Developing HEAL Pain Strategic Research Priorities: The Intersection of Pain and Substance Use Disorders

Toward phenotyping and personalized pain medicine

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Definitions

Phenotyping is the process of analyzing, determining, or predicting an organism's phenotype (observable properties determined by the set of genes and environmental factors) including its physical appearance, development, and behavior.

Personalized medicine (precision medicine):

- A form of medicine that uses information about a person's genes, proteins, environment, and lifestyle to prevent, diagnose, or treat disease *(National Cancer Institute).*
- A medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention *(The European Commission).*

Do we need phenotyping for managing pain and OUD?

	Comparisons*	Participants†	Active pain relief	Placebo	Number needed to treat (95% CI)
Tricyclic antidepressants	15	948	217/473	85/475	3·6 (3·0–4·4)
Serotonin-noradrenaline reuptake inhibitors	10	2541	676/1559	278/982	6·4 (5·2–8·4)
Pregabalin	25	5940	1359/3530	578/2410	7·7 (6·5–9·4)
Gabapentin§	14	3503	719/2073	291/1430	7·2 (5·9–9·1)
Tramadol	6	741	176/380	96/361	4·7 (3·6–6·7)
Strong opioids	7	838	211/426	108/412	4·3 (3·4–5·8)

Buprenorphine/Methadone maintenance:

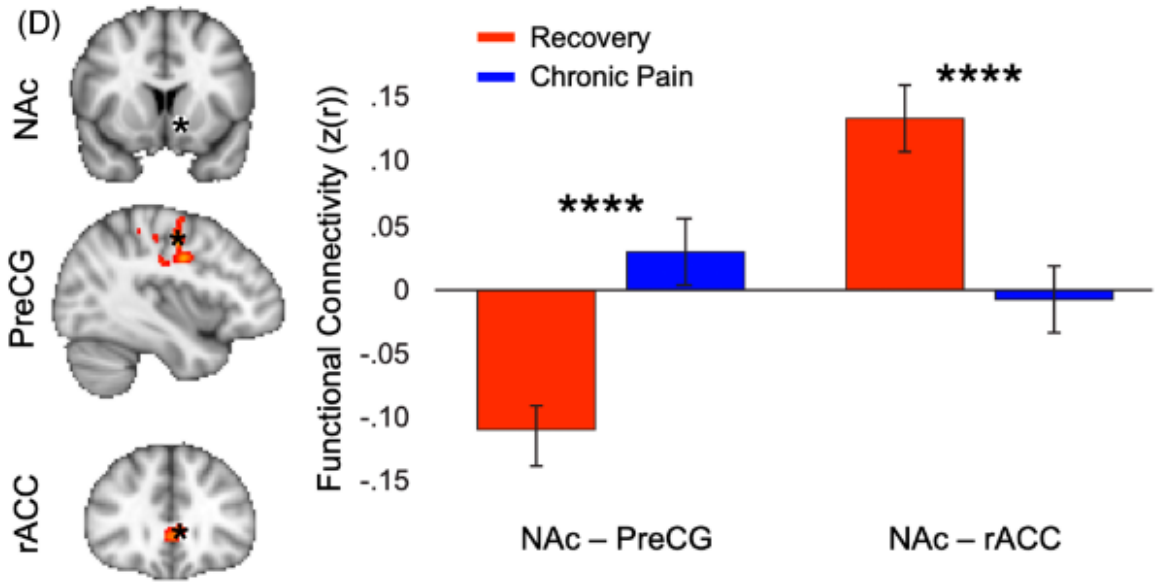
- NNT 2-3 for retention in treatment
- NNT ≈40 for prevention of an opioid overdose death

Finnerup et al, Lancet Neurol 2015; Schoenfeld et al, JAMA Network Open 2020

Examples of phenotyping-based approaches

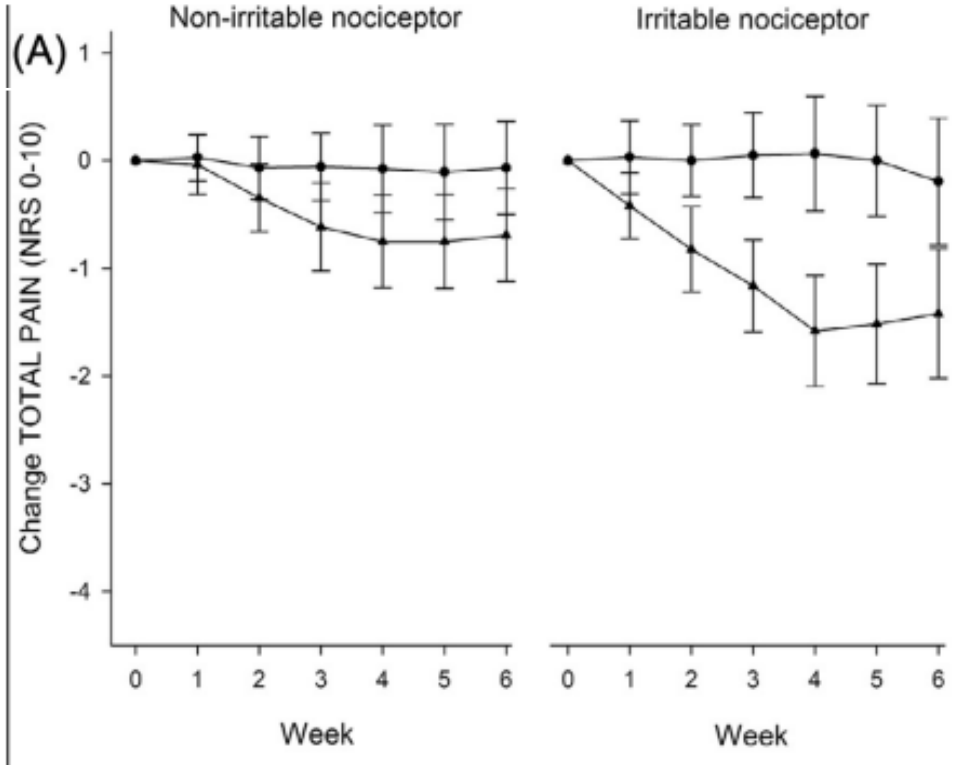
Brain Connectivity Predicts Chronic Pain in Acute Mild Traumatic Brain Injury

