Federal Pain Research Strategy

Executive Summary

The Federal Pain Research Strategy is an effort of the Interagency Pain Research Coordinating Committee and the Office of Pain Policy of the National Institutes of Health to oversee development of a long-term strategic plan for those federal agencies and departments that support pain research. A diverse and balanced group of scientific experts, patient advocates, and federal representatives identified and prioritized research recommendations as a basis for this long-term strategic plan to coordinate and advance the federal pain research agenda. The key areas of prevention of acute and chronic pain, acute pain and acute pain management, the transition from acute to chronic pain, chronic pain and chronic pain management, and disparities in pain and pain care provided the framework for development of the strategy. In addition, the task force identified and then merged a set of cross-cutting research priorities in which similar research recommendations were developed across multiples work groups. Priorities were identified across groups as "top priorities" and within groups as having "greatest near-term value" and as "most impactful".

Introduction

The Federal Pain Research Strategy (FPRS) is a long term strategic plan to guide the federal agencies and departments that support pain research and to advance the science to better understand pain and improve pain care. Development of the strategy was overseen and coordinated by the Interagency Pain Research Coordinating Committee (IPRCC) and the Office of Pain Policy of the National Institutes of Health. The strategy identifies a set of research priorities that align with the missions of numerous agencies within the Department of Health and Human Services, the Department of Defense and the Department of Veterans Affairs. Overall, the priorities cover basic through clinical, dissemination, and implementation research to support the translation of scientific discoveries into clinical practice and improve the lives of people with pain.

The significant public health crisis and individual burden of pain has received increasing recognition since release of the 2011 Institute of Medicine (IOM) report, "Relieving Pain in America"[1]. The IOM report noted that over 100 million adults report having chronic pain. Subsequent large population studies provided more detail on how pain affects our nation; more than 25 million adults suffer daily from pain; over 10 million people report high levels of pain most days, and 8 million have pain severe enough to interfere

[1] (2011). Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC, Institute of Medicine.

with their lives[2]. Pain severity is associated with worsening overall health status, greater disability, and increased use of health care services. The huge cost of health care and lost productivity associated with pain (approximately $600 billion per year)[1] far exceeds the investment in research to improve understanding of pain, develop safe and effective treatments, and translate discoveries into clinical practice. Efforts to reduce the burden of pain at the population level and for individuals must be guided by population-based data and evidence-based pain management practices. Associated with this "population-level pain" crisis is the dependence on prescription opioids in pain management. As opioid prescribing for pain care increased exponentially over the past two decades, alarming increases occurred in opioid use disorder, creating an epidemic of opioid overdoses and deaths [3,4]. In light of the millions of people with people with pain and the consequences of opioids, there is an urgent need for research to improve pain management and reduce reliance on prescription opioid medications.

After assessing the state of pain and pain care in the U.S., the IOM called for a cultural transformation in pain prevention, care, education, and research and development of a comprehensive population health-level strategy to address these issues. In response to their core recommendations, the National Pain Strategy (NPS)[5] was developed and released in 2016. The NPS is a broad-ranging plan with discrete, achievable steps intended to change how the nation perceives and manages pain. Its implementation is the government's first coordinated effort to improve pain care in America. The NPS notes that "efforts to reduce the burden of pain in the United States cannot be achieved without an expanded and sustained investment in basic and clinical research on the biopsychosocial mechanisms that produce and maintain chronic pain and development of safe and effective pain treatments". The FPRS provides guidance for an expanded pain research agenda that aligns with the vision and objectives of the NPS and serves as its companion effort to address the IOM's call for further research.

In planning for the FPRS development, a structural framework was established that fits with the NPS's definition of the continuum of pain, from prevention through chronic high impact pain. The key thematic areas of prevention of acute and chronic pain, acute pain and acute pain management, the transition from acute to chronic pain, and chronic pain and chronic pain management were assigned to work groups within a broad and diverse task force. The heterogeneity of the population of people with pain, the range of pain conditions and their heterogeneous etiology creates great challenges in developing a research agenda. It was considered essential, therefore, also to assemble an expert group specifically tasked to develop research priorities for disparities in pain and pain care. The operational structure for the FPRS development ensured engagement of scientific experts, patient advocates, and federal representatives within thematic work groups, communication across thematic workgroups, coordination through an expert steering committee, and feedback and approval from the IPRCC[6].

The work groups began their deliberations with an analysis of the current research landscape, a literature review, and a survey of additional experts. A long series of thoughtful discussions within and across work

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[2] Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012.*Journal of Pain.* 2015;16(8):769-780.
[3] IMS's Source Prescription Audit & Vector One: National
[4] National Center for Health Statistics CDC Wonder https://wonder.cdc.gov/
[5] https://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm
[6] https://iprcc.nih.gov/FPRS/FPRS.htm

groups led to identification and prioritization of a set of research priorities, specific for each thematic area and covering basic through clinical, dissemination, and implementation research. Only those priorities considered of high importance by the work groups were submitted for inclusion in the FPRS. Several priorities identified by the work groups addressed research gaps that cut across the thematic areas of the FPRS. This set of cross-cutting research priorities, which spanned the key themes, were refined and agreed upon by all work groups and as such were considered especially important recommendations. These recommendations are included in the FPRS under Cross- Cutting Themes. The entire task force anonymously scored the full set of priorities based on merit criteria. The priorities were then rank ordered by score. Those with scores in the highest quartile across all the work groups' submissions are marked as "top priority" in the FPRS report. In addition, individual work groups selected by vote, the one priority within its workgroup considered most likely to have the greatest impact on the science and in the clinic over the long term. For this process, they were asked to consider research priorities for which knowledge and technical resources currently exist to move the work forward, as well as those for which resources are yet to be developed or supporting research is needed prior to moving the work forward. The work groups also were asked to identify the one priority within its work group most likely to have the greatest near-term value, in that it is ready to move forward now. These priorities are marked respectively as "most impactful" and of "greatest near-term value" in the report. See Appendix A for a summary of ranked and selected priorities.

The task force recognized that while their recommendations applied to research relevant to all people with pain, knowledge gaps related to individual and group variability in the experience of pain and pain care need to be filled. Many research priorities in the FPRS highlight the need to identify biological and psychosocial mechanisms contributing to acute and chronic pain across the population. The task force agreed that because biopsychosocial mechanisms may influence pain differently in demographic subgroups, these research efforts must consider disparate populations. Research also is needed to elucidate biological (e.g., disease-specific, neurologic, immunologic, genetic), psychological (e.g. mood/affect, cognition, resilience), and social (e.g. discrimination, cultural influences, social support) mechanisms that contribute to and perpetuate population group differences in pain. Several workgroups highlighted the need for research to enhance assessment and treatment of pain across multiple contexts and clinical populations. It was agreed that such research must be tailored for disparate populations, to include both age- and population-appropriate pain measures and treatments. Intervention studies should be conducted to determine treatment outcomes, and their mediators in subgroups of patients based on clinical (e.g., those taking multiple medications, those with varying levels of cognitive impairment, those with physical or psychiatric comorbidities) and demographic (e.g., races/ethnicities, sex/gender, age, socioeconomic status) characteristics.

