Special article

A Rehabilomics framework for personalized and translational rehabilitation research and care for individuals with disabilities: Perspectives and considerations for spinal cord injury

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Despite many people having similar clinical presentation, demographic factors, and clinical care, outcome can differ for those sustaining significant injury such as spinal cord injury (SCI) and traumatic brain injury (TBI). In addition to traditional demographic, social, and clinical factors, variability also may be attributable to innate (including genetic, transcriptomic, proteomic, epigenetic) biological variation that individuals bring to recovery and their unique response to their care and environment. Technologies collectively called “-omics” enable simultaneous measurement of an enormous number of biomolecules that can capture many potential biological contributors to heterogeneity of injury/disease course and outcome. Due to the nature of injury and complex disease, and its associations with impairment, disability, and recovery, rehabilitation does not lend itself to a singular “protocolized” plan of therapy. Yet, by nature and by necessity, rehabilitation medicine operates as a functional model of “Personalized Care”. Thus, the challenge for successful programs of translational rehabilitation care and research is to identify viable approaches to examine broad populations, with varied impairments and functional limitations, and to identify effective treatment responses that incorporate personalized protocols to optimize functional recovery. The Rehabilomics framework is a translational model that provides an “-omics” overlay to the scientific study of rehabilitation processes and multidimensional outcomes. Rehabilomics research provides novel opportunities to evaluate the neurobiology of complex injury or chronic disease and can be used to examine methods and treatments for person-centered care among populations with disabilities. Exemplars for application in SCI and other neurorehabilitation populations are discussed.

Keywords: Rehabilomics, Personalized medicine, Biomarkers, Spinal cord injury, Disability

Personalized medicine and theranostics: a culture shift in medical practice and research

Clinically, biomarkers are routinely used in medicine to monitor biological and pathological processes that ultimately aid in patient management and assessment of treatments. To date, almost every area of medicine utilizes biomarkers in some capacity to aid in clinical care. Other fields (e.g. oncology) have embraced an

“omics”-based theranostic approach to tailor and individualize care based on specific test results generated to guide these treatments.¹ Yet, the degree to which biomarkers are used in clinical care across the medical field is variable. While there is a significant demand for biomarker research, much of the research in rehabilitation populations is exploratory in nature and discovery-based, with much work still to be done to operationalize viable candidate biomarkers into clinical care algorithms. There are a wide variety of molecular biomarkers to consider across each area of medicine, making a clear understanding of how to apply a biomarkers-based approach to

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a specific research and/or clinical care question seem daunting, yet the tools and processes by which to conduct biomarker measurements are similar across the medical field.

“Personalized Medicine” compares individual genetic make-up and other molecular marker “read-outs” that represent a heterogeneous population in order to assess individual relationships with a specific disease or complication and to compare profiles to other healthy populations. Major advancements in genomics and proteomics technology have been instrumental in developing biomarkers for clinical and research purposes. In addition to disease or complication susceptibility, comparisons may include how individuals respond to certain treatments types or intensity. “Personal genomics” refers to sequencing and analysis of the genome of a specific individual. The molecules generated from genes are the target of proteomics explorations and also are subject to regulation over time due to the physiological and external environment associated with each individual. Epigenetics specifically studies this interface between genetics and environment, giving the concepts of “nature and nurture” a molecular signature.

Injury and environmental exposures (e.g. rehabilitation), can uniquely and dynamically influence individual physiology. Despite many with complex injury and disease having similar clinical presentations, demographic profiles and risk assessments, and clinical care, outcome can be very different. Thus, this variability may be attributable to the innate molecular background that individuals bring to recovery and the unique response to each person’s care and environment. Thus, an individual’s biological profile could be used to tailor treatments that optimize outcome.

Personalized approaches to rehabilitation: function as a foundation for Rehabilomics research

The field of rehabilitation is faced with ongoing challenges to justify treatment effectiveness to payors and other regulatory entities for many of its procedures and treatments. Also, it is well recognized that rehabilitation does not lend itself to a singular “protocolized” plan of care or therapy, and the evaluation of each person must include an individualized assessment of physical, cognitive, emotional, and social systems, each of which uniquely interacts to affect recovery. Traditionally, rehabilitation practitioners customize individual rehabilitation protocols for their patients based on the specific needs, supports, and barriers identified, making traditional protocol standardization a challenge. Furthermore, there is a paucity of biomarkers

available to aid as examples for similar research and to guide rehabilitation research and care. Yet, the same issues that the rehabilitation field has historically struggled with, such as the difficulties with conducting rigorous clinical trials while preserving the theranostic principles of individualized care, may be able to be addressed viably by the successful adoption and integration of biomarkers into mainstream rehabilitation care. Although the expanse of biomechanical, demographic, clinical, and molecular heterogeneity involved with the injury response, interventions, and recovery trajectory is difficult to conceptualize, this idea using genetic and molecular signatures to guide personalized care is not very different from what we do *functionally* with a wide range of target populations to individualize and tailor rehabilitation programs.

