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Biomarkers as Common Data Elements for Symptom and Self-Management Science

Gayle G. Page, PhD, RN, FAAN^{1,*}, Elizabeth J. Corwin, PhD, RN, FAAN^{2,*}, Susan G. Dorsey, PhD, RN, FAAN^{3,*}, Nancy S. Redeker, PhD, RN, FAHA, FAAN^{4,*}, Donna Jo McCloskey, PhD, RN, FAAN^{5,*}, Joan K. Austin, PhD, RN, FAAN^{6,*}, Barbara J. Guthrie, PhD, RN, FAAN⁷, Shirley M. Moore, PhD, RN, FAHA, FAAN⁸, Debra Barton, PhD, RN, AOCN, FAAN⁹, Miyong T. Kim, PhD, RN, FAAN¹⁰, Sharron L. Docherty, PhD, PNP-BC, FAAN¹¹, Drenna Waldrop-Valverde, PhD¹², Donald E. Bailey Jr., PhD, RN, FAAN¹³, Rachel F. Schiffman, PhD, RN, FAAN¹⁴, Angela Starkweather, PhD, ACNP-BC, CNRN, FAAN¹⁵, Teresa M. Ward, RN, PhD¹⁶, Suzanne Bakken, PhD, RN, FAAN, FACMI¹⁷, Kathleen T. Hickey, EdD, FNP, ANP, APNG, FAHA, FAAN¹⁸, Cynthia L. Renn, PhD, RN, FAAN¹⁹, and Patricia Grady, PhD, RN, FAAN²⁰

¹Professor and Independence Foundation Chair in Nursing Education, Johns Hopkins University School of Nursing, Baltimore, MD, USA

²Professor and Associate Dean for Research, Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA, USA

³Professor and Chair, Department of Pain and Translational Symptom Science, University of Maryland Baltimore, Baltimore, MD, USA

⁴Beatrice Renfield Term Professor of Nursing, Professor, Section of Pulmonary, Critical Care and Sleep Medicine, Yale University, New Haven, CT

⁵Clinical Advisor, Contractor, National Institute of Nursing Research, NIH, Bethesda, MD, USA

⁶Distinguished Professor Emerita, Indiana University School of Nursing, Indianapolis, IN and National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA

⁷Professor, Director of the PhD Program, Northeastern University, Boston, MA, USA

⁸Edward J. and Louise Mellen Professor of Nursing, Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, OH, USA

⁹Mary Lou Willard French Professor of Oncology Nursing, University of Michigan, Ann Arbor, MI, USA

¹⁰Professor, Associate Vice President for Community Health Engagement, University of Texas at Austin, Austin, TX, USA

¹¹Associate Professor, School of Nursing; Associate Professor, Department of Pediatrics, School of Medicine, Duke University, Durham, NC, USA

Correspondence: Dr. Gayle G. Page, Professor and Independence Chair, School of Nursing, Johns Hopkins University, 100 Stauffer Rd., Severna Park, MD 21146. gpage1@jhu.edu.

*Writing team member

¹²Associate Professor and Assistant Dean for Research, Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA, USA

¹³Associate Professor, Duke University, Durham, NC, USA

¹⁴Professor and Associate Dean for Research, College of Nursing, University of Wisconsin-Milwaukee, Milwaukee, WI, USA

¹⁵Professor, University of Connecticut School of Nursing, Storrs, CT, USA

¹⁶Associate Professor, University of Washington School of Nursing, Seattle, WA, USA

¹⁷The Alumni Professor of Nursing and Professor of Biomedical Informatics Director, Columbia University, New York, NY, USA

¹⁸Professor of Nursing at Columbia University Medical Center, Columbia University, New York, NY, USA

¹⁹Associate Professor Department of Pain and Translational Symptom Science, University of Maryland Baltimore, Baltimore, MD, USA

²⁰Director, National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA

Abstract

Purpose—Biomarkers as common data elements (CDEs) are important for the characterization of biobehavioral symptoms given that once a biologic moderator or mediator is identified, biologically based strategies can be investigated for treatment efforts. Just as a symptom inventory reflects a symptom experience, a biomarker is an indicator of the symptom, though not the symptom per se. The purposes of this position paper are to (a) identify a “minimum set” of biomarkers for consideration as CDEs in symptom and self-management science, specifically biochemical biomarkers; (b) evaluate the benefits and limitations of such a limited array of biomarkers with implications for symptom science; (c) propose a strategy for the collection of the endorsed minimum set of biologic samples to be employed as CDEs for symptom science; and (d) conceptualize this minimum set of biomarkers consistent with National Institute of Nursing Research (NINR) symptoms of fatigue, depression, cognition, pain, and sleep disturbance.

Design and Methods—From May 2016 through January 2017, a working group consisting of a subset of the Directors of the NINR Centers of Excellence funded by P20 or P30 mechanisms and NINR staff met bimonthly via telephone to develop this position paper suggesting the addition of biomarkers as CDEs. The full group of Directors reviewed drafts, provided critiques and suggestions, recommended the minimum set of biomarkers, and approved the completed document. Best practices for selecting, identifying, and using biological CDEs as well as challenges to the use of biological CDEs for symptom and self-management science are described. Current platforms for sample outcome sharing are presented. Finally, biological CDEs for symptom and self-management science are proposed along with implications for future research and use of CDEs in these areas.

Findings—The recommended minimum set of biomarker CDEs include pro- and anti-inflammatory cytokines, a hypothalamic-pituitary-adrenal axis marker, cortisol, the neuropeptide brain-derived neurotrophic factor, and DNA polymorphisms.

Conclusions—It is anticipated that this minimum set of biomarker CDEs will be refined as knowledge regarding biologic mechanisms underlying symptom and self-management science further develop. The incorporation of biological CDEs may provide insights into mechanisms of symptoms, effectiveness of proposed interventions, and applicability of chosen theoretical frameworks. Similarly, as for the previously suggested NINR CDEs for behavioral symptoms and self-management of chronic conditions, biological CDEs offer the potential for collaborative efforts that will strengthen symptom and self-management science.

