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HEAL Initiative

NIH HEAL INITIATIVE

Helping to End Addiction Long-Term Initiative

Report to the National Advisory Committee to the Director

Walter J. Koroshetz, MD
Director, National Institute of Neurological Disorders and Stroke
For the HEAL Pain IC Directors,
and Co-Chairs Drs. Lindsey Criswell & Helene Langevin
June 14, 2024

NIH National Institute on Drug Abuse

Pain – A Public Health Crisis

Nationwide prevalence

50 million adults with chronic pain

25 million report severe pain daily

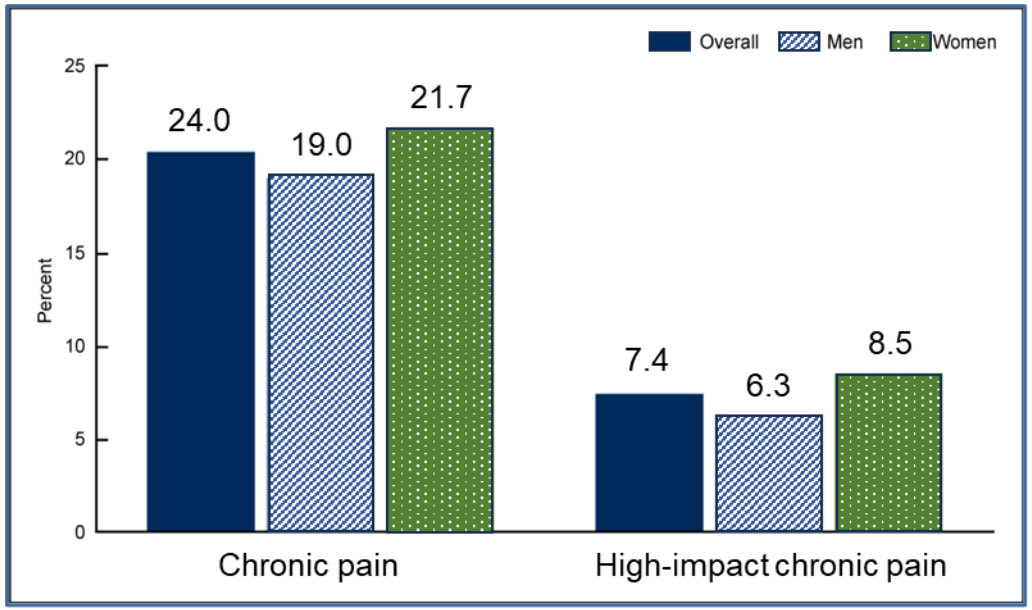
20 million with high impact chronic pain*

More rural than urban dwellers report pain

28% of rural & 16% of urban residents with chronic pain

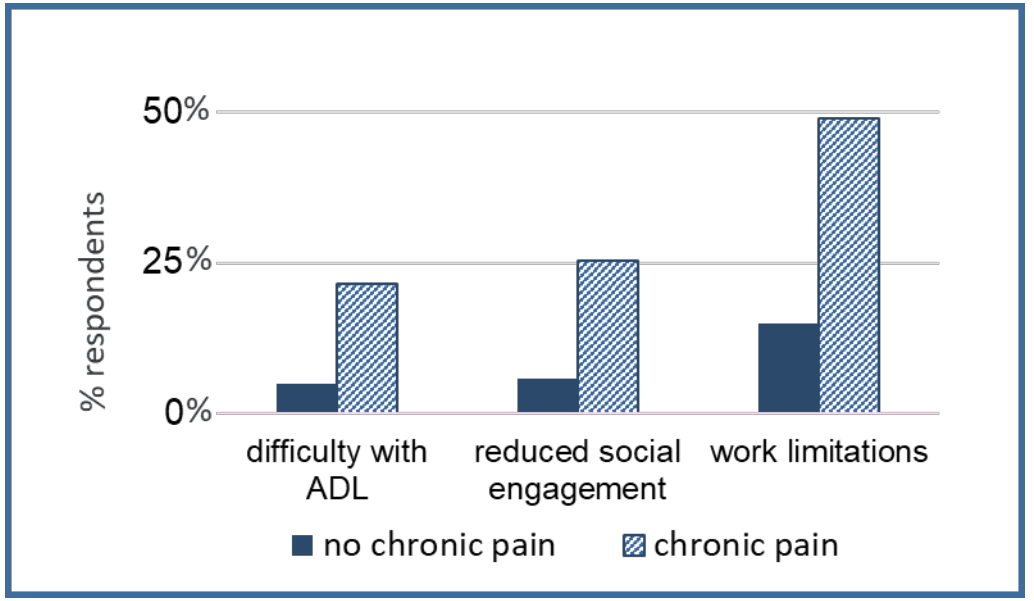
11% of rural & 6% of urban residents with hi impact chronic pain

More women than men report pain



National Center for Health Statistics: NHIS 2019
Pain and Therapy **volume 10**, pages287–314 (2021)