Rehabilomics is a novel framework from which to discuss biomarkers in research and clinical care that addresses research gaps and clinical treatment needs specific to physical medicine and rehabilitation and the unique populations we treat.² Within this framework, we have defined *Rehabilomics* as a field of research that incorporates 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.² Essentially, this biologically grounded conceptual framework provides an “-omic” overlay to the scientific study of rehabilitation processes and outcomes – personalizing a biomolecular approach to rehabilitation care that is aimed at optimizing individual recovery.

“Omics”-based considerations for Rehabilomics as a model of care and research

Although biomarkers are often used to characterize the acute pathophysiology cascades associated with injury or disease onset, they are also important in characterizing relevant pathophysiology during rehabilitation and recovery. Also, while clinical measurement scales, for example, the Glasgow coma scale and injury severity score in populations with traumatic brain injury (TBI), can be sensitive in predicting outcome,³ less is known about possible interrelationships between biomarkers and other innate factors, along with their collective influence on long-term functional outcome, disability, and recovery path. Recently, both structural and functional neuroimaging have been recognized as potential biomarkers of injury, recovery, and outcome in neurorhabilitation populations.⁴⁻⁷ Contemporary research has begun to integrate these imaging indices to

understand the structural framework for specific changes in brain function. From a rehabilitation perspective, functional and cognitive testing results have typically been viewed as phenotypic measures of outcome, but cognitive testing results or behavioral profiles may also be considered “biomarkers” proximally linked to disease, complications, or condition affecting health status.

Although Rehabilomics research can and does involve the use of biomarkers for diagnosis and prognosis, perhaps even more vital is the impact that a Rehabilomics program of research can have in the context of evidence-based medicine.^{2,8,9} Leveraging the individuality captured through a biomarkers-based approach can help identify individuals susceptible to complications and amenable to targeted treatments. Similarly, the theranostic principles embedded in the Rehabilomics framework can be used when considering the need for patient stratification in both treatment efficacy and comparative effectiveness research, the latter of which can enrich our understanding of what works for whom and help determine under what circumstances the intervention produces maximum benefit in the real-world clinical setting.⁹ Conversely, Rehabilomics approaches may have some utility in identifying who may not benefit from a particular intervention. Importantly, an effective Rehabilomics approach to treatment intervention and assessment can also address other common challenges such as dose, timing, and duration of interventions, as well as the biological veracity of functionally guided treatment algorithms. However, more work needs to be done in identifying appropriate markers of chronic pathology and recovery, and in understanding the sensitivity of these markers to disease progression, symptom profiles, recovery, and treatment response.

WHO-ICF: a clinically relevant Rehabilomics research framework for assessing functioning, disability, and health

One major challenge in identifying and evaluating effective rehabilitation therapies for individuals with either injury or complex disease is the inherent heterogeneity that accompanies the disease or condition. 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. Rehabilitation-focused phenotyping also requires an intimate understanding of how disease or injury impacts impairments, disability, and quality of life. Multimodal assessments are particularly important to reflect the complexities

affecting patient outcome in our target populations. For our rehabilitation populations, appropriate phenotype (or phenomic) profiling requires tracking individuals from the bedside to the community. Rehabilitation-based phenomic characterization should incorporate the use of adaptive strategies and technologies that limit both impairments and disabilities associated with an injury or disease process. In short, Rehabilomics-relevant approaches to capture the complex, changing interface between injury/disease and its corresponding physiology and treatment/personal environment, requires an integrated approach that blends biomarker platforms, data collection technology, and a metric structure that captures function.