Clinical Relevance—The use of biomarker CDEs in biobehavioral symptoms research will facilitate the reproducibility and generalizability of research findings and benefit symptom and self-management science.

Keywords

Biomarker; common data elements; self-management; symptoms

This position paper is the third in a series, authored by the Directors of National Institute of Nursing Research (NINR) Centers of Excellence (P30) and Exploratory Centers (P20) that focus upon advancing symptom and self-management science through the utilization of common data elements (CDEs). The goal is to conceptually define, operationalize, and measure outcomes across research studies. The first paper focused upon the identification and development of CDEs for self-reported symptoms, their use, data-sharing platforms, benefits and challenges of CDEs in symptom science, and future research implications of CDEs for symptom science (Redeker et al., 2015). The second paper focused upon CDEs for research addressing self-management of chronic conditions (Moore et al., 2016). This third paper proposes biochemical biomarkers as CDEs for symptom and self-management science as a means by which to integrate biological with behavioral characterizations of symptoms and self-management. Once biological mechanisms for symptoms can be discerned, treatment efforts can focus on these biological mediators and moderators. This is an important endeavor given the National Institutes of Health (NIH) NINR strategic emphasis on symptom science. In 1998, the NIH Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (Strimbu & Tavel, 2010, p. XXX).

The purposes of this paper are to (a) identify a minimum set of biomarkers for consideration as CDEs in symptom and self-management science, (b) evaluate the benefits and limitations of such a limited array of biomarkers with implications for symptom science, (c) propose a strategy for the collection of the endorsed minimum set of biologic samples to be employed as CDEs for symptom science, and (d) conceptualize this minimum set of biomarkers consistent with NINR symptoms of fatigue, depression, cognition, pain, and sleep disturbance and aligned with a framework of the biobehavioral characterization of sickness

behavior, a longstanding heuristic model that is of reasonable complexity with regard to brain and behavior interactions.

Best Practices for Selecting and Using Biological Common Data Elements

Several principles warrant consideration when planning for the integration of biological and behavioral outcomes in symptom and self-management science and more specific recommendations of biomarkers as CDEs. The first principle is analytic validity, that is, determining whether specific biomarkers are consistently reflective of a given symptom such that changes in biomarker levels are accompanied by changes in report of that symptom. Depending upon the approach, it would also be theoretically and conceptually important to evaluate whether interventions that alter symptoms also alter biomarker levels in a consistent way. If a biomarker is hypothesized to underlie the symptom or self-management phenomenon under study, it should be altered by the intervention if the biomarker mediates the symptom. Adding to the complexity of these relationships, however, is the recognition that individual biomarkers may mediate or moderate multiple pathways or multiple biomarkers may impact a single pathway (Miaskowski, 2016). The second principle is the quality of the evidence for each biomarker as it relates to the behavioral phenomenon, particularly with regard to the consistency of the “pairing” between behavioral and biomarker findings. Meta-analytic and rigorous experimental design are the most desirable approaches for building scientific support for these relationships. The third principle relates to our ability to measure biomarkers with precision, sensitivity, and specificity in any appropriately equipped laboratory. This principle also assumes appropriate sample collection, processing, and preservation before measurement, assuring sample quality as well as administrative precision and appropriate attribution of sample to participant. Continuing validation of biomarker and behavioral relationships contributes to their usefulness as CDEs. These three principles guided the deliberations of the writing team throughout the 8 months of meetings during which the recommendations for biomarker inclusion in symptom science were developed and consensus was reached. Compared to self-management science, there is a much greater body of literature supporting biomarkers for symptom science.

Sickness behavior offers an exemplar of relationships among a constellation of symptoms that accompany infection in both humans and animals. Symptoms including fatigue, sleep disturbance, reduced appetite, anhedonia, fever, myalgia, depressive symptoms, and pain emerge along with the immune activation mounted in response to the infection (Dantzer, 2001; McCusker & Kelley, 2013). Although it remains unclear exactly how a localized or systemic inflammatory response is transmitted to the central nervous system and initiates the sickness symptom response (Poon, Ho, Chiu, Wong, & Chang, 2015), studies in rats and mice have demonstrated that this symptom constellation is caused by increased pro-inflammatory cytokine levels in the brain. Mechanisms by which this may occur are several, including (a) entry of peripherally elevated cytokines into the brain through the blood–brain barrier; (b) activation of the afferent arm of the vagus nerve, which then conveys an inflammatory signal to the brain; or (c) cytokine production in the brain as a consequence of the immune activation in response to the infection (Poon et al., 2015). Pro-inflammatory tumor necrosis factor alpha (TNF- α) or interleukin (IL)-1 beta (IL-1 β) are necessary for the

development of sickness behaviors (McCusker & Kelley, 2013). Human experimental endotoxemia via the administration of small doses of lipopolysaccharide (LPS), cell wall components of Gram-negative bacteria, is a strategy to study inflammation-induced changes in cognition and motivation. The exemplar of sickness behavior is consistent with the NIH Symptom Science Model (Cashion & Grady, 2015) that describes how complex symptoms reflect the outcome of an individual's phenotype, including biological, genetic, psychosocial, and behavioral factors. Sickness behavior likewise reflects a constellation of symptoms that arise in an individual based on an inflammatory phenotype, overlaid on personal factors. As such, sickness behavior offers a mechanistic framework to better predict, track, and target the biology underlying individual symptom experiences.

