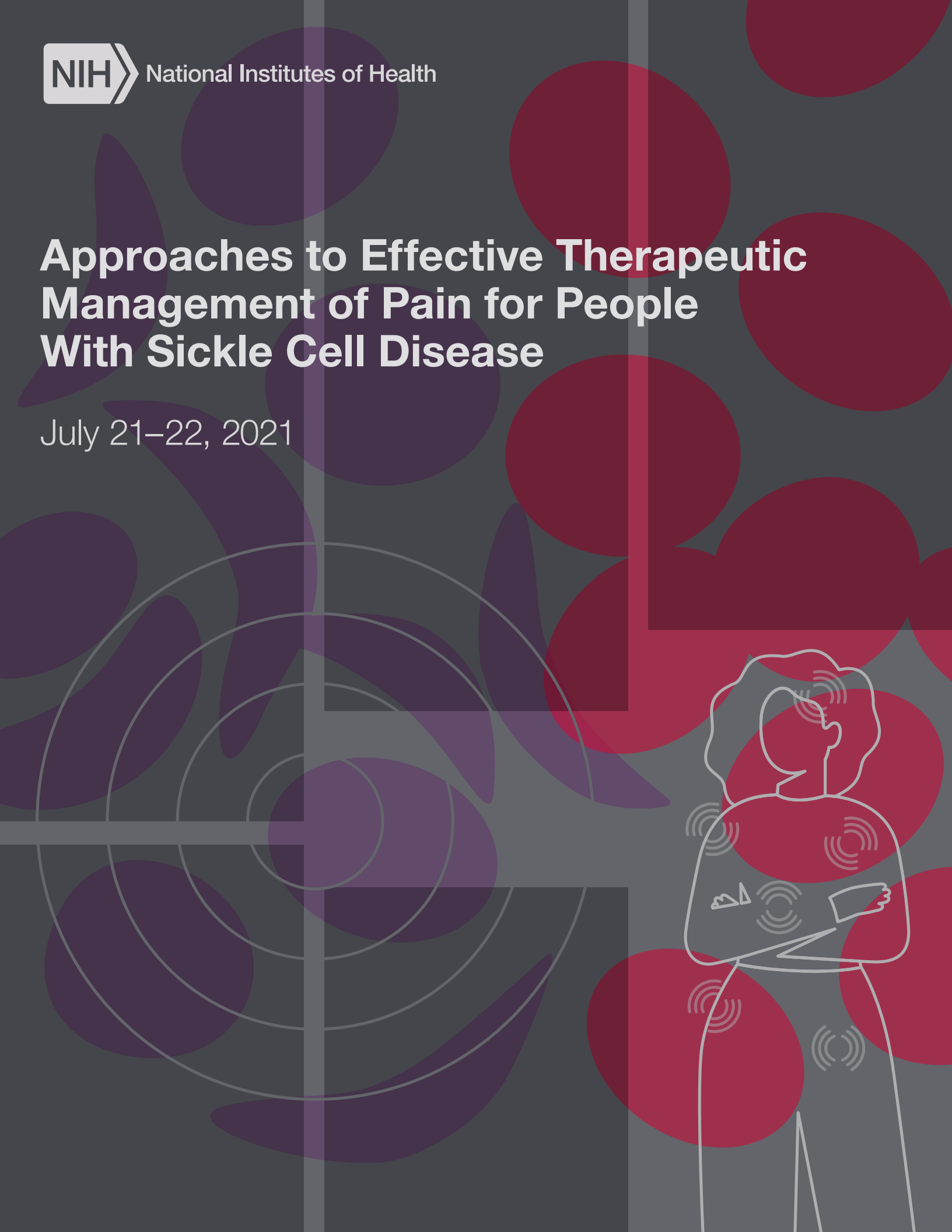
National Institutes of Health

Approaches to Effective Therapeutic Management of Pain for People With Sickle Cell Disease

July 21–22, 2021



Acknowledgments

Co-Leads

National Center for Complementary and Integrative Health (NCCIH)

National Heart, Lung, and Blood Institute (NHLBI)

National Institutes of Health (NIH) Collaboration Partners

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

National Institute on Drug Abuse (NIDA)

National Institute on Minority Health and Health Disparities (NIMHD)

National Institute of Neurological Disorders and Stroke (NINDS)

National Institute of Nursing Research (NINR)

Agenda

Approaches to Effective Therapeutic Management of Pain for People With Sickle Cell Disease

National Institutes of Health Virtual Workshop

July 21–22, 2021
11:30 a.m.–5:30 p.m. ET

Day 1: July 21, 2021

11:30 a.m. **Welcome**

Helene Langevin, M.D., Director, NCCIH

11:45 a.m. **Opening Remarks**

Francis S. Collins, M.D., Ph.D., Director, NIH

12:00 p.m. **Keynote**

Wally Smith, M.D., Virginia Commonwealth University
Reconceptualizing pain in sickle cell disease (SCD)

12:30 p.m. **Questions and Answers From NIH VideoCast Audience**

Session 1: Understanding Acute and Chronic SCD Pain: What Do We Know?

12:35 p.m. **Expert Group 1—Biology of SCD Pain**

Robert Hebbel, M.D., University of Minnesota
Sickle cell anemia: vaso-occlusion

Kalpna Gupta, Ph.D., University of California, Irvine
Chronic pain in SCD: molecular mechanisms and the contribution of the environment

1:05 p.m. **Panel Commentary**

Jay Shah, M.D., NIH Clinical Center
Potential connections between myofascial and skeletal tissues and acute and chronic SCD pain

Anjulika Chawla, M.D., Brown University
Gaps in knowledge in the musculoskeletal aspects of SCD pain

Richard Harris, Ph.D., University of Michigan
Neuroimaging of chronic SCD pain

Allison King, M.D., Ph.D., Washington University in St. Louis
Cognitive aspects of acute and chronic SCD pain

1:15 p.m. **Panel Discussion**

Moderators: Wen Chen, Ph.D., NCCIH, and William Tonkins, Ph.D., NHLBI

- What are the major gaps in our current knowledge of the biology underlying acute and chronic SCD pain?
- What tools, methodology, technology, animal models, or additional resources are needed to fill these knowledge gaps?

1:45 p.m. **Questions and Answers From NIH VideoCast Audience**

1:55 p.m. ***Break***

2:05 p.m. **Expert Group 2—Psychosocial and Environmental Factors Impacting SCD Pain**

Cecelia Valrie, Ph.D., Virginia Commonwealth University
The impact of psychological factors and sleep on acute or chronic SCD pain

Shawn Bediako, Ph.D., NHLBI
Social and ecological contexts of acute and chronic SCD pain

2:25 p.m. **Panel Commentary**

Soumitri Sil, Ph.D., Emory University
Pediatric acute and chronic SCD pain: psychosocial outcomes

Lori Crosby, Psy.D., Cincinnati Children's Hospital Medical Center
Socioeconomic effects on acute and chronic SCD pain

2:35 p.m. **Panel Discussion**

Moderators: Shawn Bediako, Ph.D., NHLBI, and Nishadi Rajapakse, Ph.D., NHLBI, formerly NIMHD

- What are the major gaps in current knowledge regarding the psychosocial and environmental factors influencing acute and chronic SCD pain?
- What tools, methodology, technology, policies, guidelines, or additional resources are needed to fill these knowledge gaps?

3:00 p.m. **Questions and Answers From NIH VideoCast Audience**

3:05 p.m. **Expert Group 3—Genetics/Microbiome Factors Impacting SCD Pain**

Amanda Brandow, D.O., M.S., Medical College of Wisconsin
The role of the microbiome in the development of acute and chronic SCD pain

Zaijie (Jim) Wang, Ph.D., University of Illinois, Chicago
Genetic factors influencing acute and chronic SCD pain

3:25 p.m. **Panel Commentary**

Seena Ajit, Ph.D., Drexel University
Molecular mechanisms underlying acute and chronic pain, with emphasis on epigenetics

3:30 p.m. **Panel Discussion**

Moderators: Inna Belfer, M.D., Ph.D., NCCIH, and Karen C. Lee, M.D., M.P.H., NICHD

- What are the major gaps in current knowledge related to the genetic, epigenetic, and microbiome factors influencing acute and chronic SCD pain?
- What tools, methodology, technology, animal models, or additional resources are needed to fill these knowledge gaps?

3:55 p.m. **Questions and Answers From NIH VideoCast Audience**

4:00 p.m. ***Break***

4:10 p.m. **Patient Perspective**

Lakiea Bailey, Ph.D., Sickle Cell Consortium
Living with SCD: my pain story

4:20 p.m. **Roundtable Discussion 1—Challenges and Opportunities for Understanding Acute and Chronic SCD Pain**

Lead discussants:

Daniel Clauw, M.D., University of Michigan
Summary of responses from invited participants to the question about knowledge gaps and research opportunities for research on acute and chronic SCD pain

Theodore Price, Ph.D., University of Texas at Dallas
Summary of responses from invited participants to the question about the tools, methodology, technology, policies, guidelines, animal models, and additional resources needed to address acute and chronic SCD pain

Roger Fillingim, Ph.D., University of Florida
Summary of responses from invited participants to the question about aspects of research on other pain conditions that could be applied to research on acute and chronic SCD pain

5:20 p.m. **Closing Remarks**

Emmeline Edwards, Ph.D., Division of Extramural Research Director, NCCIH

5:30 p.m. ***Adjourn***

Day 2: July 22, 2021

11:30 a.m. **Welcome Back**

Gary H. Gibbons, M.D., Director, NHLBI

11:40 a.m. **Opening Remarks**

Rebecca G. Baker, Ph.D., Director of the NIH HEAL (Helping To End Addiction Long-term[SM]) Initiative

11:50 a.m. **Keynote**

Cheryl Stucky, Ph.D., Medical College of Wisconsin
Sickle cell pain chasm 2021: knowns, unknowns, and bridges forward

Session 2: Challenges and Opportunities for Optimizing SCD Pain Management

12:20 p.m. **Expert Group 4—Measuring Pain and Sequelae in Patients for Clinical Trials**

Thomas Coates, M.D., University of Southern California
Acute and experimental pain

Diana Wilkie, Ph.D., R.N., University of Florida
Clinical presentation of chronic SCD pain: descriptors and phenotypes

12:40 p.m. **Panel Commentary**

William Zempsky, M.D., M.P.H., University of Connecticut
Systematic approaches to pediatric acute and chronic SCD pain, location of pain, and PhenX measures

Carlton Dampier, M.D., Emory University
Quality of life in children with chronic SCD pain, epidemiology

Nitya Bakshi, M.D., M.S., Emory University
Pain variability and pain phenotypes in SCD

Laura De Castro, M.D., M.H.Sc., University of Pittsburgh
Patterns and correlates of daily chronic SCD pain, lessons from contemporary drug trials in acute and chronic pain measurement

12:50 p.m. **Panel Discussion**

Moderators: Will Aklin, Ph.D., NIDA, and Smriti Iyengar, Ph.D., NINDS

- Other than pain severity, what outcomes should be measured in clinical trials studying SCD pain management interventions?
- What functional outcomes, co-occurring conditions, or social determinants of health measures are important to patients or are critical confounders that should be considered in analytic plans?

