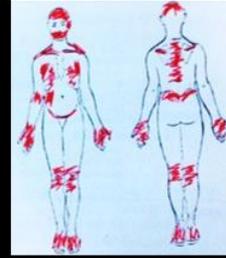
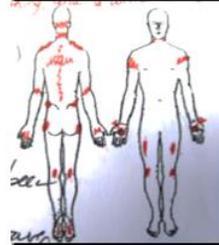
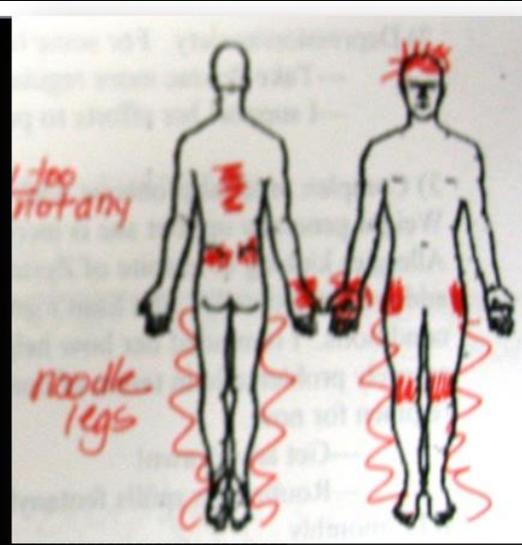
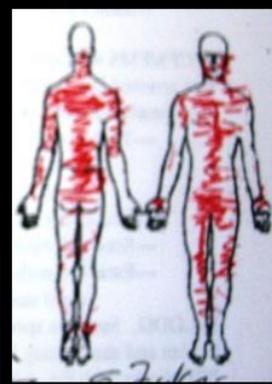
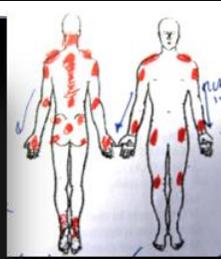
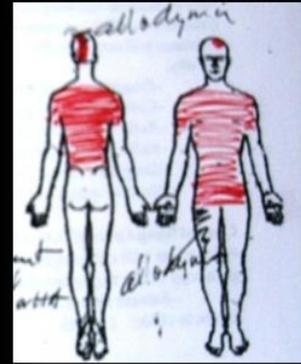
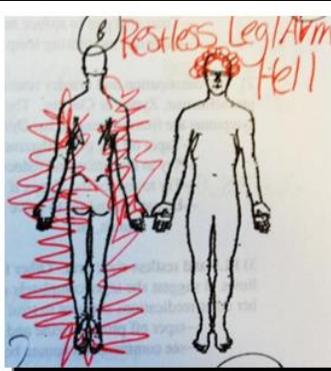


# Patient Perspective on Pain Research

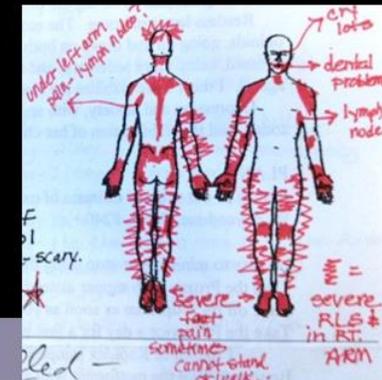
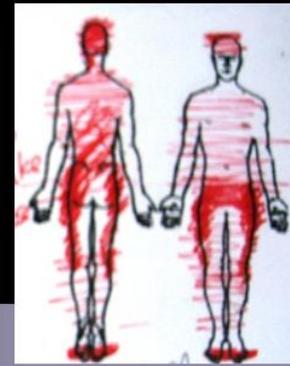
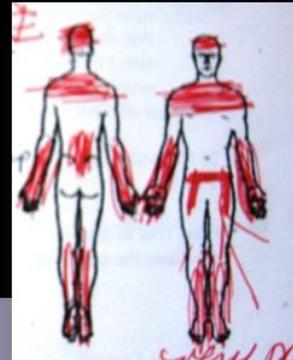
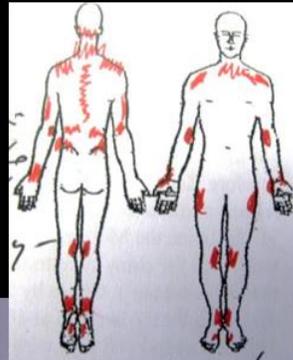
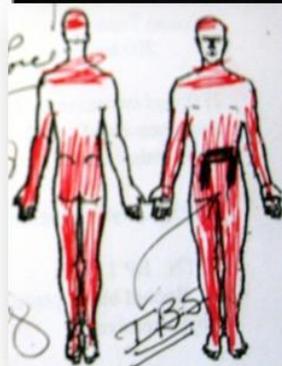
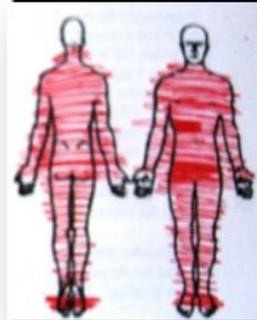
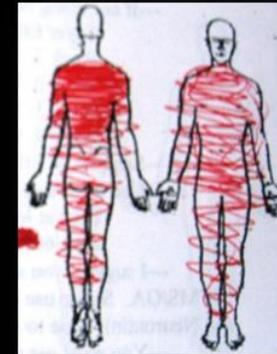
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CHRISTIN VEASLEY

CO-FOUNDER & DIRECTOR, CHRONIC PAIN RESEARCH ALLIANCE



Pain affects **100 million Americans**  
at an annual cost of **\$635 billion**  
More than **COMBINED** cost of  
cancer + heart disease + diabetes



What does pain research  
mean to patients?

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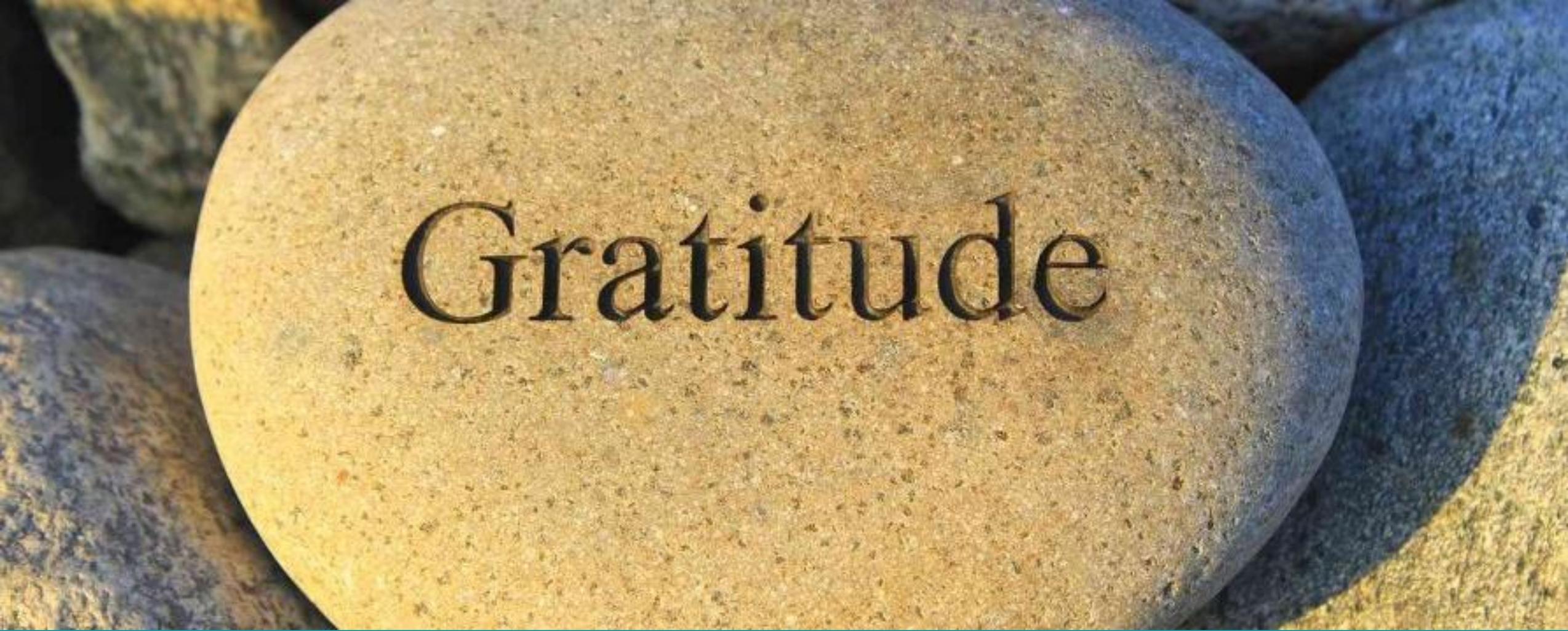


# PAIN RESEARCH EFFORT



=





# Gratitude

*“My chronic pain continues to worsen, despite my best efforts and those of my health care providers. Research is one of a few things that still gives me hope. I’m so grateful to pain researchers who devote their todays to making my tomorrow better.”*

# Where are we?

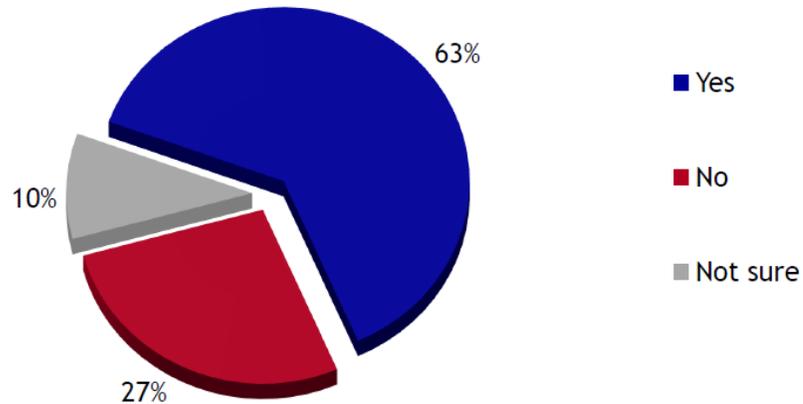
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AN HONEST ASSESSMENT

# Public Health Impact of Chronic Pain

## Most Americans Know Someone Who Sought Pain Medicine

Do you know anyone who experienced pain so severe that they sought prescription medicines to treat it?



