Precision Health
Use of Omics to Optimize Self-Management of Chronic Pain in Aging

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ABSTRACT
Chronic pain has become a public health epidemic based on the number of Americans affected and its associated health care costs. Unfortunately, there are few efficacious treatments to manage chronic pain and as the population of older adults and centenarians who are at high risk for chronic pain continues to grow, the chronic pain epidemic will continue to worsen unless new therapeutic strategies are discovered. In the current era of precision medicine, there is a major emphasis being placed on the use of self-management and omics to discover new therapeutic targets and design treatment strategies that are tailored to the individual patient. This commentary discusses the current state of the science related to omics and self-management of chronic pain in older adults, the role of gerontological nurses in this process, and future directions.


Given the recent and projected growth in the number of individuals who are older adults and centenarians, a primary challenge is the ability to provide optimal care for this segment of the population, 50% of whom have three or more chronic illnesses. One symptom that resonates across most chronic illnesses is pain. More than one half of Americans experience chronic pain associated with comorbidities and mortality (Grey, Schulman-Green, Knafl, & Reynolds, 2015). The risk of experiencing pain increases for females and older adults (Nahin, 2015). Although acute pain serves a biological purpose, for example to warn of impending tissue damage or protect an injury until healed, chronic pain serves no such purpose. This is reflected in the International Association for the Study of Pain definition of pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey et al., 1986, p. S217). Pain is debilitating and can either occur as a symptom of a chronic condition or a primary problem (Ersek, Turner, Cain, & Kemp, 2008). According to the Institute of Medicine (IOM) report on “Relieving Pain in America” (Pizzo, Clark, & Pokras, 2011), chronic pain is a public health epidemic affecting more than 116 million Americans and costing more than $600 billion per year in health care expenses and lost work productivity. Despite advances in conventional pharmacological and nonphar-
macological treatments for pain that are informed by the current understanding of basic biological mechanisms of chronic pain, most individuals do not obtain adequate pain relief.

There are few effective pharmacological agents that can completely alleviate chronic pain in dosages that do not produce debilitating reductions in functional status or quality of life. There is also considerable risk for addiction to prescription pain medications, which is a growing problem in the United States. In addition to pain, these patients also experience significant negative physical, psychological, social, and emotional consequences, all of which can reduce quality of life (Pizzo et al., 2011). In conjunction with reduced quality of life, pain-related disability is the single biggest contributor to years lived with a disability (Murray et al., 2013).

As noted, older adults are particularly at risk for experiencing chronic pain (Patel, Guralnik, Dansie, & Turk, 2013), which has a significant impact not only on quality of life but on function and physical activity. Pain is frequently cited as a primary symptom underlying disability (Ettinger et al., 1994; Leveille, Fried, & Guralnik, 2002; Melzer, Gardener, & Guralnik, 2005), and as many as 50% of individuals with dementia experience pain. There are challenges to identification of pain among these individuals, particularly those with cognitive impairment (Corbett et al., 2016; Klapwijk, Caljouw, Pieper, van der Steen, & Achterberg, 2016). Pain among these individuals often presents as aggression, agitation, withdrawal, confusion, and impaired or worsening function (Corbett & Ballard, 2012; McAuliffe, Brown, & Fetherstonhaugh, 2012). Thus, the effects of a decline in cognitive function on the ability to self-report pain may render prevalence data uncertain (Patel et al., 2013). This commentary will explain the role omics has played in advancing the understanding of pain perception, pain interpretation, and the pathophysiology of chronic pain. Current technologies for omics research are introduced. Recommendations are made for applying omics and precision health to the science of pain self-management.

MECHANISMS OF PAIN ARE MULTIFACTORIAL IN OLDER ADULTS

Given the challenges in identification and management of pain in older adults, the association of omics with pain is particularly important for older adults. Prior work has shown that there is evidence to suggest that single nucleotide polymorphisms (SNPs) in multiple genes influence pain perception and interpretation. Genetic influences of pain contribute to the modulation of pain in the central nervous system (CNS) and periphery; SNPs in genes that participate in synaptic plasticity or the activation of spinal microglia have been associated with pain. Genetic variation can also influence nerve conduction and synaptic transmission, which could lead to altered pain sensation. To date, candidate gene analyses in pain research have focused mainly on 10 genes that were identified either in animal models or humans to be associated with pain (Belfer et al., 2013; Di Lorenzo et al., 2014; Mogil, 2012; Rennt, Leitch, & Dorsey, 2009). These genes include: brain-derived neurotrophic factor (BDNF), FK506 binding protein 5 (FKBP5), neurotrophic receptor tyrosine kinase 1 (NTRK1), neurotrophic receptor tyrosine kinase 2 (NTRK2), neurotrophic receptor tyrosine kinase 3 (NTRK3), oxytocin receptor (OXTR), dopamine receptor D4 (DRD4), serotonin transporter 1 (SLC6A4), catechol-O-methyltransferase (COMT), and monoamine oxidase A (MAOA). Although replications of these findings are limited, a recent study noted that there was an association between pain and BDNF, FKBP5, NTRK2, NTRK3, and OXTR (Rennt et al., 2016). The neurotrophin BDNF has repeatedly been shown to be a potent modulator of pain processing in the CNS (Merighi et al., 2008). Noxious stimulation increases BDNF production in the spinal dorsal horn (SDH) (Coull et al., 2005) and brainstem (Rennt, Lin, Thomas, & Dorsey, 2006) leading to hyperalgesia and the formation of mechanical allodynia.

