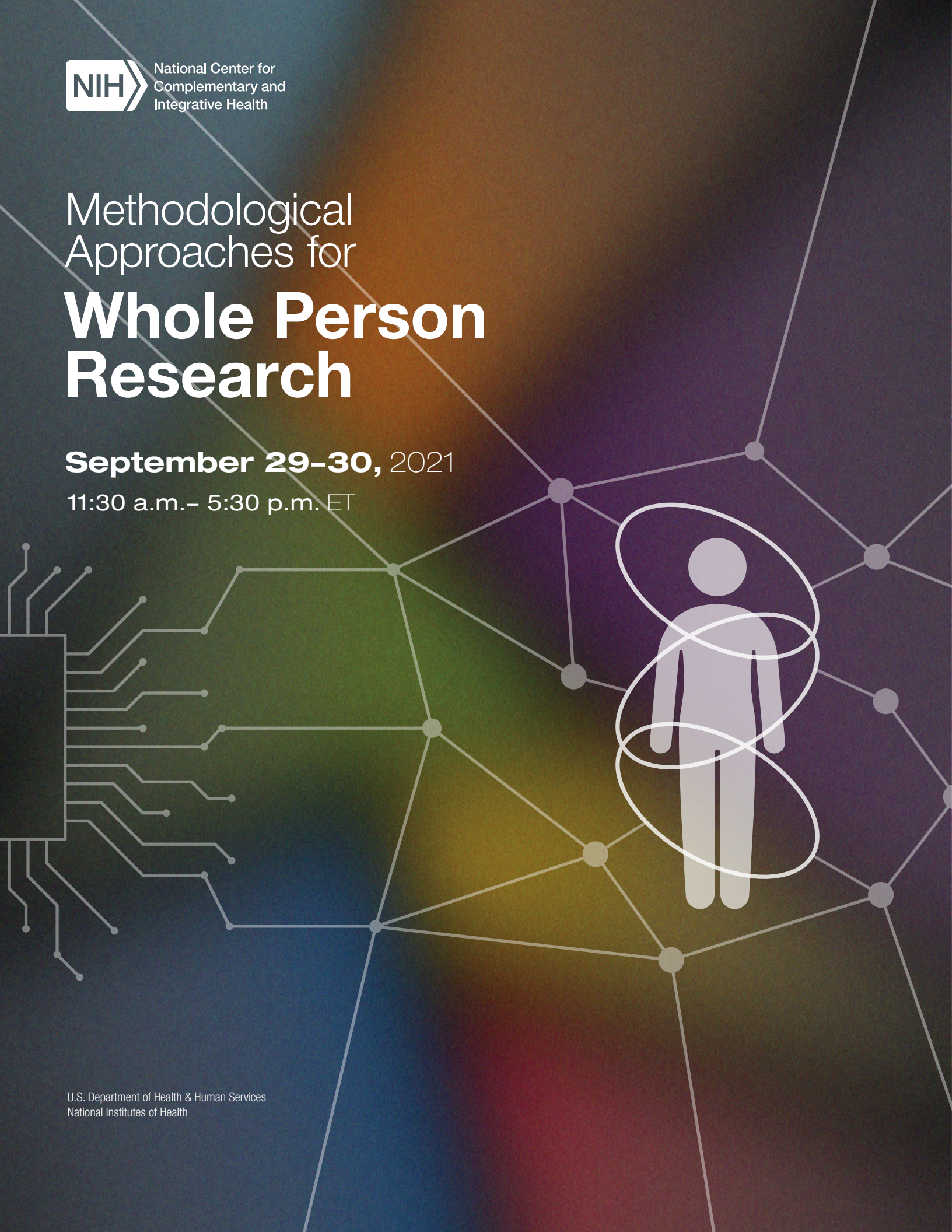
National Center for Complementary and Integrative Health

Methodological Approaches for **Whole Person Research**

September 29–30, 2021

11:30 a.m.– 5:30 p.m. ET



U.S. Department of Health & Human Services
National Institutes of Health

Table of Contents

Agenda

September 29, 2021

11:30–11:35 a.m. Welcome

11:35 a.m.–12:20 p.m. Opening Remarks and Setting the Stage

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

12:20–2:25 p.m. Session One: How To Study Interconnected Systems: Observational Studies

Moderators:

Janine Simmons, M.D., Ph.D., National Institute on Aging

Qilu Yu, Ph.D., NCCIH

Speakers:

Cynthia Rudin, Ph.D., Duke University. *A toolbox for isolating and studying parts of interconnected systems: almost matching exactly for observational causal inference*

Ziv Bar-Joseph, Ph.D., M.Sc., Carnegie Mellon University. *Machine learning methods for studying dynamic, interconnected multisystems*

Daniel Bauer, Ph.D., University of North Carolina at Chapel Hill. *A person-oriented approach to the analysis of interconnected, multicomponent systems: using latent class/profile analysis to identify prototypical profiles of risk*

Trey Ideker, Ph.D., University of California, San Diego. *Towards a precision medicine based on interpretable machine learning*

Terrie Moffitt, Ph.D., Duke University. *Measuring patients' pace of biological aging with longitudinal data, growth curves, and elastic net regression of DNA methylation*

Panel Discussion

2:25–2:40 p.m. Break

2:40–4:25 p.m. Session Two: How To Study the Impact of Single Component Interventions or Manipulation on Interconnected Multiple Systems

Moderators:

Bramaramba Kowtha, M.S., R.D.N., L.D.N., Office of Disease Prevention, National Institutes of Health (NIH) Office of the Director

Elizabeth Barr, Ph.D., Office of Research on Women's Health, NIH Office of the Director

Speakers:

Mimi Ghosh, Ph.D., George Washington University. *Impact of sexual trauma on the interconnected outcomes of mental health and immune response*

Ramsey D. Badawi, Ph.D., University of California, Davis. *Total-body positron emission tomography—a transformative tool for quantitative whole-person research*

Karyn Esser, Ph.D., University of Florida. *Preclinical approaches for whole person research: lessons from the Molecular Transducers of Physical Activity Consortium (MoTrPAC)*

David Amar, Ph.D., Stanford University. *Challenges and opportunities from the multiomic MoTrPAC project*

Panel Discussion

4:25–5:25 p.m. Roundtable Discussion I

Moderators:

Wen Chen, Ph.D., M.M.Sc., NCCIH

Judith Arroyo, Ph.D., National Institute on Minority Health and Health Disparities

Panelists:

Marybel Robledo Gonzalez, Ph.D., University of California, San Diego

Elaine Y. Hsiao, Ph.D., University of California, Los Angeles

5:25–5:30 p.m. Closing Remarks

Emmeline Edwards, Ph.D., NCCIH

5:30 p.m. Adjourn

September 30, 2021

11:30–11:35 a.m. Welcome

11:35 a.m.–1:50 p.m. Session Three: How To Investigate the Impact of Multicomponent Interventions or Therapeutic Systems on a Single Outcome

Moderators:

Ranjan Gupta, Ph.D., Fogarty International Center, NIH

Miya Whitaker, Psy.D., M.A., Office of Research on Women's Health, NIH

Speakers:

Lynne Shinto, N.D., M.P.H., Oregon Health & Science University. *Methods for designing multicomponent interventions based on naturopathy*

Lynda Powell, Ph.D., M.Ed., Rush University. *Addition of a mindfulness component to a conventional lifestyle intervention for sustained remission of the metabolic syndrome*

Linda Collins, Ph.D., New York University. *Achieving intervention EASE (effectiveness, affordability, scalability, and efficiency) using the multiphase optimization strategy (MOST)*

Liliane Windsor, Ph.D., The University of Illinois at Urbana-Champaign. *Community Wise: development of a multilevel intervention to reduce alcohol and substance misuse among formerly incarcerated men*

Mark P. Jensen, Ph.D., University of Washington. *Identifying the mechanisms underlying multicomponent pain interventions*

Nadja Cech, Ph.D., University of North Carolina at Greensboro. *Mass spectrometry metabolomics to identify bioactives and synergists in botanical medicines*

Panel Discussion

1:50–2:00 p.m. Break

2:00–4:00 p.m. Session Four: How To Examine the Impact of Complex Multicomponent Interventions on Multisystem or Multiorgan Outcomes

Moderators:

Yvonne Bryan, Ph.D., National Institute of Nursing Research

Hye-Sook Kim, Ph.D., NCCIH

Speakers:

Rob Knight, Ph.D., University of California, San Diego. *The microbiome and metabolome as a readout of complex interventions throughout the body*

Nicholas Schork, Ph.D., *The Translational Genomics Research Institute. N-of-1 and aggregated N-of-1 studies for exploring multicomponent intervention effects on multiple health outcomes*

Inbal Nahum-Shani, Ph.D., University of Michigan. *Multicomponent interventions: an organizing framework for selecting an experimental design*

Ross Hammond, Ph.D., The Brookings Institution. *Using systems science for a multifaceted multioutcome whole-of-community intervention to prevent childhood obesity*

Atul Butte, M.D., Ph.D., University of California, San Francisco. *Precisely practicing medicine from 700 trillion points of data*

Panel Discussion

4:00–5:00 p.m. Roundtable Discussion II

Moderators:

Wendy Weber, N.D., Ph.D., M.P.H., NCCIH

Craig Hopp, Ph.D., NCCIH

Panelists:

Scott Mist, Ph.D., M.Ac.O.M., Oregon Health & Science University

Irene Headen, Ph.D., M.S., Drexel University

5:00–5:25 p.m. Workshop Synthesis: Whole Person Research Methods

Bruce Y. Lee, M.D., M.B.A., City University of New York

5:25–5:30 p.m. Closing Remarks

Helene Langevin, M.D., NCCIH

5:30 p.m. Adjourn

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.

