

National Institutes of Health (NIH), Office of Disease Prevention

# **NIH Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**

## **Program Book**

**December 9–10, 2014**

**William H. Natcher Conference Center  
National Institutes of Health  
Bethesda, Maryland**



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### **Co-Sponsored by**

NIH Office of Disease Prevention  
Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)  
Research Working Group





Dear Workshop Attendees:

It is with great pleasure that I welcome you to the National Institutes of Health (NIH) Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. The U.S. Centers for Disease Control and Prevention (CDC) reports over 1 million adults with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) in the United States, and recent evidence has shown a higher prevalence in females compared with males. Certain racial/ethnic groups have also been found to be at an increased risk, most notably, Native American and African American populations. The economic burden of ME/CFS, including annual health care costs, is estimated to be well over \$1 billion.

The Office of Disease Prevention (ODP) is pleased to co-sponsor this event with the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group. I would like to thank Dr. Janine Clayton, Director of the Office of Research on Women's Health, for her leadership in this endeavor and extend a special thank you to Drs. Susan Maier and Mariela Shirley, who led the day-to-day development of the workshop alongside ODP staff. The goal of the Pathways to Prevention program is to host workshops that identify research gaps in a selected scientific area, identify methodological and scientific weaknesses in that scientific area, suggest research needs, and move the field forward through an unbiased, evidence-based assessment.

The ODP provides leadership for the development, coordination, and implementation of activities across the NIH and with other public and private partners to increase the scope, support, public health impact, and dissemination of health promotion and disease prevention research. This workshop is just one example of how the ODP promotes methodologically sound research to reduce the incidence of disease and increase healthy years of life. The workshop is designed to be interactive, so we encourage you to share your insights during audience discussion sessions about:

- How the research on ME/CFS using multiple case definitions has contributed to the state of the current scientific literature on diagnosis, pathophysiology, treatment, cure, and prevention of ME/CFS
- How the measurement outcomes (tools and measures) currently used by researchers of ME/CFS are able to distinguish among those patients diagnosed with ME/CFS, including the sensitivity of the tools and measures to identify subsets of patients according to duration, severity, nature of the illness, onset characteristics, and other categorizations
- How the research on treatments or therapies shown to be effective in addressing symptoms of ME/CFS will lead to an understanding of the underlying pathology associated with ME/CFS
- How innovative research approaches have provided an understanding of the pathophysiology of ME/CFS, and how this knowledge can be applied to the development of effective and safe treatments.

The draft report will be posted on the ODP website, and public comments will be accepted for 4 weeks.

It is an exciting time for the ODP as we have begun implementing our first Strategic Plan for Fiscal Years 2014–2018. We identified six strategic priorities that will guide the work of the Office during this time. The Pathways to Prevention Workshops were developed to address Strategic Priority II and provide an avenue for stakeholders to identify needs for prevention research, compare those needs with the current NIH portfolio, and collaborate with NIH Institutes and Centers to prioritize gaps in prevention research for additional investment.

On behalf of the NIH and the ODP, thank you in advance for your contributions. We look forward to an informative and engaging workshop.

David M. Murray, Ph.D.  
Associate Director for Prevention  
Director  
Office of Disease Prevention  
Division of Program Coordination, Planning, and Strategic Initiatives  
Office of the Director  
National Institutes of Health

Dear Colleagues:

I am pleased to welcome you to the National Institutes of Health (NIH) Pathways to Prevention Workshop, titled “Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).”

I am delighted that the NIH Office of Disease Prevention (ODP) undertook this important topic at the request of the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group through the Office of Research on Women’s Health. There are far too many individuals suffering from this disorder, and there is very little ongoing translational research to lead to effective therapeutics to treat symptoms and ultimately cure the illness.

One purpose of this workshop is to bring clarity to the assessment of the previous research conducted in this area, and suggest the means to move the research forward. Research on ME/CFS has progressed based on some of the outcomes from the NIH State of the Knowledge Workshop ([http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH\\_SKW\\_Report.pdf](http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf)); for example, a seminal study in well-characterized CFS patients showed no link between XMRV and CFS (PMID:22991430), and other studies have shown marked alterations in key immunological biomarkers present in patients with CFS (PMID:23570606). However, the translation of these important research findings into demonstrable clinical application and identification of therapeutic targets based on underlying etiology have progressed slowly. Expanding understanding of underlying pathophysiology and etiology can accelerate the development of therapeutics and optimize treatments for ME/CFS. Certainly, the outcomes from this workshop will advance the research on ME/CFS through an assessment of the current status of the field, and identification of research gaps and strategies for new investigative approaches.

I would like to thank the members of the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group for developing and submitting the application to ODP, our federal partners for their role in supporting many types of ME/CFS activities, and patients, caregivers, advocacy groups, and members of the public for their valuable input on the process that made this meeting a reality.

I truly appreciate your participation, and I look forward to reviewing the recommendations.

Sincerely,

Janine Austin Clayton, M.D.  
NIH Associate Director of Research on Women’s Health



# About the Workshop

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex, multifaceted disorder characterized by extreme fatigue and a host of other symptoms that can worsen after physical or mental activity, but do not improve with rest. In addition to extreme fatigue, people with ME/CFS may also experience:

- Widespread muscle and joint pain
- Sore throat
- Tender lymph nodes in the neck or armpit
- Headaches
- Sleep problems
- Difficulty with short-term memory or concentration.

Effects of the illness can range from moderate to debilitating and can substantially impact everyday functioning. Routine daily activities such as cooking meals, brushing teeth, and caring for children become difficult. In addition, sensitivity to environmental factors (e.g., noise, light, chemicals) may force many individuals with ME/CFS into seclusion or withdrawal from society.

The onset of ME/CFS symptoms may be sudden—for example, immediately following a viral illness such as the flu—or gradual, with no discernible attachment to a specific event or time. The Centers for Disease Control and Prevention reports over 1 million adults with ME/CFS in the United States, with higher prevalence in females compared with males. Certain racial/ethnic groups have also been found to be at an increased risk for ME/CFS, most notably, Native American and African American populations. The economic burden of ME/CFS, including annual health care costs, is estimated to be between \$1.9 billion and \$7.2 billion.

There are many aspects of ME/CFS that are problematic. First, the underlying mechanisms are unclear. Causal and/or contributing factors to ME/CFS include central nervous system, metabolic, infectious or post-infectious, cardiovascular, immune system, or other types of disorders. Second, there is little agreement among clinical and research professionals, as well as patient groups, regarding the name of the illness. The name myalgic encephalomyelitis or ME is more commonly used in Europe and Canada, while the name chronic fatigue syndrome or CFS is used more often in the United States and Australia. Yet the acronym ME/CFS is increasingly being used worldwide. Third, no laboratory tests exist for diagnosing ME/CFS, and its diagnosis is one of exclusion. All other illnesses with overlapping symptoms must be ruled out prior to an ME/CFS diagnosis. Fourth, there are no drugs or therapies approved by the U.S. Food and Drug Administration to treat ME/CFS. Clinical trials to test drug or therapy effectiveness, and drug development to target the underlying cause, are difficult to conduct because of the unknown causes, varied symptom profile, and lack of concurrence regarding diagnostic criteria. Lastly, medical professionals disagree on many aspects of ME/CFS, including whether the illness is real, and there is no definitive answer about the effectiveness of current therapies (e.g., diet, use of off-label or experimental drugs).

The 2014 Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome will seek to clarify:

- How the research on ME/CFS using multiple case definitions has contributed to the state of the current scientific literature on diagnosis, pathophysiology, treatment, cure, and prevention of ME/CFS

- How the measurement outcomes (tools and measures) currently used by researchers of ME/CFS are able to distinguish among those patients diagnosed with ME/CFS, including the sensitivity of the tools and measures to identify subsets of patients according to illness characteristics that include duration, severity, nature of the illness, onset characteristics, outcomes, and other categorizations
- How the research on treatments or therapies shown to be effective in addressing symptoms of ME/CFS will lead to an understanding of the underlying pathology associated with ME/CFS
- How innovative research approaches have provided an understanding of the pathophysiology of ME/CFS, and how this knowledge can be applied to the development of effective and safe treatments.