In addition to the consideration of the relationship of specific genes, microRNAs (miRNAs) have been evaluated as contributing to the development and pathophysiology of chronic pain (Follert, Cremer, & Béclin, 2014; Sakai & Suzuki, 2014; Sun & Shi, 2015). The protein expressions of hundreds of genes are post transcriptionally regulated by a single type of miRNA in a sequence specific manner. miRNA expressions are globally changed in various pain states in the dorsal root ganglion, spinal cord, and brain regions, such as the limbic system and prefrontal cortex. Chronic pain arises from a variety of pathologies, such as damage to the somatosensory system, cancers, or musculoskeletal problems. The miRNA expression profiles are highly distinctive depending on the cause of the pain. miRNAs have repeatedly been associated with the pathogenesis of diseases such as osteoarthritis as well as the associated symptom of pain (Barter & Young, 2013; Papageorgiou, Stivarou, & Tsidroni, 2016; Yu, Chen, & Wang, 2011; Zhang, Lygrisse, & Wang, 2017). For example, expression changes in miRNA-146a among other miRNAs were associated with cartilage change as well as inflammation in...
osteoarthritis (Barter & Young, 2013; Yu et al., 2011; Zhang et al., 2017). In animal models, rats with osteoarthritis experiencing pain expressed lower levels of miRNA-146a in their dorsal root ganglion and SDH. In addition, the role of miRNA-146a in the clinical manifestations of pain in osteoarthritis was substantiated by the fact that miRNA-146a dampens the expression of a set of inflammatory molecules associated with pain perception in hymen glial cells and the expression of transient receptor potential cation channel subfamily V member 1 (TRPV-1), an ion channel (Premkumar & Sikand, 2008). This finding has important implications for the detection of pain among older adults and the development of analgesic agents or behavioral interventions to target this pain. Moreover, these findings provide critically important information toward the development of precision health.

SELF-MANAGEMENT

Self-Management Defined

Although self-management of chronic conditions such as pain is a complex construct, it is typically defined as an interactive and dynamic process that individuals or caregivers engage in daily to manage chronic conditions (Grey et al., 2015; Ruggiero et al., 1997). Self-management is a deliberative process with patients, either alone or with the help of caregivers, to assuming responsibility for their own health care and engaging a set of self-regulation skills that include goal setting, self-monitoring, and reflective thinking to manage change and improve chronic conditions (Ryan, 2009). Self-management also requires sufficient frontal lobe function and cognitive ability on the part of the older adult to establish goals and plan a program of care. In some situations, more involvement of the caregiver is needed to facilitate this process. For example, learning from a caregiver that an older individual previously liked to swim can be used to establish swimming as an intervention to manage pain associated with osteoarthritis.

Self-Management Strategies for Chronic Pain Relief

Given the lack of efficacy and burdensome, as well as addictive, side effects of pharmacological treatments for chronic pain, there have been several self-management interventions designed and tested to reduce or eliminate this symptom. Examples of self-management interventions include educational programs (e.g., coping, social support) delivered in person or via technology (Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003), physical activity, exercise, relaxation, mindfulness, cognitive behavioral programs, coping/social support strategies, and others (Bruckenthal, Marino, & Snelling, 2016; Du et al., 2011; Kroon et al., 2014; Liu & Petrini, 2015; Park, McCaffrey, Newman, Liehr, & Ouslander, 2017; Reid et al., 2008).