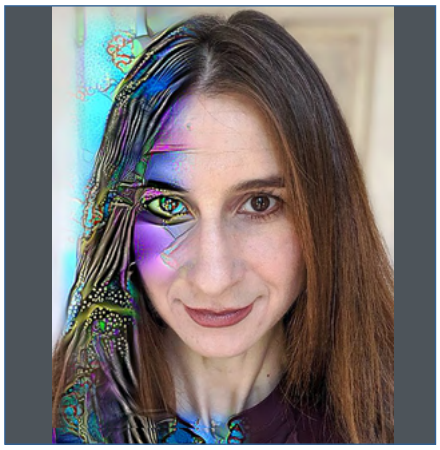
Session One Biographies and Abstracts

Moderator: Janine M. Simmons, M.D., Ph.D., National Institute on Aging

Dr. Simmons serves as the chief of the Individual Behavioral Processes Branch within the Division of Behavioral and Social Research at the National Institute on Aging. Her program focuses on stress and resilience, emotional processing, mental health, and well-being across the lifespan. Prior to taking this position, she ran the Social and Affective Neuroscience Program at the National Institute of Mental Health (NIMH). She also serves as the co-chair of the Behavioral Ontology Development Working Group within the Office of Basic and Social Sciences Research. Dr. Simmons attended Yale University and obtained a medical degree and a doctorate in neurosciences from the University of California, Los Angeles School of Medicine, trained in general and adult psychiatry at Western Psychiatric Institute and Clinic, and completed a postdoctoral fellowship within the NIMH Intramural Program.

Moderator: Qilu Yu, Ph.D., National Center for Complementary and Integrative Health

Dr. Yu is a lead statistician in the Office of Clinical and Regulatory Affairs at the National Center for Complementary and Integrative Health (NCCIH). She is a senior collaborator and expert statistical advisor for NCCIH-funded clinical trials and provides guidance on clinical trials for the National Institutes of Health's (NIH) Health Care Systems Research Collaboratory and the NIH-Department of Defense-Veterans Administration Pain Management Collaboratory. Her interests also include big data and machine learning methods in medical research. Previously, Dr. Yu served as a senior biostatistician and senior supervisory study director at Westat, Inc., where she researched electronic health records and linked/harmonized databases for studies on diabetes, tobacco use, chronic diseases in aging, and multimorbidity. As a research faculty member at the Johns Hopkins Center on Aging and Health from 2006 to 2011, Dr. Yu was co-director of data management and analysis for the Baltimore Experience Corps Study. She also supported randomized clinical trials, comparative effectiveness research, and other types of studies and taught in the School of Medicine.



Cynthia Rudin, Ph.D., Duke University

Dr. Rudin is a professor of computer science, electrical and computer engineering, and statistical science at Duke University. She directs the Prediction Analysis Lab, which focuses on interpretable machine learning. Previously, she held positions at Massachusetts Institute of Technology (MIT), Columbia University, and New York University. Her projects include developing practical code for optimal decision trees and sparse scoring systems to create models for high stakes decisions, leading the first effort in New York City to maintain a power distribution network with machine learning, developing algorithms that allow police detectives to find patterns of housebreaks, solving several previously open theoretical problems about the convergence of AdaBoost and related boosting methods, and co-leading the Almost-Matching-Exactly lab, which develops matching methods for interpretable causal inference. A three-time winner of the Innovative Applications in Analytics Award, in 2015, she was selected as a "Top 40 Under 40" professor by Poets and Quants and as 1 of the 12 most impressive professors at MIT by Businessinsider.com. She holds an undergraduate degree from the University at Buffalo and a doctorate from Princeton University, and she is a fellow of the American Statistical Association and the Institute of Mathematical Statistics.

A Toolbox for Isolating and Studying Parts of Interconnected Systems: Almost Matching Exactly for Observational Causal Inference

How can we hope to perform data-driven causal analyses from complex interconnected systems? I will present an approach that aims to match a current situation with almost identical situations from the past, in order to use these past situations to predict the future. This approach has proven invaluable in the study of complex systems where causal effects can easily be confused with correlations. The matching framework I will present, called Almost Matching Exactly, is useful for causal inference in the potential outcomes setting. This framework has several important elements: (1) Its algorithms create matched groups that are interpretable. The goal is to match treatment and control units as closely as possible, or "almost exactly." (2) Its algorithms create accurate estimates of individual treatment effects. This is because we use machine learning on a separate training set to learn which features are important for matching. Variables that are important are "stretched" so that the matched groups agree closely on these variables. (3) Our methods are fast and scalable. In summary, these methods rival black box machine learning methods in their estimation accuracy but have the benefit of being interpretable and easier to troubleshoot. Our lab website is here: https://almost-matching-exactly.github.io.

Ziv Bar-Joseph, Ph.D., Carnegie Mellon University

Dr. Bar-Joseph is the FORE Systems Professor of Computer Science at the Machine Learning and Computational Biology Departments in the School of Computer Science at Carnegie Mellon University. His work focuses on the development of machine learning methods for processing, analyzing, visualizing, and modeling high throughput biological data. He is involved in several national efforts to use single cell data to create 3D reference human maps, and he has a particular interest in analyzing and modeling time series biological data and methods for integrating this data with static interaction datasets. He leads the Computational Tools Center for the National Institutes of Health's Human Biomolecular Atlas Program and is the co-director of the Carnegie Mellon-University of Pittsburgh Ph.D. Program in Computational Biology. Previously, he led other large centers focused on the analysis of disease expression data. He received the Overton Prize—the annual award of the International Society for Computational Biology—and the National Science Foundation CAREER award, and he has won several best paper awards, including at the Research in Computational Molecular Biology and the Intelligent Systems for Molecular Biology conferences. He earned a doctorate in computer science from the Massachusetts Institute of Technology in 2003.

Machine Learning Methods for Studying Dynamic, Interconnected Multisystems

Molecular interconnected systems, both at the cell and at the tissue or organ levels, are composed of several interacting entities that, together, play a critical role in all biological and biomedical processes. In this talk, I will provide a brief overview of machine learning methods, both supervised and unsupervised, that have been used to study and model various dynamic interconnected networks within and between cells. These will include active learning methods for designing experiments to study such systems, methods for determining interactions between proteins and cells, and methods to integrate time series and static, snapshot data to reconstruct the dynamics of biological processes.

Daniel J. Bauer, Ph.D., University of North Carolina at Chapel Hill

Dr. Bauer is a professor and the director of the L.L. Thurstone Psychometric Laboratory in the Department of Psychology and Neuroscience at the University of North Carolina. His research interests lie at the intersection of quantitative and developmental psychology, particularly the development of problem health-related behaviors in childhood and adolescence. He has published over 100 scientific papers, been principal investigator on grants from the National Institutes of Health and National Science Foundation, and served as associate editor for *Psychological Methods* and on the editorial boards of several other journals. He received early career awards from the Society for

Multivariate Experimental Psychology (2004) and the American Psychological Association (2009). He teaches graduate and undergraduate courses in statistical methods and has won teaching awards from the University of North Carolina and the American Psychological Association. Endeavoring to make advanced statistical techniques more accessible, he co-founded CenterStat.org and has spent the last 15 years developing and teaching workshops in the United States and abroad on topics including multilevel modeling, mixture modeling, longitudinal data analysis, structural equation modeling, latent curve analysis, missing data analysis, measurement, and integrative data analysis.

A Person-Oriented Approach to the Analysis of Interconnected, Multicomponent Systems: Using Latent Class/Profile Analysis to Identify Prototypical Profiles of Risk

In developmental psychology, a distinction has long been made between *variable-oriented* and *person-oriented* approaches to research. The variable-oriented approach, reflected in many contemporary statistical methods, is characterized by the estimation of unique effects for specific variables, such as examining the predictive relationship between blood pressure and heart disease when controlling for other risk factors. In contrast, the person-oriented approach eschews this atomistic focus on the (often additive) effects of specific variables in favor of a more holistic representation of the individual. Motivated from the perspective of systems theory, person-oriented research typically seeks to identify prototypical individual profiles across a set of variables characterizing the process under study. Often, these profiles are obtained using heuristic clustering algorithms like K-Means or, increasingly, model-based approaches like latent class/profile analysis and other finite mixture models. What these *unsupervised learning* techniques share in common is the ability to identify configurations, or points in multivariate space, that reflect representative patterns of individual functioning across multiple domains, and which can be used as predictors or outcomes. For instance, a person-oriented approach would be ideal for evaluating hypotheses regarding *metabolic syndrome*, defined as a constellation of risk factors (high blood pressure, high blood glucose, low high-density lipoprotein (HDL), high triglycerides, large waist circumference), and its relation to heart disease and other health problems. More broadly, it is argued that the person-oriented approach and its attendant research methods are well suited for studying interconnected systems in whole person health research.

Trey Ideker, Ph.D., University of California, San Diego

Dr. Ideker is a professor in the Departments of Medicine, Bioengineering, and Computer Science at the University of California, San Diego (UCSD). He directs or co-directs the National Resource for Network Biology, the Cancer Cell Map Initiative, the Psychiatric Cell Map Initiative, and the UCSD Bioinformatics and Systems Biology Ph.D. Program. A pioneer in using genome-scale measurements to construct network models of cellular processes and disease, he founded the Cytoscape ecosystem for biological network analysis, a tool that has been cited more than 22,000 times. He serves on the editorial boards for *Cell, Cell Reports, Molecular Systems Biology,* and *PLoS Computational Biology* and is a fellow of the American Association for the

Advancement of Science and the American Institute for Medical and Biological Engineering. He was included in the 2020 Web of Science Highly Cited Researchers list, named a Top 10 Innovator by *MIT Technology Review,* and received the Overton Prize from the International Society for Computational Biology. He earned his bachelor's and master's degrees in electrical engineering and computer science from the Massachusetts Institute of Technology and a doctorate in molecular biology from the University of Washington.

