Drug Research and Development for Adults Across the Older Age Span

The National Academies of SCIENCES ENGINEERING MEDICINE

August 5-6, 2020

A Virtual Workshop

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Drug Research and Development for Adults Across the Older Age Span: A Workshop

August 5-6, 2020
Virtual Webinar

Table of Contents

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Forum on Aging, Disability, and Independence
Forum on Drug Discovery, Development, and Translation
National Cancer Policy Forum

Drug Research and Development for Adults Across the Older Age Span

A Virtual Workshop

August 5-6, 2020

Despite the widespread recognition of the "graying of America," and the need for health care among older adults, there is a dearth of information about the appropriate use of drugs in this population. Older adults are vastly underrepresented in clinical trials. Yet older adults have higher rates of comorbidities and polypharmacy than the general population, and are the majority users of many medications. Additionally, age-related physiological and pathological changes, particularly for adults 80+, can lead to significant differences in the pharmacokinetic and pharmacodynamics of a given drug compared to the general population. There is a void in evidence-based information for making informed decisions on how to best optimize care for older adults, particularly those 80+.

This virtual public workshop will provide a venue for stakeholders to discuss the challenges and opportunities in drug research and development (R&D) for older adult populations, explore barriers that impede safety and efficacy studies in these populations, and share lessons learned for better understanding the clinical pharmacology for 65+ and 80+ populations.

The workshop will feature invited presentations and discussions to:

- Review the current landscape of drug R&D for 65+ and 80+ populations across public and private sectors;
- Consider medication issues for older adult populations (e.g. dosage forms, adherence, polypharmacy, differences in PK/PD);
- Explore methodologies that are currently used or could be implemented to study differences in pharmacology for older adult populations (e.g. minimal sampling);
- Examine barriers to conducting clinical research for 65+ and 80+ populations (e.g. funding, data, co-morbidity, polypharmacy, recruitment, access); and
- Explore approaches to engage 65+ and 80+ populations in clinical research and strategies generate evidence-based information on how to best optimize treatment for older adults.

A planning committee will organize the workshop, develop the agenda, select and invite speakers and discussants, and moderate or identify moderators for the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

Planning Committee

James Appleby (Chair), The Gerontological Society of America

Barry S. Coller, The Rockefeller University

Robert Temple, U.S. Food & Drug Administration, Center for Drug Evaluation and Research

Jonathan Watanabe, University of California Irvine Samueli College of Health Sciences

Donald Harvey, Emory University School of Medicine

Alex John London, Carnegie Mellon University

Mark Rogge, Takeda Pharmaceuticals

Marie A. Bernard, National Institutes of Health, National Institute on Aging

Barbara Zarowitz, University of Maryland School of Pharmacy, The Peter Lamy Center on Drug Therapy and Aging

Miriam Mobley Smith, Northeastern University Bouvé College of Health Sciences School of Pharmacy

David Reuben, University of California, Los Angeles

Janice Schwartz, University of California, San Francisco

Deborah Collyar, Patient Advocates in Research

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Forum on Drug Discovery, Development, and Translation
Forum on Aging, Disability, and Independence
National Cancer Policy Forum

Drug Research and Development for Adults Across the Older Age Span

A Virtual Workshop

August 5-6 2020

10:00 a.m. – 3:00 p.m. (ET)

ZOOM WEBINAR REGISTRATION:
https://nasem.zoom.us/webinar/register/WN_1IN7kZ-ESdWppXPNGVPPQw

Agenda

Despite the widespread recognition of the "graying of America," and the need for health care among older adults, there is a dearth of information about the appropriate use of drugs in this population. Older adults are vastly underrepresented in clinical trials. Yet older adults have higher rates of comorbidities and polypharmacy than the general population, and are the majority users of many medications. Additionally, age-related physiological and pathological changes, particularly for adults 80+, can lead to significant differences in the pharmacokinetic and pharmacodynamics of a given drug compared to the general population. There is a void in evidence-based information for making informed decisions on how to best optimize care for older adults, particularly those 80+.

This public workshop will provide a venue for stakeholders to discuss the challenges and opportunities in drug research and development (R&D) for older adult populations, explore barriers that impede safety and efficacy studies in these populations, and share lessons learned for better understanding the clinical pharmacology for 65+ and 80+ populations.

The workshop will feature invited presentations and discussions to:

- Review the current landscape of drug R&D for 65+ and 80+ populations across public and private sectors;
- Consider medication issues for older adult populations (e.g. dosage forms, adherence, polypharmacy, differences in PK/PD);
- Explore methodologies that are currently used or could be implemented to study differences in pharmacology for older adult populations (e.g. minimal sampling);
- Examine barriers to conducting clinical research for 65+ and 80+ populations (e.g. funding, data, co-morbidity, polypharmacy, recruitment, access); and
- Explore approaches to engage 65+ and 80+ populations in clinical research and strategies generate evidence-based information on how to best optimize treatment for older adults.

DAY 1: August 5, 2020

10:00 a.m. **Welcome and opening remarks**
JAMES APPLEBY, *Workshop Chair*
Chief Executive Officer
The Gerontological Society of America

SESSION I INCLUSION OF OLDER ADULTS IN CLINICAL TRIALS: AN EVOLVING LANDSCAPE

Session Objectives:

- Review the current landscape of drug R&D for 65+ and 80+ populations across public and private sectors;
- Consider medication issues for older adult populations (e.g., dosage forms, adherence, polypharmacy, differences in PK/PD);
- Examine barriers to conducting clinical research for 65+ and 80+ populations (e.g., funding, data, co-morbidity, polypharmacy, recruitment, access).