Noam Bosak, MD,[1,2*] Paulo Branco, PhD,[3*] Pora Kuperman, PhD,[1] Chen Buxbaum, MD,[1,2] Ruth Manor Cohen, MA,[1] Shiri Fadel, BSc,[2] Rabab Zubeidat, MHA,[1] Rafi Hadad, MD,[2] Amir Lawen, BSc,[1] Noam Saadon-Grosman, PhD,[4] Michele Sterling, PhD,[5] Yelena Granovsky, PhD,[1] Apkar Vania Apkarian, PhD,[3*] David Yarnitsky, MD,[1,2*] and Itamar Kahn, PhD[1]



The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study

Dyveke T. Demant [a], Karen Lund [b], Jan Vollert [c], Christoph Maier [c], Märtha Segerdahl [d,e], Nanna B. Finnerup [b], Troels S. Jensen [b], Søren H. Sindrup [a,*]



Opportunities to examine phenotypes of pain and OUD

Surgery

- 10-20% (not everyone!) will develop chronic post-surgical pain (CPSP)
- 6-9% will start using opioids chronically

Cancer chemotherapy

- 10-20% (not everyone!) receiving certain types of chemotherapy will develop painful peripheral neuropathy (CIPN)
- Double the rates of opioid use compared to cancer patients without CIPN

Non-personalized medicine: opioid use after surgery

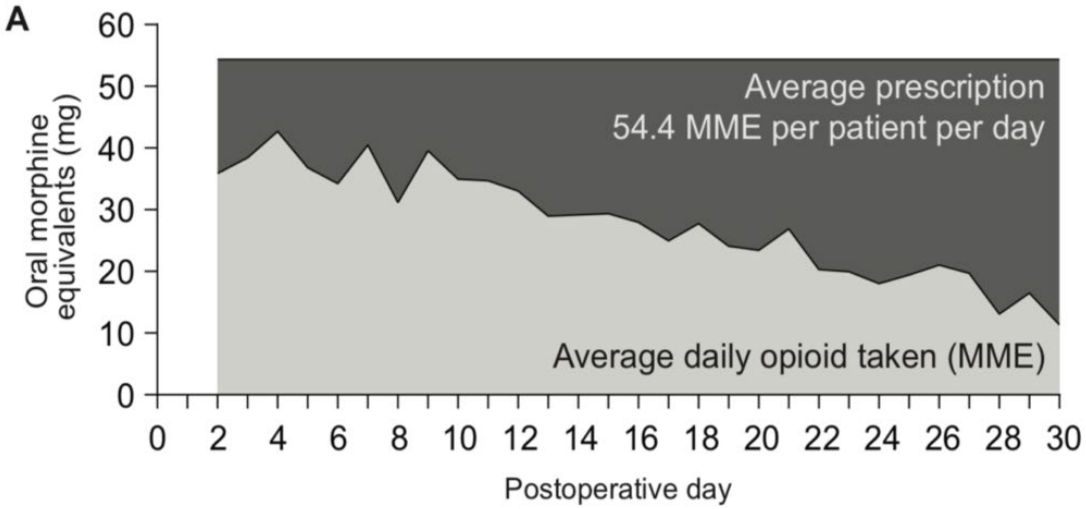
Stanford MEDICINE | medicine X
PEOPLE. TECHNOLOGY. DESIGN.


Michael Bottros, MD


Lara Crock, MD, PhD


Kate Meacham, MD, PhD

- 36 patients undergoing total knee arthroplasty procedure (TKA)
- Actigraphy monitoring with Activité Steel HR watch
- Mobile app-based recording of pain scores, opioid use and sleep quality



Opioid prescription at discharge: 54.4 MME/day

Actual opioid use: 28.1 MME/day

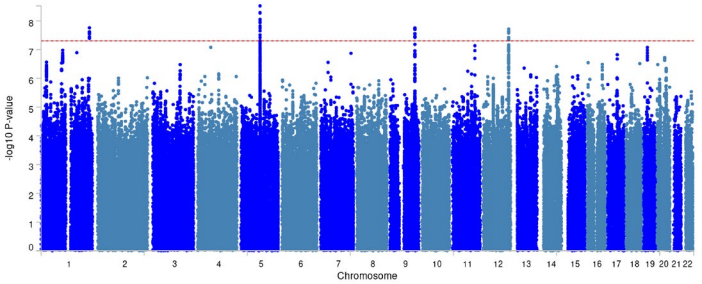
Cumulative unused excess: 28,404 MME

* Equivalent to 3,787 **unused** Oxycodone 5mg pills

MME: oral morphine mg equivalents

Do genomic factors interact with social determinants of health to influence risk of pain and OUD?

