The TBI Model Systems Program:
- Demonstrates a system of care for TBI
- Performs several types of research
  - A comprehensive longitudinal database already containing over 14,000 cases with up to 20 years of follow-up.
  - National Database Studies
  - Several center-specific clinical trials and other types of studies
  - Innovative module (collaborative) studies
    - Internet and technology utilization
    - Local Projects
      - Dopamine genetics and dynamic gene modifiers for TBI prognostication
      - Mental Health Tele-rehabilitation Tracking Tool Development
- Functional outcome tool development/validation
- Internet and technology utilization
- Local Projects
  - Dopamine genetics and dynamic gene modifiers for TBI prognostication
  - Mental Health Tele-rehabilitation Tracking Tool Development

TBI MS: Education & Dissemination
- Model System Knowledge Translation Center: [www.msptc.org/tbi](http://www.msptc.org/tbi)
- Fact Sheet Menu: Living with TBI
  - Targeting Inpatients and Caregivers
- Local Research Impact: Quick Reviews of Model System Research
  - Acute Inflammatory Biomarker Profiles Predict Risk for Depression After Moderate to Severe Traumatic Brain Injury.
  - Exploratory Associations With Tumor Necrosis Factor-α, Disinhibition, and Suicidal Endorsement After Traumatic Brain Injury.
  - Chronic Inflammation After Severe Traumatic Brain Injury: Characterization and Associations With Outcomes 6 and 12 Months Post-injury
TBI Model Systems of Care: National Trends and Local Experiences/Impact

5th Annual Current Concepts in Brain Injury Rehabilitation
November 1-2, 2014

**TBI MS: Education & Dissemination**

- Brain Injury Association of America (BIAA)

  - Challenge

- Inflammation: A new biological paradigm for Understanding TBI as a Chronic Condition

- BIAA /Mount Sinai TBI Rehabilitation Guidelines Project Under Way
  - 3 year project to develop guidelines for rehabilitation and disease management of individuals with TBI
  - Panelist: Medical Management and Outcomes

**2012-2017 Project Priorities**

“Conduct research that contributes to evidence-based rehabilitation interventions and clinical and practice guidelines which improve the lives of individuals with TBI.”

**National Database Objectives**

- Study the clinical course of individuals with TBI from time of injury through discharge from acute care and rehabilitation care.
- Evaluate the recovery and long-term outcome of individuals with TBI.
- Establish a basis for comparison with other data sources.
TBIMS Database Enrollment Criteria

- Moderate to severe TBI requiring inpatient rehab
- Age 16 or older at the time of injury
- Presenting to UPMC Mercy or Presby for acute care hospitalization within 72 hours of injury
- Must receive both acute hospital care and comprehensive rehabilitation in a designated brain injury inpatient rehabilitation program within the TBIMS
- Medical and rehabilitation care are supervised on a regular basis by a physician affiliated with the TBIMS

Database Study Procedures

- During Inpatient Stay (Form I): Medical record abstraction, pre-injury questionnaire, brief neuropsych battery.
- Follow-up (Form II): Follow up information is to be collected post injury 1 year, 2 year, 5 year, 10 year and every fifth year thereafter or until the subject expires, or requests removal from the study.
- All information is entered online and housed at the National Data Center at Craig Hospital in Englewood, Colorado.

Long Term Outcomes

- How much can we learn about how individuals with TBI feel about life as they return to the community after injury?
- Is there something more we can do long after inpatient rehabilitation is over?
- Where should we aim programs/treatment?
- Longitudinal Assessment of Life Roles after TBI and Relationships to Life Satisfaction
Satisfaction with Life Trajectories after TBI:
A TBI-MS National Database Project

- Individuals with TBI often report low life satisfaction for many years.
- We are examining unique life satisfaction trajectories after TBI and what factors influence those trajectories.
- Initial results indicate that
  - Depression
  - Functional Independence
  - Life Roles (Worker, Friend, Leisure Participant)
- are the most important factors contributing to life satisfaction trajectories after injury.
- Identify long term support and resources for life roles participation