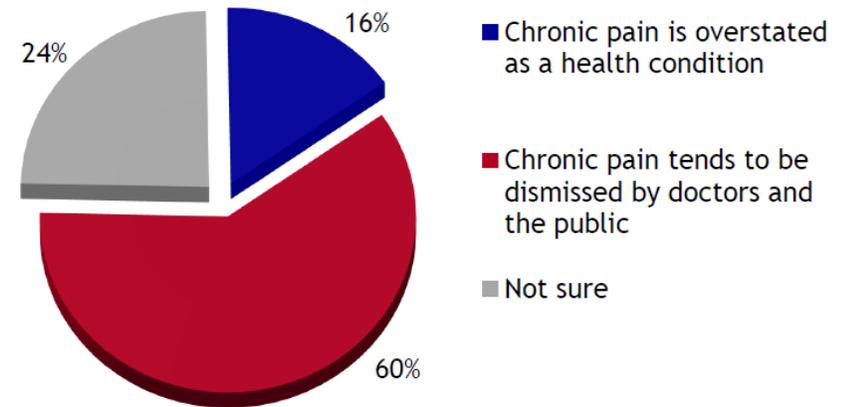
Zogby Analytics

Source: A Research!America poll of U.S. adults conducted in partnership with Zogby Analytics in March 2013.



## Majority: Chronic Pain Tends to be Dismissed by Doctors, Public

Which statement is closer to your view?



Zogby Analytics

Source: A Research!America poll of U.S. adults conducted in partnership with Zogby Analytics in March 2013.



# Major Public Disconnect – Public Health Impact of Chronic Pain

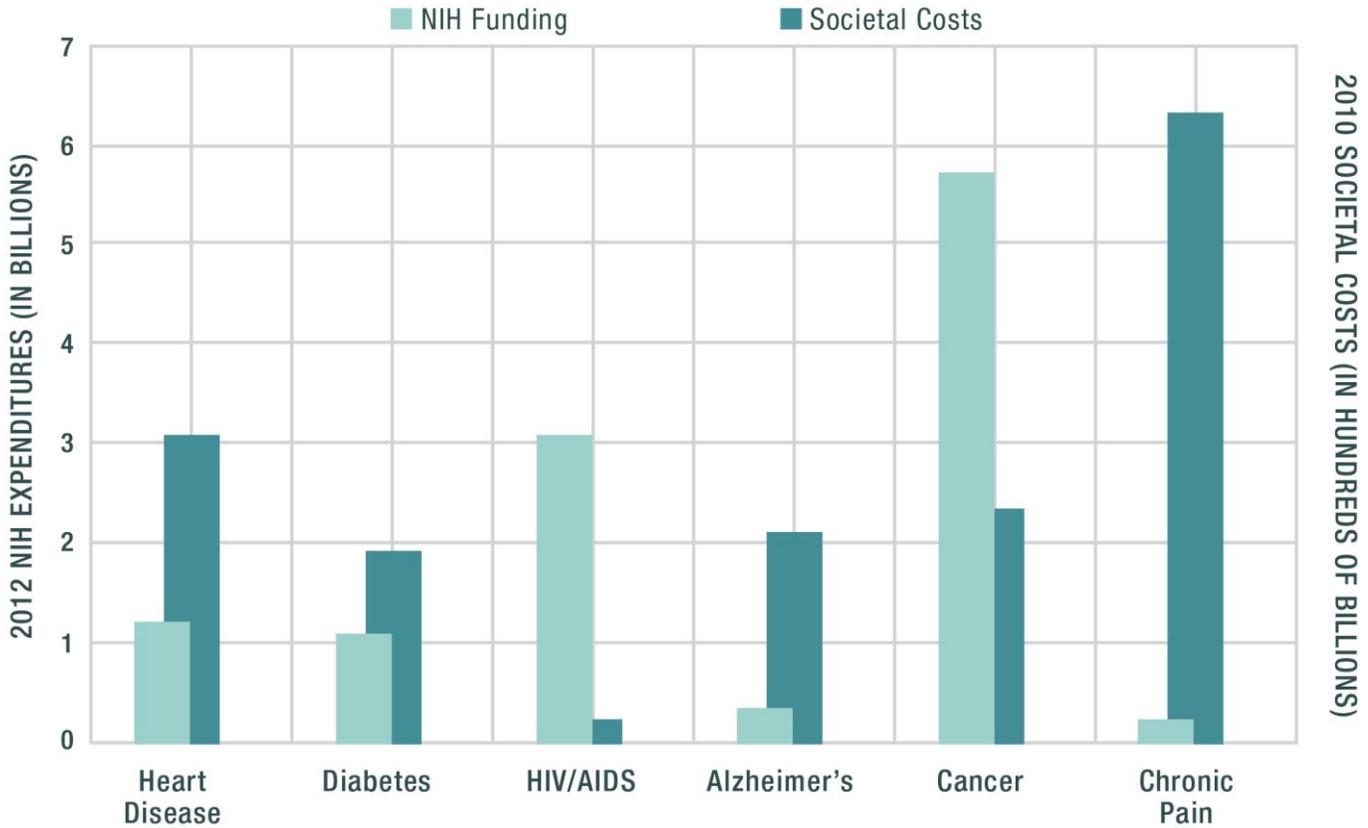
## Chronic Pain Ranks Below Many Other Conditions as Major Health Problem

Which of the following would you describe as a major health problem in the U.S.? (multiple responses allowed)

Cancer	59%
Heart disease	52%
Diabetes	52%
Drug addiction	47%
Depression	42%
Alcoholism	37%
Alzheimer's disease	34%
<b>Chronic pain</b>	<b>18%</b>
Parkinson's disease	15%
Not sure	15%



# Current Federal Investment in Pain Research

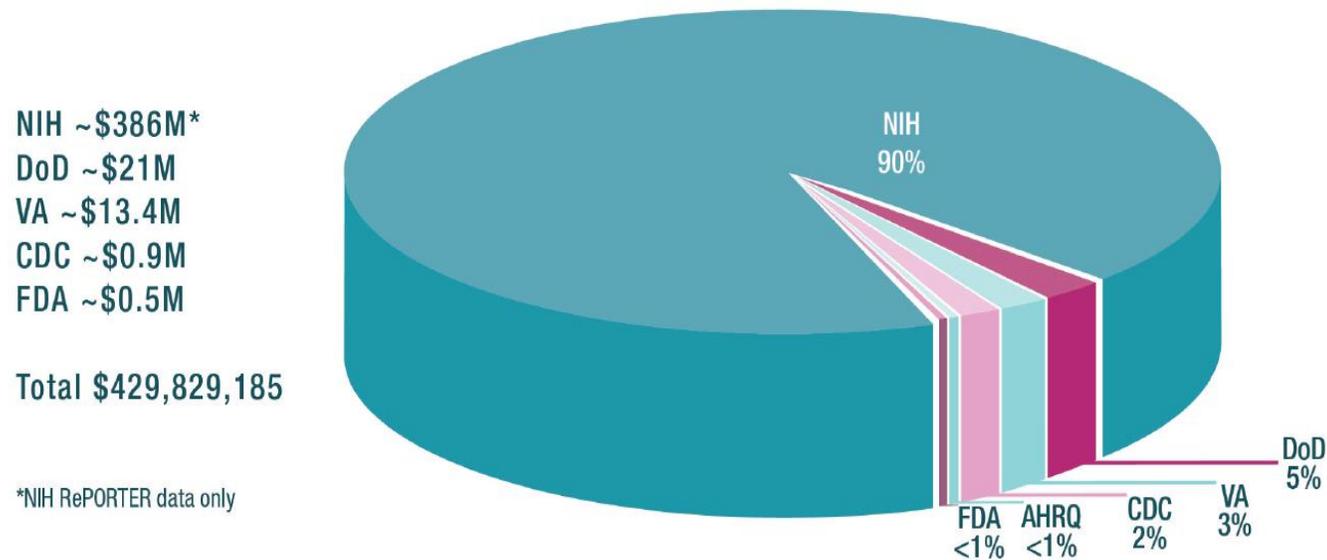


# Current Federal Investment in Pain Research

Figure 6. FY2011 Total Pain Research Expenditures by Federal Agencies

Source: Interagency Pain Research Coordinating Committee

[http://iprcc.nih.gov/docs/102212\\_mtg\\_presentations/IPRCC\\_prelim\\_portfolio\\_analysis\\_508comp.pdf](http://iprcc.nih.gov/docs/102212_mtg_presentations/IPRCC_prelim_portfolio_analysis_508comp.pdf)



Note: NIH: National Institutes of Health; DoD: Department of Defense; VA: Veterans Affairs Administration; CDC: Centers for Disease Control and Prevention; AHRQ: Agency for Healthcare Research and Quality; FDA: Food and Drug Administration