The World Health Organization’s (WHO) International Classification of Functioning Disability and Health (ICF) is central to defining and operationalizing a formula for characterizing function across multiple domains.¹⁰ The ICF model specifies common constructs and language for assessing function in clinical care and rehabilitation research that, along with innovative technology linking biorelevant symptoms to both biomarker and outcomes, is central to the Rehabilomics concept. The ICF represents rehabilitation has a health strategy, with the primary goal of rehabilitation as a health strategy being function.¹¹

The ICF framework is complementary to the International Classification of Disease (ICD) framework,^{12,13} and its elements build upon the biomedical model, which focuses on function primarily from a physical health and disease perspective, to include interrelationships between disease-specific impairments and the subsequent limitations and restrictions that co-occur (Fig. 1A). The model also captures elements important from a biopsychosocial perspective, where function is gauged also in the context of disability and reintegration.¹³ Within the biopsychosocial model, ways in which personal factors and environmental exposures (positive and negative) interact are considered,¹³ enabling further elaboration on how these factors influence function (Fig. 1A). When we consider this WHO-ICF model of health within the context of injury or complex disease (Fig. 1B), the WHO model demonstrates how injury/disease leads to body impairments lead to limitations and restrictions, including loss of independence with daily activities, difficulty resuming pre-injury life roles, and community integration. The framework also shows how individual and environmental factors can impact these domains. We have adapted the WHO-ICF framework to capture the essence of “Rehabilomics” as a field of study that intertwines biophysiological components associated

Figure 1 (A) ICF is complementary to the WHO ICD and represents a biopsychosocial model to understanding health. (B) Individual and environmental factors influence multimodal function within an adapted WHO-ICF model that is contextualized for complex injury/disease within traditional ICF framework. (C) WHO adapted Rehabilomics model overlays the impact of innate individual biology, and the unique interplay of personal biology and environmental factors to influence physiology, that contribute to the conditions and complications affecting individuals with complex injury and disease. With this model, biophysiological relationships on conditions and complications associated with disease and injury are proposed to impact multidimensional outcomes reflecting impairment, disability (represented by activities), and participation.

with personal and environmental factors, as well as with complicating conditions, that impact multidimensional outcomes and recovery across heterogeneous populations with complex injury or disease (Fig. 1C).

Research tools and capacity needed for Rehabilomics research

A carefully constructed *Rehabilomics* framework that combines state-of-the-art biomarker approaches with real-time monitoring technology, and applies the ICF model of functioning, disability, and health to reflect multimodal outcomes, can be used to: (1) understand the biological substrates of recovery across the continuum after injury or disease onset; (2) effectively identify and capture ecologically valid symptom profiles in real time for people at risk for complications and/or poor outcome; and the nature of the interactions between complications and outcome; (3) generate additional research on how individualized treatments or therapeutic targets may improve recovery, with the aim of translating this work to clinical care through the implementation of portable point-of-care (POC) technology. To generate a viable framework, multiple research tools are needed, and the infrastructure and capacity to translate Rehabilomics research to clinical care are substantial.

No matter what area of study or target population, state-of-the-art *biorepository development* is needed, with care and attention placed on sample collection, processing, labeling, storage, and access. Patient registries, as well as other means for access to target populations for biosample collection and phenotyping are needed. However, to date, most rehabilitation target populations are relatively underserved in this area, and established multisite research networks are limited. However, some possible sources from which to develop the capacity for well-phenotyped and large-scale populations might include the National Institute for Rehabilitation and Research (NIDRR) TBI, spinal cord injury (SCI), and burn. These resources may be reasonable to consider in the context of appropriate additional funding opportunities to support repository development.^{14–16} Best practices in sample handling and bioinformatics are necessary to ensure high-quality results using samples derived from a repository resource, and best practice guidelines can be found in the literature.^{17–20} When considering the potential benefits of establishing a database from which to link biorepository data, consistency, and comparability with other ongoing research efforts is a central consideration, and the NIH Toolbox as well as the NIH Common Data Elements projects can be effective

resources, in addition to the TBI model systems data elements dictionaries, in establishing informative data collection tools.^{21,22}

The National Institutes of Health (NIH) has been a primary source of federal medical research funding, particularly in the areas of disease-based mechanisms and hypothesis-driven research, though contributions from agencies like NIDRR and the Veterans Administration are also substantial with regard to rehabilitation research. Several years ago, the NIH began developing its Roadmap for Medical Research in the 21st century by identifying new pathways to discovery, developing interdisciplinary research teams, and re-inventing the clinical research process. The NIH Roadmap for Medical Research was launched by 2004, and in 2006, the NIH Common Fund was created to support the programs implemented through this NIH Roadmap. As a part of this initiative, NIH has funded ~60 *Clinical and Translational Science Awards* (CTSA) to medical research institutions to improve the way biomedical research is conducted across the country.²³ These large-scale awards have increased accessibility to cutting edge biomolecular 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. Centers for genomics, epigenomics, proteomics, imaging, systems biology, and computational/bioinformatics research, as well as statistical and human subjects compliance support, have been emphasized as central components of these large infrastructure program projects, and these types of research and infrastructure initiatives have paved the way for biomarkers research to expand across numerous disciplines. These resources have been important to the successful implementation of Rehabilomics research in the area of TBI, and can be of tremendous benefit for rehabilitation researchers whose institutions hold a CTSA.

