Report of the HEAL Pain Strategic Research Priorities Working Group – a Working Group of the National Advisory Neurological Disorders and Stroke Council

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Message from the Co-chairs

Chronic pain impacts millions of US citizens, leading to suffering and impacting every facet of life. The enormity of the problem is contrasted by the dearth of safe and effective medications. This highlights the need for research that advances our understanding of the underpinnings of pain to aid in the development of new therapies. Further, despite evidence of efficacy and safety, non-drug treatments are greatly underutilized for pain management, highlighting a need for studies aimed at implementation to improve utilization. For decades, pain science languished due to shockingly low levels of federal funding relative to the disease burden. The lack of a dedicated institute for funding pain research certainly contributed to this and necessitated additional steps to advance pain research. Despite years of advocacy efforts from the pain community and responsive efforts within the NIH and other federal agencies to advance pain care and research – funding levels for pain science remained low, and progress in improving outcomes for individuals with chronic pain was slow. Funding changed markedly with the establishment of the NIH Helping to End Addiction Long-term® (HEAL) Initiative – the NIH's effort to address the opioid epidemic.

In its first year, the HEAL Initiative brought an additional $500M – with increases since then – to the annual NIH base appropriation "for a new initiative to research opioid addiction, development of opioid alternatives, pain management, and addiction treatment." The HEAL Pain mission is "to reduce pain and the risk of opioid use disorder by developing safe and effective pain treatment and prevention strategies to improve quality of life for all people." Notably, the HEAL pain mission does not span all domains of pain research. Rather this specific subset of goals focuses on dramatically speeding improvements in pain care. To develop HEAL Initiative programs in those first years, NIH program officials were initially guided by the Federal Pain Research Strategy and a 2017 series of "Cutting Edge Science Meetings to End the Opioid Crisis."

The first phase of HEAL Initiative funding has seen great progress. Since 2018, HEAL Initiative investments totaling over $3.9 billion have funded over 2200 research projects in all 50 states, and includes collaborations across 19 NIH Institutes, Centers and Offices. This investment has generated over 40 FDA approvals for investigational new drugs or devices, and over 300 clinical trials currently under way. In addition, HEAL has developed an impressive array of programs to support development of new pain therapeutics from target validation to phase II clinical trials, as well as real-world clinical trials and implementation studies to enhance use of safe and effective pain-management strategies. This represents remarkable progress.

In 2023, the HEAL Multidisciplinary Working Group recommended development of a strategic plan to guide future HEAL investments. We were charged with forming a Working Group of the National Advisory Neurological Disorders and Stroke Council to provide guidance on how best to advance pain research by proposing and prioritizing strategic research priorities that will advance the HEAL pain research mission. Our goal is not to re-invent HEAL pain research, but to evaluate existing HEAL programs with an eye to what has worked well, what has not, and identify gaps that should be prioritized to advance the HEAL mission of ultimately improving quality of life for all people with chronic pain. Core principles of this process were that there would be broad stakeholder engagement to allow public input into programs that will be developed going forward, inclusion of people with lived experience, and inclusion of broad expertise across subcommittees. Here, we respectfully present the ten research priorities generated through the process described in detail under "Charge and Process" below.

Robert W. Gereau, PhD, Co-chair
Washington University School of Medicine
St. Louis, MO

Kathleen A. Sluka, PT, PhD, FAPTA, Co-chair
University of Iowa Carver College of Medicine
Iowa City, IA

Introduction

The public health crisis of chronic pain affects one in five adults and children in the U.S. and worldwide. High-impact chronic pain that significantly interferes with daily life including daily personal, occupational, and social activities affects approximately 25 million Americans. Further, 20 to 50% of individuals who experience an acute pain event such as trauma or surgery go on to experience persistent pain that can last months, years or even decades. Chronic pain, defined as pain lasting more than three months, can result in life-long impacts on the person, their family and society. Importantly, chronic pain is not a single disease or condition, but rather a variety of conditions with varying etiologies and mechanisms. As such, understanding and addressing the complexity of chronic pain will require significant efforts to understand the factors that contribute to the risk and resilience to development of chronic pain and recovery from chronic pain.

The prevalence, severity, and treatment of chronic pain differ between men and women, younger and older adults and in underrepresented populations. Women, older adults, underrepresented minorities, and rural residents are more likely to report pain. Women have a higher overall incidence of pain than men, and particularly of musculoskeletal pain and widespread pain. Pain incidence varies across the lifespan with older adults showing a greater incidence of pain than young adults: only about 12 percent of women under 30 have chronic pain, whereas more than a third of women over 65 do. Lower socioeconomic status, lower education level, and unemployment are also associated with higher prevalence of pain and greater disability. Thus, chronic pain is multifactorial and is influenced by biological, psychological, social, cultural, and environmental factors.

Pain has been defined by the International Association for Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Pain is a complex, multidimensional experience associated with varying degrees of biological, psychological and social factors that is influenced by life experiences. Chronic pain not only leads to reduced function and increased disability, but is often associated with psychological distress, anxiety and depression. Individuals rarely have pain in only one area, and the number of affected sites is directly related to disability, psychological distress and function. Pain is unique to each individual; even two individuals with the same condition may have variations in the underlying biological mechanisms and will have different experiences of psychological dysfunction and social impact. Thus, a better understanding of the biological mechanisms and clinical phenotyping of an individuals' experience of pain will help to guide future pain-management approaches.