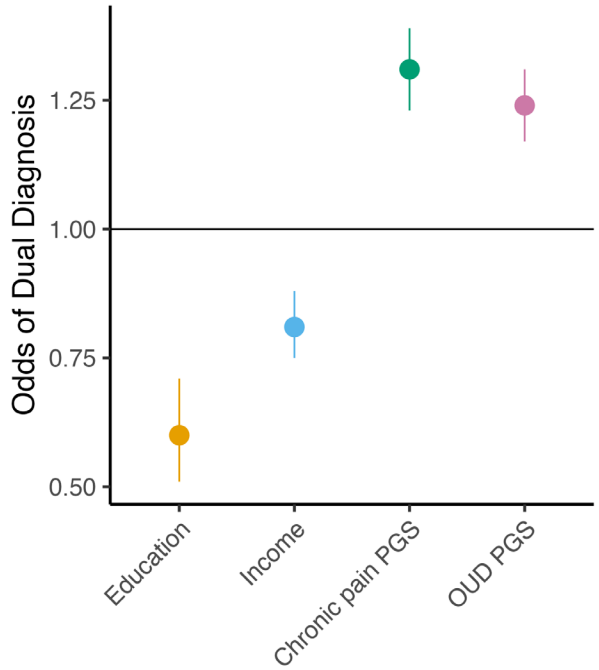
Multi-ancestral genome-wide association study to identify genetic variants and genes associated with chronic pain conditions



Emma Johnson, PhD

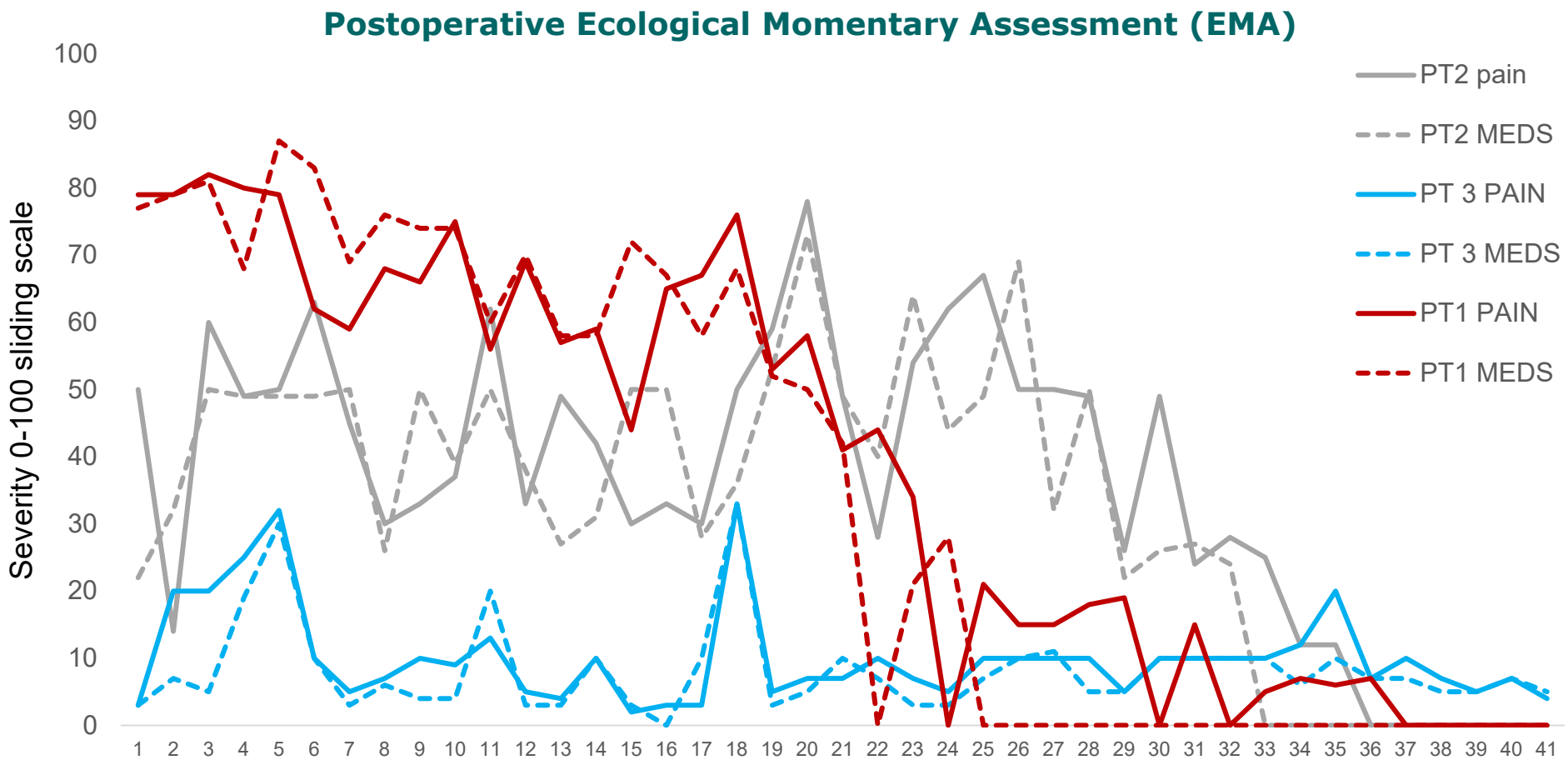
Use GWAS to develop polygenic scores (PGS)

Individuals with co-occurring chronic pain + opioid use disorder (OUD) have lower SES and higher genetic liability than those with only one diagnosis



Supported by R03DA059747 through All of Us' Extramural Program to Advance Research (EPAR)

Individual trajectories: Pain and analgesic needs after surgery



Unpublished data, **P5** (**P**ersonalized **P**rediction of **P**ersistent **P**ost-surgical **P**ain) study

What will determine an individual patient's trajectory?

CPSP – How do we identify patients at risk?