10:10 a.m. **Introduction by session moderator**
JERRY GURWITZ
Executive Director, Meyers Primary Care Institute
Division Chief of Geriatric Medicine, University of Massachusetts Medical School

10:15 a.m. **Knowledge gaps & issues unique to older adults**
ROSANNE M. LEIPZIG
Professor of Geriatrics and Palliative Medicine
Icahn School of Medicine at Mount Sinai

Age-related changes that impact drug metabolism
GEORGE A. KUCHEL
Travelers Chair in Geriatrics and Gerontology, Professor of Medicine
University of Connecticut Center on Aging

Barriers to conducting clinical trials that include older adults
NIH perspective
MARIE A. BERNARD
Deputy Director
National Institutes of Health, National Institute on Aging

Industry perspective
KATHERINE DAWSON
Senior Vice President of the Therapeutics Development Group
Biogen

11:00 a.m. *Moderated panel discussion*

11:30 a.m. **BREAK**

SESSION II CONCOMITANT ILLNESS AND POLYPHARMACY: OVERCOMING KEY BARRIERS

Session Objectives:

- Explore methodologies that are currently used or could be implemented to study differences in pharmacology for older adult populations (e.g., minimal sampling);

11:40 a.m. **Opening remarks by panel moderator**
JONATHAN WATANABE
Professor of Clinical Pharmacy, Associate Dean of Assessment and Quality
University of California Irvine Samueli College of Health Sciences

11:45 a.m. **Clinical trial considerations [Panel]**
Inclusion / exclusion criteria and trial design
HEATHER ALLORE
Professor of Medicine (Geriatrics) and Biostatistics
Yale University

Organ function criteria expansion
STUART M. LICHTMAN
Medical Oncologist
Memorial Sloan Kettering Cancer Center

FDA experience
RAJESHWARI SRIDHARA
Biostatistician Contractor (Retd. Director of the Division of Biometrics V, CDER)
U.S. Food and Drug Administration, Oncology Center of Excellence

Ethics perspective
JASON KARLAWISH
Professor of Medicine
University of Pennsylvania Perelman School of Medicine

12:30 p.m. *Moderated panel discussion*

1:00 p.m. **BREAK**

1:20 p.m. **Opening remarks by panel moderator**
ROBERT TEMPLE
Deputy Center Director for Clinical Science, Office of New Drugs
U.S. Food and Drug Administration, Center for Drug Evaluation and Research

Alternative study approaches [Panel]
Adaptive design
SCOTT BERRY
Co-Founder and President
Berry Consultants

Home-based clinical trials
STEVEN R. CUMMINGS
Executive Director, S.F. Coordinating Center
University of California, San Francisco

Quantitative systems pharmacology models: Mechanistic science perspective
CHRISTINA FRIEDRICH
Chief Engineer
Rosa & Co.

Clinical trial simulation
N. SETH BERRY
Senior Director, Decision Sciences Group
IQVIA

Real world trials
STEVEN CHEN
Associate Dean for Clinical Affairs
University of Southern California School of Pharmacy

2:20 p.m. *Moderated panel discussion*

DAY 1 REFLECTIONS

2:50 p.m. **Closing remarks**
JAMES APPLEBY, *Workshop Chair*
Chief Executive Officer
The Gerontological Society of America

3:00 p.m. **ADJOURN WORKSHOP DAY 1**

DAY 2: August 6, 2020

10:00 a.m. **Welcome and overview of Day 1**
JAMES APPLEBY, *Workshop Chair*
Chief Executive Officer
The Gerontological Society of America

SESSION III THE ERA OF COVID-19 AND BEYOND

Session Objectives:

- Explore methodologies that are currently used or could be implemented to study differences in pharmacology for older adult populations (e.g., minimal sampling);
- Explore approaches to engage 65+ and 80+ populations in clinical research and strategies generate evidence-based information on how to best optimize treatment for older adults.

10:10 a.m. **Opening remarks by panel moderator**
DEBORAH COLLYAR
President
Patient Advocates in Research

10:15 a.m. **Older adult outreach & networking strategies**
JONATHAN TOBIN
President/CEO
Clinical Directors Network

Barbershop-based outreach programs: Case study
CIANTEL BLYLER
Clinical Research Pharmacist
Cedars-Sinai Medical Center

Patient perspective
SUSAN STRONG
Director of Patient Engagement
Heart Valve Voice US

Caregiver perspective
LAUREL J. PRACHT
Research Patient Advocate and Patient Representative
NCI Symptom Management and Health-Related Quality of Life Steering Committee

Education for older adults and healthcare practitioners
STEVEN ROTHSCHILD
Vice Chairperson, Department of Preventive Medicine
Rush Medical College

11:15 a.m. *Moderated panel discussion*

11:45 a.m. **BREAK**

12:00 p.m. **Opening remarks by panel moderator, European perspective**
SVEN STEGEMANN
Professor for Patient Centric Drug Development and Manufacturing
Graz University of Technology

Lessons learned from COVID-19
U.S. regulatory changes
HARPREET SINGH
Division Director (Acting)
U.S. Food and Drug Administration, Division of Oncology 2

Infectious disease perspective
JOHN POWERS
Professor of Clinical Medicine
George Washington University School of Medicine

Telehealth / Physician perspective
ERIKA RAMSDALE
Assistant Professor
University of Rochester Medical Center

