Final Report of the HEAL Pain Strategic Planning Executive Committee – a Working Group of the National Advisory Neurological Disorders and Stroke Council

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Message from the Co-chairs

Chronic diseases are the major health challenge in America today. Chronic pain contributes heavily to this epidemic, affecting 24% of the US population, leading to tremendous suffering. The enormity of the problem is magnified by the dearth of safe, effective medications. We need more research that advances our understanding of pain to aid in the development of new therapies. Existing non-drug treatments are greatly underutilized for pain management despite evidence of their effectiveness, demonstrating the need for research on how best to implement these therapies. 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. But research 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 the HEAL Pain Strategic Planning Executive Committee (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.

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Introduction

Chronic diseases have reached epidemic proportions, with 50 to 60% of the US population experiencing one and 40% of Americans experiencing two or more. Most health care expenditures are attributed to managing chronic diseases, which significantly reduce people's quality of life and function and have wide-ranging impacts on families and society. Chronic pain is a burdensome facet of many chronic diseases, and chronic pain itself is considered a disease with its own pathological changes requiring unique, effective management strategies.

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 Executive Committee

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

This Committee 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 Committee 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 Executive Committee was co-chaired by Dr. Kathleen Sluka and Dr. Robert Gereau. Eleven other members were appointed to the Executive Committee (as described in Appendix 1) based on their scientific and lived experience expertise. To appropriately deliberate and develop strategic research priorities, the Executive Committee 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 Planning Executive Committee, 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, which are available for review in Appendix 2. 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 Executive Committee considered and refined these summaries and proposed a unified list of 28 research priorities. These were submitted to members of the seven subcommittee 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 Executive Committee at an in-person meeting at Washington University in St. Louis on January 8-9, 2025. The Executive Committee 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

"Chronic Pain" describes a group of chronic diseases 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. Indeed, chronic pain 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 committee 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 Executive Committee 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

The Executive Committee would like to thank all of the participants in the subcommittees, those who attended and participated in the virtual workshops, and the NIH staff who facilitated this process.

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Appendix 2: Subcommittee Research Priority Summaries

Biomarkers and Predictors Subcommittee

Subcommittee co-chairs:
Yenisel Cruz-Almeida, MSPH, PhD, University of Florida
Vivianne Tawfik, MD, PhD, Stanford University

I. Relevant background, assumptions, and definitions

Relevant Background: Biomarkers are defined as measurable characteristics that indicate normal or pathological biological processes or responses to an intervention (FDA-NIH Biomarker Working Group, 2016; Davis et al., 2020). Biomarkers hold promise for improving pain management, accelerating therapeutic development, and enhancing our understanding of pain mechanisms (Davis et al., 2020; Eldabe et al., 2022; Shirvalkar et al., 2023).

Assumptions: A key assumption in biomarker research is that objective, measurable biological indicators can provide valuable insights into the complex experience of pain, which is often subjective and difficult to quantify (Eldabe et al., 2022). Another assumption is that biomarkers can differentiate between various pain conditions (e.g., inflammatory vs. neuropathic) and predict treatment outcomes, allowing for more personalized pain management (Kawi et al., 2016; Reckziegel et al., 2019; Davis et al., 2020). However, it's important to note that chronic pain is multifactorial influenced by various biological, psychological, social, and environmental factors. Therefore, relying solely on single biomarkers may not capture the complexity of chronic pain conditions, and a panel of biomarkers representing multiple domains might be more effective (Tracey et al., 2019).

Definitions: There are various types of biomarkers, each serving a specific purpose:

- **Diagnostic biomarkers:** These are used to confirm the presence or absence of a condition or a specific subtype.
- **Monitoring biomarkers:** These track condition progression, treatment response, or safety.
- **Pharmacodynamic/response biomarkers:** These indicate a biological response to a medical product or an environmental agent.
- **Predictive biomarkers:** These identify individuals likely to respond to a specific treatment or experience an effect following an intervention.
- **Prognostic biomarkers:** These determine the likelihood of a clinical event, disease recurrence, or progression.
- **Safety biomarkers:** These indicate the potential for toxicity associated with a therapeutic agent.
- **Susceptibility/risk biomarkers:** These identify individuals predisposed to developing a particular condition.

II. Statement of the problem

Biomarkers are measurable biological indicators that can shed light on pain mechanisms, disease progression, and treatment response. They hold the potential to personalize pain management and accelerate drug development. Research is exploring a wide array of pain biomarkers, including serum and urine metabolites, neuroimaging data, genetic and epigenetic markers, and electrophysiological recordings. However, translating these biomarkers into clinically useful tools remains challenging. One

key challenge is the complexity of chronic pain, which is influenced by biological, psychological, social, and environmental factors. This heterogeneity makes it difficult to find single, universally applicable biomarkers. However, analysis of complex biomarker data sets integrated with reliable human phenotypes remains challenging. Another challenge is the need for rigorous validation to ensure the accuracy, reliability, and clinical utility of biomarkers requiring large-scale studies with diverse, well-characterized patient populations and standardized protocols to ensure generalizability. Additionally, practical considerations such as cost-effectiveness, ease of use, and ethical implications need to be addressed before biomarkers can be integrated into routine clinical practice.

Biomarkers and predictors for pain are critical tools to ultimately improve the lives of persons with pain. Above and beyond any one specific research priority, it is also extremely important that biomarker research:

1) **Addresses priorities of people with lived experience:** Research should consider patient preferences along the process of biomarker discovery and development.

2) **Advances health equity in pain biomarker research:** Research should consider societal and ethical implications of potential biomarkers, particularly concerning potential disparities/inequities in access and application, access to technologies, performance in people across the lifespan, biological sex, marginalized groups, insurance coverage, and in persons unable to communicate pain via self-report (e.g., infants, children, patients who are intubated in intensive care environments and those with cognitive impairments).

3) **Employs a team science approach:** A team science approach is essential for advancing pain biomarker research. By bringing together experts from various fields, we can more effectively identify and validate biomarkers, leading to better understanding of pain and its treatment. Multidisciplinary collaborations accelerate the translation of research into clinical applications, improving patient outcomes. Engaging researchers from different disciplines is needed to develop bioinformatic platforms that integrate diverse biomarker data with multi-modal phenotypes. These platforms can create clinical decision support tools for diagnosis, prognosis, and treatment.

III. Priorities shortlist

Proposed research priority 1. *Develop composite biomarker signatures that capture the complexity and multidimensional nature of clinical pain phenotypes.*

The development of composite biomarkers, incorporating multiple measurements from different domains, is essential to capture the multidimensional nature of pain. For example, composite biomarker signatures could incorporate both systemic and tissue-specific or peripheral and central biomarkers to gain a comprehensive understanding of pain biology. Systemic biomarkers, measurable in blood, urine, or saliva, can reflect overall physiological processes (e.g., immune activation, inflammation) that contribute to pain perception and modulation. Tissue-specific biomarkers, obtained from specific tissues like joints, muscles, or the nervous system, can provide insights into localized pain mechanisms and potentially identify the primary source of pain in some cases.

