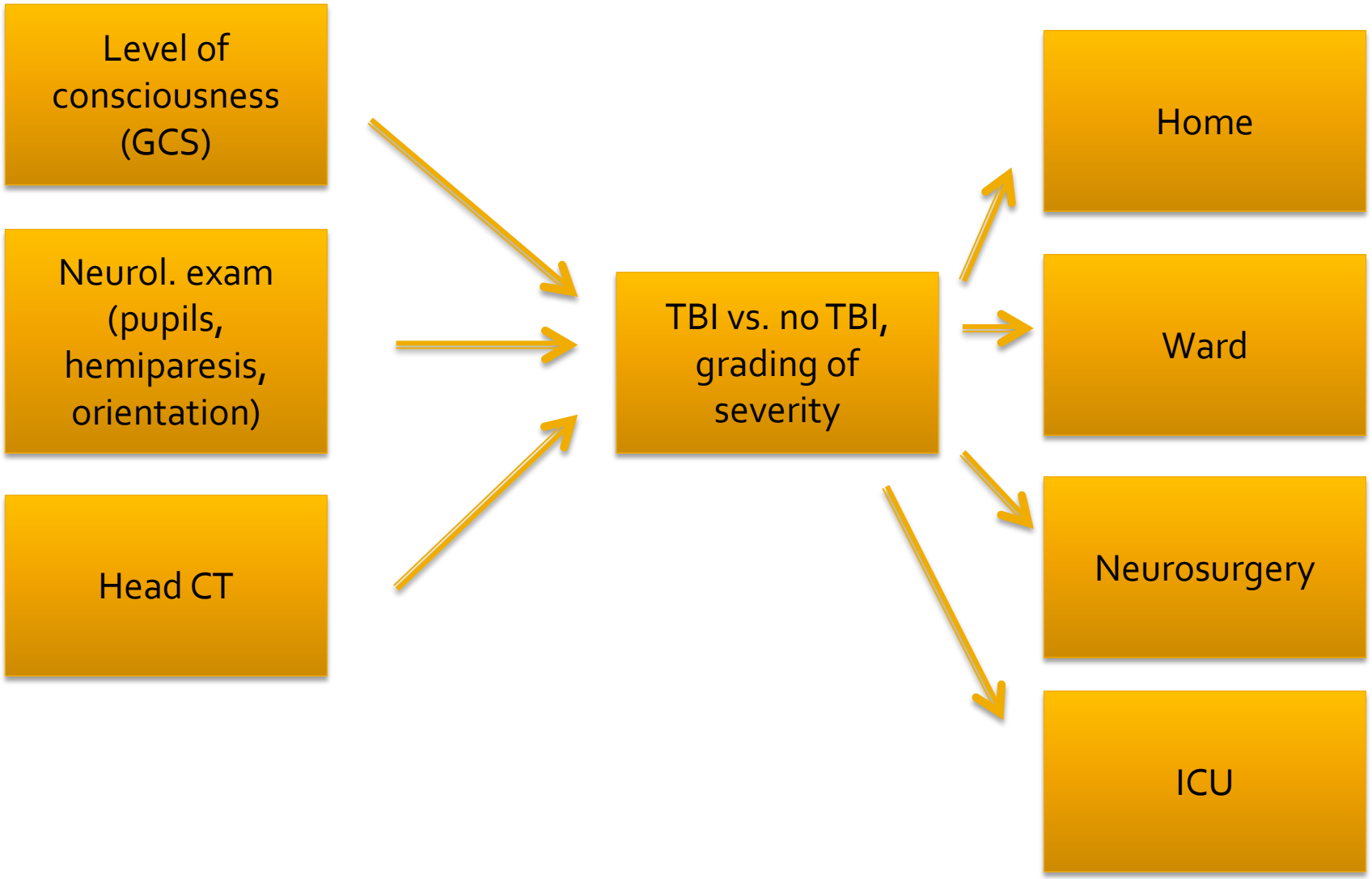
- If the order of temporal evolution is considered, the number of combinations is 6! = 720

Factors Influencing Neuropsychiatric Outcome after TBI



(Adapted from Silver and Arciniegas 2006)

Current diagnostic approach



Issues usually not sufficiently considered

Pre-injury

- Age
- Gender
- Medications
- Drug / alcohol abuse
- Earlier TBIs
- General health
- Genetics

Injury-related

- Delays
- Amnesia
- Confounding factors
- Other injuries
- Injury mechanism

Questions to be asked – without answers…

- Should 20- and 60-yr old victim be treated similarly?
- Does earlier TBI predispose to complications?
- Should patients with ApoE4 genotype be treated differently?
- How should delays be taken into account in diagnostics and treatment decisions?
- In multitraumas, what is the optimal order of treatments?