Physical activity has been one of the most commonly used and effective interventions for managing pain and pain associated symptoms such as functional changes and depression among older adults. Some early evidence for the efficacy of physical activity and exercise to reduce pain was provided by pre-clinical rodent studies. Physical activity (timed treadmill training and voluntary wheel running) was shown to reverse peripheral nerve injury–induced neuropathic thermal hyperalgesia (i.e., heightened response to a stimulation that is normally painful) and mechanical allodynia (i.e., a noxious response to a normally innocuous stimulation) (Cobianchi, Casals-Diaz, Jaramillo, & Navarro, 2013; Cobianchi, Marinelli, Florenzano, Pavone, & Luvisetto, 2010; Sheahan, Copits, Golden, & Gereau, 2013; Stagg et al., 2011). Non-weight bearing exercise (e.g., swim therapy) has also been shown to reduce neuropathic pain in rats following peripheral nerve injury (Shen, Fox, & Cheng, 2013), and regular physical activity can prevent the development of chronic pain in rats (Grace et al., 2016; Sluka, O’Donnell, Danielson, & Rasmussen, 2013).

In humans, there have been a number of studies that have tested the use of physical activity as a self-management intervention to reduce chronic pain across a variety of clinical pain conditions alone and in combination with other self-management strategies (Arnstein & Herr, 2017; Daeenen, Varkey, Kellmann, & Nijs, 2015). Physical activity has been shown to alleviate inflammatory and neuropathic pain conditions and chronic pain experienced by patients with musculoskeletal disorders (Courneya et al., 2013; Dixit, Maiya, & Shastry, 2014; Hurkmans, van der Giesen, Vliet Vlieland, Schoones, & Van den Ende, 2009; Wright & Sluka, 2001). Meta-analyses of physical activity to reduce pain can be found for several conditions (Devos-Comby, Cronan, & Roesch, 2006; Kelley, Kelley, Hootman, & Jones, 2011; Nguyen et al., 2017). Devos-Comby et al. (2006) examined physical activity with and without other self-management interventions to improve osteoarthritis outcomes including pain. Of the studies reviewed, 16 met inclusion criteria. The findings revealed only a modest effect of physical activity to improve pain, psychological well-being, and physical well-being. Among other conclusions, the authors speculated that small sample sizes and the need to intensify the physical activity intervention might explain the lack of a more robust response (Devos-Comby et al., 2006). In another meta-analysis of community delivered physical activity to improve pain and physical function in adults with osteo-
arthritis and other types of rheumatic disease, statistical analysis of 33 published studies showed a decrease in pain (Kelley et al., 2011). Of note, across these studies, treatment fidelity was not well controlled, and dose delivered versus dose received of physical activity were not comprehensively evaluated. Based on these findings and research to date, the dose of physical activity needed to achieve optimal pain relief cannot be established.

Other modalities such as ice, heat, and positioning have consistently been used to manage chronic pain (Hawamdeh et al., 2012; Iversen, 2012). Although there is some evidence for the effectiveness of these nonpharmacological treatments (Petrofsky, Laymon, Alshammari, Khowailed, & Lee, 2014), the evidence is limited and, as with physical activity, the mechanism of action is unknown.

Although the efficacy of physical activity and exercise to reduce chronic pain seems promising, there are questions regarding the mechanisms underlying pain reduction, particularly in older adults. An increasing number of studies point to a link between physical activity/exercise and the endogenous pain modulatory system (Ellingson, Shields, Stegger, & Cook, 2012; Geva & Defrin, 2013; Naugle, Ohlman, Naugle, Riley, & Keith, 2017). In brief, increased physical activity and exercise have been shown to increase the efficacy of the endogenous pain modulatory system, producing analgesia. To this point, a recent study showed that self-reported levels of exercise and total physical activity were related to the function of the endogenous pain modulatory system in healthy young and old adults (Naugle & Riley, 2014). Because older adults are less active, it may be that reduced physical activity is associated with a decline in endogenous analgesia, leading to increased chronic pain (Naugle et al., 2017). This hypothesis was tested in a recent study of older adults, which demonstrated that less sedentary time and increased light physical activity significantly increased pain inhibition (Naugle et al., 2017).

**PRECISION HEALTH**

**Precision Health Defined**

*Precision medicine,* or health, can broadly be defined as the tailoring of prevention or treatment strategies to a person’s individual characteristics (e.g., genomics, environment, lifestyle), rather than using clinical practices that are based on what works for the aggregate (Collins & Varmus, 2015). Nurse scientists are uniquely poised to use precision health methods to address symptoms such as chronic pain. The National Institute of Nursing Research (NINR) Extramural Program supports studies that aim to predict who is at risk for symptoms related to chronic conditions and those that test tailored interventions to improve symptoms. In the NINR Intramural Program, scientists use the National Institutes of Health Symptom Science Model (NIH/SSM) (Cashion & Grady, 2015) to guide symptom science and precision health studies aimed at addressing cancer treatment–related fatigue, mechanisms of oxidative stress in congenital myopathy, pain and related symptoms in digestive disorders, and cognitive dysfunction following traumatic brain injury (Cashion, Gill, Hawes, Henderson, & Saligan, 2016). Thus, nursing science has fully engaged and embraced the use of precision health to move symptom science forward, including studies of chronic pain.