Deep phenotyping is a cornerstone of all biomarker research. By carefully characterizing pain and patient reported outcomes/ social determinants of health (SDOH)/ behavioral/ psychosocial phenotypes (i.e., multi-modal phenotypes) research teams can match multidimensional biomarkers to specific pain

subtypes, which likely do not fall neatly into classic diagnostic categories. Such biomarker-phenotype matching would allow for the development of more targeted and effective diagnostic tools and identify individuals who will benefit most from specific treatments. For example, identifying biomarkers that correlate with pain severity and its impact on physical and emotional functioning, as well as connecting them with common comorbid conditions, such as depression, anxiety, fatigue, or sleep disorders, could facilitate integrated treatment approaches that are critical for assessing treatment outcomes.
A biomarker validation framework needs to also include the validation of clinical phenotypes. Clinical diagnoses serve as a starting point for categorizing pain conditions based on observable symptoms, medical history, and physical examinations. They provide a broad framework for communication among healthcare providers and for guiding initial treatment strategies. Phenotypes, on the other hand, represent a more detailed and individualized description of the patient's experience, encompassing not only their symptoms but also their underlying biological predispositions, environmental influences, and psychosocial factors. However, clinical diagnoses often lack specificity and fail to reflect the underlying mechanisms driving pain. Phenotyping can help identify subgroups of patients within a diagnostic category who share common characteristics.

Proposed research priority 2. *Establish and Develop a Pain Biomarker Validation Framework.*
The process of developing biomarkers for clinical use is a systematic and directed endeavor that requires increasing validation as the biomarker moves from pre-clinical discovery to clinical trials to clinical practice. This process is a continuum that starts with biomarker discovery and development, likely in disease-relevant animal models, and progresses through various levels of validation, ultimately leading to clinical application. Preclinical work is additionally needed to identify, validate and confirm causality of such biomarkers before they can be fully translated to humans. Thus, pain biomarker research requires a rigorous validation process to ensure clear criteria for evaluating accuracy, specificity, and clinical validity depending on context of use and clinical phenotypes.
Proposed research priority 3. *Identify biomarkers on the causal path to pain and incorporate pre-clinical models to determine mechanistic underpinnings & context of use.*
Nociceptive information is carried from the periphery to the central nervous system through specific neural circuits, influenced by immune and glial inputs. Biomarkers which capture underlying mechanisms representative of this pain transmission (e.g., peripheral or CNS imaging, serum immune markers) are important to understanding different pain subtypes. Furthermore, developing biomarkers for confidently discriminating between different sources of pain is important for solidifying treatment targets. This is important because the mechanisms of pain are not fully understood, and there is a need to develop more reliable animal models of pain including larger animal models which develop similar conditions to humans.
Proposed research priority 4. *Develop biomarkers for predicting treatment response, safety, target engagement and/or that may serve as surrogate endpoints in clinical trials.*
Identifying biomarkers that can predict safe and effective treatment response, on/off target effects, safety and/or serve as surrogate endpoint are a critical priority, as it would allow for personalized pain management strategies and more efficient clinical trials. For treatment response, identifying responders and non-responders early on, allows researchers to streamline trial design, increase the probability of success, and expedite the development of effective therapies. Clarification is needed on the meaning of success (e.g., reduce the heterogeneity in treatment effect, selection subjects for clinical trials who are most likely to respond, or other criteria). Further, predicting long-term treatment response along with

adverse effects is needed. Using biomarkers as surrogate and/or intermediate endpoints (e.g., thermal or capsaicin-evoked transient receptor potential ion channel activity) could reduce the duration and cost of clinical trials, leading to faster approval of effective pain treatments after rigorous validation to demonstrate the biomarker's relevance to the disease and its ability to predict clinical outcomes before it can be used in phase III trials.

Proposed research priority 5. *Develop a core, minimal dataset to create biomarker repository for future use.*

All HEAL funded studies should collect biological samples when feasible for use by the research community for biomarker development and/or validation. Sample collection should include detailed guidance regarding sample collection methods, tube type (blood, saliva, urine, etc.), storage methods and shipping details. Well-characterized, deeply phenotyped datasets with biological samples may accelerate research discovery and progress and will enable larger sample size research across multiple geographic areas, which could improve generalizability of results.

Appendix 1: Parking lot

- Develop biomarkers in persons unable to communication pain via self-report (ex. ICU patients, young children), although it is part of considering health equity in biomarker research (see over-arching theme 3).
- Strengthen and diversify the pain biomarker research workforce across the translational research continuum.
- Foster innovation and partnerships with the biomedical industry for biomarker pain research.

Health Equity and Pain Across the Life Course Subcommittee

Subcommittee co-chairs:
Tamara Baker, PhD, University of North Carolina, Chapel Hill
Susmita Kashikar-Zuck, PhD, University of Cincinnati & Cincinnati Children's Hospital

Statement of the Problem

Biopsychosocial risk and protective factors for pain are not evenly distributed across the population and certain populations bear a disproportionate risk for poor pain treatment and outcomes. Sub- optimal pain management faced by children, the elderly, and those from disadvantaged communities arise from their pain experiences being poorly understood, often dismissed and compounded by structural barriers in healthcare and society at large. Intersectionality can add cumulative biopsychosocial risk that is also not well understood or addressed in pain research. The following priorities are considered urgent and important for strategic planning and setting of NIH HEAL priorities for the next 5 years. Some of these priorities are of a crosscutting nature and should be incorporated into topics selected by other committees in this initiative.

Strategic Priority #1

*Conduct studies on the communication and expression of pain in different ages, developmental groups, sex/gender, and cultures (*Make pain VISIBLE).

The last decade has seen progress on developing and validating standardized measures of pain and consensus statements around the domains of pain outcomes that are important to include in pain clinical trials, treatment and research. However, these measures often are not feasible or accurate in different ages, developmental groups and cultures. More cross-disciplinary research is needed to study diverse pain expression and communication preferences/patterns, with particular attention to those who are unable to verbally communicate about pain using currently available measures due to cognitive, developmental, cultural or language barriers. Novel methods (including technology, artistic expression, or other methods) to communicate about pain should be considered.

Strategic Priority #2

Identify impact, and test interventions aimed at mitigating, false beliefs, stereotypes and trauma about pain in children, the elderly, and minoritized communities (Make pain MATTER).

There continues to be pain dismissal and insufficient recognition of *myths and stereotypes* regarding pain in children, older adults and minoritized communities based on their race, ethnicity, gender identification, disability or socioeconomic status. It is important to *test impact of stigma (including internalized stigma/shame), trauma (including historical and generational trauma), injustice and isolation on pain experience in order to develop and test appropriate interventions.*

Strategic Priority #3

Study the impact of socially driven modulators that affect pain biology (Make pain better UNDERSTOOD).

The importance of early life experiences and exposure to adverse social and environmental circumstances with regard to their impact on biologic pain processing mechanisms and risk/ susceptibility for chronic pain cannot be underestimated. Studies on biologic aging, epigenetic and

neurobiologic alterations that are driven by social factors need to be identified and understood. Examination of *intersectionality* and its cumulative impact on risk for pain and pain-related outcomes should be included.

Implementation and Health Services Subcommittee

Subcommittee co-chairs:
Lynn DeBar, PhD, MPH, Kaiser Permanente Northwest
Steven George, PT, PhD, FAPTA, Dule University School of Medicine

Relevant background, assumptions, and definitions

The HEAL Initiative, launched by NIH in 2018, aims to address the opioid and chronic pain crises through research. With over $3 billion invested in more than 1800 projects, HEAL focuses on developing effective pain management, treatment of opioid use disorder, and overdose prevention strategies. Chronic pain affects millions, leading to significant healthcare costs and lost productivity. In 2024, $285 million was allocated specifically for pain research. The initiative's mission is to reduce pain and opioid use disorder risk by developing safe, effective treatments and prevention strategies. The HEAL pain research portfolio includes identifying pain mechanisms, treatment targets, biomarkers, and tools, as well as validating these targets and tools. Further, a strong emphasis on real world implementation and sustained practice is imperative to quality to improve pain care at a population level.