Confounders of TBI diagnosis

- Uncertain LOC
- Uncertain amnesia
- Inebriated (alcohol/drugs)
- CNS active medications
- Operative measures
- Other injuries
- Uncertain trauma event
- Seizure
- Other brain disorder
- Psychiatric causes
- Communication problems
- Only nonspecific symptoms

Diagnostic confusion

Diagnosing Mild Traumatic Brain Injury: Where Are We Now?

Richard P. Dutton, MD, MBA, Kate Prior, MD, Robin Cohen, MD, Christine Wade, RN, John Sewell, MA, Yvette Fouche, MD, Deborah Stein, MD, Bizhan Aarabi, MD, and Thomas M. Scalea, MD

Methods: We prospectively studied 369 patients with mechanism of injury consistent with TBI. The diagnosis was evaluated by five methods: (a) study enrollment (i.e., mechanism of injury), (b) signs of head trauma, (c) expert physician assessment, (d) presence of initial symptoms (loss of consciousness [LOC]; amnesia), and (e) BAM. All patients had a head CT scan. We compared the BAM screen results with the diagnosis of mTBI and BAM data from 50 normal volunteers and 49 trauma control patients not thought to have TBI.

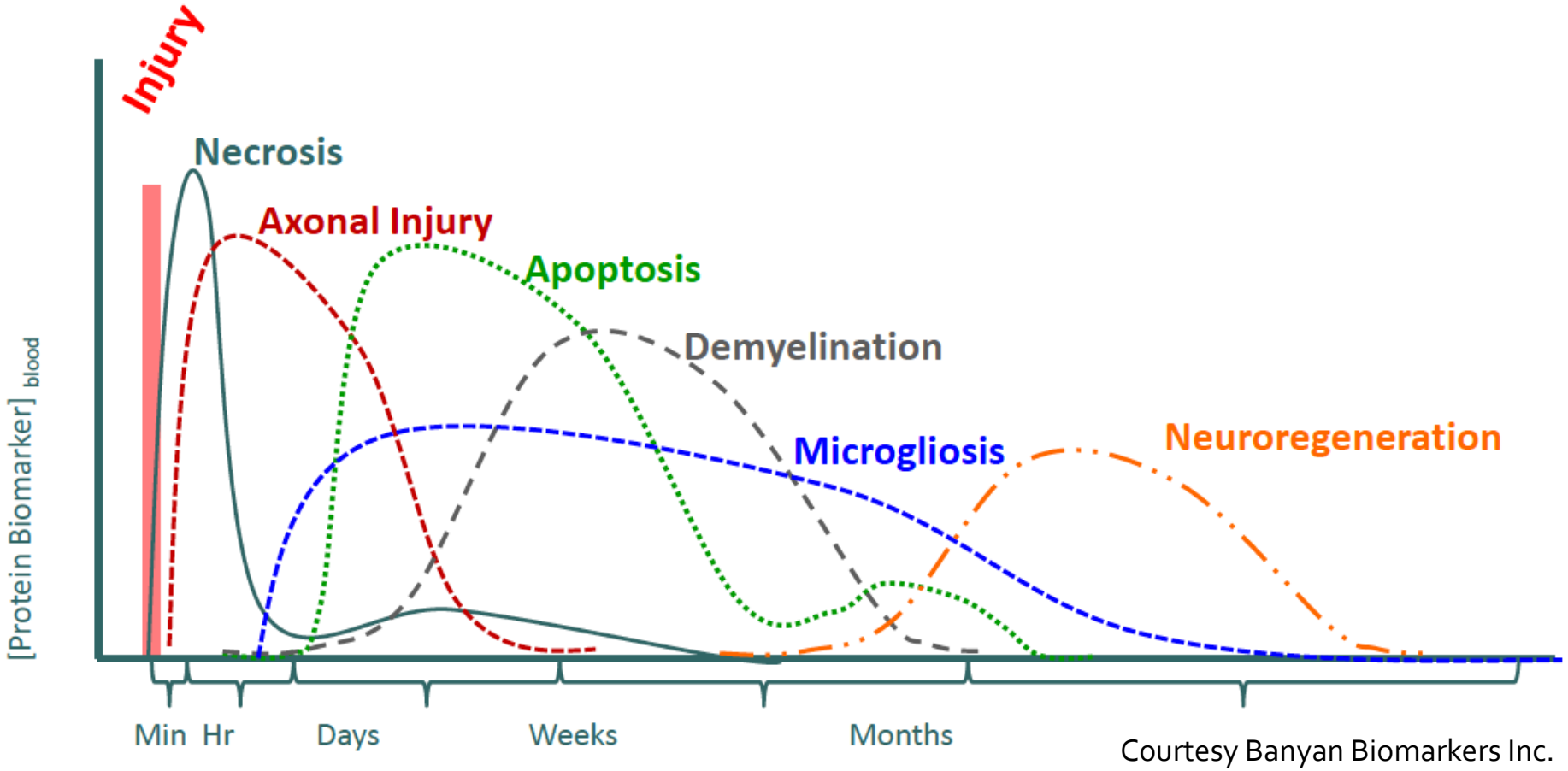
Results: None of the diagnostic methods correlated well with the others. Correlation between the methods ranged from 21% to 71%. BAM discrim-