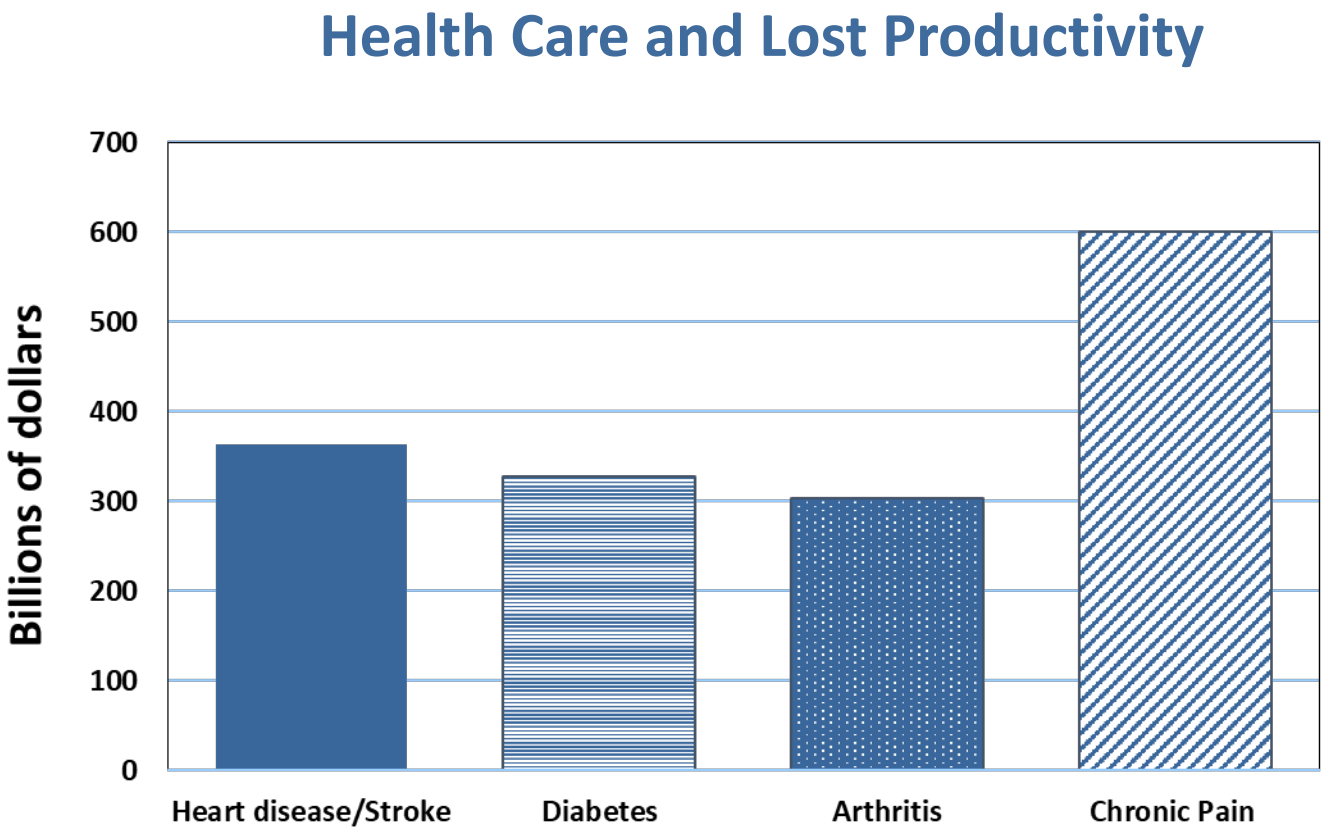
Chronic pain interferes with life



*high impact chronic pain = pain lasting more than 3 months that interferes with life (school, work, social life, etc.) https://www.cdc.gov/nchs/products/databriefs/db390.htm

Chronic Pain Costs in the U.S.

- Pain is the most common reason people seek medical care
- There are now more new cases of chronic pain compared to diabetes, depression, and high blood pressure
- ~ $600 billion/year in health care and lost productivity*



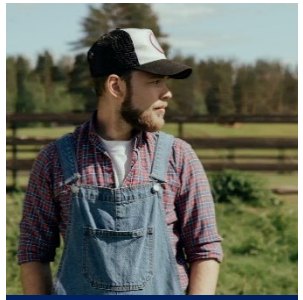
https://www.cdc.gov/chronicdisease/about/costs/index.htm

*2012 study - likely much more now

Why is Pain Management so Challenging?

Reimbursement

- Not insured
- Not covered



Access

- Geographic
- Demographic

Disparities

- Bias
- Stigma
- Population differences

Training

- Limited education
- Poor cross discipline integration disciplines

Work Force

- No protected time to mentor
- Mentors retiring

Complexity

- Overlapping pain conditions
- Other chronic conditions
- Different pain mechanisms

Lifespan

- Age related risks
- Age related changes

Research is aimed to develop treatments and inform evidence-based pain care

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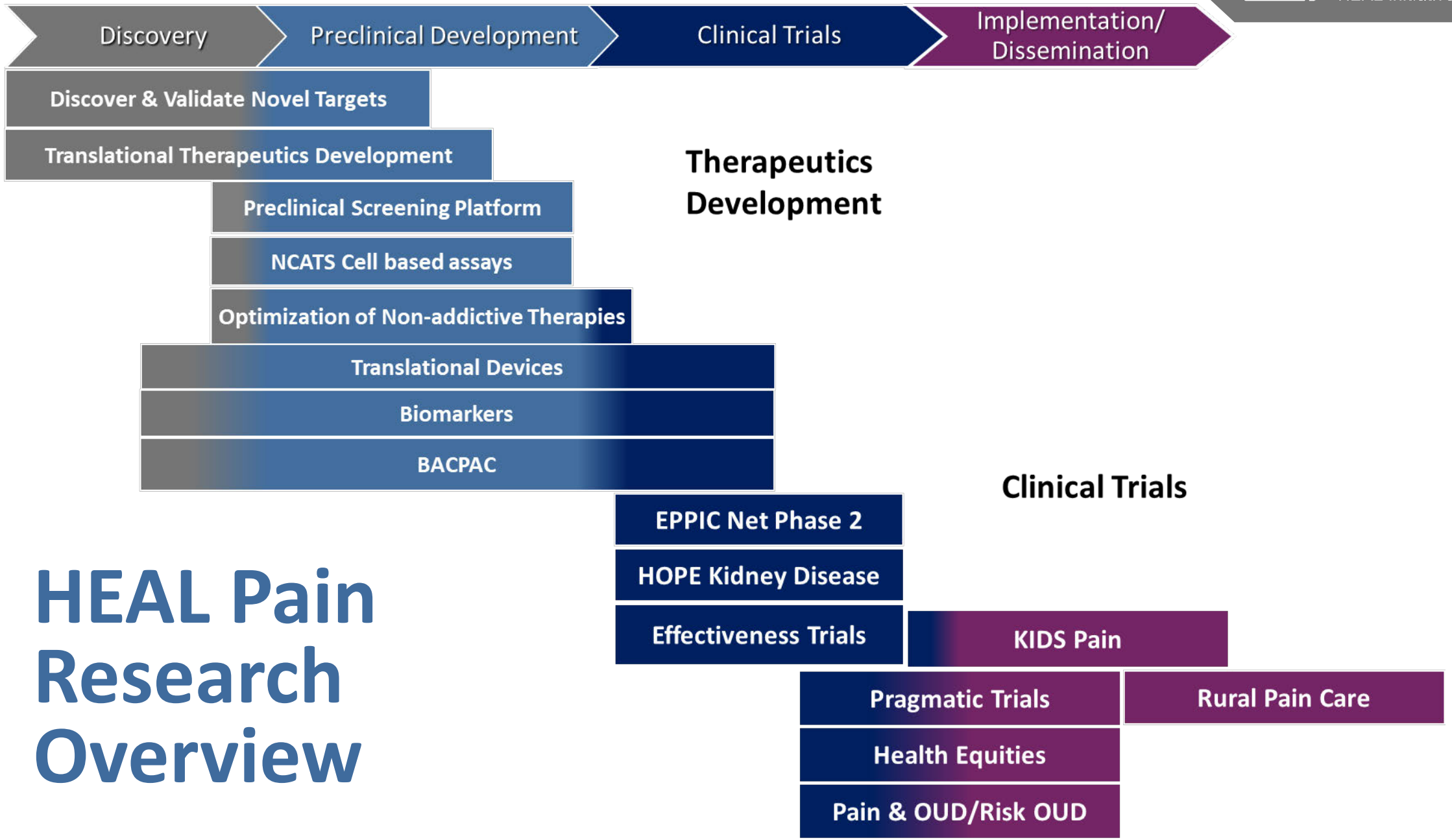