Current treatments for chronic pain remain inadequate due to a poor understanding of the pathobiological mechanisms of pain and its treatment, few available effective treatments, and inadequate use of existing evidence-based approaches. Disparities in care also contribute to the burden of chronic pain. Underrepresented minorities are often undertreated for pain, lower socioeconomic status may result in limited access to care, and rural residents may not have access to providers who specialize in pain management.

For individuals with chronic pain, treatment may entail months or even years of a trial-and-error approach to obtain adequate pain management. Experts generally agree that an individualized, personalized approach to pain management should be taken, yet whether this approach is superior to a standardized one size fits all approach has not been rigorously tested. Further, while there are a variety of evidence-based treatments available, not all individuals will respond to all treatments, and access to

treatments may be limited. The optimal combination and timing of interventions remains unknown. Often individuals are treated with low-value, higher-risk interventions (e.g. opioid, surgery), which are often covered by insurance, before being treated with high-value, low-risk interventions (e.g. psychology, physical therapy), which are often not sufficiently covered. Lastly, clinical trials often focus on reducing pain intensity as a primary outcome, yet the primary goal of individuals with chronic pain is often to improve physical, cognitive, and social function. Understanding the factors that can guide treatment with an individualized approach, and identification of factors that can identify responders to treatments for both pain and function or disability outcomes, will be important to improving pain management. Further understanding how to apply and implement high-value interventions while simultaneously minimizing use of low-value interventions will be critical to successfully reducing the burden of chronic pain.

Although safety and efficacy have been established for many non-drug approaches (e.g., behavioral therapies, exercise, acupuncture), these approaches are often not well utilized clinically. While there is increasing evidence for the mechanisms by which some treatments reduce pain, understanding these underlying mechanisms and the factors that identify responders to these interventions will help to bolster future studies and management of chronic pain. Further, methods to improve implementation and use of these non-drug approaches for management of pain are imperative to improve outcomes for those with chronic pain.

The complexity of the human pain experience and the unique challenges faced in clinical trials for new pain therapeutics have contributed to a high failure rate in these trials. Consequently, we have seen dramatically reduced investment by pharmaceutical companies in development of new therapies for pain. To encourage industry partners to re-engage in pain therapeutics development, researchers should expand mechanistic research to better predict efficacy of potential therapies in patients and to mitigate risks in potential targets at the preclinical stage. Advances in pain science are providing unprecedented insights into the various mechanisms of chronic pain. Recent technological breakthroughs will enable more precise identification of therapeutic targets and innovative approaches to address them. Additionally, insights from studying human biology will inform the development of preclinical models and help prioritize mechanisms for clinical development.

To accomplish the priorities listed herein, it is imperative that we build a strong workforce to focus on pain and its management across the spectrum from basic mechanistic work, therapeutic development, as well as translational and clinical science. A particular concern is the lack of clinical and translational researchers, and people with expertise in implementation science. This will require significant efforts to bolster and support individuals currently training in the field, as well as efforts to bring new and diverse backgrounds to the field.

Charge and Process

Charge and Formation of Working Group

The HEAL Pain Strategic Research Priorities Working Group was formed as a Working Group of the National Advisory Neurological Disorders and Stroke Council (NANDSC).

This Working Group was charged with providing scientific guidance on how best to advance pain research through the HEAL Initiative by proposing and prioritizing future-looking strategic research priorities that will advance the HEAL Initiative pain research mission for the next phase (approximately five years).

Mission Statement

HEAL pain research aims to reduce pain and the risk of opioid use disorder by developing safe and effective pain treatment and prevention strategies to improve quality of life for all people.

Specifically, the Working Group was tasked with:

- Assessing the progress the HEAL Initiative has made to date in pain research by specifying successes and lessons learned from programs supported in the first phase of the Initiative.
- Recommending better ways to achieve the goals of valuable HEAL programs supported in the first phase of the Initiative.
- Identifying gap areas in the current or past HEAL pain research portfolio that should be addressed to advance the HEAL mission.
- Suggesting new opportunities for advancing the HEAL mission through new partnerships, technologies, breaking developments in science, research infrastructure, or other methods of administering the program.

The Working Group was co-chaired by Dr. Kathleen Sluka and Dr. Robert Gereau. Eleven other members were appointed (as described in Appendix 1) based on their scientific and lived experience expertise. To appropriately deliberate and develop strategic research priorities, the Working Group members formed seven subcommittees based on distinct "focus areas" of pain research, which were supplemented with additional expertise (see Appendix 1). Each subcommittee hosted public, online workshops to garner input from the additional experts and broader public. NIH staff aided in organizing, coordinating, and providing context to each of these subcommittees. The seven subcommittees focus areas were:

1. Non-addictive pain therapeutics development
2. Biomarkers and predictors
3. Optimizing interventions to improve pain management
4. Implementation and health services
5. Health equity and pain across the life course
6. Intersection of pain and substance use
7. Research workforce and training

RFI

NIH invited email-based input from the public to inform research priorities for the HEAL Initiative via a Request for Information (RFI; NOT-NS-24-106) from June 24, 2024, to July 31, 2024. Analysis of public responses to this RFI will be provided in a forthcoming publication from NIH. For the purposes of the HEAL Pain Strategic Research Priorities Working Group, members were provided with de-identified summaries of comments relevant to the seven focus areas, which they considered as part of their deliberations.

Workshops

Each subcommittee held a virtual workshop dedicated to their focus area, including scientific presentations and input from people with lived experience, followed by discussion and input from attendees. Workshops were open to the public and publicized by NIH. The workshops were held online between late November and early December 2024; each lasted three to four hours. Recordings, Executive Summaries and other materials from the workshops are available on the NIH HEAL Initiative website.

