National Institutes of Health
HEAL Initiative

Integrating biomarkers and predictors to advance precision pain management

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BIOMARKERS & PREDICTORS SUBCOMMITTEE

PUBLIC VIRTUAL SESSION

WEDNESDAY, NOVEMBER 6TH, 2024

Outline

Neuroimaging biomarkers of pain

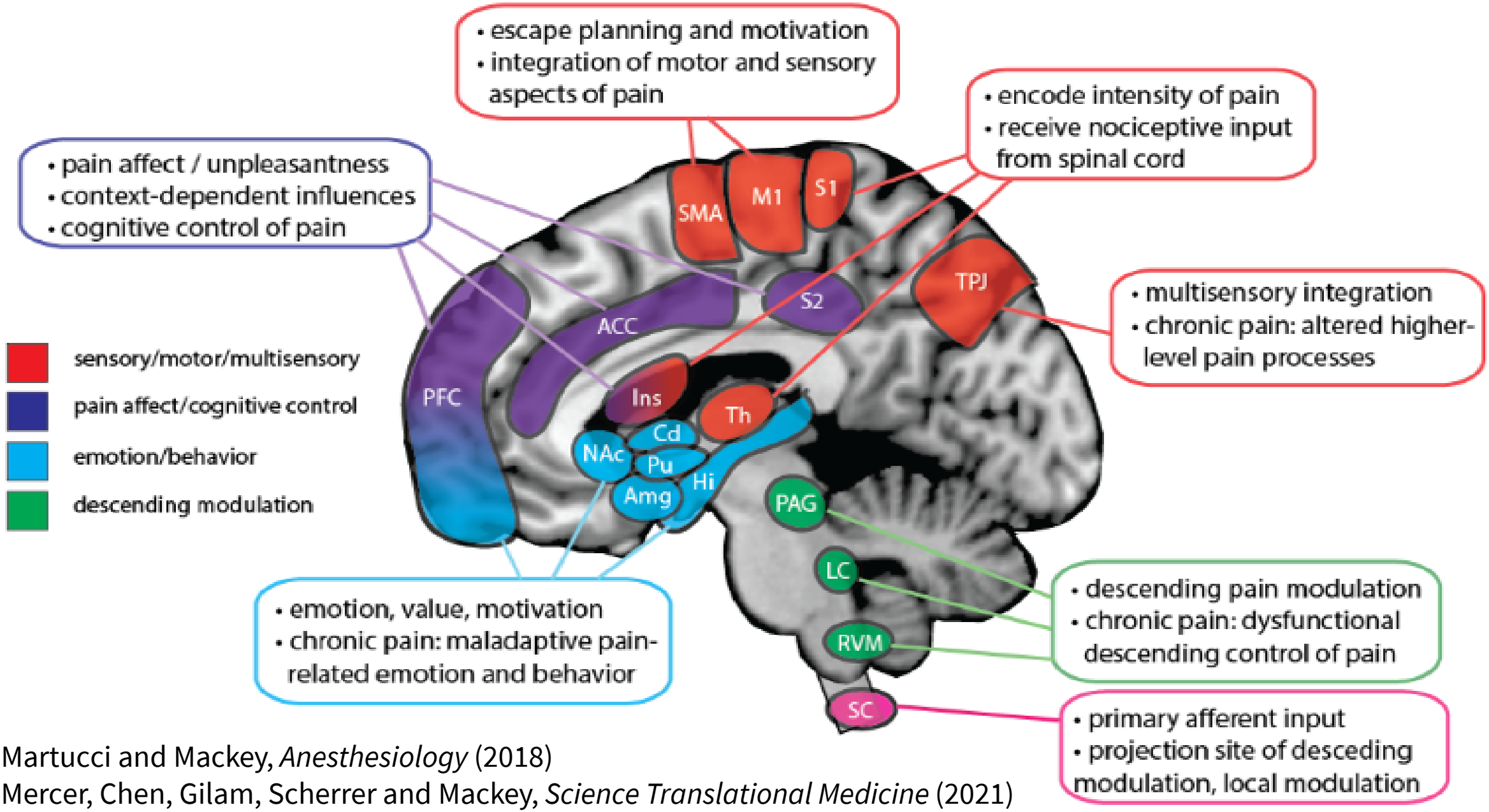
Predictors or Markers of pain

Multimodal integration

Clinical translation and utility

Neuroimaging of Pain

Pain is a product of the brain, brainstem and spinal cord and periphery



Martucci and Mackey, *Anesthesiology* (2018)
Mercer, Chen, Gilam, Scherrer and Mackey, *Science Translational Medicine* (2021)

CONSENSUS STATEMENT

OPEN

Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations

Karen D. Davis[1,2,3], Herta Flor[4], Henry T. Greely[5], Gian Domenico Iannetti[6], Sean Mackey[7], Markus Ploner[8], Amanda Pustilnik[9,10], Irene Tracey[11], Rolf-Detlef Treede[12] and Tor D. Wager[13,14]

Potential misuses of pain biomarkers

- Consequences of false-negative findings
  - Doctor–patient, employee–patient, family–patient trust issues
  - Denial of medical treatment or insurance coverage
  - Mental health, stress, spousal and/or family issues