It was considered essential to solicit and consider comments and input from the public at the planning phase and prior to finalizing the FPRS. A Request for Information solicited input on topics for discussion prior to convening work groups. A public comment period was held after release of the draft recommendations. Input was solicited by email and through an open Public Forum held at the NIH campus. All comments were reviewed, considered by the workgroups and are incorporated as deemed appropriate into the final set of research priorities.

The FPRS is directed to all federal agencies and departments that support pain research. The priorities of the FPRS were developed with input from representatives of all relevant federal entities and cover the range of mission-relevant pain research interests across the federal government. A ten year timeframe is anticipated to achieve the priorities, with some, especially those identified as having the greatest near-term value, to be supported within a shorter period of time. The FPRS is not a mandate for agencies and departments to fund the research priorities. Rather, the FPRS is intended to serve as a guidance document to coordinate and advance the federal pain research agenda, facilitate collaborative research efforts across government agencies and departments, and to optimize their resources. It is a comprehensive and thoughtful compilation of prioritized pain research recommendations developed by expert advisors and based on the current state of the science, ongoing research, technological advances, and needs of people with pain. The federal agencies and departments are asked to incorporate the research recommendations prioritized in the FPRS into their mission-specific research strategic planning. They are encouraged to note those priorities identified by the FPRS work groups as "top", "most impactful" and with "greatest near term" value as funding decisions are made.

CROSS-CUTTING THEMES

NOVEL DRUGS AND NON-PHARMACOLOGICAL TREATMENTS FOR PAIN

Statement of the Problem

Current mainstays of pain management, including analgesics and anesthetics, are used despite known side effects and uncertain efficacy. Novel pharmacologic treatments for pain have not emerged for some time. Instead, modifications and combinations of established therapeutic molecules were developed and evaluated with little improvements in efficacy or reduction of adverse effects. Given the adverse effects, risks of tolerance, dependence, and addiction associated with opioids, new safer and more effective pharmacologic and non-pharmacologic approaches for pain management are needed. Data and knowledge gaps in basic research have prevented promising targets from being translated into safe and effective therapies.

Research Priorities

Top Priority: *Develop Safer Opioids, New, Non-opioid Analgesics and the First Generation of Disease Modifying Agents.*

Development of safe and effective pharmacologic approaches for pain is an important goal that will greatly benefit patients and healthcare providers. To achieve this goal, drug discovery efforts that target endogenous resolution mechanisms and/or mechanisms that can move patients toward new, acceptable set-points should be prioritized. Government support of early stage drug development in this area should be enhanced.

Evaluate Efficacy, Safety and Interactions of New Therapies.

As part of any evaluation of a new therapy for pain management, data need to be collected on efficacy, adverse effects, interactive effects with other treatments, and interactions with and impact on patient's comorbid conditions. Determination of optimal dosing and adherence strategies for non-pharmacological treatments should be included in this evaluation process. Differential effects of novel therapies on disparate groups (e.g. young, elderly), should be explored. Of note, it may be inappropriate to expect that therapeutics, which are effective in men also are effective in women. Further research on neuraxial and peripheral regional analgesia is needed, including methods of delivery and prevention of rare adverse effects.

Explore Novel Biological Targets.
Discovery and evaluation of biologics as new pharmacologic and non-pharmacologic treatments for pain that are safe and effective is needed. Research on these targets should be based on knowledge of the biopsychosocial mechanisms underlying pain.

SCREENING TOOLS AND OUTCOME MEASURES FOR ASSESSMENTS ACROSS THE CONTINUUM OF PAIN

Statement of the Problem

Pain is a subjective experience and difficult to measure objectively. Biomarkers could provide means to objectify an inherently subjective measurement. In addition to identifying pain states and helping clinicians classify pain, biomarkers could guide treatment and prognosis, and help predict effectiveness and risks of treatment. This concept is especially important in those individuals who cannot provide self-reports of pain or response to treatment. Functional imaging and measures of inflammatory markers (e.g. cytokines, nerve growth factors) have potential to identify unique pain "signatures", but have not yet yielded appropriate clinical measures. It is generally acknowledged that pain cannot be measured in isolation, but rather in conjunction with other outcome measures in "non-pain domains" that may be affected by- and affect- pain including sleep, mood, cognition, function, and quality of life. For example, although minimal clinically important differences have been established for pain and for most other non-pain outcome measures (e.g. sleep, function, mood), improvement in pain without concomitant improvement in other domains may not constitute a clinically meaningful outcome. Combined outcome measures are being used more often in clinical trials as their utility is recognized. Objectively measuring pain and predicting which patients are at risk for developing persistent or recurrent pain and responsiveness to treatment are of utmost importance.

Research Priorities

Standardize Outcome Measures and Define Treatment Effects
Research to develop, evaluate, and disseminate standardized outcome measures for different clinical conditions, determine what constitutes a clinically meaningful effect, and determine which outcome domains to measure is crucial to successful implementation and interpretation of clinical trials of pain treatments. This research should address what constitutes a clinically meaningful outcome in the various relevant core domains and whether these outcomes differ across disparate populations.

Discover and Evaluate Biomarker Information

Research is needed that leverages quality patient-reported outcomes data across a variety of domains and correlates these data with biomarker information. This research needs to be done for acute pain and across a variety of common chronic pain conditions.

Develop Screeners for Predictor Variables of Persistent and/or Recurrent Pain
Research is needed to develop and optimize the accuracy of screening tools that are predictive of development of or resilience to persistent or recurrent pain. Such tools need to be developed across the translational spectrum including biological, psychological, and social approaches.

NATIONAL REGISTRIES, DATASETS & RESEARCH NETWORKS

Statement of the Problem

The paucity of large data sets and prospective registries of well-characterized patients has delayed our understanding of acute and chronic pain and development of safe and effective pain management. Such resources will allow researchers to follow prospectively, sizable patient populations, pool large data sets through standardized data-sharing repositories, and utilize "big data" approaches, including comparative and cost effectiveness analyses. Information generated from these resources will help to elucidate the complex heterogeneity of pain, identify populations vulnerable to developing chronic pain, and discriminate subgroups who benefit from different pharmacological and non-pharmacologic treatments and treatment algorithms. Furthermore, given the heterogeneity within and across chronic pain disorders and populations, large data sets will increase the likelihood of delineating the complex interplay among genetic, environmental, occupational, physiological, psychological and clinical characteristics that contribute to the risk of developing, clinical course, and treatment of chronic pain.