Sex

Age

Genetic Factors

Pre-operative chronic pain and analgesic use

Catastrophizing

Pain processing / Sensory Phenotype

Smoking

Cognitive parameters

Anesthetic approach

Anxiety and Depression

Expectations

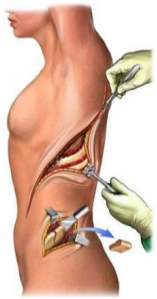
Acute Pain Experience

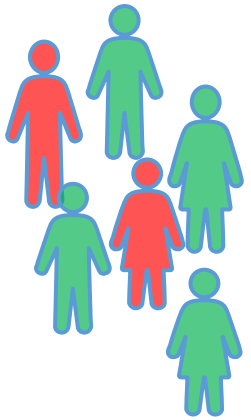
Inadvertent nerve injury

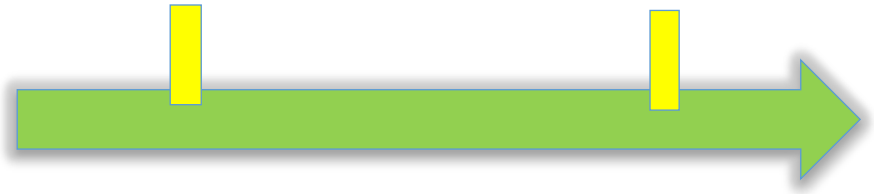
Other complications of surgery

Surgeon's training level

SURGERY **ASSESSMENT** **CLASSIFICATION**







CPSP risk and its prediction

Systematic Review and Meta-Analysis

PAIN®

Risk factors for persistent pain after breast and thoracic surgeries: a systematic literature review and meta-analysis

Joshua Lim[a], Dili Chen[b], Ewan McNicol[c], Lokesh Sharma[d], Grihith Varaday[d], Anshuman Sharma[d], Elizabeth Wilson[d], Tiffany Wright-Yatsko[d], Lauren Yaeger[e], Ian Gilron[f], Nanna B. Finnerup[g], Simon Haroutounian[d,*]

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Review Article

Perioperative Risk Factors for Persistent Postsurgical Pain After Inguinal Hernia Repair: Systematic Review and Meta-Analysis

Harutyun Alaverdyan,* Jooyoung Maeng,* Peter K. Park,† Kavya Narayana Reddy,‡ Michael P. Gaume,§ Lauren Yaeger,¶ Michael M. Awad,‖ and Simon Haroutounian*

Systematic Review and Meta-Analysis

PAIN®

Perioperative factors associated with persistent postsurgical pain after hysterectomy, cesarean section, prostatectomy, and donor nephrectomy: a systematic review and meta-analysis

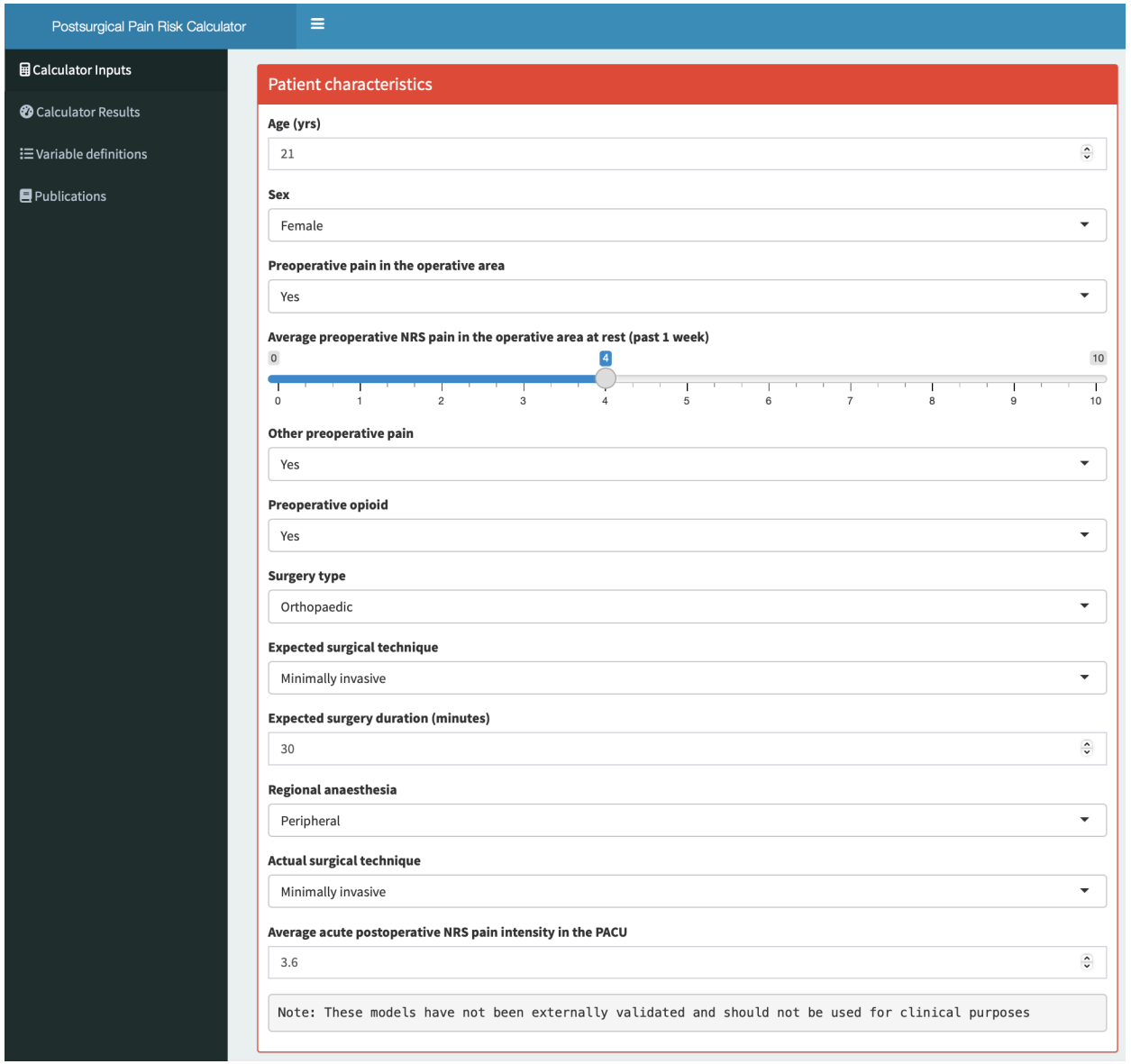
Lokesh R. Sharma[a], Ellen Lund Schaldemose[b], Harutyun Alaverdyan[a], Lone Nikolajsen[b], Dili Chen[c], Shivam Bhanvadia[d], Helga Komen[a], Lauren Yaeger[e], Simon Haroutounian[a,*]