The workshop is co-sponsored by the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group (<http://orwh.od.nih.gov/research/me-cfs/aboutgroup.asp>).

Initial planning for all Pathways to Prevention workshops, regardless of disease category/condition, is coordinated by a Working Group that nominates panelists and speakers, and develops and finalizes questions that frame the workshop agenda. After finalizing the questions, an evidence report is prepared by an Evidence-based Practice Center, through a contract with the Agency for Healthcare Research and Quality. During the 2-day workshop, subject matter experts in the workshop topic area discuss the body of evidence, and attendees have opportunities to provide comments during open discussion periods. After weighing evidence from the evidence report, expert presentations, and public comments, an unbiased, independent panel prepares a draft report that identifies research gaps and recommendations for future research priorities. The draft report is posted on the Office of Disease Prevention website, and public comments are accepted for 4 weeks. The final report is then released approximately 2 weeks later.

# Financial Disclosures

The National Institutes of Health, Centers for Disease Control and Prevention, our planners, and our presenters wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of the following:

Name	Organization	Nature of Conflict of Interest AND Mechanism to Resolve*
<b>Speakers</b>		
Clauw, Daniel J.	Abbott, Astra Zeneca, Cerephex, Cypress Biosciences, Eli Lilly, Forest, Iroko, Jazz, Johnson & Johnson, Merck, Nuvo, Pfizer, Pierre Fabre, Theravance, Tonix, UCB, University of Michigan, and Wyeth	Research funding, consulting fees, licensing fees, and honorarium. Resolved through a discussion.
Kogelnik, Andreas M.	Open Medicine Institute	Salary and stock ownership. Resolved through a discussion.
Snell, Christopher R.	WorkWell Foundation	Consultant. Resolved through a discussion.

\*All other planners, speakers, and panelists signed statements that they have no financial or other conflicts of interest pertaining to the topic under consideration.

There is no commercial support for this activity.

Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of presentations by Nancy G. Klimas, M.D., Andreas M. Kogelnik, M.D., Ph.D., and Heidi D. Nelson, M.D., M.P.H. Dr. Klimas's review of the current literature of biomarker discovery may include biomarkers that are not yet licensed for this application. Dr. Kogelnik's presentation may include a discussion of his clinic's use of several medications beyond their approved indications. Dr. Nelson's presentation on the results of a systematic review of treatments for ME/CFS will include trials of medications that are investigational or off-label.



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# Agenda

**Tuesday, December 9, 2014**

- 8:30 a.m.      **Opening Remarks**  
*James M. Anderson, M.D., Ph.D.*  
Director  
Division of Program Coordination, Planning, and Strategic Initiatives  
Office of the Director  
National Institutes of Health
- 8:40 a.m.      **Charge to the Panel**  
*David M. Murray, Ph.D.*  
Associate Director for Prevention  
Director  
Office of Disease Prevention  
Division of Program Coordination, Planning, and Strategic Initiatives  
Office of the Director  
National Institutes of Health
- 8:50 a.m.      **Workshop Overview and Panel Activities**  
*Carmen R. Green, M.D.*  
Associate Vice President and Associate Dean for Health Equity and Inclusion  
Professor of Health Management and Policy, Anesthesiology, and Obstetrics  
and Gynecology  
Office for Health Equity and Inclusion  
University of Michigan Health System
- 9:00 a.m.      **Overview of Topic**  
*Susan E. Maier, Ph.D.*  
Deputy Director  
Office of Research on Women's Health  
Office of the Director  
National Institutes of Health
- 9:20 a.m.      **Patient Perspective**  
*Robert Miller*  
Patient and Advocate
- 9:40 a.m.      **Case Definition Presentation**  
*Leonard A. Jason, Ph.D.*  
Professor of Psychology  
Director  
Center for Community Research  
DePaul University
- 10:00 a.m.      **Break**

Attendees will be responsible for meals and/or light refreshments on their own, at their own expense. The government and/or government contractors are not involved in facilitating the provision of food and/or light refreshments.

**Tuesday, December 9, 2014 (continued)**

**Session 1: What is the incidence and prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and whom does it affect?**

- 10:20 a.m.     **Evidence-based Practice Center I: Overview of Systematic Review Methodology**  
*Heidi D. Nelson, M.D., M.P.H.*  
Medical Director of Cancer Prevention and Screening  
Providence Cancer Center  
Providence Health and Service  
Vice-Chair and Research Professor  
Departments of Medical Informatics and Clinical Epidemiology  
Pacific Northwest Evidence-based Practice Center  
Oregon Health & Science University
- 10:40 a.m.     **Quantifying ME/CFS in the Population: Consideration of Case Definition and Insights From Gulf War Illness and Other Symptom-Defined Conditions**  
*Lea Steele, Ph.D.*  
Director  
Veterans Health Research Program  
Institute of Biomedical Studies  
Baylor University
- 11:00 a.m.     **Social Determinants of Health**  
*Abigail A. Brown, M.A.*  
Doctoral Candidate  
Clinical-Community Psychology  
DePaul University
- 11:20 a.m.     **Epidemiology of ME/CFS: Making Sense of What We Know**  
*Luis Nacul, M.D., Ph.D., M.F.P.H.*  
Chief Investigator  
CURE-ME  
London School of Hygiene & Tropical Medicine
- 11:40 a.m.     **Discussion**
- 12:20 p.m.     **Lunch (at the expense of the attendee)**

**Session 2: Given the unique challenges to ME/CFS, how can we foster innovative research to enhance the development of treatments for patients?**

- 1:20 p.m.     **Incorporating Multiple Study Designs Into ME/CFS Research**  
*Dedra Buchwald, M.D.*  
Professor of Epidemiology and General Internal Medicine  
Center for Clinical and Epidemiological Research  
University of Washington School of Public Health

**Tuesday, December 9, 2014 (continued)**

- 1:40 p.m.      **Maximizing Approaches and Results From the Study of Other Illnesses and Complex Chronic Conditions**  
*Daniel J. Clauw, M.D.*  
 Professor of Anesthesiology, Medicine, and Psychiatry  
 University of Michigan Medical School  
 Director  
 Chronic Pain and Fatigue Research Center  
 University of Michigan Medical Center
- 2:00 p.m.      **Using Research on Co-Morbidities to Understand ME/CFS**  
*Nilloofar Afari, Ph.D.*  
 Associate Professor  
 University of California, San Diego Healthcare System  
 Director of Clinical Research  
 Veterans Affairs (VA) Center of Excellence for Stress and Mental Health  
 Division Co-Director  
 Mental Health Integrative and Consultative Services  
 VA San Diego Healthcare System
- 2:20 p.m.      **Discussion**
- 3:00 p.m.      **Break**

**Session 3: What does research on ME/CFS tell us about the presentation and diagnosis of ME/CFS in the clinic?**

- 3:20 p.m.      **Evidence-based Practice Center II: Studies of Diagnostic Methods**  
*M.E. Beth Smith, D.O.*  
 Associate Professor  
 Department of Medical Informatics and Clinical Epidemiology  
 Pacific Northwest Evidence-based Practice Center  
 Oregon Health & Science University
- 3:40 p.m.      **Leading Questions Always Collect Inaccurate Information: Lessons From Current Treatments and Clinical Trials**  
*Christopher R. Snell, Ph.D.*  
 Scientific Advisory Committee Chair  
 The Workwell Foundation
- 4:00 p.m.      **Comparative Effectiveness Research**  
*Andreas M. Kogelnik, M.D., Ph.D.*  
 Founder and Director  
 Open Medicine Institute
- 4:20 p.m.      **The Future of Self-Management in ME/CFS**  
*Fred Friedberg, Ph.D.*  
 Research Associate Professor of Psychiatry and Behavioral Science  
 Stony Brook University
- 4:40 p.m.      **Discussion**
- 5:15 p.m.      **Adjourn**