Identifying and Selecting Biological Common Data Elements

Identifying and selecting biomarkers to include in a given research study ultimately depends upon the research question and the evidence in the literature. For nurse scientists, such biomarkers might include those known or suspected of playing a role in mechanistic pathways associated with symptoms or symptom clusters of acute or chronic illness, or stress. Within the sickness symptom framework described above, biomarkers associated with inflammation are often a choice for study inclusion given the reported associations between inflammation and fatigue (Kim, Miller, Stefanek, & Miller, 2015; Louati & Berenbaum, 2015; Morris, Berk, Walder, & Maes, 2015), pain (DeVon, Piano, Rosenfeld, & Hoppensteadt, 2014; Diatchenko, Nackley, Slade, Fillingim, & Maixner, 2006; Ji, Chameissian, & Zhang, 2016; Klyne, Barbe, & Hodges, 2017), depressive symptoms (Cai, Huang, & Hao, 2015; Huang & Sheng, 2010; Kiecolt-Glaser, Derry, & Faundes, 2015; Miller & Raison, 2016) cognitive function (Harden, Kent, Pittman, & Roth, 2015), and sleep disturbance (Harden et al., 2015; Kamath, Prpich, & Jillani, 2015).

Biomarkers associated with exposure to acute or chronic stress are also often measured in nursing science protocols, reflecting the recognition by many that emotional, physical, neighborhood, financial, relational, and societal stressors have a significant impact on health and well-being. Studies focusing upon self-management of symptoms and including biomarkers have been conducted, but are less common in the literature. For example, an abbreviated progressive muscle relaxation stress-management technique yielded reductions in psychological stress measures and diurnal cortisol secretion among first year university students (Chellew, Evans, Fornes-Vives, Pérez, & Garcia-Banda, 2015); and a 10-week guided imagery intervention in women with fibromyalgia improved self-reported self-efficacy and reduced perceived stress, fatigue, pain severity, and depressive symptoms compared to usual care, although immune biomarkers were not significantly impacted (Menzies, Lyon, Elswick, McCain, & Gray, 2014). Biomarkers that are more specifically linked to a given symptom or condition are also included in many research protocols. For example, investigators may measure specific hormones or neuroimaging biomarkers to explore mechanisms, risks, or treatments for hyperalgesia (Matic, van den Bosch, de Wildt, Tibboel, & van Schalk, 2016; Maurer, Lissounov, Knezevic, Candido, & Knezevic, 2016). Likewise, measuring changes in levels of brain-derived neurotrophic factor (BDNF), a peptide involved in neurogenesis, may be useful to evaluate how interventions such as exercise improve cognition (Meeusen, 2014), which, in turn, may improve self-management.

Immune and Inflammatory Markers

The immune response includes both innate and specific reactions driven by the increased production of white blood cells (WBCs) and the secretion from those cells of chemical products, including cytokines (Paul, 2013). Cytokines, defined as small peptides secreted by WBCs drawn to sites of injury or infection (Dinarello, 2007), provide communication between different types of WBCs. By this means, cytokines direct the immune and inflammatory response, and play a key role in host defense. Since normal or abnormal levels of cytokines remain imprecisely defined, cytokine levels are typically compared between groups or within one group before and after an event or intervention. Often cytokines are grouped as pro- or anti-inflammatory, or as contributing to the innate or active immune response.

The innate immune response involves the secretion of pro-inflammatory cytokines, including IL-1 β , IL-2, IL-6, interferon-gamma (IFN- γ), and TNF- α , from type 1 T helper (Th1) lymphocyte activation of peripheral blood mononuclear cells, including macrophages, monocytes, and natural killer cells (Dinarello, 2007). Elevated levels of pro-inflammatory cytokines initiate cell-mediated and phagocytic-protective responses, and have been linked to the development of sickness symptoms (Dantzer & Kelley, 2007) as well as a variety of chronic and acute disease states (Godbout & Glaser, 2006; Wang et al., 2014). Other cytokines, including IL-4, IL-10, and IL-13, are generally considered anti-inflammatory and are responsible for various aspects of the specific immune response such as antibody production and eosinophil accumulation. The release of anti-inflammatory cytokines is primarily under the control of a different subset of T lymphocytes called T helper 2 (Th2) cells. Th2 responses are characteristic of humoral, or B cell, immunity. These cytokines are considered anti-inflammatory to a large extent because of their ability to inhibit the production of the pro-inflammatory cytokine transcription factor nuclear factor-kappa beta (NFkappaB), thereby suppressing pro-inflammatory cytokine gene activation and cytokine production. Measuring levels of pro- and anti-inflammatory cytokines, or the ratio of pro- to anti-inflammatory cytokines, provides a sensitive measure of cytokine equilibrium or disequilibrium (Petrovsky, 2001).

Cytokines are typically measured in plasma or serum samples collected from a study participant using sterile technique and processed according to specific protocols. Cytokine levels have also been reported in urine and saliva.

Markers of Stress

Biomarkers of acute and chronic stress of interest to nursing scientists often include the hormones of the hypothalamic-pituitary-adrenal (HPA) axis: corticotropin-releasing hormone (CRH), adrenal corticotropin hormone (ACTH), and cortisol. Elevation in any of the HPA axis hormones may occur with exposure to acute or chronic stress, and each has been associated with sickness symptoms, including depressive symptoms (Raison & Miller, 2013), heightened pain sensitivity and sleep disturbance (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Moreover, given the accumulating evidence that chronic stress interferes with cognitive functioning, exposure to chronic stress may interfere with an individual's ability to self-manage his or her health or a caregiver's ability to be an effective

contributor to the self-management of another's health (Allen et al., 2017; Arnsten, 2015). Collection and analysis of plasma, serum, or cerebral spinal fluid levels of CRH and ACTH require strict consideration of sample collection methods, sample processing, and bioassay techniques. Cortisol levels are easily measured in plasma, serum, hair, or saliva, but consideration of free (salivary) versus bound (blood) cortisol, and of the strong diurnal rhythm of all HPA axis hormones, must be considered when planning studies involving these biomarkers (Segerstrom, Boggero, Smith, & Sephton, 2014). If serum or plasma samples are chosen, separation of free versus bound cortisol or concurrent measurement of cortisol-binding globulin would be required.