Research Priorities

Top Priority: *Develop a Research Network.*

Development of a research network that would study diverse chronic pain conditions using standardized phenotyping and mechanistic techniques is needed. This will require a core for data coordinating and other functions and discovery sites for specific pain conditions, which will add to the scientific power of the network. Discovery sites should cover a wide variety of pain conditions (from nociceptive, neuropathic to centralized), and longitudinally follow individuals who undergo standardized outcome batteries in mechanistic studies, and are exposed to active (pharmacological and non-pharmacological) treatments. This may be accomplished by incorporating the registry/database into primary healthcare settings and cross-linking with broader healthcare registries. These longitudinal studies should include participants from disparate populations, span the lifespan, and include all socioeconomic strata. Registries and databases should target the general patient population rather than only those seen in specialty pain clinics. A crucial component of these networks should be to integrate preclinical researchers that can reverse translate findings into animal and other models to further elucidate mechanisms.

Determine Similarities and Difference across Chronic Pain States.
Utilize these data resources to determine the similarities and difference across chronic pain states, as well as the crucial phenotypic and biomarker features that predict responsiveness to treatments. This structure also will help optimize the value of preclinical pain research, by enabling clinical studies to drive the most

important scientific questions that can be answered only by reverse translation. By studying clinical pain conditions side by side, and probing potential mechanisms from the periphery to the CNS while individuals are receiving treatments, we will be able to translate basic research into the clinic.

Standardize Data Collection and Evaluation.
Develop and utilize minimum data sets and common data elements (including those within electronic health records) that provide a comprehensive assessment of the chronic pain experience.

Leverage and Expand Current Data Resources.
Expand large healthcare databases to facilitate studies of chronic pain risk factors and potential resilience factors across the lifespan with unprecedented patient numbers.

EFFECTIVE MODELS OF CARE DELIVERY FOR PAIN MANAGEMENT

Statement of the Problem

Despite the significant burden of pain, effective programs, services, and interventions are not always accessible, available, or utilized. In particular, disparate groups such as socioeconomically disadvantaged individuals may not have access to many care services, interventions or preventative health care programs. A void exists in understanding models of care outside the hospital such as in emergency (e.g., ambulance) and home care settings. Health system and financial arrangements do not consistently support effective, low cost, low risk interventions over those interventions that are higher cost and higher risk. While clinical research has established some effective and cost-effective chronic pain interventions, there is a significant number of interventions that have not been evaluated adequately.

Research Priorities

Top Priority: *Develop, Evaluate, Improve Models of Pain Care.*

Research is needed to develop new or improve current models of primary, secondary, tertiary care to improve pain management along the continuum of the pain experience. Research should address all levels of care, in varied care settings, and across the lifespan, including palliative care. Research should include studies on models of integrated care, team care delivery, and reimbursement innovations. Such studies should incorporate and evaluate new and existing technologies to identify the best approaches to balance safety, effectiveness, and costs of care for individuals with pain to inform models of service delivery and reimbursement and to improve access to quality pain management.

Determine the Benefits, Risks, and Costs of Pain Treatments.
Utilize knowledge translation, clinical trials, and cost-effectiveness studies to determine the benefits, risks, and costs of various pain treatments alone and in combinations including patient-centered primary care chronic pain management, the roles of specialty and tertiary care, optimal strategies for tailoring pain therapies to individuals, and strategies to reduce disparities in chronic pain management. It also is important to assess provider education, patient education, decision support resources and care coordination, along with other issues that can inform realignment of financial incentives to support more effective care.

Assess Effects of Policy Changes on Pain Care.
Research to determine how regulatory and legislative policies impact access to care and which methods best incentivize innovation in models of care are needed. Research should address organizational, provider, and patient barriers to engagement in effective treatments including understanding of stigma related to chronic pain. Particular attention should be paid to understanding barriers and stigmas in disparate populations. Rigorous evaluation is needed on the impact of reimbursement innovations on pain care quality measures and cost savings. Effective methods to disseminate research findings and incentives to incorporate them into clinical practice need to be studied.

PRECISION MEDICINE METHODOLOGY TO PREVENT AND TREAT PAIN

Statement of the Problem

Precision medicine is an approach to disease prevention and treatment that takes into account biological, psychological, environmental and other patient-specific factors. This approach directly addresses the wide inter-individual differences typically observed in pain severity, treatment responsiveness, and side effect frequency. The significance of this approach for pain care will be profound as we move from generalized to personalized treatment approaches.

Research Priorities

Top Priority: ***Develop Approaches Incorporating the Principles of Precision Medicine to Prevent and Effectively Treat Chronic Pain.***
The discovery and validation of markers, measures, and combinations of these factors predictive of an individual's susceptibility to chronic pain of specific types is needed. Identification of patient-specific factors associated with favorable versus poor responsiveness to specific treatments. Establish genetic and environmental factors predictive of adverse treatment outcomes such as medication-related side effects, organ toxicity and addiction. Develop biostatistical methodologies to combine and weight patient specific factors for the purposes of enhancing diagnostic accuracy and optimizing treatment selection.

PAIN PREVENTION PRIORITIES

Statement of the problem

The morbidity and costs of pain-related conditions often are driven by injuries or acute conditions that are refractory to care and eventually become chronic. Comorbid medical conditions, psychosocial disorders, personal behaviors, living and working conditions, and lifestyle factors may contribute to the onset, persistence, and related disability of chronic pain. Primary prevention of pain is defined as preventing acute pain and may be approached best through a public health model of care aimed at both the general population and high-risk groups. Secondary prevention is defined as prevention of the transition from acute to chronic pain. Tertiary prevention is aimed at reducing the frequency, severity and disability of

chronic pain. Although a small proportion of patients with acute pain go on to experience persistent pain, they account for most of the expenditures and disability associated with pain conditions.

Research Priorities

Greatest Near-Term Value: *Optimize Public Health Strategies to Educate Patients on Managing Pain.*

Public understanding of pain should address the complex biological and psychosocial aspects of pain. Evidence-based materials should be developed on the nature of pain and ways to use self-management strategies to prevent, cope with, and reduce pain. Research is needed on methods and materials that are most effective in targeting the public at large, patients, and health-care providers. Research topics should include determining which public health strategies, interventions, and modes of delivery, for awareness and education are effective, and what population level interventions are useful for primary, secondary, and tertiary pain prevention (e.g., lifestyle changes and workplace modifications to prevent acute injuries or chronic pain and best practices to implement these strategies.

Most Impactful: *Determine Association between Patient and Intervention Factors and Psychosocial Interventions.*

Matching of patients to interventions, based on relevant predictive characteristics, would be an effective means of secondary and tertiary prevention of pain. Research is needed to explore variation in individual responses to interventions to identify appropriate matching variables. Use randomized controlled trials or observational studies and real-world data to determine patient factors, intervention factors, and psychosocial interventions that are associated with better outcomes for pain management assessed by responder analysis with matching treatments to subgroups based on subgroup characteristics

Epidemiology of Acute Pain from Health Care Procedures

Data are needed to inform health care providers in guiding patient expectations on painful procedures that may occur throughout their lives and the severity and duration of procedure-associated pain. This data would guide development of patient-education resources to alleviate fear or anxiety of pain from common procedures. The focus should be on establishing the onset, severity, duration, and impact of acute pain from common medical (e.g. spinal tap) and surgical (e.g. thoracotomy) procedures. Additional research should examine the incidence of chronic pain that develops secondary to acute pain from such procedures and the impact of chronic post-procedure pain on other aspects of health and healthcare. Research is particularly encouraged on this topic in vulnerable populations (e.g. premature infants, cancer patients, and people with chronic pain).