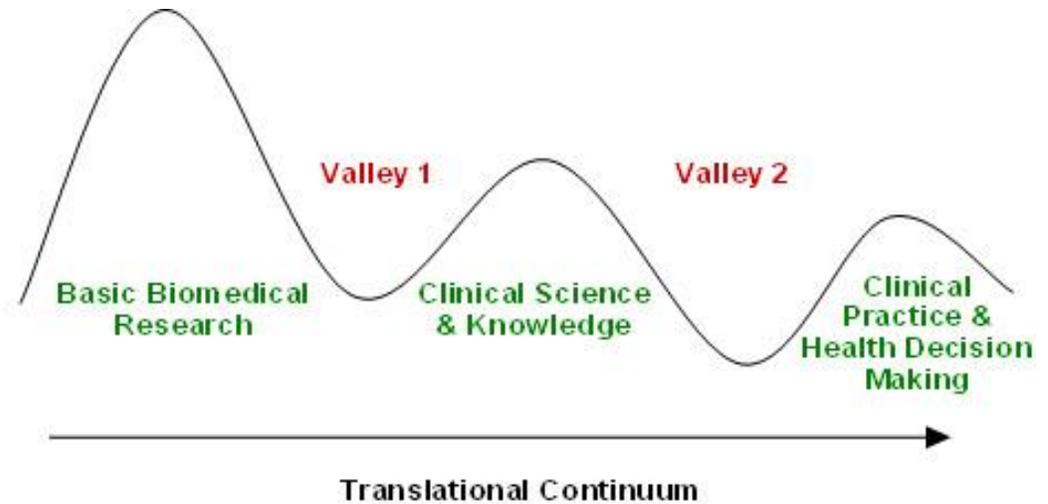
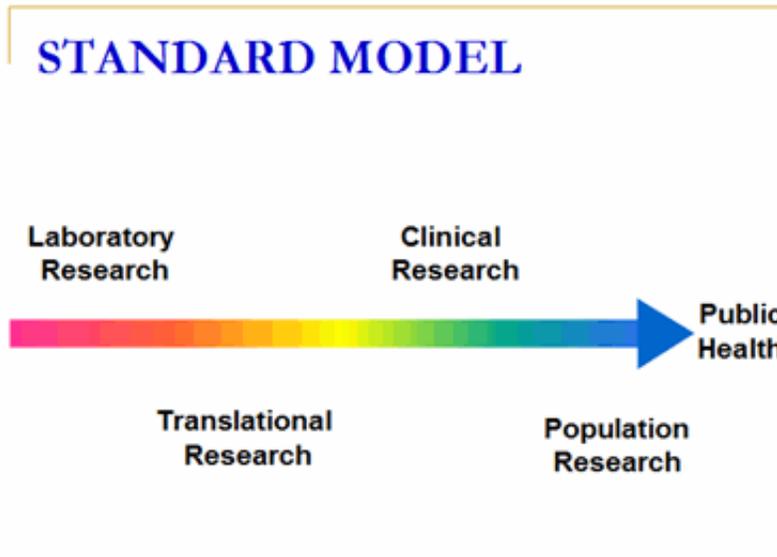


The federal investment in chronic pain research equals less than 5 cents per affected American adult!

# Translation – Research to Patient Care

IS THE STANDARD RESEARCH MODEL WORKING?

ARE SCIENTIFIC DISCOVERIES SURVIVING THE VALLEY(S) OF DEATH AND TRANSLATING TO IMPROVED PATIENT CARE?



# Where are we going?

---

RECENT DEVELOPMENTS

# Dr. Collins: “10 for 10” 10 Predictions for Scientific Breakthroughs Over Next 10 Years

Subcommittee Hearing

## Hearing on FY2017 National Institutes of Health Budget Request

Labor, Health and Human Services, Education, and Related Agencies

**Date:** Thursday, April 7, 2016

**Time:** 10:00 AM

**Location:** Dirksen Senate Office Building 138



*#8: “Genomics, neuroscience and structural biology will collaborate to unveil entirely new targets for the treatment of pain, allowing researchers in the public and private sectors to develop highly effective, non addictive medications for pain management... We need new alternatives for pain management and NIH and our partners will develop them.”*



# National Pain Strategy

A Comprehensive Population Health Level Strategy for Pain

---

## National Pain Strategy outlines actions for improving pain care in America

---

*Plan seeks to reduce the burden and prevalence of pain and to improve the treatment of pain*

**FOR IMMEDIATE RELEASE**

**Friday, March 18, 2016**

**Contact: ASH Media Office**

**202-205-0143**

[ashmedia@hhs.gov](mailto:ashmedia@hhs.gov)

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The Office of the Assistant Secretary for Health at the U.S. Department of Health and Human Services today released a [National Pain Strategy](#), outlining the federal government's first coordinated plan for reducing the burden of chronic pain that affects millions of Americans. Developed by a diverse team of experts from around the nation, the National Pain Strategy is a roadmap toward achieving a system of care in which all people receive appropriate, high quality and evidence-based care for pain.



# National Pain Strategy

A Comprehensive Population Health Level Strategy for Pain

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## Population Research Working Group

**Intent:**

Provide methods and metrics to guide progress toward achieving improved prevention (primary, secondary, and tertiary) and management of pain in the United States.

3 Major Objectives

Short-, Medium- & Long-Term Deliverables

Key Federal & Non-Federal Stakeholders



# National Pain Strategy

A Comprehensive Population Health Level Strategy for Pain

## Population Research Working Group

Short-Term Deliverable

HealthyPeople2020

A screenshot of the HealthyPeople.gov website. The header includes the site name, a search bar, and a navigation menu with items like 'Topics &amp; Objectives', 'Leading Health Indicators', 'Data Search', 'Healthy People in Action', 'Tools &amp; Resources', 'Webinars &amp; Events', and 'About'. The main content area features a large banner for a 'Progress Review Webinar Series' with a laptop displaying the 'Healthy People 2020' logo. To the right of the banner is a call to action: 'Join Us for a Progress Review Webinar' with a 'Register today' link. Below the banner are several featured content blocks: 'DATA2020 Search' (an interactive data tool), 'Leading Health Indicators: Progress Update' (a new report), 'Tools on HealthyPeople.gov' (evidence-based resources and program planning), and 'Federal Prevention Initiatives' (infographics showing an 82.4% target).



### DATA2020 Search

This interactive data tool allows users to explore data and technical information related to the Healthy People 2020 objectives. [Search Healthy People data.](#)



### Leading Health Indicators: Progress Update

[Read the report](#) to learn about progress that's been made in each of the 26 Leading Health Indicators.



### Evidence-Based Resources

Find evidence-based interventions and resources to improve health in your community. [Search our database.](#)



### Program Planning

Learn how to plan and evaluate public health interventions in your community. [Get started.](#)



[View Healthy People Infographics.](#)



### Federal Prevention Initiatives

The Healthy People objectives are the foundation for many federal prevention initiatives. Select a topic area, government office, or initiative to begin exploring these connections.

[Learn more about Federal Prevention Initiatives.](#)

To direct the NIH to intensify and coordinate fundamental, translational, and clinical research with respect to the understanding of pain, the discovery and development of therapies for chronic pain, and the development of alternatives to opioids for effective pain treatments.

---

IN THE SENATE OF THE UNITED STATES

MARCH 15, 2016

Mr. SCHATZ (for himself, Mr. HATCH, Mr. TESTER, Mr. COCHRAN, Ms. COLLINS, and Ms. BALDWIN) introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

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**A BILL**

To direct the NIH to intensify and coordinate fundamental, translational, and clinical research with respect to the understanding of pain, the discovery and development of therapies for chronic pain, and the development of alternatives to opioids for effective pain treatments.

*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,*

**SECTION 1. SHORT TITLE.**

This Act may be cited as the “Safe Treatments and Opportunities to Prevent Pain Act” or the “STOP Pain Act”.

**SEC. 2. ENHANCING BASIC AND APPLIED RESEARCH ON PAIN TO DISCOVER THERAPIES, INCLUDING ALTERNATIVES TO OPIOIDS, FOR EFFECTIVE PAIN MANAGEMENT.**

(a) **IN GENERAL.**—The Director of the National Institutes of Health (referred to in this section as the “NIH”) may intensify and coordinate fundamental, translational, and clinical research of the NIH with respect to—

- (1) the understanding of pain;
- (2) the discovery and development of therapies for chronic pain; and
- (3) the development of alternatives to opioids for effective pain treatments.

(b) **PRIORITY AND DIRECTION.**—The prioritization and direction of the federally funded portfolio of pain research studies shall consider recommendations made by the Interagency Pain Research Coordinating Committee in concert with the Pain Management Best Practices Inter-Agency Task Force, and in accordance with the National Pain Strategy, the Federal Pain Research Strategy, and the NIH-Wide Strategic Plan for Fiscal Years 2016–2020, the latter which calls for the relative burdens of individual diseases and medical disorders to be regarded as crucial considerations in balancing the priorities of the Federal research portfolio.

# STOP Pain Act

## Safe Treatments and Opportunities to Prevent Pain Act

Introduced in  
U.S. Senate  
in March 2016

Introduced in  
U.S. House of Representatives  
in May 2016

# STOP Pain Act Provisions Included in Senate HELP Committee Legislation

U.S. SENATE COMMITTEE  
ON

Health, Education  
Labor & Pensions

CHAIRMAN

RANKING MEMBER

HEARINGS

COMMITTEE ACTIONS

ABOUT

[Home](#) [Chairman](#) [Chairman's Newsroom](#) [Press](#)

03.16.16

## Senate Health Committee Passes Alexander, Murray, Cassidy, Murphy Legislation to Help Address Mental Health Crisis in America

The Mental Health Reform Act of 2016 will help Americans suffering from mental health and substance use disorders

### **SEC. 804. NIH OPIOID RESEARCH.**

*(a) IN GENERAL.—The Director of the National Institutes of Health (referred to in this section as the “NIH”) may intensify and coordinate fundamental, translational, and clinical research of the NIH with respect to—*

*(1) the understanding of pain;*

*(2) the discovery and development of therapies for chronic pain; and*

*(3) the development of alternatives to opioids for effective pain treatments.*

*(b) PRIORITY AND DIRECTION.—The prioritization and direction of the Federally funded portfolio of pain research studies shall consider recommendations made by the Interagency Pain Research Coordinating Committee in concert with the Pain Management Best Practices Inter-Agency Task Force, and in accordance with the National Pain Strategy, the Federal Pain Research Strategy, and the NIH-Wide Strategic Plan for Fiscal Years 2016-2020, the latter which calls for the relative burdens of individual diseases and medical disorders to be regarded as crucial considerations in balancing the priorities of the Federal research portfolio.*