Also, frequently studied when considering biologic responses to chronic stress is the interaction between the inflammatory response and cortisol levels. Pro-inflammatory cytokines, released in response to infection, trauma, or psychological stress, are potent stimulators of the HPA axis, leading to increased levels of circulating cortisol (Petrovsky, 2001; Steptoe, Hamer, & Chida, 2007). Circulating cortisol binds to the cytoplasmic glucocorticoid receptors of WBCs, and once bound, the cortisol-receptor complex translocates to the nucleus where it inhibits the production of key cytokine transcription factors, effectively halting pro-inflammatory cytokine production (Pace & Miller, 2009; Ratman et al., 2013). This cytokine-glucocorticoid negative feedback cycle is an important homeostatic mechanism by which the inflammatory response is controlled. This negative feedback cycle can be disrupted in persons exposed to chronic stress due to a decreased sensitivity of the glucocorticoid receptor to chronically elevated cortisol, contributing to overproduction or dysregulated production of pro-inflammatory cytokines (Corwin et al., 2013; Pace & Miller, 2009). Biomarkers measured in studies of glucocorticoid resistance may include cortisol and pro-inflammatory cytokine ratios or levels of cytokine transcription factors such as NFkappaB. NFkappaB can be measured in blood samples using enzyme-linked immunosorbent assay (ELISA) kits.

Other Biomarkers of Frequent Interest to Nursing Science

BDNF is a peptide required for brain neurogenesis, including axonal growth and synaptic plasticity. BDNF is linked to fetal and infant neurodevelopment, as well as memory, neuronal plasticity, cognition, and affect across the lifespan (Angelucci, Brenè, & Mathè, 2005). The BDNF locus is on chromosome 11, and a relatively common single nucleotide polymorphism within the BDNF gene, Val66met, has been linked to the development of depressive symptoms in response to stress exposure (Gatt et al., 2009). Serum BDNF protein levels vary depending upon genotype (Lang, Hellweg, Sander, & Gallinat, 2009), and have been reported to increase with exercise in a sex-dependent manner (Szuhany, Bugatti, & Otto, 2015), but decrease with chronic stress (Gatt et al., 2009), inflammation (Tong et al., 2012), and aging (Patterson, 2015). Compared to a control group, older heart failure patients undergoing a cognitive training intervention, Brain Fitness, improved working memory and exhibited increased BDNF protein levels (Pressler et al., 2015). Recently, epigenetic changes in the BDNF gene were identified as possible links between environmental stressors and psychological disorders (Mitchelmore & Gede, 2014). BDNF upregulation in the spinal dorsal horn following noxious stimulation plays an important role in the development of central sensitization, a maladaptive neuroplasticity that drives long-term and persistent pain

(Merighi et al., 2008; Nijs et al., 2015; Smith, 2014). As a biomarker in nursing research studies, BDNF may be measured before and after an intervention such as exercise, or in patients with chronic disease, or may be compared across populations. BDNF protein can be measured using an ELISA method, and BDNF mRNA can be measured via quantitative polymerase chain reaction (qPCR) in serum, leukocytes extracted from serum, or plasma samples. The decision of how and when to measure BDNF, however, can be complex, as there are other factors, including time of blood draw, sex, blood storage time, food intake prior to blood draw, smoking status, and other sociodemographic factors, that are critically important for consideration prior to designing the experiment (for review see Cattaneo, Cattane, Begni, Pariante, & Riva, 2016).

Another category of biomarkers frequently evaluated in nursing research is genetic polymorphisms. As with BDNF, genetic polymorphisms have been identified that influence whether and to what degree an individual might experience a particular symptom, and thus their presence or absence may be considered a risk or protective factor for symptom development. For example, polymorphisms of genes coding for cytokines have been linked to increased risk of fatigue (Lee, Gay, Lerdal, Pullinger, & Aouizerat, 2014), sleep disturbance (Miaskowski et al., 2012), depressive symptoms (Kim et al., 2013; Tartter, Hammen, Bower, Brennan, & Cole, 2015), and pain hypersensitivity among cancer patients (Oliveira et al., 2014; Shi et al., 2015). Other studies have linked genetic polymorphisms of the BDNF gene to pain and depressive symptoms in older adults (Klinedinst, Resnick, Yerges-Armstrong, & Dorsey, 2015), to dysmenorrhea (Lee et al., 2014), and to chronic musculoskeletal pain (Generaal et al., 2016). These and similar examples emphasize the range of clinically relevant research studies utilizing genetic biomarkers.

Measuring genetic polymorphisms requires first isolating the DNA and then sequencing the samples using PCR. Each of these steps requires careful consideration of the sample source (whole blood or serum) and access to DNA sequencing technology.

Platforms for Sample Outcome Sharing

Identifying and selecting biomarkers in symptom and self-management research is extremely important; however, equally important are electronic platforms by which stored sample sets can be explored and leveraged, and expert collaborators can be identified to enhance research.

NINR center collaboration involves identifying and leveraging opportunities within universities and clinical centers and potentially across other NIH centers or other universities (Dorsey et al., 2014). Big data science is an exploding field in which data sharing and collaboration have become the norm, and awareness of where to find these opportunities is key. There are many informative and comprehensive web-based platforms that are now available for obtaining biospecimens or datasets, or finding other scientists with whom to collaborate in utilizing profiling platforms, research collaboration platforms, and biorepository platforms (Redeker et al., 2015). Table S1 offers examples of these platforms.

Sample Quality and Administrative Oversight

The ability to utilize biological CDEs across studies depends upon the quality of the samples and the rigor by which they are collected, maintained, and assayed. Key to ensuring sample quality is consideration of, and strict adherence to, the methods by which each sample is collected. This may include time of day if the biomarker has a diurnal rhythm, may require subjects to be fasting, or may or may not require that a sample be kept on ice prior to processing and may or may not need to adhere to certain time constraints. For many types of biological sample collections, specific tubes with additives may be required (e.g., Tempus Blood RNA tube [Fisher or Paxgene Blood RNA tubes would both be viable tubes for measurement of DNA]). The sample may need to be centrifuged prior to aliquoting and freezing. In some cases, a sample may need to be incubated at a certain temperature, for a specified period of time. Similar detail will be required to ensure consistency in assay procedures. For example, if a commercial kit will be used in assaying a particular analyte, the same kit is recommended to be used by other investigators if possible, and details on all procedures need to be consistent across laboratories. These and other considerations must be discussed a priori, based on best practices from the literature. It will also be essential that collected samples are cataloged as they come into a laboratory and as they are assayed there or sent to other laboratories. Tracing the course of a sample from its collection, to processing, to storage, to assay or transport also contributes to the scientific rigor, transparency, and reproducibility of the data generated from that sample.

