Globally, traumatic brain injury (TBI) is a leading cause of death and persistent disability. Although improvements in standard of care have reduced the overall mortality rates associated with this disease, there is a paucity of effective neuroprotective therapies. However, some rehabilitation focused strategies have shown promise with enhancing neurorecovery. One major challenge in identifying effective therapies is that TBI is an inherently heterogeneous disease. Despite many patients having similar injury factors and clinical care after their TBI, recovery and outcomes can be very different. This commentary discusses the value of treatment effectiveness research that also incorporates theranostic principles of individualized care. Key to this concept is the utilization of state-of-the-art biomarker platforms and technologies that can identify relevant molecular or physiological fingerprints that can assist rehabilitation practitioners in delineating long term outcome that can be linked to plasticity, treatment response, and natural recovery. This commentary proposes a unique concept of “Rehabilomics” as a field of study involving the systematic collection and study of rehabilitation relevant phenotypes, in conjunction with a transdisciplinary evaluation of biomarkers, in order to better understand the biology, function, prognosis, complications, treatments, adaptation, and recovery for persons with disabilities. Specific Rehabilomics applications to TBI research, as well as relevance to the National Institutes of Health Roadmap, are discussed.

Key words: Brain injuries - Rehabilitation - Biological markers - Evidence based medicine - Rehabilomics.

Approximately 1.4 million TBIs occur each year in the United States. Of these, approximately 50,000 result in death, and 1.1 million are mild injuries, for which individuals are treated and released from the emergency room. The remaining 235,000 individuals who survive moderate to severe TBI, generally require significant medical care and hospitalization. Aside from traditional mechanisms of injury like motor vehicle collisions and falls, other less discussed and/or emerging mechanisms significantly contribute to the incidence and prevalence. In the US, approximately 1 million children are severely abused each year, and many of these children sustain serious brain injury as a result. Also, an emerging group at risk for sustaining TBI is members of the military. Walter Reed Army Medical Center in Washington DC, USA reports that 30% of service members evacuated from the field had sustained a TBI between 2003 and 2005, almost three quarters of which sustained blast injury. Globally, TBI is a leading cause of death and disability. While exact worldwide statistics are difficult.
to obtain, a recent review estimated approximately 775,000 new TBI hospitalizations per year in Europe. Available information suggests that the epidemiology of TBI on a global scale is similar to trends found in the USA. Incidence of TBI by age and gender vary slightly across regions, but overall appear to follow patterns similar to those found in the USA. For example, the distribution of mild, moderate and severe TBI is consistent across U.S., Europe, Australia and Asia.

The Growth and Development of Omics research in medicine in the United States

The National Institutes of Health (NIH) has been the primary pillar of medical research funding in the USA, particularly in the areas of mechanistic and hypothesis driven research. In addition to funding through other institutes like the National Institute on Aging (NIA), the National institute for Neurological Disease and Stroke (NINDS), and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), the National Center for Medical Rehabilitation Research (NCMRR) has been a consistent supporter of rehabilitation focused clinical and translational research. In 2002, the NIH began developing its Roadmap for Medical Research in the 21st century by identifying new pathways to discovery, developing interdisciplinary research teams of the future, and re-engineering the clinical research enterprise. The NIH Roadmap for Medical Research was launched by 2004, and by 2006, the US Congress passed legislation to create the NIH Common Fund to support the programs implemented through the NIH Roadmap for Medical Research. To date, the common fund supports initiatives directed by the Office of Strategic Coordination that foster high-risk/high-reward research, enable the development of transformative tools and methodologies, fill fundamental knowledge gaps, and supports academic cultures that foster collaboration.

Many clinical research training programs are a part of the NIH’s efforts to re-engineer the clinical research enterprise as are Institutional Clinical and Translational Science Awards. These types of large scale awards have been set up to help increase accessibility to cutting edge techniques and to appropriate expertise wherein the technology is “brought to the masses” of clinician scientists who can leverage these resources for conducting innovative and contemporary research with high translational impact to patients and clinical care. Centers for genomics, epigenomics, proteomics, imaging, systems biology, and computational/bioinformatics research have been emphasized as key components of these large infrastructure program projects. These and other areas are also central themes from which a program of requests for applications (RFAs) for investigator initiated, exploratory, and consortium or network based, and exploration applications have been funded. Within this framework, infrastructure is needed for the rigorous development, tracking and maintenance of bio-repositories, linked with relevant clinical information, which can be accessed by interested users. These types of research and infrastructure initiatives have paved the way for programs of biomarkers research to flourish across numerous disciplines including rehabilitation. Further, entities like the non-profit Foundation for NIH have helped facilitate ground breaking findings in biomarker research as a part of its mission and regularly partner with small business entities to help translate these biomarkers research discoveries into clinically useful assays and technology.