Digitization of medicine
ERIC TOPOL
Founder and Director
Scripps Research Translational Institute

Patient perspective
BEVERLY CANIN
Patient Advocate
Cancer and Aging Research Group

1:00 p.m. *Moderated panel discussion*

1:30 p.m. **BREAK**

1:45 p.m. **Reflections: Looking forward to the future**

Session moderator
JAMES APPLEBY, *Workshop Chair*
Chief Executive Officer
The Gerontological Society of America

1:50 p.m. AMY ABERNETHY
Principal Deputy Commissioner – Office of the Commissioner
U.S. Food and Drug Administration

ROBERT CALIFF
Head of Clinical Policy and Strategy
Verily and Google Health

MARIE A. BERNARD
Deputy Director
National Institutes of Health, National Institute on Aging

2:20 p.m. *Moderated panel discussion*

2:50 p.m. **Next Steps**
JAMES APPLEBY, *Workshop Chair*
Chief Executive Officer
The Gerontological Society of America

3:00 p.m. **ADJOURN WORKSHOP DAY 2**

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Forum on Aging, Disability, and Independence
Forum on Drug Discovery, Development, and Translation
National Cancer Policy Forum

Drug Research and Development for Adults Across the Older Age Span

A Virtual Workshop

Planning Committee Biographies

CHAIR

JAMES APPLEBY, SC.D (HON), M.P.H., is the Chief Executive Officer of The Gerontological Society of America (GSA), the nation's largest interdisciplinary organization devoted to research, education, and practice in the field of aging. The Society works to advance innovation in aging and disseminate information among scientists, clinicians, policy makers, and the public. He is leading the Society's current initiative to "reframe aging" in America by fostering accurate narratives of aging to replace the outdated "conventional wisdom" that dominates public understanding. The 5,500-member Society is advancing major initiatives related to improving adult immunization rates, earlier detection of cognitive impairment, improving oral health, and demonstrating the impact of the longevity economy. Appleby also is currently serving a four-year term on the National Advisory Council on Aging after being appointed by the U.S. Secretary for Health and Human Services. Prior to joining GSA, he had a 17-year career with the American Pharmacists Association (APhA) where he served in a variety of roles before being appointed Chief Operating Officer. Before joining APhA, he was on faculty at the Philadelphia College of Pharmacy and Science (PCPS). Appleby holds a bachelor of science degree in pharmacy from PCPS and a master of public health degree from Temple University. He has been awarded an honorary Doctor of Science degree from the University of the Sciences in Philadelphia.

MEMBERS

MARIE A. BERNARD, M.D., serves as Deputy Director of the National Institute on Aging (NIA) at the National Institutes of Health. As NIA's senior geriatrician, she serves as the principal advisor to the NIA director, working closely with the director in overseeing approximately $3.1 billion in aging and Alzheimer's disease research conducted and supported annually by the Institute. She co-chairs two new Department of Health and Human Services Healthy People 2020 objectives: 1) Older Adults and 2) Dementias, including Alzheimer's Disease. Within NIH she co-chairs the Inclusion Governance Committee, which oversees inclusion in clinical research by sex/gender, race/ethnicity, and age – inclusive of pediatric and older adult subjects. She has been recognized for her leadership in geriatrics by receipt in the Clark Tibbitts Award from the Academy for Gerontology in Higher Education (2013), and the Donald P Kent Award from the Gerontological Society of America (2014). Until October 2008 she was the endowed professor and founding chairman of the Donald W. Reynolds Department of Geriatric Medicine at the University of Oklahoma College of Medicine (the third department of geriatrics in the U.S.), and

Associate Chief of Staff for Geriatrics and Extended Care at the Oklahoma City Veterans Affairs Medical Center. She has held numerous national leadership roles, including chair of the Clinical Medicine Section of the Gerontological Society of America, chair of the Department of Veterans Affairs National Research
Advisory Committee, board member of the American Geriatrics Society, president of the Academy for Gerontology in Higher Education, and president of the Association of Directors of Geriatric Academic Programs. She has lectured and published widely in her area of research, nutrition and function in older populations, as well as related to geriatric education. She received her undergraduate education at Bryn Mawr College and her MD from University of Pennsylvania. She trained in internal medicine at Temple University Hospital in Philadelphia, PA, where she also served as chief resident. She has received additional training through the AAMC Health Services Research Institute, the Geriatric Education Center of Pennsylvania, and the Wharton School Executive Development program.

BARRY S. COLLER, M.D., serves as Physician in Chief, Vice President for Medical Affairs and the David Rockefeller Professor at The Rockefeller University. An authority on the cardiovascular biology of integrins and TGF-beta, Dr. Coller is a member of the Institute of Medicine, the National Academy of Sciences and was founding president of the Society for Clinical and Translational Science. Dr. Coller is a pioneer in the discovery and development of monoclonal antibodies for use as human therapeutics. He played the central role in discovering the active component and mechanism of abciximab (ReoPro(R)), and he was a leader in its subsequent clinical development resulting in one of the first FDA approvals of and antibody medicine. He has been a Member of Scientific Advisory Board at Scholar Rock, Inc. since September 2014.