OPEN

PAIN® REPORTS

Factors associated with persistent postsurgical pain after total knee or hip joint replacement: a systematic review and meta-analysis

Arunangshu Ghoshal[a], Shivam Bhanvadia[b], Som Singh[c], Lauren Yaeger[d], Simon Haroutounian[e,*]



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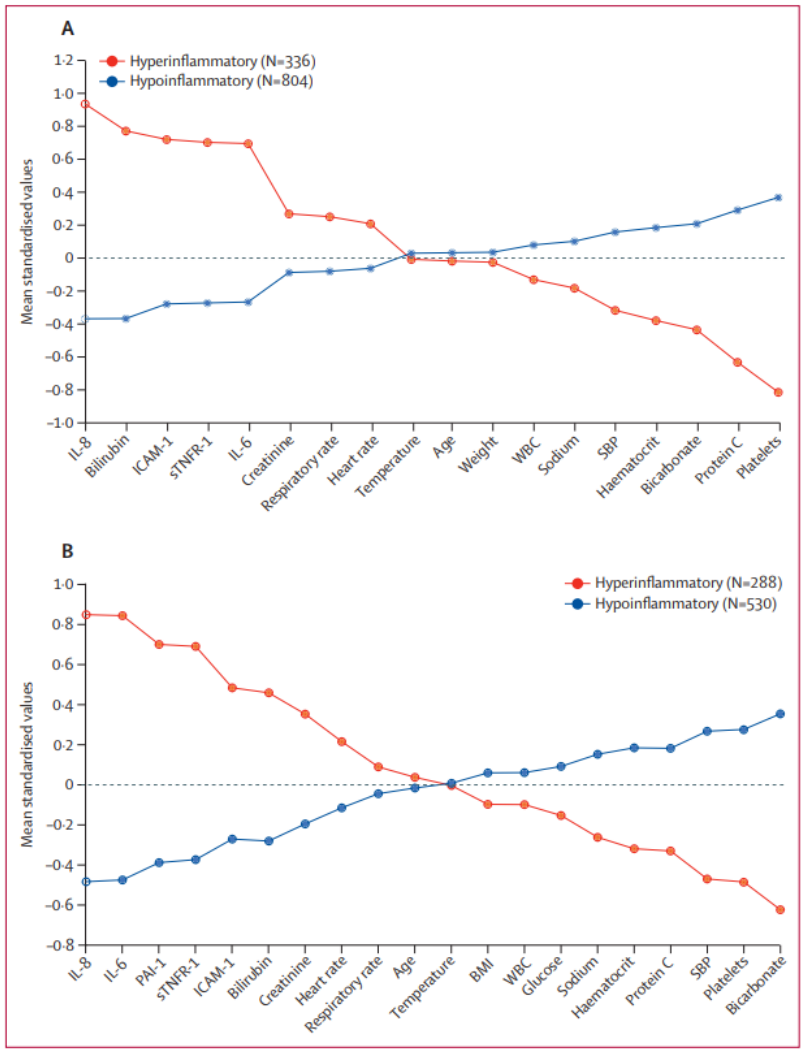
Development and internal validation of a clinical risk tool to predict chronic postsurgical pain in adults: a prospective multicentre cohort study

Nicholas Papadomanolakis-Pakis[a,b,*], Simon Haroutounian[c], Johan Kløvgaard Sørensen[a,d], Charlotte Runge[d], Lone Dragnes Brix[a,e], Christian Fynbo Christiansen[a,f], Lone Nikolajsen[a,b]

https://psp-risktools.shinyapps.io/psp_risk/

Sepsis - Example of Comprehensive Phenotyping



Pratik Sinha, MD

	Hypoinflammatory			Hyperinflammatory			p value	
	N	ICU-free days (IQR)	Mortality	N	ICU-free days (IQR)	Mortality	ICU-free days	Mortality
VALID*	804	21 (11–24)	133 (16·5%)	336	7 (0–22)	143 (42·6%)	<0·0001	<0·0001
EARLI*	530	23 (17–25)	107 (20·2%)	288	12 (0–23)	129 (44·8%)	<0·0001	<0·0001
VALID* ARDS excluded	532	23 (17–25)	70 (13·2%)	236	16 (0–23)	80 (33·4%)	<0·0001	<0·0001
EARLI* ARDS excluded	346	24 (21–25)	48 (13·9%)	226	22 (0–24)	77 (34·1%)	<0·0001	<0·0001
PROWESS-SHOCK†	1142	13 (0–20)	233 (20·4%)	538	0 (0–14)	192 (35·7%)	<0·0001	<0·0001
VASST†	455	11 (0–20)	127 (27·9%)	323	0 (0–12)	163 (50·5%)	<0·0001	<0·0001

ICU-free days were censored at day 28, such that patients that died before day 28 were assigned zero ICU-free days. p values for ICU-free days were generated using the Wilcoxon rank test and for mortality using the χ^2 test. Class 1=hypoinflammatory and Class 2=hyperinflammatory in VALID and EARLI. ICU=intensive care unit. VALID=Validating Acute Lung Injury biomarkers for Diagnosis trial. EARLI=Early Assessment of Renal and Lung Injury trial. ARDS=acute respiratory distress syndrome. PROWESS-SHOCK=Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock trial. VASST=Vasopressin and Septic Shock Trial. *In-hospital mortality. †Mortality at day 28.