Rehabilomics research: keys to research exploration for evidence based treatment and theranostics

As rehabilitation researchers, we are also ideal candidates to partner with basic scientists and utilize core facilities to conduct “omics” research that is relevant to the rehabilitation research mission. Our training naturally allows us to think in terms of innovative treatment and care teams, systems based and best practices approaches to treatments, and in the importance of individualized and customized care that maximally impacts function for each patient. Our field is faced with the constant strain of having to prove and justify treatment effectiveness. Additionally, our field has historically struggled with the uniqueness of our skill set and necessary tools to effectively conduct rigorous clinical trials that allow us to establish treatment effectiveness, yet preserve the theranostic principles of individualized care. In many ways, these seemingly opposed dual goals can be achieved through an “-omics” based approach where in we can utilize the necessary mo-
molecular tools to understand the mechanistic underpinnings of current treatments and care algorithms as well as use molecular biomarker information systematically to guide individualized treatments and optimize outcomes. Clinically, biomarkers are routinely used in medicine to monitor biological and pathological processes that ultimately aid in patient management and care. Much of biomarkers research is exploratory in its nature, and the tools and processes by which to conduct biomarker measurements are similar across disciplines. Biomarker profiles, or molecular fingerprints, have the potential to assist rehabilitation practitioners in delineating long-term outcomes that can be linked to plasticity, treatment response, and natural recovery. Biomarkers studies can also serve as dynamic and manipulable endophenotypes that reflect treatment response. Key to these concepts is the development of advanced statistical modeling approaches that can be used to predict a broad range of phenotypes, including complications, and the use of advanced biomathematics that utilize time-series data and machine learning algorithms. Biosample repositories, including samples from healthy subject and other control groups, with links to rich clinical data are also a necessary resource for effective and informative biomarkers research.

The term phenomics is generally derived from the resultant phenotypes or observable traits that result from genetic variability. More recently and as a part of the NIH Roadmap Initiatives, the term phenomics has been adopted to advance understanding of neuropsychiatric phenotypes on a genome-wide scale. An evolution in the concept of phenomics has emerged with the need to efficiently and effectively evaluate the large amounts of data generated using the high-throughput technology platforms available for biomarkers research. To this end, phenomics research may be further defined as a means to link variation in several types of biomarker data to specific syndromes, traits, outcome, or behavior. Although a new field, effective phenomics strategies can provide a central platform by which to integrate biomarker associations across multiple domains to best inform the biological basis for a particular condition, syndrome, or complication. Phenomic strategies that span across species are particularly important when making the link between bench and bedside for specific treatments or therapies. Since the human phenome is vast and dynamic, approaches to capture the complex and changing interface between patients and their treatment environment require an integrated approach that is not dissimilar from the integrative and transdisciplinary approach that characterizes rehabilitation clinical care models.

In the rehabilitation setting, relevant phenotypes must be anchored across the multiple domains of impairment, disability, and handicap, as this framework guides our treatment and management strategies clinically. The World Health Organization (WHO) has provided widely accepted definitions of impairment, disability, and handicap that have resulted in a conceptual framework by which worldwide research has been conducted investigating the impact of injury and illness on individual function. This system later was replaced by the International Classification of Functioning, Disability and Health (ICF), providing an updated framework for rehabilitation research. Several existing assessments measure outcome within more than one domain. However, multimodal assessments are often necessary to effectively reflect the complex range of factors affecting outcome. No single measurement tool can encompass all relevant areas of outcome. Ceiling effects, sensitivity to change over time, cultural biases with test administration, mode of administration, and applicability to the test population are all considerations to keep in mind. However, as physiatrists and rehabilitation practitioners, we can be well equipped to develop and apply innovative phenotyping tools, such as online symptoms and activity diaries and wearable biosensors for activity, physiology, and kinematic data acquisition. For our rehabilitation populations, appropriate phenomic profiling requires tracking individuals from the bedside to the community. It also requires an intimate understanding of how disease impacts impairments, disability, and quality of life. Rehabilitation based phenomic strategies also must incorporate the use the adaptive strategies and technologies that limit both impairments and the disabilities associated with a disease.