Multiple diagnostic needs

- Presence / lack of TBI
- "Severity" of TBI (risk of death, need for surgery, need for observation, risk of worsening, prognosis short-/long-term)
- Macroscopic pathological processes
- Pathophysiological processes
- Clinical follow-up (improving/deteriorating)
- Treatment responses

Complex pathophysiology

Pathophysiology



Courtesy Banyan Biomarkers Inc.

Complexity in practice…

- Currently we know about 100 variables which are known or suspected to affect the outcome. Many of them are not dichotomous, but simply with alternatives yes/no we have 2^{100}
  = 1267650600228229401496703205376 combinations

→ How can we ever reach evidence-based medicine in treating individual subjects with TBI?

Never, but we can approach it…

Clinical decision support systems

- Clinical decision support systems (CDSS) help clinicians or other health professionals with their decision making tasks.
- CDSS techniques are typically
  - knowledge-driven based on IF-THEN rules, or
  - data-driven based on artificial intelligence.
- There is a clear need for CDSS especially in complex diseases where the rules to diagnose are easily highly complex or fuzzy and subjective.

The TBIcare project

The idea:

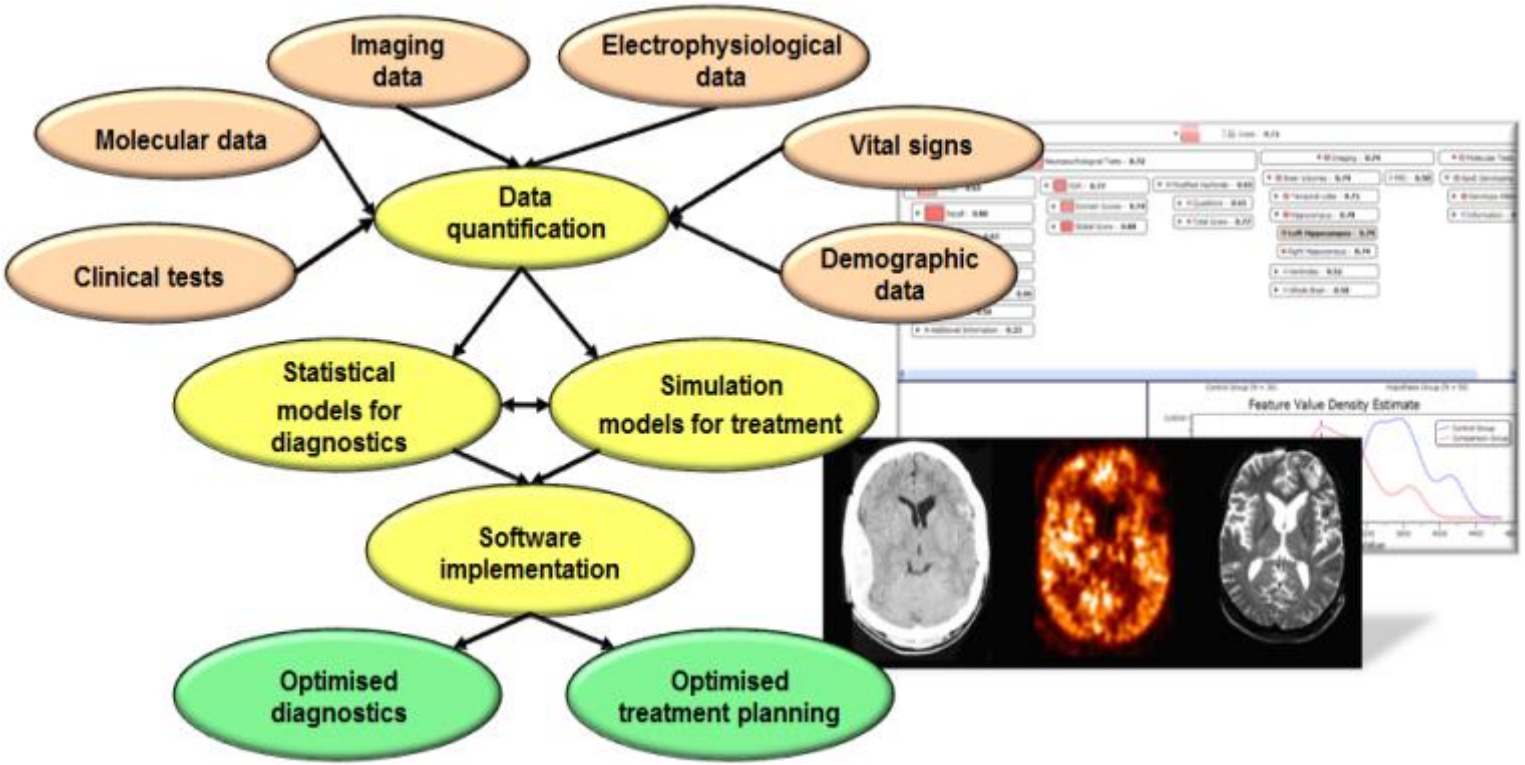
- **To combine modern statistical methods and system simulation modeling, and**
- **Data mining methodology, and**
- **Modern automatic tools to quantify heterogeneous physiological data, and**
- **Large databases with clinical TBI data (including outcome)**