The strategic planning process involves the HEAL Strategic Planning Executive Committee and subcommittees, tasked with developing research priorities for the next five years. These priorities will guide the NIH HEAL Pain Strategic Plan and are informed by public input. For implementation science and health services research, the focus is on integrating evidence-based and/or guideline concordant practices into clinical settings, improving care pathways, leveraging technology like EHRs, and aligning research with real-world clinical metrics. Training programs specific to the challenges of implementation science and health services research are needed to emphasize mentoring and support early-career scientists to have success in these areas that are vital for improving care delivery options for individuals with chronic pain conditions that limit quality of life.

Statement of problem

Implementation science and health services research are crucial for translating research findings into practice, ensuring that effective interventions reach patients and improve outcomes. By focusing on system-level changes and outcomes such as: acceptability, adoption, appropriateness, equity, feasibility, fidelity, implementation cost, penetration, and sustainability, these fields can help reduce reliance on ineffective treatments, enhance patient engagement, and promote sustainable care interventions. The integration of various partners (particularly persons with lived experience and partners with expertise in policy, informatics, health economics, and implementation science) in research ensures that the developed strategies are practical, scalable, and aligned with the needs of the healthcare system. Despite significant investments in pain research, there remains a critical gap in translating research findings into clinical practice. Implementation science and health services research are essential for bridging this gap, ensuring that effective interventions reach patients in an equitable fashion and improve outcomes. The current healthcare system often relies on ineffective treatments, leading to suboptimal patient outcomes and increased healthcare costs. There is an urgent need for system-level changes that can reduce reliance on these treatments and promote sustainable, evidence-based care interventions.

Moreover, the integration of technology, such as electronic health records (EHRs), is underutilized in supporting multidisciplinary care teams and engaging patients effectively. Aligning research with real-world clinical metrics (including NCQA and CDC [Healthy People] guidelines) is crucial to ensure that the developed strategies are practical, scalable, and meet the needs of the healthcare system. Additionally, there is a pressing need to train early-career scientists in implementation science and health services research, emphasizing mentoring and interdisciplinary collaboration to build a workforce capable of addressing these challenges. By focusing on these areas, the HEAL Initiative can make significant strides in improving pain management and reducing the burden of chronic pain on individuals and the healthcare system.

Priorities shortlist

These priorities highlight the pressing need for implementation science and health services research to improve patient care and ensure that evidence-based practices are effectively integrated into primary care and other clinical settings. By focusing on these priorities, we can make significant strides in enhancing healthcare delivery so that it improves the quality of life for individuals seeking care for chronic pain conditions.

1. **Integrating implementation principles broadly into all phases of clinically focused research is needed to ensure delivery of evidence-based pain interventions in real world settings.**
    - **Couple 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) 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 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. This approach is essential for optimizing healthcare delivery and ensuring that patients receive the best possible care.
    - **Design and conduct implementation research aimed at dissemination and sustainment.** In the early phase of translational research for pain, apply frameworks (e.g., Designing for Dissemination and Sustainment (D4DS)) to both the pain intervention and the implementation strategies needed to support implementation to maximize potential for dissemination and sustainability. Similarly, later stage research needs to specifically test strategies to achieve wide-scale spread and sustainment.

2. **Develop and optimize secure, equitable, digitally-facilitated approaches for delivering and implementing effective multi-modal pain care using extant and emergent tools that improve clinical, process, health services, quality outcomes, and have a primary care and population health focus.**
    - Strategy selection and refinement should emphasize patient centeredness, health literacy, engagement and adherence as well as consider use of a variety of tools including: electronic health records, apps, artificial intelligence, machine learning, and related tools.

- Successful approaches will enhance primary care-based multidisciplinary team (primary care providers, physical therapists, integrative medicine providers, and mental health professionals) care planning and coordination, workflow efficiency, and use of validated approaches to maximize therapeutic alliance and shared clinical decision-making.
- Proven effective digital strategies from non-clinical contexts such as direct-to-consumer communication models should be critically considered and tested.
- System evaluation should consider usability, access, patient and provider experience, as well as potential to aggravate disparities among demographics with limited digital fluency and access.

3. **Prioritize clinical- and community-embedded research, hybrid implementation-effectiveness studies, and pragmatic trials for real-world impact, scalability, and sustainability:**
    - **Align research with real-world clinical care metrics.** Research that evaluates and aligns the effectiveness of metrics meaningful to various stakeholders, 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 diverse settings.** Research that gauges the implementation and outcomes of integrated care models in various healthcare 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.

Parking lot

1. **Establish training programs that are specific to the needs of early-career scientists interested implementation, embedded trials and other real world research approaches to enhance patient care.** Developing training programs that emphasize mentoring and interdisciplinary collaboration is essential for building a workforce capable of addressing the challenges in pain management and health services research. These programs should focus on practical skills and competencies needed for effective implementation and dissemination of research findings, ultimately improving patient care. Investing in the next generation of scientists ensures that we have the expertise needed to advance healthcare practices and improve patient outcomes.
2. **Studying adaptation to better understand core and peripheral and more flexible components of implementation strategies to optimize delivery and sustainability across different settings.** Empirical testing of pragmatic packages of implementation support strategies (i.e., “bundles” of strategies for implementation along with the trial results to make them more adaptable). Focus on adaptable and sustainable care interventions that retain core evidence-based components.

3. **Address patient and provider behavior change and engagement for long-term adoption of pain treatments and care pathways with existing evidence.** Science of behavior change critical to advancing and focusing this work.

Intersection of pain and substance use Subcommittee

Subcommittee co-chairs:
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Joanna Starrels, MD, MS, Albert Einstein College of Medicine

I. Relevant background, assumptions, and definitions

Pain and substance use, including substance use and use disorder, are inextricably intertwined. Ditre et al (1) have proposed a reciprocal model of pain and substance use, wherein these conditions interrelate in the manner of positive feedback loop such that pain promotes substance use (through a variety of mechanisms, including self-treatment due to the substance's acute analgesic effects), and in turn, substance use further exacerbates pain (through a variety of mechanisms, including withdrawal and hyperalgesia). Research investigating this intersection must also consider comorbidities and contextual factors that are common to people with pain and substance use. These include co-occurring mental health problems such as depression, anxiety, and PTSD, medical conditions (e.g., joint or spine disorders, HIV) and use of multiple substances, which is the norm rather than the exception. Individuals' lived experiences are also shaped by their multiple and intersecting social categories or identities (e.g., Black woman, transgender disabled person), as described by Kimberlé Crenshaw (2). These intersecting social categories may impact how individuals interact with systems of power like the healthcare system, and influence experiences of intersectional stigma. Additionally, as Booker et al (3) have described, pain is fundamentally an issue of health iniquities which lead to disparate outcomes, in that social factors such as inequities in healthcare lead to pain and to disparate outcomes in individuals living with pain. Individuals with specific identities (e.g., Black race, woman gender, older age) have higher rates of pain and disproportionate barriers to accessing pain and substance use treatment.

II. Statement of the problem

As scientists, we are often encouraged by peers and funders to focus on one problem to the exclusion of all others. As is evident from the description in the prior paragraph, this is not possible when studying pain. We recommend that the NIH embrace the complexity inherent in studying pain. People are not the sum of multiple individual problems, and treating them as such reduces the impact of research findings. Rather, addressing the whole person is critical to moving the scientific needle in individuals with co-occurring substance use and pain. We provide cross-cutting priorities with specific recommendations that facilitate this whole-person approach. We anticipate some of these cross-cutting priorities will be relevant to other domains and sub-committees (e.g., health equity across the lifespan). In addition, we recommend five content-specific priorities.