HEAL Pain Research Overview

Challenge: Lack of industry interest in pain therapeutics

- The industry pipeline for analgesics **declined 44%** in the past five years.
- Venture capital for novel pain drug programs were $860 **million** over the last 10 years compared to $35.7 **billion** for cancer.
- No drugs with novel targets approved in the last five years for pain other than migraine.

HEAL Therapeutics Progress

➢ NCATS collaborative partnerships

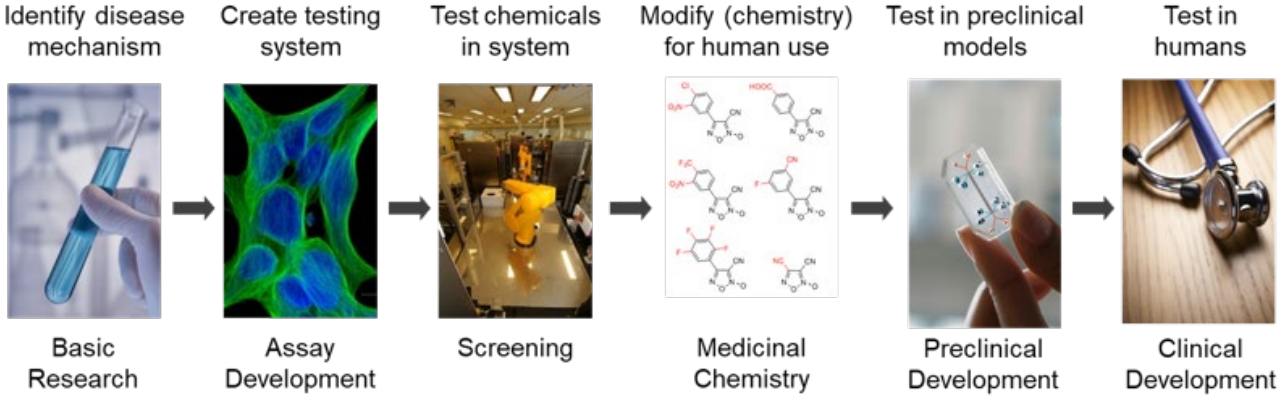
- Drug discovery - 14 projects
- Assy development – tissue chip and iPSC
- Compound library

➢ PSPP therapeutics characterization for acute & chronic pain

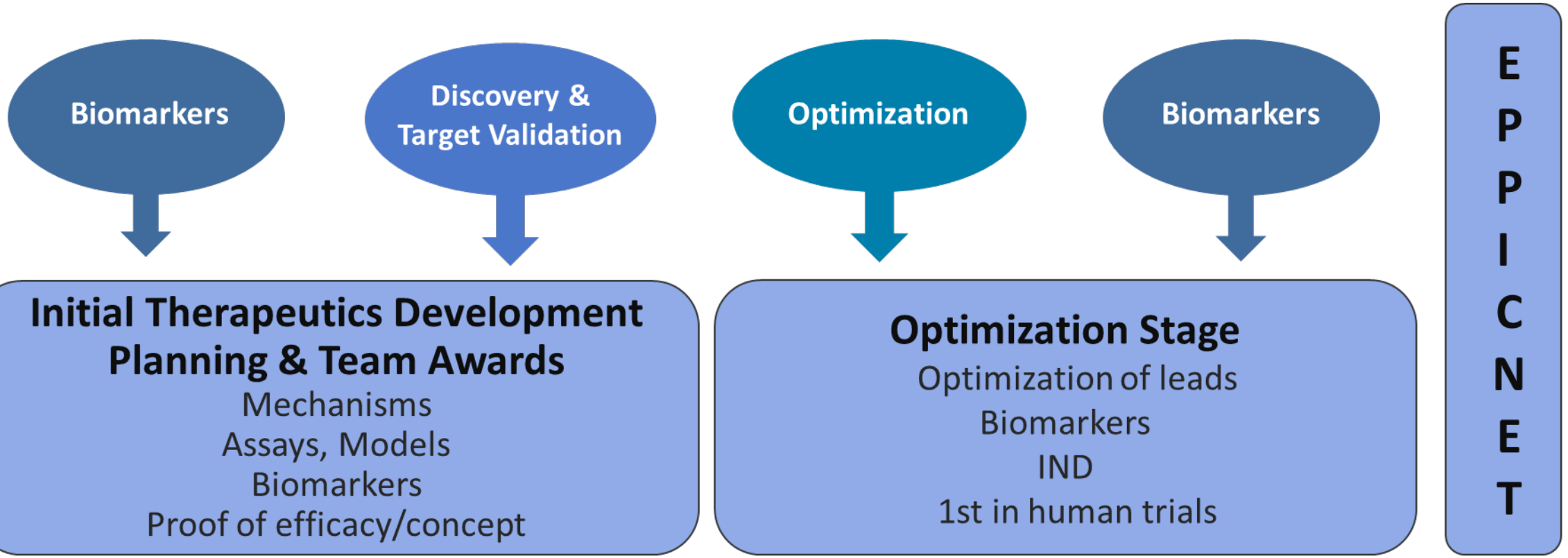
- >40 assets – *In vitro*, PK, behavioral models, side effects, specific disease models