Seizure after Injury

- Who is at risk for seizure after injury?
- How do seizures and seizure meds impact treatment and outcome?
- Are risk factors
  - Biological?
  - Medical?
  - Demographic?
- How can we improve treatment?
- Large Population Epidemiological Studies to Assess Post-traumatic Epilepsy Risk Factors are Lacking

Epidemiology of Post-Traumatic Epilepsy:
A TBI-MS National Database Project

Objective: To evaluate the impact of PTE on long-term outcomes in a longitudinal, multi-center, observational study of TBI by:
- Calculating the prevalence of PTE at 1-20 years post-injury.
- Assessing the unique demographic and injury specific factors significantly associated with seizure prevalence and seizure frequency at each time point.
- Assessing the unique clinical and demographic risk factors for hospitalization due to seizure across recovery.
- Assess multidimensional outcomes for individuals with/without PTE

**Hypothesis**: Individuals with PTE will have more comorbid conditions, rehospitalizations, and worse outcome over time compared to those without PTE.
Probabilistic Matching: TBI-MS and NTDB

**Question:** How do acute trauma factors (e.g., acute care complications) affect long-term outcomes after TBI?

**Methods:**
- Patient data from the National Trauma Data Bank (NTDB) and TBI-MS were matched using probabilistic matching.
  - Use of common non-identifiable data elements (ICD-9 codes, mechanism of injury, birth year, payer status, GCS scores)
  - Matched using a well-defined statistical algorithm.

Probabilistic Matching: TBI-MS & NTDB

**Preliminary Results:**
- Successfully matched using our local trauma registry and local TBI-MS cohort.
- Found that acute nosocomial pneumonia can negatively affect global outcome 5 years after TBI.

**Future Directions:**
- Our goal is to extend this technique to the national TBI-MS and NTDB to answer additional questions regarding long-term consequences of acute care complications after TBI.

Personalized Medicine & Rehabilitation Research

**Challenge:** Rehabilitation involves broad populations with a wide range of impairments, functional limitations, and treatment responses.

**Goal:** provide an “-omics” overlay to the scientific study of rehabilitation processes & multidimensional outcomes
- novel opportunities for person-centered care among populations with disabilities.
Health & Function: A Rehabilomics Framework

- **Pristarini 2011**: The WHO-ICF Model is clinically intended for—
  - Understanding disease beyond the traditional medical model
  - Allows for needs assessment across functional domains of impairment, activity, participation
  - Matching interventions to specific health conditions and complications
  - Rehabilitation and outcome evaluation
- The Rehabilomics adaptation of the WHO-ICF model is a viable framework to integrate a biomarkers based understanding of secondary injury/disease pathology with a rehabilitation relevant and multidimensional view of the recovery process.
  - Biomarkers provide unique information about disease pathology and biosusceptibility (risk) for complications.
  - Framework that can be used to evaluate if biomarkers carry some capacity to discriminate multidimensional outcomes
  - Biomarkers may provide the ability to personalize rehabilitation care and management

Personalized Rehabilitation Medicine
- Diagnostic and Prognostic Biomarkers
- Biomarker guided clinical decision algorithms
- Endophenotypes for treatment effects and symptom monitoring
- Biosusceptibility tools and screening and prevention programs.
- Biological stratification for RCT and Comparative Effectiveness

TBI-MS Local Project

- Two Part Project:
  - Evaluation of how dysfunction in the dopamine systems after TBI might impact outcomes after injury.
    - **Aim**: To assess Dopamine (DA) genetic variant associations with function and recovery, and to develop effective DA-Gene Prognosis Scores
      - Previously recruited Subjects
      - Newly recruited Subjects
  - Pilot study of if/how smartphone apps or other similar electronic resources might be used to collect “real time” data about symptoms and functioning after injury.
    - **Aim**: to develop valid tracking modality of mood and affective symptoms in a community sample of individuals with cognitive impairment after TBI

Why Dopamine?