III. Cross-cutting priorities

We recommend that the NIH HEAL program:

a. Require research programs to incorporate equity considerations into pain research. Lack of data on disparities and iniquities leads to the challenge of "we can't address what we don't know." *We propose* a three-pronged approach to address this challenge:

1) Improve the scope and quality of data that are collected. We recommend mandating the collection of data elements key to answering disparities questions, such as Social Determinants

of Health. *We also recommend* approaching research questions at the intersection of pain and substance use that employ designs that mitigate disparities (e.g., a large prospective cohort study like the Framingham Heart study, preceded by meaningful community engagement and earning trustworthiness, while providing appropriate monetary incentives for participation commensurate with or above a livable wage). Qualitative methods can be particularly valuable for engaging the voices of people with lived experience, and generating hypotheses for, or providing context in response to, quantitative analyses. Investigators should be encouraged to carefully consider the negative repercussions of approaches that may perpetuate disparities (e.g., unnecessary age limits in clinical trials, Artificial Intelligence using biased data inputs). Outcomes should be patient-centered include equity-specific outcomes (e.g., equitable access to treatment).

2) In the meantime, *we recommend* engaging experts in health equity to guide approaches to analyzing existing data, and to ensure optimal data quality when new studies are proposed.
3) *We also recommend* working with experts in community-engaged research to raise the bar for the definition of meaningful community engagement. This is a crucial way to center the voices of people with lived experience, identify patient-centered research questions and outcomes, and earn the trust from the community necessary to co-create the large-scale studies that will be needed to answer the biggest scientific questions. This would include developing funding mechanisms or modifying existing mechanisms that promote community engagement as early on in the research process as possible (e.g., idea generation), something that can be very difficult to accomplish within a traditional NIH grant (e.g., R01).

<u>b. Require investigators to measure co-occurring conditions and identities in pain research.</u> Minimally, this can be accomplished by assessing substance use, mental health comorbidities, and identities (e.g., race, gender, disability status, Veteran status) in all individuals. These data can then be used to assess the impact of these conditions and identities on pain outcomes.

<u>c. Encourage scientific questions that inform policy.</u> Policy work per se is beyond the scope of NIH research priorities. *We therefore recommend* supporting research at the intersection of pain and substance use that has the potential to inform policy. This research should include studies of the impact of existing public policy on health outcomes pertaining to the intersection of pain and substance use, studies that contextualize policy analyses (e.g., through community-engaged research and qualitative studies), and implementation studies that can lead to policy change to improve outcomes.

<u>d. Incorporate both treatment and prevention into priorities.</u> *We recommend* that studies examine the reciprocal pathways by which pain can lead to and exacerbate substance use and substance use can lead to and exacerbate pain. There is a need for studies that examine mechanisms, prevention, harm reduction strategies, strategies to engage people in care, and interventions aimed at treatment of pain and substance use-related problems.

<u>e. Encourage the use of existing data sets whenever possible.</u> *We recommend* that the HEAL initiative find ways to encourage investigators to utilize existing data (e.g., HEAL CDEs, phenotyping data). These data are expensive to collect and can often provide insights into co-occurring conditions and identities, with some notable exceptions (e.g., Social Determinants of Health is a HEAL CDE only as of 2023).

f. Facilitate ways to assess pain intervention outcomes that are patient-centered and long-term. *We recommend* studying patient-centered outcomes, particularly functional outcomes, pain tolerability, quality of life, mental health and suicidality, and other outcomes important to people with lived experience of pain and substance use. *We recommend* that HEAL create mechanisms that allow for intervention studies with long-term outcomes. While chronic pain and substance use are chronic conditions and often life-long, most extant studies of pharmacologic and non-pharmacologic treatment in the pain and substance use literatures focus on only short-term, proximal outcomes (e.g., pain or retention in medication for opioid use disorder [OUD] treatment at 6 months). Examination of long-term, more distal outcome measures can shed light on complex temporal relations between the pain and substance use, and highlight important protective and risk factors. Use of cohort or registry studies is one solution, in addition to novel grant mechanisms or new uses of old grant mechanisms that could be used to address this challenge.

IV. Content-specific priorities (the "shortlist")

a. 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. These populations can include demographic groups (Black Americans, individuals who are Hispanic/Latinx, American Indian, Alaskan Native, or Pacific Islander, older adults, people with disabilities, people who have lower incomes, people who live in rural areas, Veterans) and/or conditions (people with cancer, sickle cell disease, HIV, PTSD, serious mental illness, multimorbidity). These groups often have higher-than-average rates of opioid prescribing (e.g., opioids remain first-line cancer pain treatment and is more common in older vs. younger adults), differential access to medications for substance use treatment (e.g., Black and Hispanic/Latinx patients are more likely than white patients with OUD to receive methadone, and less likely to receive buprenorphine), polypharmacy (e.g., opioids + benzodiazepines + gabapentinoids + muscle relaxants + other disease-directed treatments), non-prescribed opioid use and OUD, comorbid non-opioid substance use (e.g., Veterans experience higher-than-average rates of alcohol and stimulant use). Additionally, these populations are disproportionately impacted by health disparities (e.g., Black Americans less frequently receive non-pharmacologic pain therapies). *We recommend* prioritizing these populations in research on the intersection of pain and substance use. Mechanistic understanding is further described in IV part c below (precision medicine). Epidemiology can be addressed as described in III part a, above. 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, see recommendation part e), and buprenorphine (as an initiation strategy, or switching from full agonists to buprenorphine), and interventions that address mechanisms of the reciprocal relationship between pain and substance use are key. 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. *Finally, we recommend* engaging health equity experts with expertise in community engagement to ensure collection of high-quality data collection as described in III part a above.

b. Develop a program of research that explicitly investigates and addresses the interconnectedness of pain and substance use, including non-opioid substance use. *We recommend* specific acknowledgement of the reciprocal relationship of pain and substance use, and soliciting research that expands existing knowledge of mechanisms. *We also recommend* developing treatment approaches that address existing knowledge of bidirectional mechanisms, and therefore, address pain as a perpetuator of substance use (e.g., due to acute analgesia), substance use as a perpetuator of pain (e.g., due to withdrawal and hyperalgesia). We recommend studying approaches to treatment of acute and chronic pain in people with substance use disorders, and treatment of substance use disorders in individuals living with chronic pain, in different treatment settings. Treatment approaches that are transdiagnostic are of particular interest to treat both pain and substance use together (e.g., behavioral interventions that directly address pain, substance use, their reciprocal relationship, and shared determinants). Intervention studies should ask whether and how pain impacts substance use outcomes, and whether and how substance use treatment impacts pain outcomes. *We also recommend* integration of personalized approaches as described in IV part c, below. While prior work has prioritized opioids, in the coming years we recommend additionally focus on investigating the interconnectedness of pain with use of non-opioid substances, including alcohol, nicotine/tobacco, cannabis, and stimulants, as both directions of the reciprocal pain-substance use relationship are understudied yet common (i.e., pain motivates use of these substances and their use can impact and exacerbate pain).

c. Expand research on personalized prediction/prevention and treatment of pain and substance use. With regard to prevention, *we recommend use* of existing data and development of prospective cohort studies as described in III part a and III part e. These data may allow for mechanistic studies that could include pre-clinical to clinical translation, or clinical studies that go beyond association to causation. Further collection of specific phenotyping data combining biological metrics (e.g., genomics, Quantitative Sensory Testing, neuroimaging) with psychological and social metrics (e.g., patient-reported outcomes) will also be warranted. Ecological Momentary Assessment (EMA) is particularly useful when studying proximal and longitudinal patient-reported experiences such as pain and cravings. With regard to treatment, *we recommend* considering biomedical (e.g., medications, surgery) as well as behavioral (e.g., personalized feedback) approaches, and investigating optimal ways to combine such approaches (e.g., through SMART trials). *We also recommend* developing and implementing personalized interventions, and engaging patients and provider perspectives on these personalized interventions using human-centered design. Additionally, this work can be augmented by pain phenotyping, which can be used to investigate individual responses to treatment, and will lead to important insights about which treatments work for whom, when, and why.