➔ To produce a software tool which is able to:

1. **Give an accurate estimate about the nature of the injury (= improved diagnostics)**
2. **Assist in selecting the most appropriate treatment for a particular patient (= improved care)**

This project is partially funded by the European Commission under the 7th Framework Programme (FP7-270259-TBIcare)

Project structure



Partners: **VTT** (FIN), GE Healthcare Ltd. (UK),
Turku University Central Hospital (FIN),
University of Cambridge (UK), Imperial College London (UK),
Complexio (FRA), Kaunas University of Technology (LT),
GE Healthcare Finland Oy (FIN)

Feb 2011 – Jul 2014
Budget 4.2 M€, EC contribution 3.2 M€

more info: www.tbicare.eu

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Data used for modelling and validation

The following datasets will be used for modelling of TBI-related clinical data:

Dataset	Size	Severity
IMPACT-database (www.tbi-impact.org) (global)	11 235	Mostly severe
University of Cambridge, prospective (UK)	400	Mostly severe
Turku University Hospital, retrospective (Finland)	> 1000	All severities
TBIcare prospective* (UK + Finland)	400	All severities
TRACK-TBI (USA)	650	All severities

* From University of Cambridge and Turku University Hospital, incl. detailed clinical data + blood biomarkers + acute and late MRI + multifactorial outcome

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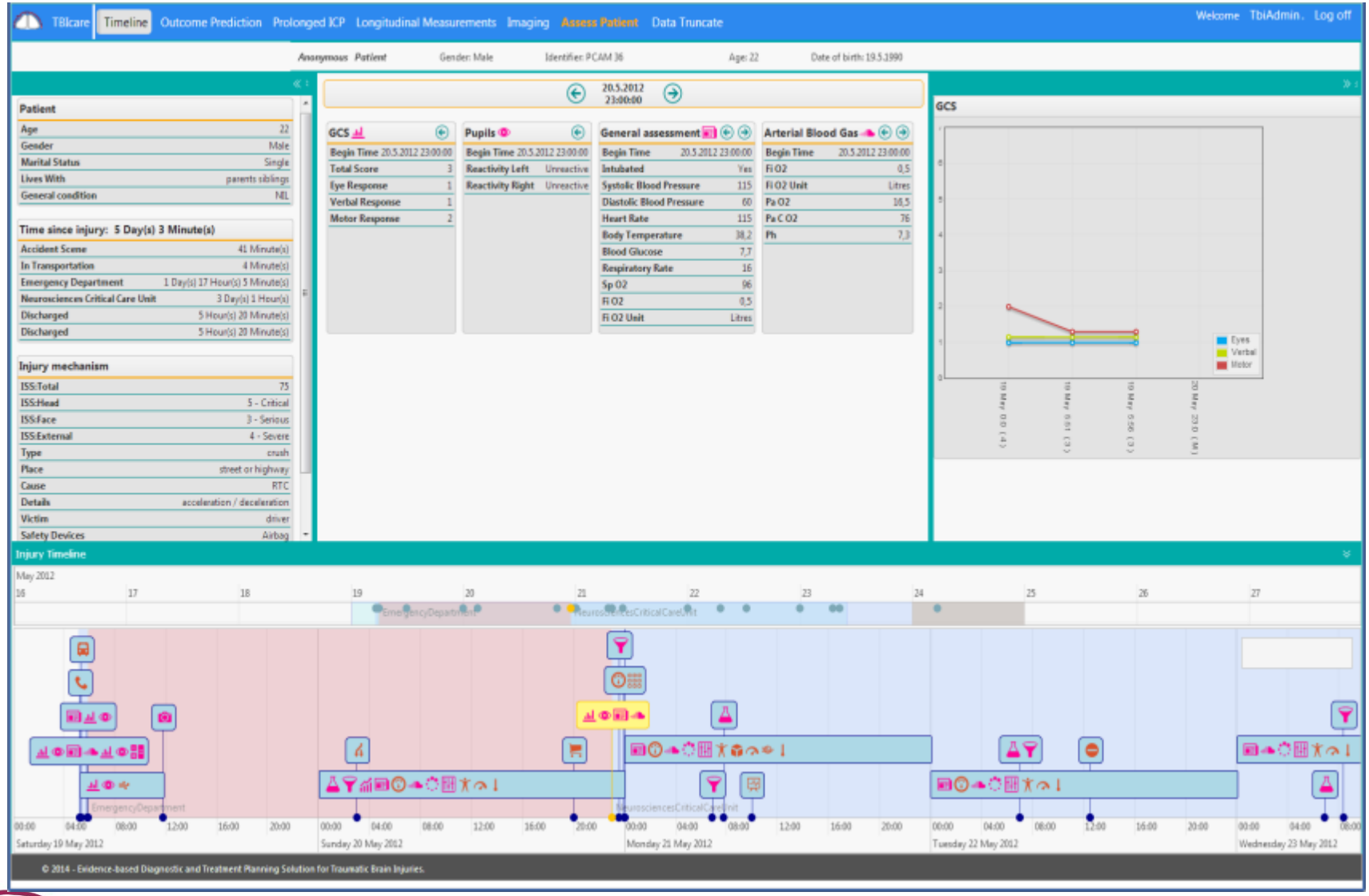
Injury overview



