Executive Summary: HEAL Pain Strategic Planning Workshop

Biomarkers & Predictors

November 6th, 2024, 1:00-4:00pm ET

Subcommittee members: Yenisel Cruz-Almeida, PhD, University of Florida; Vivianne Tawfik, MD, PhD, Stanford University; Christine Von Raesfeld, PWLE; Christin Veasley, PWLE, Chronic Pain Research Alliance; Susan Dorsey, PhD, University of Maryland, Baltimore; Tor Wager, PhD, Dartmouth College; Peter Grace, PhD, MD Anderson Cancer Center; Sean Mackey, MD, PhD Stanford University; Aaron Fields, PhD, University of California, San Francisco; Sandip Biswal, MD, Stanford Medicine

Recording available at: Developing HEAL Pain Strategic Research Priorities: Biomarkers and Predictors

- Welcome remarks and overview from HEAL Strategic Planning Executive Co-Chair **Kathleen Sluka, PhD, University of Iowa**
- Introduction from co-chair **Yenisel Cruz-Almeida** including the basic definition of biomarkers and types of biomarkers particularly important in addressing pain: prognostic, diagnostic, predictive, pharmacodynamic, recurrence.

- **Christin Veasley and Christine Von Raesfeld**, persons with lived experience of pain (PWLE), presented about their lifelong journeys as they pertain to this topic. Veasley, director and co-founder of the Chronic Pain Research Alliance, highlighted types of biomarkers particularly salient to patients: diagnostic and predictive. Von Raesfeld shared her experience with pharmacogenetic testing, cognitive behavioral therapy as an effective coping tool, and a multidisciplinary team.

- **Peter Grace, PhD, MD Anderson Cancer Center,** presented on preclinical pain models being used to develop multimodal biomarkers. Understanding markers' biological role helps understand their utility.

- **Susan Dorsey, PhD, RN, FAAN, University of Maryland, Baltimore,** talked about the multiple ways that multi-omics markers could be used for pain, with a focus on predictive markers.

- **Howard Scher, MD, Memorial Sloan Kettering Cancer Center,** described a biomarker development program for cancer that works much the same as a drug development program. Key considerations included practicality of the biomarkers, funding and trial design. Funding is scarce for the necessary clinical trials to validate **symptom** biomarkers.

- **Jackson Brougher, PhD, Chief Scientific Officer, Doloromics,** offered an industry perspective on biomarker development, focusing on the Doloromics pipeline for precision therapeutics development for pain.

- **Sean Mackey, MD, PhD, Stanford University,** presented an overview of biomarker research (including a 2018 NIH workshop) to advance pain management, including brain imaging work and ethical considerations. Mackey stressed the importance of integrating patient-reported outcomes (PROs) into "signatures" made up of multiple markers – but current HEAL funding opportunities exclude PROs. They have incredibly high clinical value, validity, and practicality, despite being "non-biological" subjective measures. He shared his perspective that multimodal biomarkers are going to lead the field toward the ultimate goal of prediction and effective pain management.

Discussion:

- Mackey added that he believes that the field will someday have more biologically-based biomarkers and predictors for pain that are rooted in mechanism – but in the meantime, why not use the rich resource of PROs. Tawfik reminded the audience that a patient's report of pain is the ground-zero truth. Christin Veasley argued for using the best possible science available now to address patient care (including PROs). Christine Von Raesfeld made the point that patients need training to effectively self-report. Scher invited her input and said that should be included in studies.

Panel Discussions - Comments from additional subcommittee members:

- **Tor Wager, PhD, Dartmouth College**, stressed that we need biological indicators of mechanisms that drive pain for two reasons: to validate pain as a biological experience (like cancer, e.g.); and as biological treatment targets. We also need markers for parts of the chronic pain experience beyond pain itself. Think of biomarkers to identify targets in trials – then deploy them to patients.

- **Aaron Fields, PhD, UCSF**, argued for biomarkers of an individual's pain mechanism, which is difficult to identify. Also, deep phenotyping of patients' experiences could help inform the best markers to use in each patient but has challenges of generating and managing large volumes of multimetric data. How can we determine what type of pain people have – nociceptive, nociplastic, neuropathic?

- Dorsey emphasized the importance of **common data elements** across research programs so that large datasets can be combined and repurposed. PROs are mainly static measures; momentary ecological assessments use technology to get more dynamic information. This work requires interdisciplinary teams.

- Wager also commented on the interface of pain biology with the **placebo effect**, and the effect of screening out patients who are placebo "responders" in clinical trials. Pain is very susceptible to placebo effects over short and long time periods. One longstanding goal is identifying biomarkers that respond to pain but not to placebo.

- We need biomarkers of disease processes *and* biomarkers for pain and its chronification. Because disease progression and pain are often not linked, they may be separate (though not mutually exclusive). There won't be just one type of biomarker. Kathleen Sluka pointed out the utility in the combination of human and preclinical data. Grace added that the measures in animals are different from the measures in humans; the two are complementary. Tawfik used the term "clinically informed basic science research" to describe back-translation of human data to animal models. Dorsey asked about large animal models in biomarker research. Grace responded that large animals allow for study of natural disease models that is not possible in rodent.

- Veasley concluded with a perspective from a PWLE on the multidimensional impacts of chronic pain. Markers of disease process may differ from pain, but what are biomarkers for the amplification of the pain state? Those likely include the known contributors to pain: sleep, mood, cognitive dysfunction, fatigue, etc., which can be omni-directional and have a big impact on quality of life (beyond pain intensity). Von Raesfeld concluded that patient education and awareness is critical to bring into clinical care.