DEBORAH COLLYAR has been a leader in cancer patient advocacy since 1991, utilizing successful business, leadership, IT and communication skills to bridge research gaps between science, medical providers and patients. Her patient advocacy work encompasses many diseases, programs and policies at grassroots, national and international levels. She also gives guidance to organizations, institutions, universities, cancer centers, nonprofits, government agencies, companies, and most importantly, to patients. Ms. Collyar founded the PAIR international network, helped initiate the NCI SPORE program and served as Program Director for their Patient Advocate Research Team (PART) Program. She also started patient advocacy in many cooperative groups and cancer centers, and has helped plan national and international biobanks. Deborah has also served on many committees and boards, including: the NCI Experimental Therapeutics (NExT) program, and Board of Scientific Counselors; Princeton Physical Sciences in Oncology Center (PS-OC); AHRQ Comparative Effectiveness Research (CER) Stakeholder Council; as Chair of the CALGB Committee on Advocacy, Research Communication, Ethics, and Disparities (CARE); and as Vice Chair of the Alliance for Clinical Trials in Oncology (Alliance) Publications Committee. Deborah and her husband have survived 3 cancers.

DONALD HARVEY, PHARM.D., is Professor in the Department of Hematology and Medical Oncology with a joint appointment in the Department of Pharmacology and Chemical Biology at Emory University School of Medicine. A board certified oncology pharmacist, Dr. Harvey serves as director of Winship Cancer Institute's Phase I Clinical Trials Unit and as chair of the Data and Safety Monitoring Committee. He is a Fellow of the American College of Clinical Pharmacy and a Fellow of the Hematology/Oncology Pharmacy Association. Dr. Harvey has established an active clinical pharmacology research program in cancer at Emory with the goal of using pharmacokinetic, pharmacodynamic, and other tools to improve individualization of therapy and clinical outcomes. An active principal and co-investigator on multiple trials, he also consults on experimental design of preclinical and clinical studies with a focus on optimizing correlative measures. Dr. Harvey's research interests include the clinical application of pharmacokinetic, pharmacodynamic, and pharmacogenomic data to patient care. Specific areas of research interest include agent tolerability and disposition in renal and hepatic impairment, effects of novel immunotherapeutics on hepatic metabolism, and use of therapeutic drug monitoring for anticancer agents. He is also active nationally and internationally in several cancer and pharmacology professional organizations. Dr. Harvey is also a past President of the Hematology and Oncology Pharmacy Association, an international professional organization.

ALEX JOHN LONDON, PH.D., is the Clara L. West Professor of Ethics and Philosophy and Director of the Center for Ethics and Policy at Carnegie Mellon University. An elected Fellow of the Hastings Center, Professor London's work focuses on ethical and policy issues surrounding the development and deployment of novel technologies in medicine, biotechnology and artificial intelligence, on methodological issues in theoretical and practical ethics, and on cross-national issues of justice and fairness. His papers have appeared in Mind, The Philosopher's Imprint, Science, JAMA, The Lancet, The BMJ, PLoS Medicine, Statistics In Medicine, The Hastings Center Report, and numerous other journals and collections. He is also co-editor of Ethical Issues in Modern Medicine, one of the most widely used textbooks in medical ethics.

DAVID REUBEN, M.D., is Director of the Multicampus Program in Geriatrics Medicine and Gerontology and also Chief of the Division of Geriatrics at the University of California, Los Angeles (UCLA) Center for Health Sciences. He is the Archstone Foundation Chair and Professor at the David Geffen School of Medicine at UCLA and Director of the UCLA Claude D. Pepper Older Americans Independence Center and the UCLA Alzheimer's and Dementia Care program. Dr. Reuben sustains professional interests in clinical care, education, research and administrative aspects of geriatrics, maintaining a clinical primary care practice of frail older persons and attending on inpatient and geriatric psychiatry units at UCLA. His bibliography includes more than 220 peerreviewed publications in medical journals, 39 books and numerous chapters. Dr. Reuben is lead author of the widely distributed book, Geriatrics at Your Fingertips. Dr. Reuben is a past President of the American Geriatrics Society and the Association of Directors of Geriatric Academic Programs. He served for 11 years on the Geriatrics Test Writing Committee for the American Board of Internal Medicine (ABIM) and for 8 years on the ABIM's Board of Directors, including as Chair from 2010-2011. Research Interests: Health services delivery to older persons; Functional assessment; Predictors of survival and functional impairment; Alzheimer's and Dementia Care; Falls. Technical Research Interests: Clinical and social epidemiology; Health services research, including economics; Interventional and behavioral research; Measurement. Past President of the American Geriatrics Society; Past President of Directors of Geriatric Academic Programs (ADGAP); Past Chair of the Board of Directors of the American Board of Internal Medicine; Chief, Division of Geriatrics Medicine at UCLA.

MARK ROGGE, PH.D., F.C.P., serves as Global Head of Quantitative Translational Science at Takeda Pharmaceuticals, International. He oversees all discovery and development modeling & simulation, clinical pharmacology, imaging, and Bioanalytical Sciences. In this role and throughout his career he has promoted the application of advanced modeling & simulation to pharmacokinetic and pharmacologic processes in the preclinical and clinical realms, and applied these principles to both efficacy and to safety. His work has encompassed small molecules, glycoproteins, antisense constructs, and most recently, gene/cellular therapy. Mark has given numerous plenary presentations related to drug development at scientific and regulatory conferences; he has more than 80 peer-reviewed publications and invited presentations at scientific symposia. He is Past Chair of the AAPS PPDM Section, Past Chair of BIO's Safety and Pharmacokinetics scientific advisory section and Past Chair of the Clinical Pharmacology Leadership Group for the International Consortium for Innovation and Quality in Pharmaceutical Development. Mark completed his undergraduate studies at the University of Wisconsin, where he is a Citation of Merit recipient, and completed his graduate work at the University of Michigan.

