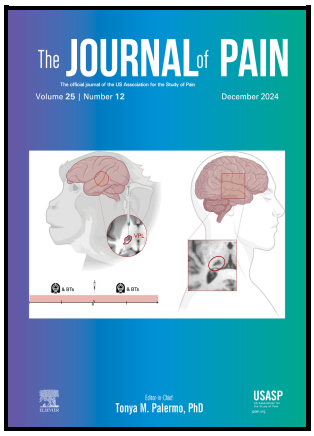

Research recommendations for the HEAL Initiative: a path forward for pain researchRunning title: Research recommendations for the HEAL Initiative

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Research recommendations for the HEAL Initiative: a path forward for pain research

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Running title: Research recommendations for the HEAL Initiative

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Abstract

Chronic pain conditions affect 24% of the US population and account for the greatest cause of disability, leading to tremendous suffering and lost productivity. 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. The NIH Helping End Addiction Long-term® Initiative (the NIH HEAL Initiative®) was launched in response to the opioid overdose crisis and set out to increase research and improve treatments for addiction disorders and chronic pain conditions. The HEAL Initiative® has made tremendous strides toward these goals since its initial launch in 2018. In 2024, the NIH convened a working group of external experts to assess its progress and strategize for the next five years of HEAL funding specifically for pain research. That process culminated in the production of an accepted Report containing these ten Research Priorities and five Core Principles to guide NIH leadership in planning and funding pain research within the HEAL initiative over the next five years. Here, we present these recommendations for consideration by the wider pain research community and invite further active discussion.

Perspective

Chronic pain remains a major public health crisis in the U.S. that has been insufficiently addressed. The research priorities outlined here were created to build the HEAL Initiative's pain research portfolio over the next five years. The primary aims are to develop and advance treatments for chronic pain.

Introduction

The public health crisis of chronic pain affects 1 in 5 people worldwide[1] and impacts individuals, families, and society. Pain is a burdensome facet of many chronic diseases[2], which now affect over half of US adults[3], and chronic pain itself is considered a disease with its own pathological changes requiring unique, effective management strategies[1, 4]. Further, 20 to 50% of individuals who experience an acute pain event, such as trauma or surgery, go on to experience persistent pain[5, 6] Chronic pain has no cure, and individuals often experience pain for months, years or decades. Importantly, chronic pain conditions have varying etiologies and mechanisms. As such, understanding and addressing the complexity of chronic pain requires significant ongoing efforts to elucidate the factors that contribute to the risk and resilience for the development of and recovery from chronic pain.

The experience of pain and its impacts are highly individualized[7-10] and may change considerably over the life course[11]. In addition, the neurological mechanisms that make pain persist are often different from the pain's initial cause, such that removing the initiating cause does not necessarily mitigate ongoing pain. The risk for chronic pain is influenced not only by underlying biological factors but also by environmental, cultural, and lifestyle factors, and life experiences, all of which can interact[12]. Further, harmful biases and a limited understanding of pain from clinicians and the public can lead to stigma, poor pain care, and ultimately worse outcomes[13]. Thus, it is necessary to understand pain comprehensively, considering biological, psychological, and social influences. All these aspects should be addressed with research to improve care.

Research funding for pain was augmented substantially with the establishment of the National Institutes of Health's (NIH) Helping to End Addiction Long-term® (HEAL) Initiative. The NIH HEAL Initiative® is an NIH-wide effort with the mission to improve prevention and treatment strategies for opioid misuse and addiction and to enhance pain management. HEAL provides yearly resources in addition to the NIH's base appropriation, or usual funding mechanisms by individual Institutes and Centers. Within HEAL, the stated mission with regard to pain is "to reduce pain and the risk of opioid use disorder by developing safe and effective pain treatments 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 its early years, NIH program officials did not use a strategic planning process nor develop HEAL Research Priorities; instead, they were guided by the Federal Pain Research Strategy and by a 2017 series of "Cutting Edge Science Meetings to End the Opioid Crisis"[14]. Despite not having a targeted plan for HEAL, the first phase of HEAL Initiative funding has seen great progress, which is detailed in multiple publicly available annual reports. Since 2018, HEAL Initiative investments totaling over $3.9 billion have funded over 2200 research projects in all 50 states, and include 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 are currently under way[15]. In addition, HEAL has developed the Pain Therapeutics Development Program to support pharmaceutical development from target validation to Phase II clinical trials – which historically has been very difficult for academic labs to achieve within the existing pipeline structure. HEAL also supports real-world clinical trials and implementation studies to enhance use of safe and effective pain-management strategies[16]. Although outside of HEAL, the NIH Pragmatic Trials Collaboratory also provides critical infrastructure for clinical effectiveness studies and pragmatic trials of new therapeutics, many of which are HEAL supported.