d. Evaluate the therapeutic benefits and harms of commonly-used non-opioid substances, including but not limited to those with potential for misuse or addiction. *We recommend* specific investigation of substances that are commonly or increasingly used for pain and substance use disorders that also have potential for misuse or addiction, such as cannabis/cannabinoids, ketamine, gabapentinoids, benzodiazepines, kratom, and psychedelics. These substances are increasingly utilized for treatment of pain and substance use disorders, are mostly not FDA-approved nor regulated, and are often perceived as having reduced risk as compared to opioids. *We recommend* epidemiologic surveillance studies that answer the questions: who is using them, patterns of use (products, frequency of use, motivations for use), , and what benefits and adverse effects are experienced? Non-addictive novel treatments for other

indications (e.g., obesity and its complications) such as GLP-1 agonists should also be investigated for pain and substance use disorders in this way. *We also recommend* clinical trials of these substances to rigorously evaluate their safety and efficacy, as well as other important clinical considerations (e.g., dosing, self-directed or clinician-directed use for pain, and co-use with opioids).

e. Support research on non-pharmacologic approaches to treatment and prevention of co-occurring chronic pain and substance use. These include primarily behavioral approaches (e.g., approaches that derive from cognitive behavioral therapy and mindfulness-based interventions, and incorporate pain psychoeducation, such as Acceptance and Commitment Therapy, mindfulness-based stress reduction, and other pain self-management approaches), movement-based approaches (e.g., yoga, physical therapy) and complementary and integrative health approaches. *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. This could also include trials that assess various combinations of the above (i.e., multimodal pain treatment). SMART trials could be a particularly useful method to identify impactful combinations of non-pharmacologic treatment, opportune times to incorporate pharmacologic treatments, and personalized treatment approaches based on phenotyping (see IV part c above).

Appendix 1: Parking lot

Additional potential priorities were discussed throughout our process (see Appendix 2). Those of sufficient importance are included here.

There is a need to examine the cost-effectiveness and scalability of interventions addressing pain and substance use in a wide range of healthcare and community settings.

There is a need to identify, develop, implement, and disseminate effective interventions to educate and support the workforce (e.g., physicians, nurses, pharmacists, peers, community leaders, etc.) to reduce stigma and improve quality and delivery of SUD and pain care in different settings.

Non-Addictive Pain Therapeutics Development

Subcommittee co-chairs:
John Markman, MD, Eli Lilly & Company
Ted Price, PhD, University of Texas, Dallas

Relevant Background, Assumptions and Definitions:

Non-addictive pain medicine development is a cornerstone of the HEAL Initiative. Twelve funding opportunities have been created to address this major need with an allocation of more than $520M in funding. Many of these programs seem to have been very successful, leading to identification of new targets and development of new drugs that are now making their way into clinical development programs.

One of the main themes emerging from the first years of the HEAL initiative is an increased emphasis on human molecular data for identification of new targets, refinement of models, and support of existing development programs. Given the way technology is changing, and early success of PRECISION and RE-JOIN, this theme should be prioritized for discussion. Preclinical drug discovery programs have also been successful.

Overall, there have been many important successes for HEAL funded programs including INDs filed for drugs and devices, new companies developed and funded to commercialize technologies, and major advances in our understanding of human pain conditions.

Statement of the Problem:

The clinical treatment of nearly every type of chronic pain remains a challenge. Outside of migraine, few new drugs have been approved for pain in the past 2 decades, and the number of Americans living with chronic pain continues to increase. More efficacious, safer, and better tolerated therapeutics of all kinds are needed for the treatment of chronic pain. Early-phase clinical trials focused on translating mechanistic insights into novel analgesics continue to be a major innovation bottleneck to bring new non-opioid analgesics to patients.

Priorities Shortlist:

Research Priority 1: ***Invest in discovery research with a focus on human biology to identify high-quality targets for development of new effective pain therapeutics.***

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. While limited studies to date have shown strong conservation of many cell types, and even some cell states, they have also revealed differences in target expression that predict clinical failures and differences in underlying disease mechanisms from animal models. Investment in more work in this area is necessary for identifying 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.

Research Priority 2: ***Support the development of a new generation of highly predictive disease specific animal and cellular models informed by recent advances in our understanding of human biology.***
Advances in our understanding of the human nervous system and how it changes in people who have chronic pain disorders creates enormous opportunity for "back translation" of these human findings to create a new generation of highly predictive animal and cellular models. These models will be necessary for testing basic science hypotheses, validating therapeutic targets, and testing efficacy of new drug candidates. These models need to consider important biological variables like age which does not receive enough attention in the field.

Research Priority 3: ***Support early phase clinical development through detailed phenotypic characterization of prevalent chronic pain conditions to allow the matching of clinical features to potential targets.***
Phenotypic characterization of homogeneous chronic pain populations in highly prevalent syndromes is required to deliver on the potential of mechanism-based analgesic development for the vast majority of patients. One consensus focus area is the need for improved study population definition in osteoarthritis, peripheral nerve entrapment, and chronic low back pain subtypes. Matching clinical features such as a medical history, sensory profile, and pain quality to targets is in need of refinement. Platform trial approaches that build on the EPPIC-Net first generations learnings offer one practical way to improve the assay sensitivity of clinical trial methods. In addition to improvements to study population definition, more sensitive endpoints relevant to the outcome of modulation of pain intensity are needed.

Research Priority 4: ***Support the development of novel analgesic modalities.*** **In contrast to other areas of clinical development, the potential benefit of antibodies, peptides, and mRNA therapeutics 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. Diverse routes of administration, neuroanatomic and neuromodulatory targets, and dosing regimens with these technologies will overcome the serious liabilities of small molecule analgesics. Strategic investment in these technologies in refractory pain populations in phase 1B would help emulate the success observed in oncology and infectious diseases in chronic pain populations.

Appendix 1: Parking Lot
Research Priority 5: Support small Business innovation for pain to drive the development of new therapeutics
In order for new treatments to make it to the marketplace, commercialization will eventually be required. Small business innovation is a driver of innovation in commercialization and many small companies funded by HEAL initiative grants have now progressed from the pre-clinical to clinical development stage. Investment in small business research can be a key driver of innovation in development of new therapeutics for pain. A public/private partnership to support investment in this area would be advantageous

Optimization of existing and novel interventions to improve pain management Subcommittee

Subcommittee co-chairs:
Claudia Campbell, PhD, Johns Hopkins Medicine
John T. Farrar, MD, PhD, Hospital of the University of Pennsylvania

Relevant background, assumptions, and definitions

Although it is very clear that the development of new and expanded therapies for pain is a significant area ripe for research, it is also important to pursue effective pain management by applying our rapidly expanding clinical evidence to the prevention and treatment of pain across the lifespan using a wide variety of modalities. As our understanding of the multiple approaches to pain evolves, it has become increasingly clear that we have significant gaps in our knowledge of the issues preventing the widespread adoption of effective therapies and in the evidence necessary to guide the appropriate use of an expanding pool of pharmaceutical, psychological, physical and integrative medicine therapies for pain.