➢ Pain therapeutics development

16 awards, 8 INDs/IDEs, 2-3 INDs expected



HEAL Analgesic Development Program

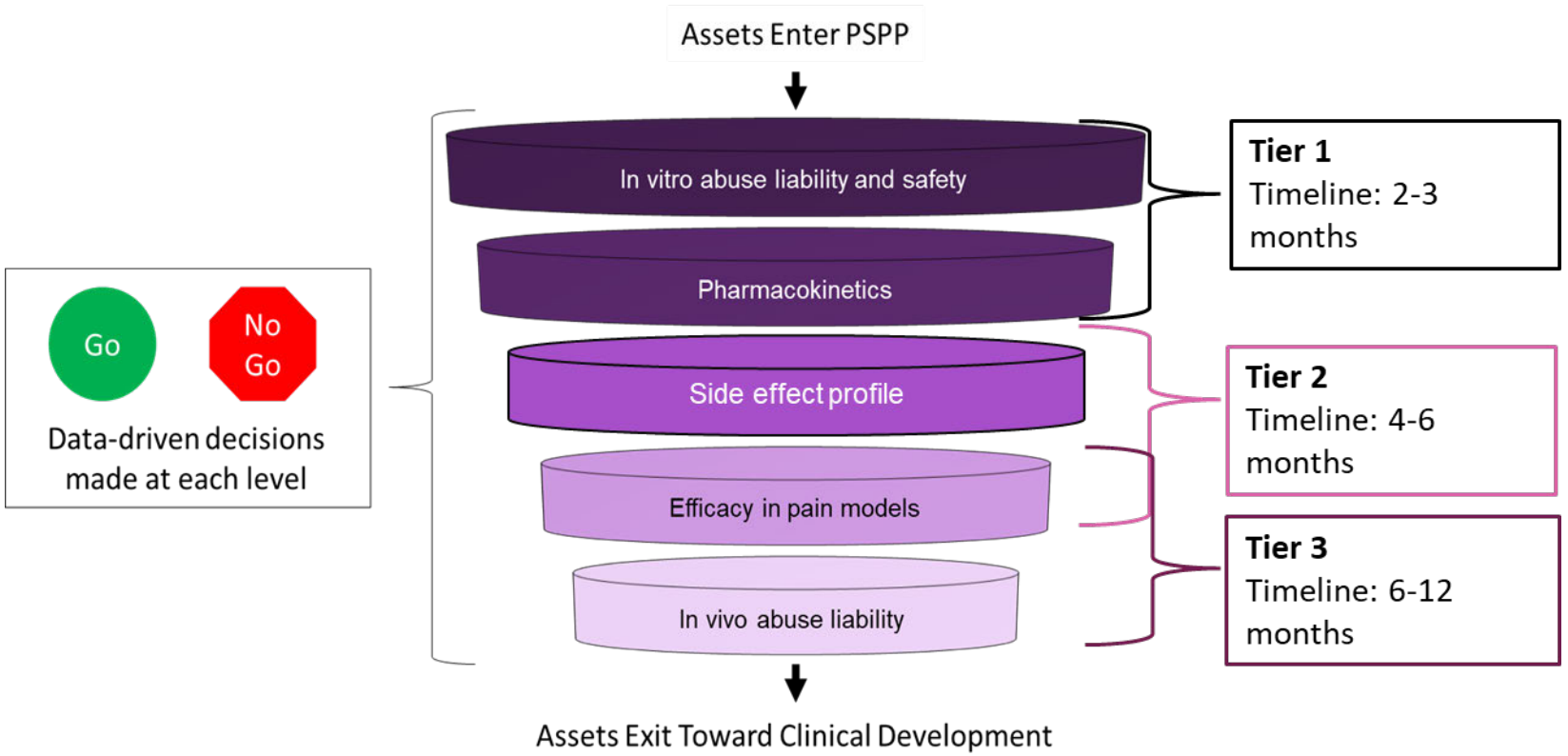


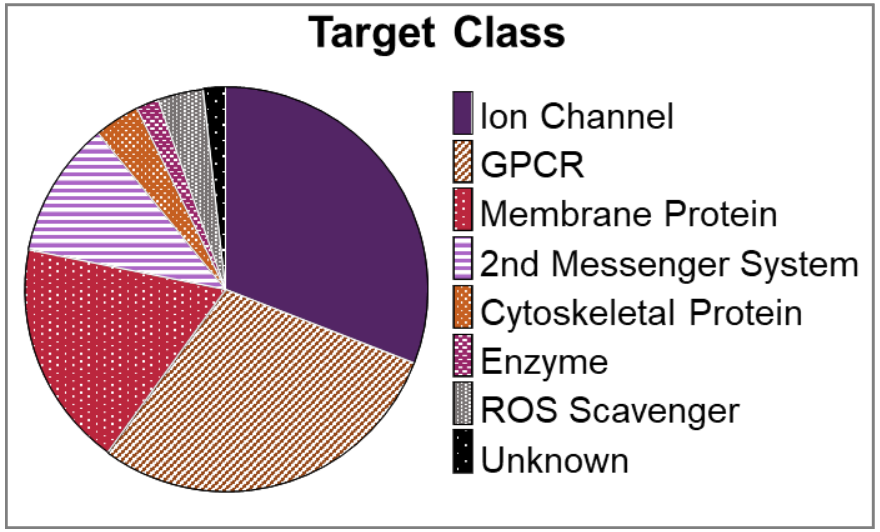
Small molecules, Biologics

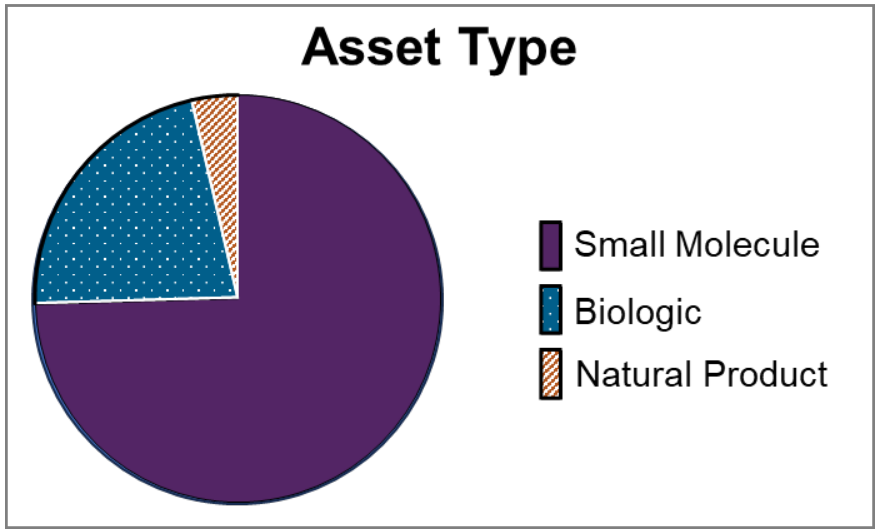
Lead compound

IND-approved, Phase 1 complete asset

HEAL Programs to Align animal models of pain to the human experience Preclinical Screening Platform for Pain (PSPP)