Table 2: **Differences in clinical outcomes between the hypoinflammatory and hyperinflammatory phenotypes across four sepsis cohorts**

Sinha et al, Lancet Respir Med 2023

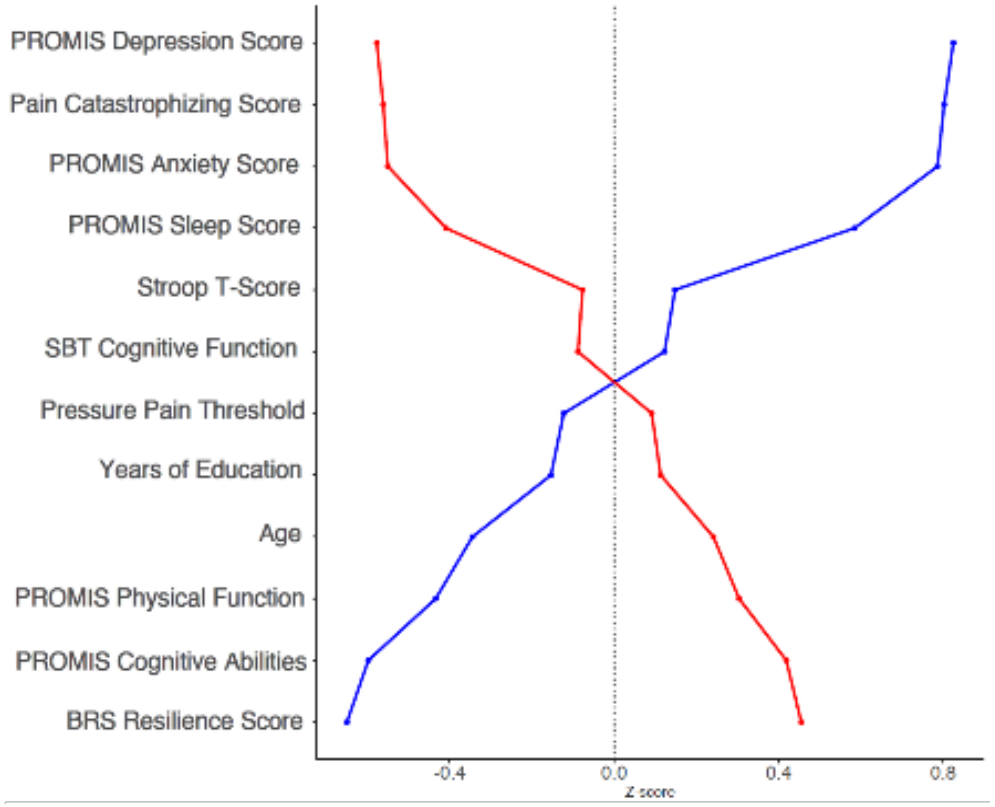
Applying Patient Phenotyping approaches to CPSP

684 patients from P5 cohort who developed chronic post-surgical pain (CPSP)

Preoperative data used to generate clusters, using K-mean clustering

Cluster 1 (blue):

- High depression
- High anxiety
- High catastrophizing
- Poor sleep
- Poor cognitive abilities
- Younger age
- Poor physical function
- Low self-reported resilience



Unpublished data, Haroutounian lab

Our view of next step in phenotyping approaches to CPSP

WashU P5 Cohort: 3,000 patients with preoperative phenotyping, >1,440 abdominal surgeries

Postoperative follow-up 6 months

No CPSP
>900 expected

CPSP
>400 expected

CPSP: 220

Matched controls: 100

IMPETUS

Aim 1

Sensory symptoms
skin biopsy
immune phenotyping

Peripheral domain-specific clustering and comparison to no-CPSP controls

Peripheral domain correlates: mouse

Sensory testing
skin biopsy
immune phenotyping

Aim 2

Activity
Affective, cognitive
phenotyping

Central domain-specific clustering and comparison to no-CPSP controls

Central domain correlates: mouse

Activity
Affective, cognitive
phenotyping

Aim 3 Multi-Domain Clustering Along Central and Peripheral Mechanisms • Polygenic Risk

Heterogeneous patient populations stratified by mechanistic clusters

Clinically meaningful animal models recapitulating mechanistic clusters

Inform personalized treatment approaches and clinical trials with patient groups stratified by mechanistic clusters

Supported by HEAL 1RM1NS135283

Patient perspectives for phenotyping and personalized medicine

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Patient engagement in designing, conducting, and disseminating clinical pain research: IMMPACT recommended considerations

Simon Haroutounian[a,*], Katherine J. Holzer[a], Robert D. Kerns[b], Christin Veasley[c], Robert H. Dworkin[d], Dennis C. Turk[e], Kristin L. Carman[f], Christine T. Chambers[g], Penney Cowan[h], Robert R. Edwards[i], James C. Eisenach[j], John T. Farrar[k], McKenzie Ferguson[l], Laura P. Forsythe[f], Roy Freeman[m], Jennifer S. Gewandter[d], Ian Gilron[n], Christine Goertz[o], Hanna Grol-Prokopczyk[p], Smriti Iyengar[q], Isabel Jordan[g], Cornelia Kamp[r], Bethea A. Kleykamp[s], Rachel L. Knowles[t], Dale J. Langford[u], Sean Mackey[v], Richard Malamut[w], John Markman[x], Kathryn R. Martin[y], Ewan McNicol[z], Kushang V. Patel[e], Andrew S.C. Rice[aa], Michael Rowbotham[ab], Friedhelm Sandbrink[ac], Lee S. Simon[ad], Deborah J. Steiner[ae], Jan Vollert[aa,af,ag,ah]