Prioritization process

Each subcommittee developed a summary of their deliberations including a list of proposed research priorities relevant to their focus area. These summaries will be provided in a forthcoming publication from the NIH. Several groups also included overarching principles or crosscutting themes that arose as important to pain research broadly. The co-chairs of the Working Group considered and refined these summaries and proposed a unified list of 28 research priorities. These were submitted to members of the seven subcommittees to rank based on their ability to advance the HEAL Pain mission and their feasibility. Results of that ranking informed the final deliberations of the Working Group at an in-person meeting at Washington University in St. Louis on January 8-9, 2025. The Working Group extensively discussed the top 16 of these proposed scientific research priorities for final consideration. This deliberation resulted in a final prioritization of ten scientific research priorities and associated “Core Principles” as described in the following sections.

Core Principles

"Pain" describes a group of clinical conditions that significantly impact individuals from all walks of life and at all stages of life. In addition to affecting a person's life and function, chronic pain also impacts families and society. Chronic pain has no cure, and individuals often experience pain for months, years or decades. The experience of pain and its impacts are highly individualized and may change considerably over the life course. The risk for chronic pain is influenced not only by underlying biological factors, such as genetics, but also by environmental, cultural, and lifestyle factors, as well as by life experiences, all of which can interact. Thus, it is necessary to understand pain comprehensively, considering biological, psychological, and social influences. Many individuals have multiple pain conditions and co-occurring pain, substance use, mental health, or other medical conditions. Harmful false beliefs about pain from clinicians and the public can lead to stigma, poor pain care, and ultimately worse outcomes. Given these concerns, the Working Group developed the following "Core Principles" for the HEAL Initiative to consider in their programs to enhance pain research, increase rigor, and ensure translatability to the public.

These core principles differ from the scientific research priorities that follow in that they are general themes that arose across different subcommittees and should be considered across different scientific focus areas of pain research. The Working Group recommends that HEAL incorporate these principles across its pain programs to advance the HEAL Pain Mission.

1. **Involvement of People with Lived Experience in NIH HEAL research.** HEAL-funded research should involve persons with lived experience (PWLE) as part of pain research teams to ensure that research questions and outcomes are patient-centered and impactful. Input from PWLE should be included across the research spectrum (from basic to clinical), and from study design through data analysis and dissemination. This would include PWLE involvement in training and career development awards where they would have input into the training and research plan. Achieving this goal will require adequate training for investigators in how to engage PWLE in the research process, as well as adequate training and opportunities for PWLE in working with a research team.

2. **Education of Public and Providers.** A common theme across subcommittees was the need to educate healthcare students, clinicians, and the public in the current science of pain and its management. This could be achieved by studying methods for dissemination of findings from ongoing research, methods to enhance education of entry-level healthcare practitioners, and public outreach campaigns. Community engagement methods could be included for clinical trials and implementation studies to further enhance knowledge in local communities and healthcare systems on pain management.

3. **Methodological principles for preclinical and clinical trial research.** As part of the current NIH policy both preclinical and clinical studies should consider sex as a biological variable. Beyond this, both preclinical and clinical research should consider reporting data by sex, age should be collected, considered, and reported, and longer-term outcomes should be collected. In preclinical work, for example, animal models of chronic human conditions could be developed using aging animals and longer outcomes. Studies of clinical therapies or interventions should measure longer outcomes to account for the variability of pain and function, and to measure

treatment effectiveness over time. Clinical studies should consider and collect data related to co-occurring pain, substance use, mental health, and medical conditions.

Influence of social factors - There has been a recognition in pain research that pain will best be understood using a biopsychosocial perspective, but studies focusing on the "social" component of the causes and influences on pain are scant. Clinical studies should collect data on social determinants of health (SDoH) including (but not limited to): race, ethnicity, rurality, and socioeconomic status. Other social constructs include relationship dynamics, social support, stigma, work status, and pain expectations and acceptance. The HEAL core data elements could be revisited to ensure that adequate SDoH are represented.

Implementation - Clinical effectiveness trials, pragmatic trials, and implementation studies should embed implementation strategies during the initial design phase and consider using applied frameworks for the both the intervention and strategies needed to support implementation and maximize potential for dissemination and sustainability while maintaining fidelity.

4. **Interdisciplinary teams should be employed to capitalize on unique skills and methodologies.** To fully realize the proposed strategic plan will require a team science approach. Teams that include basic and preclinical scientists, clinicians, data scientists, and PWLE could provide transformative insights (see the HEAL Integrated Basic and Clinical Team-based Research in Pain - RM1 program). Teams that employ experts in pain with those from other fields can propel science forward, develop novel methods and techniques, and analyze data using unique approaches. For example, experts in molecular biology can provide high-quality and novel methods for analysis of tissue samples, bioinformatics experts can analyze data sets in unique ways, implementation scientists can design better methods for sustainability, and community engagement experts can enhance pain and study visibility to the public.

5. **Secondary analysis of existing data and biological samples, many of which are already stored in the HEAL Data Ecosystem, can also yield insights into the genesis and maintenance of chronic pain.** The HEAL initiative has put considerable resources into support of large programs and harmonizing studies with development and use of common data elements in these studies. Data sets from all HEAL studies are made available to the public and consolidated through the HEAL Data Ecosystem to support sharing and open science. Use of these data could combine multiple studies, perform secondary analysis on existing data sets, or test novel hypothesis on existing biological samples. Leveraging these existing resources should be prioritized and supported to advance the science of pain and its management.

Research Priorities

The following priorities are presented in a thematic sequence, but the order is not based on importance or priority. Priorities are lettered for ease of organization.