  - Financial, insurance and employment issues
  - Privacy and legal (for example, medical malpractice) issues
- Consequences of false-positive findings
  - Unnecessary, costly and potentially harmful analgesic treatment in non-communicative patients
- Human, infrastructure, financial and time resources
- Misunderstanding as a substitute for self-report

Non-Biomarker Predictors of Pain

- Original task force focused on traditional biomarkers and clinical endpoints
- Emphasis on “objective” biomarkers
- Precluded use non-biomarker predictors
- Opportunity to integrate additional high-quality data into modeling


CONSENSUS STATEMENT

OPEN

Check for updates

Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities

Karen D. Davis[1,2✉], Nima Aghaeepour[3], Andrew H. Ahn[4], Martin S. Angst[5], David Borsook[5], Ashley Brenton[6], Michael E. Burczynski[7], Christopher Crean[8], Robert Edwards[9], Brice Gaudilliere[3], Georgene W. Hergenroeder[10], Michael J. Iadarola[11], Smriti Iyengar[12], Yunyun Jiang[13], Jiang-Ti Kong[3], Sean Mackey[3], Carl Y. Saab[14], Christine N. Sang[15], Joachim Scholz[16], Marta Segerdahl[17], Irene Tracey[18], Christin Veasley[19], Jing Wang[20], Tor D. Wager[21], Ajay D. Wasan[22] and Mary Ann Pelleymounter[12]

