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# NIH Symptom Science Model Sheds Light on Patient Symptoms

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## Abstract

Since the establishment of the nursing profession, identifying and alleviating the subjective symptoms experienced by patients has been at the core of nursing practice. In supporting the scientific foundation for clinical practice, nursing science has maintained a consistent commitment to prevent, manage and eliminate symptoms. Scientists from the intramural research program at the National Institute of Nursing Research (NINR), a component of the National Institutes of Health, developed a National Institutes of Health Symptom Science Model (NIH-SSM) to guide symptom science research programs engaged in the use of emerging ‘omic’ methods such as the genotyping of symptom phenotypes. The NIH-SSM was developed based on the NINR intramural research program’s success in designing and implementing methods for examining identified symptoms or symptom clusters. The NIH-SSM identifies the research process of characterizing symptom phenotypes, identifying and testing biomarkers, and, ultimately developing clinical interventions in cancer-related fatigue, gastrointestinal disorders, and traumatic brain injuries. The purpose of this article is to demonstrate how scientists can apply the NIH-SSM, leading the broader scientific community in advancing personalized and precise clinical interventions.

## Introduction and Overview of NIH-SSM

In the field of ‘omics’, a rapidly evolving area of science that can include genomics, proteomics, and metabolomics among others, nurse scientists from the intramural research program at the National Institute of Nursing Research (NINR), a component of the National Institutes of Health, developed the National Institutes of Health Symptom Science Model (NIH-SSM) (Cashion & Grady, 2015) to guide research programs engaged in the use of emerging ‘omics’ methods to study symptoms experienced by individuals (Figure 1). Symptoms are defined as the self-reported perception of an individual’s experience of disease or physical disturbance (Dodd, et al., 2001), and can include experiences such as fatigue, pain, and cognitive dysfunction. Clustering of symptoms occurs when patients

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experience multiple related symptoms concurrently (Xiao, et al., 2010). Symptoms are of clinical, research and policy concern because they are the most common reason that patients seek healthcare (Rutledge & McGuire, 2004), and the assessment and management of symptoms is a hallmark of nursing practice (Corwin, et.al).

The NIH-SSM describes an investigative sequence for symptom science research, beginning with the identification of a symptom, or cluster of symptoms, followed by the characterization into a phenotype, a person's observable characteristics and traits. Within the NIH-SSM, phenotypes are determined by combinations of individuals' behavioral, biological and clinical data. Once a phenotype is determined, genomic and other 'omics' discovery methodologies are used to illuminate potential biomarkers – measures of normal biological processes, pathogenic processes, or pharmacologic responses (Biomarkers Definitions Working Group, 2001) – and targets for therapeutic and clinical interventions.

## NINR Intramural Research Program and Symptom Science

Novel discoveries in symptom science require integration of diverse information from the patient's biologic processes, physiologic pathways, and behaviors to predict, treat, and manage symptoms of diseases and treatments. Studying 'omics' in relation to symptom science is beginning to identify new biologic pathways that might potentially reduce the burdens associated with acute and chronic illness and enhance personalized health and identify biologic targets for precision medicine initiatives.

The environment of the NINR intramural research program, which is a collaborative, team-science centered program, using primarily shared scientific resources and supports, benefits the development of novel models, such as the NIH-SSM, to address complex areas of science. The NINR intramural research program is able to provide: flexible, agile resources that can be redirected to fit developing science areas and needs; cross-trained research support staff who can work on multiple projects, protocols or tasks; opportunities for cross-symptom discoveries as teams work in close proximity; and, a variety of laboratory and clinical research opportunities for fellows. Moreover, its location on the NIH Bethesda campus provides opportunities for NINR investigators to collaborate directly with other NIH investigators across the other NIH Institutes and Centers to address specific research questions. These scientific components and commitments exist because of the established linkages and collaborations with the NIH Clinical Center, other NIH Institutes and Centers, and the long-term commitment and support of NINR. Maximizing these resources allows the NINR intramural research program to act as a nursing science hub, where collaborative teams of diverse, interdisciplinary investigators from across the NIH, along with extramural partners, research fellows, and students, can develop, hone, and apply their research methodology skills to tackle complex, symptom research challenges, and, offer discoveries that can be translated into practical solutions for patients.

This article presents three examples of 'omics' research programs that are implementing the NIH-SSM in the NINR intramural program. These three programs of research are leading the broader scientific community in knowledge discovery in the areas of cancer-related

fatigue, irritable bowel syndrome (IBS) and associated complex gastrointestinal symptoms, and, traumatic brain injury (TBI) symptoms including cognitive changes and insomnia.