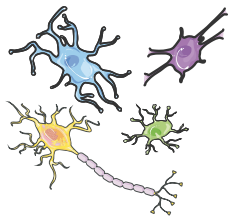
PRECISION Human Pain Network

Human tissues and cells to generate datasets of molecular signatures, cell types/phenotypes/signatures underlying human pain

Tissue Resources

- Transplant centers
- National Disease Research Interchange
- NIH NeuroBioBank Brain Bank Network

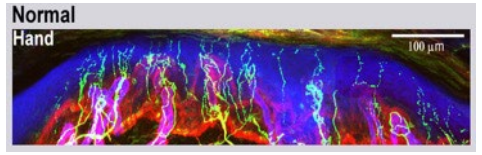
Diverse samples, specific pain & substance use conditions

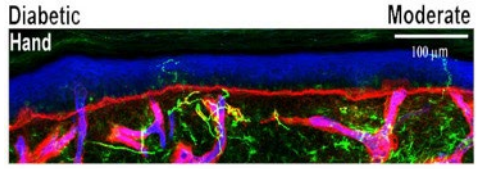


Across the nervous system

- Brain, brainstem
- Spinal cord, dorsal root ganglia
- Peripheral nerve bundles
- Skin

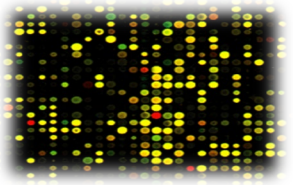
Tissue histologic phenotype mapping





- Neuronal, non-neuronal cells
- Slice preps

Transcriptomics & Proteomics



- Omics
- Functional phenotyping
- Tissue histology

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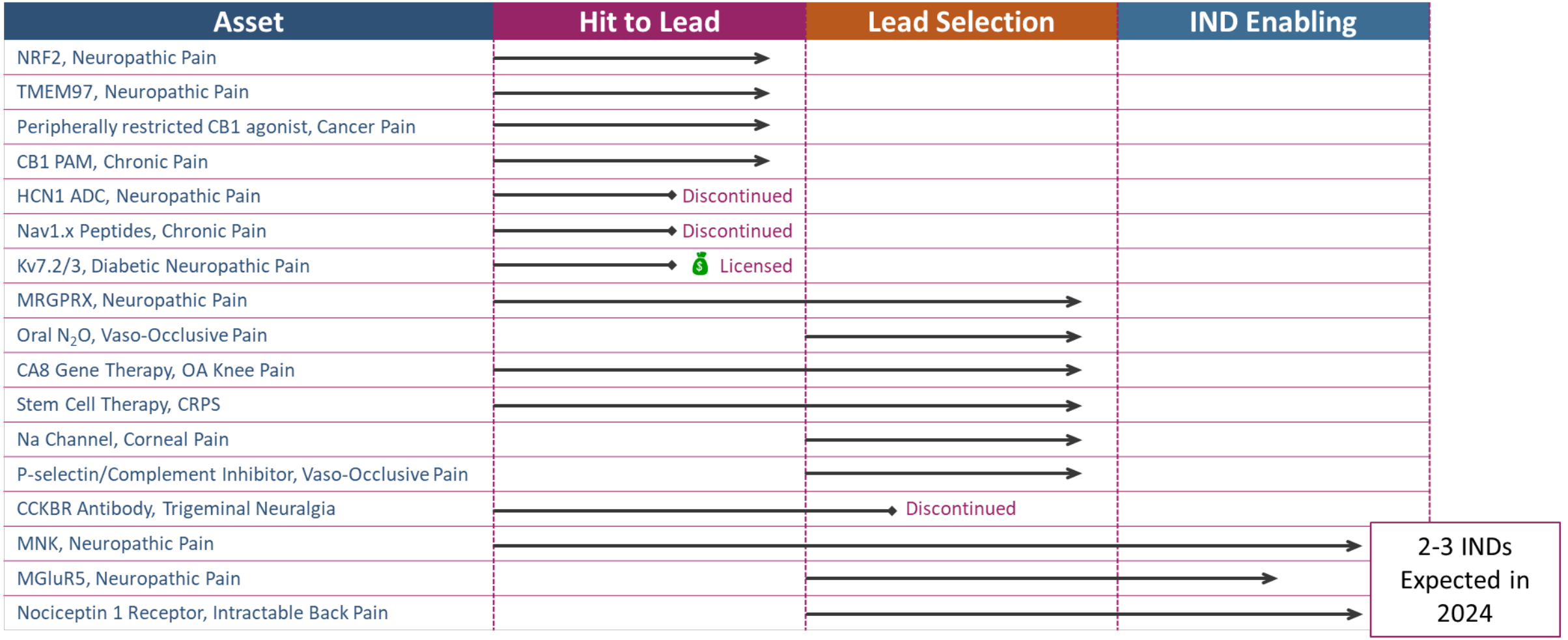
The PTDP preclinical pipeline is poised to advance several projects to Phase I



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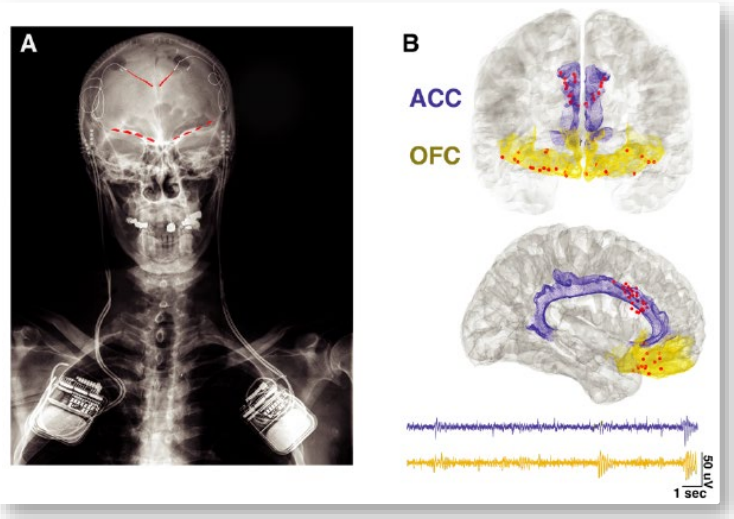
HEAL & BRAIN: Neural Signatures of Chronic Pain
Technology Development for Closed-Loop Deep Brain Stimulation to Treat Refractory Neuropathic Pain