1:20 p.m. **Questions and Answers From NIH VideoCast Audience**

1:25 p.m. ***Break***

1:35 p.m. **Expert Group 5—Current or Promising Treatments for Acute and Chronic SCD Pain**

C. Patrick Carroll, M.D., Johns Hopkins University
Treatment strategies to manage acute and chronic SCD pain

Judith Schlaeger, Ph.D., University of Illinois, Chicago
Managing chronic SCD pain with nonpharmacologic approaches

1:55 p.m. **Panel Commentary**

Ardith Doorenbos, Ph.D., R.N., University of Illinois, Chicago
Acupuncture and guided relaxation: complementary and integrative therapies for SCD pain

Michael V. Vitiello, Ph.D., University of Washington
The potential of cognitive behavioral therapy for insomnia to manage chronic pain and comorbid insomnia

Bin He, Ph.D., Carnegie Mellon University
Ultrasound neuromodulation for acute and chronic SCD pain management

Lynnette Kaid, SorsaMED
Potential therapeutic proteins infused with cannabinoids for chronic SCD pain management

Alexis Leonard, M.D., NHLBI
Residual chronic pain following gene therapy for SCD

Deepika Darbari, M.B.B.S., M.S., Children's National Hospital
Persistence of pain post stem cell transplantation in SCD

2:10 p.m. **Panel Discussion**

Moderators: Jeri Miller, Ph.D., NINR, and Della White, Ph.D., NCCIH

- What effective treatments or models relevant to SCD pain management could be adopted, adapted, integrated, or scaled up in various health care systems?
- What promising multidisciplinary and multilevel interventions or multicomponent delivery models are ready for multisite efficacy or effectiveness trials for SCD pain management and related function?

2:35 p.m. **Questions and Answers From NIH VideoCast Audience**

2:40 p.m. **Expert Group 6—Overcoming Challenges of Evidence-Based Pain Management: Patient Engagement, Stigma, Bias, and Access to Quality Care**

Patricia Kavanagh, M.D., Boston University
Addressing implementation and access to quality care challenges in SCD pain care

Coretta Jenerette, Ph.D., R.N., University of South Carolina
Addressing stigma and bias challenges in SCD pain care

3:00 p.m. **Panel Commentary**

Roger Fillingim, Ph.D., University of Florida
Addressing disparities and other potential challenges in SCD pain management

Shan-Estelle Brown, Ph.D., Rollins College
Using cultural competence/sensitivity approaches and minimizing structural barriers to improve SCD pain management

Jerlym Porter, Ph.D., M.P.H., St. Jude Children's Research Hospital
Challenges of acute and chronic SCD pain management in the transition to adult care

3:10 p.m. **Panel Discussion**

Moderators: Susan Shero, M.S., R.N., NHLBI, and Wendy Weber, N.D., Ph.D., M.P.H., NCCIH

- What successful strategies from other fields could be evaluated in trials to address stigma, enhance access to quality care, reduce bias, and overcome structural barriers in acute and chronic SCD pain management?

3:35 p.m. **Questions and Answers From NIH VideoCast Audience**

3:40 p.m. ***Break***

3:50 p.m. **Patient Perspective**

Shauna Whisenton, American Society of Hematology Research Collaborative
Living with SCD: personal experience with acute and chronic pain management after SCD cure

4:00 p.m. **Roundtable Discussion 2—Building a Future in Which SCD Pain Management Can Be Optimized**

Lead discussants:

Sophie Lanzkron, M.D., M.H.S., Johns Hopkins University
Summary of responses from invited participants to the questions about (1) multidisciplinary and multilevel interventions or multicomponent delivery models that are ready for multisite efficacy or effectiveness trials for acute and chronic pain management, and (2) important functional measures to be considered for such clinical trials

Wally Smith, M.D., Virginia Commonwealth University
Summary of responses from invited participants to the question about the barriers to and effective treatments and models for acute and chronic SCD pain management that could be adopted, adapted, integrated, and scaled up in various health care systems

Cheryl Stucky, Ph.D., Medical College of Wisconsin
Summary of responses from invited participants to the question about successful strategies from other fields that could be evaluated in trials to address stigma, enhance access to quality care, reduce bias, and overcome structural barriers in acute and chronic SCD pain management

5:20 p.m. **Closing Remarks**

Monica Webb Hooper, Ph.D., Deputy Director, NIMHD

5:30 p.m. ***Adjourn***

Biographies and Abstracts

Day 1: July 21, 2021

Welcome and Opening Remarks

Helene Langevin, M.D., Director, National Center for Complementary and Integrative Health

Dr. Langevin was sworn in as director of the National Center for Complementary and Integrative Health on November 26, 2018. Previously, she was the director of the Osher Center for Integrative Medicine in Boston, jointly based at Brigham and Women's Hospital and Harvard Medical School, and a professor in residence of medicine at Harvard Medical School. She was a professor of neurological sciences at the University of Vermont Larner College of Medicine in Burlington until 2012. Her research has centered around the role of connective tissue in chronic musculoskeletal pain and the mechanisms of acupuncture, manual, and movement-based therapies. Her more recent work has focused on the effects of stretching on inflammation resolution mechanisms within connective tissue. Dr. Langevin received her medical degree from McGill University in Montreal, Canada. She completed a postdoctoral research fellowship in neurochemistry in the Medical Research Council Neurochemical Pharmacology Unit at the University of Cambridge, England, and a residency in internal medicine and postdoctoral fellowship in endocrinology and metabolism at the Johns Hopkins Hospital in Baltimore.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health

Dr. Collins was sworn in on August 17, 2009, as the 16th director of the National Institutes of Health, where he oversees the work of the largest supporter of biomedical research in the world, spanning the spectrum from basic to clinical research. Dr. Collins is a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the international Human Genome Project, which culminated in April 2003 with the completion of a finished sequence of the human DNA instruction book. He served as director of the National Human Genome Research Institute at the National Institutes of Health from 1993 to 2008. He is an elected member of both the National Academy of Medicine and the National Academy of Sciences, was awarded the Presidential Medal of Freedom in November 2007, and received the National Medal of Science in 2009. In 2020, he was elected as a Foreign Member of the Royal Society (United Kingdom) and

was also named the 50th winner of the Templeton Prize, which celebrates scientific and spiritual curiosity.

Keynote

Keynote Speaker: Wally Smith, M.D., Virginia Commonwealth University

Dr. Smith is the Florence Neal Cooper Smith Professor of Sickle Cell Disease and the director of the Adult Sickle Cell Program at Virginia Commonwealth University. His clinical specialties include care for adults with sickle cell disease, hydroxyurea and remittive therapies for sickle cell disease, and pain management in sickle cell disease. He is an experienced implementation scientist and an expert in clinical and health services research. He was the principal investigator for the Pain in Sickle Cell Epidemiology Study, which was the largest adult cohort study of sickle cell disease pain. Dr. Smith was a member of the National Institutes of Health (NIH) Interagency Pain Research Coordinating Committee, which published the National Pain Strategy. He is a member of the multidisciplinary working group that advises the NIH HEAL (Helping to End Addiction Long-term℠) Initiative. He received his medical degree from the University of Alabama.

Reconceptualizing Pain in Sickle Cell Disease

Pain is the hallmark and chief symptom of sickle cell disease. Vaso-occlusive crises are accompanied by severe acute pain. Vaso-occlusive crises originate in infancy, are extremely variable in frequency and intensity, worsen with age, and predict morbidity and mortality. Vaso-occlusive crises usually have sudden, unpredictable onset and are typically experienced at home. Initially, vaso-occlusive crises are likely nociceptive, relate to complex sickle cell disease vasculopathy, and can be altered with disease-modifying agents. However, as patients enter adulthood, they may develop chronic or acute-on-chronic pain. This pain may involve not only tissue and organ damage–related mechanisms, but also central sensitization and/or neuropathic mechanisms. Ironically, opioids, typically a treatment for sickle cell disease pain, may themselves cause hyperalgesia. For decades, physicians and researchers have focused on eliminating sickle cell disease pain simply by eliminating vaso-occlusion and sickle cell disease vasculopathy. However, a simple Cartesian vascular nociceptive stimulus-response reflex does not explain either acute or chronic sickle cell disease pain. The mechanisms are far more complex and multidimensional. Sickle cell disease pain is difficult to objectify or distinguish using physical signs or biomarkers. Sickle cell disease pain can be measured by descriptors, quantitative sensory testing, and brain imaging. But sickle cell disease pain may result in or be worsened by a plethora of comorbid biopsychosocial factors including depression, anxiety, maladaptive coping, catastrophizing, somatization, sleep disturbances, or stigmatization. Further, sickle cell disease pain occurs in the context of conscious or unconscious bias and disbelief among health care workers, society, and sometimes, even family members. Sickle cell disease pain is negatively affected

by disparities in health care and outcomes, and often by adverse social determinants of health. What results is that patients are often stigmatized and undertreated. There is a dearth of knowledge of mechanisms that cause and contribute to sickle cell disease pain. The basic neurobiology and circuitry underlying sickle cell disease pain from peripheral vasculature to the brain remain understudied. Relationships between vasculopathy and pain are little known. Genetic and epigenetic determinants of sickle cell disease pain are only now being explored. Clinical pain treatment trials are scarce. Real advances in treatment of pain in patients with sickle cell disease will occur only when the complex model of sickle cell disease pain is acknowledged and researched at multiple levels from the biology to society, and sickle cell disease pain is treated holistically with understanding, empathy, and compassion for the patient.

Session 1: Understanding Acute and Chronic Sickle Cell Disease Pain: What Do We Know?

Expert Group 1—Biology of Sickle Cell Disease Pain

Speaker: Robert Hebbel, M.D., University of Minnesota

Dr. Hebbel is a Regents Professor Emeritus in the Division of Hematology, Oncology, and Transplantation at the University of Minnesota. Previously, he was the director of the National Institutes of Health hematology training grant and the vice chairman for research in the Department of Medicine. Dr. Hebbel's research interests include the vascular pathobiology of sickle disease, the use of blood outgrowth endothelial cells for biomedical applications, and the role of genetically determined differences in endothelial biology as a determinant of clinical phenotypic heterogeneity of vascular disease. His expertise includes hematology, red cell disorders, sickle cell anemia, and endothelial and vascular biology. He received his medical degree and a postdoctoral fellowship in hematology from the University of Minnesota.

Sickle Cell Anemia: Vaso-Occlusion

Although acute pain crises are the usual way that vaso-occlusion presents, there is more to the story. Also, the actual mechanism of vaso-occlusion triggering may vary from time to time, from organ to organ, or even among individuals. Our common understanding is that red blood cell sickling is allowed to occur when capillary passage of sickle red blood cells is slowed. There are three current candidate vaso-occlusion onset triggers. Precapillary obstruction due to loss of red blood cell deformability has not been fully excluded as a participant, as will be explained. Other mechanisms of slowed microvascular flow involve abnormal blood cell adhesion to endothelium. In the mouse, both sickle red blood cells and sickle white blood cells exhibit a capability to slow blood flow via P-selectin dependent mechanisms. Heterocellular adhesion has been heavily promoted, but such data are from a problematic experimental model. Vaso-occlusion leads to ischemia/reperfusion pathobiology,

and this ischemia/reperfusion (along with hemolysis products) drives the robust, highly complex, systemic inflammatory state characteristic of sickle cell disease. Importantly, there is nothing steady about "steady state," as inflammatory biomarker levels bounce around in the absence of overt clinical disease. It is from this inflammatory state that pain emerges. Emerging data reveal that an ischemia/reperfusion-induced excess level of HMGB1 (a driver of sterile inflammation) and hemolysis-induced free heme can converge as TLR4 signaling ligands. Of direct relevance to this workshop, HMGB1-triggered TLR4 signaling has been specifically implicated in nociceptive hypersensitivity and prolonged pain.