## Cancer-related Fatigue

Cancer-related fatigue (CRF) is the most common, troublesome, and costly side effect of many cancer treatment regimens; it is a complex symptom because of its elusive and multifaceted etiology. Currently, CRF is thought to be attributable to a cascade of physiologic events resulting in pro-inflammatory cytokine production, hypothalamic-pituitary-adrenal (HPA) activation dysfunction, and neuromuscular function abnormalities (Bower et al., 2009; Ryan et al., 2007). Although a number of biomarker investigations have been conducted in an attempt to specify the etiology of CRF, inconsistencies in phenotype stratification and data interpretation have resulted in inconclusive and possibly misleading conclusions (Saligan & Kim, 2012). Dr. Leorey Saligan and his research team at the NINR intramural research program are using the NIH-SSM to specify the clinically-relevant phenotypic characterization of CRF in order to guide the identification of CRF-related biomarkers and provide a foundation for testing clinical applications that alleviate the complex and debilitating symptoms of CRF experienced by many current and former cancer patients (National Institutes of Health, National Institute of Nursing Research, 2015) (Figure 2).

Many of the phenotyping approaches that have previously been used in determining biologic correlates of CRF have methodological drawbacks. For example, one approach uses previously identified cutoff scores for patient-reported outcomes to group study participants into categories, often in an attempt to dichotomize participants by symptom intensity (Pertl et al., 2013; Kurz et al., 2012). This approach is problematic because these cutoff scores are often based on mean symptom experience scores from the general, healthy, population, which may be quite different from the fatigue experienced by cancer patients receiving toxic therapies. Another approach to characterize the CRF phenotype is using raw fatigue scores as continuous variables, which are then correlated with gene/protein levels to determine relationships (Hsiao et al., 2012; Lukkahatai et al., 2014; Saligan et al., 2013). This approach lacks empirical evidence that the observed relationship between raw fatigue scores and gene/protein concentration has clinically relevance.

To address the above methodological limitations, Dr. Saligan's phenotype characterization approach utilizes clinically-relevant and empirically derived cut-off scores to categorize participants into high or low fatigue groups based on their change in fatigue scores during radiation therapy. The research team uses the 13-item Functional Assessment of Cancer Therapy–Fatigue (FACT-F), a well-established, validated, reliable, stand-alone measure of fatigue in cancer therapy with coefficient alphas in the mid-90s (Yellen et al., 1997). The FACT-F, which is scored from 0-52 with higher scores indicating lower fatigue symptoms, is administered at baseline and at completion of external beam radiation therapy (EBRT). Subjects with a decrease of 3 or more points in FACT-F scores are categorized into the high fatigue group, while those with less than a 3-point decrease in FACT-F scores between both time points are categorized in the low fatigue group. A greater than 3-point decrease in the FACT-F score is considered to be a minimally-important change that is clinically relevant

(Yost et al., 2011). This phenotyping approach considers the unique experience of each subject, using the perceived baseline fatigue scores as controls and following the trajectory of their fatigue experience longitudinally. In addition, this phenotyping approach comprehensively accounts for the influence of other contributing factors of the fatigue experience, such as changes in body weight, hemoglobin levels, depressive symptoms, and sleep disturbance. This approach can also be used with other valid CRF measures such as the revised Piper Fatigue Scale (Hsiao et al., 2012) and the Patient Reported Outcomes Measurement Information System-Fatigue subscale (Hsiao et al., 2013).

The phenotypic characterization described above is being used by Dr. Saligan's team in the search for CRF biomarkers through several genomic and proteomic investigations, some of which have already yielded promising results in the prediction of CRF for patients receiving EBRT. In one collaborative investigation, Dr. Saligan's team applied a novel statistical approach to identify the most predictive cluster of genes for high fatigue patients following EBRT. The identified gene cluster predicted with >75% accuracy individuals with clinically significant fatigue following EBRT (Saligan et al., 2014). Another investigation identified that increases in concentrations of two proteins (apolipoprotein E and A1) and a decrease in one (transthyretin) were significantly correlated with clinically significant fatigue intensification during EBRT (Lukkahatai et al., 2014). More recently, the team's research has revealed that a decline in brain-derived neurotrophic factor levels during EBRT is common among participants who experience high fatigue (Saligan et al., 2015).

Findings from the genomic and proteomic investigations by Dr. Saligan's team have paved the way to the development of a clinical intervention currently being investigated through a clinical trial in the NIH Clinical Center (National Institutes of Health, National Institute of Nursing Research, 2015). This trial is examining whether an N-methyl-D-aspartate receptor antagonist can alleviate CRF. Other biologic pathways discovered to be related to the CRF phenotype have led the team to begin examination of additional experimental therapeutics, including nutritional supplements, dietary modifications, physical activity, energy conservation, and cognitive-behavioral strategies to target specific biologic pathways hypothesized to explain the etiology of CRF.