Health Information Technology and Telerehabilitation Tools are a significant and important component of infrastructure needed, particularly to support large-scale, and community-based rehabilitation research designs. Ecological momentary assessment (EMA) tools have been used with some success in evaluating populations seeking emergent care²⁴ and who have chronic disease^{25–28} addiction,^{29–31} for symptom tracking (e.g. fatigue, pain),^{32–35} and self-management of health.³⁶ The ICF represents rehabilitation as a health strategy, with the primary goal of rehabilitation as a health strategy being function.¹¹ Recent work targeting SCI and spina bifida populations has focused on

developing and using relevant EMA tools, as well as ecological momentary interventions (EMI), for the prevention and management of 2° conditions. The work shows that, *engagement*, within the context of self-management of daily care activities, and with the use of telewellness mobile phone applications that provide clinical care reminders and interactions with a healthcare specialist, reduce complications and healthcare utilization.³⁷ Additional work has focused on EMA tools in populations with cognitive impairments^{38,39} with some success. Importantly, pairing biomarkers with a rehabilitation-focused rigorous research design and EMA tools and platforms^{40–43} is critical to derive meaningful information about rehabilitation as a health strategy. Interestingly, there is a wide range of biosensors, body media, and portable/wearable point-of-care technology whose data could serve as physiological and/or activity-based biomarkers to link with other POC technology and platforms to generate a rich characterization of biological processes that influence symptoms and outcome. The integration of biomarker panels with EMA tools, and to POC assays developed for these panels, has tremendous potential for implementation of large-scale pharmacogenetic and other biomarker-driven comparative effectiveness and clinical trials for rehabilitation research.

While relatively uncommon in rehabilitation research, translational research models are an essential component to building translational rehabilitation (and Rehabilomics) research capacity. *Experimental Rehabilitation Research Models and Systems* provide the opportunity to tease out mechanisms of disease or injury as well as identify therapeutic targets. Experimental models of SCI,⁴⁴ stroke,⁴⁵ TBI,^{46,47} burn,⁴⁸ musculoskeletal,^{49,50} and neurodegenerative disease^{51–54} are established, and when paired with a thoughtful experimental design, research using these models can be relevant to rehabilitation care. Developing rehabilitation-relevant outcome assessment tools for these models, as well as testing relevant clinical-translational rehabilitation modalities, can provide the pre-clinical building blocks for proof-of-concept for new treatments, for identifying treatment mechanisms of action, and for generating preliminary and pre-clinical safety, tolerability, and efficacy data to support the transition of rehabilitation-relevant treatments to a phased clinical trials pipeline.

Rehabilomics research efforts in TBI: an exemplar for researching other populations with disability

Biomarkers have been used increasingly within the field of TBI research to capture information about the injury

cascades that occur, particularly in humans, after TBI.^{55–56} Although not widely studied from this frame of reference, Rehabilomics-relevant research has the potential to capture important elements about heterogeneity in TBI and the factors/therapeutic targets that lead to heterogeneity in recovery observed with this population.^{2,8,57} We have leveraged our biosample repository to conduct analyses demonstrating how several candidate biomarkers measured from biosamples collected early after injury are sensitive as potential markers contributing to and/or reflective of outcome.^{57–60} In addition, our work has implicated genetic and proteomic markers with regard to susceptibility to post-traumatic depression⁶¹ as well as the development of post-traumatic epilepsy.^{62–64} We have used a Rehabilomics framework to delineate and dissect novel components of endogenous hormone physiology early after TBI,^{65,66} as well as characterize chronic hormonal pathology associated with post-traumatic hypogonadism.⁶⁷ Furthermore, we have demonstrated that severe TBI leads to a chronic inflammatory state that has a significant impact on outcome.⁶⁸ Other work suggests that in TBI, some dopamine pathology may be genotype specific, findings which demonstrate unique injury interactions with innate heterogeneity in dopamine system biology.^{69,70} While certainly not the entirety of work demonstrating how biomarkers are relevant to clinical TBI care and research, this work provides some poignant examples about how biomarkers have informed acute and chronic TBI pathology, early prognostication, and bio-susceptibility to secondary complications after injury. It should be noted though that despite the identification of several interesting genomic, proteomic, and hormone-based biomarkers emerging in the TBI literature, additional validation work is needed to support use of these markers as a part of clinical care. Also, additional investment is needed to make the appropriate assay engineering and platform developments required to support the clinical utility studies needed for promising biomarkers to make the transition into clinical care.⁷¹