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Graphs for longitudinal data

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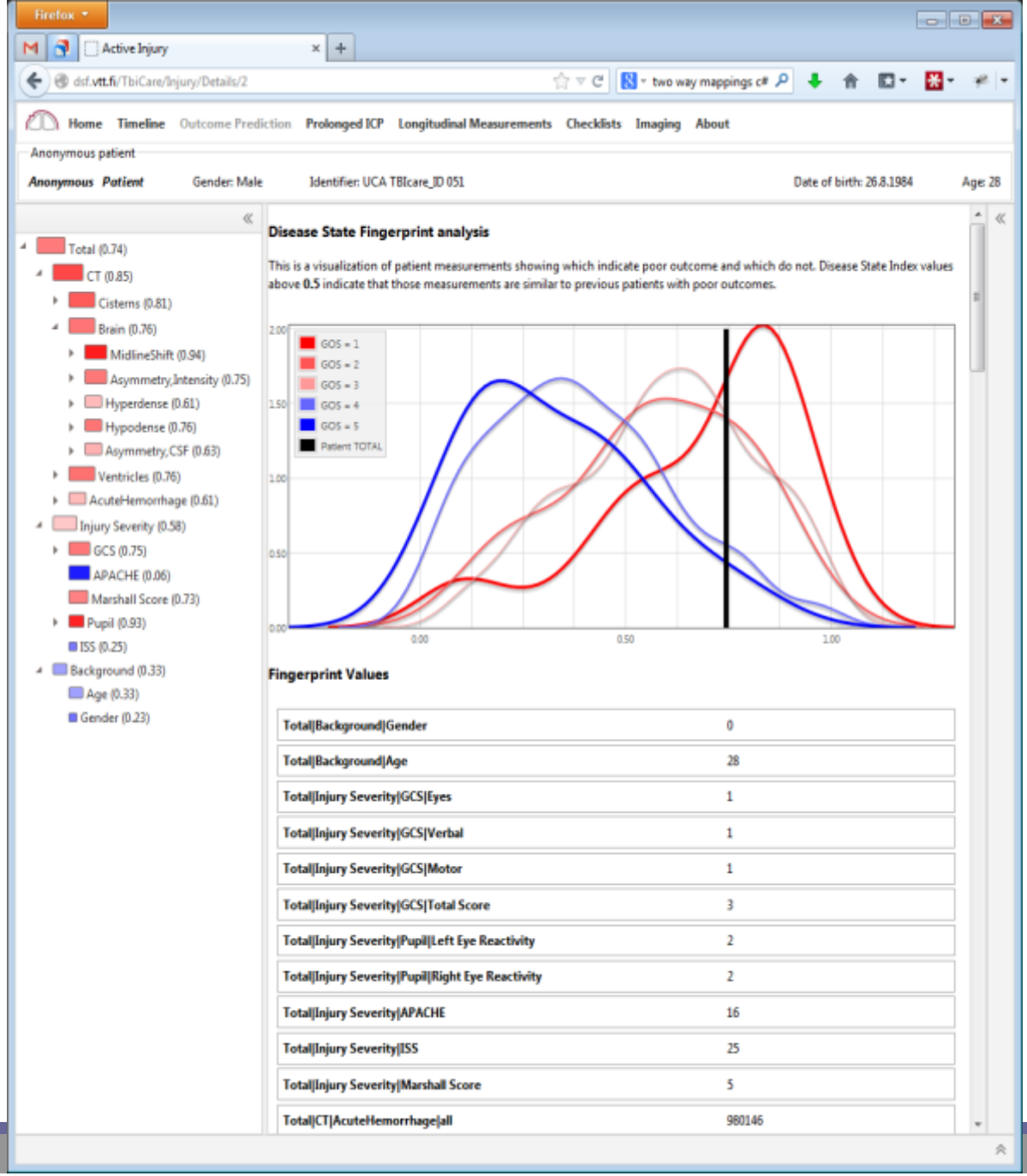