The NIH-SSM provides the foundation to guide a focused and strategic approach to advance our understanding of CRF. These findings parallel the scientific vision underlying the Precision Medicine Initiative, affirming a more personalized phenotyping approach and demonstrating the potential of the NIH-SSM model for advancing the science of CRF and improving the lives of those who experience this complex and debilitating symptom.

## Complex Gastrointestinal Symptoms

Digestive or gastrointestinal (GI) symptoms are common across populations and one of the top ten reasons for outpatient visits. The identification and specification of GI symptoms are complex, requiring careful phenotypic characterizations (Grundmann & Yoon, 2010). One condition associated with significant GI symptoms is Irritable Bowel Syndrome (IBS), a disorder with a symptom-based diagnosis of exclusion that affects over 15 million persons in the United States (Sandler, Everhart, Donowitz, et al., 2002). Overall, GI symptoms are

many, varied, and often overlapping with other physical and physiological symptoms. Gaps in treatment, research, and clinical practice remain, particularly for chronic GI symptoms of unknown origin. Consequently, there is a clinical need for real-time assessment of both subjective (patient-reported) and objective symptom assessment and improved characterization of GI symptom phenotypes. Dr. Wendy Henderson and her research team at the NINR intramural research program are actively engaged in applying the NIH-SSM to discover the mechanisms involved in GI symptom distress related to digestive disorders, specifically the biobehavioral relationships between inflammation and patient symptoms, with the goal of developing targeted treatments for patients with these chronic debilitating GI-symptoms (Figure 3).

An existing GI symptom phenotype characterization with regard to IBS involves documenting a complex mix of observed and reported symptoms (abdominal pain with changes in bowel habits) that are exacerbated by stress while organic pathology is absent -- “Rome III diagnostic criteria” (Rome III) (Drossman, et al., 2006). While the Rome III criteria aid clinicians in diagnosing IBS, Dr. Henderson’s lab provides clinicians with an integrated tool for real-time GI symptom assessment that includes location, intensity, quality, and physiologic parameters. Her team developed a tool for phenotyping general GI symptoms called the Gastrointestinal Pain Pointer (GIPP), which integrates a user interface for self-reported assessment of GI symptoms that includes a pain intensity electronic dial-up interface with a 0-100 scale, pain word descriptor/s and locations, as well as recordings of heart rate and blood pressure data (Henderson, et al., 2012; Henderson, et al., 2015).

Dr. Henderson’s research team utilizes established measures and instruments, such as the Rome III and the GIPP, to guide their clinician-scientist approach to better characterize complex GI symptom phenotypes and illuminate predictive biomarkers. Highly sensitive and specific biomarkers will aid not only in diagnosing, but in identifying therapeutic clinical applications. Their research is building on existing evidence of subclinical inflammation in IBS, including increased mast cell population in colonic samples from patients with IBS (Henderson et al., 2012), as they follow a multi-omic search for GI symptom biomarkers.

Recent research findings from Dr. Henderson’s lab suggest the presence of differential microRNA, small non-coding RNA molecule that functions in regulation of gene expression, signatures in patients with IBS vs. healthy controls. More specifically, the study identified two microRNAs (from peripheral circulation) and the pathways in which they functioned (i.e., immune, inflammatory, nervous system, metabolic) that were differentially expressed in patients suffering from IBS (Fourie, Peace, Abey, et al., 2014). The results support an underlying pathophysiology of IBS, and suggest that microRNAs may be used as either diagnostic biomarkers or targets for a clinician-led, symptom-based interventions.

The NIH-SSM model continues to provide a foundation to guide Dr. Henderson’s research team as they pursue a focused and strategic approach to advance our understanding of complex GI symptoms and IBS. Furthermore, the results provide justification for continuing use of novel phenotypic diagnostic methods to achieve the ultimate goal of providing therapeutics and other treatments for IBS and complex, chronic GI symptoms.

## Complex Symptoms of Neurological Trauma

For military personnel, deployment exerts a combination of unique stressors that include adjustment to different wake-sleep patterns (Ferrer, Bisson, et al. 1995), chronic sleep deprivation unsafe sleeping environments (Peterson, Goodie et al. 2008; Miller, Shattuck, et al. 2010), and high rates of traumatic brain injuries (TBIs) (Alosco, et al., 2015). The combination of these stressors increases the risk for symptoms of post-traumatic stress disorder (PTSD) and depression, as well as sleep disturbance (U.S. Army Medical Command, 2011; Centers for Disease Control and Prevention, 2012). Following deployment, insomnia may become chronic and likely relates to interactions of complex processes that are not well understood (Bramoweth and Germain, 2013). A better understanding of the molecular mechanisms underlying insomnia and related comorbidities including TBIs will ultimately lead to the design of novel and effective interventions.