A few reasons:

- Accumulating evidence supports a “dopaminergic hypothesis” as central to cognitive dysfunction after TBI
- DA agonist medications improve cognition
- Data suggests DA systems may impact post-traumatic depression and may interact with depression to effect recovery based outcomes.
Post-TBI cognitive performance is moderated by genetic variation within ANKK1 and DRD2

- Due to a hypo-dopaminergic state post-TBI genetic variation may impact D2 receptor physiology/function important for cognitive recovery.

- Sample Size N=109 subjects with moderate to severe TBI
- Cognitive composites developed from data collected at 6 & 12 months post-injury
- Functional Variant (Taq1A polymorphism) sits within the ANKK1 gene and affects DRD2 expression.
- Tagging SNPs within the DRD2 gene assessed for gene variation relationships with Cognition

Post-TBI cognitive performance is moderated by genetic variation within ANKK1 and DRD2

- ANKK1 Taq1A heterozygotes have better cognition at 6 and 12 months post TBI

*Significant predictor of cognitive function at 6 and 12 months in multivariate analysis

Post-TBI cognitive performance is moderated by genetic variation within ANKK1 and DRD2

- Rs6279 CC homozygotes do better on cognitive performance at 6 and 12 months

*Significant predictor of cognitive function at 6 months in multivariate analysis
COMT Val158Met Genotype and Sex Interact to Affect Cognitive Dysfunction after TBI

- *Catechol-O-Methyltransferase* (COMT) breaks down and metabolizes dopamine.
  - RS4680 is a known functional SNP in exon 4 which causes a val/met switch
    - val (G) =↑ activity, ↓ DA and more metabolite
    - Met (A) =↓ activity, ↑ DA and less metabolite (Chen 2004)
  - met/met individuals made fewer mistakes on WCST after TBI (Lipsky 2005)
  - Sexual dimorphism in how genetic variation within COMT can affects DA Levels and function
  - Population N=106 subjects
  - 6 and 12 month cognitive composite scores

![Diagram of dopamine metabolism involving COMT and MAO](image)

Cognitive Composite Sex*Gene 6 Months

![Graph showing cognitive composite scores by sex and genetic variant at 6 months](image)

Cognitive Composite Sex*Gene 12 Months

![Graph showing cognitive composite scores by sex and genetic variant at 12 months](image)
Ecological Momentary Assessment

- Traditional assessment relies on retrospective self-report
  - Recall bias using retrospective method
  - Average over a period of time
- EMA addresses limitations
  - Repeated longitudinal assessment
  - Real time
  - Natural environment
- EMA allows for more holistic measure of constructs of interest (i.e. mood)

"-omics" research paired with real-time monitoring technologies can link biology to multi-disciplinary outcomes and rehab-relevant metrics to individuals as they occur in the community setting.

Rehabilomics Research Capacity and Tools

Development/usability assessment of mobile phone apps for mood tracking in populations with TBI & cognitive dysfunction

iPerform: for iphone, android

- TBI symptoms using mAPP Technology
- Assess mental health symptoms in participants with cognitive dysfunction
  - Beta testing with patients and providers
  - Language, layout, processes user friendly
  - Reminders to enhance compliance
  - EMA Symptom profiles compared with retrospective assessment
- 2-way encrypted interactive health provider portal system to monitor chronic symptoms and intervene in the setting of suicidality.
  - First subject with known PTD, Anxiety, Memory deficits: 92.6% correct assessment completion
Overall, our long-term vision is for a POC Biomarker and EMA model of chronic, community-based care for individuals with TBI embraces the Rehabilitomics model to generate a truly translational and paradigm-shifting approach to chronic care in populations dealing with the long term effects of TBI.

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**Additional Resources**