Towards a Precision Medicine Based on Interpretable Machine Learning

Most drugs entering clinical trials fail, often related to an incomplete understanding of the mechanisms governing drug response. Machine learning techniques hold immense promise for better drug response predictions, but most have not reached clinical practice due to their lack of interpretability and their focus on monotherapies. To address these challenges, I will describe development of DrugCell, an interpretable deep learning model of human cancer cells trained on the responses of thousands of tumor cell lines to thousands of approved or exploratory therapeutic agents. The structure of the model is built from a knowledge base of molecular pathways important for cancer, which can be drawn from literature or formulated directly from integration of data from genomics, proteomics, and imaging. Based on this structure, alterations to the tumor genome induce states on specific pathways, which combine with drug structure to yield a predicted response to therapy. The key pathways in capturing a drug response lead directly to design of synergistic drug combinations, which we validate systematically by combinatorial clustered regularly interspaced short palindromic repeats (CRISPR), drug-drug screening *in vitro,* and patient-derived xenografts. We also explore a recently developed technique, few-shot machine learning, for training versatile neural network models in cell lines that can be tuned to new contexts using few additional samples. The models quickly adapt when switching among different tissue types and in moving to clinical contexts, including patient-derived xenografts and clinical samples. These results begin to outline a blueprint for constructing interpretable artificial intelligence systems for predictive medicine.

Terrie E. Moffitt, Ph.D., Duke University

Dr. Moffitt is the Nannerl O. Keohane University Professor of Psychology at Duke University and a professor at King's College, London. She is a licensed clinical psychologist who specializes in neuropsychological assessment, with expertise in lifelong aging, mental health, and longitudinal research methods. She is the associate director of the Dunedin Longitudinal Study and founder of the Environmental Risk Longitudinal Twin Study. She chairs the Board on Behavioral, Cognitive, and Sensory Sciences (National Academies of Sciences), the Data-Monitoring Board for the Health and Retirement Study (National Institute on Aging), and the jury for the Klaus J. Jacobs Prize (Switzerland). She has received the Stockholm Prize, the Klaus J. Jacobs Prize, and the National Alliance for Research on Schizophrenia and Depression's Ruane Prize for work on mental health, and the National Institutes of Health's Maltilda White Riley Award for work on aging processes in midlife adults. After receiving a doctorate in

psychology at the University of Southern California, she completed postdoctoral training at the University of California, Los Angeles Neuropsychiatric Institute. She is a fellow of the U.S. National Academy of Medicine, British Academy, U.K. Academy of Medical Sciences, and Association of Psychological Science.

Measuring Patients' Pace of Biological Aging With Longitudinal Data, Growth Curves, and Elastic Net Regression of DNA Methylation

Our team has developed a new measure of an individual's personal pace of biological aging. It is designed for use in clinical trial research and in prevention research aiming to extend years of healthy life. To develop the measure, we tracked decline in 7 organ systems by repeatedly assessing 19 biomarkers at ages 26, 32, 38, and 45 in a population-representative 1972 birth cohort of 1,000 individuals. The measure, implementable in whole blood, has strong test-retest reliability. Because it was developed in a single-year birth cohort, DunedinPACE is unconfounded by generational differences in exposures to factors that alter DNA methylation. Because it was developed from analysis of longitudinal change, DunedinPACE measures recent ongoing aging-related changes, not long-standing differences in health from early life.

Session Two Biographies and Abstracts

Moderator: Bramaramba Kowtha, M.S., R.D.N., L.D.N., Office of Disease Prevention

Ms. Kowtha is a public health advisor in the Office of Disease Prevention, where she promotes collaborative research and leads National Institutes of Health–wide disease prevention efforts. Her work includes strengthening partnerships to advance disease prevention, addressing health disparities and risk factors for morbidity and mortality, and contributing to efforts to identify prevention research gaps. Previously, she was a project officer, public health analyst, and registered dietitian nutritionist group leader at the Health Resources and Services Administration, where she developed funding opportunity announcements, managed grants with academic institutions, provided guidance to grantees, and educated staff on prevention-focused nutrition topics. She has also been a senior program analyst at the U.S. Department of Agriculture (USDA), where she monitored national child nutrition programs, provided program oversight to state and local governments, and supported implementation of the Healthy, Hunger-Free Kids Act. Ms. Kowtha has two master's degrees in food and nutrition and food science.

Moderator: Elizabeth Barr, Ph.D., Office of Research on Women's Health

Dr. Barr is a social and behavioral scientist administrator in the Office of Research on Women's Health (ORWH). She coordinates the ORWH interprofessional education program, co-leads the Diverse Voices speaker series, and supports efforts related to gendered variables in health research. Previously, Dr. Barr served on the faculties of University of Maryland, Baltimore County and Towson University and led interdisciplinary and cross-sector projects to increase women's engagement in clinical research. Her background is in community-centered research, HIV treatment, reproductive justice, and gender-based violence. Dr. Barr completed a doctorate at the University of Wisconsin-Madison and a master's degree at Towson University.

Mimi Ghosh, Ph.D., The George Washington University

Dr. Ghosh is an associate professor in the Milken Institute School of Public Health at The George Washington University. Her research interests are focused on HIV in vulnerable populations, specifically immune responses and their regulation by sex hormones. Funded by the National Institutes of Health and the Centers for AIDS Research, her current projects include work with adolescent girls, postmenopausal women, women who have experienced sexual violence and trauma, and transgender individuals. Dr. Ghosh received her doctorate in infectious diseases and microbiology from the University of Pittsburgh's Graduate School of Public Health. She did her postdoctoral training at the Geisel School of Medicine at Dartmouth, focusing on HIV acquisition and transmission in women.

Impact of Sexual Trauma on the Interconnected Outcomes of Mental Health and Immune System

Sexual violence exposure can result in localized physical trauma to the genital tract as well as severe psychological distress. Sexual violence exposure also leads to impaired immune response and increased susceptibility to sexually transmitted infections. However, immunobiological mechanisms linking sexual violence, mental health outcomes, and immune responses to pathogens are incompletely understood. Using a series of cross-sectional and longitudinal studies that include participants with both acute and chronic exposure to sexual violence, we show that mental health outcomes associate with immune biomarkers and improve over time from exposure event. We also find that immune signature associated with chronic sexual abuse exposure and depression are distinct in local (genital tract) versus systemic (plasma) compartments and impacted by HIV status. Finally, we find differential immune signatures in those who were exposed to acute sexual trauma (past 4 days) compared to those who reported chronic (life-long) sexual abuse. Studies that include mental health and immune biomarker evaluations in vulnerable populations are rare, and they face many challenges. Our data point to the interconnected outcomes of mental health and immune dysregulation in sexual trauma survivors and underscore the need for inclusion of vulnerable populations in research studies and clinical trials, improved methodology and analysis tools, and increased awareness regarding the need for trauma-informed care in sexual violence survivors.

Ramsey Badawi, Ph.D., University of California, Davis

Dr. Badawi is a professor of radiology and biomedical engineering and the vice-chair for research in the Department of Radiology at the University of California, Davis (UC Davis). He is also the co-director of the Biomedical Technology Program at the UC Davis Comprehensive Cancer Center. He currently co-directs the EXPLORER Molecular Imaging Center (part of UC Davis Health in Sacramento, California), which houses the world's first total-body clinical positron emission tomography (PET) scanner, which he co-developed with Dr. Simon Cherry from 2005 to 2018. After joining UC Davis in 2004, his lab also developed the world's first dedicated breast PET/computerized tomography scanner and several preclinical *in vivo* PET imaging scanners. In 2000, Dr. Badawi joined the Dana Farber Cancer Institute in Boston, where he helped to set up its first clinical PET service. His work in medical imaging began in 1991 in the United Kingdom, where he obtained his doctorate in PET physics in 1998. He completed a postdoctoral fellowship at the University of Washington.

Total-Body PET—A Transformative Tool for Quantitative Whole-Person Research

In September 2018, the first human subject was scanned on the world's first total-body PET scanner. This represented a watershed moment, when, for the first time, simultaneous 3D imaging of the entire living human was demonstrated. PET is a radiotracer technique that allows for quantitative *in vivo* measures of parameters such as metabolic rate, blood perfusion, receptor expression, drug biodistribution, and cell trafficking. The advent of total-body PET, funded by a $15 million Transformative R01, offers tremendous opportunities for whole person research by allowing measurement of such parameters across every tissue and organ of the body at the same time. This, in turn, provides a tool for assessment of single component and multicomponent interventions on interconnected multiorgan outcomes. Combined with our preclinical PET scanners, we can now apply this methodology to small animals, nonhuman primates and companion animals, and humans. We present the concepts of total-body PET and show a range of use-cases demonstrating the capabilities of the technology, including immune response to COVID-19, multiorgan impacts of myocardial infarction and of fatty liver disease, total-body burden of autoimmune disease, identification of viral reservoirs, impacts of time-restricted eating on glucose metabolism, and preliminary studies of changes in the whole-person glucose metabolic connectome in cachexia. Possible future uses of the technology in whole person research, including in mind-body connection, abscopal effect in radiation therapy, immune cancer therapy, and drug development through total-body regional tissue pharmacokinetics and pharmacodynamics, will also be discussed.