JANICE SCHWARTZ, M.D., is a board-certified internist and cardiologist with a distinguished record of leadership and research in clinical pharmacology and geriatric medicine. She received her medical degree from Tulane University School of Medicine and completed an internship in internal medicine at LAC/USC Medical Center and internal medicine residency training at Cedar Sinai Medical Center, Los Angeles. She began cardiology training at Cedar Sinai followed by a combined clinical and research cardiology fellowship at Stanford University, where she focused on evaluation of new cardiovascular drugs in clinical populations. She began her faculty career in the Department of Medicine at Baylor College of Medicine in the Divisions of Cardiology and Clinical Pharmacology. She has been an active member of cardiology, clinical pharmacology and geriatric professional societies, including serving as President of the Society for Geriatric Cardiology and Vice President of the American Society for Clinical Pharmacology and Therapeutics (ASCPT), past member of the Board of Directors and a former member of the ASCPT Editorial Board. She has served on NIH peer review committees for more than sixteen years during her

career and served on the Advisory Panel on Geriatrics, USP Pharmacopeial Convention, Inc., and on the Institute of Medicine's Committee on Pharmacokinetics and Drug Interactions in the Elderly.
Dr. Schwartz's research has focused on understanding drug responses to medications and especially factors leading to altered drug responses in older people. She has utilized laboratory and clinical investigations to investigate changes in cardiovascular function and rhythm, the autonomic system, and drug pharmacokinetics and pharmacodynamics in models of healthy aging and in patient populations including the frail elderly. Her work has improved the understanding of age and disease-related effects that can lead to improved use of therapeutic medications. She has also elucidated gender differences in drug metabolism and responses that are especially pertinent in the clinical care of patients. Working within both the research and clinical worlds has provided the opportunity to translate research findings into clinical practice and to train and mentor others. Her goal of improving medication therapy for older patients has also led to efforts beyond research in the form of contributing to textbooks for health care professionals, creating on-line educational content for health care professionals, and writing on medication and health- related issues in the lay press.

MIRIAM MOBLEY SMITH, PHARM.D., received her BS in Pharmacy from the University of Michigan in 1978. She went on to earn her PharmD from the University of Illinois and completed a pharmacy practice residency at Sinai Hospital of Detroit. Dr. Mobley Smith is currently the Interim Dean and Visiting Professor at Northeastern University Bouvé College of Health Sciences School of Pharmacy; she is also presently an independent pharmacy and healthcare consultant. She has held numerous leadership positions during her career, notably serving as the Director of Strategic Alliances for the Pharmacy Technician Certification Board in Washington, D.C. She spent twelve years as a clinical faculty member and eventually the Director of Experiential Education at the University of Illinois at Chicago College of Pharmacy. Dr. Mobley Smith spent eight years at the Chicago State University College of Pharmacy, ultimately servings as Dean until her departure in 2015. She has also served leadership positions in numerous professional pharmacy organizations. She was chair for the American Association of Colleges of Pharmacy Professional Affairs Committee, vice-chair of the Illinois State Board of Pharmacy, chair of the American Society of Health-System Pharmacists Council on Education and Workforce Development, a member of the Institute of Medicine Committee on the Future Healthcare Workforce for Older Americans, Pharmacy Workforce Center, Inc., Technical Advisory Panel, and on the Professional Examination Service Board of Directors. Dr. Mobley Smith has received numerous grants, professional and civic awards, including recognition as a 2013 Fellow of the American Society of Health-System Pharmacists, the 2012 National Pharmaceutical Association's Chauncey I. Cooper Award in recognition of sustained and distinguished professional service, and the 2013 Illinois Pharmacists Association Pharmacist of the Year.

ROBERT TEMPLE, M.D., serves as CDER's Deputy Center Director for Clinical Science and Senior Advisor in the Immediate Office of the Office of New Drugs (OND). As the senior advisor, Bob is a consultant to the OND director and other FDA officials on matters related to clinical program objectives. Dr. Temple received his medical degree from the New York University School of Medicine in 1967. In 1972, he joined CDER as a
Medical Officer in the Division of Metabolic and Endocrine Drug Products. He later moved into the position of Director of the Division of Cardio-Renal Drug Products. Before becoming Senior Advisor in OND, Dr. Temple was the Acting Deputy Director of OND's Office of Drug Evaluation-I (ODE-I) which is responsible for the regulation of cardiovascular and renal, neurology, and psychiatry drug products. He served in this capacity for more than 23 years—since the office's establishment in 1995.

JONATHAN WATANABE, PHARM.D., PH.D., M.S., seeks to determine factors that jeopardize appropriate medication use. Dr. Watanabe practices in Senior Care Pharmacy and focuses on outcomes in older adults and residents of extended care facilities. He has completed investigations on 1) the role of adherence on surrogate markers for chronic conditions; 2) the effect of copayment and copayment pricing on adherence; 3) the impact of polypharmacy on adherence; 4) the role of pharmacy benefit on health services; 5) methods used in health services research applying large national data. Collaborating with an interdisciplinary care team, Professor Watanabe initiated longitudinal assessments of outcomes in Post-Acute Care Settings and characterized those at risk for poor adherence and compromised health outcomes in Veterans with chronic diseases. He has served as an invited speaker at several international forums devoted to improving care for seniors in long term care settings and provided