Wednesday, December 10, 2014

**Session 4: What tools, measures, and approaches help define individuals with ME/CFS?**

- 8:30 a.m.      **Evidence-based Practice Center III: Treatment: Medications and Complementary and Alternative Medicine**  
*Heidi D. Nelson, M.D., M.P.H.*  
Medical Director of Cancer Prevention and Screening  
Providence Cancer Center  
Providence Health and Service  
Vice-Chair and Research Professor  
Departments of Medical Informatics and Clinical Epidemiology  
Pacific Northwest Evidence-based Practice Center  
Oregon Health & Science University
- 8:50 a.m.      **Evidence-based Practice Center IV: Treatment: Counseling Therapies and Exercise**  
*M.E. Beth Smith, D.O.*  
Associate Professor  
Department of Medical Informatics and Clinical Epidemiology  
Pacific Northwest Evidence-based Practice Center  
Oregon Health & Science University
- 9:10 a.m.      **Overview of Existing Tools and Measures**  
*Benjamin H. Natelson, M.D.*  
Director  
Pain and Fatigue Study Center  
Mount Sinai Beth Israel  
Professor of Neurology  
Icahn School of Medicine at Mount Sinai
- 9:30 a.m.      **Measures: Patient-Reported and Physiologic**  
*Elizabeth R. Unger, Ph.D., M.D.*  
Chief  
Chronic Viral Diseases Branch  
Division of High-Consequence Pathogens and Pathology  
National Center for Emerging and Zoonotic Infectious Diseases  
Centers for Disease Control and Prevention
- 9:50 a.m.      **Innovative Approaches in Fatigue Research: Phenotyping, Biomarker Discovery, and Statistics**  
*Leorey N. Saligan, Ph.D., R.N., CRNP, FAAN*  
Investigator  
Symptom Management Branch  
National Institute of Nursing Research  
National Institutes of Health
- 10:10 a.m.     **The Role of the Immune System in ME/CFS**  
*Mady Hornig, M.D., M.A.*  
Director of Translational Research  
Center for Infection and Immunity  
Associate Professor of Epidemiology  
Columbia University Mailman School of Public Health

**Wednesday, December 10, 2014 (continued)**

10:30 a.m.     **Discussion**

11:30 a.m.     **Break**

<b>Session 5: How are tools and measures used to distinguish subsets of patients with ME/CFS?</b>
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11:50 a.m.     **Identification of Subsets of Individuals**

Nancy G. Klimas, M.D.  
Director  
Miami Veterans Affairs Gulf War Illness and ME/CFS Research Program  
Professor and Chairperson  
Department of Clinical Immunology  
Scientific Director  
Institute for Neuro-Immune Medicine  
Nova Southeastern University

12:10 p.m.     **Subtypes of CFS/ME: New Discoveries and Unanswered Questions**

Renée R. Taylor, Ph.D.  
Vice Provost for Faculty Affairs  
Licensed Clinical Psychologist  
Professor  
Department of Occupational Therapy  
University of Illinois at Chicago College of Allied Health Sciences

12:30 p.m.     **What Outcomes Represent Improvement, Recovery, Prevention, Benefits, or Harms?**

Suzanne D. Vernon, Ph.D.  
Scientific Director  
Solve ME/CFS Initiative

12:50 p.m.     **Discussion**

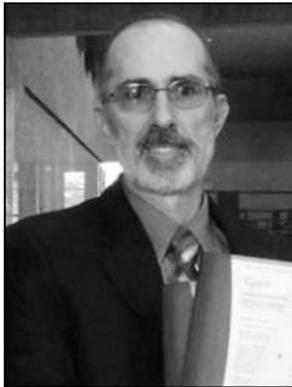
1:20 p.m.     **Workshop Wrap-Up/Next Steps**

1:30 p.m.     **Adjourn**



# Speaker Biographies and Presentation Summaries

## Opening Session



**Robert Miller**, a patient and advocate, has participated in clinical trials for more than 15 years, has served on government advisory boards, and has advocated for a stronger federal response to the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) medical crisis. He has made donations of his own DNA, blood, muscle, spinal fluid, bone marrow, and lymph node tissue. He has testified before U.S. Senator Harry Reid (D-Nevada); the Nevada Senate Commerce and Labor Committee; the U.S. Department of Health and Human Services Chronic Fatigue Syndrome Advisory Committee; and the U.S. Food and Drug Administration (FDA) Advisory Committee (for Ampligen). Mr. Miller has spoken with President Obama on the topic of ME/CFS and has met with the National Institutes of Health (NIH) Office of the Director on the subject. He has served as a panelist on an FDA Drug Development Workshop and

has spoken before the Institute of Medicine regarding diagnostic criteria for ME/CFS. Mr. Miller also has served as a reviewer for the U.S. Department of Defense on ME/CFS grant applications and has given feedback to the Centers for Disease Control and Prevention on their 5-year plan. He is a member of the National Institutes of Health Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Working Group.

**Patient Perspective.** I have had ME/CFS for more than 25 years. ME/CFS is a life-robbing illness. This panel has a profound responsibility to change the course of scientific research so that 1 million Americans like me can be healthy. I went through what most patients go through—I saw 30 doctors before being diagnosed in 1995, and many ridiculed me. I am also lucky because I found an expert who uses sophisticated diagnostic testing and treatment in this illness. I have moved my family twice in 15 years to participate in the only FDA-approved clinical trial for CFS. I have engaged with federal health officials for over a decade to compel our government to mount an urgent response to this health crisis. I urge this panel to recommend scientific funding commensurate with our substantial health and fiscal costs, and to focus research on immunological abnormalities, auto-immunity, genetics, and the higher incidence of cancers. These directions show progress and promise. I also recommend no more resources be spent researching behavioral or psychological characteristics, which, despite receiving a disproportionate share of research funding, has failed to produce any improvement in diagnosing or treating ME/CFS for 30 years.



**Leonard A. Jason, Ph.D.**, is currently a Professor of Psychology at DePaul University and the Director of the Center for Community Research. Dr. Jason is a former President of the Division of Community Psychology of the American Psychological Association. Dr. Jason has served as the Vice President of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). He also served as the Chairperson of the Research Subcommittee of the U.S. Chronic Fatigue Syndrome Advisory Committee. Dr. Jason has edited or written 23 books, and he has published over 650 articles and 75 book chapters. He has served on the editorial boards of 10 psychological journals. Dr. Jason has served on review committees of the National Institutes of Health, and he has received over \$34 million in federal research grants. He was given the Dutch ME Foundation International ME Award in 2003 for outstanding work

in the field of CFS. He also was presented in 2007 with a Special Contribution to Public Policy Award

by the Society for Research and Action. Dr. Jason was also awarded the 2011 Perpich Award for distinguished service to the International Association for CFS/ME and the CFS/ME community. In 2013, he was presented with the DePaul University College of Science and Health's Excellence in Research Award.

**Case Definition Presentation.** My talk will review current case definitions, and provide an overview of criterion variance and why it is important to deal with. I will suggest that for scientific research to progress, it is important to settle on a case definition for usage both clinically and in research areas, to decide on thresholds for what counts as a symptom, and to construct reliable and validated measures.