Speaker: Kalpna Gupta, Ph.D., University of California, Irvine

Dr. Gupta is a professor of medicine in the Division of Hematology/Oncology at the University of California, Irvine. Previously, she was a tenured professor at the University of Minnesota. She initiated pioneering work in understanding the mechanisms of pain in sickle cell disease and established mouse models of chronic and acute sickle cell disease pain. Her translational approach of bench to bedside research provides insights for treating pain and the underlying disease process that causes pain. Her laboratory has identified several mechanism-based novel targets at the intersection of the sickle cell disease process and pain, including cannabinoid receptors, mast cells, and the nociceptin receptor, in addition to integrative approaches including diet modification, acupuncture, and perception modulation to relieve pain. She received her doctorate in biochemistry from the All India Institute of Medical Sciences and completed her postdoctoral training at the University of Minnesota.

Chronic Pain in Sickle Cell Disease: Molecular Mechanisms and the Contribution of the Environment

In 1949, Linus Pauling first described sickle cell disease as a molecular disorder. About three-quarters of a century later, the molecular mechanisms of pain, a devastating sequela of sickling, remain a scientific enigma. However, the last decade has provided a launch pad for the discovery of potential mechanism-based targets for the development of nonopioid therapies to prevent and/or treat sickle pain. The unique and complex pathobiology of sickle cell disease includes hemolysis releasing cell-free heme, oxidative stress, inflammation, vascular dysfunction, hypoxia, ischemia-reperfusion injury, and organ damage, each of which can directly and/or indirectly contribute to the pathogenesis of pain. Humanized mouse models of sickle cell disease have provided insights into the characteristic features of pain sensitivity: constitutive and sustained sensitization of the peripheral and central nervous system; neuroimmune and neurovascular interactions involving mast cells, neuropeptides, and "cytokine storm"; nerve injury in the periphery; and glial activation in the central nervous system. Important insights from the transcriptomic analysis of the dorsal root ganglion of sickle mice have evinced that the system of checks and balances is diminished while the balance is tilted toward neuronal injury. This is accomplished by an increase in noxious

proteases such as neutrophil elastase and mast cell tryptase and downregulation of protective serine protease inhibitors (SERPINS) as well as the nerve repair and regeneration gene, small proline rich protein 1A (SPRR1A), which may underlie sustained neuropathic pain that may not be attenuated with curative therapies such as bone marrow transplant. Thus, SERPINS and SPRR1A offer potential targets for early interventions to prevent pain at its source. Direct involvement of the higher brain centers may further contribute to pain via the limbic system and coexistence of cognitive impairment and psychosocial mechanisms. In male sickle mice, isolation increased hyperalgesia, whereas improving their environment with a female companion and/or nutritionally enriched diet reduced hyperalgesia via a serotonergic top-down mechanism. In addition to pharmacologic interventions, many integrative approaches including acupuncture, cannabinoids, supplements including curcumin, and environment modulation have therapeutic potential by influencing sickle pathobiology as well as the nervous system. Despite these advances, major lacunae exist in the objective unbiased quantification of pain, understanding the optimal use of opioids and their side effects/potential for reward, cotreatment strategies to minimize side effects of novel treatments, understanding of specific pain features such as musculoskeletal pain, perception-based approaches, translation of preclinical observations, advanced omics, social media, contribution of environmental factors, and application of advanced engineering-based technology. A systems-wide approach involving biology, medicine, engineering, environment, complementary medicine, and social sciences is therefore warranted to develop a well-rounded management plan for sickle pain, an outcome of genetic predisposition, complex pathobiology, social stigma, and compromised environmental factors.

Expert Group 1—Panel Commentary

Panelist: Jay Shah, M.D., National Institutes of Health Clinical Center

Potential Connections Between Myofascial and Skeletal Tissues and Acute and Chronic Sickle Cell Disease Pain

Dr. Shah is a physiatrist and clinical investigator in the Rehabilitation Medicine Department at the National Institutes of Health Clinical Center. His interests include the symptoms and signs, pathogenesis, and pathophysiology of myofascial pain syndrome associated with myofascial trigger points and the integration of physical medicine techniques into the management of neuromusculoskeletal pain and dysfunction. Dr. Shah is intrigued by the roles played by neurogenic inflammation, central sensitization, somatovisceral and viscerosomatic reflexes, spinal facilitation, and limbic system dysfunction. For the past 20 years, Dr. Shah has been studying the clinical, biochemical, and imaging aspects of myofascial pain syndrome and myofascial trigger points. He has developed and successfully used novel microanalytical and ultrasound imaging techniques that have uncovered the unique biochemical milieu and the viscoelastic and blood flow properties of myofascial trigger points and surrounding soft tissue. He received his medical degree from the Cayey School of Medicine.

Panelist: Anjulika Chawla, M.D., Brown University

Gaps in Knowledge in the Musculoskeletal Aspects of Sickle Cell Disease Pain

Dr. Chawla is a professor of pediatrics in the Alpert School of Medicine at Brown University. She is a practicing pediatric hematologist/oncologist who focuses on the care of people with sickle cell disease and their families. She is interested in curative intent therapies and is a medical director in medical affairs at Bluebird Bio, where she works to understand the potential role of gene therapy in halting sickle cell disease. Sickle cell disease affects the whole person, and Dr. Chawla strives to find ways for people to drive their disease rather than allowing the disease to drive them. She received her medical degree from the University of Vermont and completed a fellowship at the University of California, San Francisco.

Panelist: Richard Harris, Ph.D., University of Michigan

Neuroimaging of Chronic Sickle Cell Disease Pain

Dr. Harris is an associate professor in the Department of Anesthesiology and a research associate professor in the Department of Internal Medicine at the University of Michigan. His background is in basic science and clinical research in alternative medicine. Currently, Dr. Harris is investigating the neurobiological mechanisms of both pharmacologic and nonpharmacologic (acupuncture/acupressure) treatments for chronic pain and fatigue conditions. His recent investigations have focused on the role of brain neurotransmitters and their receptors in humans with chronic pain. He is copresident of the Society for Acupuncture Research. He received his master's degree in clinical research design and statistical analysis from the University of Michigan and a doctorate in molecular and cellular biology from the University of California, Berkeley.

Panelist: Allison King, M.D., Ph.D., Washington University in St. Louis

Cognitive Aspects of Acute and Chronic Sickle Cell Disease Pain

Dr. King is a professor of pediatrics, medicine, and public health sciences at Washington University in St. Louis. She is a pediatric and young adult hematologist and oncologist with formal training in clinical investigation, research methods in public health and education, and implementation science. Her research focus is determining the factors, particularly factors of disparity and family function, that are related to the daily function of individuals with chronic diseases. Specifically, she studies the cognitive, educational, and functional outcomes of children with sickle cell disease. Her clinical research laboratory has been addressing the relationships between health and education in this population, evaluating the social issues related to a low socioeconomic status, in addition to the disease-related sequelae. She received her medical degree from the University of Missouri and a doctorate in education from St. Louis University.

Expert Group 1—Panel Discussion

Moderator: Wen Chen, Ph.D., National Center for Complementary and Integrative Health

Dr. Chen serves as the branch chief of the Basic and Mechanistic Research Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health. She oversees fundamental science, translational, and intervention optimization research, as well as methodology and technology development related to all complementary and integrative health approaches. Previously, she worked as a scientific editor at *Neuron,* a program coordinator at the National Institute of Mental Health, and a program director overseeing a research portfolio on sensory and motor disorders of aging at the National Institute on Aging. She received her master's degree in medical sciences as part of the Harvard-Markey Medical Scientist training program at Harvard Medical School and a doctorate in biological chemistry and molecular pharmacology from Harvard University. She did her postdoctoral training in proteomics at the Massachusetts Institute of Technology.

Moderator: William Tonkins, Ph.D., National Heart, Lung, and Blood Institute

Dr. Tonkins is a behavioral scientist serving as a health scientist administrator in the Division of Blood Diseases and Resources at the National Heart, Lung, and Blood Institute. He also is a lieutenant commander in the U.S. Public Health Service Commissioned Corps. Dr. Tonkins will serve as the project officer for the Sickle Cell Disease in Sub-Saharan Africa Research Network. Previously, he was a consumer safety officer with the U.S. Food and Drug Administration and directed a behavioral and biopsychosocial research portfolio at the National Institute of Arthritis and Musculoskeletal and Skin Diseases. His portfolio focused on innovative complementary and integrative therapies, pragmatic clinical trials, vulnerable populations, and health disparities. He also has worked as a public health analyst at the Health Resources and Services Administration. He received a doctorate in public health from Morgan State University and his law degree from North Carolina Central University.

Expert Group 2—Psychosocial and Environmental Factors Impacting Sickle Cell Disease Pain

Speaker: Cecelia Valrie, Ph.D., Virginia Commonwealth University

Dr. Valrie is an associate professor in the Department of Psychology and an adjunct associate professor in the Department of Internal Medicine at Virginia Commonwealth University. She is the director of the health psychology doctoral program and chair of the Culture, Race, and Health Transdisciplinary Core in the Institute for Inclusion, Inquiry, and Innovation. She is a developmental health psychologist whose research focuses on improving the health and well-being of youth and young adults at risk for poor health outcomes, especially youth with sickle cell disease. Her work centers on understanding pain and sleep experiences of youth with sickle cell disease. Additional interest areas include improving the transition to adulthood for pediatric patients with sickle cell disease, reducing pediatric health disparities, and developing effective pain and sleep interventions. She received her doctorate in developmental psychology from the University of North Carolina, Chapel Hill.

The Impact of Psychological Factors and Sleep on Acute or Chronic Sickle Cell Disease Pain

Previous conceptualizations of sickle cell disease pain have viewed poor psychological functioning and sleep as consequences of acute and chronic sickle cell disease pain. However, more contemporary work has indicated that psychological functioning and sleep often have bidirectional relations with sickle cell disease pain; in some cases, psychological factors and sleep may be the more dominant drivers of these relationships and thus, significant targets for reducing sickle cell disease pain experiences. This presentation will illustrate the many ways that psychological factors and sleep may impact acute and

chronic sickle cell disease pain experiences. This will be accomplished by describing the current prevailing theories of pain relevant to the sickle cell disease pain experience that incorporate psychological factors and sleep, and then critically evaluating the literature linking psychological factors and sleep with acute and chronic sickle cell disease pain. Given specific gaps in this literature base, work from other pain populations will be used to highlight possible additional associations and mechanisms linking psychological factors, sleep, and sickle cell disease pain experiences. The presentation will also highlight opportunities for leveraging existing and emerging psychological and sleep interventions to ameliorate the frequency and intensity of acute sickle cell disease pain experiences and the development and maintenance of chronic sickle cell disease pain.

Speaker: Shawn Bediako, Ph.D., National Heart, Lung, and Blood Institute

Dr. Bediako is the director of the Office of Education in the Division of Intramural Research at the National Heart, Lung, and Blood Institute, where he oversees scientific and professional development activities for fellows trained by the Institute's investigators. Previously, he was a professor at the University of Maryland, Baltimore County, where he taught interdisciplinary courses in health psychology, behavioral medicine, and social science research methods. His innovative research program focused on the adult experience of sickle cell disease, and he has received private and Federal funding to support studies on sickle cell disease stigma and the impact of "racialized" social perceptions about sickle cell disease on patient outcomes. He received his master's degree in community psychology from Florida Agricultural and Mechanical University, his doctorate in social/health psychology from Stony Brook University, and was a Carolina Postdoctoral Fellow for Faculty Equity at the University of North Carolina, Chapel Hill.