presentations on pharmacy benefit and evaluation at the National Academy of Sciences. He currently trains students, post-docs, and practitioners in multiple disciplines in clinical research and post-acute care. Professor Watanabe is a clinical consultant for the Program of All-inclusive Care for the Elderly (PACE) Clinic in San Diego, CA and the Villa Pomerado Skilled Nursing Facility in Poway, CA. He is an investigator on the Health Resources and Services Administration funded San Diego Geriatrics Workforce Enhancement Program Grant. Dr. Watanabe was the inaugural recipient of the University of Washington/Allergan Health Economics and Outcomes Research Fellowship. Watanabe serves as the advisor for the Academy of Managed Care Pharmacy student chapter. Dr. Watanabe serves the CA State Legislature as a faculty content expert for the California Health Benefits Review Program. He serves as a member of the advisory group on pain assessment and management standards for long-term care organizations for The Joint Commission. He was a contributing author to the Making Medicines Affordable consensus report from the National Academies of Sciences, Engineering, and Medicine. He is a Board Certified Geriatric Pharmacist (BCGP).

BARBARA ZAROWITZ, PHARM.D., previously served as vice president for pharmacy care management at Henry Ford Health System; vice president and chief clinical office at Omnicare, Inc; chief clinical officer for long-term care at CVS Health; and adjunct professor of pharmacy practice at the College of Pharmacy and Health Sciences, Wayne State University and the University of Michigan. She created clinical programs for Omnicare, Inc., subsequently a CVS Health Company, and developed strategies and tactics to manage drug utilization, including disease management and formulary management to optimize clinical outcomes. Omnicare provided pharmacy care for 1.4 million older adults living in long-term care facilities. Her expertise has been chronicled through attainment of board certification in pharmacotherapy (BCPS) and geriatric pharmacotherapy (BCGP). She has been recognized as a fellow of the Society of Critical Care Medicine, American College of Clinical Pharmacy, and the American Society of Consultant Pharmacists. Over her career she has published 10 book chapters; 125 peer-reviewed articles and over 120 abstracts, editorials, letters and columns. Dr. Zarowitz is a frequent speaker at national research and society meetings. She has received 11 leadership, research, teaching and practice awards, including the 2015 George F. Archambault Award for outstanding contributions to consultant and senior care pharmacy.

Drug Research and Development for Adults Across the Older Age Span

A Virtual Workshop

Speaker Biographies

SPEAKERS

AMY ABERNETHY, M.D., PH.D., is an oncologist and internationally recognized clinical data expert and clinical researcher. As the Principal Deputy Commissioner of Food and Drugs, Dr. Abernethy helps oversee FDA's day-to day functioning and directs special and high-priority cross-cutting initiatives that impact the regulation of drugs, medical devices, tobacco and food. As acting Chief Information Officer, she oversees FDA's data and technical vision, and its execution. She has held multiple executive roles at Flatiron Health and was professor of medicine at Duke University School of Medicine, where she ran the Center for Learning Health Care and the Duke Cancer Care Research Program. Dr. Abernethy received her M.D. at Duke University, where she did her internal medicine residency, served as chief resident, and completed her hematology/oncology fellowship. She received her Ph.D. from Flinders University, her B.A. from the University of Pennsylvania and is boarded in palliative medicine.

HEATHER ALLORE, PH.D., is focused on issues related to the design and analysis of trials and studies of multifactorial geriatric health conditions, especially among persons with Alzheimer's Disease and related dementia. Several projects focus upon health disparities of older adults. She developed a sub-discipline of biostatistics that focus on training and methodological development in geriatrics called "Gerontologic Biostatistics." This discipline trains biostatisticians for conducting collaborative research with clinical investigators in geriatrics and gerontology and provides the basis for the development of new statistical methodologies.

SCOTT BERRY, M.S., PH.D., is President and a Senior Statistical Scientist at Berry Consultants, LLC. He earned his MS and PhD in statistics from Carnegie Mellon University and was an Assistant Professor at Texas A&M University before co-founding Berry Consultants in 2000. He has led Berry Consultants to be widely regarded as the premier Bayesian consulting company in the world. Since 2000, he has been involved in the design of hundreds of Bayesian adaptive clinical trials of pharmaceuticals and medical devices and has become an opinion leader in the field of Bayesian adaptive clinical trials. Some of these trials have been groundbreaking trial designs, setting new standards for innovation and flexibility in trial design. These include the trials supporting the first fully Bayesian approval by the center for drug evaluation of the United States FDA (Pravastatin-Aspirin combination) and the statistical design for Time Magazine's #2 Medical Breakthrough of 2007 (Veridex's GeneSearch BLN Assay).

N. SETH BERRY, PHARMD, is a Senior Director in the Decision Sciences group at IQVIA. He obtained his PharmD from the University of Missouri-Kansas City, School of Pharmacy, completed a 2-year Post-Doctoral Pharmacokinetic / Pharmacodynamics (PK/PD) Fellowship with the University of North Carolina, and a 2-year Pharmacometrics Fellowship with the Center for Drug Development Science at Georgetown University. Since joining IQVIA (formerly Quintiles) in 2004, Dr. Berry's research has focused primarily on performing population pharmacokinetic- pharmacodynamic modeling and clinical trial simulations to optimize dose selection and study design. His work also centers on the development of precision dosing applications for individualizing pharmacotherapy, building high performance computing solutions, and authoring R packages for non-linear mixed effects modeling. Dr. Berry has numerous publications and presentations in the pharmacometrics discipline, while also mentoring students, fellows, and colleagues through various workshops and training seminars.