# Federal Pain Research Strategy

First federal interagency strategic plan for research

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*Advancing Research – Changing Lives*



# CPRA Scientific Advisory Council

Allan Basbaum, PhD (UCSF)

Ronald Dubner, PhD, DDS (Univ of MD)

Jon Levine, MD, PhD (UCSF)

Emeran Mayer, MD (UCLA)

William Maixner, DDS, PhD (Duke)

Sean Mackey, MD, PhD (Stanford)

Richard Lipton, MD (Albert Einstein)

Dan Clauw, MD (Univ of Michigan)

Alan Light, PhD (Univ of UT)

Philip Pizzo, MD (Stanford)

Allen Cowley, Jr, PhD (Medical College of WI)

Ursula Wesselmann, MD, PhD (Univ of Alabama-Birmingham)

Howard Jacob, PhD (HudsonAlpha Institute)

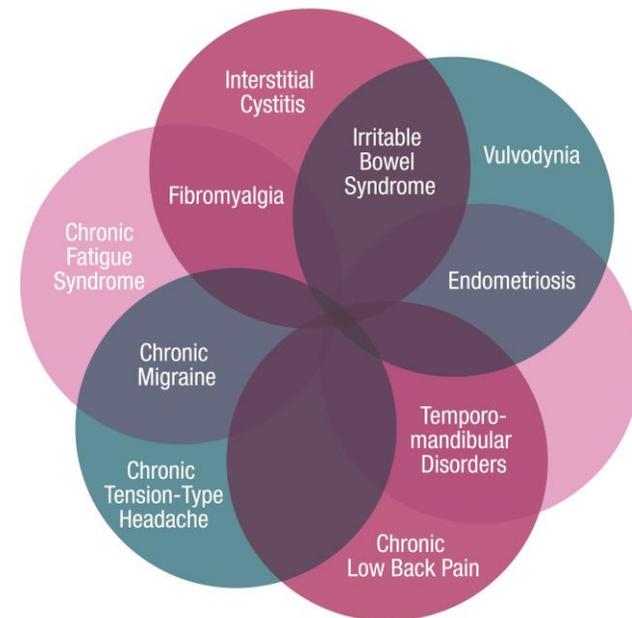
Suzanne Vernon, PhD (Bateman Horne Center of Excellence)

Martin Frank, PhD (American Physiological Society)

Ruby Nguyen, PhD, MHS (Univ of MN)

Denniz Zolnoun, MD, MPH (UNC-Chapel Hill)

Mounting scientific evidence demonstrates that a cluster of chronic pain conditions co-exist, predominantly in women - termed Chronic Overlapping Pain Conditions (COPCs)



Number of Medical Journal Articles Published on Various Combinations of COPCs Increases Five-Fold Between 1995 and 2014



Number of Medical Journal Articles Published on Various Combinations of COPCs Between January 2013 and December 2014

A total of 804 (482 non-duplicate) medical journal articles were published in this time period. Most common were publications on the relationship between ME/CFS and FM (128 articles), IBS and FM (74 articles), migraine and TMD (66 articles) and ME/CFS and IBS (58 articles).

	ENDO	FM	IBS	IC/PBS	Migraine	cTTH	Vulvodynia	cLBP	TMD
ME/CFS	9	128	58	23	15	2	6	3	6
ENDO		13	16	18	8	1	10	8	2
FM			74	32	41	3	15	38	25
IBS				33	39	1	9	6	9
IC/PBS					7	0	10	1	4
Migraine						--	0	23	66
cTTH							0	5	20
Vulvodynia								1	4
cLBP									12
TMD									

Note: ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome; ENDO: endometriosis; FM: fibromyalgia; IBS: irritable bowel syndrome; IC/PBS: interstitial cystitis/painful bladder syndrome; cTTH: chronic tension type headache; cLBP: chronic low back pain; TMD: temporomandibular disorders

# Common Underlying Disease Mechanisms

*Genetic and Environmental Factors*

*Abnormal Pain and Sensory Processing*

*Autonomic Nervous System Processing*

*Female Predominance & Role of Ovarian Hormones*

*Neuroendocrine & Neuroimmune Abnormalities*

*Role of Stress, Behavior & Psychological Behaviors*

## Section VI: Emerging Research on Common Underlying Disease Mechanisms

In addition to a growing epidemiological evidence base substantiating the overlap of conditions addressed in this report, several observations support the concept that these conditions share common underlying mechanisms of disease. Those affected by chronic overlapping pain conditions (COPCs) are more likely to be female, exhibit similar symptom profiles and benefit from similar treatments. Studies increasingly support the idea that COPCs are heterogeneous and that patient populations – both within and across disorders – cluster into phenotypic subgroups with common pathophysiologic mechanisms, and each being responsive to treatment modalities that specifically target those mechanisms.<sup>196</sup> This section summarizes the findings of emerging research on common underlying mechanisms of disease in COPCs.

### Genetic and Environmental Factors

Pain genetics research demonstrates that there are likely numerous genetic variations that determine the sensitivity of an individual's nervous system to pain and other sensory input, as well as risk for developing chronic pain.<sup>199-201</sup> Studies have identified a number of genetic variations associated with a higher risk of developing COPCs, most of which involve the regulation of the immune, neural and endocrine systems, specifically related to sensory/pain processing.<sup>202-217</sup> Likewise, research demonstrates a strong familial component to developing COPCs.<sup>218-224</sup> Twin studies have been particularly helpful in establishing that COPCs co-aggregate, are strongly genetic and are separable from anxiety and depression.<sup>225-232</sup> Gene expression studies in this area are also beginning to yield insight on molecular pathways implicated in symptom expression and treatment response.<sup>233-236</sup> As with most illnesses that have a genetic underpinning, environmental factors, such as infection, trauma, surgery and injury, may play a prominent role in triggering the onset of COPCs.<sup>237-248</sup> Genome-wide epigenetic studies have not yet

### Abnormal Pain and Sensory Processing

Once COPCs develop, the abnormalities most consistently detected are pain and sensory processing dysfunction. Compared to healthy individuals, those with COPCs report enhanced pain perception – both increased pain intensity and lower sensory and pain thresholds – with the application of a variety of sensory stimuli (e.g., pressure, thermal, vibratory, electrical). These sensitivities are found not only at the body site where a person experiences chronic pain, but at distal locations, such as the thumb, shin and arm.<sup>249-275</sup> Recent studies, including those utilizing functional MRI, also provide evidence that other sensory input, such as light, sound and odor, are biologically amplified in patients with COPCs.<sup>276-281</sup> In these studies, the insula – the brain region that plays a critical role in sensory integration – most consistently shows hyperactivity.<sup>282-283</sup>

**Using experimental pain testing, two pathogenic mechanisms have been found to contribute to enhanced pain perception and low sensory thresholds in individuals with COPCs:**

- **Attenuated Diffuse Noxious Inhibitory Control (DNIC)/Conditioned Pain Modulation (CPM)**

In healthy people as well as lab animals, application of an intense painful stimulus for two to five minutes produces generalized whole-body analgesia, i.e., “pain inhibits pain.” This analgesic effect has been consistently observed to be attenuated or absent in many, but not all, individuals with COPCs.<sup>284-297</sup>

- **Increased Wind-Up/Temporal Summation**

Studies also suggest that some individuals with COPCs exhibit evidence of “wind-up” or temporal summation, in which repeated painful stimuli cause increased pain perception, indicative of sensitization of the central nervous system.<sup>298-308</sup>

## COPCs - FY2013 & FY2014 NIH Funding Levels, Investment per Affected Individual and Primary Funding Institutes/Centers

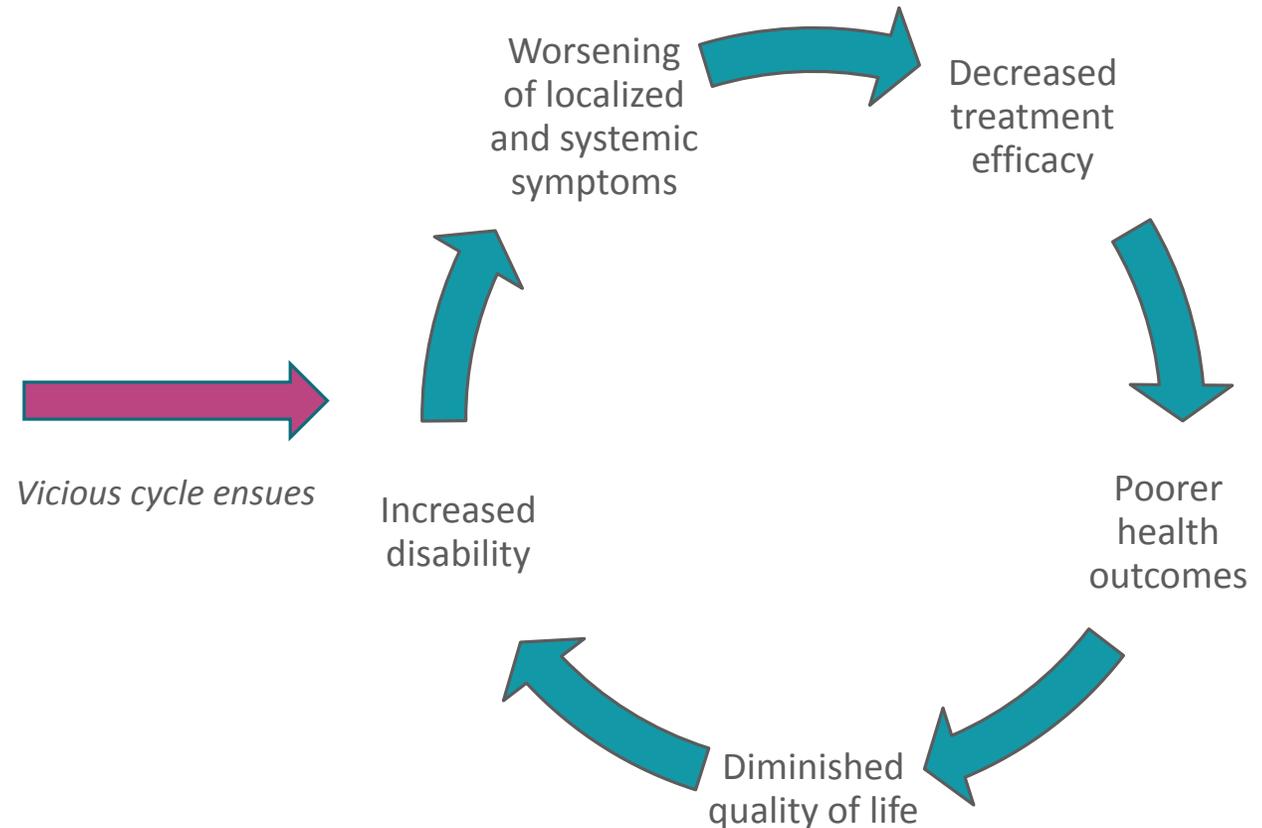
Totals derived from NIH Research Portfolio Online Reporting Tools (RePORT) Research, Condition, and Disease Categorization (RCDC) & NIH Project RePORTER, available at [http://report.nih.gov/categorical\\_spending.aspx](http://report.nih.gov/categorical_spending.aspx) & [www.projectreporter.nih.gov](http://www.projectreporter.nih.gov)