## Evidence-based Practice Center



**Heidi D. Nelson, M.D., M.P.H.**, is Research Professor and Vice-Chair of Medical Informatics and Clinical Epidemiology and Medicine at Oregon Health & Science University, and Medical Director of Cancer Prevention and Screening at Providence Health and Services, a large not-for-profit health system. Her research, teaching, and clinical activities focus on women's health, primary care, screening, prevention, clinical epidemiology, and health systems. Dr. Nelson has led over 30 systematic reviews for the U.S. Preventive Services Task Force, National Institutes of Health, Agency for Healthcare Research and Quality Effective Healthcare Program, and other partners at the Pacific Northwest Evidence-based Practice Center since 1998. This work has informed clinical practice guidelines, health policy, and coverage decisions for multiple stakeholders. She has developed and analyzed patient databases, and planned, implemented, and evaluated health care programs and practices. She served on the Institute of Medicine (IOM) Committee on Preventive Services for Women that identified health services to be included under the Affordable Care Act based on evidence of effectiveness. Dr. Nelson currently serves as a member of the National Institutes of Health Advisory Committee on Research on Women's Health and as an advisor for the National Cancer Institute's Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR) initiative. In 2014, she published a textbook on systematic review methodology based on the IOM standards for systematic reviews that incorporates previous projects.



**M.E. Beth Smith, D.O.**, is an Associate Professor in the Departments of Medicine and Medical Informatics and Clinical Epidemiology at Oregon Health & Science University. She has been a primary investigator or served as a co-investigator on multiple systematic reviews, comparative effectiveness reviews, and analyses through the Pacific Northwest Evidence-based Practice Center to inform the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality Effective Healthcare Program, the American College of Physicians, the Drug Effectiveness Review Project, and the U.S. Department of Veterans Affairs Portland Evidence-based Synthesis Program. These projects required innovative approaches to best understand the state of the evidence, gaps, limitations to the literature, and the needs for future research. Dr. Smith is also a practicing clinician sharing joint appointments with the Divisions of Health Promotion and Sports Medicine and the Division of Rheumatology. She has an active internal medicine primary care practice, has an expertise in medical orthopedics and therapeutic benefits of exercise given her background as a physical therapist, performs clinical exercise testing in the Human Performance Laboratory, and serves on the medicine teaching service. She currently is Chair-Elect for the Society of General Internal Medicine Evidence-based Medicine Task Force.

### Evidence-based Practice Center I: Overview of Systematic Review Methodology

*Heidi D. Nelson, M.D., M.P.H.*

The systematic review was commissioned specifically to inform the National Institutes of Health 2014 Pathways to Prevention Workshop on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The review evaluates and summarizes research addressing key questions about methods for diagnosing ME/CFS and the benefits and harms of treatments. In addition, it identifies limitations and gaps in the current literature, and describes future research needs. The review includes studies of adults with symptoms related to ME/CFS and treatment trials with outcomes

experienced by them including improved function, fatigue, quality of life, and involvement in daily activities. Studies were conducted in clinical settings relevant to health care practices in the United States. Experts, patients, and additional stakeholders provided essential input during all phases of the review. The systematic review follows established methods. Searches of electronic databases, including MEDLINE, PsycINFO, and the Cochrane libraries, identified relevant articles published between 1988 and September 2014. Abstracts and full-text articles were reviewed for inclusion based on predefined criteria; data were extracted from included studies; and the quality of the methods of each study was rated based on predefined criteria. Results of some of the treatment trials were statistically combined using meta-analysis. Finally, the overall strength of evidence was assessed for each key question and outcome.

**Evidence-based Practice Center II: Studies of Diagnostic Methods**

*M.E. Beth Smith, D.O.*

Eight case definitions of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are used to identify patients with ME/CFS and to distinguish ME/CFS from other conditions that also present with fatigue. Eight descriptive studies compared case definitions. Patients diagnosed using clinical criteria for ME or ME/CFS had more severe symptoms or impairment than those diagnosed using criteria for CFS alone. Twenty-three studies contributed to our understanding of the accuracy and concordance of current methods to diagnose ME/CFS but were limited by the lack of an accepted reference standard (case definition). Three studies identified differences in reported symptoms using various self-reported symptom scales. Twelve studies evaluated other self-reported symptom scales and biomarkers as methods to diagnose ME/CFS with inconclusive results. No studies evaluated these methods using an adequate size and spectrum of patients, and no studies demonstrated an accurate and reliable method for identifying patients or subgroups of patients with ME/CFS. One study found that older patients were more impaired, and two studies found that a cardiopulmonary exercise test was different for ME/CFS patients compared with healthy controls and that certain subscales of the SF-36 were associated with slow recovery after exercise, but none considered how this might contribute to diagnosis. Five studies consistently found that patients with CFS felt stigmatized by their diagnosis in terms of financial stability, work opportunities, perceived judgments of their characters, social isolation, and interactions with the health care system. Two studies indicated that medical trainees and mental health practitioners make judgments about a patient's condition based on the name it carries (ME, CFS, or other) and what treatment is being given. Substantial burden of misdiagnosis was found in the ME/CFS population.

**Evidence-based Practice Center III: Treatment: Medications and Complementary and Alternative Medicine**

*Heidi D. Nelson, M.D., M.P.H.*

Nine randomized controlled trials of the benefits and harms of medications for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and seven trials of complementary and alternative medicine therapies met predefined inclusion criteria for the systematic review. Outcomes included measures of improved function, fatigue, quality of life, and involvement in daily activities. Most trials used methods that were rated fair or poor quality based on established research standards. Trials enrolled predominantly female patients from ME/CFS specialty clinics using the Centers for Disease Control and Prevention (Fukuda, 1994) or Oxford (Sharpe, 1991) case definitions, had small sample sizes, and were conducted in the United States and Western Europe. None of the medications included in trials were U.S. Food and Drug Administration approved for ME/CFS. Rintatolimod, an immune modulator, improved measures of exercise performance compared with placebo, but requires further study. Seven trials compared complementary and alternative medicine therapies (dietary supplements, distant healing, homeopathy, melatonin, and phototherapy) with usual care, placebo, or alternative therapies. Although homeopathy, pollen extracts, and L-carnitine preparations indicated some benefit, studies were inconclusive. Other treatments either provided no benefit or results were insufficient to draw conclusions. Definitive

results of treatment trials are currently unavailable because few trials of effectiveness and adverse effects have been done, and existing trials are limited.

#### **Evidence-based Practice Center IV: Treatment: Counseling Therapies and Exercise**

*M.E. Beth Smith, D.O.*

All trials enrolled patients diagnosed primarily by the Oxford (Sharpe, 1991) or Centers for Disease Control and Prevention (Fukuda, 1994) case definitions and may not be generalizable to other patient populations. Fourteen trials compared counseling or behavioral therapy with usual care, no treatment, or other types of counseling or behavioral therapy in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients. Counseling improved fatigue (7/11 trials showed positive effect), measures of functioning (4/11 trials showed positive effect; 2/11 showed mixed results on different measures), quality of life (2/4 trials showed positive effect), and global improvement (2/2 trials showed positive effect). Six trials evaluated exercise therapies including graded exercise therapy (GET), qigong, and home orthostatic training. GET improved measures of fatigue, function, and clinical global impression of change compared with controls. Four trials compared either head-to-head interventions or combinations of two interventions. GET and cognitive behavioral therapy (CBT) had similar improvement on measures of function but mixed results on other outcomes. Harms were not well reported, although patients receiving GET reported more harms compared with CBT, adaptive pacing, or usual care in one trial, and they constituted more withdrawals in several other trials. Four trials contributed to the understanding of characteristics of patients more likely to respond to therapies for ME/CFS and suggest that younger patients who have less impairment, have less symptom focusing, and are compliant with homework are more likely to improve in some measures of fatigue and/or function. Staying within one's energy envelope also appeared beneficial; however, evidence for these factors is insufficient to determine their applicability to all patients with ME/CFS. Future trials require larger sample sizes, more rigorous adherence to methodological standards, use of a set of core outcomes measures, and more emphasis on subgroup analysis.