Karyn A. Esser, Ph.D., University of Florida

Dr. Esser is a professor of physiology and functional genomics and associate director of the Myology Institute at the University of Florida. Her lab has been working in the area of skeletal muscle adaptation, with a focus on understanding the molecular mechanisms that underly skeletal muscle adaptations to endurance and resistance exercise. In 2002, her lab discovered that the circadian clock mechanism was active in skeletal muscle, and since that time, her lab has pioneered research in this area. Currently, her lab is focusing on two main lines of research—the role of the muscle clock in homeostasis and aging and defining the transcriptional pathways downstream of exercise that regulate organ health and resilience. The latter topic builds on her work as the prinicipal investigator at one of the preclinical sites within the Molecular Transducers of Physical Activity Consortium (MoTrPAC).

Research Design to Support Systems-Level Multiomics Response to Exercise: Preclinical Studies

MoTrPAC has the goal of discovering and performing characterization of the range of molecular transducers (the "molecular map") that underlie the health benefits of physical activity. One of the challenges in the exercise field is that the health benefits are very broad, with known impacts on metabolic disease, cardiovascular disease, neurodegeneration, cancer, and mental health. However, there is still little to nothing known about the effects of exercise across many different organ systems within the body. In addition, very little is understood about the potential for sex-specific differences. Thus, the preclinical study teams were focused on developing a research design to perform well-controlled exercise interventions with sufficient rat numbers and multiple tissue/organ collections with both male and female animals. The challenge was to coordinate these studies across three separate sites, with considerations to help minimize site batch effects. The lessons learned across the preclinical MoTrPAC sites—including design decisions and post collection "corrections"—will be presented.

David Amar, Ph.D., Stanford University

Dr. Amar is a senior data scientist at the Ashley Lab at Stanford University, where he is a lead analyst for both the Molecular Transducers of Physical Activity Consortium (MoTrPAC) and the Exercise at the Limit Study. He has expertise in multiomics data analysis, systems biology, machine learning, and causal inference. He holds a doctorate in computer science and bioinformatics from Tel Aviv University and he was a fellow at the Simons Institution for the Theory of Computation at University of California, Berkeley. He completed his postdoctoral work at Stanford University in the Departments of Cardiovascular Medicine and Biomedical Data Science.

Challenges and Opportunities From the Multiomic MoTrPAC Project

Performing regular exercise is one of the most important actions by which individuals of all ages can improve their health. It prevents multisystem chronic diseases, reduces anxiety, improves cognitive function, and enhances overall quality of life. However, a gap remains in identifying the detailed molecular signals that are induced by exercise and lead to these benefits. MoTrPAC was established to address this gap and generate a molecular map of exercise as well as to assess potential sources of heterogeneity among individuals in their response to exercise. Preclinical and clinical studies are currently underway to examine the multiomic, cross-tissue, longitudinal effects of endurance and resistance exercise across a range of ages and fitness levels by molecular probing before and after acute bout and long-term training. These new, vast datasets entail computational and statistical challenges that require rigorous methodology. In this talk, we will discuss multivariate and network-biology methods that have proven to be beneficial in the preclinical data and how similar ideas can be adapted for the human data analysis. We will also briefly discuss areas in which methodological research is required.

Roundtable Discussion I

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

Dr. Chen is 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 earned a doctorate in biological chemistry and molecular pharmacology from Harvard University and a master's degree in medical sciences as part of the Harvard-Markey Medical Scientist training program at Harvard Medical School. She did her postdoctoral training in proteomics at the Massachusetts Institute of Technology.

Moderator: Judith Arroyo, Ph.D., National Institute on Minority Health and Health Disparities

Dr. Arroyo is special assistant to the director of the National Institute on Minority Health and Health Disparities, where she works to expand research on the health of underrepresented peoples and promote their leading funded research. Previously, she was the coordinator of minority health and health disparities research at the National Institute on Alcohol Abuse and Alcoholism. She has also served on the faculty of the University of New Mexico (UNM), where she researched bias in Hispanic mental health treatment, and the UNM Center on Alcohol, Substance Abuse, and Addictions, where she researched Hispanic alcoholism. She has received numerous awards for her work in mentoring and training diverse investigators and expanding the research focus to include minorities, including an American Psychological Association Early Career mentoring/training award, and several National Institutes of Health Directors' Awards and lifetime achievement awards from the Research Society on Alcoholism, the American Psychological Association Addictions Division, and the National Hispanic Science Network. Dr. Arroyo received a doctorate in clinical psychology from the University of California, Los Angeles.

Marybel Robledo Gonzalez, Ph.D., University of California, San Diego

Dr. Gonzalez is a postdoctoral scholar in the Department of Psychiatry at the University of California, San Diego (UCSD) under the mentorship of Dr. Susan Tapert and Dr. Sandra Brown. Her research, funded through a Diversity Supplement by the National Institute on Alcohol Abuse and Alcoholism, focuses on investigating the biosocial ecological systems that influence risk and resilience in adolescent substance use and cognitive and mental health. She obtained her doctorate in cognitive science at UCSD and was the recipient of the University of California, Berkeley's undergraduate Regents' and Chancellor's Scholarship, the Cota-Robles Fellowship, and the National Science Foundation Graduate Research Fellowship Award.

Elaine Y. Hsiao, Ph.D., University of California, Los Angeles

Dr. Hsiao is the De Logi Associate Professor of Biological Sciences in the Department of Integrative Biology & Physiology at the University of California, Los Angeles (UCLA), where she leads a laboratory that studies fundamental interactions between the microbiome, brain, and behavior, and their application to neurological disorders. Inspired by the interplay between microbiota and the nervous system, her laboratory mines for microbial modulators of host neuroactive molecules and investigates the impact of microbiota-immune system interactions on neurodevelopment and the role of the microbiome in gene-environment interactions in neurological diseases. Their discoveries have led to honors including the Chan Zuckerberg Initiative Ben Barres Career Award, Packard Fellowship in Science and Engineering, Alfred P. Sloan Fellowship in Neuroscience, Klingenstein-Simons Fellowship in Neuroscience, Kavli Fellowship of the National Academy of Sciences, National Institutes of Health Director's Early Independence Award, Forbes' 30 Under 30 in Science and Healthcare, and National Geographic's Emerging Explorer Award. Dr. Hsiao received her doctorate in neurobiology from the California Institute of Technology and her bachelor's degree in microbiology, immunology, and molecular genetics from UCLA.

Closing Remarks

Emmeline Edwards, Ph.D., National Center for Complementary and Integrative Health

Dr. Edwards is the director of the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH). She is responsible for development of scientific programs or areas of science that fulfill NCCIH'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.

Session Three Biographies and Abstracts

Moderator: Ranjan Gupta, Ph.D., Fogarty International Center

Dr. Gupta is the regional program director for South Asia and Eurasia at the Fogarty International Center. His work involves science policy strategic planning and evaluation, intellectual property management, negotiation of cooperative activities, and management of international scientific programs such as the Indo-U.S. Vaccine Action Program, programmatic reviews, and international scientific workshops. He established a bilateral scientific program between the United States and India, implemented through the American Society for Microbiology. Previously, Dr. Gupta held positions at GenBank, the National Library of Medicine, the Office of Technology Transfer, the National Institute of Allergy and Infectious Diseases, and the National Cancer Institute, where he began as a visiting scientist working on HIV/AIDS molecular epidemiology in 1997. From 2001 to 2003, he was a science policy fellow of the American Association for the Advancement of Science and served at the U.S. State Department's Office of the Science & Technology Advisor and the U.S. Department of Health and Human Services' Office of Global Affairs. Currently, he is a U.S. board member of the United States–India Science & Technology Endowment Fund.

Moderator: Miya Whitaker, Psy.D., M.A., Office of Research on Women's Health

Dr. Whitaker is a health scientist administrator/program officer in the Office of Research on Women's Health (ORWH). Her work in ORWH's Clinical Research Section involves supporting the U3 Administrative Supplement Program, which supports research on women from populations that are understudied, underrepresented, and underreported (U3) in biomedical research. As a social and behavioral scientist, Dr. Whitaker is passionate about geographically analyzing disease and disease risk for underserved racial and ethnic groups and low-income communities, eliminating neighborhood incivility, addressing income inequality and food insecurity, and advancing integrated health equity solutions. She has a background in cognitive behavioral therapy and research on environmental influences on health and disease development and progression among health disparity populations. She earned her doctorate and master's degree in clinical psychology from the Forest Institute of Professional Psychology and her bachelor's degree in biology from the University of Maryland, Eastern Shore. She completed a postdoctoral fellowship in drug dependence epidemiology in the Division of Clinical Pharmacology at the Johns Hopkins Bloomberg School of Public Health.

Lynne Shinto, N.D., M.P.H., Oregon Health & Science University

Dr. Shinto is a professor in the Departments of Neurology and Obstetrics and Gynecology in the Center for Women's Health Integrative Health Division at Oregon Health & Science University (OHSU). She is the principal investigator on studies that evaluate natural therapies for brain and whole person wellness, funded by the National Institutes of Health, National Multiple Sclerosis Society, and OHSU Foundation. She has expertise in conducting clinical trials to evaluate the effectiveness of dietary supplements, mindfulness, and multicomponent therapies in multiple sclerosis, Alzheimer's disease, dementia prevention, and first-episode psychosis in youth. Dr. Shinto is a member of the National Advisory Council for Complementary and Integrative Health. She has provided naturopathic medical care at OHSU's Center for Women's Health Integrative Medicine Clinic for 16 years and is deeply involved in advancing the integration of all types of medicine. She obtained her doctorate at Bastyr University in 2000, and a master's degree in public health at OHSU in 2006.

