Rehabilomics Research: A biomarkers based approach to assessing multimodal outcomes after TBI
Amy K. Wagner, MD
Associate Professor, Vice-chair Faculty Development
Department Physical Medicine and Rehabilitation
Associate Professor, Neuroscience
Associate Director, Rehabilitation Research
Safar Center for Resuscitation Research

Presentation Overview

- Rehabilomics: Conceptualizing a Framework
- Rehabilomics Exemplar: Dopamine Systems and Effects on TBI Recovery
- Rehabilomics: Using Technology to Forge a Path Towards Clinical Translation

2015
The NEW ENGLAND JOURNAL of MEDICINE
A New Initiative on Precision Medicine
Francis S. Collins, M.D., Ph.D., and Francis S. Collins, M.D.
“Tonight, I am launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”
President Barack Obama, State of the Union Address, January 20, 2015

Precision medicine: is an emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle

- Near Term Focus: Cancer
  - Already advanced in use of biomarkers and genomics
- Long Term Focus: Health and Disease
  - How does disability fit within the PMI?

2015
The NEW ENGLAND JOURNAL of MEDICINE
Goals: Improve & Personalize the ways we anticipate, prevent, diagnose & treat health conditions

- Genomic Heterogeneity; Personal Biology
- Better understanding of Disease Mechanism
- Medical and Bioinformatics
  - Molecular, cellular, clinical, behavioral, physiological and environmental
- Adaptive Clinical Trials; Stratified Clinical Trials.
  - The right drug at the right dose to the right patient.
- (2016) NIH awards $55 million to build million-person precision medicine study
  - Populations with Disabilities?

Precision Medicine
Thinking Beyond Disease to Disability

- Disability is a Global Problem
  - (WHO 2011) More than 1 billion persons in the world have some form of disability.
    - ~15% of the world's population.
    - Between 110-190 million people have very significant difficulties in functioning
  - (CDC 2015) ~53 Million Live with Disability in the US
    - 1 in 4 women
    - 3 in 10 Non-Hispanic Blacks
    - $400 Billion/Yr Healthcare Expenditures
    - More likely to have chronic disease

Precision Medicine
Thinking Beyond Disease to Disability & Function

- Neurological Injuries: Stroke, Traumatic Brain Injury, Spinal Cord Injury
- Neurological Diseases: MS, Epilepsy, Parkinson’s, Huntington’s, Alzheimer’s
Rehabilitation Defined

- World Health Organization:
  - Rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social levels of function.
  - Rehabilitation provides people with disabilities with the tools they need to attain independence.

Rehabilitation: A Personalized Path to Function

- At the core of Rehabilitation and Function is Personalization:
  - Rehabilitation represents by nature a functional model of “Personalized Care”.
  - Individualized assessment: of physical, cognitive, emotional, and social systems.
  - Medical rehabilitation and individualized therapies work synergistically to optimize functional recovery.

- Genetic and Molecular Signatures: may further guide personalized care and add to what we do functionally in clinical rehabilitation programs & treatment plans.

Rehabilomics: Moving from Personalization to Precision in Rehabilitation Medicine

- Rehabilomics Research Framework: intended to provide an “-omics” overlay to the scientific study of rehabilitation processes & multidimensional outcomes.
- Novel opportunities for precision rehabilitation medicine among populations with disabilities.
  - Diagnostic and Prognostic Biomarkers
  - Biomarker guided clinical decision algorithms
  - Biosusceptibility tools and screening and prevention programs.
  - Biological stratification for RCT and Comparative Effectiveness

WHO-ICF: Multi-Dimensional Function

- Understanding disease beyond the traditional medical model
- Allows for assessment across functional domains of impairment, activity, participation

Rehabilomics adaptation of the WHO-ICF model integrates a biomarkers based understanding of secondary injury/disease pathology with a REHABILITATION RELEVANT & multi-dimensional view of disability and recovery.