Condition	U.S. Prevalence	2013 NIH Funding Levels	2014 NIH Funding Levels	2013 Research Investment/Patient	2014 Research Investment/Patient	Primary NIH Funding ICs
Vulvodynia	6 million	\$4 million	\$3 million	\$0.67	\$0.50	1 - NICHD 2 - NIDDK 3 - NINDS
Temporo-mandibular Disorders	35 million	\$19 million	\$18 million	\$0.54	\$0.51	1 - NIDCR 2 - NINDS 3 - NIEHS
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome	4 million	\$5 million	\$5 million	\$1.25	\$1.25	1 - NIAID 2 - NINDS 3 - NINR & NIDDK
Irritable Bowel Syndrome	44 million	\$23 million	\$14 million	\$0.52	\$0.32	1 - NIDDK 2 - NCCIH 3 - NINDS
Interstitial Cystitis/ Painful Bladder Syndrome	8 million	\$10 million	\$9 million	\$1.25	\$1.13	1 - NIDDK 2 - NINDS 3 - NICHD
Fibromyalgia	6 million	\$11 million	\$10 million	\$1.83	\$1.67	1 - NIAMS 2 - NINDS 3 - NIAID, NCCIH, NINR, NIDDK
Endometriosis	6.3 million	\$7 million	\$7 million	\$1.11	\$1.11	1 - NICHD 2 - NCI 3 - NIEHS
Headache						
Chronic Tension-Type	7 million	\$990,000	\$285,000	\$0.14	\$0.04	1 - NIGMS 2 - NICHD
Chronic Migraine	7 million	\$19 million	\$20 million	\$2.71	\$2.86	1 - NINDS 2 - NIMH 3 - NICHD
Chronic Low Back Pain	19.5 million	\$28 million*	\$24 million*	\$1.44	\$1.23	1 - NCCIH 2 - NIAMS 3 - NIDA
<b>Totals</b>		<b>\$127 Million</b>	<b>\$110 Million</b>	<b>\$1.15</b>	<b>\$1.06</b>	

\*Includes NIH investment in both "chronic low back pain" and "low back pain" studies

### Current Reality for Patients

- Frequent misdiagnoses due to lack of education and training of health care providers
- Few FDA-approved treatment options
- Insufficient scientific evidence to guide clinicians and patients in making informed treatment decisions



## Our Approach

### Research

Silo effort by Dx/body site – similar studies duplicated across conditions



Collective/collaborative effort - to parse out commonalities & uniqueness across phenotypic subgroups

### Clinical Care

Fragmented medical care by specialists according to body area



Patient-centered medical home with team-based interdisciplinary treatment approach

Treatment is trial-and-error based & draws upon findings of better researched disorders



Treatment informed by scientific evidence, with proven efficacy in mechanism-based subtypes

Treatment of most painful symptom or body part



Individualized treatment of all affected domains and contributing factors (pain, sleep, mood, physical function, etc.)

### Translation of Evidence

Evidence not widely disseminated or translated into improved care or tools



Heavy focus on translation of findings into improved care and tools



## Mission

CPRA works with invested stakeholders in a collaborative model to:

- 1 – Promote a rigorous, standardized, collective and cost-effective **research** approach
- 2 – **Translate** research findings into information for patients and educational and training programs for clinicians
- 3 – Drive the development of safe and effective **treatments** for chronic overlapping pain conditions

## Vision

A future where individuals with multiple pain diagnoses will receive a **timely and accurate diagnosis**, followed by **high-quality and comprehensive medical care** and **safe and effective treatment** that is **informed by the latest and most rigorous scientific evidence**.



# National COPCs Studies: MAPP Research Network

The screenshot shows the MAPP Research Network website. The browser address bar displays 'www.mappnetwork.org'. The page title is 'Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain'. A navigation menu includes 'About MAPP', 'Discovery Sites', 'Core Sites', 'Recruiting Sites', 'Projects', 'MAPP Portal', and 'Participant Survey'. The main content area features a 'Welcome to the MAPP Research Network Home Page' header with the MAPP logo. A sidebar on the left lists various categories: MAPP News, MAPP Publications, Epidemiological Studies, Urological Phenotyping, Non-Urological Phenotyping, Neuroimaging / Neurobiology, Biomarkers, Organ Cross-Talk / Pain Pathways, MAPP Network Data Collection, MAPP Feedback Survey, and Sponsor Links. The main content area has a featured article titled 'A New Look at Urological Chronic Pelvic Pain ...' with an image of a scientist using a microscope. The article text discusses the MAPP Research Network's approach to studying urological chronic pelvic pain disorders, including interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). It mentions the establishment of the MAPP Research Network in 2008 and the Trans-MAPP Epidemiology/Phenotyping (EP) Study. The article also describes the Trans-MAPP Symptom Patterns Study (SPS) and the highly multidisciplinary nature of the network, listing key focus areas such as epidemiology of disease, phenotyping, neuroimaging, quantitative sensory testing, biomarker identification, microbiome influences, and animal models. The page concludes with information on how to participate in the research.

Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain

About MAPP Discovery Sites Core Sites Recruiting Sites Projects MAPP Portal Participant Survey

## Welcome to the MAPP Research Network Home Page

MAPP News  
MAPP Publications  
Epidemiological Studies  
Urological Phenotyping  
Non-Urological Phenotyping  
Neuroimaging / Neurobiology  
Biomarkers  
Organ Cross-Talk / Pain Pathways  
MAPP Network Data Collection  
MAPP Feedback Survey

Sponsor Links  
Department of Health & Human Services (HHS)  
National Institutes of Health (NIH)  
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)  
USA Gov  
USA.gov

### A New Look at Urological Chronic Pelvic Pain ...

To help better understand the underlying causes of the two most prominent chronic urological pain disorders—interstitial cystitis/ bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), in 2008 the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) established the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network.

The MAPP Research Network embraces a systemic—or whole-body—approach in the study of Urological Chronic Pelvic Pain Syndrome (UCPPS). UCPPS is a term adopted by the network to encompass both IC/BPS and CP/CPPS, which are proposed as related based on their similar symptom profiles. In addition to moving beyond traditional bladder- and prostate-specific research directions, MAPP Network scientists are investigating potential relationships between UCPPS and other chronic conditions that are sometimes seen in IC/BPS and CP/CPPS patients, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome.

The primary clinical research effort carried out during the MAPP Network's first 5-year project period (MAPP I) was a prospective cohort study, the Trans-MAPP Epidemiology/Phenotyping (EP) Study. From 12/14/2009 through 12/14/2012 1,039 men and women were enrolled, including persons with UCPPS (n=424), persons with other comorbid illnesses, including fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome (n=200 for all conditions), and healthy controls (n=415). Allstudy participants were extensively characterized (i.e., phenotyped) at baseline, and UCPPS participants were further assessed during an additional 12 month follow-up period.

Initial analyses of these data have identified a number of provocative findings. There are strong indications those certain subgroups of participants (albeit with small sample sizes) with urinary and non-urinary symptoms tend to improve over time; whereas other subgroups tend to worsen over time. These patterns of improving or worsening are differentially expressed according to sex, subtype of bladder pain syndrome (BPS), and pain location (e.g., localized to the pelvic region vs pain reported in the pelvic region as well as other body sites).

The second phase of the MAPP Network is now underway and is designed to conduct a prospective, observational study of men and women with UCPPS, referred to as the Trans-MAPP Symptom Patterns Study (SPS). The this collaborative study will be enriched with pre-defined subgroups and involves a longer follow-up in order to describe UCPPS symptom changes over time and associated changes in underlying biology. The Trans-MAPP SPS will further investigate and extend upon clinical and biologic insights identified in MAPP I and will examine the potential for classification of UCPPS patients into clinically meaningful sub-groups based on differing pathophysiological profiles and/or potential to respond to certain clinical interventions.