Priority A

Support comprehensive fellowship, career development, and mentored research scholar awards for individuals across all career stages, including non-U.S. citizens. To increase the number of individuals engaged in pain research, these awards should 1) foster the continued growth of established pain researchers and 2) provide targeted opportunities for individuals with no prior pain research experience but strong potential to develop impactful careers in pain science.

Rationale: To cultivate a robust and sustainable pain research workforce capable of addressing the complex challenges of pain and its treatment, it is crucial to provide individuals at all career stages, including non-U.S. citizens and PWLE, with the necessary resources and protected time required to develop field-specific expertise. To increase the number of new individuals working in the pain field, develop programs that raise awareness for the wide array of job opportunities that exist in pain science, and develop programming for individuals of all ages – from school-aged children to established investigators without pain research experience. Support for new pain investigators should include education in pain science, access to qualified mentors who have a broad range of professional expertise, and clinical exposure. To maintain the current pool of pain researchers, develop career-stage-specific programming that prioritizes stage-appropriate skill development in the following topics: mentoring, engagement of PWLE, establishing and maintaining cross-disciplinary collaborations, implementation science, leadership skills, entrepreneurship, and public relations/communications. It is vital to support researchers across the full translational spectrum (T0 to T5), particularly T4 (effectiveness and outcomes in populations) and T5 (implementation of evidence-based practice in health systems) as expertise in these areas is significantly under-represented in the pain field. Streamline the application process for these programs to reduce the up-front burden and make program acceptance more equitable. Investing in the next generation of scientists ensures that we have the expertise needed to advance healthcare practices and improve patient outcomes.

Specific Identified Needs: Two specific needs were identified: 1) increased support for training clinician scientists, and 2) increased training opportunities for clinical researchers focusing on clinical trial methodology and implementation. To fulfill specific needs, career development programs should address the unique time and financial challenges faced by clinician-scientists (e.g. MD, PT, Psych, Etc.) such as raising the maximum salary support or reducing required protected research time, and longitudinal training that integrates research with clinical practice. Further, we need to train establish training programs specific to early-career scientists interested in implementation, embedded pragmatic trials and other real-world research approaches as these types of studies have unique challenges and methodology not conducive to most training programs. Training programs that emphasize mentoring and interdisciplinary collaboration are essential to build a workforce capable of addressing the challenges in pain management and health services research. Development of these programs with a focus on practical skills and competencies is needed for effective clinical trial methodology, implementation, and dissemination of research findings to ultimately improving patient care.

Priority B

Support the development of mechanistically varied and highly efficacious pain therapeutic pharmaceutical modalities.

Rationale: The non-addictive pain therapeutics development subcommittee endorsed strong support for the programs established in the first iteration of HEAL funding of therapeutic development. These programs include novel target identification and validation and a robust ecosystem that enables interrogation of assets in areas critically important for go/no-go decisions in therapeutic development, including the pain therapeutics development and devices programs and the establishment of a robust preclinical screening platform for pain. These programs provide a pathway, even in an academic environment, to substantially advance and de-risk potential assets, increasing interest from industry partners in pursuing clinical development. There was strong consensus that the NIH should build on this success, which focused on small molecules, by including new therapeutic modalities in this ecosystem. In contrast to other areas of clinical development, the potential benefit of antibodies, peptides, mRNA therapeutics and related technologies for chronic pain remain untapped for the vast majority of the 50 million Americans with chronic pain. These modalities likely offer more tolerable, safer ways to engage thoroughly vetted targets and/or mechanisms. Varied routes of administration, neuroanatomic and neuromodulatory targets, and dosing regimens with these technologies will overcome some serious liabilities of small-molecule analgesics. Strategic investment in these technologies at the proof-of-concept stage of development, particularly in refractory pain populations, would help emulate the success observed in oncology and infectious diseases in chronic pain populations. This aim represents a previous gap in pain therapeutic development that HEAL can now fill.

Priority C

Invest in discovery research with a focus on human biology to support the development of novel therapeutics by: (1) identifying high-quality targets for development of new effective pain therapeutics and (2) supporting the development of a new generation of highly predictive disease-specific animal and cellular models.

Rationale: Enormous progress has been made in the basic science of pain using animal models, but we still know relatively little about the molecular composition of the human pain pathway from the peripheral nervous system to the brain. Further, it has become increasingly evident that the immune system plays a strong role in the generation and maintenance of pain, and that there is cross talk between non-neuronal cell (e.g. immune cells, muscle cells, keratinocytes) and neurons that are critical to development of chronic pain. While limited studies to date have shown strong conservation of many cell types - and even some cell states - across species, they have also revealed important differences across species that predict clinical failures. Investment in better preclinical models of human pain conditions is necessary to identify high-quality targets for efficacious pain therapeutics. This is necessary for all areas of therapeutic development, from small molecules to novel biologic modalities, to devices and neuromodulation.

Advances in the understanding of the human nervous system and how it changes with chronic pain create enormous opportunity for “back translation” of findings in patients to create a new generation of highly predictive animal and cellular models needed to test basic science hypotheses, validate therapeutic targets, and test efficacy of new drug candidates. These models need to consider important biological variables like sex and age.

Priority D

Develop pain prevention strategies to prevent the development of chronic pain throughout the lifespan, particularly during key transitions across the life course.