Challenges to the Use of Biological Common Data Elements for Symptom and Self-Management Science

Challenges in selecting and using biomarkers for symptom and self-management science include identifying and selecting relevant biomarkers that are components of the biological pathways of interest, and careful operationalization of symptom and self-management phenotypes, including multidimensionality, clustering, and temporal patterning.

Multiple biological pathways may contribute to symptoms and self-management, and each of these may have multiple biomarkers. Examples as described above may include the HPA axis stress pathways, inflammatory pathways, and sickness behavior. In some cases, little may be known about underlying pathways, or competing explanations may need to be tested. Understanding of putative pathways is needed to identify relevant biomarkers of interest. In the event that multiple biomarkers are examined, this may be associated with significant cost.

Distinct phenotypes of symptoms and the impact of self-management interventions must be selected with care to sensitively detect associations of biomarkers with these phenomena or to examine the effects of symptom and self-management interventions on biology. Challenges to phenotyping symptoms and self-management include the wide variety of operational definitions of symptom and self-management concepts; the inherently multidimensional, temporal, and perceptual characteristics of these phenomena; overlap and multicollinearity among symptoms; cultural, linguistic, developmental, and cognitive differences in the expression of these self-reported phenomena; and their meanings to

respondents. For example, depressive symptoms have cognitive and somatic dimensions, such as sleep disturbance and fatigue (Schaakxs, Comijs, Lamers, Beekman, & Penninx, 2017), while pain and other symptoms have sensory, affective, and functional dimensions. Care must be taken to elicit relevant dimensions because biomarkers may be differentially related to various dimensions of these self-reported phenomena, although these possible differences are not yet well described. Although CDEs for symptom (Redeker et al., 2015) and self-management science (Moore et al., 2016) have been identified, further specification is needed to fully understand how multiple dimensions interact with biomarkers of interest. Standardization across studies is also needed to make the most efficacious use of data.

Symptoms also often occur in clusters during everyday life in individuals suffering with chronic conditions, such as cancer (Dong, Butow, Costa, Lovell, & Agar, 2014) and heart disease (Moser et al., 2014). Recent evidence suggests that biomarkers, such as cytokines, are associated with membership in specific symptom clusters (e.g., Illi et al., 2012). If a single symptom is actually part of a cluster, the specificity of the biomarker to one particular symptom may be compromised. Because symptoms are also temporal phenomena, with diurnal (Van Onselen et al., 2013; Wright et al., 2015) or seasonal rhythms, these patterns should be accounted for in relation to biomarkers that may also fluctuate (e.g., salivary cortisol). Symptoms also depend upon the context in which they are perceived. For example, a symptom that may be considered mild while an individual is interacting with loved ones may become much more unpleasant or burdensome when the individual is alone or in the hospital (Corwin et al., 2014). A mismatch between the timing of symptom measurement and the biomarker may also obscure associations or effects.

Culture (Moser et al., 2014; Park & Johantgen, 2016), language, reading level, aging, sex, and developmental level (Schaakxs et al., 2017), among other factors, influence how symptoms and self-management are reported and measured (Redeker et al., 2015). Factors such as aging, race, sex, and gender may also influence biomarkers, genes, and gene expression. Therefore, these factors should be considered in analyses and selection of measures to contextualize findings and minimize bias.

The causal nature of symptoms and biomarkers must also be considered and may be bidirectional (Corwin, Meek, Cook, Lowe, & Sousa, 2012). For example, sleep disturbance may be either a cause or a consequence of sympathetic arousal and HPA axis activation; and limitations in self-management (e.g., inability to exercise or adhere to medical treatment regimens) may contribute to changes in biological pathways and relevant biomarkers as well as behavior. These challenges suggest the ongoing need for experimental and longitudinal studies to understand causal relationships.

Implications for Future Research and Use of Biological Common Data Elements for Symptom and Self-Management Science

An intended outcome of this third paper in the series is, as with the previous two, to identify a short list, minimum set, of CDEs, in this case, biological CDEs, to be recommended for inclusion in appropriate symptom and self-management research studies. These recommendations, along with brief measurement guidelines are presented in Table S2.

The Benefits of Biological Common Data Elements to Symptom and Self-Management Science