Epidemiology of Acute Pain from Work-Related Injuries

Data are needed to inform occupational and public health practitioners on prevention of work-related incidents and injuries leading to acute pain. These data would guide development of evidence-based workplace interventions. Additional research should examine: the incidence of chronic pain that develops secondary to acute pain from work-related injuries; and the impact of pain and pain treatment on the

ability to work. Research is particularly encouraged on this topic in vulnerable populations (e.g. workers in high-risk occupations).

Evaluate Safety and Effectiveness of Management of Procedure-Associated Pain.
Health care procedures are common, often cause acute pain, and affect, a large proportion of the population. They occur however, in controlled settings where it is feasible to implement interventions aimed at primary prevention of pain. Research is needed on prevention and mitigation of effects of acute pain from health care procedures. Research is needed on safety and effectiveness of management of procedure associated pain, including opioid-sparing and existing multimodal pain management protocols used to manage acute post-surgical pain. Research is encouraged to identify the optimal multimodal pain prevention protocols based on the type of health care procedure, health care resources available, patient risk/prognostic factors, and patient preferences.

Optimize Post-Surgical Approaches for Acute Pain
Surgery is a risk-factor for the development of chronic pain. Given the large number of surgeries that are performed, there is potential for many individuals to develop chronic pain. Research is needed to optimize and individualize management of acute post-surgical pain to prevent persistent or recurrent pain and related disability. Genetics, past medical history, musculoskeletal factors, and psychological perspectives are all recognized as potential factors impacting the development of chronic post-surgical pain and as such are areas of interest for the development of optimal secondary prevention strategies. Research is needed to track the number and effectiveness of surgeries to alleviate pain and the relationship of surgical procedure rates to that of chronic pain and disability.

Evaluate Safety and Effectiveness of Early Interventions for Tertiary Prevention.
Research is needed to identify effective tertiary prevention interventions that improve the quality-of-life of persons with chronic pain, as well as reduce costs of care.

ACUTE PAIN

Statement of the Problem

Acute pain often is marginalized because many assume that it is: inherent to illness, trauma, medical procedures, and surgery; necessary to diagnose disease or injury; important for recovery from illness and trauma, including surgery; or solved. However, acute pain assessment and management are commonly inadequate, pharmacologic treatments are imprecise and associated with adverse effects, little evidence exists for use, dosing, duration, or mechanism of action of biobehavioral treatments. Furthermore, acute pain can be persistent and resistant to treatment and increase the risk for development of chronic pain. Therefore, better measures and treatments are needed to effectively relieve or manage acute pain. The heterogeneity across types and causes of pain is prominent in every aspect of acute pain, from transduction of nociceptive signals to psychosocial circumstances that impact the pain experience. Understanding of molecular and circuit-level mechanisms that contribute to acute pain is far from complete. Progress in understanding these processes will

lead to better treatments for acute pain. The optimal approaches to measure and manage acute pain in order to provide tailored interventions for each patient are unknown.

Research Priorities

Greatest Near-Term Value: *What are the Cellular Mechanisms of Heterogeneity in Acute Pain Sensation?*

All forms of stimulus energy (thermal, mechanical, and chemical) can initiate nociceptor activity, although the stimulus adequate for activation is not the same for all nociceptors. Decades of research have focused on stimuli adequate to activate cutaneous nociceptors, including molecules that transduce those energies, but comparable information and understanding of bone/joint, dural, muscle, and visceral nociceptors remains to be established. Given that musculoskeletal, visceral, and cephalic pains are common, it is essential to improving pain management that research be done to bridge this gap. Nociceptors innervating cutaneous tissue are heterogeneous. It should be appreciated that nociceptors that innervate deeper tissues are similarly heterogeneous and dissimilar from cutaneous as well as other deep nociceptors with respect to chemical phenotype, expression of ligand- and ion-gated channels, neuroanatomical location in tissue, etc. Anatomic, genetic, molecular, pharmacological, and physiological approaches that address the unique properties of deep nociceptors are needed to lead to improved understanding of pain mechanisms and pain management.

Most Impactful: *Heterogeneity of the Circuitry Involved in Acute Pain Sensation and Modulation*

Beyond the peripheral nervous system, relatively little is known about distributed networks of neurons across diverse regions of the nervous system that contribute to acute pain. While many regions that integrate nociception and give rise to pain have been identified, the underlying neural circuits and the computations they perform are almost completely unknown. The acute pain experience is influenced by expectation, fear, psychological factors, and repeated exposure to the painful episode. Neural signals that enter the nervous system encounter a substrate reflecting this experience of pain, which therefore, may not reflect the state of the tissues. Active modulation of pain occurs from multiple supraspinal regions through descending circuits that act on spinal and medullary dorsal horn. However, the identity (e.g., neurochemical) of the neurons in these circuits has yet to be identified. Understanding the pain experience to better develop therapies requires defining the neuronal cell types that are involved, characterizing how they are connected, and modeling the computations that they execute. Bridging these gaps will require collaborative efforts of molecular geneticists, physiologists, behaviorists, and computational scientists using a variety of approaches including *in vivo* recordings, population imaging, real-time manipulation of neurons in awake behaving animals, advanced microscopic approaches to understand connectivity, and computational studies.

What are the Molecular Mechanisms of Heterogeneity in Acute Pain Sensation?

At the most basic level, thermal, mechanical, and chemical signals can initiate nociceptor activity or alter activation thresholds. Despite considerable progress in identifying sensors of touch and nociception, major gaps remain. Research to find the identity of mechanically activated ion channels responsible for initiating mechanical nociception (from skin, muscle, or internal organs) needs to be done. Molecular players in

sensing temperature (noxious cold) also need to be explored. Advancements in genomics technologies, for example single cell RNAseq, would help tackle these questions. Furthermore, studies on rare, inherited disorders could lead to understanding of nociceptor function that either alters sensitivity to acute noxious stimuli or results in spontaneous pain.

What are the Contributions of the Autonomic Nervous System to Acute Pain Sensation?

Nociceptor somata in DRG/TG have been the major focus of study, whereas the contribution of the autonomic nervous system to acute pain mechanisms remains largely unknown. Incorporated within the gastrointestinal (GI) track is an intrinsic nervous system, comprised of intrinsic afferents of enteric neurons within the GI wall. Knowledge of interactions between intrinsic afferents and extrinsic spinal and vagal afferents is scant. Furthermore, interactions of afferents of intrinsic and/or extrinsic nervous systems with sympathetic and parasympathetic efferent neurons conveying information from the CNS are considered important to acute pain mechanisms, but largely unstudied. Neuromodulation of these different nervous systems is a promising treatment for acute pain, although mechanisms of neuromodulation are incompletely understood. Recent developments of *in vivo* imaging, optogenetics, chemogenetics, and novel animal models should provide means to address these questions.