Methods for Designing Multicomponent Interventions Based on Naturopathy

Naturopathic medicine shares key characteristics with other whole systems of medicine, such as traditional Chinese medicine, Ayurvedic medicine, and other traditional systems that include a holistic approach to diagnosis and treatment. The intent of a naturopathic doctor is to stimulate the self-healing capacities of the individual by using therapeutic modalities that include lifestyle management, herbs, nutritional supplements, homeopathy, physical medicine (physiotherapy, hydrotherapy, manipulation), and counseling, usually in conjunction with conventional medicine. The inherent complexity of whole system medicine makes it difficult to evaluate scientifically. This presentation will focus on the methods used to design a multicomponent intervention that models whole system naturopathic medicine using examples from two studies: Naturopathic Medicine in Multiple Sclerosis and Meals, Mindfulness, and Moving Forward in First Episode Psychosis (M3 Study). The presentation will highlight the use of provider surveys, Delphi panels, and patient/community stakeholder input to inform on a "best" practice intervention model and will address qualitative methods to help identify components within the model that have potential therapeutic benefit. The advantages and disadvantages to a "best" practice model in representing whole system medicine, decreasing bias (e.g., control group choice and participant blinding), and study reproducibility will also be highlighted.

Lynda H. Powell, Ph.D., Rush University Medical Center

Dr. Powell is the Charles J. and Margaret Roberts Professor of Preventive Medicine, Medicine, Behavioral Sciences, and Pharmacology, and the chair of the Department of Preventive Medicine at Rush University Medical Center. She is the principal investigator (PI) of a multisite behavioral clinical trial on a lifestyle intervention for remission of the metabolic syndrome. Previously, she was the PI of five randomized behavioral trials, a National Heart, Lung, and Blood Institute (NHLBI) P50 center on multilevel behavioral treatments to reduce cardiopulmonary disparities, and the Chicago site of NHLBI's Obesity-Related Behavioral Intervention Trials network, where she co-developed a model for behavioral intervention development. She is a founding member of the Office of Behavioral and Social Science Research's Summer Institute for Randomized Clinical Trials Involving Behavioral Interventions and was the Institute's co-director from 2008 to 2013. She was a member of the National Advisory Council for Complementary and Integrative Health from 2011 to 2015, and a fellow at the Stanford Center for Advanced Studies in Behavioral Sciences from 2015 to 2016. In 2021, she is co-publishing a book titled *Behavioral Clinical Trials for Chronic Diseases*: *Scientific Foundations.*

Addition of a Mindfulness Component to a Conventional Lifestyle Intervention for Sustained Remission of the Metabolic Syndrome

A progressive translational science model was used to determine if adding a mindfulness component to diet and physical activity can achieve sustained remission of metabolic syndrome (MetS). The need for a stress component is drawn from basic science observations that cognitive control deteriorates in the face of stress and from convergence of focus group insights from clinicians and applied behavioral scientists that stress undercuts intention to engage in healthy behaviors. A proof-of-concept study of a three-component intervention including stress produced MetS remission in 54 percent of treated participants after 2.5 years. Component analysis of the mechanisms of MetS remission status did not support alleviation of depressed symptoms, but a 7-year follow-up revealed that participants perceived the most important skill in sustaining change was emotional nonreactivity. Using principles of human-centered design, a small group of 10 volunteers with MetS prepared and ate food together over 3 months, making it evident that fast, mindless eating was a needed target. This progressive set of studies produced a hypothesized pathway where stress was replaced with a mindfulness component that targeted emotional nonreactivity and sensory awareness. Continued development will evaluate sustainability of mindfulness over 2 years using ecological momentary assessment and mechanisms of sustainability with change score analyses to determine if change in mindfulness over 6 months predicts MetS remission over 18 months, independently of, or in interaction with, change in diet and physical activity.

Linda M. Collins, Ph.D., New York University

Dr. Collins is a professor of social and behavioral sciences and biostatistics in the School of Global Public Health, New York University. She is working to develop methods for decision making based on optimization and has collaborated on research to apply the multiphase optimization strategy (MOST) to HIV, smoking cessation, the prevention of sexually transmitted infections, and weight loss. Her research funding has come from the National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, and National Science Foundation. Previously, Dr. Collins held faculty positions at Penn State and the University of Southern California. She has been the president of the Society of Multivariate Experimental Psychology and the Society for Prevention Research and is a fellow of the American Psychological Association, the Association for Psychological Science, the Society for Prevention Research, and the Society of Behavioral Medicine. Her awards include a Fulbright Specialist grant, the President's Award from the Society for Prevention Research, and being named the 2020 Valkhov Chair by Radboud University Medical Centre in the Netherlands.

Achieving Intervention EASE (Effectiveness, Affordability, Scalability, and Efficiency) Using the Multiphase Optimization Strategy (MOST)

Multicomponent behavioral and biobehavioral interventions are used widely for prevention and treatment of health problems, improvement of academic achievement, and promotion of health. These interventions are typically developed and evaluated using a treatment package approach, in which the intervention is assembled *a priori* and evaluated by means of a two-group randomized controlled trial. I will briefly introduce an alternative methodological framework for developing, optimizing, and evaluating behavioral and biobehavioral interventions. This framework, called the multiphase optimization strategy (MOST), is a principled approach that integrates ideas from behavioral science, multivariate statistics, engineering, health economics, and decision science. MOST enables the investigator to balance intervention effectiveness, affordability, scalability, and efficiency to achieve intervention EASE. Using MOST, behavioral and biobehavioral interventions can be optimized to meet any objective chosen by the investigator. The objective may be to develop a cost-effective intervention, an intervention that achieves a specified level of effectiveness, the briefest intervention that achieves a minimum level of effectiveness, or any other reasonable goal. The MOST framework relies heavily on resource management by strategic choice of highly efficient experimental designs. I propose that MOST offers several benefits, including more rapid long-run improvement of interventions, without requiring a dramatic increase in research resources.

Liliane Windsor, Ph.D., M.S.W., University of Illinois at Urbana-Champaign

Dr. Windsor is the associate dean for research and an associate professor of social work at the University of Illinois at Urbana-Champaign. Her research focuses on the application of critical consciousness theory in multilevel interventions to promote health equity in the treatment of substance use disorders, HIV prevention, and criminal justice in marginalized communities. She is the founder and chair of the Newark Community Collaborative Board, a group of researchers, service providers, and consumers who developed Community Wise, a multilevel intervention to reduce substance misuse and health risk behaviors. She is also the principal investigator of two large randomized controlled trials funded by the National Institute on Minority Health and Health Disparities—a manualized multilevel intervention to reduce substance misuse among formerly incarcerated men and optimization of a COVID-19 treatment and prevention cascade to increase adherence to public health recommendations. Dr. Windsor was a 2019–2020 Robert Wood Johnson Health Policy Fellow in Senator Dick Durbin's office. She received her doctorate and master's degrees in social work from the University of Texas at Austin and earned a bachelor's degree in education from the Fundação Mineira de Educação e Cultura in Brazil.

Community Wise: Development of a Multilevel Intervention to Reduce Alcohol and Substance Misuse Among Formerly Incarcerated Men

Marginalized urban communities with higher rates of poverty and people of color face serious inequities related to alcohol and substance misuse (ASM) when compared to more affluent and White communities (e.g., higher incarceration and HIV/hepatitis C virus infection rates). These communities also have considerably less access to effective and affordable treatment of substance use disorders. Community Wise is an innovative multilevel behavioral group intervention created in partnership with service providers, residents of marginalized communities, and individuals with histories of substance use disorders and incarceration, to reduce health inequities related to ASM. Community Wise addresses social determinants of health (e.g., stigma, poverty, lack of treatment access, housing, and meaningful employment) and inequities related to ASM at the micro level (e.g., cognitive and behavioral processes), meso level (e.g., relationships with individuals and organizations), and macro level (e.g., political and cultural processes). Community Wise builds on critical consciousness theory, which empowers individuals, organizations, and communities to address social determinants of health while changing individual behaviors (e.g., reducing alcohol and illicit drug use). Community Wise is manualized, delivered by a trained peer-facilitator, and includes nine weekly sessions lasting 2 hours each. This presentation will discuss the application of the multiphase optimization strategy (MOST) and Community Based Participatory Research (CBPR) to optimize Community Wise over the past 10 years. The discussion will include lessons learned, advantages and challenges of implementing these frameworks in the real world, and existing methodological limitations of multilevel intervention science.

Mark P. Jensen, Ph.D., University of Washington

Dr. Jensen is a professor and the vice chair for research in the Department of Rehabilitation Medicine, University of Washington. He is also the current editor-in-chief for the *Journal of Pain*. His research program focuses on understanding the effects and mechanisms of psychological pain interventions. He has published over 590 articles in peer-reviewed journals, is the author or co-author of over 40 books chapters, and has authored or edited 11 books. A fellow of the American Psychological Association, Dr. Jensen has received numerous awards for his scientific contributions, including the Clark L. Hull Award for Scientific Excellence in Writing on Experimental Hypnosis and the American Psychological Association Division 30 Award for Distinguished Contributions to Professional Hypnosis. Dr. Jensen received his doctorate from Arizona State University and completed his postdoctoral training at the Multidisciplinary Pain Center, University of Washington Medical Center.

Identifying the Mechanisms Underlying Multicomponent Pain Interventions

This talk will describe and discuss two strategies for understanding the mechanisms underlying multicomponent pain interventions: mediation and cross-lagged panel design analyses. It will begin by making the point that the current gold standard for chronic pain treatment **is** multicomponent treatment, because chronic pain both impacts and is impacted by the whole person. One strategy for increasing our understanding of these treatments is to examine the effects they have on whole-person mechanism variables (that is, on the biological, psychological, and social factors that the treatments target for change) and the subsequent impact of these mechanism variables on outcome. Both mediation and cross-lagged analyses allow investigators to determine: (1) if the multicomponent treatments influence specific mechanism variables, as hypothesized; and (2) if treatment-related changes in these mechanism variables are associated with treatment outcome. Mediation analyses identify the mechanism variables impacted by treatment (e.g., if level of mindfulness is impacted by a treatment that includes a mindfulness training component, and if activity level is impacted by a treatment that includes a behavioral activation component) and if any treatment-related changes in the mechanism variables are associated with treatment outcome. Cross-lagged panel analyses determine if changes in mechanism variables during treatment **precede** subsequent changes in outcome. Although each approach has strengths and weaknesses, both allow investigators to identify the mechanisms that are more or less likely to explain multicomponent treatment benefits, allowing for greater understanding of the components that might be most important to include in order to maximize beneficial outcomes.