Social and Ecological Contexts of Acute and Chronic Sickle Cell Disease Pain

Pain is the hallmark characteristic of sickle cell disease; our understanding of sickle cell disease pain has primarily emphasized biological and physiological mechanisms for more than 5 decades. Consequently, it is not surprising that conceptual frameworks and theoretical models describing sickle cell disease pain sequelae principally reflect a bias for the biophysiological origins of pain. This bias ultimately relegates social, cognitive, and ecological contexts to the periphery of sickle cell disease pain research and reinforces their conceptualization as mere moderators of the pain process—and not putative causes. This presentation will incorporate recent findings from psychosomatic medicine and ecological psychology to craft an argument for the need to reconsider the body/mind dichotomy and pursue an integrative research agenda that permits a comprehensive understanding of the etiology and temporality of sickle cell disease pain. Understanding sickle cell disease pain in this manner may broaden the scope and effectiveness of interventions that mitigate or prevent negative patient experiences of both acute and chronic pain.

Expert Group 2—Panel Commentary

Panelist: Soumitri Sil, Ph.D., Emory University

Pediatric Acute and Chronic Sickle Cell Disease Pain: Psychosocial Outcomes

Dr. Sil is an associate professor of pediatrics at Emory University School of Medicine and a pediatric psychologist at the Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta. She is a clinical psychologist with specialized training in pediatric psychology. She has research and clinical expertise in pediatric pain management focused on the development and evaluation of behavioral interventions to promote the health and functioning of children and adolescents with complex chronic pain conditions. Dr. Sil's research program in pediatric pain examines coping with acute and chronic pain, therapeutic mechanisms of treatment efficacy, and long-term health outcomes. Her research centers on the assessment and treatment of chronic pain in pediatric sickle cell disease. She received her doctorate in clinical child psychology with specialization in behavioral medicine from the University of Maryland, Baltimore County.

Panelist: Lori Crosby, Psy.D., Cincinnati Children's Hospital Medical Center

Socioeconomic Effects on Acute and Chronic Sickle Cell Disease Pain

Dr. Crosby is a professor of pediatrics at the University of Cincinnati College of Medicine and the Cincinnati Children's Hospital Medical Center. She also is the director of the Community Engagement Core at the Cincinnati Center for Clinical and Translational Science and Training and a codirector of Innovations in Community Research. She specializes in treating adolescents and young adults with conditions such as chronic pain and sickle cell disease. Her areas of research include self-management, treatment adherence, health care transition, recruitment and retention of minorities in research, integrating design thinking into research, implementation science, and community engagement. She received her doctorate in clinical psychology from Wright State University.

Expert Group 2—Panel Discussion

Moderator: Shawn Bediako, Ph.D., National Heart, Lung, and Blood Institute

Dr. Bediako is the director of the Office of Education at the National Heart, Lung, and Blood Institute, where he oversees scientific and professional development activities for fellows. Previously, he was a professor at the University of Maryland, Baltimore County, where he taught interdisciplinary courses in health psychology, behavioral medicine, and social science research methods. His research program focused on the adult experience of sickle cell disease, sickle cell disease stigma, and the impact of "racialized" social perceptions about sickle cell disease on patient outcomes. He received his doctorate in social/health psychology from Stony Brook University.

Moderator: Nishadi Rajapakse, Ph.D., National Heart, Lung, and Blood Institute

Dr. Rajapakse was a program director in the Division of Scientific Programs at the National Institute on Minority Health and Health Disparities until July 2021, where she directed the Transdisciplinary Collaborative Centers for Health Disparities Research Focused on Precision Medicine initiative. She also led the Centers of Excellence on Environmental Health Disparities Research Program and was a program official for the Research Centers in Minority Institutions program. Recently, she began a new position at the National Heart, Lung, and Blood Institute. She received her master's degree in clinical research from Duke University and a doctorate in molecular medicine and translational sciences from Wake Forest University. She completed a postdoctoral fellowship in genetic epidemiology at the National Institute of Environmental Health Sciences, where she examined genetic and environmental risk factors in the development of cardiovascular disease, sepsis, and rheumatoid arthritis.

Expert Group 3—Genetics/Microbiome Factors Impacting Sickle Cell Disease Pain

Speaker: Amanda Brandow, D.O., M.S., Medical College of Wisconsin

Dr. Brandow is a professor of pediatrics at the Medical College of Wisconsin in the section of hematology/oncology/bone marrow transplantation. She is a physician-scientist who provides care for children with sickle cell disease and other nonmalignant hematologic conditions, and she conducts clinical and translational research focused on understanding the pathophysiology of acute and chronic pain in children and adults living with sickle cell disease. Specifically, she is investigating the underlying neurobiology of sickle cell pain, focusing on inflammation, the microbiome, and nervous system sensitization. She is an active advocate for comprehensive pain management for individuals living with sickle cell disease. She has served on the U.S. Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force and as chair of the American Society of Hematology's guidelines for acute and chronic pain. She received her doctorate in osteopathic medicine from Midwestern University.

The Role of the Microbiome in the Development of Acute and Chronic Sickle Cell Disease Pain

A critical knowledge gap exists in the identification of reasons other than chronic sickling that contribute to the unpredictable clinical phenotype of frequent acute and chronic daily pain in individuals living with sickle cell disease. This presentation will discuss how alterations in the intestinal microbiota or dysbiosis, a known driver of chronic inflammation, are being investigated in individuals living with sickle cell disease. Microbiome alterations have been shown to play a role in other chronic inflammatory diseases and pain-related disorders. Dysbiosis has been associated with pain in rheumatoid arthritis, migraines, chronic pelvic pain, and chemotherapy-induced pain. Dysbiosis can lead to a "leaky" intestinal barrier resulting in bacterial translocation into the blood. Bacterial translocation (i.e., systemic microbial antigen exposure) can trigger chronic inflammation, which can sensitize peripheral pain nociceptors and result in recurrent acute and chronic pain. Immune regulation of this inflammatory response can modulate the inflammatory impact on pain. Nervous system sensitization occurs in individuals living with sickle cell disease. However, the biologic factors that lead to nervous system sensitization in sickle cell disease are unknown. Thus, investigating the connection between the microbiome, inflammation, and pain could lead to novel therapeutic targets for sickle cell disease pain that are opioid sparing.

Speaker: Zaijie (Jim) Wang, Ph.D., University of Illinois, Chicago

Dr. Wang is a distinguished professor in the Department of Pharmaceutical Sciences at the University of Illinois, Chicago. He is a University of Illinois Scholar and has joint appointments in the Department of Neurology and the Department of Bioengineering. His research focuses on the molecular neurobiology of chronic pain and on the pharmacology and pharmacogenomics of analgesics. Dr. Wang has authored 120 peer-reviewed manuscripts, and his research is supported primarily by grants from the National Institutes of Health. He is a licensed pharmacist and is a fellow of the American Association of Pharmaceutical Scientists. He received his doctoral degree from the University of California, San Francisco.

Genetic Factors Influencing Acute and Chronic Sickle Cell Disease Pain

Pain in sickle cell disease is not only severe, prevalent, and frequent, it also exhibits large interindividual variability. The contributing genetic factors are not well understood. We investigated pain-related candidate gene polymorphisms in 131 sickle cell disease patients. This presentation will cover some of the candidate gene single nucleotide polymorphisms (SNPs) and their influence on acute pain (e.g., *COMT*, *DRD3*, *AVPR1A*, *PNMT*) or chronic pain (e.g., *IL1A*, *NR3C1*, *TRPA1*, *S100B*) in sickle cell disease. GCH1 polymorphisms were found to influence both acute and chronic pain. There are also sex-specific effects, for example, *S100B* rs9722 and rs1051169 minor alleles and their corresponding haplotypes show sex-specific associations with chronic pain only in female patients. We further applied pathway analysis and polygenic network-based computational approaches to tackle the limitation of the small sample size in our study. Four major molecular interaction networks, namely Reactome, BioGrid, IntAct, and MINT, were obtained and merged on Cytoscape to identify clusters of nodes with a high density of shared polygenic interactions by Markov clustering algorithm. Of the first sample of 200 candidate SNPs studied, we identified 12 polygenic SNPs accounting for 30 percent of the phenotypic variability, and the polygenic model can predict pain scores with about 70 percent overall accuracy, illustrating the utility of polygenic models in studying complex pain traits in sickle cell disease.

Expert Group 3—Panel Commentary

Panelist: Seena Ajit, Ph.D., Drexel University

Molecular Mechanisms Underlying Acute and Chronic Pain, With Emphasis on Epigenetics

Dr. Ajit is an associate professor in the Department of Pharmacology and Physiology at Drexel University College of Medicine. Previously, she was a researcher at Wyeth, where she contributed to pain drug discovery efforts and the identification and validation of pain targets. At Drexel, her research focuses on elucidating the molecular mechanisms underlying pain, with emphasis on noncoding RNA and the translation of clinical findings to basic research and vice versa. She investigates circulating microRNAs as biomarkers and their mechanistic significance in patients with complex regional pain syndrome and rodent models of pain. She is also studying the role of small extracellular vesicles in intercellular communication, their potential utility as a pain therapeutic, and the role of long, noncoding RNA X-inactive specific transcript in chronic pain disorders in women. She received her doctorate from Rutgers University.

Expert Group 3—Panel Discussion

Moderator: Inna Belfer, M.D., Ph.D., National Center for Complementary and Integrative Health

Dr. Belfer is a program director in the Basic and Mechanistic Research in Complementary and Integrative Health Branch at the National Center for Complementary and Integrative Health. Her research focuses on mechanisms underlying the effects of mind and body approaches and natural products on pain management. She leads research programs related to genetic, genomic, and epigenetic mechanisms of complementary and integrative health approaches; neural mechanisms of meditative movement practices; cannabinoids and pain; and sleep and pain. Dr. Belfer has published articles on the relationship between gene polymorphisms and complex phenotypes such as pain, psychiatric disorders, and addictions; biobehavioral aspects of acute and chronic pain; phenomics of human pain; sex-specific genetic effects on pain; genetic modifiers of pain in sickle cell disease; and genomic predictors of the transformation of acute pain into a chronic condition. She received her medical degree from Moscow Medical University and her doctorate in neurobiology from Hebrew University.

Moderator: Karen C. Lee, M.D., M.P.H., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Dr. Lee is the program director for the Behavioral Pediatrics and Health Promotion Program in the Division of Extramural Research at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Her research focuses on relationships between behaviors and clinically important health outcomes, including establishing and maintaining healthy behaviors and identifying and reducing risky behaviors from childhood through early adulthood. Previously, she worked with the U.S. Preventive Services Task Force and the Evidence-Based Practice Center Program at the Agency for Healthcare Research and Quality, the U.S. Food and Drug Administration, and the Health Resources and Services Administration. She received her master's degree in public health from Harvard University and a doctorate from Northwestern University. She completed her pediatrics internship and residency training at NewYork-Presbyterian Hospital and a pediatric research fellowship at Harvard University.