To date, rehabilitation focused biomarker research has been lacking, both at the clinical and preclinical levels, and has not taken advantage of the tremendous potential that biomarker research tools and platforms can provide. 1) to better understand these diseases from a rehabilitation perspective; 2) to gain a better understanding of long-term prognosis.
sis and recovery; and 3) to develop more biologically grounded rehabilitation treatment strategies for optimizing recovery. With the evolution of institutional core facilities and the potential that biomarkers research have in aiding rehabilitation research and discovery, the time has come to develop the concept of Rehabilomics research as a field of study. Given the unique framework required to understand the integration of biomarkers and their relevant phenotypes in rehabilitation research, we propose a unique concept of "Rehabilomics" as a field of study to reflect these interrelated research areas. Thus, Rehabilomics Research refers to the systematic collection and study of rehabilitation relevant phenotypes, in conjunction with a transdisciplinary evaluation of biomarkers, in order to better understand the biology, function, prognosis, complications, treatments, adaptation, and recovery for persons with disabilities.

Within this view, Rehabilomics research spans from bench to bedside to community, addresses common problems and issues that occur within the populations of people with disabilities, and incorporates a rehabilitation focused model. Given the needs for rehabilitation research and advances in the field of biomarker research, now is a perfect time for inception of the field of Rehabilomics. Within this research framework is the need to integrate rehabilitation structured bioinformatics tools as well as rehabilitation technologies and engineering devices into Rehabilomics research design. The study and development of Rehabilomics Research must also go beyond what is needed for adequate assessment in the research setting and have a tangible role in patient care. The ability to leverage and integrate assistive technologies as a mode of intervention, meant either to enhance functional outcome or to incorporate as an adjunct technique when monitoring biomarker response to exercise or other therapeutic activity, is a framework from which the fields of rehabilitation medicine and engineering can come together to uniquely enrich Rehabilomics Research. For example, researchers at the University of Pittsburgh are leaders in clinical neurobiology, biomarkers, developing core biomarker facilities, and assistive technology research, and they are working collaboratively to spearhead new Rehabilomics Centers of Excellence, particularly in the area of TBI (see www.rehabilomics.pitti.edu).

Building blocks for a rehabilomics model of rehabilitation research in TBI

Genomic and proteomic biomarkers used in rehabilitation research in general carry tremendous potential to unlock clues about the molecular neurobiology of injury, plasticity, and recovery as well as discover the molecular substrates for treatment effectiveness for many of our rehabilitation interventions. Biomarkers may have specific potential for further understanding of TBI specific concepts like the development and resolution of diaschisis. Molecular fingerprints can be identified to reflect neuroplasticity, cognition, and functional indices of global recovery that also serve as prognostic tool and proxy measurements for treatment effectiveness. Although biomarkers are often conceptualized from a molecular framework, cognitive and imaging markers of functional activity and structural damage can also be effective tools in TBI rehabilitation research.

Despite many patients having similar injury factors and clinical care after their TBI, recovery and outcomes can be very different. Intrinsic factors like gender and age can significantly impact response to injury and path for recovery. This variability in response to injury and treatments also may be attributable to genetic variation in DNA that patients bring to recovery, and genetic background may interact with other innate factors like gender and age to uniquely impact recovery. Genes represent a rich biomaterial for assays identifying individual-specific data for how a person may respond to an injury or treatment and degree of risk for particular complication after an injury as occurred. For traumatic injuries, genomic data can be collected and analyzed a priori for groups at high risk (e.g. military combat personnel, contact sport athletes). The majority of genomics studies in TBI have focused on apolipoprotein E (APOE). The largest study conducted in TBI evaluating possession of the APOE4 allele and outcome found a significant age-genotype interaction where adolescent-young adult patients carrying APOE4 had worse outcomes compared to younger patients without this allele.\textsuperscript{14} In addition, variability within the neprolysin gene, the primary enzyme responsible for beta-amyloid degradation, impacts the incidence of Alzheimer's type beta-amyloid plaques in TBI.\textsuperscript{15} More recently, dopamine genes have been implicated in secondary injury and outcome,\textsuperscript{16, 17} while genetic variability in the adenosine A1 recep-
The molecular consequences of injury and clinical treatments can dynamically interact with each individual’s genetic makeup to effect gene transcription and protein translation. Several examples suggest how techniques such as gene array studies have been valuable in sorting out mechanisms of secondary injury by sampling injured tissue in both humans and in experimental models of TBI, with some studies characterizing the response to treatments. Increased attention has focused also on the epigenome and how dynamic modification of chromatin can have unique implications with regard to phenotypes including outcomes from injury. Technological advances are now in place such that significant portions of the Human Methylome have been mapped and that comparative analyses could be made in relation to pathological conditions.