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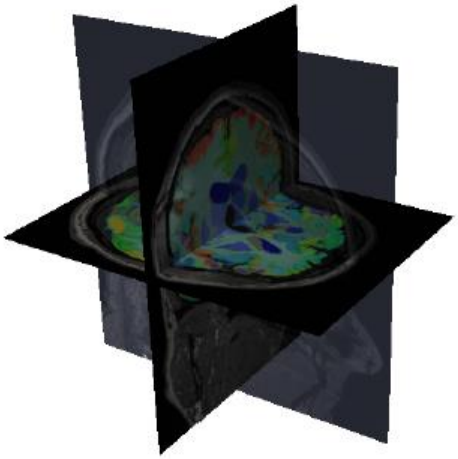
Use automatic analysis of TBI subjects to investigate structural changes

automatic
brain segmentation

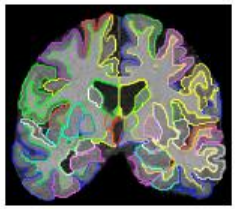


volumetric analysis

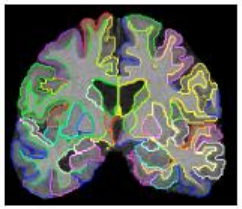
baseline

6 months follow up

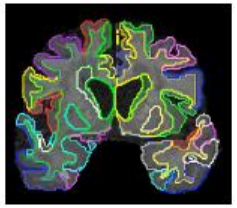
controls or
favourable outcome



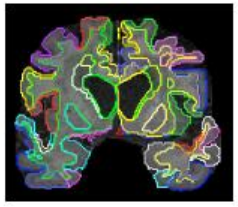
minor
changes



unfavourable outcome



severe
changes



structural changes over time

Human serum metabolites associate with severity and patient outcomes in traumatic brain injury

Matej Orešič[1,2,3], Jussi P. Posti[4,5,6], Maja H. Kamstrup-Nielsen[1], Riikka S. K. Takala[7], Hester F. Lingsma[8], Ismo Mattila[1,3], Sirkku Jäntti[3], Ari J. Katila[7], Keri L. H. Carpenter[9], Henna Ala-Seppälä[5,6], Anna Kyllönen[5,6], Henna-Riikka Maanpää[5,6], Jussi Tallus[5,6], Jonathan P. Coles[10], Iiro Heino[5,6], Janek Frantzén[4,5,6], Peter J. Hutchinson[9], David K. Menon[10], Olli Tenovuo[5,6], Tuulia Hyötyläinen[1,2,3,11]

"Here we applied comprehensive metabolic profiling of serum samples from TBI patients and controls comprised of acute orthopaedic non-brain injuries in two independent cohorts. Several medium-chain fatty acids and sugar derivatives were strongly associated with severity of TBI, and most of them were also detected at high concentrations in brain microdialysates of TBI patients."

"Adding the metabolites to the established CRASH[3] model, comprising of clinical and CT data, significantly improved prediction of patient outcomes. The identified 'TBI metabotype' in serum, that is indicative of disrupted blood-brain barrier, of protective physiological response and altered metabolism due to head trauma, offers a new avenue for the development of diagnostic and prognostic markers of broad spectrum of TBIs."