Dr. Jessica Gill and her research team at the NINR intramural program are investigating the predictors of and symptoms associated with deployment including the risk for neurological deficits following TBIs, as well as risk for comorbid symptoms of sleep disturbance, PTSD depression and pain. This program of research includes the application of the NIH-SSM to characterize symptom phenotypes and the mechanisms underlying differential responses to trauma and deployment (Figure 4). Included within this program of research is the examination of risk and resiliency factors related to clinical outcomes for TBI patients, to determine proteomics and genomic biomarkers that are prognostic of recovery. Specifically, in a recent study of military personnel Dr. Gill's team linked high concentrations of the protein tau, a protein marker of neurodegenerative processes, to chronic TBI related symptoms in military personnel (Olivera, et al., 2015). This line of research will advance knowledge of clinical and biological risks that can help identify patients at high risk for psychological and neurological impairments following a traumatic injury, and ultimately lead to the development of preventive interventions that are personalized to meet individual patient needs.

Dr. Gill and her team have recently undertaken studies utilizing gene-expression analyses to understand the comorbid symptoms that have been previously identified in studies of deployed military personnel, including insomnia, PTSD, and depression (Hoge, McGurk et al., 2008; Luxton, Greenburg, et al., 2011), as well as TBI and related neurological symptoms (Heinzelmann, et al., 2014). An example of this line of research is a study by Dr. Gill's team that used whole genome expression to identify genes that were altered in activity in military personnel with chronic TBI related symptoms. Specifically, there was an up-regulation of genes included epithelial cell transforming sequence and zinc finger proteins, which are necessary for astrocyte differentiation following injury. Protein ubiquitination genes, such as epidermal growth factor receptor, were also down-regulated and identified as the central regulators in the gene network determined by interaction pathway analysis (Heinzelmann, et al., 2014). This study provided unique insights into mechanisms related neurological symptoms following TBI, and suggests that interventions to increase protein ubiquitination may improve these chronic symptoms.

Changes in the symptoms of insomnia have been found to be attributed to interactions among genes and the environment, resulting in vulnerability to insomnia onset (Seugnet, Suzuki et al., 2009), as well as to the comorbid symptoms of PTSD and depression (Wright, Britt et al., 2011). Following the NIH-SSM model, Dr. Gill and her research team have begun identifying several 'omic' pathways related to insomnia and other complex, interrelated symptoms. Specifically, Dr. Gill's team recently published a study linking gene-expression alterations to chronic symptoms of PTSD (Guardado, et al., 2015). In this study, PTSD was associated with differentially expressed genes indicated a dysregulation of genes associated with the innate immune, neuroendocrine, and NF-κB systems. These studies form the essential foundational steps in the development of therapeutic agents that can regulate these pathways, providing novel treatments for insomnia and other sleep disorders, as well as service-related injuries.

Recent findings from Dr. Gill and her colleagues include previously unknown associations between lower health related quality of life and inflammation with TBI, PTSD, and depression (Gill, et al., 2014), and the identification of differential expression in 43 genes in military personnel with insomnia. They specifically identified one gene that was downregulated more in insomnia patients than in healthy controls. This gene has been associated with switching between different stages of sleep, which may in turn be the mechanism underlying insomnia symptoms (Gill, et al., 2015). Further, in another study, Dr. Gill's team found that for patients whose sleep improved, inflammatory genes were expressed differently compared to their own baseline expression, and, that the differential expression was also related to reductions in depression symptoms (Livingston, et al., 2015). These studies show that differential gene-expression relates to insomnia and chronic symptoms in military personnel, and that standard care can change gene-activity. Together, these studies indicate that the phenotype of insomnia as a molecular signature, and that improving sleep can change gene-activity.

By examining different models of gene expression, Dr. Gill and her research team are able to better understand how comorbid symptoms relate to different biological profiles. Findings from Dr. Gill's research indicate that interventions such as sleep restoration result in biological changes including significant reductions in depression symptoms, and improved health related quality of life which relate to reductions in inflammatory proteins including C-reactive protein (Heinzelmann, et al., 2014). In addition, the identification of genes that contribute to insomnia symptoms also provides the eventual promise of a novel pharmacological target for insomnia. For example, an orexin receptor antagonist has recently been tested and shown promise for treating insomnia (Patel, Aspesi et al., 2015), providing evidence that orexin alterations relate to insomnia and are a pharmacological target with therapeutic value.

Dr. Gill and her NINR research team are continuing to employ the NIH-SSM, using gene-expression methods to examine novel gene target candidates and biological pathways related to the symptoms of TBI, post-concussive disorder, PTSD, and depression. This research provides hope for the millions of military and civilian personnel who experience these complex and debilitating symptoms, sequelae, and who often have a complex combination of symptoms.