The NIH also invested in the HEAL Data Ecosystem, a collection of resources and support teams that promote collaboration by making HEAL data available to researchers, healthcare providers, community leaders, policy makers, and advocates. Data collected in HEAL studies must be harmonized using common data elements (CDE) and are stored and accessed via the HEAL Data Platform. Workforce training and development has also increased with HEAL-funded programs. For example, HEAL doubled the number of postdoctoral positions at pain research centers in 2024, and its investment in the National K12 Program supports investigators at institutions without a pain research infrastructure who could benefit from a national mentoring team. Both these training programs connect researchers with people with lived experience of pain. This all represents remarkable progress.

In 2024, the NIH began to strategically plan for the next phase of HEAL pain research funding and convened a working group made up of external experts from across the pain research field. That group ultimately produced the HEAL Pain Research Recommendations that are the focus of this report[17]. The purpose of this manuscript is to highlight the recommendations that were submitted to and ultimately accepted by NIH HEAL Pain leadership. These priorities were

intended to guide the next phase of the pain research portfolio for the HEAL Initiative implemented by NIH leadership. Here, we present these recommendations for consideration and invite active discussion by the wider pain research community.

Methods

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 five to eight future-looking strategic research priorities that will advance the HEAL Initiative pain research mission for the next phase (approximately five years).

Specifically, the Committee was tasked with:

- Assessing the progress that 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 future 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; the co-chairs were selected by Directors of NIH Institutes. With support from the NIH, the co-chairs selected the eleven additional members of the Executive Committee (as described in Appendix 1) based on their scientific and/ or 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 each led by two co-chairs. These co-chairs selected additional members with pertinent expertise for each sub-committee (see Appendix 1). Each of the seven subcommittees hosted public online

workshops[14] to gather input from additional experts and the 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 (Price, Markman)
2. Biomarkers and predictors (Cruz-Almeida, Tawfik)
3. Optimizing interventions to improve pain management (Farrar, Campbell)
4. Implementation and health services (DeBar, George)
5. Health equity and pain across the life course (Kashikar-Zuck, Baker)
6. Intersection of pain and substance use (Merlin, Starrels)
7. Research workforce and training (Haythornthwaite, Stucky)

Request for Information (RFI)

NIH invited public input to inform research priorities through a HEAL Initiative Request for Information (RFI; NOT-NS-24-106) from June 24, 2024, to July 31, 2024. HEAL Pain Strategic Planning Executive Committee members were provided with de-identified summaries of comments relevant to the seven focus areas, which they considered during their deliberations.

Workshops

Each subcommittee held a workshop dedicated to its focus area, including scientific presentations and input from people with lived experience, followed by discussion and input from attendees. These workshops also presented relevant background on previous HEAL research in each research area. 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 its deliberations, including a list of proposed research priorities relevant to its focus area. Several subcommittees included in their summary 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 into a proposed unified list of 28 research priorities. Members of the seven subcommittees then used an online survey to anonymously rank these priorities based on their potential to advance the HEAL Pain mission and their feasibility. Results of that ranking were reviewed by the co-chairs of the Executive Committee, several were combined to generate a list of 16 top research priorities, which is available in Supplementary Materials. These 16 priorities were brought for discussion to the Executive Committee at an in-person meeting at Washington University in St. Louis, MO, on January 8-9, 2025. That meeting also included NIH staff and leadership, including then-NINDS Director Walter Koroshetz and then-OPPP Director Linda Porter, but all discussion and prioritization was conducted by committee members. On the first day, one subcommittee co-chair made a five-minute presentation of each priority, followed by 15 minutes of discussion by the Executive Committee for final consideration. At the conclusion of that day, all Executive Committee members (but no NIH staff) cast secret online rankings for each research priority. They were instructed to consider each priority's intended aim, timeliness, feasibility to complete in five years, appropriateness to HEAL, and its uniqueness. On day two, the Committee received the results of the rankings and deliberated in discussions that ultimately resulted in the distillation of ten scientific research priorities (in no particular order) and five associated "Core Principles" as described in the following sections. The initial charge from the NIH was to recommend five to eight HEAL pain research priorities. No priorities were excluded or rejected by NIH leadership. All materials produced during strategic planning remain available to current NIH leadership.