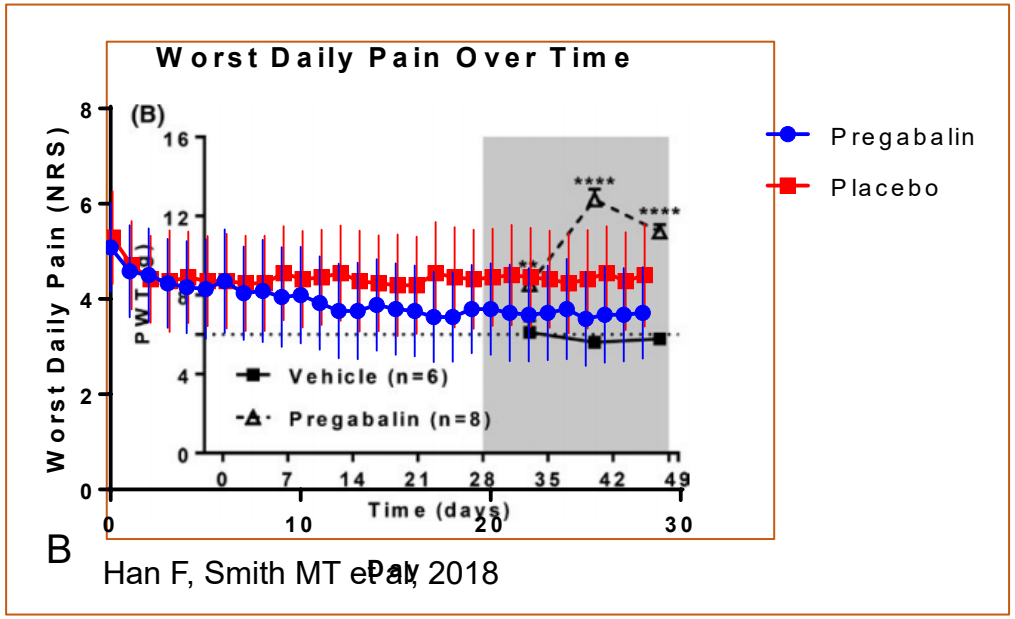
Katie Holzer

Chris Veasley

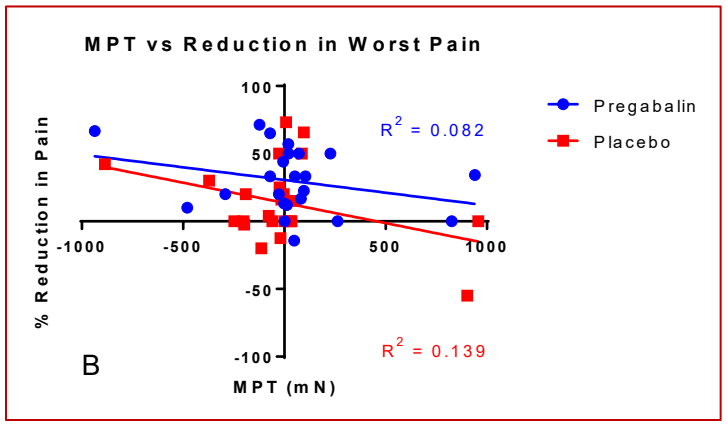
Robert Kerns

Robert Dworkin

Phenotypes, predictors, and what patients care about



Han F, Smith MT et al, Pain 2018



PAIN

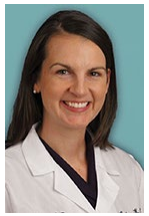
Somatosensory predictors of response to pregabalin in painful chemotherapy-induced peripheral neuropathy: a randomized, placebo-controlled, crossover study

Alexander Hincker[a,b], Karen Frey[a], Lesley Rao[a,b], Nina Wagner-Johnston[c], Arbi Ben Abdallah[a], Benjamin Tan[d], Manik Amin[d], Tanya Wildes[a,d], Rajiv Shah[a,b], Pall Karlsson[e,f], Kristopher Bakos[g], Katarzyna Kosicka[h], Leonid Kagan[i], Simon Haroutounian[a,b,*]


Alex Hincker, MD


Karen Frey


Rajiv Shah, MD


Lesley Rao, MD


Leonid Kagan, PhD


Benjamin Tan, MD

	Pregabalin	Placebo	P value
Evoked pain (NPSI), % reduction	**30%**	**12%**	**0.02**

8. Is your pain provoked or increased by <u>brushing</u> on the painful area?

No pain worst pain imaginable
0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

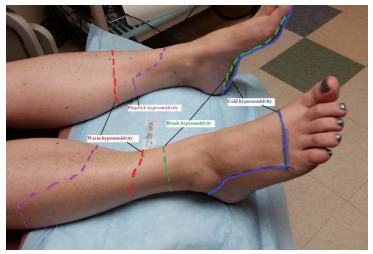
9. Is your pain provoked or increased by <u>pressure</u> on the painful area?

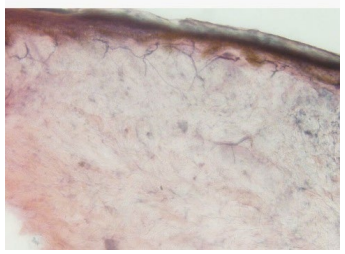
No pain worst pain imaginable
0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

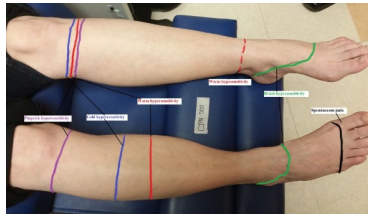
10. Is your pain provoked or increased by <u>contact with something cold</u> on the painful area?