## Conclusion/Next Steps

The three examples from the NINR intramural research program demonstrate a model of a nursing science enterprise that has successfully developed and implemented dynamic, nurse-led, interdisciplinary team science to foster symptom science research such as was recommended by Corwin, et al (2014). Organizing and supporting each of these successful research programs is the NIH-SSM, which guides the design and implementation of methods for identifying complex symptoms, and symptom clusters; characterizing phenotypes; and, identifying and testing biomarkers. In implementing the NIH-SSM with a focus on developing and evaluating novel interventions to manage symptoms, the NINR intramural program demonstrates how nursing science can lead the broader scientific community, providing a valuable model to emulate in advancing personalized and precise clinical interventions. The NIH-SSM provides the nursing science community with a clear framework for incorporating phenotypic and 'omics' data into health intervention research - a valuable and necessary tool for leading the interdisciplinary, team science programs that are critical to sustaining the future of innovative research and that hold the most promise in developing the precise and personalized interventions to treat and manage illnesses and improve health.

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## Highlights

- The NIH Symptom Science Model guides research programs engaged in ‘omics’ sciences.
- Use of the NIH-SSM is advancing the understanding of the mechanisms of fatigue in cancer and other chronic conditions.
- Use of the NIH-SSM is advancing the understanding of symptoms in complex GI symptoms.
- Use of the NIH-SSM is advancing the understanding of symptoms of traumatic brain injury and other neurological trauma.