Results

Work Group Recommendations

Core Principles

The following "Core Principles" were developed to enhance the value of pain research, increase rigor, and ensure translatability to the public. The Executive Committee recommends that HEAL incorporate these principles across its research programs to advance the HEAL Pain Mission.

1. **Partnerships with 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 partnership in training and career development awards, providing PWLE input into the training and research plans. Achieving this goal will require adequate training for investigators on how to engage PWLE in the research process, as well as adequate training and opportunities for PWLE to work with a research team.
2. **Education of the Public and Health Care Providers.** A common theme across subcommittees was the need to educate health care 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 (i.e. pre-licensure) health care 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 report data by sex, collect and consider age, and collect longer-term outcomes. 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-term 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. However, 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): gender, 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 potentially include adequate representation of SDoH.

- *Implementation* - Clinical effectiveness trials, pragmatic trials, and studies that embed implementation strategies using applied frameworks are needed. Research designs that intentionally support implementation and maximize the potential for translation of intervention strategies to settings beyond those conducting the research. In order to advance this area to improve patient care experiences, special attention is needed to identify factors that influence an intervention's fidelity and sustainability.

4. **Interdisciplinary teams should be formed to leverage unique skills and methodologies.** A team science approach will be required to fully realize the proposed research recommendations here. 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 together with experts 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 assess existing workflows and design better methods for scalability or sustainability, community engagement experts can best create partnerships with PWLE to ensure studies address PWLE's most pressing needs, and science communicators can provide outreach and education 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 invested considerable resources into supporting 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 hypotheses 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 opportunities to connect with PWLE or pain clinicians. 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.

Specific Identified Needs: 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, 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 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 improve 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. In addition to small molecules, these modalities can 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 can 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 PWLE 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 understanding pain mechanisms and developing treatments for ongoing pain. In addition, research has not effectively addressed differences in the pain experience over stages of the lifespan. The current

understanding of chronic pain conditions is evolving such that research can now take aim at preventing, mitigating, or even reversing some chronic 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.

Actualizing 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 identifying those individuals with greater resilience. It also will 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. Secondary prevention of chronic pain involves 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, cognitive-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 and its damaging impact on people's lives are preventable, including stigmatization and dismissal by health care 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 expand research on the 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, and/or target engagement 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 endpoints is 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 - for example, by reducing the heterogeneity of treatment effects, or guiding selection of trial participants most likely to respond. Biomarkers also can 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 require rigorous validation to demonstrate disease relevance and the ability to predict clinical outcomes before they are used in phase III trials. Predictive, prognostic and pharmacodynamic biomarkers likely will improve the therapeutic treatment potential of existing interventions in PWLE 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 PWLE'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 PWLE with a composite signature reflecting ongoing physiological processes. 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 PWLE can provide a detailed and individualized picture of a person'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 mechanistic signature of pain with the best available, most appropriate, and individualized treatment can then be tested against current standardized treatments.

Priority G

Develop and test the evidence base to determine an appropriate initial pain therapy, the order and timing of multimodal approaches, and non-specific effects to achieve maximal benefit for individuals 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 sociodemographic and clinical characteristics. 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 individuals' 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 people. 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, and their influence on natural recovery and pain-resolution mechanisms, is vitally 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 pain, function/disability, and responder profiles are critical.

Understanding of non-specific effects (e.g. placebo, therapeutic alliance, and PWLE's 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 PWLE-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, CDC, and the Healthy People 2030 project 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 PWLE and providers, helping to navigate their differing needs, is needed to evaluate whether such tools improve understanding, adherence, 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 PWLE 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/ or sometimes less-safe, e.g. opioid) treatments in clinical settings is critical for improving PWLE's outcomes and reducing healthcare costs, these must be coupled with aligned implementation of evidence-based viable alternative approaches (sometimes with less risk, such as exercise) to pain management. By focusing on coupled implementation/ de-implementation strategies that prioritize primary care and involve multiple stakeholders, including clinicians, payers, PWLE, and leadership, we can ensure that resources are allocated to more effective and evidence-based treatments, ultimately enhancing clinical care.