**Omics Defined**

According to the IOM committee report on the review of omics-based tests to predict patient outcomes in clinical trials (Micheel, Nass, & Omenn, 2012), the term *omics* refers to multiple molecular disciplines brought to bear to characterize various biological molecules, including protein, DNA, RNA, and metabolites, to generate high-dimensional, systems-level data. For example, genetics refers broadly to the investigation of DNA, whereas transcriptomics studies measure RNA levels to quantify gene expression. One could examine the DNA to identify SNPs that might alter gene expression. In this case, both DNA and RNA would be assayed. Or, a study might be performed to identify epigenetic changes to DNA that are known to alter gene expression. However, if single omics tests are conducted (e.g., SNP analysis), the ability to draw meaningful conclusions regarding the mechanistic influence of each SNP is lost when gene expression studies are not also included. The data generated from omics studies can then be used to either predict individual outcomes related to a specific intervention or susceptibility to develop a symptom or disease.

**Currently Available Technologies for Omics Research**

Although a comprehensive review of omics technologies is beyond the scope of the current commentary, the available technology platforms are briefly described below.

**Next Generation Sequencing.** Next generation sequencing (NGS) technologies can be used to examine a DNA, RNA, or protein sequence or conduct high-resolution mapping of 5′—C—phosphate—G—3′ (CpG) dinucleotide methylation of DNA, termed *epigenomics* (Conley et al., 2013; Lan et al., 2011; Metzker, 2010; Wickersham & Dorsey, 2017). For DNA and RNA, the sequencing is performed to identify a predetermined length of nucleotide sequence (typically 25 to 150 base pairs), each of which is termed a *short-read.* Prior genome sequencing technolo-
ologies accomplished this with assays that identified one molecule at a time using a technology known as bi-directional Sanger sequencing (Katsanis & Katsanis, 2013). Advances in technology, however, have made it possible to investigate millions of nucleotides simultaneously (Conley et al., 2013). NGS has become more efficient, with corresponding increases in sequence output, as well as less expensive (Wetterstrand, 2016), and it is likely that a sub-$1,000 whole genome sequence will soon be possible.

Microarray and Other Array-Based Technologies. DNA microarrays can be used to conduct transcriptomic, epigenomic, proteomic, or genome-wide association studies (GWAS). Microarrays are typically fabricated on silicon, glass, or plastic substrates and have tens to hundreds of thousands of probe sets or antibodies designed to capture DNA, RNA, methylated CpG sites, or proteins (Heller, 2002). Unlike NGS, where each nucleotide or amino acid is directly assayed, array-based analysis depends on transforming an analog fluorescence signal to a value representing the relative abundance of a gene or transcript, a protein, or to call a SNP for GWAS studies (DNA).

APPLYING OMICS TO SELF-MANAGEMENT OF PAIN IN OLDER ADULTS

As the study of omics continues, it is anticipated that discoveries of biomarkers for pain and the associated underlying cause of pain will be identified. This discovery of pain biomarkers will facilitate the measurement of pain and matching of treatment modalities to the cause of pain, either through discovery of new targeted pharmacological agents or via testing behavioral interventions. The ability to objectively measure pain is particularly important for older adults with cognitive impairment who may be unable to report pain and/or provide information about the location of the pain to help determine the cause. Regarding the treatment of pain, omics can be used to objectively measure outcomes following pain interventions. For example, balneotherapy was noted to modify miRNA expression levels in older adults with osteoarthritis (Giannitti et al., 2017). Furthermore, this information can be used to help guide the development of new technologies or pharmacotherapeutic agents.

ROLE OF GERONTOLOGICAL NURSE SCIENTISTS AND CLINICIANS

Incorporation of Omics into Research and Clinical Practice

Nurse researchers and clinicians are well-positioned to identify clinical problems related to pain and pain management that can drive future research questions. Identification of treatment modalities that work clinically can be tested rigorously using omics techniques as possible biomarkers of pain. Further, nurse researchers at the bench can work with nurses in the clinical setting to translate findings to practice and drive new research in animal models. Examples of this might be the replication of dosing studies with animals performed on humans or vice versa.

FUTURE DIRECTIONS

Continued research is needed to incorporate omics findings into pain research and management in real world clinical settings. Although it is a challenge to conduct research in these settings, due to the heterogeneity of older individuals, multimorbidity, and the inability to control psychosocial factors such as motivation and resilience, the findings are important to moving the science of precision health forward.

REFERENCES

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