What are the Most Sensitive and Specific Preclinical Models of Acute Pain that are Representative of Naturally Occurring Pain Conditions?

Existing preclinical models have provided valuable insights into acute pain mechanisms. However, to develop new insights and novel therapeutic approaches, preclinical models that are more representative of naturally occurring acute pain conditions need to be developed. In addition, preclinical studies of acute pain need to provide an increased understanding of the mechanisms that underlie changes over time in the experience of acute pain. As part of preclinical research, automated methods need to be developed to monitor spontaneous animal behaviors to elucidate the temporal patterns associated with acute pain. These types of approaches are needed to determine how/what spontaneous measures used in animal research will reflect the human experience of postoperative pain that lasts for days. In addition, better measures are needed to evaluate the affective dimension of acute pain in animals.

What are the Optimal Acute Pain Assessment Parameters and Biopsychosocial Predictors of Acute Pain that can be used to Optimize Individualized Acute Pain Management?

Assessment of acute pain currently relies on a unidimensional rating scale (e.g., 0 to 10 numeric rating scale) that focuses on pain intensity, which does not provide an optimal assessment of an individual's acute pain management experience or the effectiveness of pain management interventions. Research is needed to determine the parameters (e.g., physical, emotional, cognitive, and functional domains) to include in acute pain assessment to optimize acute pain management for an individual patient. Included in this type of research is a determination of the optimal timing, frequency, and duration for assessments by domain and interventions to best inform clinical decisions and patient outcomes. In addition, work is needed to develop pre-intervention assessment tools to predict the trajectory of pain following interventions. Equally important, research is needed on the appropriate assessments for pain in patients with multiple co-morbidities.

What Are the Assessment Parameters and Biopsychosocial Predictors of Acute Pain that Can Be Used to Optimize Individualized Acute Pain Management in Patients Who Cannot Self-Report?

Research is needed to develop, improve, and evaluate measures of responsiveness to pain for individuals who cannot provide self –reports of acute pain. Advanced technology and novel approaches are needed to translate findings, across all pain assessment domains, from animal models and patients who can provide self-report to individuals who cannot provide self-reports of their pain experiences.

What Are the Most Effective Strategies to Provide Optimal Individualized Acute Pain Management of Complex Patients?

Patients at the extremes of age present unique challenges. As the population ages, the numbers of patients with multiple comorbid conditions is increasing. At the other extreme, as our ability to care for premature infants improves, the lack of options for treating very young patients is increasingly problematic. In addition, the numbers of patients with a history of chronic pain with or without concurrent substance use disorders are on the rise. The development and evaluation of strategies to optimize acute pain management of complex patients is warranted.

What Are the Most Effective Approaches to Deliver Evidence-Based Effective Acute Pain Management Programs and How Can New and Existing Technologies Improve Them within/across Health Care Systems?

Research is needed that provides practical approaches to evaluate the therapeutic efficacy of acute pain management strategies. This research needs to provide cost effective approaches, incorporate real world settings (including primary care practices and pain self-management programs), and include representative samples of patients. To achieve this objective may require expansion and leveraging of existing, or development of new pain registries to track clinical and patient-reported outcomes. Research also is needed on how to incorporate new and existing technologies into existing pain management programs. The use of the electronic health record, personal health records, wearable devices, sensors, and other technologies is growing at exponential rates.

TRANSITION TO CHRONIC PAIN

Statement of the Problem

Every day many individuals have the same injury, disease, surgery, or treatment. Many of them experience associated pain, and most of them experience a resolution of pain when the disease is cured, the injury heals, or the treatment stops. However, in a significant proportion of these individuals, pain does not resolve and becomes chronic. The factors causing this persisting pain state and mechanisms that govern persistent pain are only beginning to be elucidated. This is a crucial scientific problem because these factors and mechanisms may hold the key to new therapeutic options to either prevent the development of chronic pain or reverse its course once it becomes persistent. Common risk factors may predispose people to chronic pain. From animal studies, we know that neuronal plasticity and interactions of the nervous system with the immune system are key to persistent pain states. Human brain imaging studies show changes in brain anatomy and function as pain becomes chronic. How these findings fit into a

comprehensive picture of the transition to chronic pain, whether there is such a transition, represents a key gap in knowledge for the field.

Research Priorities

Greatest Near-Term Value:

Most Impactful:

Top Priority: ***Understand and Address Plasticity Mechanisms that Promote Persistent Pain and (Endogenous) Resolution Mechanisms that May Reverse Persistent Pain.***

New tools and new lines of research are needed to bridge advances in preclinical research to gaps in our understanding of human molecular neuroscience. Examples include advances in next generation sequencing and/or imaging to enable molecular resolution of mechanisms that drive persistent pain in human patients. As human tissue banks continue to expand in capacity, new lines of research that leverage these resources with advancing technologies should be engaged to test preclinically-defined mechanisms that may give immediate insight into human persistent pain. Moreover, research that utilizes human stem cells to potentially treat and/or to discover pain mechanisms should be encouraged. Research to enable the development of new tools (e.g. optogenetics) for use in the clinic should be encouraged. Researchers using animal models of persistent pain should be encouraged to utilize clinically meaningful endpoints (e.g. assaying cerebrospinal fluid) to enhance translation of preclinical work into clinical diagnostics and/or hypothesis testing.

Whole Brain Imaging in Animal Models Compared to Human Models

Preclinical work can add considerable molecular insight that may never be within reach in the human central nervous system (technologies include light sheet microscopy and tissue clearing techniques such as SCALE, CLARITY and uDISCO). Researchers should develop and/or utilize new technologies to assess brain-wide connectivity changes in animal models that can parallel human imaging work.

Understand How Early and Life Experiences Contribute to Persistent Pain Later in Life.

Despite recent advances, it is still unclear how early life experiences influence long-lasting pain. For instance, are acute pain mechanisms different at birth and/or during adolescence as compared with later in life? In line with this, recent research suggests there are critical periods when organisms may be relatively protected from development of persistent pain from early-life injuries (e.g., brachial plexus avulsion pain in children) or illnesses (e.g., post herpetic neuralgia in younger adults), conditions that produce chronic pain in older adults with high probability. Mechanisms of developmentally-specific pain protective or pain facilitatory periods need to be explored. Research is needed to discover the mechanisms for these developmentally-specific pain protective periods (or conversely, pain facilitatory), as it has great potential to inform novel therapeutic strategies for chronic pain.