TBI translational rehabilitation research in the 21st Century: exploring a Rehabilomics research model

- Globally, traumatic brain injury (TBI) is a leading cause of death and persistent disability.
  - Vehicular Collision, Falls, Violence, Military, Sports, Child Abuse
  - Heterogeneity with Injury Mechanism & Response to Injury.
  - Heterogeneity in Recovery & Treatment Response
    - No proven neuroprotective therapies
    - Some success with neurostimulant trials: MPH Bromocriptine
    - 2012 NEJM: Amantadine Promotes TBI Recovery
    - Dopamine Systems: implicated in other neurological and mental health diseases.
Dopamine Systems and Genetic Variability

- Schizophrenia
- Addiction
- Parkinson's Disease
- ADHD
- TBI?

TBI Effects on Dopaminergic Systems
- Wagner 2005, 2009
- Functional Hypodopaminergia
  - Injury reductions in DA neuro-transmission
  - Reversal of deficits with daily Methylphenidate

TBI: Cognition, Mood, and Behavior
- Changes in behavior, emotion, cognition, and daily activities influence and interact with each other in complex ways
  - Symptoms can persist for decades post-injury
  - Can negatively affect social functioning, health, and quality of life
- 50% of individuals with moderate to severe TBI experience post-traumatic depression
- Post-acute behavioral problems are reported in ~54% of individuals with sustain a moderate to severe TBI
  - Apathy, impulsivity, anger, aggression
  - Can be amplified in the setting of other stressors (e.g. depression/PTSD)
- Cognitive and behavioral impairment and activity limitations most associated with community reintegration post-TBI.
- DA Neurotransmission: may be an important effector of cognition/mood/behavior
  - How do DA genes influence cognition?

Sex Dichotomy with DA Genetics
- Gurvich 2015: Sex effects COMT Val158Met & DRD2 6269
  - attention tasks.
- Gurvich 2015: Sex affects DRD2—rs6277 genotype
  - executive functioning tasks
- Jacobs 2011: COMT has an ERE near Val158Met functional variant
  - affects transcription status and cognition.
- Glatt 2006: Sex effects on VMAT2 genetic variation in the promoter region in risk for Parkinson’s disease
  - women selectively garner protective effects and a reduced risk with this polymorphism

DA Genetic Biosusceptibility to Cognitive Dysfunction
- JHTR 2015: DRD2 & Taq1a polymorphism associated with cognitive composite measure performance 6 & 12 months after severe TBI
- JHTR 2016: VMAT2 SNP polymorphism associated with cognitive composite scores and worse functional cognition & 6 & 12 months after severe TBI.
- JHTR 2015: A dopamine pathway gene risk score for cognitive recovery after TBI
- Hypothesis: Sex specific effects of DA Genes on Cognition

Building a DA Gene Risk Score (GRS)
GRS Considerations
- Useful when many small, incremental genetic risk effects contribute to risk associations
- Genetic “load” assumption
GRS Population
- 182 white adults w/ severe TBI (16-75 years old)
- Cognitive Composites: T-scores for Executive functioning, attention, verbal fluency, memory
- Genotyped for previously published DA gene variants
  - (ANKK1, DRD2, COMT, VMAT, DAT)
GRS Formulation
- Stratified population by sex & evaluated bivariate gene associations cognitive composites.
- Used weighted beta-coefficients derived from these bivariate regressions as sex-specific multipliers for each gene when calculating the GRS
Sex-Specific GRS Score Formulation

Behavior and TBI

- 81 adults with moderate-severe TBI in an ongoing study collecting genetic samples and outcome data at 12 months post-injury
- Hypothesis: Genetics would influence behavior in the context of depressive symptoms.
- Genetics: COMT and ANKK1 Risk Genotypes
  - COMT: Met-carrier
  - ANKK1: A2/A2 homozygotes
- Behavior: Frontal Systems Behavioral Scale (FrSBe)
  - Self-reported (primary) and family-reported (subgroup)
  - Apathy, Disinhibition, Executive Dysfunction
- Scaled T-scores used for analysis.
- Depression: Patient Health Questionnaire-9
  - Self-reported and based on DSM criteria
  - Dichotomized into Depressed/Not Depressed