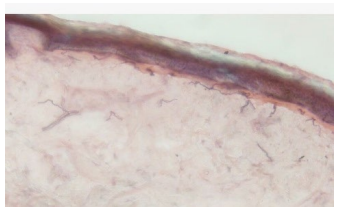
No pain worst pain imaginable
0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

Can we "dig deeper" while focusing on what patients care about?









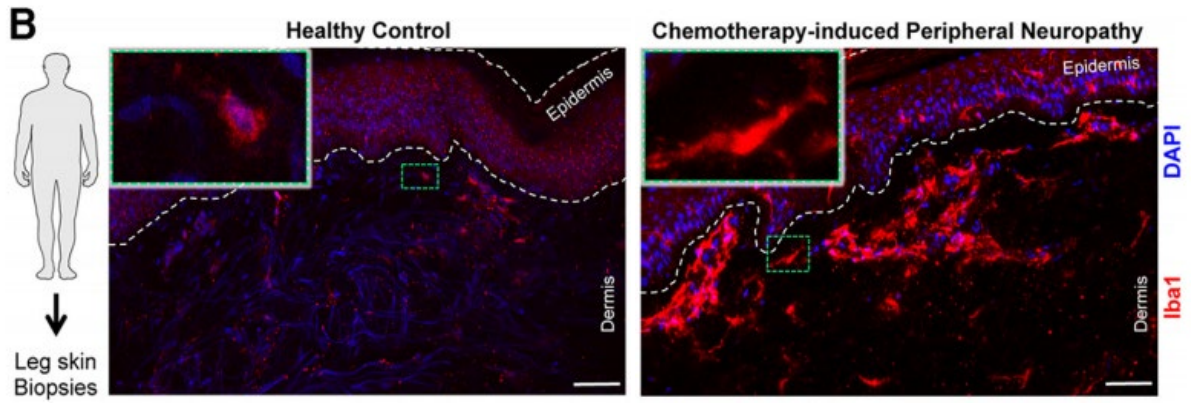
Angiotensin II Triggers Peripheral Macrophage-to-Sensory Neuron Redox Crosstalk to Elicit Pain

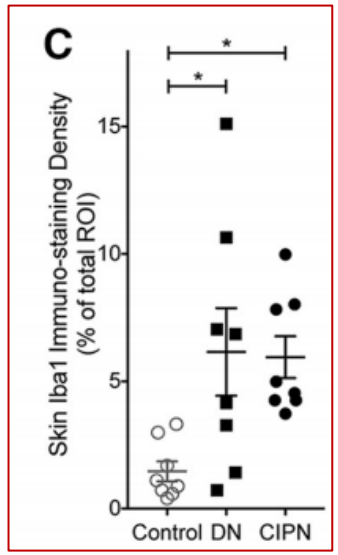
Andrew J. Shepherd,[1,2] Bryan A. Copits,[1*] Aaron D. Mickle,[1,2*] Páll Karlsson,[3,4*] Suraj Kadunganattil,[1*] Simon Haroutounian,[1] Satya M. Tadinada,[2] Annette D. de Kloet,[5] Manouela V. Valtcheva,[1] Lisa A. McIlvried,[1] Tayler D. Sheahan,[1] Sanjay Jain,[6] Pradipta R. Ray,[7] Yuriy M. Usachev,[2] Gregory Dussor,[7] Eric G. Krause,[8] Theodore J. Price,[7] Robert W. Gereau IV,[1,9] and Durga P. Mohapatra[1,2,10]

Andrew Shepherd, PhD

Pall Karlsson, PhD

Macrophage density in human skin fibers





Shepherd et al, J Neurosci 2018

Exploring Patient and Clinician Perspectives on Risk Prediction for Chemotherapy-Induced Peripheral Neuropathy (CIPN)


Joanna Abraham, PhD


Justin Stout


Katie Holzer, PhD

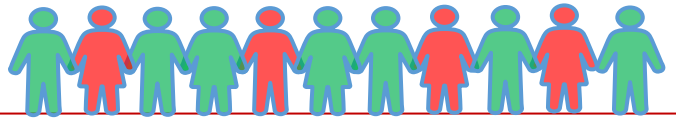

Karen Frey

Themes that are important for patients:

- Be able to attain full benefit of chemotherapy and not require dose reduction / discontinuation due to neuropathy
- Be better informed about risks of CIPN, and participate in shared decision making
- Having a sense of individual risk will help make decisions about participating in prevention trials

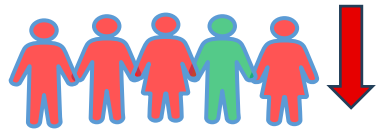
Supported by HEAL 1R41CA277875

Prediction of CIPN to inform personalized care and research

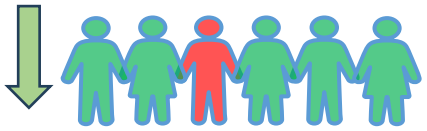


Patient cohort – chemotherapy candidates

Screening for CIPN risk



High Risk



Low Risk

Randomize to interventions

Supported by HEAL 1R41CA277875

Summary

- One-size-fits-all approach does not work for pain prediction or treatment; results in patient harm and recourse/time waste
- Phenotyping approaches has been used, mostly unimodal, with limited applicability so far
- Performing comprehensive phenotyping where mechanistic insights can be gained (e.g., with genotyping and multi-omics) likely to provide added beneficial
- Critical to maintain patient-centered focus
- Opportunity to develop animal models that are phenotypically aligned, to bridge translational gaps

Acknowledgements

Thank you to my lab members, collaborators, funding agencies and importantly – all patients who volunteer to participate in clinical studies