- Determine neural correlates of increased pain states in patients with chronic pain to enable targeted DBS treatment
- Provide pain relief with neural stimulation
- Compare the efficacy of open-loop vs closed-loop DBS paradigms. 4 patients implanted
  - Medtronic PC+S
  - 3 with post-stroke pain
  - 1 with phantom limb pain
- Data collection:
  - >5100 pain reports and 9600 recordings in the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC)
  - Over 4800 minutes of continuous intracranial neural data
- Therapeutic Results:
  - Significant pain relief (>1 NRS) in 2 subjects
  - High impact relief (>5 NRS) in 1 subject

First-in-human prediction of chronic pain state using intracranial neural biomarkers

- implanted electrodes in anterior cingulate and orbitofrontal cortex
- neural recordings over months correlate pain state with neural activity
- neural data to decode high vs low pain state
- OFC activity may provide biomarker of chronic pain: potential to inform closed-loop DBS therapy for pain management



HEAL Effectiveness Research

Fisher: Integrated Approach to Pain and Opioid Use in **Hemodialysis** Patients: Buprenorphine and self-management	**Study completed**
Clifton: Individualized approach to opioid prescribing for women who undergo a **C-Section**	**Study completed**
DeBar: Scalable modalities for CBT-based treatments to persons with high-impact chronic pain in **rural and other underserved** areas	**Enrollment completed**
Ang: Complementary treatments and Registered Nurse support to motivate patients to use pain coping skills in combination with duloxetine	**Enrollment completed**
Vowles, Witkiewitz: Integrated **psychosocial treatment** in veterans with chronic pain who are taking buprenorphine for treatment of OUD	**Enrollment 80+% completed**
Rabbitts: mHealth pain self-management intervention for the **perioperative** period to target psychosocial risk factors and teach pain self-management skills	**Enrollment 80+% completed**
Cohen: Evaluate behavioral, pharmacologic, procedural interventions for **knee osteoarthritis** pain to find conservative and nonsurgical interventions before considering surgical interventions	**Enrollment 80+% completed**
Penzien: mHealth pain coping skills training to improve self-management of chronic pain in **cancer** survivors	**Enrollment 50+% completed**
Wang: Use of **ketamine** during and/or after surgery to prevent **Post-Mastectomy** Pain Syndrome	**Enrollment 50+% completed**

Pragmatic and Implementation Studies for the Management of Pain

Doorenbos Assess effectiveness of guided Relaxation and **Acupuncture** for Chronic pain associated with Sickle Cell Disease delivered in in health care systems.

Fritz Compare and evaluate teleconsult combined with phone-based physical therapy, and sequenced pain teleconsult (first), followed by phone-based physical therapy through primary care clinics of FQHCS located in **rural** and low-income communities.

Sluka Evaluate treatment adherence and outcomes of adding **transcutaneous electrical stimulation** to physical therapy for those with fibromyalgia.

DeBar Compare effectiveness of 12 weeks of **acupuncture** to an enhanced course of acupuncture (12-week standard course, plus 12-week maintenance course) to usual medical care for cLBP in adults over 65 with low back pain.

Cheville Develop sustainable strategy to embed patient-facing and clinician-facing decision support components of an **EHR-embedded evidence-based bundled pain care** to enhance perioperative pain management with nonpharmacological options

Morone Integrate and test an evidence-based group-based **mindfulness** clinical pain program in the primary care setting for patients with cLBP.

HEAL Clinical Research Networks in Pain Management to Accelerate Research into Practice