Nadja B. Cech, Ph.D., University of North Carolina Greensboro

Dr. Cech is the Patricia A. Sullivan Distinguished Professor of Chemistry at the University of North Carolina Greensboro. She supervises a dynamic research group engaged in developing novel approaches to solve challenging problems in natural products and integrative medicine research. A major focus of this work is studying how combinations of molecules may interact to achieve biological effects (additivity, synergy, or antagonism). She is a principal investigator for the Center for High Content Functional Annotation of Natural Products, funded by the National Center for Complementary and Integrative Health and the Office of Dietary Supplements. She is also the co-director of the Medicinal Chemistry Collaborative and the Analytical Core for the Center of Excellence for Natural Product Drug Interaction Research. Dr. Cech is the recipient of the 2011 Jack L. Beal Award from the *Journal of Natural Products* and the 2017 Thomas Norwood Award for Undergraduate Research Mentorship.

Mass Spectrometry Metabolomics to Identify Bioactives and Synergists in Botanical Medicines

Botanical (plant-based) natural products, which are classified as “dietary supplements” in the United States, constitute a multibillion-dollar industry in North America. Regulation and quality control for this industry is an ongoing challenge. Myriad examples exist whereby commercially available botanical natural products are either intentionally or unintentionally adulterated or mislabeled, a situation that constitutes a major health concern for consumers. Even for correctly identified botanical natural products, composition differs depending on myriad factors, including variability in genetics, cultivation conditions, and processing methods. While there is general agreement that rigorous scientific studies are needed to evaluate the safety and efficacy of botanical natural products used by consumers, researchers conducting such studies face the challenge of dealing with inherently complex mixtures of variable composition. Unfortunately, many studies of botanical natural products are carried out with poorly characterized study material, such that the results are irreproducible and difficult to interpret. To address these challenges, our research group has developed mass spectrometry metabolomics approaches to capture and compare the chemical diversity of complex botanical natural products. We seek to identify the multiple constituents that may play a role in the biological activity of a given botanical and to uncover mechanisms by which biological effects occur. This talk will review some of the approaches employed to accomplish these goals and provide case studies of their application to the study of medicinally relevant botanicals.

Session Four Biographies and Abstracts

Moderator: Yvonne Bryan, Ph.D., National Institute of Nursing Research

Dr. Bryan is a senior advisor to the director of the National Institute of Nursing Research (NINR). Previously, she served as the acting director of the Division of Extramural Science Programs (DESP) and a special assistant to the NINR director, the DESP deputy director, and chief of DESP's Office of Extramural Research Administration and NINR's Office of Extramural Programs. In 2009, she received the National Institutes of Health (NIH) Director's Award and the NINR Director's Leadership Award and, in 2011, the NIH Equal Employment Opportunity Award of the Year. Dr. Bryan joined NINR as program director for infant, child, reproductive, and family health in 2001, after completing a 3-year fellowship at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and holding several academic and research positions. She began her career as a registered nurse in the obstetrics and gynecology unit at the University Hospital of the West Indies after receiving her nursing diploma, and later earned a bachelor's degree in psychology and her master's and doctoral degrees in experimental psychology at Concordia University, Montreal.

Moderator: Hye-Sook Kim, Ph.D., National Center for Complementary and Integrative Health

Dr. Kim is a program director in the Basic and Mechanistic Research Branch of the Division of Extramural Research at the National Center for Complementary and Integrative Health. Her research focuses on the fundamental mechanisms underlying the effects of prebiotic, probiotic, and microbiome-/microbial-based treatments. Previously, she was a senior research and development manager with the Institute of Advanced Technology at CJ-Cheil Jedang Corporation in South Korea, where she oversaw research on microbiome-based therapeutics for neurological disorders, immune-related diseases, and cancer. She has also been a project leader at DuPont, where she managed human gut microbiome and probiotic projects aimed at ameliorating metabolic disorders and improving gastrointestinal health. Dr. Kim's areas of expertise include bacteriology, molecular biology, biochemistry, bioinformatics, and host–microbe interactions. She earned her doctorate in plant pathology from the University of Wisconsin–Madison and did her postdoctoral training in the University of Chicago's Department of Biochemistry and Molecular Biology, where she studied the regulatory mechanisms of a biosafety level-3 bacterial pathogen during host adaptation.

Rob Knight, Ph.D., University of California, San Diego

Dr. Knight is the founding director of the Center for Microbiome Innovation and a professor of pediatrics, bioengineering, computer science, and engineering at the University of California, San Diego. His lab has produced software tools and laboratory techniques for high-throughput microbiome science, including the Quantitative Insights Into Microbial Ecology pipeline and UniFrac, a method for computing differences between microbial communities based on phylogenetic information. A co-founder of the Earth Microbiome Project, the American Gut Project, and the company Biota, Inc., his work has linked microbes to health conditions including obesity and inflammatory bowel disease and enhanced our understanding of microbes in environments ranging from the oceans to the tundra. He received the 2019 National Institutes of Health Director's Pioneer Award for his microbiome research and the 2017 Massry Prize. He is the author of *Follow Your Gut: The Enormous Impact of Tiny Microbes* and the co-author of *Dirt is Good: The Advantage of Germs for Your Child's Developing Immune System,* and he has written over 700 scientific articles. He is a fellow of the American Association for the Advancement of Science and the American Academy of Microbiology.

The Microbiome and Metabolome as a Readout of Complex Interventions Throughout the Body

There is increasing evidence that many different factors impact the microbiome and that it can be used to read out the impact of many interventions throughout the body. In this talk, I summarize the use of the microbiome and/or microbiome-derived metabolome as a readout for a range of different diseases and environmental exposures (including diet), some of the statistical methods used in microbiome research, and the promise of microbiome-directed drug or diet interventions that impact systems throughout the body.

Nicholas J. Schork, Ph.D., The Translational Genomics Research Institute

Dr. Schork is the deputy director and Distinguished Professor of Quantitative Medicine at The Translational Genomics Research Institute. He is also an adjunct professor of population sciences and molecular and cellular biology at City of Hope, of psychiatry and biostatistics at the University of California, San Diego (UCSD), and of integrative structural and computational biology at Scripps Research. He is a co-principal investigator (PI) and scientific director of the Longevity Consortium and the PI of Integrated Longevity Omics, both funded by the National Institute on Aging. Previously, he held faculty positions at the J. Craig Venter Institute, Scripps Research, UCSD, Case Western Reserve University, and Harvard University. He has published over 550 articles on biomedical and translation science, developed 12 patents associated with analysis

methodology, been involved with more than 10 startup companies, and mentored over 75 students and postdoctoral fellows. From 1999 to 2000, he was the vice president of statistical genomics at Genset, where he helped to construct the first high-density map of genetic variation in the human genome.

N-of-1 and Aggregated N-of-1 Studies for Exploring Multicomponent Intervention Effects on Multiple Health Outcomes

Identifying and characterizing the factors that mediate or cause a system to have the observable properties it has is not trivial given the number of factors and their complex interactions that may be involved. This is especially true for understanding human biology and effects that health-preserving interventions may have on the actual health of individuals, since ethical constraints on what can be measured limit the design and execution of appropriate studies. Nonhuman models; *in vitro*, organoid, lab-on-a-chip, and other laboratory constructs and approaches; and simulation methods can all help but are limited and cannot provide perfect substitutes for studies on humans. Focused studies on individual humans (i.e., N-of-1 studies) involving sophisticated designs, emerging health monitoring devices, and integrated analytical approaches have promise, however, and have their roots in studies of the natural history of rare diseases, therapeutic drug monitoring (TDM) studies, and early-phase clinical trials. Relevant N-of-1 and aggregated N-of-1 studies can indeed be designed to explore complex human health interventions with one very important caveat: "health" is not captured by a single parameter (e.g., differences between mental health versus physical health). It is crucial, and often overlooked, that the success of a health intervention—in terms of its actual effects and adoption in the population at large—will be dictated by not only how it modulates a primary endpoint, like blood pressure, mood, insulin levels, or weight, but also how it makes people feel and influences their health trajectory going forward. Unfortunately, such insights cannot be achieved with ingrained legacy strategies and policies for vetting health interventions. Next-generation N-of-1 studies can leverage emerging health monitoring devices and sophisticated analytical methods that focus on integration and multivariate outcomes, but they must be sensitive to phenomena such as serial correlation among observations, intra- and inter-individual variation, carryover effects, and "part-to-whole" (or "whole-to-part") inferences, as well as biological motivations for their pursuit arising from nonhuman studies.

Inbal Nahum-Shani, Ph.D., University of Michigan

Dr. Nahum-Shani is an associate professor in the Institute for Social Research and a founding member of the Data Science for Dynamic Decision-making Laboratory at the University of Michigan. Her research focuses on conceptual and methodological issues pertaining to the construction of effective adaptive interventions—a design in which regularly updated personal information is used to individualize the type/dose/modality of support or treatment—and just-in-time adaptive interventions (JITAI), which use mobile devices to provide support in a timely and ecological manner. Dr. Nahum-Shani collaborates with multiple scientific teams on the development of technology-

based interventions that deliver support in real time, including engaging individuals in self-monitoring behaviors, emotion-regulation exercises, and mental health treatments. She is a lead on three federally funded research projects to inform the development of adaptive interventions and JITAI targeting substance use and HIV (funded by the National Institute on Drug Abuse), obesity (funded by the National Institute of Diabetes and Digestive and Kidney Diseases), and smoking (funded by the National Cancer Institute).