Rationale: Historically, pain research has largely been devoted to finding treatments for established pain symptoms and associated disabilities and has treated patients at various developmental stages indiscriminately. Current understanding of chronic pain conditions is evolving such that research can now take aim at halting, preventing, or reversing pain conditions. Further, research has also revealed important differences in pain mechanisms and treatment needs across the life course, particularly during transitions such as childhood to puberty, adolescence to early adulthood, perimenopause, and later life. Each transition period brings unique biologic, psychosocial and structural risk factors for chronic pain. This priority aims to develop multilevel targets for prevention.

To actualize this research priority will require screening tools and biomarkers that can help predict who has a higher likelihood of developing persistent or recurrent pain, as well as identify those individuals with greater resilience. It will also require a better understanding of *how* to prevent primary and secondary pain, which may be gleaned from a better understanding of resilience – for example in people who experience less pain or recover more consistently. Primary prevention encompasses measures such as vaccination, preventive interventions in children (e.g. school, sport, or primary care settings), workplace injury avoidance programs, disease-modifying treatments (e.g. diabetes, osteoporosis), and lifestyle modifications aimed at long-term reduction of pain risk, which also require further study. Prevention of secondary pain could involve addressing acute pain immediately after its onset—whether due to trauma or predictable situations like post-operative scenarios—with an emphasis on preventing progression to chronic pain.

Current data shows that prior pain experience and psychological factors increase risk for chronic pain, but evidence on whether treating these factors prevents chronic pain is lacking. Thus, research should focus on testing if reducing risk for development of chronic pain using tailored interventions across the biopsychosocial spectrum (drug, behavioral, physical, social, etc.) prevents development of chronic pain and promotes resolution from acute pain. Importantly, community engagement methods and intervention and focus on primary care will be necessary to realize this priority.

Some causes of pain are entirely preventable, including stigmatization and dismissal by healthcare professionals perpetuated by false beliefs and stereotypes particularly regarding pain in children, older adults and underrepresented and underserved populations (e.g., race/ethnicity, low socioeconomic status). It is important to test impact of stigma (including internalized stigma/shame), trauma (including historical and generational trauma), injustice and isolation on the development of chronic pain to halt practices that contribute to its generation.

Preclinical studies can also promote prevention of chronic pain by elucidating underlying mechanisms of pain that can subsequently inform development of novel therapeutics and treatments aimed at pain resolution, prevention, disease modification and recovery from injury

Priority E

Develop biomarkers for predicting treatment response, safety, target engagement and/or that may serve as surrogate endpoints in clinical trials.

Rationale: Identifying biomarkers that can predict safe and effective treatment response, on- or off-target effects, safety, and/or serve as surrogate endpoints are a critical priority, as it would allow for the implementation of personalized pain management strategies and for more efficient clinical trials. Such response-related biomarkers allow researchers to streamline clinical trial design, increasing the probability of success and expediting development of effective therapies. Biomarkers could also improve clinical trials outcomes by, e.g., reducing the heterogeneity of treatment effects, or guiding selection of trail subjects most likely to respond. Biomarkers can also help predict long-term treatment responses and adverse effects. Using biomarkers as surrogate and/or intermediate endpoints could reduce the duration and cost of clinical trials, leading to faster approval of effective pain treatments. Biomarkers would require rigorous validation to demonstrate disease relevance and the ability to predict clinical outcomes before they could be used in phase III trials. Predictive, prognostic and pharmacodynamic biomarkers could also improve the therapeutic treatment potential of existing interventions in patients immediately.

Priority F

Evaluate whether individualized, tailored, mechanism-based treatments improve outcomes.

To accomplish this aim: (1) Develop composite pain "signatures," or deep phenotypes, including biological markers and patient-reported outcomes (PROs), that capture the complexity and multidimensional nature of chronic pain (2) Investigate mechanisms underlying non-drug interventions, and (3) Test personalized approaches based on matching a patient's phenotype /signature with known underlying mechanisms.

Rationale: Common sense dictates that treatments based on specific mechanisms and tailored to an individual's phenotype would be more effective than a one-size-fits-all approach, but empirical evidence to support superiority of this approach is lacking. To enact this approach will require deep phenotyping of patients with a composite pain signature. Also limiting this approach is the lack of understanding of the biological, psychological, and social mechanisms underlying many aspects of chronic pain conditions. Although the mechanism of action is well known for most pharmaceutical agents (drugs), a considerable knowledge deficit exists concerning the mechanisms underlying many non-drug interventions. To bridge these gaps will require further investigation of pain etiology and mechanisms underlying chronic pain, mechanisms behind non-drug interventions, and how these pain and treatment mechanisms intersect with one another.

This priority therefore aims to further elucidate the biological, psychological, and social underpinnings of pain conditions and pain-management approaches, while immediately testing whether a personalized approach based on known mechanisms yields superior results compared to standard evidence-based care.

Biological markers within composite signatures could include systemic and tissue-specific measures of peripheral and central processes. Systemic markers, measured in blood, urine, or saliva, can reflect physiological processes (e.g., immune activation, inflammation) that contribute to pain perception and modulation. Tissue-specific biomarkers, obtained from tissues like joints, muscles, or the nervous system, can provide insights into localized pain mechanisms. Biomarkers can improve the potential to identify the primary source of pain in some cases.

Deep phenotyping of patients can provide a detailed and individualized picture of a patient's experience, encompassing not only their diagnosis and symptoms but also their underlying biological predispositions, environmental influences, and psychosocial factors. In addition to collecting biomarkers, deep phenotyping should carefully characterize pain and patient-reported outcomes (PROs), social determinants of health (SDOH), and behavioral/ psychosocial components. Phenotypes should be multi-modal.