HEAL Pain Research Networks and Consortia

Biomarkers

Back Pain Consortium

EPPIC NET: Early phase 2 trials for therapeutics

ERN: comparative effectiveness research network

PRISM: pragmatic trials in health care systems

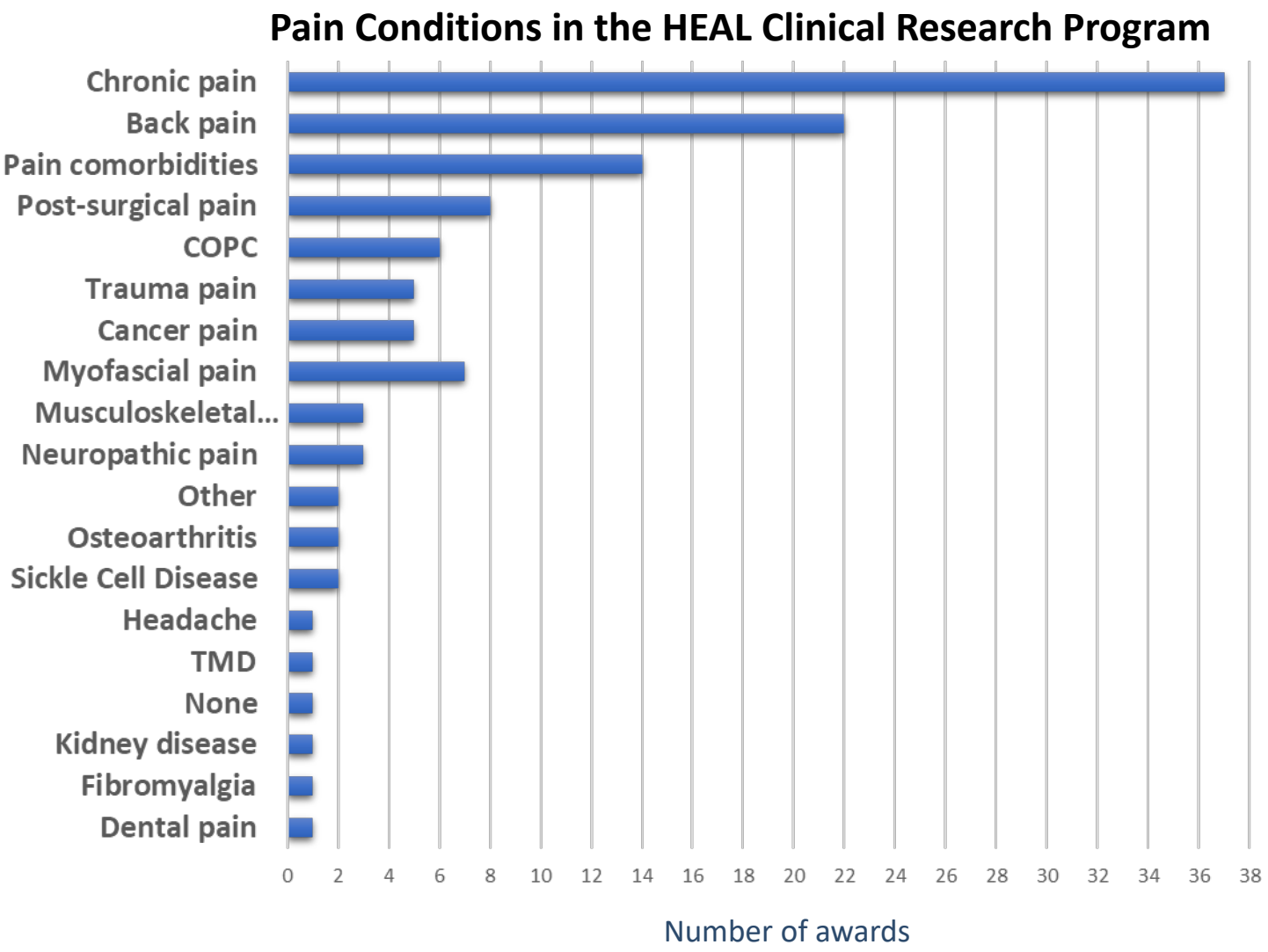
Pain and OUD

HOPE: trial for pain in late-stage renal disease

Health Equities

Rural Health

KIDS Pain: acute and chronic pain

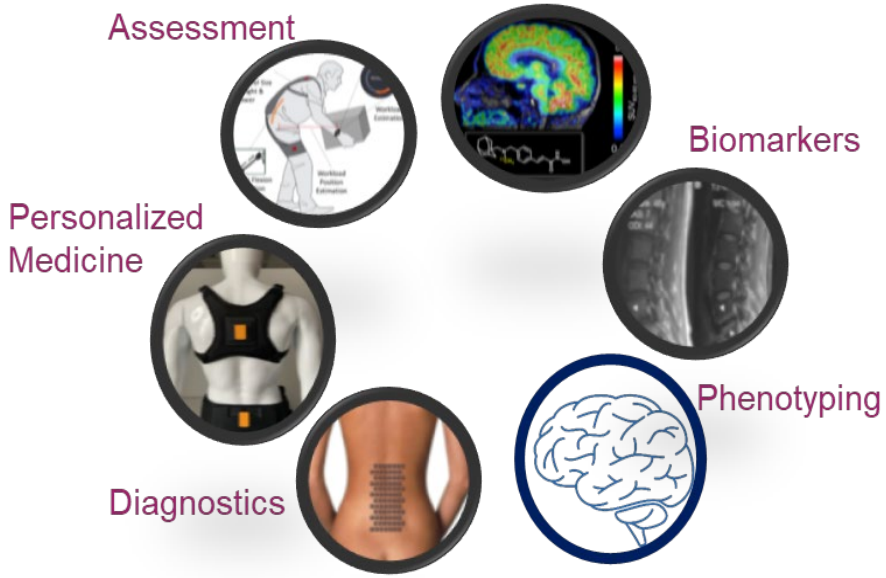


Back Pain Research Consortium: BACPAC

The BEST trial to develop personalized care for those with back pain

BEST
Biomarkers for Evaluating Spine Treatments

- Deep phenotyping to optimize personalized care
- collaborative multi-site BACPAC effort to understand what treatments are most effective for whom based on individual characteristics
- sequential randomization, such that the interventions can be maintained, added to or dropped according to the outcome from the initial randomization, reflecting real-world practice
- Enrollment complete
- Data harmonization, integration, analysis ongoing



- Predictive algorithms for personalizing treatment
- Wearable muscle to support the back
- Combination therapy: Antidepressants and physical therapy
- Deep brain stimulation to treat chronic low back pain and depression
- Virtual reality
- Wearable devices

HEAL Workforce Efforts in Pain Research

HEAL training supplements for novice researchers and investigators new to pain research

HEAL National K12 National scholar grant for enhanced mentorship for researchers who are not ready for an independent NIH grant

HEAL Initiative Partnerships to Advance Interdisciplinary Training in Clinical Pain Research: The HEAL Pain Cohort Program (T90/R90 Institutional Award)

HEAL Initiative Pain Care Clinical Training Program (Career development awards: K23s and K08s)

Advanced Postdoctoral-to-Independent Career Transition Awards in Pain and Substance Use Disorder Research

PURPOSE network. A national network that connects pain researchers across the continuum of pain research, from all disciplines and at all career stages.

R15 award: Promoting Diversity in the Pain Workforce

Why the HEAL Data Ecosystem?

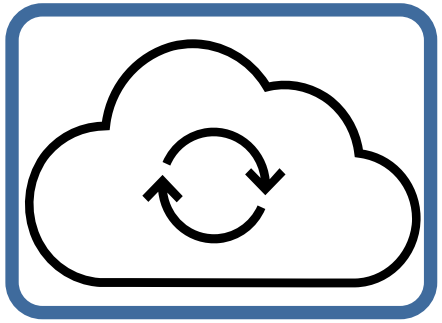
Problem: Data are highly diverse, being managed/curated to various extents, different storage needs