In support of other Rehabilomics infrastructure, capacity, and mechanistic studies, our pre-clinical work utilizing the controlled cortical impact model of experimental TBI has helped to characterize chronic DA pathology after injury. In addition, we have shown the value of rehabilitation-relevant constructs such as chronic treatment paradigms,^{72–75} environmental enrichment,^{76–78} and implicit learning and memory⁷⁹ as applicable models from which to study TBI pathology relevant to rehabilitation and recovery,

to study the beneficial mechanisms (and detrimental side effects) of common, clinically available pharmacotherapeutics, and to examine other novel interventions. Finally, our recent work examining the use of EMA tools in TBI suggests, that at least in setting of concussion, these types of telehealth tools can be both viable and valuable methods for high-resolution phenotyping that can be paired with other biomarker-based studies and EMI tools.³⁸

Contemporary SCI research: perspectives and parallels using a Rehabilomics research lens

The examples of TBI-specific Rehabilomics work above provide some frame of reference regarding study design and translational potential for biomarkers research in other rehabilitation-relevant populations such as people with SCI. Given the high co-occurrence of TBI in many individuals with SCI,^{80,81} several of biomarker associations described above could be directly applicable to SCI research and care. While large datasets like the SCI-MS^{80,81} have provided insight into clinical predictor/prognostic variables in discriminating outcome, sensitive indicators of treatment specificity or effectiveness are quite limited, thus supporting the potential impact and application that research utilizing a Rehabilomics model might have on improving SCI care and recovery.

Clinically, Rehabilomics studies may identify biomarkers that can augment the ASIA impairment scale (AIS) grading system and other clinical/injury variables^{82–85} to inform prognosis. Those studying mood and SCI may be able to draw upon existing Rehabilomics work in TBI identifying genetic and inflammatory biosusceptibility markers for depression⁶¹ when considering possible candidate markers to explore. Furthermore, parallels for SCI Rehabilomics work with the TBI Rehabilomics literature might be drawn when evaluating chronic inflammation,⁶⁹ endogenous hormone physiology,⁶⁷ and autoimmune dysfunction.^{86,87} Certainly, contusion and transection models (see above) as well as other experimental SCI models can be used to assess regeneration mechanisms,^{88,89} injury severity,^{90–93} prognosis,^{94,95} and neurological recovery.^{96–98} Pre-clinical models have also provided some insight into novel therapies and biomaterials with neurorestorative potential.^{44,99–103} Additional work using these models to evaluate daily treatment paradigms (e.g. for spasticity and pain management agents) and other potential neurorestorative strategies already used in clinical care (e.g. treadmill training¹⁰⁴) could provide more of a mechanistic evidence base from which to support their

continued use clinically and also provide more of an understanding on how their use impacts recovery. Some notable clinical biomarker examples exist in the SCI literature that nicely serve as examples where a progressive line of Rehabilomics research might inform important research areas that lead to personalized care.

Clinical biomarkers work in SCI has yielded novel insights into bone mineral physiology after SCI in response to electromyostimulation.¹⁰⁵ Within the context of this study, future work might explore whether pre-training anabolic/catabolic hormone levels, as well as bone mineral density markers, have potential to serve as stratification markers from which to identify the best responders to electromyostimulation as an osteoporosis prevention/treatment tool. Additional future work might explore the utility of these markers as screening and early intervention tools to help prevent the onset of osteoporosis as a late complication, and additional studies might establish ICF links characterizing the down-stream morbidity effects of osteoporosis (and associated fractures) on activities and participation endpoints. Other studies have reported temporal biomarker relationships associated with bone density and osteoporosis,^{106–108} laying the groundwork for studies setting predictive cutpoints and time windows for sampling, as well as future work validating these markers as informative tools for clinical decision and treatment pathways as well as endophenotypes for treatment response.

Both detrimental and possible protective effects associated with autoimmunity have been identified with SCI that warrant further study to determine risk for complications and poor outcomes as well as to identify potentially relevant autoimmunity treatment targets that optimize SCI repair and recovery of function.^{109–112} In addition, a recent imaging study suggests that magnetic resonance spectroscopy could provide brain-based biomarkers indicative of neuropathic pain in subjects with SCI.¹¹³ Brain-based neuropathic pain biomarkers may inform researchers on novel mechanisms for this common complication, and also, provide a quantifiable biomarker for pain, a condition that is notably complicated to research given the subjective nature of its presentation. Future clinical work might identify pathology associated with other secondary complications common to those dealing with the chronic effects of SCI. Embracing a Rehabilomics framework for contextualizing published and emerging biomarkers-based research may help facilitate translation to clinical care and personalize therapies for those with SCI.

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