CIANTEL BLYLER, PHARMD, CHC, is a clinical research pharmacist at Cedars-Sinai Medical Center in Los Angeles, CA. Dr. Blyler earned a Doctor of Pharmacy degree from the Eshelman School of Pharmacy at the University of North Carolina-Chapel Hill and completed her clinical work at Duke University Health System. After graduation she worked as a clinical pharmacist at Senior PharmAssist, a non-profit based in Durham, NC, where she provided free medication therapy management (MTM) services to low-income, dual-eligible geriatric patients as part of an initiative with Community Care of North Carolina. Upon moving to the West Coast, she managed an independent specialty pharmacy in Beverly Hills, CA before joining Cedars-Sinai in 2016. There she served as one of two full-time clinical research pharmacists on an NIH/NHLBI funded randomized trial that investigated a novel community-based approach to treat hypertension in African American male patients involving pharmacists, barbers and physicians. The highly successful intervention was recognized by the Clinical Research Forum as the 'Top Research Achievement of the Year. Dr. Blyler has spoken about this work at multiple national meetings including ASN Kidney Week (2019), AHA Hypertension Sessions (2018) and the National Medical Association meeting (2016). She is a co-author on publications in the *New England Journal of Medicine*, *Circulation*, and *The Journal of the American Heart Association* and has been covered in TIME Magazine, The Washington Post and CNN. She is a certified hypertension clinician and a member of the Target BP advisory board – a collaboration between AMA/AHA. Her professional interests include health disparities research, community-based practice, cardiology and geriatrics.

ROBERT CALIFF, M.D., MACC, is the Head of Clinical Policy and Strategy for Verily Life Sciences and Google Health for Verily and Google Health. Prior to this Dr. Califf was the vice chancellor for health data science for the Duke University School of Medicine; director of Duke Forge, Duke's center for health data science; and the Donald F. Fortin, MD, Professor of Cardiology. He served as Deputy Commissioner for Medical Products and Tobacco in the U.S. Food and Drug Administration (FDA) from 2015-2016, and as Commissioner of Food and Drugs from 2016-2017. A nationally and internationally recognized leader in cardiovascular medicine, health outcomes research, healthcare quality, and clinical research, Dr. Califf is a graduate of Duke University School of Medicine. Dr. Califf was the founding director of the Duke Clinical Research Institute and is one of the most frequently cited authors in biomedical science.

BEVERLY CANIN is a breast cancer survivor, is a former member of the board of directors of Breast Cancer Action, a national organization dedicated to inspiring and compelling societal changes necessary to end the breast cancer epidemic; president of Breast Cancer Options, a grassroots support, education and advocacy organization serving six counties in the Hudson Valley; patient advocate member of the Cancer and Aging Research Group (CARG), seeking to improve cancer care for older adults with cancer and chair of Stakeholders for Care in Oncology and Research for our Elders (SCOREboard), a patient and caregiver advisory group

STEVEN CHEN, PHARM.D., FASHP, FCSHP, FNAP, is an Associate Professor and Associate Dean for Clinical Affairs at the USC School of Pharmacy and the William A. Heeres and Josephine A. Heeres Chair in Community Pharmacy. He received his Pharm.D. from USC and completed a USC-affiliated residency in 1990. Before joining the faculty at USC in 1998, he was a quality assurance pharmacist and clinical pharmacy coordinator at the Department of Veterans Affairs. Dr. Chen has received honorary fellowships from the California Society of Health-System Pharmacists (CSHP), the American Society of Health-System Pharmacists (ASHP) and the National Association of Practitioners. He is a member of research and practice teams that have been awarded the Best Practices Award from ASHP twice (2002 and 2008), the American Pharmacists Association Pinnacle Award (2007) and the American Association of Colleges of Pharmacy Inaugural Community Transformative Award (2009). He received the USC School of Pharmacy Outstanding Alumnus of the Year Award and the American Pharmacists Association Pinnacle Award for individual career achievement in 2013. In 2015, he received the American Heart Association Multicultural Initiatives Award, the Schweitzer Fellowship Leadership Award and the CSHP Innovator Award. He was recognized by the Center for Medicare and Medicaid Services in 2016 for his collaboration with The Partnership for Public Service that contributed to 87,000 lives saved, 2.1 million fewer patient harms and $19.8 billion in cost savings. In 2017, Dr. Chen received a third Pinnacle Award through his partnership with the Center for Medicare and Medicaid Innovation, and in 2018, he received the Pharmacist of the Year Award from CSHP. Dr. Chen has received multiple teaching awards from USC students and residents.

STEVEN R. CUMMINGS, M.D., is a Professor of Medicine, Epidemiology, and Biostatistics Emeritus at UCSF. Executive Director of the San Francisco Coordinating Center. He designed and led numerous clinical trials including pivotal trials of therapies for FDA approvals. He co-founded the UCSF Clinical Research Training Program and is a co-author of Designing Clinical Research (Williams and Wilkins). He is an expert in clinical research on aging, leading several large studies of the biological basis of human aging and biomarkers of aging outcomes and has served on the NIA National Advisory Council on Aging. He has over 600 publications and was elected to the National Academy of Medicine for his accomplishments in clinical research. Dr. Cummings is also a pioneer in, 'direct-to-participant' AKA 'Virtual' AKA Home-based clinical trials and interactive e-consent. Pertinent to this conference, Dr. Cummings leads the NIA-funded TOPAZ trial, a randomized trial of an IV treatment for osteoporosis in patients age 65 or older with Parkinson's disease, that is being conducted entirely from patients' homes.