Classification Results – Turku

- Using the best metabolites gives the best classification performance
- Using all features gave the second best performance

	AUC	Accuracy	Sensitivity	Specificity	#favorable	#unfavorable
All	0.89	0.81	0.73	0.83	119	37
Basic Measures	0.84	0.74	0.78	0.73	119	37
Physiological	0.41	0.53	0.29	0.62	87	33
Laboratory	0.76	0.70	0.64	0.72	108	35
Metabolomics	0.90	0.80	0.81	0.79	60	22
CT	0.85	0.74	0.76	0.74	106	34

All: age, gender, GCS, pupil reactivity, secondary insults, loss of consciousness, post traumatic amnesia, ISS, Marshall Grade, physiological measures, laboratory results, metabolomics data, CT

Basic Measures: age, gender, GCS, pupil reactivity, loss of consciousness, post traumatic amnesia, ISS, Marshall Grade

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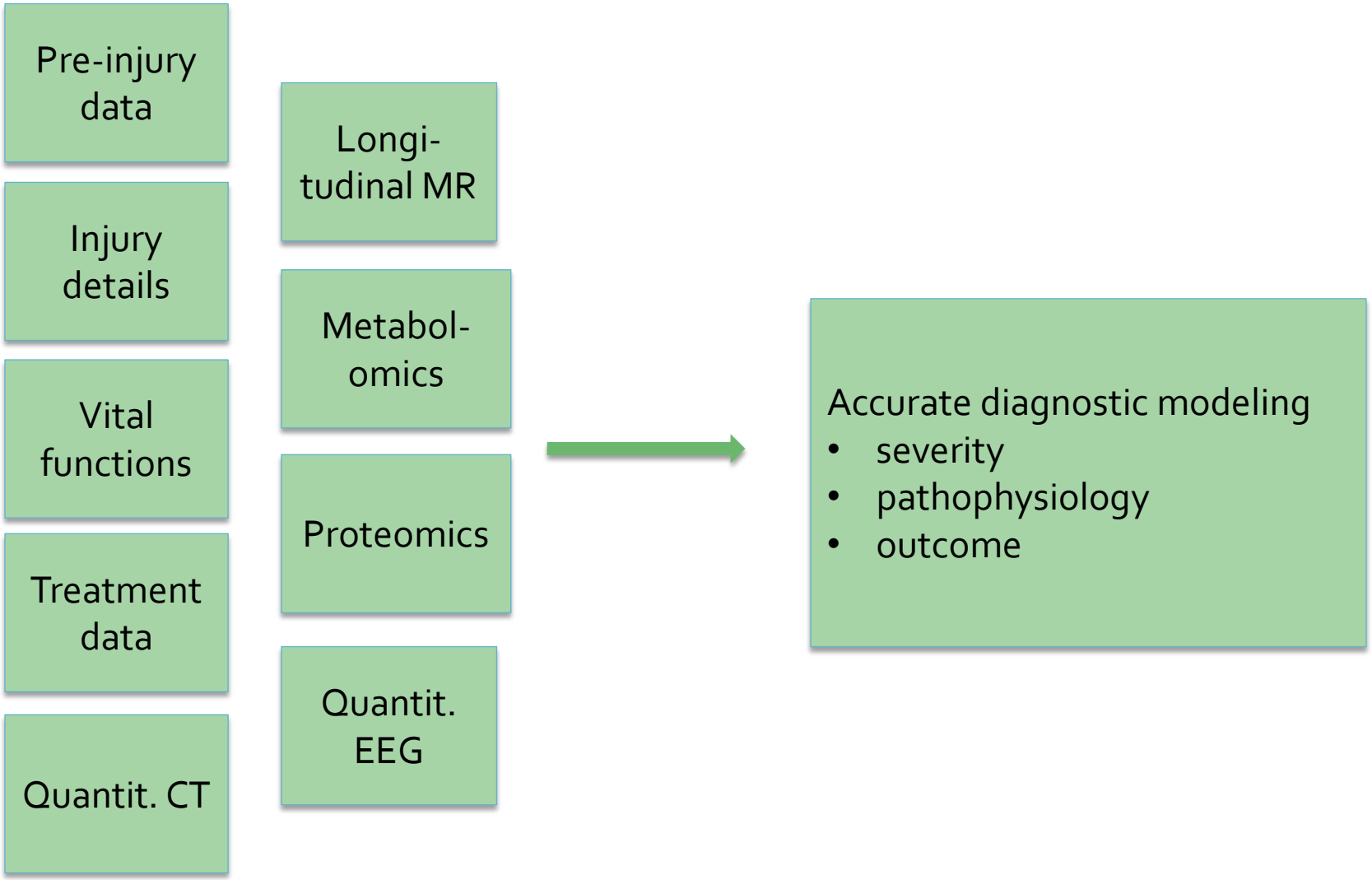
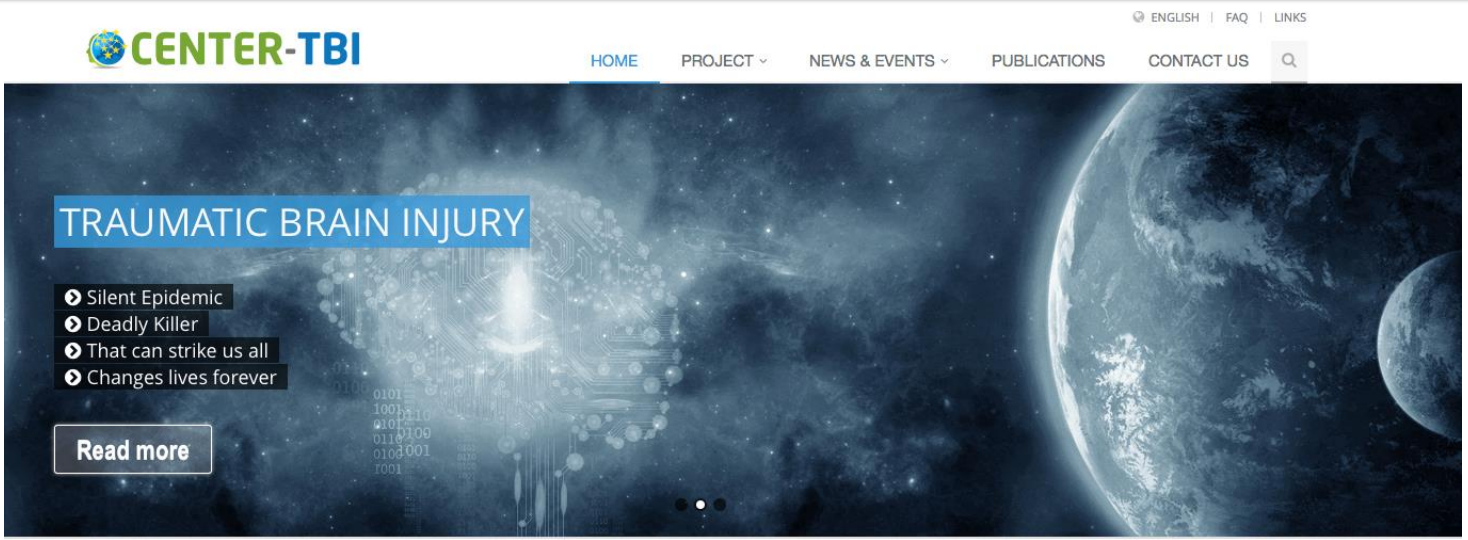
Within near future…