Non-Biomarker Predictor of Pain

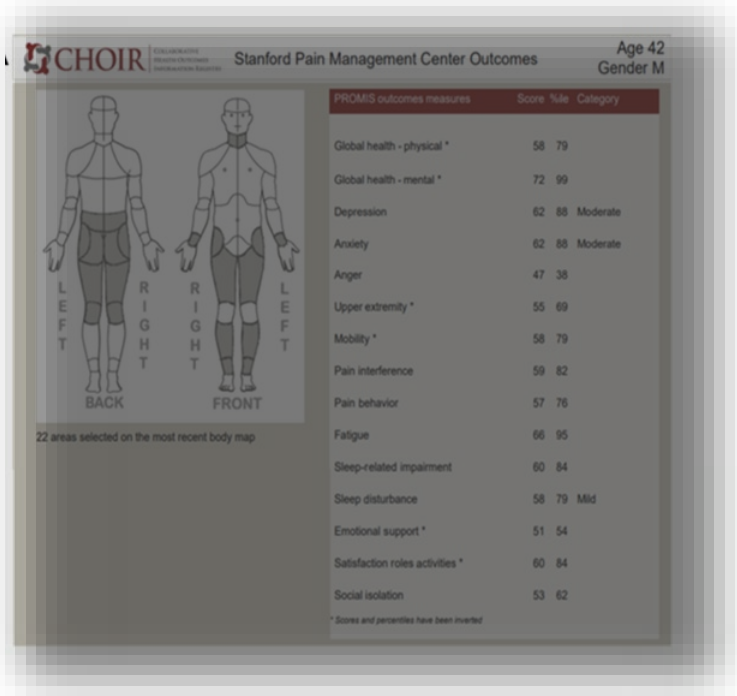
- Demographic predictors
  - Age, sex, ethnicity and race, socioeconomic status
- Behavioral and Lifestyle Predictors
  - Sleep quality, physical activity, smoking status, medication adherence, substance use
- Social and Environmental Predictors
  - Social support, work-related factors, environmental stressors, healthcare access
- Psychological predictors
  - Anxiety, depression, fear-avoidance beliefs, pain catastrophizing, self-efficacy
  - Trait, state, evoked
  - Patient reported outcome measures (PROs or PROMs)

Concerns about PROs for predictive modeling

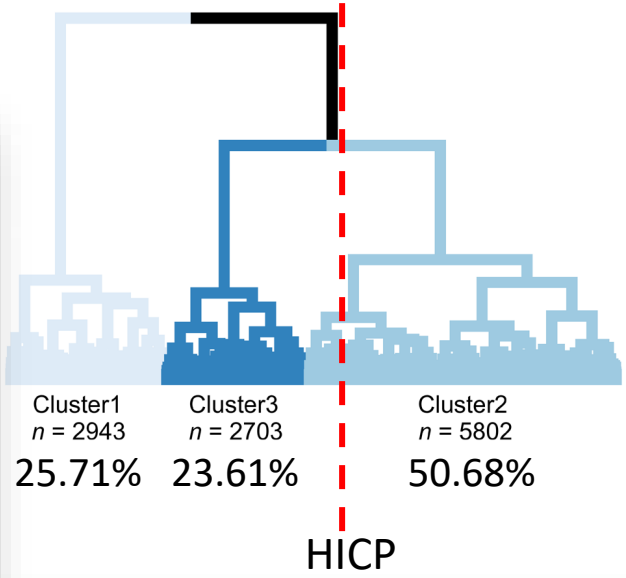
- Subjectivity and Bias making less reliable
- Standardization and Reproducibility
- Alignment with mechanistic models
- Data integration challenges
- Potential for misinterpretation or overemphasis on patient experience

- Need for balance!

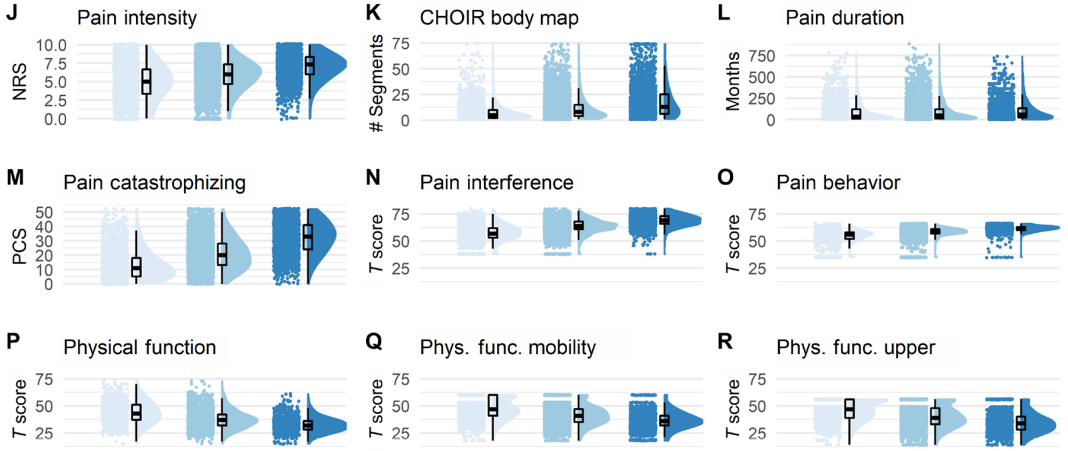
Classifying chronic pain using multidimensional pain-agnostic symptom assessments and clustering analysis