DA Genetics & Behavioral Dysregulation

- Depression was significantly associated with behavioral dysregulation
- COMT and ANKK1 are only associated with behavioral dysregulation in the context of depression

Among Depressed Individuals

Conclusions

- DA genetics may play an important role with heterogeneity and prediction of cognitive & behavioral dysfunction post-TBI
  - Validation studies are required
- Innate factors such as sex, and clinical factors such as depression, may interact with genetics to contribute to cognitive and behavioral recovery following TBI.
- A GRS reflecting the DA pathway as a whole may prove to be an effective method of examining effects of individual polymorphisms polygenic traits
- As future polymorphisms of interest are identified, they can be added to create a more inclusive GRS
- Translational Need: to identify the downstream impact that DA genetics has on functional impairment and Disability.

Behavior Dysfunction Prediction: 12 Months Post-Injury

Ecological Momentary Assessment: Toward Research Translation

- Repeated measures
- Natural environment
- Reduces errors
- Ecologically valid
- Real time
- Community-based
- Reduces bias
- Leverages technology

Part of larger technology development arena where biosensors, body media and point of care monitoring have gained increasing traction.
Rehabilomics Research Capacity and Tools
NIDILRR TBI MS 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
  - 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 symptoms of fatigue, affect depression & anxiety
  - Every other day EMA assessment for 8 weeks
  - Telephone interview every 2 weeks.
- Brain Injury (2016): 20 subjects community dwelling and with previous TBI 73.4% correct completion rate. High correlation with telephone assessments (81-93%)

**EMA after TBI: Pilot Study Results**

**Measurement-related findings:** Within-person and between-person symptoms variability (n=18)
- Positive and Negative Affect Schedule (PANAS)
- Patient Health Questionnaire 2 (PHQ2)
- Generalized Anxiety Disorders 2 (GAD2)
- Fatigue impact: Rating of agreement (1=strongly disagree to 2=strongly agree) for the statement, “Fatigue interferes with my work, family, or social life.”

**Over the 8 weeks of the study, participants reported significant within-person variability over time (p<.002)**

Psychometric validation: needs to be assessed in the context of EMA High resolution temporal symptom profiling & technology based interventions Link to handheld POC Biomarker Technology

**Overall,** our long-term vision is for an integrated Point of Care Biomarker and telehealth model of chronic, community-based care for individuals with TBI that provides Personal Biology readouts for risk stratification and clinical decision making to personalize approaches to chronic care in populations dealing with the long term disability associated with their TBI.

**Acknowledgements**
- NIH R01HD048162, P01NS030318, R01NR008424, R21HD071728
- DOD W81XWH-07-0701, W91XWH-08-1-0237 NIDILRR: 90DP0041
- Collaborators: Yvette Conley, Ph.D., Anthony Fabio, Ph.D., Joseph Ricker Ph.D, C. Edward Dixon, Ph.D, Patrick Kochanek, MD, Patricia Areth, Ph.D., Robert Ferrell, Ph.D.; Julie Price, PhD, Tomas Drabek, MD
- Post-Doctoral Research Associates: Joelle Scandon, PhD; Huichao Zou, MD, PhD; Shannon Juengst, PhD, Xiangbai Chen, MD PhD
- Technical Support: Sandra Delouches, Christian Niyonkuru, MS, Emily McCullough, MPH; Martina Santarsieri, BA.; Raj Kumar, MPH; Elizabeth Brough, BA
- Students: Megan Miller, BS, Michelle Carter Failla, PhD, Krutika Amin, MPH., Matthew Diamond, BS Jennifer Boles, MD, Akash Goyal, BS, Nasia Jamil, BS, Rashed Harun, PhD, Steven Marks, BS, John Myrva, BS, Miranda Munoz, BS, Christine Grassi, BS, Kristen Hare, BS.

**UPMC Rehabilitation Institute**