Challenges remain…

- Genetic influences
- Long-term processes
- Neuroinflammation / neurodegeneration
- Treatment windows
- Infrequent injury types
- Etc…

Within not so remote future…



www.center-tbi.eu

Welcome to the CENTER-TBI website!

CENTER-TBI is a large European project that aims to improve the care for patients with Traumatic Brain Injury (TBI).

It forms part of the larger global initiative InTBIR: International Initiative for Traumatic Brain Injury Research with projects currently ongoing in Europe, the US and Canada.

CENTER-TBI brings the newest technologies and many of the world's leading TBI experts together in a much needed effort to tackle the silent epidemic of TBI. International and multidisciplinary collaboration are key elements to the project in which past dogmas will be left behind and innovative approaches undertaken. As Coordinators of CENTER-TBI we are proud to lead this generationally unique project.

We anticipate that CENTER-TBI will revolutionize our view of leading TBI to more effective and efficient therapy, improved health care at both individual and population based levels, and better outcomes at lower costs.

We are grateful to our patients for allowing us the opportunity to advance the care for future patients, and wish all Participants and Investigators success in their efforts.

Andrew Maas
Project Coordinator

David Menon
Co-chairman

A few facts about TBI

- In Europe:
  - 2.5 million people suffer a TBI each year
  - 1 million are admitted to hospital
  - 75.000 will die
- TBI is the leading cause of death and disability in young adults.
- The incidence in elderly patients is increasing.
- TBI can strike us all, but males are about twice as likely as females to experience a TBI.
- In younger patients Road Traffic Accidents are the most frequent cause of injury; in older patients falls.
- Moderate and severe head injury (respectively) are associated with a 2.3 and 4.5 times increased risk of Alzheimer's disease.

The CENTER-TBI website provides general information and further aims to be a communication platform for Patients, Scientific Participants and Investigators. As such, you will also find secure sections on the website with more specific information – these require a login and password.