These comprehensive pain biosignatures should then be considered to guide pain treatment according to mechanisms. Such "matching" of an individual's pain signature with the best available, most appropriate, and individualized treatment can then be tested against current standardized treatments.

Priority G

Develop and test evidence-based guidance on the appropriate initial pain therapy, order and timing of multimodal approaches, and non-specific effects to achieve maximal benefit for the individual patient without undue risk.

Rationale: These approaches need to be developed in a culturally appropriate manner that includes testing in low-resource settings and across various populations, the lifespan, and sex. Emerging research indicates that multimodal therapies for pain and its prevention are more effective than single-agent treatments. Nonetheless, several questions remain unaddressed: Does the sequence in which therapies are initiated affect patient outcomes? How should treatment be adjusted if initial responses are suboptimal? What combinations or additions to therapy can further enhance outcomes and expedite pain resolution? The underlying variability of response to single treatments in clinical trials and the lack of studies that go on to evaluate whether non-responders would benefit from another intervention (drug or non-drug) for the same symptoms has created a large gap in our understanding of how to best treat individual patients. There remains a significant gap in our understanding of the number of patients that can achieve meaningful relief after a trial of multiple treatments and multimodal therapies over time. Studies should identify predictors (and biomarkers) of treatment response to specific therapies to advance efficiency of personalized pain management above the current method of trial and error.

Sequential and multimodal clinical trials must consider the growing concern that certain therapies may potentially cause harm—such as the risk of developing opioid use disorder, or a current concern based on animal research that pharmacologically reducing inflammation may impede natural healing processes and ultimately pain resolution. Thus, understanding the risks of interventions, particularly their influence on natural recovery and pain-resolution mechanisms, is critically important.

Sequential and multimodal treatments also have the potential to improve efficacy above individual treatments. Chronic pain management is a long-term process where treatments are regularly modified, and some are used intermittently. Longer term studies aimed at more real-world management that includes both scheduled and intermittent interventions to examine effectiveness on not only pain but also function/disability as well as responder profiles is critical.

Understanding of non-specific effects (e.g. placebo, therapeutic alliance, and patient choice) and their influence on effectiveness of an intervention could provide valuable data to clinicians to improve outcomes clinically. To achieve the goals of this priority it will be important to include all types of therapy with a particular emphasis on the role of non-drug approaches and patient-initiated techniques which leverage the body's intrinsic capabilities for self-regulation and control. These treatments are seldom used alone but rather are part of a broader therapeutic regimen tailored to individual needs. It is essential to define the role of non-drug approaches within the broader context of other concurrent therapies as primary or complementary strategies that aim to minimize pharmacologic intervention while promoting recovery from pain.

Priority H

Prioritize clinical- and community-embedded research, hybrid implementation-effectiveness studies, and pragmatic trials for real-world impact, scalability, and sustainability.

Rationale: Align research with real-world clinical care metrics. Research that evaluates and aligns the effectiveness of metrics meaningful to various stakeholders (PWLE, clinicians, healthcare systems, payors), including patient-reported outcomes, clinician-reported metrics, and priorities of agencies such as NCQA and CDC (Healthy People) is needed to implement evidence-based practices in real-world settings for tangible improvements in healthcare delivery.

Assess the integration of shared decision-making tools into clinical practice. Research that considers whether shared decision-making tools, such as journey maps and other decision aids, effectively facilitate communication between patients and providers, helping to navigate their differing needs, is needed to evaluate whether such tools improve understanding, satisfaction, and health outcomes.

Evaluate integrated care models in various settings. Research that gauges the implementation and outcomes of integrated care models in various healthcare and community settings, including primary care and others supporting underserved and rural communities, is needed to elucidate their impact and scalability. Ensuring that all patients have access to effective pain management is essential to reduce health disparities and improve public health and population focused care.

This research should focus on coupling implementation of higher-value pain interventions with strategies to de-implement low-value care. While addressing the widespread use of ineffective (and sometimes less-safe, e.g. opioids) treatments in clinical settings is critical for improving patient outcomes and reducing healthcare costs, these must be coupled with aligned implementation of evidence-based viable alternative approaches (sometimes with less risk, e.g. exercise) to pain management. By focusing on coupled implementation/de-implementation strategies that prioritize primary care and involve multiple stakeholders, including clinicians, payers, and leadership, we can ensure that resources are allocated to more effective and evidence-based treatments, ultimately enhancing patient care.

Importantly, these studies should also focus on integrating implementation principles broadly into all phases of clinical research, studies should include strategies and investigation aimed at dissemination and sustainment. Further, studies need to now go beyond testing efficacy of existing treatments include testing of implementation effectiveness and sustainment of the intervention.

Current existing programs include the Pragmatic Studies for Pain Management Without Opioids (PRISM) network and the Pain Management Effectiveness Research Network (ERN) which provide support to these large-scale studies.

Priority I

Identify populations that are disproportionately and highly impacted by both pain and substance use, understand mechanisms that differentially impact these populations, and develop and test interventions to address the disproportionate impact.

Rationale:

Certain populations face higher risk of chronic pain and/or for substance misuse/abuse due to disparities in treatments of these groups for pain and substance use disorder. For example, opioids are first-line pain treatment for people with cancer and are more commonly used in older adults to manage chronic pain. Black Americans are less likely to receive non-drug treatments, more likely to receive methadone for OUD and less likely to receive buprenorphine for OUD. Rural individuals have higher pain and disability and are less likely to receive non-drug therapies, yet they have higher rates of opioid use. Veterans experience higher than average rates of alcohol and stimulant use. All of these factors elevate risk for these populations. Additionally, several pain conditions have higher rates of opioid prescribing including cancer, sickle cell disease, and HIV. Further, those with multimorbidity (e.g. PTSD, mental illness), polypharmacy prescription (e.g., opioids + benzodiazepines + gabapentinoids + muscle relaxants), non-prescribed opioid use and OUD, comorbid non-opioid substance use are of particular concern due to increased risk, difficult pain management, and substance use disorders.