There are multiple benefits to incorporating biological CDEs into symptom and self-management science. First, measuring biological CDEs can provide insights into the mechanistic underpinnings of patient symptoms, including symptom clusters. For example, data showing that IL-6/IL-10 ratios increase over time in patients with worsening heart failure compared to patients with stable disease, while at the same time, cognitive deficits and fatigue increase as well, potentially provide insights into the mechanisms by which cognitive deficits and fatigue develop in those patients, that is, that these symptoms may be driven by a similar increase in the pro- or decrease in the anti-inflammatory response (Petrovsky, 2001). Second, when developing an intervention to relieve or manage a given symptom, investigators often propose a theoretical or conceptual model that includes a pathway by which the intervention is hypothesized to work. When testing the intervention, measuring a biomarker known to be associated with that pathway before and after the intervention could provide evidence of both the efficacy of the intervention and the applicability of the model (Corwin & Ferranti, 2016). For example, again considering cognitive deficit and fatigue in heart failure patients, if a 6-month exercise intervention hypothesized to improve cognitive function and reduce fatigue by reducing inflammatory pathways does indeed lead to an improvement in symptoms compared to baseline and if that improvement is accompanied by a corresponding decrease in the IL-6/IL-10 ratio pre- to postintervention, this would suggest that the intervention is effective and the proposed model is supported. However, if there is symptom improvement in the absence of change in the cytokine ratio, the hypothesized mechanism by which the intervention is thought to be effective might need to be reconsidered. Other studies have been published recently as well, wherein biomarker status at baseline has been reported to predict the efficacy of an intervention, potentially allowing clinicians the ability to identify individuals up front who might or might not respond to the intervention in the future. For example, baseline levels of certain cytokines were identified as predictive of who would respond to a mindfulness-based stress reduction intervention and who would not (Reich et al., 2014), and in a separate study, baseline levels of certain cytokines were identified as predictive of which patients with treatment-resistant depression would benefit from the addition of an anti-inflammatory drug to their standard depression therapy and who would not (Raison et al., 2013). These latter examples demonstrate the power of measuring biomarkers to advance precision health care. Lastly, and perhaps most importantly, including biological CDEs offers the potential for collaboration across nursing research studies, which in turn will increase sample size, generalizability of findings, and data reproducibility. This is especially true if the biological CDEs are used in conjunction with the previously suggested NINR CDEs for behavioral symptoms and for research addressing self-management of chronic conditions. In this way the scientific impact of nursing research will continue to grow, and patients, families, and communities will benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- Allen AP, Curran EA, Duggan A, Cryan JF, Chorcornain AN, Dinan TG, ... Clarke G. A systematic review of the psychobiological burden of informal caregiving for patients with dementia: Focus on cognitive and biological markers of chronic stress. *Neuroscience and Biobehavioral Reviews*. 2017; 73:123–164. [PubMed: 27986469]
- Arnsten AF. Stress weakens prefrontal networks: Molecular insults to higher cognition. *Nature Neuroscience*. 2015; 18:1376–1385. [PubMed: 26404712]
- Angelucci F, Brenè S, Mathè AA. BDNF in schizophrenia, depression and corresponding animal models. *Molecular Psychiatry*. 2005; 10:345–352. [PubMed: 15655562]
- Cai S, Huang S, Hao W. New hypothesis and treatment targets of depression: An integrated view of key findings. *Neuroscience Bulletin*. 2015; 31:61–74. [PubMed: 25575479]
- Cashion AK, Grady PA. The National Institutes of Health/National Institutes of Nursing Research intramural research program and the development of the National Institutes of Health Symptom Science Model. *Nursing Outlook*. 2015; 63:484–487. [PubMed: 26187087]
- Cattaneo A, Cattane N, Begni V, Pariante CM, Riva MA. The human BDNF gene: Peripheral gene expression and protein levels as biomarkers for psychiatric disorders. *Translational Psychiatry*. 2016; 6:e958. [PubMed: 27874848]
- Chelley K, Evans P, Fornes-Vives J, Pérez G, Garcia-Banda G. The effect of progressive muscle relaxation on daily cortisol secretion. *Stress*. 2015; 18:538–544. [PubMed: 26130387]
- Corwin EJ, Berg JA, Armstrong TS, DeVito DA, Lee KA, Meek P, Redeker N. Envisioning the future in symptom science. *Nursing Outlook*. 2014; 62:346–351. [PubMed: 25085330]
- Corwin EJ, Ferranti EP. Integration of biomarkers to advance precision nursing interventions for family research across the life span. *Nursing Outlook*. 2016; 64:292–298. [PubMed: 27298194]
- Corwin EJ, Guo Y, Pajer K, Lowe NK, McCarthy D, Schmiede S, ... Stafford B. Immune dysregulation and glucocorticoid resistance in minority and low income pregnant women. *Psychoneuroendocrinology*. 2013; 38:1786–1796. [PubMed: 23541234]
- Corwin EJ, Meek P, Cook PF, Lowe NK, Sousa KH. Shape shifters: Biobehavioral determinants and phenomena in symptom research. *Nursing Outlook*. 2012; 60:191–197. [PubMed: 22789451]
- Dantzer R. Cytokine-induced sickness behavior: Mechanisms and implications. *Annals of the New York Academy of Science*. 2001; 933:222–234.
- Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity*. 2007; 21:153–160.
- Dantzer R, O'Connor JC, Freund GC, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*. 2008; 9:46–57. [PubMed: 18073775]
- DeVon HA, Piano MR, Rosenfeld AG, Hoppensteadt DA. The association of pain with proinflammatory biomarkers: A review of the literature. *Nursing Research*. 2014; 63:51–62. [PubMed: 24335913]
- Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders—Pathways of vulnerability. *Pain*. 2006; 123:226–230. [PubMed: 16777329]
- Dinarello CA. Historical insights into cytokines. *European Journal of Immunology*. 2007; 37:S34–S45. [PubMed: 17972343]
- Dong ST, Butow PN, Costa DS, Lovell MR, Agar M. Symptom clusters in patients with advanced cancer: A systematic review of observational studies. *Journal of Pain and Symptom Management*. 2014; 48:411–450. [PubMed: 24703941]
- Dorsey SG, Schiffman R, Redeker NS, Heitkemper MM, McCloskey DJ, Weglicki LS. ... NINR Center Directors. NINR Centers of Excellence: A logic model for sustainability, leveraging resources and collaboration to accelerate cross-disciplinary science. *Nursing Outlook*. 2014; 62:384–393. [PubMed: 25085328]
- Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, ... Williams LM. Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular Psychiatry*. 2009; 14:681–695. [PubMed: 19153574]