**Session 1: What is the incidence and prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and whom does it affect?**



**Lea Steele, Ph.D.**, directs the Veterans Health Research Program at the Baylor University Institute of Biomedical Studies. She is a neuroepidemiologist whose research focuses on the health consequences of military service in the 1991 Persian Gulf War. Current projects include a study to evaluate the health of Gulf War veterans nationwide to determine current prevalence of Gulf War illness and to support an updated case definition for this condition. Additional projects include assessment of brain, immune, endocrine, and hematological processes that underlie the symptoms of Gulf War illness, and an innovative project to develop a clinical diagnostic test for this complex condition. Dr. Steele previously served as Scientific Director of the federal Research Advisory Committee on Gulf War Veterans' Illnesses and Director of the Kansas Persian Gulf War Veterans' Health Initiative. As an epidemiology research fellow at the

Centers for Disease Control and Prevention in the 1990s, she directed the San Francisco Fatigue Study and was a member of the international study group that developed the 1994 case definition for chronic fatigue syndrome. She received her undergraduate degree from Northwestern University and her doctoral training in epidemiology and human ecology at the University of Texas School of Public Health.

**Quantifying ME/CFS in the Population: Consideration of Case Definition and Insights From Gulf War Illness and Other Symptom-Defined Conditions.** Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) refers to a complex of chronic and debilitating symptoms that are not explained by other medical or psychiatric diagnoses, and cannot currently be diagnosed using standard clinical testing methods. Although the impact of ME/CFS on the general population is an issue of central importance, a clear understanding of its prevalence and who is most affected has been hindered by challenges involved in clearly determining who is a "case" and consistent use of an accepted case definition. This presentation will summarize the current literature describing the occurrence of ME/CFS in the population, with attention to the role of case definition in characterizing the prevalence and patterns of ME/CFS. Insights also will be provided from research on prevalence and case definition of Gulf War illness and other symptom-defined conditions.



**Abigail A. Brown, M.A.**, is a Doctoral Candidate in the Department of Psychology at DePaul University. She specializes in clinical and community psychology under the mentorship of Dr. Leonard Jason at the Center for Community Research. Her research interests include myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) case definitions and ME/CFS-related stigma. She is currently a Graduate Research Assistant on a community-based epidemiological study of pediatric ME/CFS. She also oversees a paraprofessional social support intervention for patients in the Chicago area. Previously, she worked on the final wave of a community-based, natural history study of ME/CFS in adults and on secondary analysis of a non-pharmacological, randomized controlled trial in a tertiary care sample. Ms. Brown has co-authored over 20 articles and multiple book chapters on ME/CFS. For her master's thesis, she helped

design and validate a measure of ME/CFS symptomatology. Ms. Brown is currently working on a dissertation investigating ME/CFS-related mortality.

**Social Determinants of Health.** The phrase “social determinants of health” refers to the conditions in which people are born, develop, and live, as well as the societal systems put in place to manage health issues. This talk will briefly review findings regarding sociodemographic, psychosocial, and health risk factors for illness onset, as well as factors that may be predictive of poorer prognosis or improvement over time. Limitations of these studies will be discussed, with a specific focus on case definition issues. Finally, the adequacy of the current state of health care in serving individuals with this illness will also be addressed, particularly with regard to medical provider attitudes and knowledge about the illness, and the impact of these factors on the patient-provider relationship.



**Luis Nacul, M.D., Ph.D., M.F.P.H.,** has been researching myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in the United Kingdom (UK) and overseas. He was the Principal Investigator for the feasibility studies on establishing a disease-specific post-mortem tissue bank and biobank for the study of ME/CFS and the London lead for the ME/CFS Observatory project. He currently directs the CURE-ME Research Programme at the International Centre for Evidence on Disability at the London School of Hygiene & Tropical Medicine in London, where he is the Chief Investigator of the UK ME-CFS Biobank, which hosts the National Institutes of Health-funded project “Longitudinal Immunological and Virological Study for ME/CFS Biomarker Discovery.” Dr. Nacul has wide experience in epidemiology, teaching, and public health, including public health genomics, as well as clinical. He is a member of the Faculty of

Public Health, associate member of the Royal College of General Practitioners, and Fellow of the Higher Education Academy in the UK, and member of the Brazilian Society of Family and Community Medicine. In addition to clinical and research work, with emphasis on chronic and disabling diseases, he has contributed to teaching epidemiology and public health at both the London and Cambridge universities in the UK and internationally.

**Epidemiology of ME/CFS: Making Sense of What We Know.** The reported prevalence of ME/CFS varies 32-fold from 0.2% to 6.4% and higher in some high-risk subgroups. While population and geographical variations are possible, the most likely explanations for these variations relate to methodological differences in studies, including in data collection procedures and case definitions used. Methodological limitations also restrict the interpretation of findings on risk factors, although female gender, young age, and some infections are the factors most consistently associated with disease incidence. The distribution and disabling nature of the disease has a high burden and economic impact on individuals and society. The presentation will discuss epidemiological data on ME/CFS and their limitations, and how they can be used to guide research and services planning.

**Session 2: Given the unique challenges to ME/CFS, how can we foster innovative research to enhance the development of treatments for patients?**



**Dedra Buchwald, M.D.**, is the Principal Investigator of the University of Washington Community Networks Program Center, also known as the Native People for Cancer Control. Dr. Buchwald leads one of the largest research programs on American Indian and Alaska Native health in the nation, through the University of Washington Partnerships for Native Health Program, which works with over 200 tribal partners and 35 scientists in diverse disciplines. Dr. Buchwald has a broad background in public health and primary care, with special emphases on culturally competent care and the health of American Indians and Alaska Natives. Her work considers health at the level of the individual, the community, and the health system. Dr. Buchwald's scientific programs adhere to the principles of community-based participatory research, as she typically works in partnership with tribal and community leaders and strives to ensure that her work brings

tangible benefits to the populations under study. Dr. Buchwald has also been the Principal Investigator or Co-Principal Investigator of more than 20 grants funded by the National Institutes of Health and other major organizations. She currently leads or co-leads four multisite program projects of Native health that focus on population health and health disparities; two of these focus on cancer. As Co-Principal Investigator on more than two dozen funded projects, her team uses an array of quantitative and qualitative methodologies. Dr. Buchwald has also been involved in numerous educational and training efforts. She is the National Institutes of Health-funded Director of the Native Investigator Development Program jointly administered by the University of Washington-University of Colorado Denver. In this role, she is primarily responsible for engaging and training American Indian and Alaska Native junior faculty in the research enterprise and helping them implement bidirectional scholarly efforts.

**Incorporating Multiple Study Designs Into ME/CFS Research.**

Summary not available at time of print.



**Daniel J. Clauw, M.D.**, is a Professor of Anesthesiology, Medicine, and Psychiatry. He attended undergraduate and medical school at the University of Michigan, and then did his internal medicine residency and rheumatology fellowships at Georgetown University, where he eventually held roles including Chief of Rheumatology and Vice Chair of Medicine. He moved back to Michigan in 2002, bringing with him one of the leading pain research groups. This group has helped identify the prominent central nervous system contributions to a number of chronic pain disorders, as well as the most effective pharmacological and non-pharmacological treatments for chronic pain. Dr. Clauw was also the first Principal Investigator of the University of Michigan Clinical and Translational Science Award, Associate Dean for Clinical and Translational Research, and founding Director of the Michigan Institute for Clinical and Health

Research. Although he stepped down from these latter roles in 2009 to rededicate himself to pain research, he remains very active in institutional clinical research training programs and is a very active and recognized mentor of clinical and translational researchers.