Although we have an expanding understanding of the underlying etiologies and mechanisms that can result in pain, we are not yet able to make accurate mechanistic diagnoses in our patient based on their symptoms and signs, even with a growing array of genetic and metabolomic biomarkers being investigated. To reach our goal of providing comprehensive care plans tailored to individual patient needs, we need to fill the gaps in accurate mechanistic diagnosis, extensive data on the mechanism of action and efficacy of treatments, and appropriate outreach to the practitioners seeing patients and the incorporation of patient innate differences and preferences into the treatment plan.
While many of these issues cut across all areas of pain research, this summary outlines the research priority areas necessary to maximize the utilization of current clinical evidence across the spectrum of the concept of types of pain prevention namely primary prevention which prevents pain from occurring (e.g. healthy lifestyles or the shingles vaccine), secondary prevention (e.g., treating pain as it occurs targeting a resolution of the pain and prevention of any transition to chronic pain), and tertiary prevention (e.g. aiming to minimize the consequences of chronic pain once it has developed). Notably, most pain research has concentrated on tertiary prevention, neglecting the critical early stages where intervention could yield the most significant benefits. Although healthcare providers may recognize the risk of developing chronic pain, there is a substantial gap in evidence to inform prevention strategies, particularly in childhood, where many chronic pain issues originate. By developing research approaches to optimizing the application of evidence-based prevention strategies and therapeutics, we can enhance patient outcomes, improve quality of life, and establish a more holistic framework for pain management.

Statement of the problem

The significant gaps in the provision of effective prevention and management of pain include not only more research but also leveraging existing clinical evidence to maximize the efficacy of multimodal approaches to prevention and treatment to individual patient needs. Current pain management strategies rely on generalized, one-size-fits-all models that fail to account for the complex and varied nature of pain, resulting in suboptimal outcomes. Pain arises from multiple mechanisms, yet most treatments target only a limited number of pathways and yield moderate, variable effects. While there is a significant amount of data on the efficacy of individual treatments, there is a substantial gap in our

understanding of how and when to initiate, modify, and maintain multimodal therapies to maximize patient benefit.

Priorities Shortlist

Proposed research priority 1. ***Evaluate whether an individualized, tailored treatment based on pain and treatment mechanisms improves efficacy.*** Despite widespread belief in the effectiveness of tailored treatments based on specific mechanisms or patient characteristics, there is a paucity of empirical evidence to support superiority of a tailored approach compared to more generalized one-size fits all approach. A considerable knowledge deficit exists concerning the mechanisms that underlie pain syndromes and current therapies, and how these align with the varied responses seen in patients. To bridge this gap, it is imperative to deepen our understanding of pain etiology and mechanisms that lead to chronic pain, mechanisms of non-pharmacological interventions, and how pain mechanisms intersect with mechanisms of proposed interventions. This priority should therefore determine biological, psychological, and social underpinnings of prevalent pain management approaches, identify individuals at risk for poor outcomes, identify responders and non-responders to interventions, and determine if a personalized approach based on mechanisms, risk and responder profiles yields superior results compared to standardized evidence-based care. Through this endeavor, we strive toward a model of evidence-based personalized pain care that refines treatment effectiveness while curtailing unwarranted interventions—a step forward in achieving a more sophisticated approach to pain management.

Proposed research priority 2. ***Evaluate if incorporating patient choice in the selection of study treatments and individualized outcomes improves engagement, adherence, clinical effectiveness, and more equitable pain management strategies.*** There is a significant gap in our understanding of the impact of patient choice in selecting both study treatments and targeted individualized outcomes on patient engagement, adherence, clinical effectiveness, and equitable pain management strategies. Current clinical trials typically employ standardized protocols with little room for accommodating patient preferences. This approach often overlooks the complexities encountered in real-world settings, such as patients' desired benefits, lifestyle needs, and cultural or personal values. To gain better insights into the role of patient choice, it is essential to design clinical trials that incorporate patient preferences and patient-centered outcomes.

Despite this potential, few studies have thoroughly investigated the effects of providing patients with options regarding their treatment choices or personalized healthcare goals. Research into how patient preference interacts with various factors—including pain mechanisms, psychosocial profiles, and access to healthcare services—may reveal ways to develop more effective and equitable pain management strategies.

Future research should prioritize systematic investigations to evaluate whether therapies that are aligned with patients' outcome preferences, required efficacy level, and side effect tolerability result in better health outcomes when compared to standard approaches. These studies should be inclusive of diverse populations and aim at overcoming barriers related to patient healthcare needs, access, and adherence.

Proposed research priority 3. ***Develop pain prevention strategies to prevent the development of chronic pain throughout the lifespan especially during key transitions during the life course.***
Historically, pain research has largely been devoted to treating established pain symptoms and associated disabilities—categorized as tertiary prevention. The are important gaps in our knowledge about pain mechanisms and treatment needs during crucial life course transitions especially during puberty, adolescence to early adulthood, perimenopause, and later life (e.g., retirement, bereavement). Each of these life transitions brings unique biologic, psychosocial and structural risk factors for chronic pain or risk factors for acute to chronic pain transition. Developing multilevel targets for prevention should be included in this priority.

To actualize this research priority, there is a pressing need to develop and refine screening tools and biomarkers that can accurately predict the likelihood of developing persistent or recurrent pain, as well as identify those individuals with greater resilience. A substantial gap persists in our comprehension of both primary prevention (preventing the onset of pain) and secondary prevention (managing acute pain to prevent chronicity), as well as understanding which patients are most likely to experience less pain or recover more consistently (resilience).

Primary prevention encompasses diverse tactics such as vaccination (e.g. shingles), 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 (e.g., stress reduction, physical activity). The objective is to concentrate on developing and testing primary prevention strategies that prevent development of pain. Secondary prevention involves addressing pain immediately after its onset—whether due to trauma or predictable situations like post-operative scenarios—with an emphasis on preventing acute episodes from progressing into chronic conditions. Current data shows that the level of pain experienced and psychological factors heighten the risk for chronicity; however, there's an absence of evidence on whether treating these factors prevents chronic pain. Thus, research should focus on testing if reducing risk for development of chronic pain using tailored interventions across the biopsychosocial spectrum (pharmacological, behavioral, physical, social, etc.) prevents development of chronic pain and promotes resolution from acute pain.

Proposed research priority 4. ***Develop and test evidence-based guidance on the appropriate initial pain therapy and the order and timing of multimodal approaches to achieve maximal benefit for the individual patient without undue risk*.** These approaches need to be developed in a culturally appropriate manner that includes testing in low resource settings, diverse populations, across the lifespan, and sex and gender. 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 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. As described in Priority 1 such studies should identify predictors 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 take into account the growing concern that certain therapies may potentially cause harm—such as the risk of developing opioid use disorder or the current animal study based concern that reducing inflammation may impede the natural healing processes and ultimate level of pain resolution. Therefore, also understanding risk of the interventions, particularly their influence natural recovery and pain resolution mechanisms, is critically important.
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-pharmacological treatments (NPTs) 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's essential to define the role of NPTs within the broader context of other concurrent therapies as primary or complementary strategies that aim to minimize pharmacologic intervention while promoting recovery from pain.

Proposed research priority 5. **Development and prospective evaluation of novel research designs to improve study assay sensitivities of individual clinical trials and the translation of the research results to real-world outcomes that include those who are underrepresented in pain research and treatment.** To enhance clinical study validity (both clinical trials and causal inference prospective cohort studies), and ensure the clinical applicability of research findings, there is a need to promote and evaluate innovative research designs. An area of focus should be the integration of learning health systems with patient-reported outcomes and detailed histories of prior treatments and their effects. A key feature of the learning health system is that collecting comprehensive data directly from patients can enrich medical records with valuable insights into treatment efficacy and potential side effects. In addition to formal studies using this data, AI-generated care summaries of this data could play a significant role in informing healthcare decisions, but their impact has not been studied.