Top Priority: ***Prospective Studies for Susceptibility and Resilience Factors Underlying the Transition from Acute to Chronic Pain***

A general clinical assumption is that there is a linear transition from acute, to subacute, to chronic pain, despite sparse evidence of the basic epidemiology and natural history of the transition. Research is needed to evaluate the course of pain from an acute episode to chronic pain, disability, and flare ups, to

understand the complex transition mechanisms and to prevent chronic pain. Trajectories from an acute episode to chronic pain may vary in duration, severity and level of disability. Such information is vital to tailored interventions at critical windows of opportunity. Research should be conducted prospectively to determine causes for susceptibility to the transition to chronic pain. A goal should be identifying protective factors, including psychosocial and economic factors that can be integrated with other known risk factors. A longitudinal research study is needed on one of the most prevalent and costly pain conditions (e.g., low back pain, headache) to evaluate the different trajectories that occur.

Top Priority: *Mechanistic Trials of Risk & Resilience to Chronic Pain with Meaningful Outcome Measures*

Mechanistic clinical trials should be conducted that target risk and/or resilience and push beyond mere correlation. For example, does therapeutic intervention to decrease catastrophizing prior to surgery reduce chronic pain in this high-risk population? These trials should assess outcomes that are meaningful to patients in addition to simply measuring pain.

Trials to Determine Acute Pain Management Strategies that Promote or Prevent Development of Chronic Pain

Preclinical work suggests that certain acute pain management strategies may either promote or prevent the development of persistent pain. It is possible that some strategies for acute pain treatment may impair endogenous resolution mechanisms. This question should be investigated prospectively in targeted clinical trials.

CHRONIC PAIN

Statement of the Problem

The prevalence of chronic pain and the paucity of evidence-based treatments, as well as the rapid rise in opioid misuse and overdose constitute major public health crises. Significant advances have been made in understanding the basic mechanisms of nociception and pain that have led to new potential targets for pain assessment and treatment strategies. Furthermore, recent advances in the neuroscience, biomarkers, and the behavioral sciences have validated a comprehensive approach to the management of pain that includes the individual's inherent biology, behavior, and psychological makeup and reactions, and their environmental influences. However, data and knowledge gaps remain and have prevented research translation into safe and effective therapies. This is particularly true for chronic pain that occurs in the context of comorbid medical conditions, overlapping comorbid symptoms, and in certain populations including older adults and children. In addition, there is increasing recognition that while numerous self-management strategies exist, crucial questions remain regarding their efficacy and effectiveness alone or in combination with other therapeutics. Despite important research advances on chronic pain, there remain major gaps in our understanding of mechanisms and effective treatments for most chronic pain conditions.

Research Priorities

Greatest Near-Term Value:

Top Priority: ***Determine Optimal Safe and Effective Chronic Pain Management.***

Chronic pain management, with or without opioids, requires individualization of treatment. Gaps exist in our knowledge base of the effectiveness of drug and nondrug interventions, in large measure due to the lack of long-term outcomes data of the most commonly employed interventions for chronic pain management. While fully implemented and supported multimodality treatment approaches based on the biopsychosocial model are the long-term goal, a systematic evaluation of the long-term effectiveness of available pharmacologic and non-pharmacologic treatments for chronic pain alone and in combination is needed. The immediate objective is to identify subpopulations of chronic pain patients who benefit from treatments and those that do not. These studies should be extended to define the mechanisms at the preclinical and clinical levels that are responsible for the adverse effects of available treatments (e.g., liability for misuse, addiction and respiratory depression). Studies at the clinical level should include real-world pragmatic trials and randomized controlled trials.

Most Impactful:

Top Priority: ***Determine the Mechanisms that Sustain or Resolve Chronic Pain and which of these Elements Can Be Intrinsically and Extrinsically Modulated.***

Clinical phenotypic features of chronic pain conditions are well characterized. Research is needed however, to determine the neural, genetic, and epigenetic factors that sustain or resolve chronic pain, and the relative contributions of peripheral and central factors. Within a chronic pain condition, there may be tremendous heterogeneity in the roles of these factors. There may be more commonality of mechanisms across pain conditions however, than within a pain condition. Whereas, any single drug or non-drug treatment often works only in a small subset of individuals with a single pain state, it may work in many individuals across chronic pain conditions. Alternatively, few, if any, specific mechanisms have been discovered which differentiate chronic pain conditions and as such would point to important differential treatment opportunities. These commonalities and unique mechanisms need to be explored.

Top priority: ***Determine the Bidirectional Relationship Between Common Comorbidities and Chronic Pain.***

Chronic pain occurs in the context of both comorbid medical conditions (e.g., cancer, diabetes, obesity) and overlapping comorbid symptoms (e.g., fatigue, sleep deficiency, mood disturbances) that may impact pain and modify effectiveness of interventions. Studies of neurobiological and psychosocial mechanisms of pain that strive to isolate pain-specific mechanisms and understand important relationships and connectivity across multiple comorbidities are needed. Efforts to enhance the precision and validity of brain imaging, genetic/genomic and psychosocial methods to distinguish pain from overlapping and confounding factors are especially important. Novel theories and conceptual models that explicitly incorporate putative mediators and moderators of relationships among pain and comorbidities are needed to understand the human experience of chronic pain. These efforts should inform development and

evaluation of more innovative, integrated approaches to clinical assessment and treatment taking into account relevant comorbidities in patients across the lifespan.

Top Priority: ***Understand Mechanisms of Childhood Chronic Pain.***

Chronic pain often begins in childhood and research has demonstrated that it confers risk for adult chronic pain and psychiatric disorders. In addition, early adversity may alter the central nervous system. Research is needed to understand the developmental mechanisms (e.g., psychological, social, neurobiological) that contribute to chronic pain in children. During childhood, critical pain memories form and are influenced by social-environmental factors such as parenting behaviors and neurobiological processes. Research is needed to determine the contribution of psychological and social environmental processes in development and maintenance of chronic pain in childhood, characterize the link between early life adversity and subsequent chronic pain, and identify key neurobiological substrates of stress and sex hormones that may contribute to behavioral alterations in pain responses. Availability of psychological and family environment measures, psychophysical pain measures, genetic and immune markers, and brain imaging technologies should accelerate research in this area. In parallel, advances in conceptual models to incorporate developmentally relevant dimensions and to understand basic socio-behavioral mechanisms and processes are needed to explain children's experience of chronic pain. We need to expand our conceptual understanding of developmentally relevant targets for interventions to reduce or prevent childhood chronic pain. Determining the role of timely intervention in modifying developmental mechanisms of chronic pain is crucial. Research in this domain will significantly advance understanding of pain mechanisms and is expected to lead to identification of developmentally relevant targets for specific therapies.