**Maximizing Approaches and Results From the Study of Other Illnesses and Complex Chronic Conditions.** The study of the pathogenesis and treatment of chronic fatigue syndrome (CFS) presents challenges similar to the study of many other complex chronic conditions. Issues include reliance on subjective patient-reported outcomes, the heterogeneity of the disorder which leads to many different subsets of patients with differing underlying etiologies, and the need to delineate which biological measures are causing the illness and which are epiphenomenon or due to co-morbidities. The National Institutes of Health has developed interdisciplinary networks to study several conditions that share many features of CFS, including the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) network and the Orofacial Pain: Prospective Evaluation and Risk Assessment network studying temporomandibular joint disorder. The structure and function of the MAPP network will be presented as a potential model for the future study of CFS.



**Niloofar Afari, Ph.D.**, is Associate Professor of Psychiatry at the University of California, San Diego, Director of Clinical Research at the U.S. Department of Veterans Affairs (VA) Center of Excellence for Stress and Mental Health, and Division Director of the Mental Health Integrative and Consultative Services unit at the VA San Diego Healthcare System. Dr. Afari received her Ph.D. in clinical psychology from the University of Nevada, Reno in 1996. She completed a predoctoral internship and postdoctoral training at the University of Washington School of Medicine in Seattle, where she also was a faculty member from 2000 to 2006. Dr. Afari's interdisciplinary research, funded by the National Institutes of Health and the VA, involves twin studies to examine genetic and environmental influences on unexplained clinical conditions and their co-morbidities; treatment studies of health conditions using acceptance and commitment therapy; and implementation of eHealth technology for evidence-based screening and outcomes monitoring of mental health symptoms.

**Using Research on Co-Morbidities to Understand ME/CFS.** Despite years of research, there remain many challenges in the diagnosis and treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). One area of consistent findings is the co-occurrence of ME/CFS with other unexplained clinical conditions such as fibromyalgia, temporomandibular disorder, irritable bowel disorder, and interstitial cystitis/painful bladder syndrome. This set of conditions is characterized by overlapping symptoms, lack of currently understood physical or biological etiology, and inconsistent laboratory abnormalities, and is defined by expert consensus or research diagnostic criteria. Given the consistency of these co-morbidities, examining ME/CFS and other unexplained clinical conditions in a way that focuses both on the similarities and differences between conditions and the potential mechanisms that underlie the co-morbidities may provide a better understanding of the pathophysiology of ME/CFS and inform treatment development. In this presentation, Dr. Afari will briefly review research on co-morbidities with ME/CFS and discuss areas of innovative research on co-morbidities that may facilitate understanding of ME/CFS and lead to the development of effective interventions.

### **Session 3: What does research on ME/CFS tell us about the presentation and diagnosis of ME/CFS in the clinic?**



**Christopher R. Snell, Ph.D.**, has over 15 years experience studying myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and in particular the postexertional fatigue and malaise that typifies this illness. He is part of a group that was among the first to advocate for use of cardiopulmonary exercise testing to measure fatigue in CFS research. Together, they have probably conducted more exercise tests with patients than anyone. Their 2-day exercise testing protocol has potential to be a biomarker for both pathology and function in ME/CFS. Dr. Snell is a former Chair of the Chronic Fatigue Advisory Committee to the U.S. Secretary of Health and Human Services. He has lectured and published extensively on ME/CFS including invited presentations for the National Institutes of Health and the U.S. Food and Drug Administration.

**Leading Questions Always Collect Inaccurate Information: Lessons From Current Treatments and Clinical Trials.** If research evidence is to be believed, the most effective treatments for ME/CFS are graded exercise therapy (GET) and cognitive behavioral therapy (CBT). However, compelling evidence from both patients and clinicians suggests that neither remedy truly benefits ME/CFS symptoms. CBT may help some patients better cope with their illnesses but does not constitute a cure, and GET frequently prompts relapse. To understand how the science and experience of ME/CFS can be so divergent, it might be helpful to examine current diagnostic approaches. The problem of multiple case definitions is widely acknowledged. Less obvious is the requirement that all other explanatory etiologies be excluded before conferring an ME/CFS diagnosis. Two alternative explanations seldom well controlled in most treatment trials are depression and low fitness. Even more problematic is when deconditioning and/or psychosomatic hypotheses drive the research. Such studies are, to quote Florence Nightingale, merely “means of obtaining inaccurate information.” Objective assessment of major ME/CFS symptoms while excluding other pathologies is key to conducting meaningful research. To this end, cardiopulmonary exercise testing can provide quantifiable measures of fatigue and postexertional malaise while differentiating ME/CFS from other fatiguing conditions. Testing parameters may also be useful for subtyping patients.



**Andreas M. Kogelnik, M.D., Ph.D.**, received his M.D. from Emory University and his Ph.D. in bioengineering from the Georgia Institute of Technology. He completed a residency in internal medicine and a fellowship in infectious diseases at Stanford University. After 8 years at Stanford University as a National Institutes of Health- and Hewlett Packard-funded physician-scientist working at the intersection of genomics, microbiology/immunology, bioinformatics, and clinical medicine with Dr. Ellen Jo Baron, Dr. Stanley Falkow, and Dr. Atul Butte, he left Stanford University to found the Open Medicine Institute (OMI). At OMI, he has successfully driven forward a new collaborative model for patient-centric clinical research networks through OpenMedNet by leveraging information and biotechnology to bring together physicians and patients, pharmaceutical and diagnostic companies, government agencies,

and foundations. OMI has pioneered a big data approach to personalized medicine, leading a community and patient-centric registry and biobank across medicine. Dr. Kogelnik’s group has focused on big data analytics for Lyme disease, chronic fatigue syndrome, and neuroimmune disease. Dr. Kogelnik’s research interests include longitudinal outcomes measurement of

populations from preconception to advanced age with a particular focus around rapidly emerging complex conditions such as autism, diabetes, and various viral and immunologic syndromes.

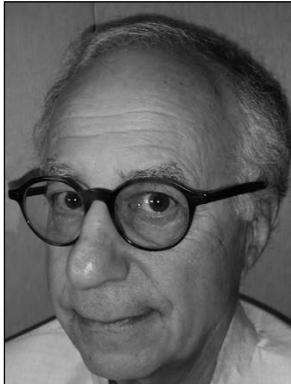
**Comparative Effectiveness Research.** Dr. Kogelnik will discuss current research and its implications on clinical diagnosis and treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) with a particular focus on -omic and informatics-driven analyses. He will touch on his experiences as a Principal Investigator in the multisite Centers for Disease Control and Prevention evaluation of ME/CFS as well as numerous private foundation-funded molecular diagnostic and treatment studies that are underway.



**Fred Friedberg, Ph.D.**, is a Research Associate Professor at Stony Brook University Medical Center in Stony Brook, New York. He was a psychologist in private practice for 30 years specializing in the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia, and other chronic pain conditions. Since 2001, he has been conducting research, funded by the National Institutes of Health (NIH) on lifestyle, stress factors, and self-management programs related to ME/CFS and fibromyalgia. Dr. Friedberg is the founder and editor of a new peer-review journal, *Fatigue: Biomedicine, Health and Behavior*, published by Routledge/Taylor and Francis. In addition, he is President of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME), an organization of professionals and patients dedicated to advancing scientific research and improving patient care. Dr. Friedberg has authored or co-authored seven books and a number of scientific articles on ME/CFS and fibromyalgia. He has also served as chair of the NIH grant review panel on ME/CFS. He is the lead author of the *IACFS/ME Primer for Clinical Practitioners* (2012, 2014), which provides guidelines for diagnosis and management of ME/CFS.

**The Future of Self-Management in ME/CFS.** Effective and appropriate lifestyle management as utilized by ME/CFS patients and taught by clinical practitioners involves targeted, individualized plans. These types of assistance work more effectively with higher functioning patients and with those who are more recently ill. Management strategies are also more successful if patients are given explicit guidance with user-friendly, take-home materials. Health policy implications of effective illness management include lower health care utilization, reduced health costs, and improved quality of life for the patient. This talk will focus on clinical management issues and their relevance to health policy.