We recommend prioritizing *disproportionately and highly impacted* populations in research on the intersection of pain and substance use through development and testing of interventions with high potential for impact, such as shared decision-making regarding full agonist opioid prescription, de-prescribing opioids and other pain medications, multimodal care (including non-pharmacologic approaches), buprenorphine (as an initiation strategy, or switching from full agonists to buprenorphine). Preclinical studies and development of interventions that address mechanisms of the reciprocal relationship between pain and substance use are critical to the management of pain and substance use in these populations. In addition, studies that investigate equitable implementation of evidence-informed approaches that address opioid complexity (e.g., treatment of opioid use disorder with FDA-approved medications, employment of opioid risk mitigation strategies) are critical to change the outcome for all individuals with pain and substance use. Finally, we recommend engaging health equity experts with expertise in community engagement to ensure collection of high-quality data collection and improve public outreach.

Priority J

Support research on non-drug approaches to treatment and prevention of chronic pain, including in patients with co-occurring substance use disorder.

Rationale: Even though safety and efficacy are established for a number of non-drug approaches (e.g. behavioral therapies, exercise, acupuncture) these approaches are often not well utilized clinically. While there is increasing evidence for how some of these treatments reduce pain or improve quality of life, the underlying mechanisms for how many non-drug treatments reduce pain are unknown. Non-drug treatments are seldom used in isolation, but little is known about the effects of combining non-drug treatments with drugs or other non-drug approaches. Non-drug approaches include behavioral and self-management approaches (e.g., derive from cognitive behavioral therapy, mindfulness-based interventions, and incorporate pain science education), movement-based approaches (e.g., yoga, exercise), devices (e.g. neuromodulation approaches such as TENS, laser therapy, wearables) and complementary and integrative health approaches (e.g. acupuncture, massage, manual therapy). Importantly, efficacy of most non-drug interventions for reductions in pain and/or improved function is known, and thus the next steps should focus on improving delivery and usage.

We recommend identifying existing evidence-based approaches for pain and/or addiction treatment, tailoring them to people with co-occurring conditions, and conducting hybrid implementation trials. Preclinical and clinical studies evaluating underlying mechanisms, and clinical studies performing responder analyses with predictors and biomarkers, could a) identify methods to improve use and implementation of the interventions, and b) select appropriate treatment options and individualize the treatment plan. This priority could also include trials that assess various combinations of non-drug treatments or drug and non-drug treatments (i.e., multimodal/multidisciplinary pain treatment). Optimal timing of the initiating the intervention, effects of shared decision making, and person-centered care could be included. Sequential Multiple Assignment Randomized Trials (SMART) trials could be a particularly useful method to identify impactful combinations of non-drug treatment, opportune times to incorporate drug treatments, and personalized treatment approaches based on phenotyping.

Appendix 1: Rosters & Acknowledgements

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HEAL Pain Strategic Research Priorities Working Group Members

Robert Gereau, PhD, Washington University School of Medicine, St. Louis, Co-chair
Kathleen Sluka, PT, PhD, FAPTA, University of Iowa, Co-chair
Tamara Baker, PhD, University of North Carolina, Chapel Hill
Yenisel Cruz-Almeida, MSPH, PhD, University of Florida
Lynn DeBar, PhD, MPH, Kaiser Permanente Northwest
Michael Falcon, OTD, OTR/L, MHA, Hawaii Pacific University and Global Alliance of Partners for Pain Advocacy, Lived Experience Advisor
John T. Farrar, MD, PhD, Hospital of the University of Pennsylvania
Susmita Kashikar-Zuck, PhD, University of Cincinnati & Cincinnati Children's Hospital
John Markman, MD, Eli Lilly & Company
Jessica Merlin, MD, PhD, MBA, University of Pittsburgh
Ted Price, PhD, University of Texas, Dallas
Cheryl L. Stucky, PhD, Medical College of Wisconsin
Vivianne Tawfik, MD, PhD, Stanford University

Lived Experience Expertise

Joletta Belton
Eden Buell
Kristy Fischmann
Katryna Joubert
Quána Madison
Kate Nicholson
Tom Norris
Will Schwalbe
Christin Veasley
Christine Von Raesfeld
David White

Subcommittee Members

Non-addictive pain therapeutics development

John Markman, MD, Eli Lilly & Company, Co-Lead
Ted Price, PhD, University of Texas, Dallas, Co-Lead
Kristy Fischmann, Lived Experience Expert
David Julius, PhD, University of California, San Francisco
Anne-Marie Malfait, MD, PhD, Rush University
Ana Moreno, PhD, Navega Therapeutics

Daniela Salvemini, PhD, Saint Louis University
Will Schwalbe, Lived Experience Expert
Prasad Shirvalkar, MD, PhD, University of California, San Francisco
Joyce Teixeira Da Silva, PhD, University of Maryland, Baltimore
Todd Vanderah, PhD, University of Arizona
Beth Winkelstein, PhD, University of Pennsylvania