Multicomponent Interventions: An Organizing Framework for Selecting an Experimental Design

A variety of experimental designs can be used to inform the construction of multicomponent behavioral interventions. These include factorial designs, sequential multiple assignment randomized trials (SMART), and micro-randomized trials (MRT). This presentation is a nontechnical introduction to different types of multicomponent interventions, including fixed interventions, adaptive interventions, and JITAI. An organizing framework will be presented to help scientists select an experimental approach to inform intervention development. The connection between several experimental approaches will be discussed, and a variety of case studies will be used for illustration.

Ross Hammond, Ph.D., The Brookings Institution

Dr. Hammond is the director of the Center on Social Dynamics & Policy and a senior fellow in economics at The Brookings Institution. He is also the Betty Bofinger Brown Distinguished Associate Professor in Public Health and Social Policy in the Brown School at Washington University in St Louis. He holds additional academic appointments at the Harvard School of Public Health, the Santa Fe Institute, and the Australian National University. For the past two decades, his research has focused on applying complex systems science to challenging policy problems. Current topics include pandemic containment, obesity prevention, tobacco control, implementation science, the food system, health disparities, and decision making. Dr. Hammond is also an advisory special government employee at the U.S. Food and Drug Administration and serves on the Food and Nutrition Board of the National Academies of Sciences, Engineering, and Medicine. He has been a member of multiple National Institutes of Health–sponsored scientific networks focused on computational modeling and served on several National Academy of Sciences consensus panels as well as the Lancet Commission on Obesity. His articles have been published in journals including *Lancet, Science, JAMA, Nature Medicine, PNAS,* and the *American Journal of Public Health*.

Using Systems Science for a Multifaceted Multioutcome Whole-of-Community Intervention to Prevent Childhood Obesity

This presentation will cover the approach and key results from a multifaceted multioutcome research study funded by the National Institutes of Health, using multiple complex systems methods, for which the author served as the principal investigator. The project focused on obesity prevention at the community level.

Atul Butte, M.D., Ph.D., University of California, San Francisco

Dr. Butte is the Priscilla Chan and Mark Zuckerberg Distinguished Professor and inaugural director of the Bakar Computational Health Sciences Institute at the University of California, San Francisco. He is also the chief data scientist for the University of California Health System. With funding from the National Institutes of Health, Dr. Butte is an inventor on 24 patents and has authored over 200 publications. In 2015, he was elected to the National Academy of Medicine and in 2013, he was recognized by the Obama Administration as a White House Champion of Change in Open Science. He is a founder of three companies: Personalis, which provides medical genome sequencing services; Carmenta (acquired by Progenity, 2015), which develops diagnostics for pregnancy complications; and NuMedii, which finds new uses for drugs through open molecular data. He has also worked as a software engineer at Apple and Microsoft. Dr. Butte received his medical degree at Brown University and trained in pediatrics and pediatric endocrinology at Children's Hospital Boston. He earned his doctorate from Harvard Medical School and the Massachusetts Institute of Technology and trained in computer science at Brown University.

Precisely Practicing Medicine From 700 Trillion Points of Data

There is an urgent need to take what we have learned in our new data-driven era of medicine and use it to create a new system of precision medicine, delivering the best, safest, and cost-effective preventative or therapeutic intervention at the right time, for the right patients. As the chief data scientist for the University of California Health system, covering 20 health professional schools, 6 medical schools, 5 academic medical centers, 10 hospitals, and over 1,000 care delivery sites, Dr. Butte, a computer scientist and pediatrician, will highlight his center's recent work on integrating electronic health records data across the entire University of California, and how analytics of this "real world data" can lead to a better understanding of patients and provide new evidence for drug efficacy, new savings from better medication choices, and new methods to teach intelligence—real and artificial—to more precisely practice medicine.

Roundtable Discussion II

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

Dr. Weber is the branch chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH). She oversees a portfolio of pragmatic clinical trials, natural product clinical trials, studies of complementary medicine to promote healthy behavior, and complex complementary/integrative medicine intervention research. Dr. Weber is also one of the programmatic leads for the Health Care Systems Research Collaboratory Program and the Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing Program. A member of the planning and oversight team for the Nonpharmacologic Approaches to Pain Management Collaboratory, an initiative of the National Institutes of Health, the Department of Defense, and the Veterans Administration, she serves as a project scientist for its Coordinating Center. Prior to joining NCCIH as a program director in 2009, Dr. Weber earned a naturopathic medicine degree from Bastyr University as well as a doctorate in epidemiology and a master's degree in public health from the University of Washington.

Moderator: D. Craig Hopp, Ph.D., National Center for Complementary and Integrative Health

Dr. Hopp is a program director and the deputy director for the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH). He is also the coordinator for the Consortium for Advancing Research on Botanical and Other Natural Products Program and oversees other natural products projects supported by NCCIH. He administers NCCIH's Natural Product Integrity Policy and helps to shape priorities in the field of natural products. Previously, he was a senior research scientist at AMRI, where he isolated and identified natural compounds for therapeutics, He also worked on the research and development of complex herbal formulas used in traditional Chinese medicine at Phyto-Technologies. Dr. Hopp received his doctorate in pharmacognosy from Purdue University and his bachelor's degree in chemistry from James Madison University. While completing his postdoctoral research at Shaman Pharmaceuticals, he was an author on multiple patents after discovering several antihyperglycemic compounds through his work.

Scott Mist, Ph.D., M.Ac.O.M., Oregon Health & Science University

Dr. Mist is an associate professor in the Anesthesiology & Perioperative Department at the Oregon Health & Science University. A licensed acupuncturist and a pain researcher with a background in systems sciences, his research focuses on whole systems treatment of chronic pain conditions such as temporomandibular joint disorders and fibromyalgia. Dr. Mist is also investigating the role of light sensitivity in traumatic brain injury and post-traumatic stress disorders.

Irene Headen, Ph.D., M.S., Drexel University

Dr. Headen is an assistant professor of Black health in the Department of Community Health and Prevention in the Dornsife School of Public Health at Drexel University. Interested in the social and structural determinants of racial/ethnic inequities in adverse pregnancy outcomes, her research focuses on identifying neighborhood and community factors underlying these inequities and translating these factors into multilevel interventions to improve Black maternal health outcomes. She uses epidemiologic, systems science, and mixed methods approaches to conduct her research. The recipient of a K01 award (K01MD015291-01), Dr. Headen is further harnessing participatory system dynamics methods to improve understanding of dynamic neighborhood processes and severe maternal morbidity among Black birthing people. She received her doctorate in epidemiology from the University of California, Berkeley in 2015, and completed a postdoctoral training fellowship through the Maternal and Child Health Bureau's Centers of Excellence in Maternal Health Postdoctoral Training Program. She was a postdoctoral fellow at the Drexel Urban Health Collaborative before joining the faculty in 2019.

Workshop Synthesis: Whole Person Research Methods

Bruce Y. Lee, M.D., M.B.A., City University of New York

Dr. Lee is a professor of health policy and management at the Graduate School of Public Health & Health Policy and the executive director of the Center for Advanced Technology and Communication in Health at the City University of New York. He is also the executive director of Public Health Computational and Operations Research and the founder and chief executive officer of Symsilico. A systems modeler, computational and digital health expert, writer, and health journalist, Dr. Lee has over two decades of experience in developing mathematical and computational models for health decisioning. He has authored over 245 scientific publications and written over 1,200 health-related articles for the general media, including as a senior contributor for Forbes. His writing has also appeared in media outlets including *Time, The Guardian,* and *MIT Technology Review, The New York Times, USA Today,* the *Los Angeles Times,* CBS News, *U.S. News and World Report, Bloomberg News,* and National Public Radio. He received his medical and bachelor's degrees from Harvard University and his master's degree from the Stanford Graduate School of Business.

Workshop Synthesis: Whole Person Research Methods

The human body is a complex system, and it interacts with many surrounding complex systems, including behavioral, social, and environmental systems. Therefore, the impact and value of various treatments and health improvement strategies that affect multiple organ systems may be quite complex and difficult to understand. The recent years have seen growth of different computer-based approaches, methods, and tools, such as modeling, that can help better understand and address these complex systems. Such systems approaches have the potential of transforming whole body research as they have other fields, such as meteorology, manufacturing, and transportation. Here we cover some examples of how we have used systems methods, models, and tools for a variety of health-related issues.

Closing Remarks

Helene Langevin, M.D., Director, National Center for Complementary and Integrative Health (see biography on page 7)

Panelists' Questions

SESSION ONE

1. What methodologies can be used in preclinical models, human subjects, or both for studying interconnected systems, and what are the advantages/strengths/pros (e.g., ability to assess temporal dynamic range and responses) and limitations/cons (e.g., some approaches are considered fishing expeditions; need to adjustment for multiple comparisons, lack of causality analysis of machine learning) of these methodologies?
2. What methodologies can be commonly used in both preclinical and clinical studies to analyze interconnected systems, and which types of data can be captured in both preclinical and human subject studies?
3. Which computational and analytic methods are unique to preclinical studies vs. human subject research to study interconnected systems, and what types of data can be captured in preclinical models or human subjects uniquely?

SESSION TWO

1. What methodologies can be used in preclinical models, human subjects, or both for studying interconnected systems, and what are the advantages/strengths/pros (e.g., ability to assess temporal dynamic range and responses) and limitations/cons (e.g., some approaches are considered fishing expeditions; need to adjustment for multiple comparisons, lack of causality analysis of machine learning) of these methodologies?
2. What methodologies can be commonly used in both preclinical and clinical studies to analyze interconnected systems, and which types of data can be captured in both preclinical and human subject studies?
3. Which computational and analytic methods are unique to preclinical studies vs. human subject research to study interconnected systems, and what types of data can be captured in preclinical models or human subjects uniquely?