Importantly, these studies should also focus on integrating implementation principles broadly

into all phases of clinical research and include strategies and investigation aimed at dissemination and sustainment. Further, studies need to now go beyond testing efficacy of existing treatments, including testing of implementation effectiveness and sustainment of the intervention.

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:

Pain and substance use, including substance use disorder, are inextricably intertwined. Researchers have proposed a reciprocal model of pain and 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 the intersection of pain and substance use 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. These intersecting social categories and identities may impact how individuals interact with systems of power like the healthcare system, and influence experiences of intersectional stigma. Additionally, pain is fundamentally an issue of health inequities that 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.

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. Highly impacted populations include demographic groups (Black Americans, Hispanic/Latinx, American Indian, Alaskan Native, Pacific Islander, older adults, disability, lower income, rural environment, Veterans) and/or conditions (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, polypharmacy 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., opioids + benzodiazepines + gabapentinoids + muscle relaxants + other disease-directed treatments). 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, and interventions that address mechanisms of the reciprocal relationship between pain and substance use are key.

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 PWLE are effectively partnered with in the research process, ensuring studies are designed in a way that is most meaningful to these populations and results will reach community members.

Priority J

Support research on non-drug approaches to treatment and prevention of chronic pain, including in people with chronic pain 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., derived from cognitive behavioral therapy, mindfulness-based interventions, and 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, the 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 effectiveness-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 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.

Discussion

Several themes emerged from the discussions within the working groups and from the generation of the research priorities. It became clear that there were overlapping themes that arose consistently and independently within several subcommittees across multiple priorities. During the in-person meeting of the Executive Committee, these themes were pooled into what are now the Core Principles. These core principles are generally designed to guide high-quality and rigorous research, include broad outcomes, particularly social factors and function, and promote an interdisciplinary team science approach. The core values also highlighted opportunities to perform secondary analysis of existing databases and additional analysis on banked samples, particularly considering standardization across trials, and larger clinical observation and clinical trial studies. The ongoing use of shared data from multiple HEAL studies is made possible by the HEAL Data Ecosystem of support at the NIH.

Forging partnerships with individuals with lived experience in all HEAL initiative projects was deemed the first Core Principle. PWLE should be considered or included in research from basic science to clinical trials, and from design to dissemination. PWLE can provide unique insights into the research study design and interpretation of outcomes as well as reduce biases by researchers and medical professionals[9]. The accompanying commentary (Letzen & Falcon) will provide more detail.

With regard to the second Core Principle, Education of the Public and Health Care Providers: the need for increased, educated public awareness of pain arose overwhelmingly across subcommittees. The Principle emphasizes “the need to educate health care students, clinicians, and the public in the current science of pain and its management.” Outreach, education and broad dissemination of research, however, is beyond the purview of the HEAL Initiative and the NIH altogether. But, the Principle states, “this could be achieved by *studying* methods for dissemination of findings from ongoing research, methods to enhance education of entry-level (i.e. pre-licensure) health care practitioners, and public outreach campaigns,” reflecting the fact that *research of* public education or dissemination falls under the purview of the NIH. The Principle continues, “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,” citing those public-facing research modalities as ongoing opportunities for researchers to continue to increase community engagement in pain research.

We have presented here the unaltered, accepted Priorities. As described in the Introduction, the Priorities arose from summaries presented by each subcommittee, who provided in some cases vastly different levels of detail. The Executive Committee made every effort to make the Priorities reflect the intentions that arose in discussions. The intent was to provide high-level direction to move the HEAL mission forward while not imposing overly specific recommendations on how to achieve these aims. The Committee leaves the execution of these Priorities to the research community, and we encourage further discussion to guide the research.

Nearly all priorities were aimed toward developing personalized and tailored approaches to pain management. Clinically, this approach requires a comprehensive assessment that includes measures across the biopsychosocial spectrum. Pain is a complex, multidimensional disease process that is experienced differently by each individual and is associated with varying degrees of biological, psychological, and social factors that interact with life experiences[18]. Chronic pain not only leads to reduced function and increased disability, but is often associated with psychological distress, anxiety, and depression[19-21]. It has become clear that 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 psychological and social experiences[20, 22, 23]. Several research recommendations recognize this complexity and call for adequate phenotyping of individuals using multimodal data including biological, psychological, social, and functional measures. People with co-occurring pain and substance use are highlighted as meriting special consideration given that these conditions have an important bidirectional relationship.