Top Priority: ***Determine Optimal Approaches for Use of Self-Management Strategies in Chronic Pain.***

Self-management for pain refers to interventions that can be learned and adopted by an individual or initiated in the context of therapy and subsequently maintained by the individual. Such interventions include physical and mind-body activities (e.g., exercise, yoga, tai chi, meditation, etc.), dietary supplements, over-the-counter medications, behavioral and physical therapies, education about pain, and complementary health approaches. While a number of self-management strategies are promoted, crucial questions remain regarding efficacy and effectiveness, combined use with prescribed treatments, proper dosing, patient adherence, and the identification of biological mechanisms. Research is needed to address these issues and would be facilitated by studies identifying cost-effective and sustainable delivery mechanisms, ways of creating a patient-centric practice culture that values self-management, reduces stigma, and includes self-management in the continuum of care with documentation in the electronic medical record. Self-management is included as a recommendation of many meta-analytic studies, government documents (e.g., National Pain Strategy) and guidelines addressing optimal pain care. Research on this topic would support the shared-decision making process between providers and patients in developing long-term chronic pain management plans.

DISPARITIES

Statement of the Problem

Research has documented major age, sex, gender, racial/ethnic, and socioeconomic group differences in the development and persistence of pain conditions across the lifespan. For example, women suffer from persistent pain more frequently than men, and there is preclinical evidence that mechanisms which promote persistent pain are molecularly distinct between the sexes. Moreover, it is recognized that hormone and neuroendocrine levels, which change across the lifespan and can be dramatically different based on sex, play an important role in mechanisms of transition to persistent pain. The developmental effects of pain and pain treatments may have long term implications for susceptibility for chronic pain throughout the lifespan. Older adults suffer from persistent pain more commonly than all others, yet quality evidence based treatments are lacking. Whereas lower SES has been related to poorer health and poorer pain-related outcomes, the mechanisms driving the SES-pain link are not understood. The components of social economic position factors, both personal resource and environmental, that may be more strongly associated with pain, have yet to be identified. The extent to which SES differences contribute to ethnic group disparities in pain remains poorly understood. Evidence is needed to establish whether and how individual characteristics, patient preferences, and treatment decisions influence susceptibility to chronic pain, treatment benefits and risks. These mechanisms are poorly understood and could lead to insight into development of personalized medicine for pain.

Research Priorities

Greatest Near-Term Value: ***Better Define the Epidemiology of Pain in Disparate Populations, Including Children, Women vs. Men, Specific Racial and Ethnic Groups, Older Adults, and Socioeconomically Disadvantaged People.***

Research is needed to define the prevalence, incidence, and impact of pain, patterns of treatment, and risk factors that predispose disparate populations to pain. Research is needed on the epidemiology of single and overlapping pain conditions in disparate populations to identify societal consequences of pain in understudied groups, document effectiveness of specific treatments, and guide intervention efforts. Investigations on either acute or chronic pain and longitudinal investigations that document trajectories of specific pain conditions should employ standardized questions to facilitate comparisons across studies. Studies across disparate populations are needed to characterize factors (e.g., clinical, genetic, psychological, metabolic, lifestyle, environmental) and investigate interactions across factors that differentially affect risk for pain incidence and/or persistence. Studies that document health services received and/or preferred for pain and complementary treatments used by these populations are encouraged. Efforts to identify specific mechanisms that underlie the incidence, maintenance, or remission of pain disorders in these populations are needed. Further, analyzing existing data sources (public and private) to shed light on the epidemiology and impact of pain in these disparate populations is encouraged.

Most Impactful:

Top Priority: *Investigate Biological, Psychological, Social Mechanisms that Contribute to Population Group Differences in Chronic Pain.*

The burden of chronic pain is unequally distributed across the population, and there is an urgent need to understand the biological and psychosocial factors that drive the disproportionate impact of pain in specific population groups. Research addressing this priority should cover the spectrum of basic,

translational, and clinical methodologies and include longitudinal studies that examine changes in mechanisms and their effects over time and the lifespan. For example, low-income individuals may be at higher risk for pain due to nutritional deficits that occur in early life (in utero and/or childhood) and impair nervous system development, which may interact with psychological factors to increase the risk for chronic pain. This increased risk may be compounded or buffered by the quality of social support networks. Research that identifies these fundamental mechanisms will advance our understanding of why differences emerge and/or persist across different groups and inform prevention and intervention strategies that specifically target these underlying factors.

Determine Optimal Methods for Assessing and Treating Pain in Disparate Populations.
Effective pain management requires appropriate assessment and personalized treatment. Research is needed to determine whether the safety, efficacy, and comparative effectiveness of existing and emerging pharmacotherapies for acute and chronic pain differ across disparate populations (e.g., races/ethnicities, sex/gender, age/lifespan, socioeconomic status). Research also is needed to determine population group differences in responses to nonpharmacological therapies, with a focus on establishing their long-term safety and benefits and approaches that can be readily implemented and disseminated widely.

Identify Developmental Periods and Life Stages that Confer Risk for or Protection against Pain Conditions.
Exposures to certain events in a developmental period (neonatal, childhood, adolescence, adulthood and late life/end-of-life) can have negative or positive impacts in other life periods. For example, low SES in childhood is associated with decreased psychological and physical functioning and increased mortality in adulthood. Studies are needed to identify specific factors and their mechanisms that influence the risk of pain occurrence or persistence across the lifespan, including whether events in one developmental period (e.g., family stress exposure in childhood) predispose to increased (or decreased) risk of pain in another life period. These studies should systematically investigate environmental exposures and risk/protective factors that differentially influence onset and persistence of pain across life periods. In addition, studies are needed that apply biopsychosocial theoretical perspectives to examine how genetic factors, environmental exposures, social resources, SES, and race/ethnicity can lead to cumulative advantages or disadvantages over the life course. Studies that examine the independent impact of factors suggested by life course biopsychosocial models and their interactions (e.g., gene-environment interactions) across life periods are needed. Longitudinal studies and innovative design approaches are needed to provide insights into predisposition to pain, develop preventive and therapeutic strategies, and inform translation into diverse practice settings.

Characterize within-group Variability in the Experience of Pain across Disparate Population Subgroups.
Research documents between-group differences in the experience of pain across age, gender, racial/ethnic, and socioeconomic categories. There is a need for research to elucidate within-group variability in the experience of pain and determine factors that contribute to this variability, given that there may be more variation in biopsychosocial factors relevant to pain within, than between groups. For example, this work may identify protective factors against development and persistence of pain among

individuals who are members of disparate groups that are at increased risk for pain. Basic and clinical studies are needed. Greater understanding of within-group variability and its potential association to between-group variability in pain will advance efforts to reduce pain-related disparities at the individual- and population group-level.

Evaluate the Impact and Long-Term Consequences of Pharmacological Interventions for Pain across the Life Span, Especially on the Developing Nervous Systems of Infants and Children.

Studies that targeted acute and chronic pain treatment show variability in the effectiveness of the approaches for pain relief and improved functioning. Studies typically focus on single treatment approaches in a circumscribed population. Thus, little is known about how pain treatments, administered individually or combined, vary in their efficacy across the lifespan. There also are few data documenting long-term benefits and risks of specific treatments. A striking dearth of studies have documented the efficacy and adverse effects of pharmacological approaches for pain in infants, children, and adolescents, which is particularly problematic given the potential impact of pharmacologic pain treatments on the developing nervous system. Therefore, it is critical to conduct studies of individual and multimodal pain treatments with long-term follow-up and include analyses of efficacy and adverse effects in patients across the lifespan.