Patient Perspective

Speaker: Lakiea Bailey, Ph.D., Sickle Cell Consortium

Living With Sickle Cell Disease: My Pain Story

Dr. Bailey is the director of the Sickle Cell Consortium, a network of sickle cell community-based organizations, patient and caregiver advocates, community partners, and health care and research advisers. Diagnosed with sickle cell disease at age 3, she has become an advocate, educator, and research scientist in the sickle cell disease field. Her research has investigated the molecular mechanisms involved in the induction and regulation of the gamma globin gene. Dr. Bailey has served as a consultant with Bluebird Bio and a patient engagement expert for Pfizer, and she is an advisory board member for the Foundation for Sickle Cell Disease Research. Her goal is to amplify patient voices to ensure that patients with sickle cell disease and their caregivers take leadership roles in research, policy, advocacy, legislation, and education. She received her doctorate in molecular hematology and regenerative medicine from the Medical College of Georgia, Augusta University.

Roundtable Discussion 1—Challenges and Opportunities for Understanding Acute and Chronic Sickle Cell Disease Pain

Roundtable Discussant: Daniel Clauw, M.D., University of Michigan

Knowledge Gaps and Research Opportunities for Research on Acute and Chronic Sickle Cell Disease Pain

Dr. Clauw is a professor of anesthesiology, medicine (rheumatology), and psychiatry at the University of Michigan, where he is an active mentor to clinical and pain researchers. Previously, he was the chief of the Division of Rheumatology and vice chair of medicine at Georgetown University, where he founded the Chronic Pain and Fatigue Research Center. In 2002, he was recruited to bring the center to the University of Michigan, where it has become one of the most successful pain research groups in the world. His research areas include fibromyalgia, chronic pain, mechanisms of pain processing, functional somatic syndromes, opioids, and cannabinoids. He has published more than 450 peer-reviewed articles and currently is a coprincipal investigator for four National Institutes of Health grants studying various aspects of chronic pain. He received his medical degree from the University of Michigan and completed fellowships at Georgetown University.

Roundtable Discussant: Theodore Price, Ph.D., University of Texas at Dallas

Tools, Methodology, Technology, Policies, Guidelines, Animal Models, and Additional Resources Needed To Address Acute and Chronic Sickle Cell Disease Pain

Dr. Price is the Eugene McDermott Professor and cochair of the Department of Neuroscience in the School of Behavioral and Brain Sciences and is the director of the Center for Advanced Pain Studies at the University of Texas at Dallas. His laboratory investigates molecular mechanisms driving the transition to chronic pain and focuses on drug development for chronic pain disease modification and the peripheral and central mechanisms of neuronal plasticity in response to injury. He has been continuously funded by the National Institutes of Health for more than 10 years, has published more than 150 peer-reviewed articles, and is an associate editor for the *Journal of Neuroscience*. He has cofounded many companies, including CerSci Therapeutics, which was acquired by Acadia in 2020, and Doloromics, which is currently in the Illumina Accelerator program. He received his doctorate from the University of Texas Health Science Center at San Antonio.

Roundtable Discussant: Roger Fillingim, Ph.D., University of Florida

Aspects of Research on Other Pain Conditions That Could Be Applied to Research on Acute and Chronic Sickle Cell Disease Pain

Dr. Fillingim is a distinguished professor in the College of Dentistry and director of the Pain Research and Intervention Center of Excellence at the University of Florida. He also serves as director of the Center for Advancing Minority Pain and Aging Science. His research investigates biopsychosocial mechanisms mediating individual differences in pain, including racial and ethnic disparities in pain, as well as age-related changes in pain processing. His federally funded research investigates individual differences in pain. He received his doctorate in clinical psychology from the University of Alabama at Birmingham.

Closing Remarks

Closing Remarks: Emmeline Edwards, Ph.D., Director, National Center for Complementary and Integrative Health Division of Extramural Research

Dr. Edwards is the director of the Division of Extramural Research at the National Center for Complementary and Integrative Health. She is responsible for development of scientific programs or areas of science that fulfill the National Center for Complementary and Integrative Health's mission as well as planning, implementation, and policy. Previously, Dr. Edwards served as deputy director of the extramural program at the National Institute of Neurological Disorders and Stroke. Her research there focused on the neural mechanisms of complex behaviors and characterization of a genetic model of affective disorders. Dr. Edwards is chair of Women in World Neuroscience, an independent mentoring and networking organization with the primary mission of identifying, promoting, and implementing mentoring and networking opportunities for women neuroscientists across the world. Dr. Edwards earned her doctorate in neurochemistry from Fordham University, did postdoctoral research in behavioral pharmacology and neuroscience at the State University of New York, and was a tenured associate professor in the Department of Pharmacology at the University of Maryland.

Biographies and Abstracts

Day 2: July 22, 2021

Welcome Back and Opening Remarks

Welcome Back: Gary H. Gibbons, M.D., National Heart, Lung, and Blood Institute

Dr. Gibbons is the director of the National Heart, Lung, and Blood Institute, where he oversees the third largest institute at the National Institutes of Health. Previously, he served as the founding director of the Cardiovascular Research Institute, chairperson of the Department of Physiology, and professor of physiology and medicine at the Morehouse School of Medicine in Atlanta. At the Cardiovascular Research Institute, he directed research in the fields of vascular biology, genomic medicine, and the pathogenesis of vascular diseases and received several patents for innovations derived from his research. He was a member of the faculty at Stanford University from 1990 to 1996 and at Harvard Medical School from 1996 to 1999. He received his medical degree from Harvard Medical School and completed his residency and cardiology fellowship at the Harvard-affiliated Brigham and Women's Hospital in Boston.

Opening Remarks: Rebecca G. Baker, Ph.D., Director, National Institutes of Health HEAL (Helping to End Addiction Long-term℠)

Dr. Baker is director of the National Institutes of Health Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative, in the Office of the Director, NIH. Dr. Baker helped develop the Initiative and leads coordination of NIH HEAL Initiative programmatic activities between the NIH Office of the Director and relevant Institutes and Centers. She also provides expert advice to and represents the NIH director on Initiative-related activities, including interagency efforts in pain and opioid research and policy. Prior to this position, Dr. Baker served as special assistant to the NIH director and the principal deputy director working directly with NIH leadership to analyze complex biomedical research policy issues and assist in the development of new science and policy initiatives. She earned her Ph.D. from the University of Pennsylvania and her bachelor's degree from Cornell University.

Keynote

Keynote Speaker: Cheryl Stucky, Ph.D., Medical College of Wisconsin

Dr. Stucky is the Marvin Wagner Endowed Professor in the Department of Cell Biology, Neurobiology and Anatomy at the Medical College of Wisconsin and the director of the neuroscience doctoral program and of the Pain Division in the Neuroscience Research Center. She has more than 27 years of experience studying pain mechanisms at the behavioral, physiological, cellular, and molecular levels. The National Institutes of Health has funded her laboratory for more than 21 years, and she is currently the principal investigator for a Javits Neuroscience Investigator award from the National Institute of Neurological Disorders and Stroke. Dr. Stucky is an expert in modeling painful injury and disease conditions in rodents. Previous studies in her laboratory used mouse models of sickle cell disease to identify channels and receptors on sensory neurons that contribute to sickle cell disease pain. She received her doctorate in neuroscience, physiology, and immunity from the University of Minnesota.

Sickle Cell Pain Chasm 2021: Knowns, Unknowns, and Bridges Forward

We know far more about the pathophysiology and management of sickle cell disease vascular complications than we know about the pathophysiology and management of the chief symptom of sickle cell disease—pain. For example, pioneering studies in the 1940s and 1950s discovered the genetic cause of sickle cell disease and placed it as a leading example at the cutting edge of identification of the molecular basis of human diseases. Elegant studies over the past 70 years have identified a wealth of biological information about the malfunctions of the red blood cell, sickling, vaso-occlusion, hemolysis, anemia, and major organ damage. Yet we have not explored the complex relationships between sickle cell disease pain and the malfunction of the red cell. We have not moved beyond recognition of the enormity of the pain experienced by patients with sickle cell disease in the past 10 years. Many still vastly underappreciate and often ignore this enormity. Patients know this and stay away from pain care as a result. Researchers have not delved into mechanisms of pain that could be palliative treatment targets. Similarly, they have not studied well how to apply what we already know about pain to sickle cell disease. This keynote highlights what was learned on Day 1 of this workshop, recapitulating the biopsychosocial mechanisms identified that underlie acute and chronic sickle cell disease pain and its related sequelae and comorbidities. More importantly, it recapitulates the unknowns—the enormous chunk of information beneath the tip of the iceberg regarding sickle cell disease pain. As daunting as the iceberg of pain and of knowledge seems, Day 2 of this workshop presents a massive, exciting opportunity to plot a path forward to move sickle cell disease pain research to the cutting edge.

Session 2: Challenges and Opportunities for Optimizing Sickle Cell Disease Pain Management

Expert Group 4—Measuring Pain and Sequelae in Patients for Clinical Trials

Speaker: Thomas Coates, M.D., University of Southern California

Dr. Coates is a professor of pediatrics and pathology at the University of Southern California Keck School of Medicine and the section head of hematology in the Division of Hematology Oncology at Children's Hospital Los Angeles. His research interests are sickle cell disease pain, thalassemia, disorders of neutrophils, and iron overload in children and adults. His research employs various engineering-intensive methodologies, such as magnetic resonance imaging, laser Doppler flowmetry, digital image analysis, and signal processing, to explore the basic mechanisms of sickle cell disease by using direct measures of microvascular blood flow to monitor the process of vaso-occlusion and how that relates to simultaneous measures of autonomic nervous system function. He was the lead principal investigator for a National Heart, Lung, and Blood Institute research award that examined multimodal biophysical biomarkers of vascular disease in hemoglobinopathies. He received his medical degree from the University of Michigan.

Acute and Experimental Pain

Pain responses are often assessed in the laboratory in humans by exposing the subject to heat or cold temperature applied to the skin and having the subject indicate the level of pain using a standard scale of some type. We wanted to noninvasively assess the physiological response to a painful stimulus. In particular, we were interested in perfusion as a biomarker, as decreased perfusion is thought to promote sickle vaso-occlusive crisis. We will discuss this methodology, show significant vasoconstriction in response to pain, and present data that humans have an inherent quantifiable vasoconstriction propensity that strongly predicts the frequency of sickle vaso-occlusion over the subsequent 2 years. This data demonstrates a clear role of vasoconstriction/perfusion in the pathophysiology of sickle cell disease and provides a mechanistic link between pain, stress, and vaso-occlusive crisis frequency. Vasoconstriction is a viable biomarker for the response to experimental pain and is mechanistically linked to the pathophysiology of sickle cell vaso-occlusion.

Speaker: Diana Wilkie, Ph.D., R.N., University of Florida

Dr. Wilkie is a professor and nurse scientist at the University of Florida. Her research focuses on the management of pain experienced by individuals with serious illnesses, such as sickle cell disease and cancer. Her biobehavioral and informatics research led to the development of a tablet-based pain reporting system that allows people to describe their pain. Her recent work includes characterization of sickle cell pain using patient-reported outcome measures, quantitative sensory testing, and genomics. She works with researchers and clinicians to effectively combine pharmacologic and nonpharmacologic therapies to manage pain and reduce health disparities. Her research has been continuously funded for 35 years, and she is committed to mentoring biobehavioral scientists, especially underrepresented minorities, focused on improving pain management or eliminating health disparities. She is a member of the National Academy of Medicine and received her doctorate from the University of California, San Francisco.