Dendrogram of training dataset (n=11448)

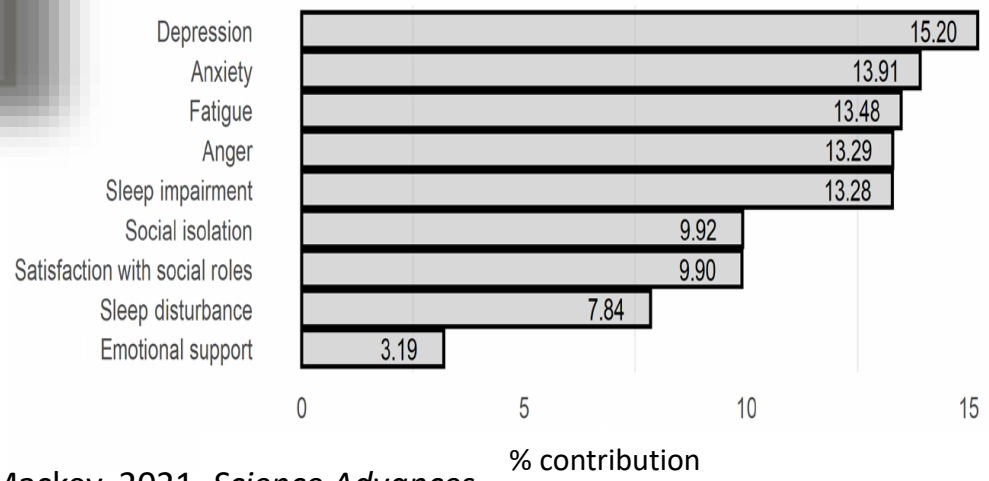


Differences between clusters across pain specific measures

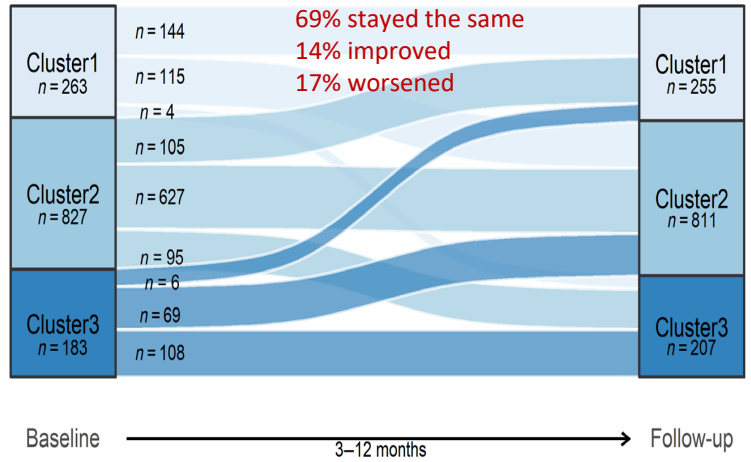


Replicated in two more data sets of n=3817 and n=1273

Symptom contribution to cluster assignment



Patients' transition across clusters over time



Gilam, Cramer, Weber, Ziadni, Kao and Mackey, 2021, *Science Advances*