The highly multidisciplinary (i.e., scientists employing a variety of research approaches) MAPP Network includes researchers with clinical, epidemiological, and basic research expertise, all working collaboratively:

- Clinical researchers bring experience treating patients
- Epidemiological investigators study the occurrence of, and identify risk factors for, IC/BPS and CP/CPPS
- Basic research scientists examine what's happening on a cellular level

The MAPP Network includes multiple key focus areas, including:

- Epidemiology of Disease
- Phenotyping of Urological and Non-Urological symptoms
- Neuroimaging / Neurobiology Studies
- Quantitative Sensory Testing
- Identification of Biomarkers of Disease
- Potential influences of the microbiome
- Studies of relevant UCPPS animal models

The MAPP Research Network is comprised of six Discovery Sites that recruit participants and conduct the research studies and two Core Sites that coordinate data collection, analyze tissue samples, and provide technical support. In addition, the network supports three non-recruiting Discovery Sites that are focused in specific research areas of interest. To further broaden the scope and investigator base beyond the Discovery and Core sites, the MAPP Network also fosters the incorporation of ancillary study sites tasked with the conduct of clinical, basic, and translational research performed in collaboration within the network.

By promoting novel and innovative research approaches, the MAPP Network aims to discover new and clinically relevant insights that may lead to improved treatment options and better patient care.

### How Can You Participate?

There are currently opportunities for interested participants to get involved with this important research. Your interest and willingness to enroll in the research studies now being initiated by the MAPP Research Network is vitally important to achieving the goals for improved treatment options and better patient care. Please follow this participant link for updates and for information on how you can get involved. ([Learn more](#))

# National COPCs Studies

## OPPERA I & II

NIH National Institute of Dental and Craniofacial Research

A-Z Index | Staff Directory | Español

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NIDCR Home | Oral Health | Clinical Trials | Research | Grants & Funding | Careers & Training

NIDCR > Research > Research Results > Interviews with Oral Health Researchers > Let's Talk OPFERA: A New Study on TMJ Disorders

### Let's Talk OPFERA: A New Study on TMJ Disorders

## The Inside Scoop

January 2006

The National Institute of Dental and Craniofacial Research (NIDCR), announced recently the study that could accelerate research on better pain-controlling treatments for a jaw condition called orofacial pain and muscle disorders (TMJDs). Called Orofacial Pain: Prospective Evaluation and Risk Assessment, this \$100 million project marks the first-ever large, prospective clinical study to identify risk factors that could lead to developing a TMJ disorder. A prospective study looks forward in time, tracking volunteers over time to monitor the onset and natural course of a disease. The *Inside Scoop* recently spoke with Dr. V. Ravitsky, principal investigator and a scientist at the University of North Carolina in Chapel Hill, to hear more about the study design, and possible benefits to people with TMJD.

The adjective that has been used to describe the OPFERA study is "novel." Is that a fair description?

Yes, I think it's very novel. We intend to identify key risk factors for painful TMJDs, using a prospective design. By prospective design, I mean we are enrolling individuals who are initially free of TMJD. We will follow them from three to five years to see who develops a TMJD.

Obviously not everyone will develop TMJD. Based on your best estimates, how many might develop TMJD? Approximately five or six percent of enrollees. That translates to roughly 200 people in the study.

What might these cases tell you?

A tremendous amount about the initial risk factors for TMJ disorders. Right now, we know very little about the initial risk factors for TMJ disorders. How so? Each study participant will undergo a baseline evaluation of his or her jaw function, receive an initial pain sensitivity test, undergo a genetic analysis, and volunteer other potentially relevant information. Thereafter, participants will complete a questionnaire with high sensitivity and specificity for the onset of TMJD. They will then respond in certain ways to visit the clinic, and we will examine them to see whether they meet the criteria for TMJD. For those who do, we can compare their baseline data with those at the time of diagnosis to see what variables changed and possibly are predictive of TMJD. As far as I know, and I've been in the field for over 20 years, OPFERA is the first large, prospective risk factor study in the field of chronic pain.

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## Genetic and Psychosocial Influences on Transition to Chronic TMD and Related Pain

Maixner, William | Diatchenko, Luda | Fillingim, Roger B. | Greenspan, Joel D. | Knott, Charles | Ohrbach, Richard | Slade, Gary Douglas | Sunyaev, Shamil | Weir, Bruce S. | University of North Carolina Chapel Hill, Chapel Hill, NC, United States

### Abstract

While virtually everyone experiences acute pain at some time, it is chronic pain that exacts a profound burden on the public health, reducing quality of life for tens of millions of Americans, and incurring substantial health care costs. Yet little is known about mechanisms that cause a transition from acute to chronic pain; subsequently, even the best of treatments have limited efficacy. One likely clue regarding etiology is that patients who have one form of chronic pain often experience chronic pain elsewhere in the body. In this project, we hypothesize that the transition from acute to chronic pain and the development of multiple chronic pain conditions, are caused by specific constellations of genetic variants and phenotypic risk factors (ie. psychological distress, pain amplification and clinical pain characteristics). This hypothesis is based on our studies of temporomandibular disorder (TMD) in the multi-site OPFERA project (Orofacial Pain, Prospective Evaluation and Risk Assessment; NIH/NIDCR U01-DE017018). In 2006-08, we enrolled 3,263 healthy adults, 233 of whom developed acute TMD during the 3-year follow-up period. Risk factors for acute TMD differed conspicuously from genetic and phenotypic risk factors for chronic TMD. Furthermore, 86% of chronic TMD cases had one or more of four chronic, idiopathic pain conditions: headache (HA), low back pain (LBP), irritable bowel syndrome (IBS) or widespread bodily pain (WBP). In this competitive renewal application, we propose three new aims designed to reveal novel information regarding the etiology and pathophysiology of chronic pain.

**Aim 1:** To identify phenotypes and genotypes that predict risk of transition from acute TMD to chronic TMD, we will enroll a new cohort of 1,000 adults who have acute TMD, following them for six months to identify an expected 400 who progress to chronic TMD.

**Aim 2** will identify risk factors for one or more of five: idiopathic pain conditions (IPCs): TMD, HA, LBP, IBS and/or WBP. Follow-up assessments will be conducted among people in the OPFERA-I prospective cohort study, identifying an expected 640 people who have  $\geq 1$  IPC. Existing phenotypes and genotypes measured at baseline will be used to predict risk of 1 IPC vs.  $\geq 2$  IPCs relative to controls.

**Aim 3** will identify genetic variants associated with chronic TMD. A discovery-phase genome wide association study (GWAS) will use existing DNA from 1,000 OPFERA-I chronic TMD cases and 1,000 OPFERA-I controls. Replication will use a new cohort of n=1,000 chronic TMD cases and n=1,000 controls. Those findings will be contrasted with GWAS analysis of the cohort for Aim 1 to identify genes that contribute differentially to acute and chronic TMD. Based on these findings and validated associations from other studies, twelve genes will be selected for exon sequencing of rare genetic variants. Knowledge generated from these proposed studies will have a significant impact on scientific understanding of risk factors for multiple, overlapping pain conditions. Moreover, the findings will be of direct benefit for clinicians and for their patients, elucidating mechanisms underlying chronic and idiopathic pain in people with TMD.

# National COPCs Studies

## *Complex Persistent Pain Conditions: Unique & Shared Pathways of Vulnerability*

### Complex Persistent Pain Conditions: Unique & Shared Pathways of Vulnerability

Maixner, William

University of North Carolina Chapel Hill, Chapel Hill, NC, United States

#### Abstract

Complex persistent pain conditions (CPPCs) such as headache conditions, fibromyalgia, temporomandibular disorders, irritable bowel syndrome, and vulvar vestibulitis are high prevalent and shared or comorbid chronic pain conditions. There are two features of CPPCs that are fundamental to the aims and goals of this proposal: 1) the etiology of CPPCs is multifactorial and 2) the clinical manifestations of CPPCs are diverse. In this Program Project, we expect to identify a mosaic of risk factors for each of five CPPCs: fibromyalgia (FM), episodic migraine (EM), vulvar vestibulitis (VVS), irritable bowel syndrome (IBS), and temporomandibular joint disorders (TMD). Furthermore, we expect to characterize clusters of patients within each CPPC that vary significantly according to manifestations of their condition in addition to its painful characteristics (e.g., fatigue, dysfunction, sleep loss). Importantly, we expect some clusters of patients to be more alike across CPPCs than within any single CPPC, consistent with our view that there is some overlap in the manifestations of CPPCs. A unifying hypothesis integrating this Program is that multiple genetic factors, when coupled with environmental exposures (e.g. injury, infections, physical and psychological stress), increase the susceptibility to highly prevalent CPPCs by enhancing pain sensitivity and/or increasing psychological distress. To address the aims and goals of the subprojects and cores described in this application, a group of accomplished pain clinicians, pain researchers, psychophysicists, molecular and cellular geneticists, biostatisticians and epidemiologists have been brought together to form this Program. Studies proposed in this Program Project application seek to identify the psychological and physiological risk factors, clusters, and associated genetic polymorphisms, that influence pain amplification and psychological profiles in enrollees who have established CPPDs. Additionally, the proposed studies seek to characterize the biological pathways through which these genetic variations causally influence CPPCs.

#### Funding Agency

<b>Agency</b>	National Institute of Health (NIH)	<b>Project Start</b>	2003-03-01
<b>Institute</b>	National Institute of Neurological Disorders and Stroke (NINDS)	<b>Project End</b>	2015-03-31
<b>Type</b>	Research Program Projects (P01)	<b>Budget Start</b>	2013-04-01
<b>Project #</b>	5P01NS045685-09	<b>Budget End</b>	2014-03-31
<b>Application #</b>	8457063	<b>Support Year</b>	9
<b>Study Section</b>	National Institute of Neurological Disorders and Stroke Initial	<b>Fiscal Year</b>	2013
		<b>Total Cost</b>	\$1,297,314
		<b>Indirect Cost</b>	\$603,425

# National COPCs Studies

## *PAIN Repository: Pain and Interoception Imaging Network*

### Current Data

Our growing body of data contains structural and functional brain scans from patients with chronic pain conditions and healthy controls contributed by members and available for analysis. In addition, the PAIN Standardized Repository also offers clinical, psychosocial and behavioral data.

The Executive Committee evaluates all requests for data, and encourages collaborations among multiple researchers and institutions.