- Generaal E, Milaneschi Y, Jansen R, Elzinga B, Dekker J, Penninx BW. The brain-derived neurotrophic factor pathway, life stress, and chronic multi-site musculoskeletal pain. *Molecular Pain*. 2016; 12doi: 10.1177/1744806916646783
- Godbout JP, Glaser R. Stress-induced immune dysregulation: Implications for wound healing, infectious disease and cancer. *Journal of Neuroimmune Pharmacology*. 2006; 1:421–427. [PubMed: 18040814]
- Harden LM, Kent S, Pittman QJ, Roth J. Fever and sickness behavior: Friend or foe? *Brain, Behavior, and Immunity*. 2015; 50:322–333.
- Huang ZB, Sheng GQ. Interleukin-1 β with learning and memory. *Neuroscience Bulletin*. 2010; 26:455–468. [PubMed: 21113196]
- Illi J, Miaskowski C, Cooper B, Levine JD, Dunn L, West C, ... Aouizerat BE. Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. *Cytokine*. 2012; 58:437–447. [PubMed: 22450224]
- Ji RR, Chamesian A, Zhang YQ. Pain regulation by non-neuronal cells and inflammation. *Science*. 2016; 354:572–577. [PubMed: 27811267]
- Kamath J, Prpich G, Jillani S. Sleep disturbances in patients with medical conditions. *Psychiatric Clinics of North America*. 2015; 38:825–841. [PubMed: 26600111]
- Kiecolt-Glaser JK, Derry HM, Faundes CP. Inflammation: Depression fans the flames and feasts on the heat. *American Journal of Psychiatry*. 2015; 172:1075–1091. [PubMed: 26357876]
- Kim JM, Stewart R, Kim SY, Kang HJ, Jang JE, Kim SW, ... Yoon J-S. A one year longitudinal study of cytokine genes and depression in breast cancer. *Journal of Affective Disorders*. 2013; 148:57–65. [PubMed: 23276701]
- Kim S, Miller BJ, Stefanek ME, Miller AH. Inflammation-induced activation of the indoleamine 2,3-dioxygenase pathway: Relevance to cancer-related fatigue. *Cancer*. 2015; 121:2129–2136. [PubMed: 25728366]
- Klinedinst NJ, Resnick B, Yerges-Armstrong LM, Dorsey SG. The interplay of genetics, behavior, and pain with depressive symptoms in the elderly. *Gerontologist*. 2015; 55:S67–S77. [PubMed: 26055783]
- Klyne DM, Barbe ME, Hodges PW. Systemic inflammatory profiles and their relationships with demographic, behavioural and clinical features in acute low back pain. *Brain, Behavior, and Immunity*. 2017; 60:84–92.
- Lang UE, Hellweg R, Sander T, Gallinat J. The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations. *Molecular Psychiatry*. 2009; 14:120–122. [PubMed: 19156154]
- Lee KA, Gay CL, Lerdal A, Pullinger CR, Aouizerat BE. Cytokine polymorphisms are associated with fatigue in adults living with HIV/AIDS. *Brain, Behavior, and Immunity*. 2014; 40:95–103.
- Louati K, Berenbaum F. Fatigue in chronic inflammation—A link to pain pathways. *Arthritis Research and Therapy*. 2015; 17:254. [PubMed: 26435495]
- Matic M, van den Bosch GE, de Wildt SN, Tibboel D, van Schalk RH. Genetic variants associated with thermal pain sensitivity in a paediatric population. *Pain*. 2016; 157:2476–2482. [PubMed: 27541715]
- Maurer AJ, Lissounov A, Knezevic I, Candido KD, Knezevic NN. Pain and sex hormones: A review of current understanding. *Pain Management*. 2016; 3:285–296.
- McCusker RH, Kelley KW. Immune-neural connections: How the immune system's response to infectious agents influences behavior. *Journal of Experimental Biology*. 2013; 216:84–98. [PubMed: 23225871]
- Meeusen R. Exercise, nutrition and the brain. *Sports Medicine*. 2014; 44(Suppl 1):47–56.
- Menzies V, Lyon DE, Elswick RK, McCain NL, Gray DP. Effects of guided imagery on biobehavioral factors in women with fibromyalgia. *Journal of Behavioral Medicine*. 2014; 37:70–80. [PubMed: 23124538]
- Merighi A, Salio C, Ghirri A, Lossi L, Ferrini F, Betelli C, Bardoni R. BDNF as a pain modulator. *Progress in Neurobiology*. 2008; 85:297–317. [PubMed: 18514997]
- Miaskowski C. Future directions in symptom cluster research. *Seminars in Oncology Nursing*. 2016; 32:405–415. [PubMed: 27776833]