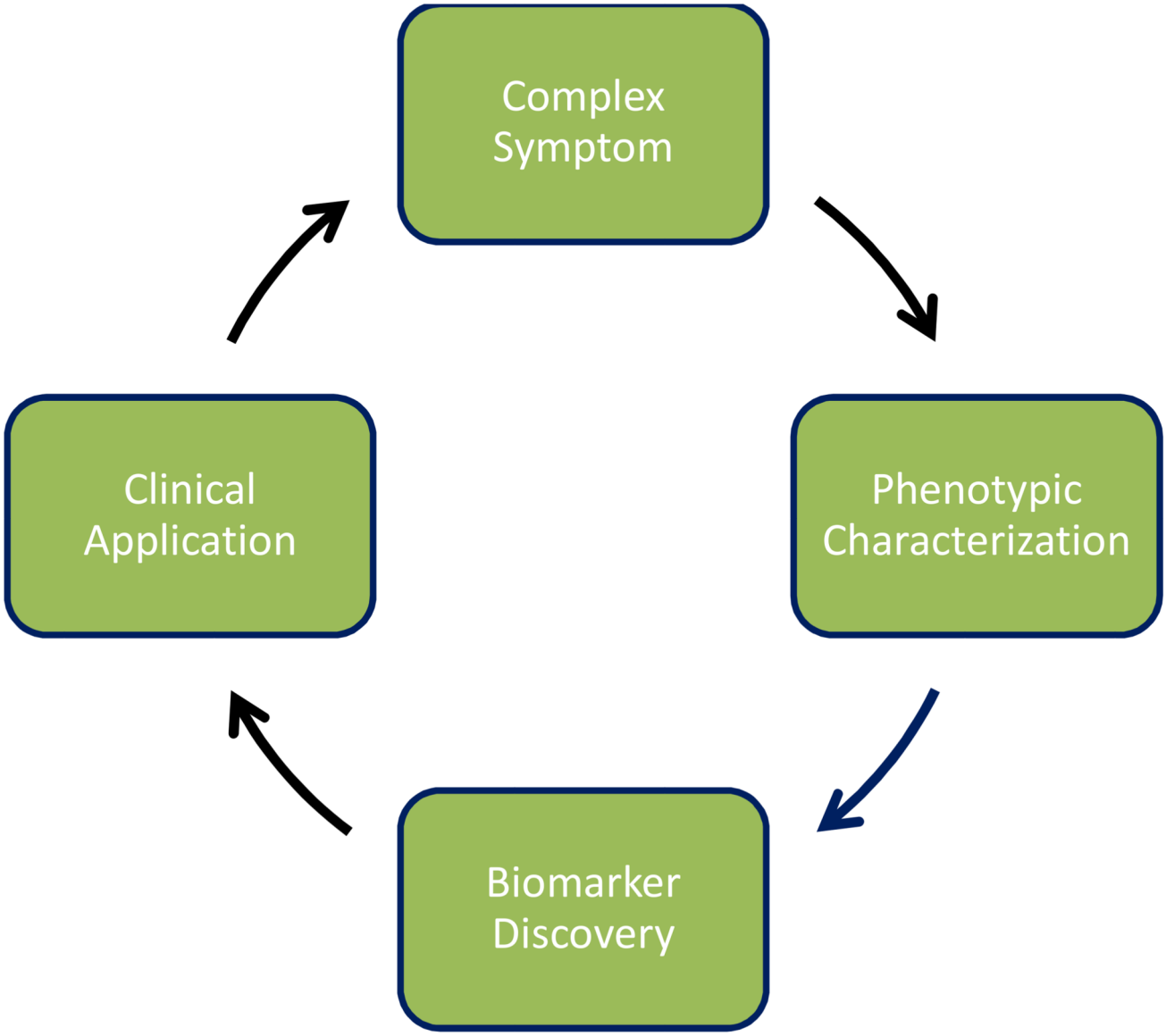


**Figure 1. NIH Symptom Science Model**

The NIH-SSM was developed to guide research. It begins with the presentation of a symptom; the symptom undergoes phenotypic characterization; then biomarkers are identified; and this ultimately leads to clinical applications, resulting in symptom reduction and improvement.

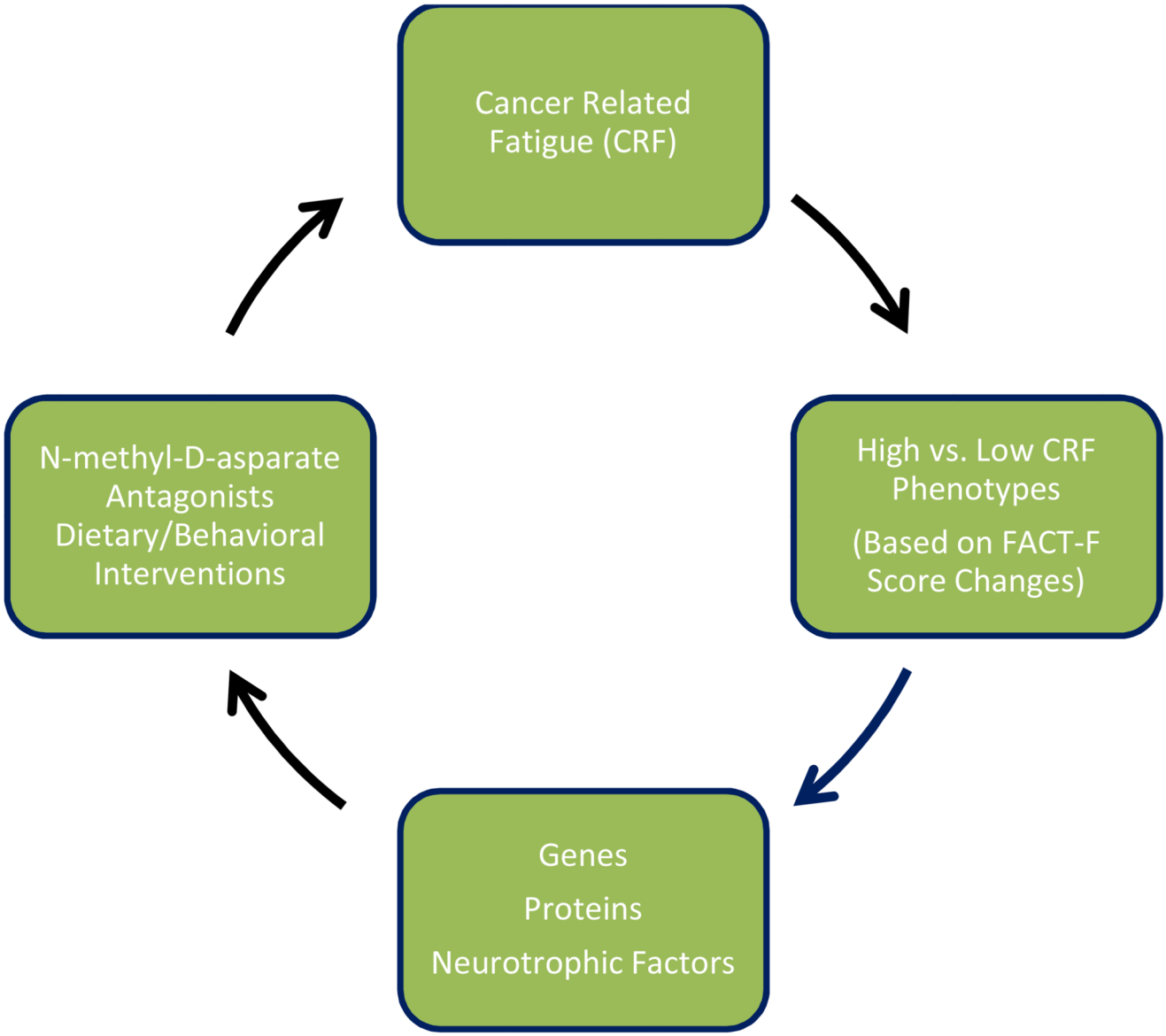


**Figure 2. NIH Symptom Science Model Applied to Fatigue**

The NIH-SSM is applied to research into cancer-related fatigue (CRF). It begins with the presentation of the symptom (CRF); the symptom undergoes phenotypic characterization (High vs. Low CRF Phenotypes Based on FACT-F Score Changes); then biomarkers are identified (Genes, Proteins, Neurotrophic Factors); and this ultimately leads to clinical applications (N-methyl-D-asparate Antagonists and Dietary/Behavioral Interventions) under evaluation for results in symptom reduction and improvement.