nature reviews neurology

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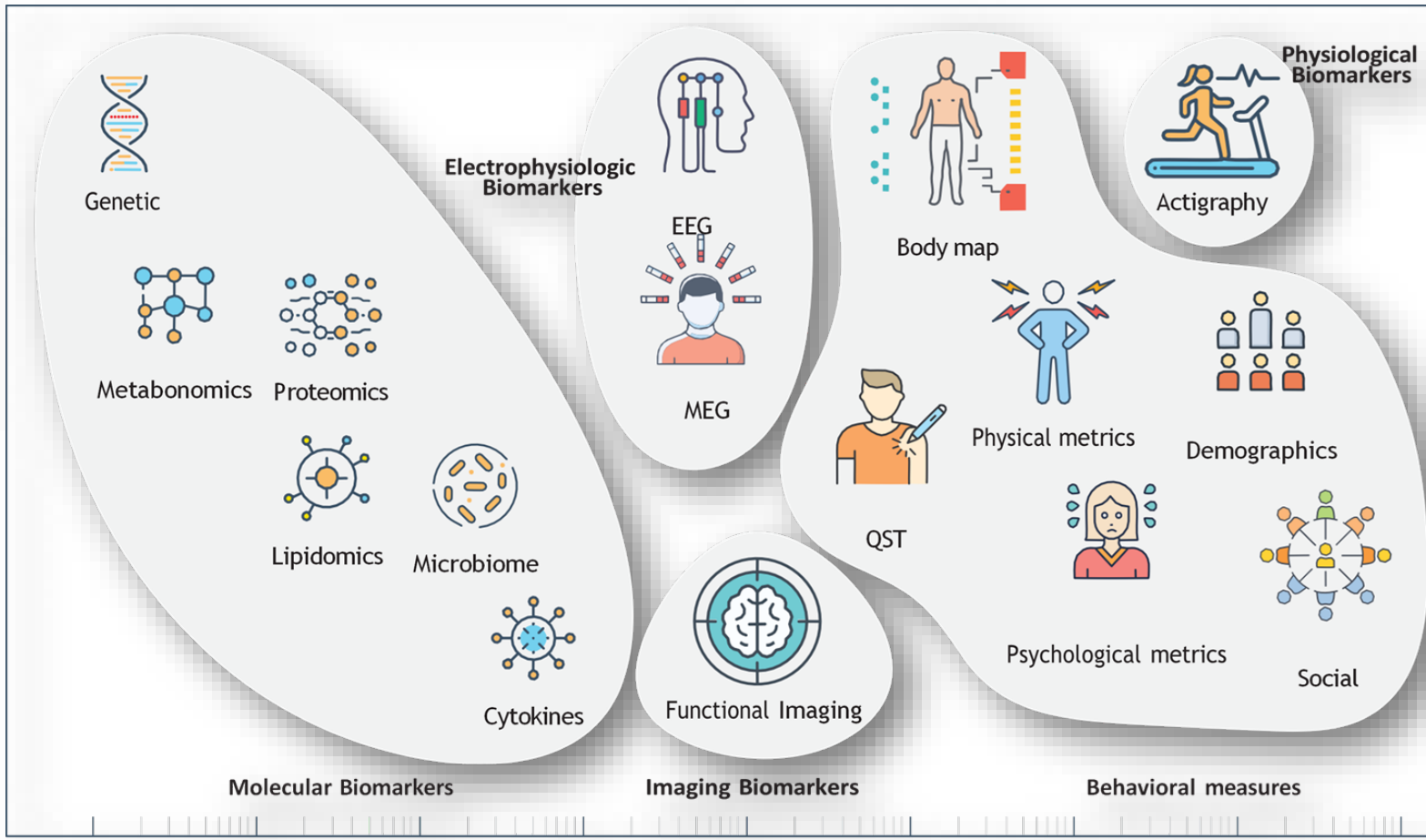
Nature Reviews Neurology 16, 381–400(2020)

Multimodal Pain Biomarkers



Mackey, S., et al, Innovations in Acute and Chronic Pain Biomarkers: Enhancing Diagnosis and Personalized Therapy, *Regional Anesthesia and Pain Medicine* (2024)