- Miaskowski C, Cooper B, Dhruva A, Dunn LB, Langford DJ, Cataldo JK, ... Aouizerat BE. Evidence of associations between cytokine genes and subjective reports of sleep disturbance in oncology patients and their family caregivers. *PLoS One*. 2012; 7:e40560. [PubMed: 22844404]
- Miller AH, Raison CL. The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*. 2016; 16:22–34.
- Mitchellmore C, Gede L. Brain derived neurotrophic factor: Epigenetic regulation in psychiatric disorders. *Brain Research*. 2014; 1586:162–172. [PubMed: 25223903]
- Moore SM, Schiffman R, Waldrop-Valverde D, Redeker NS, McCloskey DJ, Kim MT, ... Grady P. Recommendations of common data elements to advance the science of self-management of chronic conditions. *Journal of Nursing Scholarship*. 2016; 48:437–447. [PubMed: 27486851]
- Morris G, Berk M, Walder K, Maes M. Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses. *BMC Medicine*. 2015; 13:28. [PubMed: 25856766]
- Moser DK, Lee KS, Wu JR, Mudd-Martin G, Jaarsma T, Huang TY, ... Riegel B. Identification of symptom clusters among patients with heart failure: An international observational study. *International Journal of Nursing Studies*. 2014; 51:1366–1372. [PubMed: 24636665]
- Nijs J, Meeus M, Versijpt J, Moens M, Bos I, Knaepen K, Meeusen R. Brain-derived neurotrophic factor as a driving force behind neuroplasticity in neuropathic and central sensitization pain: a new therapeutic target? *Expert Opinion on Therapeutic Targets*. 2015; 19:465–476.
- Oliveira A, Dinis-Oliveira RJ, Nogueira A, Gonçalves F, Silva P, Vieira C, Medeiros R. Interleukin-1b genotype and circulating levels in cancer patients: Metastatic status and pain perception. *Clinical Biochemistry*. 2014; 47:1209–1213. [PubMed: 24747159]
- Pace TW, Miller AH. Cytokines and glucocorticoid receptor signaling. Relevance to major depression. *Annals of the New York Academy of Science*. 2009; 1179:86–105.
- Paul, WE. *Fundamental immunology*. 7. Philadelphia, PA: Lippincott Williams & Wilkins, Wolters Kluwer; 2013.
- Park J, Johantgen ME. A cross-cultural comparison of symptom reporting and symptom clusters in heart failure. *Journal of Transcultural Nursing*. 2016; 28doi: 10.1177/1043659616651673
- Patterson SL. Immune dysregulation and cognitive vulnerability in the aging brain: Interactions of microglia, IL-1b, BDNF and synaptic plasticity. *Neuropharmacology*. 2015; 96:11–18. [PubMed: 25549562]
- Petrovsky N. Towards a unified model of neuroendocrine-immune interaction. *Immunology and Cell Biology*. 2001; 79:350–357. [PubMed: 11488982]
- Poon DCH, Ho YS, Chiu K, Wong HL, Chang RCC. Sickness: From the focus on cytokines, prostaglandins, and complement factors to the perspectives of neurons. *Neuroscience and Biobehavioral Reviews*. 2015; 57:30–45. [PubMed: 26363665]
- Pressler SJ, Titler M, Koelling TM, Riley PL, Jung M, Hoyland-Domenico L, ... Giordani B. Nurse-enhanced computerized cognitive training increases serum brain-derived neurotrophic factor levels and improves working memory in heart failure. *Journal of Cardiac Failure*. 2015; 21:630–641. [PubMed: 25982826]
- Raison CL, Miller AH. Malaise, melancholia and madness: The evolutionary legacy of an inflammatory bias. *Brain, Behavior, and Immunity*. 2013; 31:1–8.
- Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, ... Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *Journal of the American Medical Association Psychiatry*. 2013; 70:31–41. [PubMed: 22945416]
- Ratman D, Vanden Berghe W, Dejager L, Libert C, Tavernier J, Beck IM, De Bosscher K. How glucocorticoid receptors modulate the activity of other transcription factors: A scope beyond tethering. *Molecular and Cellular Endocrinology*. 2013; 380:41–54. [PubMed: 23267834]
- Redeker NS, Anderson S, Bakken S, Corwin EJ, Docherty SL, Dorsey SG, ... Grady P. Advancing symptom science through use of common data elements. *Journal of Nursing Scholarship*. 2015; 47:379–388. [PubMed: 26250061]
- Reich RR, Lengacher CA, Kip KE, Shivers SC, Schell MJ, Shelton MM, ... Klein TW. Baseline immune biomarkers as predictors of MBSR(BC) treatment success in off-treatment breast cancer patients. *Biological Research for Nursing*. 2014; 16:429–437. [PubMed: 24477514]

- Schaakxs R, Comijs HC, Lamers F, Beekman AG, Penninx BW. Age-related variability in the presentation of symptoms of major depressive disorder. *Psychological Medicine*. 2017; 47:543–552. [PubMed: 27786143]
- Segerstrom SC, Boggero IA, Smith GT, Sephton SE. Variability and reliability of diurnal cortisol in younger and older adults: Implications for design decisions. *Psychoneuroendocrinology*. 2014; 49:299–309. [PubMed: 25137484]
- Shi Q, Wang XS, Li G, Shah ND, Orlowski RZ, Williams LA, ... Cleeland CS. Racial/ethnic disparities in inflammatory gene single-nucleotide polymorphisms as predictors of a high risk for symptom burden in patients with multiple myeloma 1 year after diagnosis. *Cancer*. 2015; 121:1138–1146. [PubMed: 25469832]
- Smith PA. BDNF: No gain without pain? *Neuroscience*. 2014; 283:107–123. [PubMed: 24887639]
- Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity*. 2007; 21:901–912.
- Strimbu K, Tavel JA. What are biomarkers? *Current Opinion in HIV and AIDS*. 2010; 5:463–466. [PubMed: 20978388]
- Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *Journal of Psychiatric Research*. 2015; 60:56–64. [PubMed: 25455510]
- Tartter M, Hammen C, Bower JE, Brennan PA, Cole S. Effects of chronic interpersonal stress exposure on depressive symptoms are moderated by genetic variation at IL6 and IL1b in youth. *Brain, Behavior, and Immunity*. 2015; 46:104–111.
- Tong L, Prieto GA, Kramár EA, Smith ED, Cribbs DH, Lynch G, Cotman CW. Brain-derived neurotrophic factor-dependent synaptic plasticity is suppressed by interleukin-1 β via p38 mitogen-activated protein kinase. *Journal of Neuroscience*. 2012; 32:17714–17724. [PubMed: 23223292]
- Van Onselen C, Paul SM, Lee K, Dunn L, Aouizerat BE, West C, ... Miaskowski C. Trajectories of sleep disturbance and daytime sleepiness in women before and after surgery for breast cancer. *Journal of Pain and Symptom Management*. 2013; 45:244–260. [PubMed: 22921179]
- Wang P, Guan PP, Wang T, Yu X, Guo JJ, Wang ZY. Aggravation of Alzheimer's disease due to the COX-2-mediated reciprocal regulation of IL-1 β and A β between glial and neuron cells. *Aging Cell*. 2014; 13:605–615. [PubMed: 24621265]
- Wright F, D'Eramo Melkus G, Hammer M, Schmidt BL, Knobf MT, Paul SM, ... Miaskowski C. Predictors and trajectories of morning fatigue are distinct from evening fatigue. *Journal of Pain and Symptom Management*. 2015; 50:176–189. [PubMed: 25828559]

Clinical Resources

- National Institute of Neurological Disorders and Stroke. NINDS common data elements. <https://www.ninds.nih.gov/Funding/Apply-Funding/Application-Support-Library/NINDS-Common-Data-Elements>
- National Institute of Nursing Research. Common data elements at NINR. <https://www.ninr.nih.gov/site-structure/cde-portal>
- National Institutes of Health, U.S. National Library of Medicine. Summary Table for NIH CDE initiatives. https://www.nlm.nih.gov/cde/summary_table_1.html