## Session 4: What tools, measures, and approaches help define individuals with ME/CFS?



**Benjamin H. Natelson, M.D.**, received his bachelor's and medical degrees from the University of Pennsylvania in Philadelphia and then did his neurology residency at the Albert Einstein College of Medicine in New York City. Following that, he did two postdoctoral fellowships: one in behavioral neurosciences at the Cornell University Medical Center in White Plains, New York, and one in physiological psychology at the Walter Reed Army Institute of Research in Washington, DC. He then moved to the New Jersey Medical School in Newark and the Veterans Administration (VA) Medical Center in East Orange. He rose through the ranks, attaining the rank of Professor of Neurosciences in 1981 and leaving in 2008 as an Emeritus Professor. He had continual funding from the VA through 1999 for his experimental work on stress and chronobiology. With the award of a federally funded research center to explore the causes of chronic

fatigue syndrome (CFS) in 1991, he shifted his research to studies of humans with CFS and more recently has extended those studies to include those with fibromyalgia (FM). He has served as President of the Pavlovian Society and of the Academy of Behavioral Medicine Research. He has over 240 papers published in peer-review journals and has authored three books. Since 2008, Dr. Natelson has moved his activities to the Department of Pain Medicine and Palliative Care at Mount Sinai Beth Israel in Manhattan where he directs the Pain & Fatigue Study Center (see [www.painandfatigue.com](http://www.painandfatigue.com)). In that capacity, he is also a Professor of Neurology at the Icahn College of Medicine at Mount Sinai.

**Overview of Existing Tools and Measures.** The 1994 Centers for Disease Control and Prevention (CDC) case definition for CFS called for the identification of subgroups. One common overlapping diagnosis is FM, a syndrome of widespread pain with tenderness on palpation. We have developed a straightforward, operational method of diagnosing CFS. Using this plus the 1990 criteria for diagnosing FM, we have sought to determine if patients with CFS alone differ from those with CFS+FM and have found some differences. Besides having more pain, CFS+FM patients more often fulfill the more demanding 1988 CDC criteria for CFS than those with CFS alone. In addition, those with CFS+FM show a different response to a submaximal exercise test than those with CFS alone—specifically, reduced blood pressure and increased stroke index. In contrast, those with CFS alone showed neuropsychological dysfunction and an increased brain serotonergic response to tryptophan infusion relative to controls, while those with CFS+FM did not. Finding these differences suggests that CFS and FM are not necessarily manifestations of the same pathophysiological disease process. Other important stratifiers include the identification of patients with (a) physiological evidence of orthostatic dysfunction—namely orthostatic tachycardia, hypocapnia, or delayed onset of hypotension or (b) low natural killer cell function. Data from other groups suggest that patients in these groups are more symptomatic than patients without these co-morbidities.



**Elizabeth R. Unger, Ph.D., M.D.**, is Chief, Chronic Viral Disease Branch, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. Dr. Unger received an undergraduate degree in chemistry from Lebanon Valley College, Annville, Pennsylvania. She earned her Ph.D. and M.D. in the Division of Biologic Sciences from the University of Chicago where she also began a residency in anatomic pathology. She completed her residency and fellowship at The Pennsylvania State University Medical Center and joined the Emory University School of Medicine Department of Pathology and Laboratory Medicine faculty in 1986. She moved to the CDC in 1997 and in 2010 became Acting Chief of the CDC Chronic Viral Diseases Branch. She is currently responsible for guiding public health programs addressing chronic fatigue syndrome and human papillomavirus-associated diseases. As part of her CDC tenure, Dr. Unger has served as a consultant for the World Health Organization and the U.S. Food and Drug Administration and was a key member of the laboratory team initiating microarray technology to study gene expression in peripheral blood mononuclear cells. She is co-author of 200 peer-reviewed publications and 30 book chapters and serves on the editorial boards of the *Journal of Molecular Diagnostics* and the *Journal of Histochemistry and Cytochemistry*.

**Measures: Patient-Reported and Physiologic.** Studies of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have been challenged by difficulties in measuring the illness. This is true for treatment trials, hypothesis-driven studies of pathophysiology, analyses of biomarkers, and those aimed at defining disease course and risk factors. Ensuring that study participants meet a particular case definition is a starting point, but case definitions have limited ability to identify homogenous groups of patients whose illness characteristics can be easily compared with those in other studies. Demographic and illness variables, such as sex, age, race, duration of illness, type of onset, co-morbid conditions, and medication use, are all significant variables that need to be considered. Some of the major domains of illness experienced by ME/CFS patients, such as fatigue, pain, and symptom profile, can be assessed by validated tools or instruments (e.g., self-reported or clinician-rated measures) that have been used in CFS and other conditions. Other illness characteristics, such as difficulties with cognition and sleep, have been assessed by a combination of self-reported measures and tests, but optimal methods for ME/CFS patients have not yet been determined. However, critical domains, such as neuroendocrine and autonomic dysfunction as well as postexertional malaise, either do not have standardized self-reported measures validated to correlate with specific problems or require physiologic measures or testing that have not yet been standardized or optimized for ME/CFS.



**Leorey N. Saligan, Ph.D., R.N., CRNP, FAAN**, has been a nurse for 22 years, evolving into various roles from a nurse aide, staff nurse, nursing faculty, nurse practitioner, and currently a nurse scientist. Dr. Saligan is a Tenure-Track Investigator and Chief of the Symptoms Biology Unit of the National Institute of Nursing Research of the National Institutes of Health. His research interest is focused on understanding the role of bioenergetics in fatigue. As a nurse scholar, he makes highly visible contributions to nursing by initiating innovative clinical trials, translating genomic discoveries into practice aimed at reducing polysymptomatic distress, and engaging individuals to promote self-care. Further, he models strong collaborative interinstitutional and multidisciplinary relationships to advance symptoms science, as well as create opportunities for students interested in nursing research and scholarship. In addition to his publication record,

he has been asked to conduct scholarly presentations on translational investigations in symptom science by various research societies, academic institutions, and professional organizations

across the United States and internationally. He also provides leadership in minority nursing organizations in improving the genetic and genomic knowledge of their members to improve clinical practice. He is a recipient of several recognitions from national organizations and international multidisciplinary groups.

**Innovative Approaches in Fatigue Research: Phenotyping, Biomarker Discovery, and Statistics.** The presentation will address three aims: (1) describe a method to phenotype clinically relevant change of fatigue, (2) identify genomic and proteomic approaches to pursue discovery of biologic correlates of fatigue, and (3) describe innovative statistical approaches to assist in the discovery of biologic correlates of fatigue. The first aim will be addressed by describing a unique approach to phenotype clinically relevant change in fatigue, based on published reports of a minimally important difference in fatigue scores using a validated fatigue scale. The second aim will be addressed by presenting genomic and proteomic findings using unbiased approaches to identify biologic correlates of fatigue, based on the phenotyping approach utilized. The third aim will be addressed by describing innovative statistical approaches used to predict risk for developing a clinically relevant change in fatigue, especially in cancer patients receiving treatment.



**Mady Hornig, M.D., M.A.**, is a physician-scientist and Director of Translational Research at the Center for Infection and Immunity at the Columbia University Mailman School of Public Health where she is also Associate Professor of Epidemiology. Her research focuses on the role of microbial and toxic factors and specific immune signatures in the development of brain conditions including autism, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, mood disorders, and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). She is particularly interested in fetal programming of central nervous system disorders that manifest across the life span, ranging from neurodevelopmental disorders such as autism to mood and cognitive disorders in adulthood and later life. She is widely known for establishing animal models focused on how genes and age-related factors interact with microbes and how other environmental agents lead to autism, mood disorders, schizophrenia, and brain inflammation (encephalitis) across the life span. She is identifying birth biomarkers for autism using immune profiling and metabolomic and proteomic approaches in the prospective Autism Birth Cohort Study in Norway. She also leads projects examining the role of the microbiome and metabolome in the altered immunity associated with ME/CFS with support from the Hutchins Family Foundation/Chronic Fatigue Initiative.