Biomarkers and Predictors
Yenisel Cruz-Almeida, MSPH, PhD, University of Florida, Co-Lead
Vivianne Tawfik, MD, PhD, Stanford University, Co-lead
Sandip Biswal, MD, University of Wisconsin-Madison
Susan Dorsey, PhD, RN, FAAN, University of Maryland, Baltimore
Aaron Fields, PhD, University of California, San Francisco
Peter Grace, PhD, MD Anderson Cancer Center
Sean Mackey, MD, PhD, Stanford Medicine
Christin Veasley, Lived Experience Expert
Christine Von Raesfeld, Lived Experience Expert
Tor Wager, PhD, Dartmouth College

Optimizing Interventions to improve pain management
Claudia Campbell, PhD, Johns Hopkins Medicine, Co-Lead
John T. Farrar, MD, PhD, Hospital of the University of Pennsylvania, Co-Lead
Meryl Alappattu, DPT, PhD, University of Florida
Benedict Alter, MD, PhD, university of Pittsburgh
Ausaf Bari, MA, MD, PhD, University of California, Los Angeles
Joletta Belton, Lived Experience Expert
Katie Butera, PT, DPT, PhD, University of Delaware
Jeffery Dusek, PhD, University of California, Irvine
Jennifer Gewandter, PhD, MPH, University of Rochester Medical Center
Renee Manworren, PhD, University of Texas, Arlington
Jennifer Rabbitts, MD, Stanford Medicine
Fenan Rassu, PhD, Johns Hopkins School of Medicine
David White, Lived Experience Expert

Implementation/Health Services
Lynn DeBar, PhD, MPH, Kaiser Permanente Northwest, Co-Lead
Steven George, PT, PhD, FAPTA, Dule University School of Medicine, Co-Lead
Lindsay Ballangee, PT, DPT, Duke University
Will Becker, MD, Yale School of Medicine
Andrea Cheville, MD, Mayo Clinic
Michael Falcon, Lived Experience Expert
Julie Fritz, PT, PhD, FAPTA, University of Utah
Susan Nicole Hastings, MD, Duke University
Steve Martino, PhD, Yale School of Medicine

Natalia Morone, MD, Boston Medical Center
Kate Nicholson, Lived Experience Expert
Natasha Parman, PT, DPT, University of Washington
Justin D. Smith, PhD, University of Utah

Health Equity and Pain Across the Lifecourse
Tamara Baker, PhD, University of North Carolina, Chapel Hill, Co-Lead
Susmita Kashikar-Zuck, PhD, University of Cincinnati & Cincinnati Children's Hospital, Co-Lead
Edwin Aroke, PhD, CRNA, University of Alabama, Birmingham
Staja Booker, PhD, RN, FAAN, University of Florida
Mary Janevic, PhD, MPH, University of Michigan
Quána Madison, Lived Experience Expert
Vani Mathur, PhD, Texas A&M
Tonya Palermo, PhD, University of Washington
Soumitri Sil, PhD, Children's Healthcare of Atlanta

Intersecting SUD and Pain
Jessica Merlin, MD, PhD, MBA, University of Pittsburgh, Co-Lead
Joanna Starrels, MD, MS, Albert Einstein College of Medicine, Co-Lead
Amy Bohnert, PhD, MHS, University of Michigan
Hailey Bulls, PhD, University of Pittsburgh
Ziva Cooper, PhD, University of California, Los Angeles
Joseph W. Ditre, PhD, Syracuse University
Karlyn Edwards, PhD, University of Pittsburgh
Michael Falcon, Lived Experience Expert
Scott Fishman, MD, University of California, Davis
Katie Fitzgerald Jones, PhD, APRN, VA Boston
Jennifer Hah, MD, MS, Stanford Medicine
Katryna Joubert, Lived Experience Expert
Lakeya McGill, PhD, University of Pittsburgh
Hector Perez, MD, Albert Einstein College of Medicine

Research Workforce and Training
Jennifer Haythornthwaite, PhD, Johns Hopkins University, Co-Lead
Cheryl L. Stucky, PhD, Medical College of Wisconsin, Co-Lead
Eden Buell, Lived Experience Expert
Alex Chamessian, MD, PhD, Washington University, St. Louis
Daniel Clauw, MD, University of Michigan Medical School
Roger Fillingim, PhD, University of Florida
Laura Frey Law, MPT, MS, PhD, University of Iowa
Bryan McKiver, MS, PhD, Yale School of Medicine
Tom Norris, Lived Experience Expert
Flavia Penteado Kapos, PhD, University of Washington
Jamie Rhudy, PhD, University of Oklahoma Health Sciences Center

Katelyn Sadler, PhD, University of Texas, Dallas
Carolina Valencia, PhD, University of Texas, El Paso

NIH Staff
Sam Ananthan (NIDA)
Ram Arudchandran (NINDS)
Vivi Bauman (NINDS)
Dave Clark (NICHD)
Rachel Desai (NIAMS)
Rachel Diamond (OD/DPCPSI)
Joel Islam (NIDA)
Kat Le Blanc (NINDS)
Janelle Letzen (NINDS)
Aron Marquitz (NIAMS)
Diana Morales (NINDS)
Michael Oshinsky (NINDS)
Mary Ann Pelleymounter (NINDS)
Steven Pittenger (NCATS)
Linda Porter (NINDS)
Michele Rankin (NIDA)
Whitney Ratliff (NCCIH)
Cheryse Sankar (NINDS)
Shelley Su (NIDA)
Stephani Sutherland (NINDS)
Elizabeth Sypek (NINDS)
Alex Tuttle (NCCIH)
Yolanda Vallejo (NCATS)
Laura Wandner (NINDS)
Jackie Ward (NINDS)
Wendy Weber (NCCIH)
Alynda Wood (NINDS)
Andrew Wright (NINDS)