Clinical Presentation of Chronic Sickle Cell Disease Pain: Descriptors and Phenotypes

The chronic pain experience of individuals with sickle cell disease is complex, which poses challenges and opportunities for improving pain management. Further complicating the complexity of this pain is a health care context relying nearly exclusively on pain intensity and valuing unreliable or redundant indicators of pain. Within this context, not uncommon is dismissal of the individual's report, which contributes to additional stress, intensified pain, varied attempts to obtain adequate pain control, increased bidirectional mistrust, and resultant disparities in pain control for this vulnerable population. This context contributes to excessive heterogeneity with clinical trial risk of rejecting therapies that could be effective. The context, therefore, poses challenges for clinical trial design, sample size, and selection of pain measures. Several unrealized opportunities exist to optimize clinical trials focused on improving management of the pain of sickle cell disease. Preparing the health care context to reduce mistrust is central and requires education and dedicated efforts toward building a culture of respect, inclusion, and trust; effective methods of doing so are yet to be discovered. Critical is the characterization of sickle cell pain phenotypes relative to pain **etiology and mechanisms** (e.g., central or peripheral neuropathic, inflammatory, or nociceptive components), **sensory dimension** (e.g., pain location and distribution, intensity, quality, and temporal and seasonal patterns; sensitivities to mechanical stimuli), **affective dimension** (e.g., catastrophizing, anxiety, depression, anger), **cognitive dimension** (e.g., beliefs about pain and pain management, meaning of the pain, expectations about the pain, goals for pain control, past pain, neurocognitive status), and **behavioral dimension** (e.g., pain control behaviors, pain expression, coping strategies, self-management, functional status, health care utilization), **disease and comorbid conditions**, and **social determinants of health**. For young children with sickle cell disease, the parents are the individuals with critical understanding of and potential contributions to the pain experience. Therefore, trials with children are complicated further by the need for measures appropriate for the developmental

age of the child or adolescent and for their parents. Sample selection by phenotype and pain outcome measure selection matched to the expected therapeutic effect and duration are essential for well-designed clinical trials to test effects of new therapies and interventions.

Expert Group 4—Panel Commentary

Panelist: William Zempsky, M.D., M.P.H., University of Connecticut

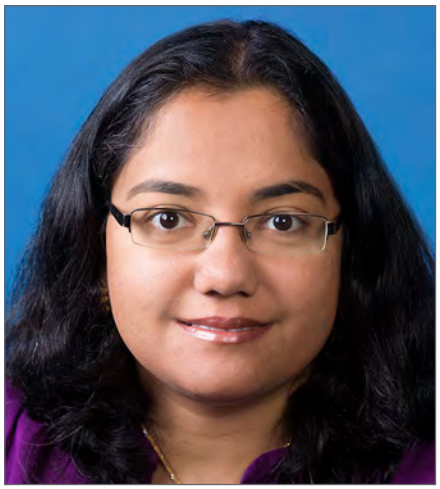
Systematic Approaches to Pediatric Acute and Chronic Sickle Cell Disease Pain, Location of Pain, and PhenX Measures

Dr. Zempsky is a professor of pediatrics and nursing at the University of Connecticut and the Francine L. and Robert B. Goldfarb Endowed Chair for Pain and Palliative Medicine and the associate chair for research at Connecticut Children's Medical Center. He is an international expert on pediatric pain management. He has published numerous research papers and received several National Institutes of Health grants, including an ongoing grant focused on improving the lives of children with severe functional disability associated with pain. Dr. Zempsky was elected chair of the Pediatric Special Interest Group of the American Pain Society in 2015 and was appointed as the pediatric representative to the physicians medical marijuana board for the State of Connecticut in 2016. He received a master's degree in public health from the University of Massachusetts, Amherst, and his medical degree from Johns Hopkins University.

Panelist: Carlton Dampier, M.D., Emory University

Quality of Life in Children With Chronic Sickle Cell Disease Pain, Epidemiology

Dr. Dampier is a professor of pediatrics at Emory University and a pediatric hematologist/oncologist at the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta. His research focuses on assessment of patient-reported outcomes and symptom management among children and adolescents, particularly those with pain from sickle cell disease. He is a coprincipal investigator on a clinical trial of an mHealth intervention for adolescents with sickle cell pain. He is interested in clinical trial process improvement, quality management, research ethics, and scientific integrity. Previously, he was a site principal investigator for the Cooperative Study of Sickle Cell Disease and led or participated in studies validating assessment tools, including the pediatric Patient-Reported Outcomes Measurement Information System, and in longitudinal observation studies. An experienced clinical trialist, he has participated in numerous phase 2 and 3 trials for new sickle cell therapies. He received his medical degree from the University of Chicago.



Panelist: Nitya Bakshi, M.D., M.S., Emory University

Pain Variability and Pain Phenotypes in Sickle Cell Disease

Dr. Bakshi is an assistant professor of pediatrics at Emory University and a pediatric hematologist/oncologist at the Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta. Her research interests include chronic pain, ecological momentary assessment of pain, decision science, and patient-reported outcomes. Her work with sickle cell disease patients, their caregivers, and health care providers is revealing barriers to care and approaches that improve access to care and curative therapies such as bone marrow transplant. She received her medical degree from Christian Medical College and Hospital, Vellore, India, and a master's degree in clinical research from the University of Pittsburgh.

Panelist: Laura De Castro, M.D., M.H.Sc., University of Pittsburgh

Patterns and Correlates of Daily Chronic Sickle Cell Disease Pain, Lessons From Contemporary Drug Trials in Acute and Chronic Pain Measurement

Dr. De Castro is a professor of medicine and the clinical chief of benign hematology in the Division of Hematology/Oncology at the University of Pittsburgh Medical Center. Previously, she was director of the Duke University Sickle Cell Center. As a clinician, she provides acute and longitudinal care to patients with sickle cell disease and other benign blood disorders and addresses and manages disease complications, chronic pain, preventive medicine, and psychosocial support. She has been a principal or coprincipal investigator for more than 30 clinical research studies and has coauthored more than 45 articles on research related to sickle cell disease, including topics such as psychosocial issues, pulmonary hypertension, use of social media and mobile technology for health-related outcomes, drug development, and pregnancy outcomes among women with sickle cell disease. She received her medical degree from the Universidad Autónoma de Santo Domingo in the Dominican Republic.

Expert Group 4—Panel Discussion

Moderator: Will Aklin, Ph.D., National Institute on Drug Abuse

Dr. Aklin is the director of the Behavioral Therapy Development Program within the Division of Therapeutics and Medical Consequences at the National Institute on Drug Abuse. His areas of research include development of treatments with theory-derived behavioral targets, studies that integrate behavioral/pharmacologic treatment, and clinical validation/optimization of digital therapeutic interventions (e.g., mobile or web-based). He has extensive clinical and research experience in behavioral and cognitive behavioral treatment for substance use disorders, adaptive brief interventions, and adherence trials. He has worked on several initiatives, including National Institutes of Health Common Fund initiatives and the National Institutes of Health HEAL (Helping to End Addiction Long-term℠) Initiative, and he has partnered with the National Institute on Alcohol Abuse and Alcoholism and the National Cancer Institute on the development and testing of behavioral therapies for drug and alcohol use disorders. He received his doctorate in clinical psychology from the University of Maryland.

Moderator: Smriti Iyengar, Ph.D., National Institute of Neurological Disorders and Stroke

Dr. Iyengar is the director of the Preclinical Screening Platform for Pain program and a program director in the Division of Translational Research at the National Institute of Neurological Disorders and Stroke. She is an adjunct senior research professor in the Departments of Anesthesia and Clinical Pharmacology at the Indiana University School of Medicine. Previously, she worked at Eli Lilly, G.D. Searle, Schering-Plough, and Ciba Geigy. Her research experience has focused on mechanisms underlying neurodisorders, including pain and headache. Her drug discovery expertise includes target, lead, and clinical candidate identification and characterization, as well as translational and clinical development, regulatory strategy, and commercialization. She has served on several national and international committees established to evaluate research issues and accelerate translational medicine for pain. She received her doctorate from Maharaja Sayajirao University of Baroda, India, and completed a postdoctoral fellowship as a Charles and Johanna Busch fellow at Rutgers University.

Expert Group 5—Current or Promising Treatments for Acute and Chronic Sickle Cell Disease Pain

Speaker: C. Patrick Carroll, M.D., Johns Hopkins University

Dr. Carroll is an associate professor in the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins School of Medicine and the director of psychiatric services at the Sickle Cell Center for Adults at the Johns Hopkins Hospital. He is an internationally recognized expert in multidisciplinary management of patients with sickle cell disease, particularly in the management of acute-on-chronic pain and psychiatric comorbidities. He is an attending physician in the Pain Treatment Program, an intensive, multidisciplinary program for patients with refractory chronic pain. He has worked with the American Society of Hematology, the National Institutes of Health, and other organizations to improve care of people with sickle cell disease and helped develop the American Society of Hematology's guidelines for managing acute and chronic sickle cell disease pain. Recently, he has supported incorporating patient-reported outcomes into clinical trials and research. He received his medical degree from Washington University in St. Louis.

Treatment Strategies To Manage Acute and Chronic Sickle Cell Disease Pain

While pain, particularly painful crisis, is the hallmark of sickle cell disease, clinicians and patients must manage this aspect of the condition with a remarkably poor foundation of evidence. This is particularly true of noncrisis and chronic pain. This presentation will briefly summarize what is known and unknown with respect to treatment of acute and chronic pain in sickle cell disease, with implications for long-term management strategy. The presentation will focus on three arguments: (1) How to integrate new or newly proven interventions into the strategy of care is at least as important as proving they work. (2) There are several interventions known to benefit chronic pain in other conditions that are not being tested in sickle cell disease and should be. (3) While rapid assessment and treatment with individualized opioid dosing probably helps those presenting in acute crisis pain, what to do beyond this—to either improve outcomes or alter treatment in response to failure—is unknown but ripe for investigation.

Speaker: Judith Schlaeger, Ph.D., University of Illinois, Chicago

Dr. Schlaeger is an associate professor in the Department of Human Development Nursing Science at the University of Illinois, Chicago. She is a pain scientist focused on the development of translational treatments for chronic pain. She developed her interests in researching pain and treatments for vulvodynia, a chronic pain syndrome, from her extensive background as a practicing licensed acupuncturist and certified nurse midwife. Dr. Schlaeger is grounded in Western medicine and trained in traditional Chinese medicine and understands the limitations and strengths of both paradigms. Her understanding of the origins of chronic pain allows her to contribute to the evaluation of people with sickle cell disease. She received her doctorate in acupuncture science from Guangzhou University of Chinese Medicine.

Managing Chronic Sickle Cell Disease Pain With Nonpharmacologic Approaches

Pain, both acute and chronic, is a constant companion to the 100,000 people in the United States, mostly of African background, and millions more worldwide living with sickle cell disease. Pain is sickle cell disease's hallmark symptom, the leading cause for almost 200,000 annual emergency department admissions, and is the leading cause of hospitalization, with estimated annual health care costs in the United States of $2.4 billion. The use of nonpharmacologic approaches by those with sickle cell disease to reduce pain, reduce opioid use, and enable themselves to better cope with their pain is well known, but there are few studies that evaluate the effectiveness of these therapies. Preliminary studies suggest that acupuncture, massage, yoga, guided relaxation, mindfulness-based interventions, biofeedback, and aquatic rehabilitation are promising therapies. Guided relaxation and mindfulness-based interventions have been tested with well-designed feasibility and acceptability studies and efficacy pilot randomized controlled trials. Overall, the preliminary studies on managing chronic sickle cell disease pain with nonpharmacologic approaches have methodological issues that hamper generalizability of results. Weaknesses include reliance on retrospective chart reviews and case studies, lack of control group comparisons, and small sample sizes. Future rigorous randomized controlled trials conducted on nonpharmacologic approaches are needed to reduce pain and opioid use in individuals with sickle cell disease.