Integrated biosignatures, including biological markers in combination with psychosocial, demographic and self-reported data, are also clearly important in a personalized medicine approach and have emerged in medicine as having the potential to screen for the risk of disease, assist with diagnosis, predict prognosis, and evaluate treatment response[24]. The group discussed the classical biological markers but expanded and highlighted the need to consider psychosocial and other patient-reported outcomes together with classical biological markers. This broader conceptualization aligns with integrated biopsychosocial signatures, which move beyond isolated biomarkers to capture the multidimensional nature of persistent pain[25]. Indeed, the HEAL initiative has developed a biomarker program, and several large biomarker studies

are currently being completed[12, 25-29]. The research priorities[30] described in the current study focus on a variety of biomarkers and have been incorporated into numerous priorities.

How, when, and why treatments are applied may be critical to their outcome and are key principles of a personalized medicine approach. The priorities outlined here propose testing models of care, including timing of intervention delivery. There has been a focus on several principles in pain management including a patient-centered approach[31, 32], shared decision making[33], and a mechanism-based approach[34] yet these models have not been rigorously tested in clinical studies. These models all have a strong theoretical base and are often used clinically. However, it will be important to identify whether using novel models of care provides better outcomes than the current standard of care.

It was also clear through discussions that there is a need to test effectiveness of interventions and implementation methods in real-world settings, for both pharmaceutical and non-pharmaceutical treatments. Randomized, placebo-controlled trials generally test intervention efficacy under ideal conditions and often eliminate participants with co-morbidities. However, individuals with chronic pain rarely have just one pain condition and often have other health co-morbidities[35-37]. Thus, many of these individuals have not been included in efficacy trials conducted to date. In addition, randomized, placebo-controlled clinical trials often test single interventions and, by its nature, treating chronic pain usually requires a multimodal approach. Having broader inclusion criteria for trial participants and testing real-world effectiveness is a way to expand the evidence base to better match the requirements of individuals seeking care for chronic pain. A related issue is that non-pharmaceutical interventions as a whole are underutilized.[38] Understanding methods to implement effective drug and non-drug treatments, often in a multimodal manner, while de-implementing low-value interventions, will be critical to improving healthcare for individuals with chronic pain.

It remains critically important to develop novel therapeutics aimed at underlying mechanisms that have the potential to be disease-modifying for those experiencing chronic pain. Further, these interventions need to not only be efficacious; they also need to be safe and non-addictive as they may need to be used for long periods. To do this, we need to focus on a better understanding of biomarkers and mechanisms, particularly in human tissues, and use novel delivery approaches. With HEAL, the NIH made a clear effort to fulfill the great need to develop novel therapeutics for the management of chronic pain. The priorities here were developed to

gain a better understanding of mechanisms in humans, provide the infrastructure necessary to develop novel therapeutics, and support novel target development.

Lastly, it was recognized that, to make sufficient progress, the pain research community needs to expand the research and practitioner workforce, particularly with respect to those who have expertise in all aspects of pain research, with areas of highest need likely to be in biomarkers, clinical trials, and implementation. Cultivating and supporting a robust and highly skilled pain research workforce will be critical to the success of the HEAL initiative and to improve outcomes for those with chronic pain.

Conclusion

In this paper, we have summarized the HEAL pain strategic plan accepted by NINDS council in May 2025 that will guide the next five years of the HEAL Initiative for pain research. These priorities are broad-based and intended to advance the HEAL mission 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.

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Conflict of Interest

YCA is Associate Editor for the Journal of Pain and Treasurer of the US Association for the Study of Pain, with no other conflicts. SZG receives an honoraria from the American Physical Therapy Association for his Editor-in-Chief role for the Physical Therapy Journal and Royalties from Rehab Essentials, LLC for an online pain science education module. JM is an employee of and holds equity in Eli Lilly. TJP is founder and equity holder in 4E Therapeutics, Nerveli, Ted and Greg's, NuvoNuro, and PARMedics. SPS received support for manuscript preparation from KAS and RG. JW is currently employed by and shareholder of Veeva Systems Inc. SPS, JEL, JMW, and LLP were formerly employed by NIH but all contributions to this manuscript have been provided in their personal capacities and are not associated in any official capacity with NIH.

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Highlights

- Here we present strategic pain research recommendations for the HEAL Initiative for the NIH.
- An NINDS Advisory Council working group developed the priorities with scientific and public input.
- 5 core principles and 10 research priorities aim to improve the lives of people with chronic pain.