These techniques then allow scientists to begin to understand the interplay between genes and environment. Leveraging the power of transcript changes or epigenetic marking in rehabilitation research may provide another unique avenue from which to study the molecular mechanisms of complex treatments like cognitive rehabilitation programs or mass practice techniques in treating patients with TBI.

Proteomic biomarkers are a part of mainstream clinical care to quantitatively assess and define injury in almost every organ system other than the brain. However, biomarkers have the potential to assist clinicians with TBI diagnosis, prognosis, and treatment and management strategies. TBI proteomic markers of structural damage such as myelin basic protein (MBP), neuron specific enolase (NSE) and glial fibrillary acidic protein (GFAP) have been identified that represent damage to neurons and glia. Other proteomic markers reflect secondary injury, many of which also have prognostic potential. Whether markers of structural damage or mediators of secondary injury and recovery, proteomic biomarkers have the potential to serve as a physiological proxy for measuring treatment effects for TBI, particularly for treatment endpoints important for rehabilitation based trials such as timing and dose as well as carryover and maintenance effects of treatments.

While injury scales such as the Glasgow coma scale (GCS) and injury severity score (ISS) have shown sensitivity in predicting outcome in multiple populations with TBI, less is known about the ability to establish interrelationships between TBI biomarkers, injury and intrinsic factors, and measures of long term functional outcome, disability and cognitive performance. Most biomarker work in the TBI field has focused on associations between a singular marker of interest and global outcome or survival status. Further, primarily point estimates of biomarkers have been utilized, (e.g., max, mean) and less is known if or how temporal modeling strategies such as area under the curve (AUC) or group based trajectory analysis (TRAJ) are more informative. Also, the field of molecular bioinformatics has exploded such that there is easy access to databases capable of providing end-users with complex and informative systems biology models of cellular function. As such, novel statistical modeling systems are emerging to allow one to more fully describe the complex relationships that exist between biomarkers thought to act within a shared biochemical pathway and a disease/injury and their collective relationship with outcome. Structural equations modeling (SEQM) is one statistical application that has been used to represent these biological relationships with respect to hormonal influences in TBI. Specifically, clinical research applications of TRAJ and SEQM have been applied to hormone profiles and outcome prediction after TBI.

It has been suggested that both structural and functional neuroimaging could be considered as potential “biomarkers” of injury, recovery, and outcome in neurorehabilitation populations. This potential has begun to be realized through the incorporation of diffusion tensor imaging (DTI), functional connectivity indices, and functional MRI (fMRI). Contemporary research in these fields has now begun integrating these imaging indices to understand the structural framework for specific changes in brain function. Functional and cognitive testing results have typically been viewed as phenotypic measures of outcome, but cognitive testing results or functional profiles may also be considered “biomarkers.” As an example from related fields, early memory deficits have been recognized as predictive of future onset of Alzheimer’s dementia in people with a family history of the disease. Likewise, our field uses neuropsychological or functional status frequently...
to predict further progression or recovery from deficits after acquired brain injury.

Previously, the NINDS May 2000 Clinical Trials in Head Injury Study Group identified and discussed many of the issues associated with failure to produce positive results with several recent randomized clinical trials (RCTs) aimed at neuroprotection.31 Group recommendations are consistent with the development of a TBI Rehabilomics Program of study, and although discussed from the perspective of RCT, the themes conveyed represent key elements of biomarker research across a wide range of applications. The group concluded that in order for RCT’s to be effective, it is essential to: 1) establish that a drug or proposed intervention is having the desired effect on a specific mechanism of injury in vivo; 2) obtain adequate pre-clinical data; 3) target subpopulations of patients most likely to benefit from the treatment; 4) standardize clinical care; 5) choose appropriate outcome measures or endpoints; and 6) have reasonable expectations for treatment effects. From a Rehabilomics perspective, utilizing injury related prognostic (biomarker) variables, as well as innate variables like genetic makeup, in the selection criteria for studies may allow investigators to effectively target subpopulations for particular interventions. Functional status at the time of entry into rehabilitation trials in particular may be more prognostic of outcome and a more relevant biomarker than acute injury variables. Finally, smaller effect sizes, the careful design and use of sensitive outcomes as well as the judicious use of relevant proxy variables (biomarkers) as phenotypes may allow investigators to appreciate subtle treatment effects for specific interventions. These points support future viable Rehabilomics focused strategies for effective RCT design in TBI, the product of which will be clinical relevant treatment and management strategies that materially improve the lives and future of persons living with TBI.

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