Determine How the Affective-motivational Components of Pain Contribute to the Overall Pain Experience and Functional Outcomes in Disparate Populations.

Pain is not simply a discriminative sensation generated by nociceptors and activation of pain pathways. Rather, pain is a complex, highly-individual, subjective, perceptual phenomenon with emotional qualities that underlie the "unpleasantness" of the experience. Pain is influenced by motivation, emotions (e.g. empathy, fear, relief), past experiences, the social setting, and environmental factors. The sensory-discriminative dimensions are processed in the primary and secondary somatosensory cortex. The affective-motivational dimensions of pain reflect the perceived unpleasantness of the painful event and these involve processing in specialized areas of the brain. Studies that have sought to understand the complex affective-motivational dimensions of pain suggest that these components – including psychological, contextual, anticipatory, and prior experience factors – may powerfully influence the experience and functional outcomes of pain in humans. These factors may be particularly influential in disparate populations such as racial-ethnic minority, socioeconomically disadvantaged, geriatric, pediatric, and gender-specific groups. It is essential to examine how affective-motivational factors uniquely influence pain in each of these disparate groups.

Elucidate Sex-Specific Pain Mechanisms and Determine their Implications for Optimal Treatment of Pain in Females and Males.

Preclinical and clinical evidence reveals sex differences in pain responses. However, sex-specific pain mechanisms that underlie these differences have received relatively little empirical attention. Sex-specific influences on pain may emerge from biological processes that differ between sexes, such as organizational (i.e. developmental) and ongoing effects of sex hormones. In addition, different environmental exposures for females and males could produce sex-specific influences on pain. Female children, adolescents, adults, and seniors remain neglected across many cultures through nutritional deprivation, family disparities between male and female genders, and increased work-load among females. In addition to age-dependent hormonal changes, the psychosocial stressors that differ for females versus males may impact pain

responses. There is a need for studies that increase our understanding of sex-specific biological, psychological, and social mechanisms contributing to pain to reduce the increased burden of pain among females. Due to age-dependent hormonal changes, mechanisms are likely to vary at different life stages (e.g. pre- vs. post-puberty, pre- vs. post-menopausal). Therefore, it is crucial to study sex-specific pain mechanisms across the lifespan. Likewise, sex differences in environmental exposures can vary across ethnic, age, and SES groups. Therefore, sex-specific mechanisms need to be studied across these disparate groups.

Advance Knowledge of the Relationship between Socioeconomic Status and Pain.

Social determinants play a key role in a variety of health statuses. Some argue that lifestyle, environmental, and economic factors are more important than biological factors in the etiology of health and disability. Others argue that the patterning of effects over time may implicate social and economic factors, occupational risks, and low educational attainment as fundamental causes of poor health. Others suggest that environmental exposures play a direct role in causing unhealthy conditions, which in turn influence health outcomes. The lack of socioeconomic and related resources, is clearly related to help-seeking and access to care and may influence treatments for physical and mental health conditions related to pain. This is especially true for high impact chronic pain. It has been more difficult to explicate whether social and environmental resource factors play a direct role in the experience of pain. Integrative research adopting a biopsychosocial perspective is needed to: (a) elucidate the associations of SES with psychological and physical mechanisms and progression of pain and treatment response, (b) clarify the contribution of SES to ethnic differences in pain, and (c) understand the potential etiologic role that lack of long term access to social and economic resources plays in the psychological and physical experiences of pain. Recent advances in research have provided innovative tools for understanding the biological underpinnings of lower SES. These tools will allow for analyses of gene-by-gene and gene-by-environment interactions as well as epigenetic and transcriptional changes (e.g. the conserved transcriptional response to adversity) that may serve as pathways whereby social, economic, and environmental resource factors influence the experience of pain.

Appendix A

Selected Priorities

Top Priorities (highest quartile scores across all work groups)

Develop Safer Opioids, New, Non-opioid Analgesics, and the First Generation of Disease Modifying Agents.

Develop a Research Network.

Develop, Evaluate, Improve Models of Pain Care.

Develop Approaches Incorporating Principles of Precision Medicine to Prevent and Effectively Treat Chronic Pain.

Prospective Studies for Susceptibility and Resilience Factors Underlying the Transition from Acute to Chronic Pain

Understanding and Addressing Plasticity Mechanisms that Promote Persistent Pain and (Endogenous) Resolution Mechanisms that May Reverse Persistent Pain

Mechanistic Trials of Risk & Resilience to Chronic Pain with Meaningful Outcome Measures

Determine the Mechanisms that Sustain or Resolve Chronic Pain and Which of these Elements Can Be Intrinsically and Extrinsically Modulated.

Determine Optimal Safe and Effective Chronic Pain Management.

Determine Optimal Approaches for Use of Self-Management Strategies in Chronic Pain.

Determine the Bidirectional Relationship Between Common Comorbidities and Chronic Pain.

Understand Mechanisms of Childhood Chronic Pain.

Investigate Biological, Psychological, Social Mechanisms that Underlie Development and Persistence of Chronic Pain in Disparate Populations.

Most Impactful Priorities (selected within each work group)

Prevention: Determine Association between Patient and Intervention Factors and Psychosocial Interventions.

Acute Pain and Acute Pain Management: Heterogeneity of the Circuitry Involved in Acute Pain Sensation and Modulation

Transition from Acute to Chronic Pain: Understand and Address Plasticity Mechanisms that Promote Persistent Pain and (Endogenous) Resolution Mechanisms that May Reverse Persistent Pain.

Chronic Pain and Chronic Pain Management: Determine the Mechanisms that Sustain or Resolve Chronic Pain and which of these Elements Can Be Intrinsically and Extrinsically Modulated.
Disparities in Pain and Pain Care: Investigate Biological, Psychological, Social Mechanisms that Contribute to Population Group Differences in Chronic Pain.

Greatest Near-Term Value Priorities (selected within each work group)

Prevention: Optimize Public Health Strategies to Educate Patients on Managing Pain.

Acute Pain and Acute Pain Management: What are the Cellular Mechanisms of Heterogeneity in Acute Pain Sensation?

Transition from Acute to Chronic Pain: Understand and Address Plasticity Mechanisms that Promote Persistent Pain and (Endogenous) Resolution Mechanisms that May Reverse Persistent Pain.

Chronic Pain and Chronic Pain Management: Determine Optimal Safe and Effective Chronic Pain Management.

Disparities in Pain and Pain Care: Better Define the Epidemiology of Pain in Disparate Populations, Including Children, Women vs. Men, Specific Racial and Ethnic Groups, Older Adults, and Socioeconomically Disadvantaged People.

Appendix B

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