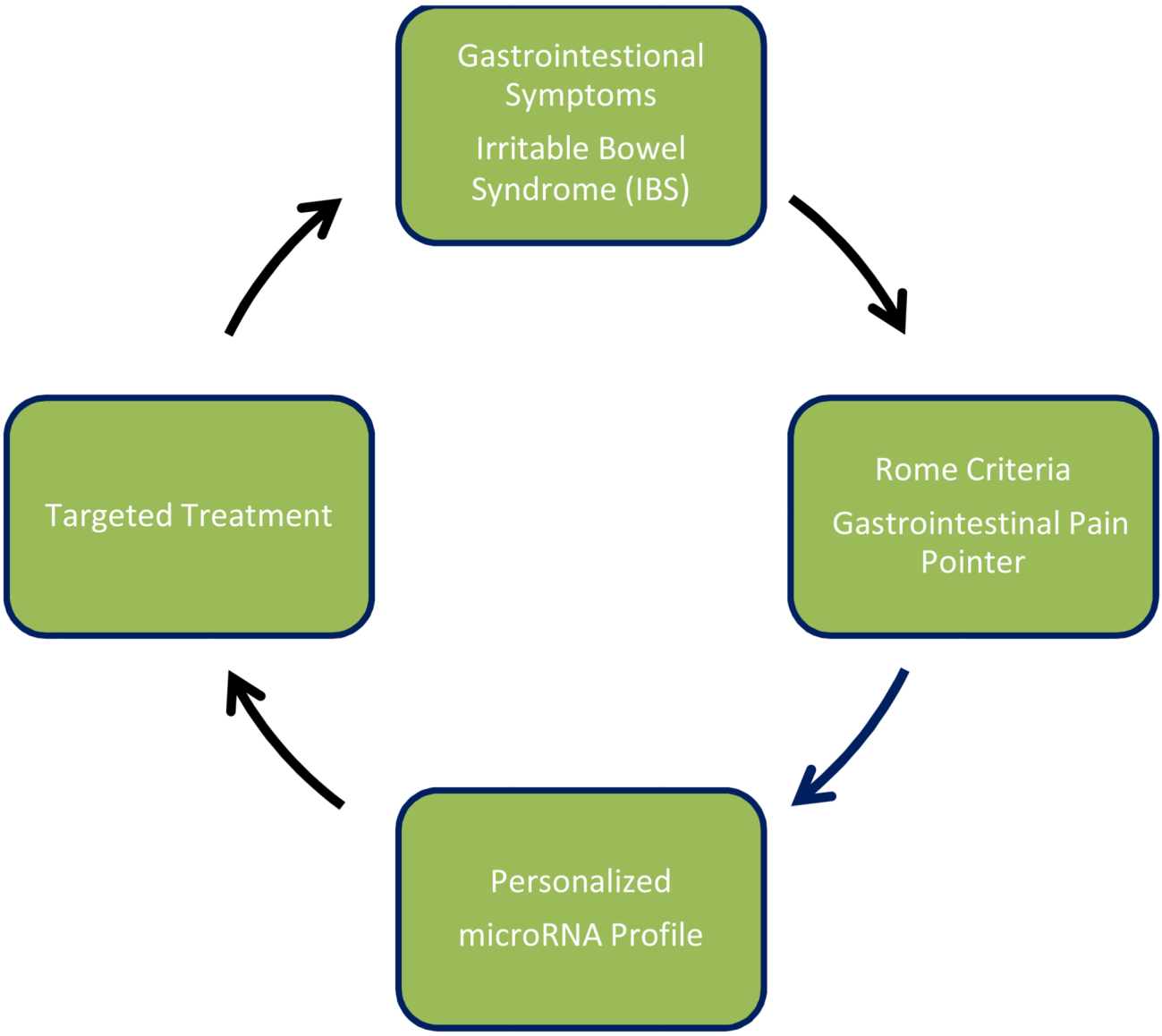


**Figure 3. NIH Symptom Science Model Applied to GI Symptoms**

The NIH-SSM is applied to research into gastrointestinal symptoms. It begins with the presentation of the symptoms (Gastrointestinal Symptoms/Irritable Bowel Syndrome); the symptoms undergo phenotypic characterization (Rome Criteria/Gastrointestinal Pain Pointer); then biomarkers are identified (personalized microRNA Profile); and this ultimately leads to clinical applications (Targeted Treatments) under development that can be evaluated for results in symptom reduction and improvement.