Current pain conditions include: **chronic back pain (CBP), fibromyalgia (FM), migraine, irritable bowel syndrome (IBS), vulvodynia (Vlvd), inflammatory bowel disease (IBD)**

#### Standardized Repository

**Standardized Structural Scans:** 323

**Standardized Resting State Scans:**  
195\*

**Standardized DTI Scans:** 146\*

**Total Standardized Scans:** 664

[Go to List of Scans \(Member login required\)](#)

#### Archived Repository

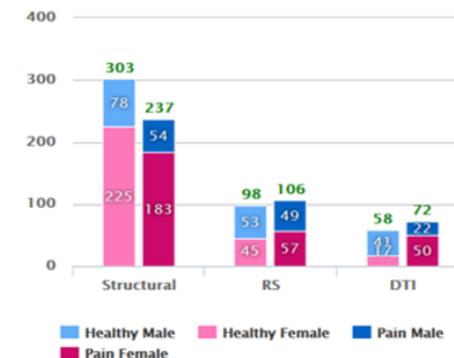
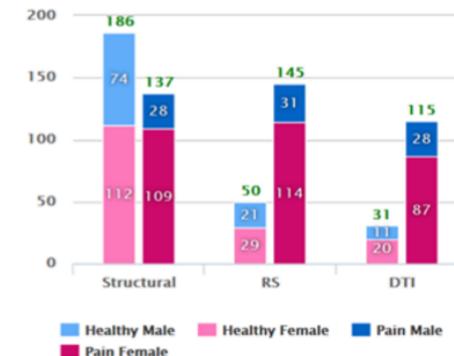
**Structural Scans:** 540

**Resting State Scans:** 204\*

**DTI Scans:** 130\*

**Total Archived Scans:** 874

[Go to List of Scans \(Member login required\)](#)



# Recent Publications from National Studies

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Pain. 2016 Jun;157(6):1266-78. doi: 10.1097/j.pain.0000000000000518.

**Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the CRPFA study.**

Baird Transl Res. 2015 Dec;166(6):706-720.e11. doi: 10.1016/j.trsl.2015.06.008. Epub 2015 Jun 24.

o L, Maixner W.

**MicroRNA expression profiles differentiate chronic pain condition subtypes**

Ciszel Clin J Pain. 2015 Jan;31(1):73-8. doi: 10.1097/AJP.0000000000000087.

**Natural history of comorbid orofacial pain among women with vestibulodynia.**

Bair E Brain Behav Immun. 2015 Oct;49:66-74. doi: 10.1016/j.bbi.2015.03.003. Epub 2015 Mar 11.

**Toll-like receptor 4 and comorbid pain in Interstitial Cystitis/Bladder Pain Syndrome: a multidisciplinary approach**

JUrol. 2015 Apr;193(4):1254-62. doi: 10.1016/j.juro.2014.10.086. Epub 2014 Oct 22.

Schri  
Rese **Relationship between chronic nonurological associated somatic syndromes and symptom severity in urological chronic pelvic pain syndromes: baseline evaluation of the MAPP study.**

Krieger JN, Stephens AJ, Landis JR, Clemens JQ, Kreder K, Lai HH, Afari N, Rodríguez L, Schaeffer A, Mackey S, Andriole GL, Williams DA; MAPP Research Network.

## **Initiatives & Accomplishments Since Inception:**

2010: Inclusion of first US Congressional appropriations language, directing the NIH to develop a research program on COPCs

2011: NIH Establishes first Trans-NIH Working Group (12 NIH Institutes/Centers)

2012: First US Senate hearing on chronic pain, including COPCs

2012: First federal workshop convened and research priorities developed for COPCs

2014: Release of first federal funding announcement on COPCs

## **Initiatives & Accomplishments – 2015/2016:**

To maximize COPCs research investment & facilitate data pooling/analysis across studies, working with NIH to:

- 1) Develop a case definition
- 2) Common Data Elements program (including rigorous screening tool)
- 3) Data-Sharing Repository

# Research Recommendations

*Provides recommendations for advancing a coordinated, standardized and cost-effective research effort*

*PDF Available on CPRA's web site:  
[www.ChronicPainResearch.org](http://www.ChronicPainResearch.org)*

## Section VIII: Recommendations for Advancing Research

### Learning from Past Successes and Failures

The NIH Pain Consortium recently established the NIH Task Force on Research Standards for Chronic Low Back Pain (cLBP) after a review of cLBP studies demonstrated that researchers use "variable inclusion and exclusion criteria, case definitions for LBP chronicity or recurrence, baseline assessments, stratification criteria, and outcome measures," and that "as a result, it is difficult to compare studies of similar or competing interventions, replicate findings, pool data from multiple studies, resolve conflicting conclusions, develop multidisciplinary consensus, or even achieve consensus within a discipline regarding interpretation of findings."<sup>472</sup> The resultant manuscript summarizes the Task Force's recommendations for definitions, a minimum dataset, reporting outcomes, and future research.<sup>473</sup>

The NIH Pain Consortium has approved the recommendations, which investigators are now asked to incorporate into their NIH grant applications. The Task Force believes that these recommendations will advance the field, help to resolve controversies, and facilitate future research, as greater consistency in reporting should facilitate comparison among studies.

Deliberations of the August 2012 Workshop on Chronic Overlapping Pain Conditions (COPCs) revealed almost identical findings. As no Research Diagnostic Criteria (RDC) for COPCs currently exist, investigators from different institutions are using different ontology, case definitions and outcome measures. High-caliber research on COPCs has recently begun and we have a historic opportunity – responsibility even – to ensure that current and future research efforts are conducted in a strategic coordinated fashion. This will maximize the federal investment in COPCs research and reduce taxpayer waste from incomparable study findings. Most importantly, this will benefit those for whom scientific research is conducted – individuals affected by these life-altering disorders.

### Vision for the Future

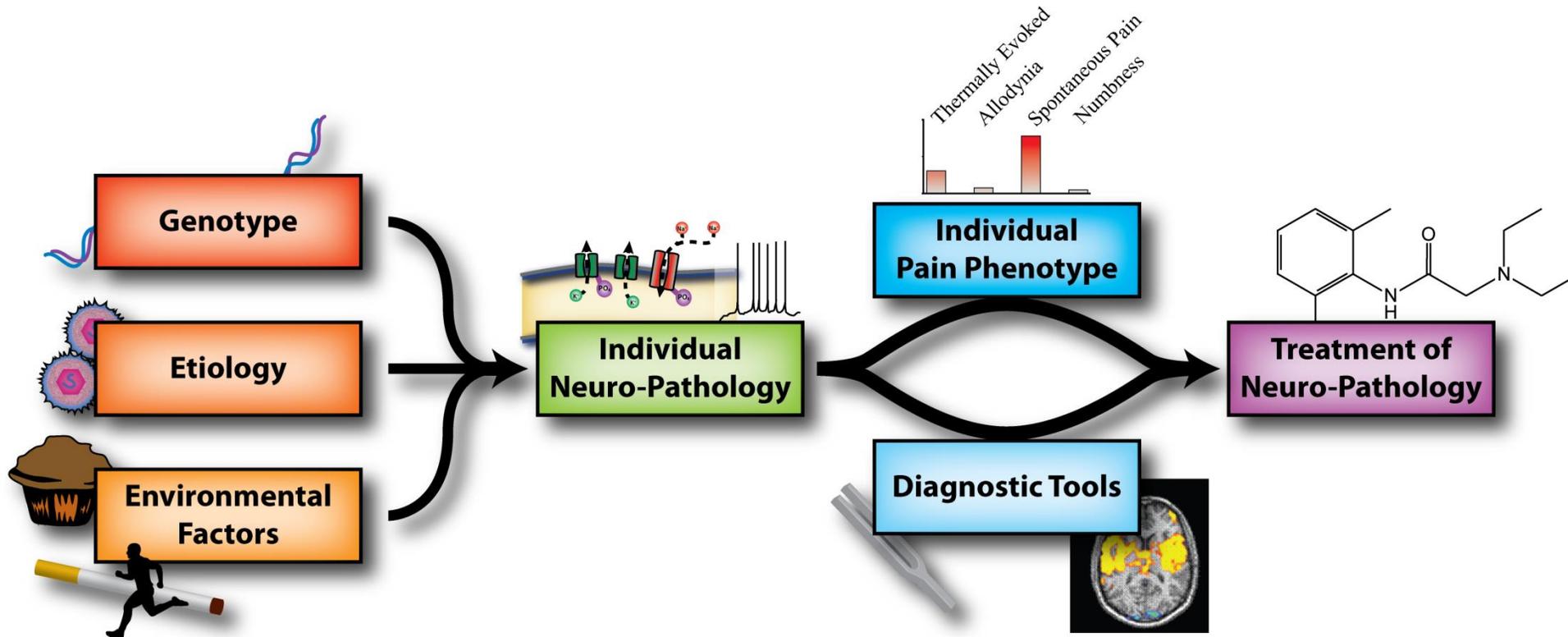
With an increased federal and private investment to implement the initiatives called for by the Chronic Pain Research Alliance, taxpayer dollars would be maximized through a coordinated, standardized and collaborative research effort, generating urgently needed scientific evidence on chronic overlapping pain conditions. This evidence would be used to develop diagnostic and treatment guidelines for the training of health care professionals, enabling them to provide high-quality, evidence-based medical care to those suffering from these life-altering conditions, improving their health, quality of life, dignity and ability to fully contribute to society.