Novel designs will also be needed to explore different modalities for delivering care. This includes telehealth services, hybrid models that combine in-person and virtual care, outreach via text messaging, and AI-driven solutions. Building on Priority 3 above, it is also crucial to consider how preventive measures and treatments impact individuals throughout their lives, examining how intervention type and timing influence lasting responses. Given the ongoing difficulties described by researchers in the conduct of pain clinical trials, innovation in study designs remain important to assess other priority areas including: 1) direct evidence pertaining to appropriate therapy selection aimed at maximizing effectiveness while minimizing side effects; 2) the incremental benefits derived from sequential multimodal approaches; 3) effective combinations of therapies tailored to enhance patient care outcomes.

Treatments should be designed to *better matched to the needs of those who are under-represented* in pain research and treatment. Multilevel interventions that address structural and systemic barriers to safe and effective pain treatment should be designed and include issues related to access to care, equity focused interventions, and addressing the root social causes of pain risk and poor outcomes. Culturally

transformative approaches that engage and empower those with lived experiences of pain to live full and productive lives should be prioritized. Evaluate the responsible use of AI and novel technologies to support pain management across the life course and to provide equitable and accessible care. Prioritizing inclusivity in research is paramount to ensure that studies specifically aiming to meet the needs of vulnerable or historically underserved groups and are designed with input from patient about what is required. Broadening the scope of research to include various populations and settings—such as urban, suburban, rural environments; age-specific groups like children, elderly, individuals of childbearing age; minoritized populations; and consideration of access to resources—is essential for addressing our countries diverse healthcare needs.

Appendix 1: Parking lot [For all proposed priorities that did not fit above, along with additional examples that may add additional understanding. This does not have a limit as to the number but should be formatted similarly to the one above.

1) Study Design Issues to consider in the evaluation of pain-related proposals:
    a. Adequate length follow-up after pain treatment to know if the response is durable.
        i. A clear definition of intermediate outcomes can be used to shorten trials that are not able to continue for the full effect of treatment to manifest. The relationship of such outcomes to the real goal must be defined and documented.
    b. Defined methods for inclusion of appropriate participants by determining the patient's pain phenotype and assessing the likelihood of response to the treatment is effective.
    c. The selection of outcomes is based on what is important to the patients experiencing the pain. It will provide clinically applicable information easily transmitted to the broad range of healthcare practitioners involved in treating pain.
    d. Selection of clinical trial methodologies that maximize the use of available data or the collection of new data and are most likely to provide a clinically interpretable answer. Examples include:
        i. SMART, Pragmatic, and other research methods.
        ii. Studies of the barriers and facilitation of acceptance and maintenance of therapeutic involvement, especially with non-drug treatments.
        iii. Planning for evaluation of the fidelity of treatment and adjustments to improve this is not adequate.
        iv. Studies using learning health systems and data registries.
    e. Patient partners should be included to clarify the issues to be studied and the relevant outcomes and contribute to the design to enhance recruitment and patient engagement.
2) Promote multidisciplinary research, including experts outside pain and medicine, to maximize the use of novel technologies and basic science discoveries.
    f. Computer scientist
    g. Neuropsychology/Psychiatry
    h. Engineers and lifting teams for built-in job safety.
    i. Community engagement to address
        i. Acceptance of therapies
        ii. Access to therapies

iii. Support for essential therapies in areas where they are not provided.

Training and Workforce Development Subcommittee:
Subcommittee co-chairs:
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Cheryl L. Stucky, PhD, Medical College of Wisconsin

Relevant background, assumptions, and definitions

Over 20 percent of US adults (<60 million people) experience chronic pain with a cost of ~$600 billion each year. Chronic pain typically consumes patients' lives into a vicious cyclone that disrupts their physical, emotional, intellectual, and social health. Given the life-impacting, broad and encompassing effect of chronic pain, far more research spanning from underlying mechanisms to patient treatments must be done. A fundamental foundation of all pain research is the availability of a workforce capable of and committed to conducting a broad range of science, from basic mechanisms, to treating patients. Ensuring such a research workforce requires training everyone, in all roles and at all levels, including academic, clinical constituents, industry and the community. One of the most challenging features of pain research, education, and treatment is that pain is a symptom common to most diseases and medical conditions, thus no subspecialty or discipline "owns" it. More than 50 years of research, including missteps and breakthroughs, highlight the requirement that numerous disciplines and subspecialties collaborate in developing pain researchers if we are to understand and effectively treat pain, particularly chronic pain. While the pain field values interdisciplinary collaboration, this model is too often thwarted by the siloed institutional structures generating future scientists who might choose to pursue a career in pain research. While a single lecture on pain might be included in a neuroscience course, few undergraduates are exposed to a full course, let alone a series of courses, on pain. A full course on pain is also rare at the medical student level in the US, as is the case for graduate students or postdoctoral fellows. In the field of pain, the science that contributes to the field builds on a large body of knowledge that is complex, multidimensional, and translational and often integrates expertise from other areas (e.g., clinicians' input into the pre-clinical models of a pain condition). Thus, in addition to coursework in pain and its treatment, adequate preparation of the pain researcher requires mentoring by experts in the field and training within an interdisciplinary team experienced in pain and its treatment. Despite its longstanding interdisciplinary nature, the pain field has not managed to fully integrate researchers in some critically relevant areas, such as epidemiology and implementation science. And finally, while pain is an inherently patient-centered experience, the field has not developed a sophisticated and systematic integration of people with lived experience (PWLE) with pain into the research and training enterprise.

Three <u>common themes</u> cross all priorities this subcommittee identified:

1. **Involving PWLE in training, research centers, and educating the public is vital**. PWLE with pain offer a unique perspective for all aspects of the training and research enterprise through their daily experiences living with chronic pain. To effectively integrate this valuable expertise, it is necessary to 1) train researchers to effectively integrate PWLE as equal partners, and conversely, to 2) train PWLE to effectively engage with pain researchers at all stages of career maturity.
2. **Mentoring of trainees and mentors at all career stages.** Healthy, robust mentoring is a vital part of trainees' success and advancement in the pain research pipeline. Yet few programs or existing pain institutes focus on healthy, effective mentoring. Further, experienced pain scientists can benefit from learning how to mentor their trainees most effectively at all stages of development.

3. **Pain education is fundamental for all trainees in pain research from T0 to T5, and for pain clinicians**. Yet there is very little focus on providing quality, robust, consistent education about the underlying mechanisms driving chronic pain from the peripheral to central nervous systems, or on effective pain treatments or how they work. All trainees and institutes will benefit from focused efforts to improve pain education.

A related concept, brought up in another subcommittee, is the need for more efforts to *promote education and knowledge about pain across intersecting identities*. There is a need for increased education and training about pain across the life course and how it affects those of diverse racial, ethnic, gender, disability and other minoritized communities. Intersecting identities may confer cumulative risk/protective factors and targeted educational approaches for training providers, as well as patients, caregivers and the broader community (e.g., schools, nursing homes and other organizations) are needed. In addition, it is essential for research studies to routinely *measure* key social, structural, and biobehavioral determinants of health -including for those studies that are not specifically focused on these topics to better contextualize findings and understand gaps in evidence.