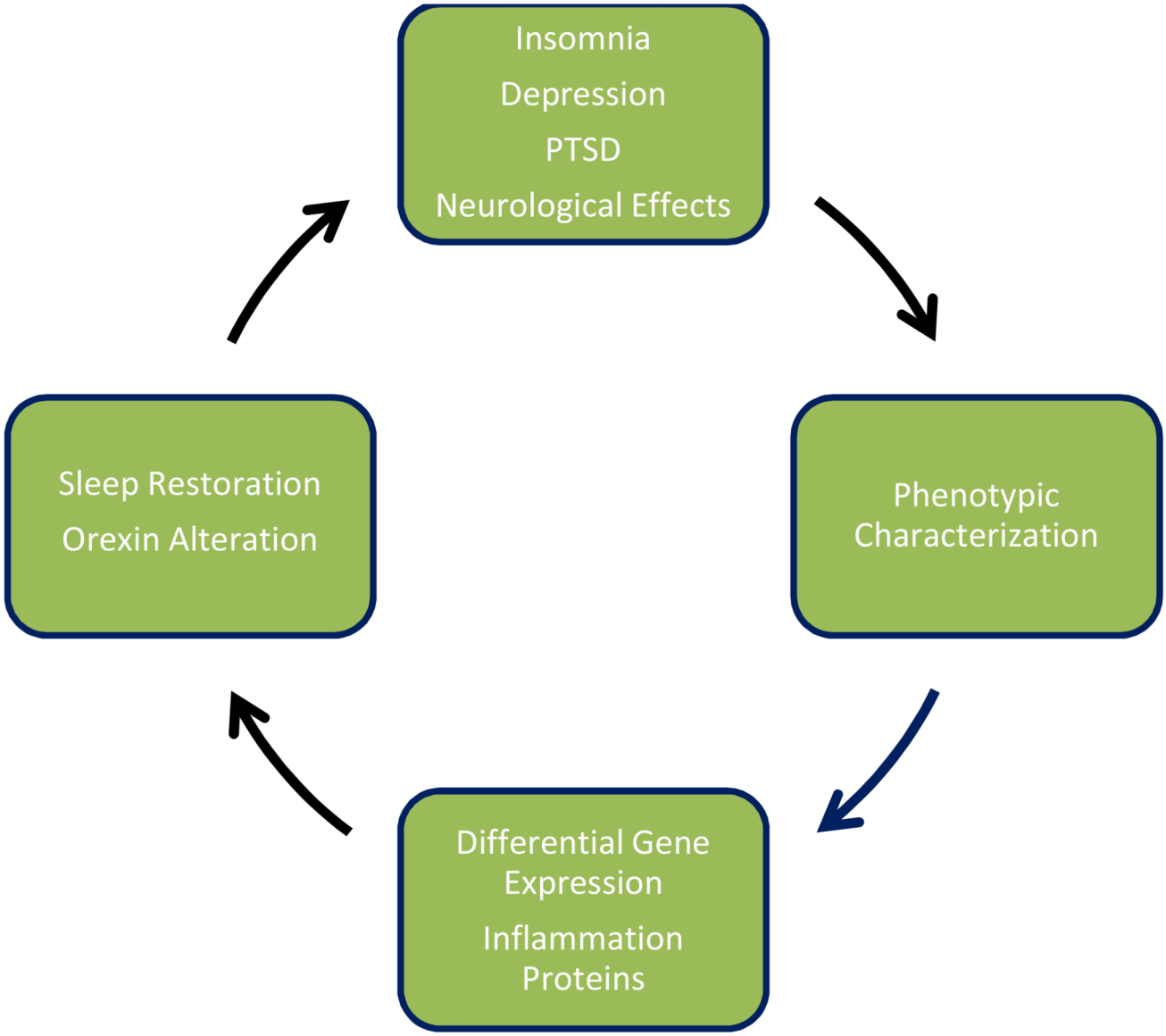


**Figure 4. NIH Symptom Science Model Applied to Differential Responses to Neurological Trauma**

The NIH-SSM is applied to research into symptoms of differential responses to neurological trauma. It begins with the presentation of the symptoms (Insomnia, Depression, PTSD, Neurological Effects); the symptoms undergo phenotypic characterization; then biomarkers are identified (Differential Gene Expression, Inflammation Proteins); and this ultimately leads to clinical applications (Sleep Restoration, Orexin Alteration) under development that can be evaluated for results in symptom reduction and improvement.