Expert Group 5—Panel Commentary

Panelist: Ardith Doorenbos, Ph.D., R.N., University of Illinois, Chicago

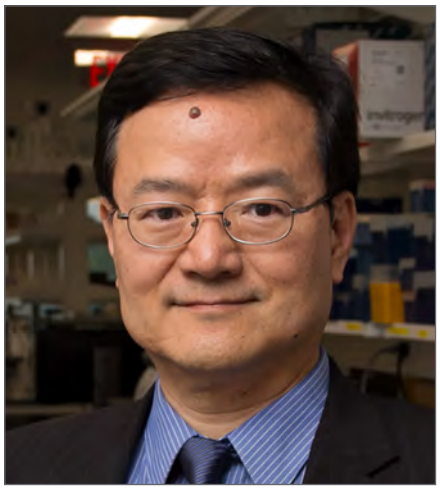
Acupuncture and Guided Relaxation: Complementary and Integrative Therapies for Sickle Cell Disease Pain

Dr. Doorenbos is a nursing collegiate professor in the Department of Biobehavioral Nursing Science in the College of Nursing at the University of Illinois, Chicago. Her research is centered on pain and symptom management. Her grant portfolio is funded by the National Institutes of Health, congressionally directed medical research programs, and other professional sources. She has published more than 150 peer-reviewed, data-based articles in nursing and multidisciplinary journals. In 2010, she became a fellow of the American Academy of Nursing, and in 2018 she was inducted into the Sigma Theta Tau International Nurse Researcher Hall of Fame.

Panelist: Michael V. Vitiello, Ph.D., University of Washington

The Potential of Cognitive Behavioral Therapy for Insomnia To Manage Chronic Pain and Comorbid Insomnia

Dr. Vitiello is a professor of psychiatry and behavioral sciences at the University of Washington. He is an internationally recognized expert in sleep, circadian rhythms, and sleep disorders of aging. His research is funded by the National Institutes of Health and focuses on the causes, consequences, and treatments of disturbed sleep, circadian rhythms, and cognition in older adults. His current work focuses on improving the sleep of people with osteoarthritis to reduce their osteoarthritis-related symptoms, such as pain, fatigue, and depression; health care utilization; and health care–related costs. He has written more than 500 scientific articles, reviews, chapters, and editorials and is the editor in chief of *Sleep Medicine Reviews*. He has served in leadership roles for many sleep-related societies, including as president of the Sleep Research Society. He received his doctorate in psychology from the University of Washington.



Panelist: Bin He, Ph.D., Carnegie Mellon University

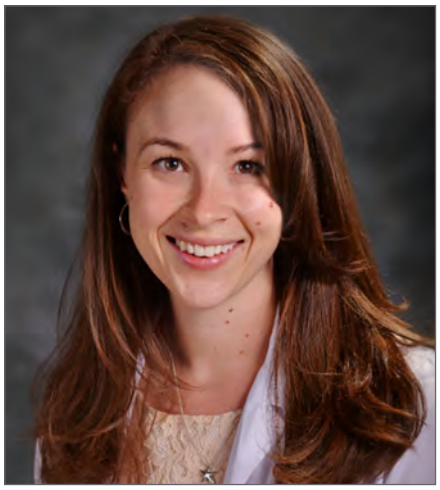
Ultrasound Neuromodulation for Acute and Chronic Sickle Cell Disease Pain Management

Dr. He is the Trustee Professor of Biomedical Engineering and Neuroscience at Carnegie Mellon University. He has research expertise in neural engineering, including noninvasive neuromodulation, neural interfacing, and neuroimaging. He develops and investigates noninvasive techniques to quantify sickle cell disease pain using electroencephalography and functional magnetic resonance imaging and to reduce or suppress sickle cell disease pain using focused ultrasound neuromodulation. He is the chair of the International Academy of Medical and Biological Engineering, has published more than 280 peer-reviewed articles, and has served as a member of the National Advisory Council for Complementary and Integrative Health. He was the department head of biomedical engineering at Carnegie Mellon University and the director of the Institute for Engineering in Medicine at the University of Minnesota. He received his doctorate in bioelectrical engineering from the Tokyo Institute of Technology and completed a postdoctoral fellowship at Harvard University—Massachusetts Institute of Technology.

Panelist: Lynnette Kaid, SorsaMED

Potential Therapeutic Proteins Infused With Cannabinoids for Chronic Sickle Cell Disease Pain Management

Ms. Kaid is a cofounder of SorsaMED, which promotes socially equitable treatment options for sickle cell disease sufferers through innovative biomedical technologies. A defining moment for Ms. Kaid was when her mother died at age 33 from complications related to sickle cell disease. Ms. Kaid remembers her mother's daily struggles and frequent trips to the hospital and the day her mother never returned home from the hospital. While attending a cannabis and health conference with her business partner, Lisa Yancey, Ms. Kaid noticed that sickle cell disease was not on the agenda. Although the life expectancy of sickle cell patients has increased and advances have been made toward a cure, an opioid alternative for current sufferers of sickle cell disease is still needed. Thinking of her mother, her cousins, and countless others affected by the disease, Ms. Kaid used her background in marketing, graphic arts, and music to bring together experts and innovators to develop solutions for sufferers of sickle cell disease.



Panelist: Alexis Leonard, M.D., National Heart, Lung, and Blood Institute

Residual Chronic Pain Following Gene Therapy for Sickle Cell Disease

Dr. Leonard is a clinical researcher in Dr. John Tisdale's cellular and molecular therapeutics laboratory at the National Heart, Lung, and Blood Institute. She also provides clinical care at Children's National Hospital. Her research focuses on curative strategies, including gene therapy, for sickle cell disease. The sickle cell program focuses on preclinical and clinical testing of drugs and innovative compounds, elucidating genetic modifiers that may affect disease severity, studying and preventing organ damage that may lead to increased morbidity and mortality, and developing potentially curative stem cell transplantation strategies. She received her medical degree from Tufts University and completed her pediatric residency and fellowship training in pediatric hematology/oncology at Children's National Hospital.

Panelist: Deepika Darbari, M.B.B.S., M.S., Children's National Hospital

Persistence of Pain Post Stem Cell Transplantation in Sickle Cell Disease

Dr. Darbari is a pediatric hematologist-oncologist at Children's National Hospital, which serves a large population of youth with sickle cell disease. She conducts clinical and translational studies on mechanisms of sickle cell pain and its management through pharmacologic and nonpharmacologic integrative modalities. Her research has investigated pain experience variability and the risk factors associated with sickle cell disease pain, and she has contributed to developing diagnostic criteria for acute and chronic sickle cell disease pain. She served as a chair at the Sickle Cell Disease Clinical Endpoints Workshop, which was cohosted by the U.S. Food and Drug Administration and the American Society of Hematology, and contributed to the Centers for Disease Control and Prevention amended guidelines on opioid use in sickle cell disease. She received her medical degree from Gandhi Medical College and training in pediatric hematology oncology from a joint Johns Hopkins University and National Institutes of Health fellowship program.

Expert Group 5—Panel Discussion

Moderator: Jeri Miller, Ph.D., National Institute of Nursing Research

Dr. Miller is the chief of the Office of End-of-Life and Palliative Care Research in the Division of Extramural Science Programs at the National Institute of Nursing Research. She coordinates the development, implementation, and evaluation of end-of-life and palliative care research in direct collaboration with other National Institutes of Health Institutes and Centers, Federal research agencies, and outside constituencies. In addition, she oversees the pain research portfolio and the Research Centers Program at the National Institute of Nursing Research. At the National Institutes of Health, she completed her postdoctoral work, was an intramural scientist, and was a principal investigator for numerous research protocols.

Moderator: Della White, Ph.D., National Center for Complementary and Integrative Health

Dr. White is a program director in the Division of Extramural Research at the National Center for Complementary and Integrative Health. Her research portfolio includes studies of complementary and integrative health approaches for health promotion and disease prevention across the lifespan in diverse populations. She is interested in the role of social and structural determinants of health in the use of complementary and integrative health approaches to improve health outcomes, particularly among minority and underserved populations. Previously, she was a program director at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, where she managed research on reproductive health, community-based participation, health disparities, and administrative capacity building. She received her doctorate in health education and health promotion from the University of Alabama at Birmingham. She completed postdoctoral training in public health genomics at the National Human Genome Research Institute.

Expert Group 6—Overcoming Challenges of Evidence-Based Pain Management: Patient Engagement, Stigma, Bias, and Access to Quality Care

Speaker: Patricia Kavanagh, M.D., Boston University

Dr. Kavanagh is an associate professor in the Department of Pediatrics at Boston University School of Medicine and is an attending physician in the pediatric emergency department at Boston Medical Center. She has a national reputation in systems approaches that improve emergency department care for people with sickle cell disease. She has defined and refined treatment standards for sickle cell disease through guideline-based care pathways and individualized pain protocols. In addition, she is examining how screening and referring families with unmet basic needs may impact health outcomes of children with sickle cell disease. She cofounded and chairs the Emergency Department Sickle Cell Care Coalition, serves on the oversight steering committee of the Health Resources and Services Administration's Sickle Cell Disease Treatment Demonstration Program, and serves on the steering committee for the American Society of Hematology's Sickle Cell Disease Coalition. She received her medical degree from Boston University.

Addressing Implementation and Access to Quality Care Challenges in Sickle Cell Disease Pain Care

Accessing high-quality, guideline-based care for acute pain due to a sickle cell crisis is a considerable challenge for many individuals living with sickle cell disease. The lack of knowledgeable providers in the acute care setting, compounded by the stigma associated with sickle cell disease and the reluctance to use opioids to treat pain due to the opioid overdose epidemic, has left patients with sickle cell disease "choosing between death or dignity" when deciding whether to seek care for their acute pain. Several alternative care settings have been used as an alternative to the emergency department to provide care for acute sickle cell disease pain, including day hospitals or infusion centers and hospital-based observation units. However, many patients with sickle cell disease do not have access to institutions offering these services. Significant improvements in emergency department care have been achieved with the implementation of standardized protocols for sickle cell disease that include high-priority triage, parenteral pain medications initiated within 1 hour of arrival, frequent pain reassessment and redosing of pain medications, and starting patient-controlled analgesia for those being admitted. The use of pain protocols individualized to adult patients with sickle cell disease has shown promise over weight-based approaches; the definitive study is currently underway. Other successful strategies used in the emergency department setting have focused on shortening the time to the first dose of pain medications, including providing pain medications via the subcutaneous route

when obtaining intravenous access is difficult, and using nurse-driven protocols to conduct patient assessments and deliver the first dose of pain medications.