Statement of the problem

The lack of a dedicated scientific "home" in most universities and the NIH has contributed to a lack of unified and consistent support for pain research and training in the US. As a result of this inconsistent investment, the field of pain research is inadequately equipped to effectively address the public health challenge of pain and its treatment. At present, the current infrastructure is insufficient to produce and support the workforce required to advance pain research, to prepare all clinicians to treat pain, and to encourage the public's informed participation in treatment and discovery. The research pipeline is essential for the ongoing advancement of knowledge and treatment, thus strengthening this pipeline at every stage is vital. Effective pain care, education, and research requires interdisciplinary collaboration and is now just beginning to embed people with lived experience of pain at some stages of program development. Currently, most pain researchers are not experienced in engaging with the public, particularly fully integrating people with lived experience of pain into all phases of the research and education enterprise. While most institutions have pain treatment centers, many of these are fractured by departmental structures and finances which impede the true integration of subspecialties. Some institutions have pain research groups built from infrastructures that support the interdisciplinary collaborations and training programs required to develop and sustain success, however, these programs are limited in number, experience funding inconsistencies, and are splintered by the typical institutional departmental structure that affects pain treatment centers.

Pain Research Workgroup Priorities

PRIORITY #1: Support comprehensive fellowship, career development, and mentored research scholar awards for individuals across all career stages, including non-U.S. citizens. In order 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.

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, programs should be developed that raise awareness for the diverse array of job opportunities that exist in pain science. Programming should be developed for individuals of all ages – from school-aged children to established investigators with no prior 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, career-stage specific programming is needed. All such programs should prioritize stage-appropriate skill development that may include training in the following topics: mentoring, engagement of PWLE, establishing and maintaining cross-disciplinary collaborations, implementation science, leadership skills, entrepreneurship, and public relations/communications. Engaging PWLE in the research process and designing career development programming specifically for this group of individuals ensures that PWLEs become equal partners who are embedded into the fabric of pain research and that outcomes are truly patient-centered and impactful. Career development programs for faculty must address the unique time and financial challenges faced by academic scientists – particularly physician scientists – offering institutional support for protected research time, partial matching of funds, and longitudinal training that integrates research with clinical practice. Furthermore, 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 T4 and T5 translation is significantly under-represented in the pain field. The application process for these programs should be streamlined to reduce the up-front burden and make program acceptance more equitable.
An identified need was to establish training programs that are specific to the needs of early-career scientists interested implementation, embedded trials and other real world research approaches to enhance patient care. Developing training programs that emphasize mentoring and interdisciplinary collaboration is essential for building a workforce capable of addressing the challenges in pain management and health services research. These programs should focus on practical skills and competencies needed for effective implementation and dissemination of research findings, ultimately improving patient care. Investing in the next generation of scientists ensures that we have the expertise needed to advance healthcare practices and improve patient outcomes.

PRIORITY #2: Develop Translational Pain Research Centers of Excellence. In order to expand the T0-T5 translational pain research across the US, efforts should support the development of new pain centers that will harness novel resources at new institutes and expand and strengthen existing pain centers. The lack of robust NIH support for interdisciplinary pain research centers is a critical barrier to advancing future pain research given the widespread prevalence and devastating impact of pain in the U.S. Much like cancer, pain research requires a robust "center" approach that fosters integration and collaboration across multiple disciplines and financial units within institutions. Existing pain research centers have been built on dedicated institutional and individual leadership, limited NIH funding that includes training programs, and a culture of mentorship that supports individuals at all career stages. These centers are essential in advancing pain research and care by offering comprehensive training, nurturing interdisciplinary collaborations, and guiding trainees and early career faculty toward independence. It is imperative that both the number and size of these centers be increased if the US is to amplify the pain research workforce. Translational Pain Research Centers of Excellence should create cross-disciplinary collaborations, involve a broad range of trainees at all stages of maturity, and include human research with direct clinical translation. This would enable existing comprehensive pain centers to develop or

expand core resources, establish research collaborations across the full translational spectrum (T0 to T5), integrate clinical research within clinical settings, expand opportunities for preclinical research, and support the development of pain curricula. Such centers are expected to create educational and career development programs covering pain science, treatment, leadership, and entrepreneurship for learners at all career stages. It is crucial that both new and existing pain centers actively involve PWLE as members of the collaborative interdisciplinary team across all aspects of research, education, and clinical programming. Centers should actively strive to increase the visibility of chronic pain as a public health concern through interaction with the public at local through national levels. Centers would also foster collaboration with other existing centers (cancer, diabetes, pediatrics) and partner with industry to conduct efficacy and effectiveness trials and perform research on rare conditions.

PRIORITY #3: Train pain researchers in effective methods for educating diverse learners, including the public, health care providers, and patients, in understanding pain, its prevention, and appropriate use of evidence-based pain treatments.

Our understanding of pain and its treatment has advanced significantly in the past fifty years, yet understanding of these advances by the public and non-pain providers is quite limited. Thus, the translation of knowledge from the laboratory to the clinic and health care system is incomplete and, in part, contributed to the over-prescribing of opioids and the opioid epidemic. Too often pain management is equated with opioid management, even by providers who recently completed their training, as few medical schools offer comprehensive education about pain and its treatment to medical students. There is a critical need to equip experts in pain research and treatment with the skills and knowledge required to communicate effectively with the public and health care professionals and systems to ensure that evidence-based pain care becomes the standard of care. This will not only promote better understanding of pain but also encourage more informed consumption of pain treatments and promote patient-centered care. Since most pain is managed by non-pain professionals, it is essential that pain researchers and clinicians partner with PWLE to learn about how communities impacted by pain obtain information on effective pain management and how to partner in amplifying awareness of pain, its impact, and its effective management. Pain researchers and clinicians require training in providing accessible and effective educational programming that empowers the public in requesting and non-pain clinicians in implementing evidence-based pain management. Additionally, training pain researchers in engaging persons with lived experience (PWLE), developing leadership skills, fostering entrepreneurship, and enhancing communication with the public will help improve both the delivery and accessibility of pain care, thereby bridging the gap between public awareness and professional competency in pain management.

Parking Lot Priorities

1. Compensation for trainees and PWLEs needs to be addressed.
2. Institutional resources limit job opportunities and NIH support for career development mechanisms and Translational Pain Research Centers of Excellence will encourage institutional investment. Institutional investment, which occurred for Cancer Centers, will validate pain as a field and increase the perception, especially among early career scientists, that it is a viable career.
3. Develop better partnerships with industry and encourage cross-fertilization.

4. Develop mechanisms that support physician scientists in fields such as Anesthesiology and Physical Medicine & Rehabilitation, which feed into clinical pain medicine yet often do not have dedicated programs to facilitate research training and strong internal financial pressures to produce clinically. This is a critical issue, as the number of physician-scientists has remained stable over recent years.
5. Expand the number and breadth of career development programs for graduate students across many disciplines to work in pain labs.
6. We need more study sections with expertise in pain research.
7. Training mechanisms for PWLEs who want to train in pain research.
8. Training of mentors and mentees in effective mentoring relationships; this is particularly important to ease the transition from mid to senior career. Ideas generated in the breakout room at the workshop included creating mentoring circles and peer-to-peer workshops which could be local, national, or international.
9. Protected/funded time for mentors, who are already spread thin, and many are overwhelmed with training, funding, and institutional demands.
10. Training in transferable skills for working in industry: regulatory affairs, clinical trials, science communication, product development, financial management.
11. Expand the number of positions on existing T32 training programs and fund additional programs dedicated to pain research. Dr. Wandner presented compelling data on the small number (6) in 2022 compared to alcohol use disorder (27), Alzheimer's (35), and diabetes (37).
12. The development of small grants would be helpful for investigators at all career stages.
13. Consider a mechanism like the K99 that is for individuals earlier in their post-doc and provides funding for a period of post-doc and then resources to take with them to a new institution.
14. Develop mechanisms to provide salary support for individuals wanting to complete an internship placement in a laboratory. This would address issues of economic accessibility, as most internships are unpaid.
15. Fund investigators rather than specific projects.
16. Fund workshops to develop the communication and community outreach skills for pain researchers.