ROUNDTABLE DISCUSSION I

1. Which methodologies for studying interconnected multisystem outcomes are also suitable for studying the impact of single component interventions on multisystem outcomes?
2. What are the gaps and challenges in methodological approaches for preclinical studies, translational research, and clinical studies of interconnected multisystem outcomes and their impact on single component interventions?
3. What are the opportunities for innovation and further advancements in computational and analytic methods to study interconnected multisystem outcomes and the impact of single component interventions in preclinical, translational, and clinical research?

4. What methods from other fields that we have not discussed would be useful to study interconnected systems and the impact of a single component intervention on interconnected systems?

5. How do the social determinants of health disparities—*see below for table (e.g., race/ethnicity, socioeconomic status, place) enter into the study of interconnected systems and the impact of single component interventions?

6. Limitations in data collection could lead to bias in the application of machine learning/artificial intelligence-based models to underrepresented populations. What kind of data collection and data analysis techniques ensure equitable whole person research?

* https://www.nimhd.nih.gov/about/overview/research-framework/nimhd-framework.html

SESSION THREE

1. What methodologies can be used in preclinical models, human subjects, or both for studying multicomponent interventions or therapeutic systems, and what are the advantages/strengths/pros (e.g., ability to assess temporal dynamic range and responses) and limitations/cons (e.g., some approaches are considered fishing expeditions; need to adjustment for multiple comparisons, lack of causality analysis of machine learning) of these methodologies?

2. What methodologies can be commonly used in both preclinical and clinical studies to study multicomponent interventions or therapeutic systems, and which types of data can be captured in both preclinical and human subject studies?

3. Which computational and analytic methods are unique to preclinical studies vs. human subject research to study multicomponent interventions or therapeutic systems, and what types of data can be captured in preclinical models or human subjects uniquely?

4. What rigorous methods exist for developing multicomponent interventions?

SESSION FOUR

1. What methodologies can be used in preclinical models, human subjects, or both for studying the impact of multicomponent interventions or therapeutic systems on multisystem or multiorgan outcomes, and what are the advantages/strengths/pros (e.g., ability to assess temporal dynamic range and responses) and limitations/cons (e.g., some approaches are considered fishing expeditions; need to adjustment for multiple comparisons, lack of causality analysis of machine learning) of these methodologies?

2. What methodologies can be commonly used in both preclinical and clinical studies to study the impact of multicomponent interventions or therapeutic systems on multisystem or multiorgan outcomes, and which types of data can be captured in both preclinical and human subject studies?

3. Which computational and analytic methods are unique to preclinical studies vs. human subject research to study the impact of multicomponent interventions or therapeutic

systems on multisystem or multiorgan outcomes, and what types of data can be captured in preclinical models or human subjects uniquely?

ROUNDTABLE DISCUSSION II

1. Which methodologies for studying interconnected multisystem outcomes or multicomponent interventions are also suitable for studying the impact multicomponent interventions on multisystem outcomes?
2. What are the gaps and challenges in methodological approaches for preclinical studies, translational research, and clinical studies of multicomponent interventions and their impact on interconnected multisystem outcomes?
3. What are the opportunities for innovation and further advancements in computational and analytic methods to study multicomponent interventions and their impact on interconnected multisystem outcomes in preclinical, translational, and clinical research?
4. What methods from other fields that we have not discussed would be useful to study multicomponent interventions and their impact on interconnected multisystem outcomes?
5. How do the social determinants of health disparities—*see below for table (e.g., race/ethnicity, socioeconomic status, place) enter into the study of multicomponent interventions and their impact on interconnected multisystem outcomes?
6. Limitations in data collection could lead to bias in the application of machine learning/ artificial intelligence-based models to under-represented populations. What kind of data collection and data analysis techniques ensure equitable whole person research?

* https://www.nimhd.nih.gov/about/overview/research-framework/nimhd-framework.html

NIH Planning Committee

Judith Arroyo, Ph.D., National Institute on Minority Health and Health Disparities (see biography on page 19)

Elizabeth Barr, Ph.D., Office of Research on Women's Health (see biography on page 14)

Yvonne Bryan, Ph.D., National Institute of Nursing Research (see biography on page 29)

Wen Chen, Ph.D., M.M.Sc., National Center for Complementary and Integrative Health (see biography on page 19)

Roberto Flores, Ph.D., M.P.H., Office of Nutrition Research

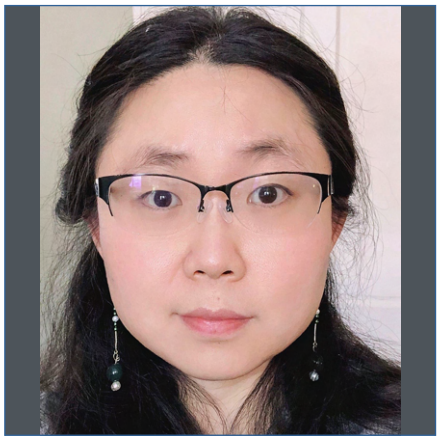
Dr. Flores is a coordinator for the Nutrition Research Implementation Working Groups (IWGs) in the Office of Nutrition Research in the Office of the Director at the National Institutes of Health (NIH). In this role, he facilitates the implementation of the 2020–2030 Strategic Plan for NIH Nutrition Research and supports the activities of the IWGs. Dr. Flores also serves as co-chair for the Microbiome, Diet & Health Interrelationships Implementation Working Group. His areas of expertise include human microbiome and nutrition research, infectious disease epidemiology, bioassay development and validation, molecular screening of viral infections, next generation sequencing technologies in cancer research and infectious disease, cancer prevention and control, grant management, and scientific program coordination and development.

Margaret Grisius, D.D.S., National Institute of Dental and Craniofacial Research

Dr. Grisius is the director of the National Institute of Dental and Craniofacial Research's Oral & Comprehensive Health Program, which focuses on epidemiologic and patient-oriented studies aimed at improving dental, oral, and craniofacial health. She served as an officer in the U.S. Public Health Service, stationed at the National Institutes of Health (NIH) Clinical Center, where she completed an oral medicine fellowship. Prior to joining the Clinical Center, she was an assistant professor in the Department of Oral Medicine at the University of Pennsylvania School of Dental Medicine. She then returned to NIH as an associate investigator in the Salivary Gland Dysfunction/Sjogren's Syndrome Clinic at the NIH Clinical Center. She received her dental degree from Georgetown University School of Dentistry and completed her general practice residency at the Washington, D.C. Veterans Administration Hospital and a geriatric fellowship through the University of Pennsylvania Department of Geriatric Medicine and the Veterans Administration Hospital of Philadelphia.

Ranjan Gupta, Ph.D., Fogarty International Center (see biography on page 22)

D. Craig Hopp, Ph.D., National Center for Complementary and Integrative Health (see biography on page 34)



Diane Joss, Ph.D., National Center for Complementary and Integrative Health

Dr. Joss is a scientific program analyst in the Basic and Mechanistic Research Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health. She supports administrative and scientific activities including numerous National Institutes of Health–wide initiatives led by program directors in the Basic and Mechanistic Research Branch. Previously, Dr. Joss was an instructor of psychiatry at Harvard Medical School and an assistant neuroscientist at McLean Hospital. She also worked as a research fellow in the Department of Psychiatry at Massachusetts General Hospital.

Hye-Sook Kim, Ph.D., National Center for Complementary and Integrative Health (see biography on page 29)

Bramaramba Kowtha, M.S., R.D.N., L.D.N., Office of Disease Prevention (see biography on page 14)

Sreenivasan Rajamoni Nadar, Ph.D., M.B.A., National Center for Complementary and Integrative Health

Dr. Nadar is an analyst/special volunteer in the Division of Extramural Research at the National Center for Complementary and Integrative Health. He has worked with the Division of Extramural Research for 3 years and served as a scientific review officer, clinical risk consultant, and scientific program analyst. He has over two decades of research and teaching experience on nonlinear dynamics and its applications to biology, medicine, biomedical signal processing, multimodal neuroimaging, computational neuroscience, and the science of science.

Janine M. Simmons, M.D., Ph.D., National Institute on Aging (see biography on page 8)

Wendy B. Smith, Ph.D., Office of Behavioral and Social Sciences Research

Dr. Smith is the associate director of the Office of Behavioral and Social Sciences Research. She advises the director on programmatic and scientific issues related to behavioral and social sciences, interdisciplinary research, and public-private partnerships. She also leads new National Institutes of Health (NIH)–wide research initiatives. Previously, she was the program director for clinical research partnerships in the Office of Science Policy and the inaugural deputy director of the National Cancer Institute's Office of Cancer Complementary and Alternative Medicine, where she created and directed the Research Development and Support Program. She has been a research psychologist in the intramural research program within the Neurobiology and Anesthesiology Branch's Pain Section at the National Institute of Dental and Craniofacial Research. A founding member of the NIH Pain Consortium, her publications include research on pain memory, psychophysics of pain perception, psychological aspects of pain, complementary and alternative medicine, and research methodologies. She has a doctorate in applied experimental psychology and a master's degree in health psychology, and is a licensed experimental psychologist and a nationally certified biofeedback therapist with advanced training in the use of hypnosis for pain.

Wendy J. Weber, N.D., Ph.D., M.P.H., National Center for Complementary and Integrative Health (see biography on page 34)

Miya Whitaker, Psy.D., M.A., Office of Research on Women's Health (see biography on page 22)

Qilu Yu, Ph.D., National Center for Complementary and Integrative Health (see biography on page 8)