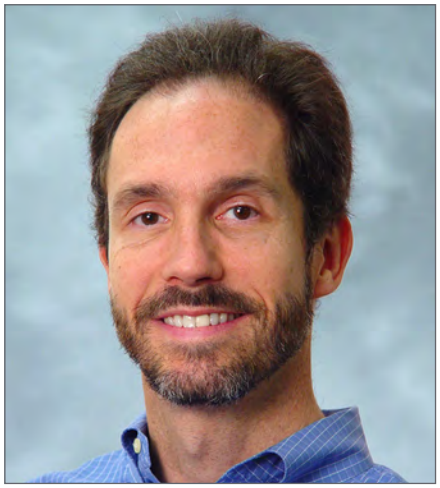
Speaker: Coretta Jenerette, Ph.D., R.N., University of South Carolina

Dr. Jenerette is the associate dean for the Office of Diversity, Equity, and Inclusion at South Carolina University. After entering the nursing profession, she became aware of the plight of adults with sickle cell disease and learned that much inequity of care for individuals with sickle cell disease is due to structural and social determinants of health, implicit and explicit bias, lack of knowledge, myths about Black people, and racism. Her research focuses on improving holistic health outcomes for people with sickle cell disease and other vulnerable populations. In 2020, Sickle Cell 101 named her the National Sickle Cell Advocate of the Year. She received her master's degree in nursing and a doctorate from the University of South Carolina. She completed her certification in nursing education at the University of North Carolina, Chapel Hill and completed postdoctoral fellowships at Yale University and the University of North Carolina, Chapel Hill.

Addressing Stigma and Bias Challenges in Sickle Cell Disease Pain Care

Dr. Martin Luther King, Jr. stated, "Of all the forms of inequality, injustice in health is the most shocking and inhuman." Thus, those involved in health care and research should be social justice advocates for optimal outcomes for all patients. Unfortunately, the health care system is a microcosm of society. As noted by recent events in the United States, leading to the Black Lives Matter movement, Black Americans have significant challenges based on the color of their skin that lead to biases (implicit or explicit) in treatment, stereotyping, labeling, and poor outcomes. Similarly, individuals with sickle cell disease, most often Black in the United States, encounter stereotyping, labeling, and poor health outcomes. The plight of Black people in society is also visible in the lack of humanity and empathy experienced by many individuals with sickle cell disease during care-seeking and in research. It may be challenging to change the hearts of health care providers and researchers to be empathetic toward individuals with sickle cell disease; however, appropriate accountability may compel a behavior change.

Expert Group 6—Panel Commentary



Panelist: Roger Fillingim, Ph.D., University of Florida

Addressing Disparities and Other Potential Challenges in Sickle Cell Disease Pain Management

Dr. Fillingim is a distinguished professor in the College of Dentistry and director of the Pain Research and Intervention Center of Excellence at the University of Florida. He also serves as director of the Center for Advancing Minority Pain and Aging Science. His research investigates biopsychosocial mechanisms mediating individual differences in pain, including racial and ethnic disparities in pain, as well as age-related changes in pain processing. His research program investigating individual differences in pain has been continuously funded by the National Institutes of Health for more than 25 years, and he currently holds multiple grants from the National Institute on Aging. He has published more than 390 scientific articles and is a frequent speaker at national and international conferences. He received his doctorate in clinical psychology from the University of Alabama at Birmingham.

Panelist: Shan-Estelle Brown, Ph.D., Rollins College

Using Cultural Competence/Sensitivity Approaches and Minimizing Structural Barriers To Improve Sickle Cell Disease Pain Management

Dr. Brown is an assistant professor in the Department of Anthropology and the coordinator of the Global Health Program at Rollins College. Previously, she was a postdoctoral research associate in the AIDS Program at the Yale School of Medicine. She is a mixed-methods medical anthropologist with training in qualitative research and pedagogy on writing. Her research interests include conducting community-engaged research, improving patient-centered outcomes with medical technologies, understanding patient perceptions of risk and well-being, and identifying structural facilitators and barriers to health care access and retention in care. She has researched these issues for people with HIV and for people with sickle cell disease. She is the author of *Writing in Anthropology: A Brief Guide* and received her doctorate in anthropology from the University of Connecticut.

Panelist: Jerlym Porter, Ph.D., M.P.H., St. Jude Children's Research Hospital

Challenges of Acute and Chronic Sickle Cell Disease Pain Management in the Transition to Adult Care

Dr. Porter is an associate member in the Department of Psychology at St. Jude Children's Research Hospital. Her research interests include issues related to the transition process from pediatric care to adult care for patients with sickle cell disease and the psychosocial factors impacting health promotion, treatment adherence, and disease management. She received her master's degree in public health from Northwestern University and a doctorate in counseling psychology from Virginia Commonwealth University.

Contributor: Paula Tanabe, Ph.D., Duke University

Dr. Tanabe is the Laurel B. Chadwick Distinguished Professor of Nursing and vice dean of research at the Duke University School of Nursing. Her work advances the care of individuals with sickle cell disease and focuses on improving emergency department pain management during vaso-occlusive crises. Currently, the National Heart, Lung, and Blood Institute funds two of her clinical trials. She is the principal investigator for a randomized controlled trial comparing pain scores of patients in the emergency department who have had vaso-occlusive episodes and have been treated with individualized or weight-based opioids. She also is a coprincipal investigator for an implementation science project that embeds individualized pain plans into electronic health records that can be accessed by patients and emergency department providers. The goal of the project is to improve emergency department treatment of vaso-occlusive episodes. She received her doctorate from the University of Illinois.

Expert Group 6—Panel Discussion

Moderator: Susan Shero, R.N., M.S., National Heart, Lung, and Blood Institute

Ms. Shero is a program officer within the Center for Translation Research and Implementation Science at the National Heart, Lung, and Blood Institute. She leads the Implementation Science and Health Care Innovation program with a focus on rigorous evidence review, integration of evidence into practice, and implementation research to accelerate innovation in health care delivery in clinical and community settings. Her portfolio includes research in innovative strategies, methods, tools, and technologies to quicken implementation and deimplementation research, inclusion of data from pragmatic trials, and decision support tools for patients and health care professionals. She is an experienced project manager and has led several clinical practice guidelines development projects, national health education programs, and a variety of health awareness campaigns. She has a clinical background in emergency department nursing and several years of experience in community health nursing in military, government, worksite, and university settings.

Moderator: Wendy Weber, N.D., Ph.D., M.P.H., National Center for Complementary and Integrative Health

Dr. Weber is branch chief at the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health, where she coordinates clinical trial–specific funding opportunity announcements. She oversees a portfolio of pragmatic clinical trials, natural product clinical trials, studies of complementary medicine that promote healthy behavior, and complex complementary/integrative health intervention research. Her interests include the use of complementary health interventions for common pediatric conditions, mental health conditions, promoting healthy behaviors, and health services research. Previously, she was a research associate professor at Bastyr University, where her research included the study of herbal treatments for pediatric conditions. She received her master's degree in public health and a doctorate from the University of Washington.

Patient Perspective

Speaker: Shauna Whisenton, American Society of Hematology Research Collaborative

Living With Sickle Cell Disease: Personal Experience With Acute and Chronic Pain Management After Sickle Cell Disease Cure

Ms. Whisenton is a sickle cell disease community engagement manager for the American Society of Hematology Research Collaborative's sickle cell disease clinical trials network. She manages and assists with the development and implementation of the network's community engagement and outreach activities at the local and national levels. She also supports engagement activities for local, site-specific community advisory boards. She is a passionate sickle cell disease advocate who was born with sickle cell disease but conquered the disease through participation in a curative clinical trial. She also is passionate about ensuring that individuals directly affected by sickle cell disease have a voice in creating community-centric clinical research. She has participated in many minority health awareness activities, including advocacy discussion panels and video productions. Her story has been featured in Mediaplanet's *Clinical Trials,* and she has contributed to numerous health care news articles.

Roundtable Discussion 2—Building a Future in Which Sickle Cell Disease Pain Management Can Be Optimized

Roundtable Discussant: Sophie Lanzkron, M.D., M.H.S., Johns Hopkins University

1. Multidisciplinary and Multilevel Interventions or Multicomponent Delivery Models That Are Ready for Multisite Efficacy or Effectiveness Trials for Acute and Chronic Pain Management
2. Important Functional Measures To Be Considered for Such Clinical Trials

Dr. Lanzkron is a professor of medicine and oncology, a hematologist, and the director of the Sickle Cell Center for Adults at the Johns Hopkins University School of Medicine. She is internationally recognized for her research on the optimal care and management of people with sickle cell disease. She has served on the expert panel for the National Institutes of Health report on the management of sickle cell disease, on the American Society of Hematology's panel for the development of its sickle cell disease practice guidelines, and as chair of the patient engagement and education subcommittee for the American Society of Hematology Research Collaborative's Sickle Cell Disease Clinical Trials Network. Her

research focuses on improving the quality of care provided to this historically underserved population, and she is considered an expert in health services research. She received her medical degree from the Albert Einstein College of Medicine.

Roundtable Discussant: Wally Smith, M.D., Virginia Commonwealth University

Barriers to and Effective Treatments and Models for Acute and Chronic Sickle Cell Disease Pain Management That Could Be Adopted, Adapted, Integrated, and Scaled Up in Various Health Care Systems

Dr. Smith is the Florence Neal Cooper Smith Professor of Sickle Cell Disease and the director of the Adult Sickle Cell Program at Virginia Commonwealth University. His clinical specialties include care for adults with sickle cell disease, hydroxyurea and remittive therapies for sickle cell disease, and pain management in sickle cell disease. He is an experienced implementation scientist and an expert in clinical and health services research. He was the principal investigator for the Pain in Sickle Cell Epidemiology Study, which was the largest adult cohort study of sickle cell disease pain. He received his medical degree from the University of Alabama.

Roundtable Discussant: Cheryl Stucky, Ph.D., Medical College of Wisconsin

Successful Strategies From Other Fields That Could Be Evaluated in Trials To Address Stigma, Enhance Access to Quality Care, Reduce Bias, and Overcome Structural Barriers in Acute and Chronic Sickle Cell Disease Pain Management

Dr. Stucky is the Marvin Wagner Endowed Professor in the Department of Cell Biology, Neurobiology and Anatomy at the Medical College of Wisconsin and the director of the neuroscience doctoral program and of the Pain Division in the Neuroscience Research Center. Dr. Stucky has more than 27 years of experience studying pain mechanisms at the behavioral, physiological, cellular, and molecular levels and is an expert in modeling painful injury and disease conditions in rodents. Her previous studies have used mouse models of sickle cell disease to identify channels and receptors on sensory neurons that contribute to sickle cell disease pain. She received her doctorate in neuroscience, physiology, and immunity from the University of Minnesota.

Closing Remarks

Closing Remarks: Monica Webb Hooper, Ph.D., National Institute on Minority Health and Health Disparities

Dr. Monica Webb Hooper is Deputy Director of the National Institute on Minority Health and Health Disparities. She works closely with the director, Dr. Pérez-Stable, and the leadership, to oversee all aspects of the Institute and to support the implementation of the science visioning recommendations to improve minority health, reduce health disparities, and promote health equity.

Before joining the National Institute on Minority Health and Health Disparities, Dr. Webb Hooper was a professor of oncology, family medicine and community health and psychological sciences at Case Western Reserve University. She was also associate director for Cancer Disparities Research and director of the Office of Cancer Disparities Research in the Case Comprehensive Cancer Center.

Dr. Webb Hooper completed her doctorate in clinical psychology from the University of South Florida, internship in medical psychology from the University of Florida Health Sciences Center, and her Bachelor of Science from the University of Miami.