Solution: Thread data + details in one place that is machine-readable, shareable

Call to Action: "GET THE DATA" to maximize return on investment

Data and resources diverse and siloed

Data trapped in field-specific databases and journals



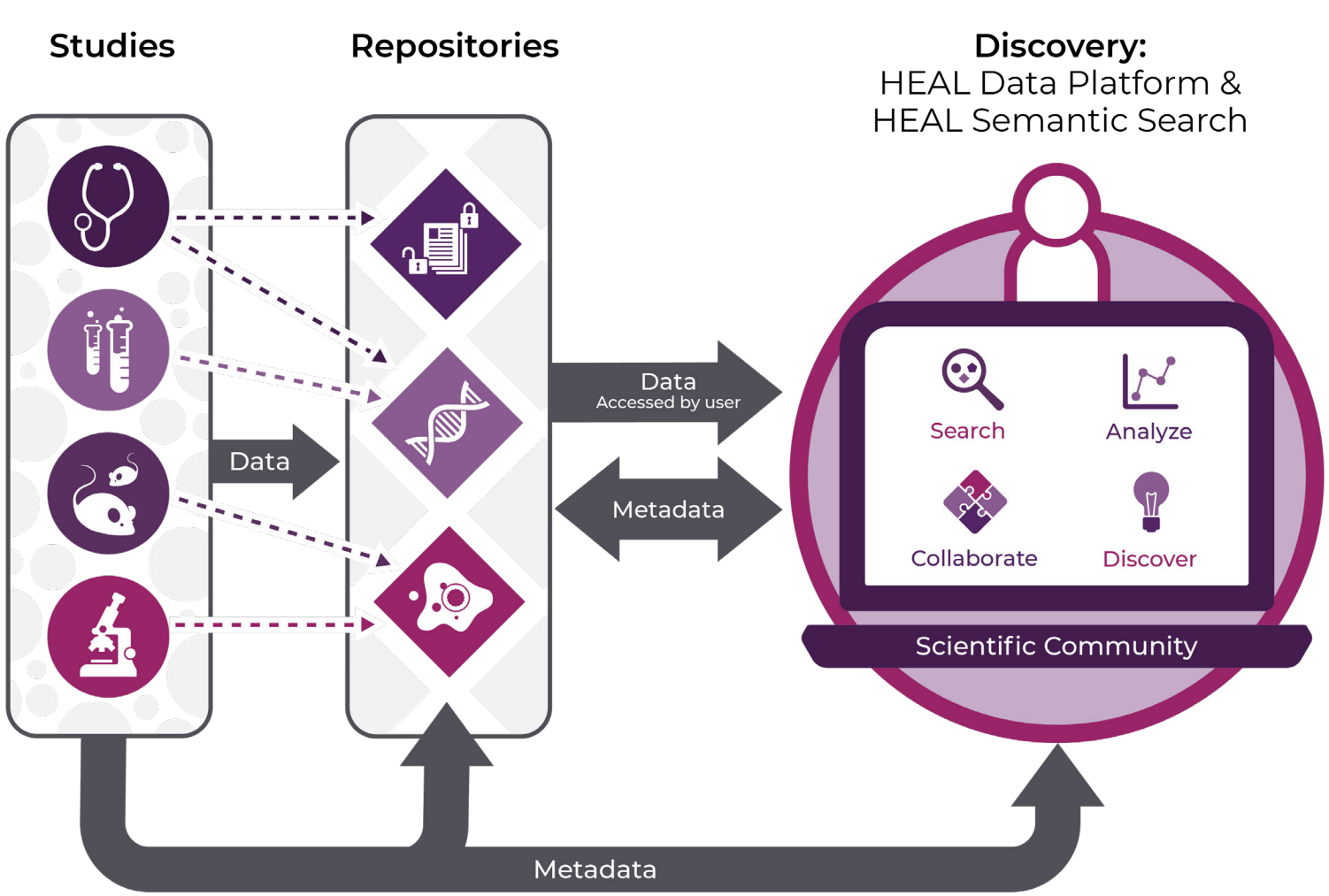
HEAL Data Platform

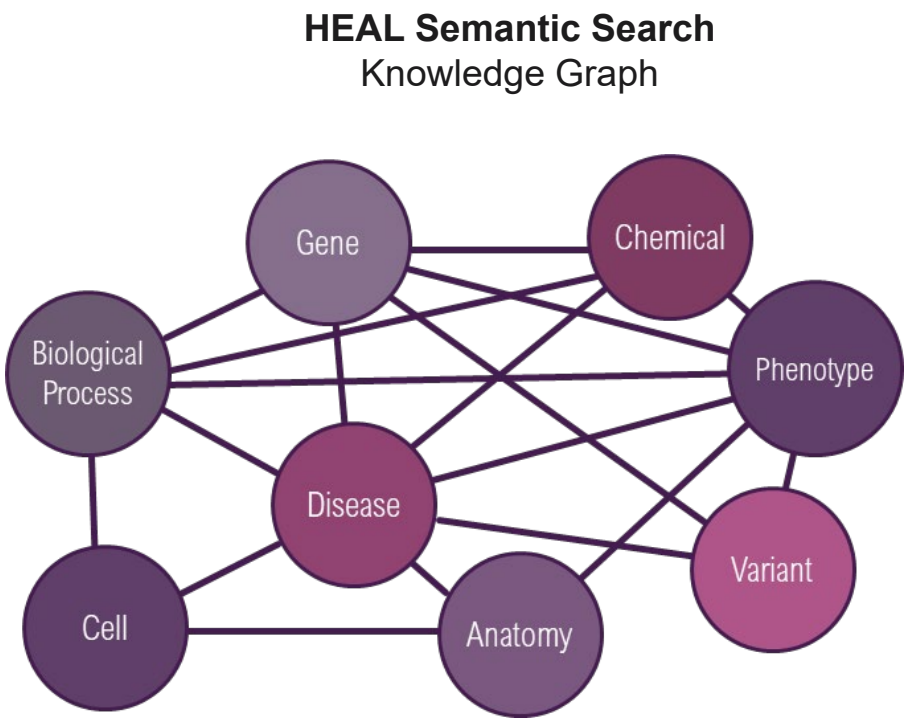
Environment for data search, access, analyses

Needs full participation, more connections between data

Get data connected and drive secondary use

A Distributed Approach: Leveraging Existing Resources





HEAL Pain Strategic Plan

- NIH HEAL Initiative was established in 2018
- Looking to the future: developing a strategic plan to guide the next phase of the initiative
  - development research priorities for HEAL Pain
  - pair with NIDA's strategic plan on research priorities for OUD/overdose
- Working Group of Council to provide scientific guidance on how best to advance pain research through the HEAL Initiative.
- **Charge:** prioritize strategic research priorities for the next phase of pain research to advance the HEAL mission.
  - Assess progress from successes and lessons learned from early programs Recommendations to achieve the goals of HEAL programs in the first phase of the initiative.
  - Identify gaps in the current HEAL pain research portfolio that should be addressed to advance the HEAL mission.
  - Identify opportunities to advance the HEAL mission through partnerships, technologies, breaking developments in science, research infrastructure

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.

Co-chairs

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