### Basic, Translational and Clinical Research

*National Institutes of Health (NIH) | Patient Centered Outcomes Research Institute (PCORI) | Department of Veterans Affairs (VA) | Department of Defense (DOD) | Industry*

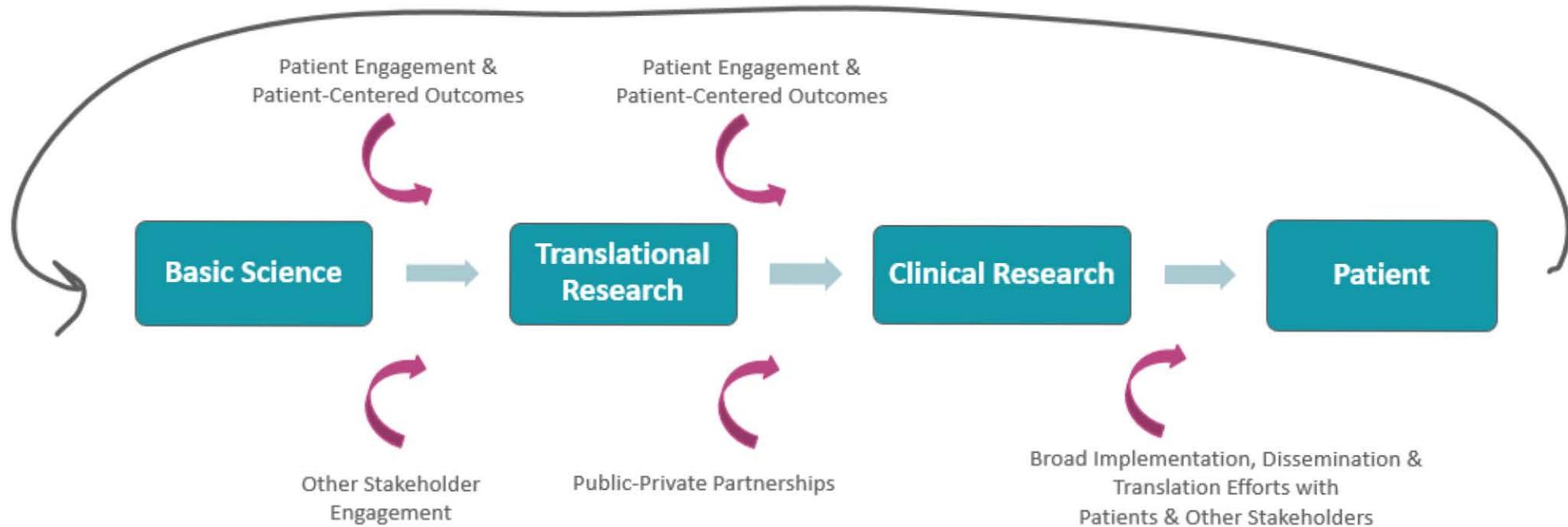
A comprehensive, coordinated and cost-effective effort – that spans the basic, translational and clinical research continuum – is urgently needed to advance understanding of the risks, causes and mechanisms of COPCs, and should yield safe and effective treatments for these disorders. The NIH should lead this effort through the developed Trans-NIH Working Group on Chronic Overlapping Pain Conditions, and should include all relevant agencies and organizations, such as the Patient Centered Outcomes Research Institute, Department of Defense and Department of Veteran Affairs. The research recommendations put forth from the August 2012 Workshop on Chronic Overlapping Pain Conditions should be used as a starting point. Further, in an effort to maximize the research investment in COPCs research, the large program projects already funded by the NIH and described in the prior section (MAPP, OPPERA, etc.), should be expanded upon to include all COPCs.

# Research Model – Shift Towards Mechanism-Based Individualized Treatment



# COPCs Research/Translation Model

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# CPRA 2015 White Paper

*Reviews latest data on:*

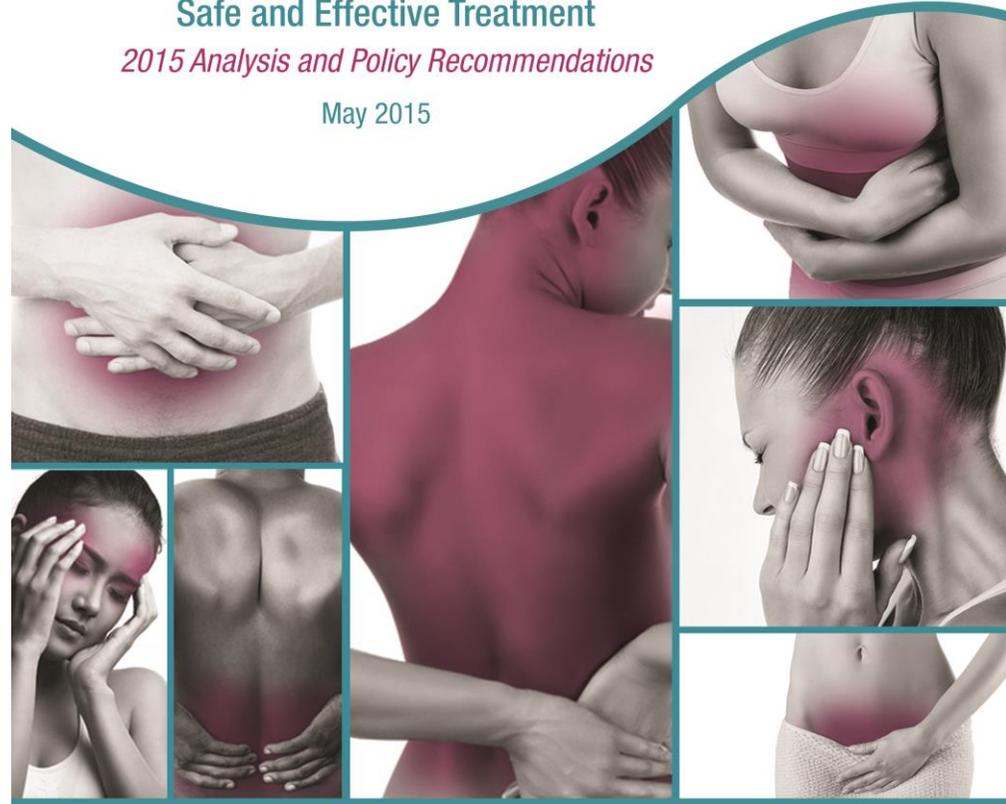
- *Prevalence, Burden of Illness & Societal Impact*
- *Research Disparities*
- *Safety & Efficacy of FDA-Approved Therapies*
- *Emerging Research on Common Underlying Disease Mechanisms*
- *Promising National Studies*

*PDF Available on CPRA's web site:  
[www.ChronicPainResearch.org](http://www.ChronicPainResearch.org)*

## Impact of Chronic Overlapping Pain Conditions on Public Health and the Urgent Need for Safe and Effective Treatment

*2015 Analysis and Policy Recommendations*

May 2015



Produced by



*Advancing Research – Changing Lives*

# COPCs Research Advances

*Purpose: Bimonthly electronic publication developed to keep the medical-scientific community abreast of recent scientific publications on COPCs*

*Provides: Compiled list of recently published abstracts on the epidemiology, pathophysiology and clinical management of COPCs*

*Sign-up & PDFs available at:  
[www.ChronicPainResearch.org](http://www.ChronicPainResearch.org)*



## FEATURE EDITORIAL

### **Challenges in drug discovery for overcoming 'dysfunctional pain': an emerging category of chronic pain.**

Nagakura Y.

Expert Opin Drug Discov. 2015 Oct;10(10):1043-5. doi: 10.1517/17460441.2015.1066776.

<http://www.tandfonline.com/doi/full/10.1517/17460441.2015.1066776>

'Dysfunctional pain', a type of chronic pain, is associated with a broad range of clinical disorders, including fibromyalgia, irritable bowel syndrome and interstitial cystitis. It is emerging as a serious issue due to the negative impact of inexplicable pain on quality of life, lack of effective therapies and health care cost. Although drug discovery efforts in pain research have so far focused primarily on inflammatory and neuropathic pain, this editorial attracts attention to dysfunctional pain research and discusses a possible fundamental framework for tackling this difficult issue. While dysfunctional pain is characterized by chronic widespread or regional pain symptoms and occurrence of pain amplification, underlying pathophysiologies remain to be identified. Thus, a pivotal step in future research would be the exploration of pathophysiological pathways, such as relevant molecular networks, which are responsible for dysfunctional pain. Utilization of developing technologies paves the way for the identification of underlying pathophysiologies and the development of effective drugs which would eventually solve the clinical issues associated with dysfunctional pain.

## NATIONAL STUDIES

### **Pain and Interoception Imaging Network (PAIN): A multimodal, multisite, brain-imaging repository for chronic somatic and visceral pain disorders.**

Labus JS, Naliboff B, Kilpatrick L, Liu C, Ashe-McNalley C, Dos Santos IR, Alaverdyan M, Woodworth D, Gupta A, Ellingson BM, Tillisch K, Mayer EA.  
Neuroimage. 2015 Apr 19. pii: S1053-8119(15)00308-0. doi:10.1016/j.neuroimage.2015.04.018.

The Pain and Interoception Imaging Network (PAIN) repository ([painrepository.org](http://painrepository.org)) is a newly created NIH (NIDA/NCCAM) funded neuroimaging data repository that aims to accelerate scientific discovery regarding brain mechanisms in pain and to provide more rapid benefits to pain patients through the harmonization of efforts and data sharing. The PAIN Repository consists of two components, an Archived Repository and a Standardized Repository. Similar to other 'open' imaging repositories, neuroimaging researchers can deposit any dataset of chronic pain patients and healthy controls into the Archived Repository. Scans in the Archived Repository can be very diverse in terms of scanning procedures and clinical metadata, complicating the merging of datasets for analyses. The Standardized Repository overcomes these limitations through the use of standardized scanning protocols along with a standardized set of clinical metadata, allowing an unprecedented ability to perform pooled analyses. The Archived Repository currently includes 741 scans and is rapidly growing. The Standardized Repository currently includes 433 scans. Pain conditions currently represented in the PAIN repository include: irritable bowel syndrome, vulvodynia, migraine, chronic back pain, and inflammatory bowel disease. Both the PAIN Archived and Standardized Repositories promise to be important resources in the field of chronic pain research. The enhanced ability of the Standardized Repository to combine imaging, clinical and other biological datasets from multiple sites in particular make it a unique resource for significant scientific discoveries.