**The Role of the Immune System in ME/CFS.** Infectious triggers of immune and metabolic derangements are hypothesized to play a broad role in the pathogenesis of ME/CFS; however, no single infectious agent has been conclusively implicated. Increasing evidence suggests that immune and metabolomic markers provide potent clues to the existence of an infectious process, especially in the early phases after microbial exposures. We have found elevations of both proinflammatory and allergy-related cytokines in ME/CFS subjects with more recent onset of illness, as compared with long duration patients and healthy controls from the multisite Chronic Fatigue Initiative cohort study. Serotonin was more often undetectable in this subgroup. Peripheral indices of immune function and metabolism were abnormal and highly interrelated in ME/CFS subjects with a more recent onset of illness. Given the importance of serotonin in neurovegetative functions, these findings suggest that convergent biochemical pathways alter immunity, and specific intestinal bacterial community structures may contribute to the manifestations of ME/CFS in the early phases of illness. These results have important implications for diagnosis and discovery of novel treatment strategies.

## Session 5: How are tools and measures used to distinguish subsets of patients with ME/CFS?



**Nancy G. Klimas, M.D.**, has more than 30 years of professional experience and has achieved international recognition for her research and clinical efforts in multisymptom disorders, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Gulf War illness, fibromyalgia, and other neuro-immune disorders. She currently directs the Nova Southeastern University Institute for Neuro-Immune Medicine, an integrated clinical and research institute treating and studying complex medical illnesses such as ME/CFS. She is Past President of the International Association for CFS/ME, a professional organization of clinicians and investigators, and also a member of the U.S. Department of Veterans Affairs Research Advisory Committee on Gulf War Veterans' Illnesses, the National Institutes of Health Pathways to Prevention

Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Working Group, the Institute of Medicine ME/CFS Review Panel, and the NASA Immunology Integration Panel. Dr. Klimas has advised three U.S. Secretaries of Health and Human Services during her repeated service on the U.S. Department of Health and Human Services CFS Advisory Committee. Dr. Klimas has been featured on *Good Morning America* and in *USA Today* and the *New York Times*.

**Identification of Subsets of Individuals.** In this presentation, the use of various strategies to subgroup ME/CFS will be discussed. The purpose of subgrouping will be reviewed from clinical and research perspectives. Studies that subgroup by symptom clusters, mode of onset, duration, severity, and co-morbid conditions will be reviewed. Biomarkers are defined as measurable indicators of the severity or presence of some disease state. In ME/CFS, these have included studies of blood, urine, and spinal fluid as well as neuroimaging studies. In this presentation, the focus will be on laboratory studies used to define subgroups and strategies to increase the sensitivity and specificity of biomarker signatures. Clinical trials targeting specific mediators already employ biomarkers to define appropriate subgroups for intervention. Measures of natural killer cell function have sufficient data to meet evidence-based criteria as a marker of ME/CFS, and the availability of biorepository samples from clearly defined cases increases optimism that other biomarkers will be validated. The use of exertional challenges to increase the biologic signal and measure the dynamics of illness relapse have resulted in a rich source of data useful in studying the nature of relapse and promise a better understanding of subgrouping relevant to treatment strategies and clinical trials design.



**Renée R. Taylor, Ph.D.**, is a Licensed Clinical Psychologist who also serves as Vice Provost for Faculty Affairs and Professor of Occupational therapy at the University of Illinois at Chicago. She holds master's and Ph.D. degrees in clinical-community psychology from DePaul University, where she first began study of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in 1992 under the guidance of Professor Leonard Jason. At DePaul University, Dr. Taylor served as Project Director for a National Institutes of Health (NIH) R01 project focusing on the epidemiology of CFS in a random community-based sample. As Principal Investigator, Dr. Taylor subsequently completed two additional, federally funded studies. The first of these evaluated the effectiveness of a consumer-driven rehabilitation program for adults with CFS/ME. For the second, Dr. Taylor completed a prospective follow-up study of adolescents

with postinfectious fatigue following infectious mononucleosis. Dr. Taylor also served as a Co-Investigator for Brigitte Huber's R01 study of HERV K-18 as a risk factor for CFS/ME. Her 24-year career has focused on the topic of CFS/ME. She has published extensively in the area of quality of life and subtyping, with a specialty in the complementarity and differentiation of symptoms of CFS/ME and those of certain classifications of psychiatric disorders.

**Subtypes of CFS/ME: New Discoveries and Unanswered Questions.** Findings from an NIH R01 prospective study of fatigue following infectious mononucleosis in adolescents will be presented. Prior to this study, there was little understanding of the causes and extent of long-term fatigue and disability following acute infection in adolescents. Based on the work of Dr. Taylor and her colleagues, a series of recently published studies indicated that 6, 12, and 24 months after infectious mononucleosis, 13%, 7%, and 4%, respectively, of adolescents met criteria for CFS. Consistent with findings from studies of adults, severity of initial infection and self-reported autonomic symptoms appear to be strong predictors of postinfectious fatigue following acute infectious mononucleosis and could serve as foundational variables in continued work in the area of subtyping. The question of how qualitative data and relevant research designs might be used to explicate these subtypes will be entertained.



**Suzanne D. Vernon, Ph.D.**, is the Scientific Director of the Solve ME/CFS Initiative. She has dedicated the past 20 years of her professional research career working to solve myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). As a team lead member of the Centers for Disease Control and Prevention's (CDC) CFS research group, Dr. Vernon recruited an eclectic team of molecular biologists and computational biologists to merge data collected in laboratory, clinical, and epidemiology studies with the goal of identifying biomarkers to objectively define ME/CFS. Dr. Vernon's tenure at the CDC culminated with the publication of a special issue of the journal *Pharmacogenomics* that included 14 peer-reviewed articles resulting from a computational challenge she conceived and organized. Dr. Vernon joined the Solve ME/CFS Initiative in 2007 as Scientific Director, and now she leads the organization's Research Institute

Without Walls (RIWW), the first initiative focused on identifying diagnostic biomarkers and disease-modifying treatment for ME/CFS. Since 2008, two competitive funding cycles that awarded \$1.1 million to 11 investigators have resulted in more than \$12 million in follow-on funding for several of the organization's grantees. At the core of the RIWW is the SolveCFS BioBank, an integrated patient registry and sample biorepository to conduct patient-centered research. More than 1,000 patients and controls are in the SolveCFS BioBank.

**What Outcomes Represent Improvement, Recovery, Prevention, Benefits, or Harms?** This presentation will describe how well outcomes that are meaningful to patients are measured in the research being conducted on ME/CFS. In April 2013, the U.S. Food and Drug Administration (FDA) hosted its first Patient-Focused Drug Development Initiative Workshop on ME/CFS. ME/CFS was the first of 20 disease-specific meetings where the FDA gathered patients' perspectives on the severity of ME/CFS, its impact on daily life, and available treatment options. The FDA posed a series of questions to begin to build the benefit-risk assessment framework for ME/CFS. Understanding that the majority of affected patients would not be able to attend the workshop in person, the Solve ME/CFS Initiative conducted a survey in our ME/CFS community using the FDA questions on disease symptoms, daily impact, and treatments. There were 1,500 respondents to the survey. Only 18% of the respondents indicated that ME/CFS was the only condition that had been diagnosed. The remaining 82% of respondents indicated that their symptoms, treatments, and impact on their lives was further complicated by multiple conditions and diagnoses that require management. To understand if the patients' symptom and treatment experience ascertained by this survey were reflected in the ME/CFS and overlapping conditions biomedical literature, we used natural language processing of the colloquial text from the survey and medical text from 511,000 PubMed abstracts.

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Working group members provided their input at a meeting held January 6–7, 2014. The information provided here was accurate at the time of that meeting.

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