KATHERINE DAWSON, M.D., senior vice president, Therapeutics Development Group started at Biogen in 2004 from Massachusetts General Hospital, where she trained and was as an attending Physician in the Neuromuscular Group. During her initial 9 years in clinical development, Kate worked on Tysabri, Avonex, Plegridy, and brought Tecfidera through Phase 3 trials and approval in the US and EU. For the next 4 years, she worked on the Medical Affairs leadership team, first as VP, Global Medical Neurology and then VP, US Medical. In June Kate transitioned back to Development and her current role. Kate received her Medical Degree from Albert Einstein College of Medicine in New York graduating AΩA honors. She is currently the Chair of the Biogen Foundation, our non-profit organization, and proudly dates her participation in WIN to its earliest days.

CHRISTINA FRIEDRICH, PH.D., brings over 17 years of leadership expertise in applying mathematical models of biologic/physiologic systems for overcoming development challenges faced by pharmaceutical and consumer product companies. At Rosa (and previously at Entelos, Inc.), she has developed significant experience in the fields of diabetes, blood disorders, CNS disorders, oncology, immune-oncology, rheumatoid arthritis, respiratory diseases, skin diseases, gastrointestinal disorders, and other immune system dysfunctions and inflammatory processes. While at Rosa, Dr. Friedrich developed and published the first peer-reviewed journal article on the qualification of mechanistic mathematical models. Before Rosa, Dr. Friedrich was the Director of Core Product Development at Entelos, Inc., the first –generation leader in PhysioPD-style models. Dr. Friedrich has spearheaded numerous modeling methodologies and contributed to foundational patents, including on the use of virtual patients and populations to explore biological variability and uncertainty, and on the identification of biomarkers. Dr. Friedrich completed her BS at MIT and a PhD in Management Science and Engineering at Stanford University.

JASON KARLAWISH, M.D., is a physician and writer. He is a Professor of Medicine, Medical Ethics and Health Policy, and Neurology at Penn and cares for patients at the Penn Memory Center (www.pennmemorycenter.org), which he co-directs. His research focuses on issues at the intersections of bioethics, aging and the neurosciences. He leads the Penn Program for Precision Medicine for the Brain (P3MB). He has investigated the development and translation of Alzheimer's disease treatments and biomarker-based diagnostics, informed consent, quality of life, research and treatment decision making, and voting by persons with cognitive impairment and residents of long term care facilities. P3MB has developed standards for Alzheimer's disease biomarker disclosure and investigated the clinical impacts of this knowledge on persons and their families.

GEORGE A. KUCHEL, M.D., F.R.C.P., is professor of medicine, Travelers Chair and Director of the University of Connecticut Center on Aging. This center brings together clinicians, educators, clinical investigators, basic scientists and researchers conducting health outcome/population studies who are all committed to the discovery of strategies for promoting independence and health in old age. Dr. Kuchel's research funded by NIH and other agencies is focused on Precision Gerontology, an approach designed to help older adults remain and healthy independent in a manner that is both individualized and guided by mechanisms. To that end, his work focused on potentially-targetable pathways contributing to functional declines involving host defense, mobility, continence and cognition.

ROSANNE M. LEIPZIG, M.D., PH.D., is an internationally recognized leader in the field of geriatrics and has received numerous awards for her work, including the American College of Physicians Richard and Hinda Rosenthal Foundation Award, Joy McCann Scholar, Dennis W. Jahnigen Memorial Award from the American Geriatrics Society (2008), Brookdale National Fellowship in Geriatric Medicine, and the Paula Ettelbrick Community Service Award from Services & Advocacy for GLBT Elders (2014). She also received the Jacobi Medallion, one of the highest honors from the Mount Sinai Health System (2016). She is the editor-in-chief of *Focus on Healthy Aging*, a monthly newsletter. Dr. Leipzig has published over 100 articles and published two groundbreaking books on geriatrics. During her career as a doctor, she has been named as one of the Best Doctors in America (Woodward/White, Inc.), Best Doctors in the New York Metro Area (The Castle Connolly Guide), America's Top Physicians (Consumers Research Council of America), a *New York Times* SuperDoc, and one of *New York* Magazine's Top Doctors for Geriatric Medicine. She has appeared on *The Today Show*, *CBS Evening News*, *CBS Sunday Morning*, CNN, and AARP Webinars, and has been published in *TIME* magazine, the *New York Times*, the *Wall Street Journal*, Bottom Line Health, *AARP The Magazine*, and American Medical News, among others. Dr. Leipzig is currently writing a book about what to expect as you age, which will provide valuable advice and unparalleled expertise for everyone who is in the process of aging.

STUART M. LICHTMAN, M.D., is an Attending Physician and Member, Memorial Hospital for Cancer and Allied Diseases, Member, Memorial Sloan-Kettering Cancer Center and Professor of Medicine, Weill Cornell Medical College. He is a member of the 65+ Clinical Geriatrics Program and Gynecologic Oncology Disease Management Team at the Center. He has been on the Board of Directors and Treasurer of SIOG since 2010 and has participated in multiple taskforces (Chemotherapy, as chair, Geriatric Assessment, Renal Dysfunction, Lymphoma, Oral Chemotherapy), US National Representative and Scientific Chair of the 2011 meeting. He has been a participant in the Alliance for Clinical Trials in Oncology (formerly CALGB) as a member of the Pharmacology and Experimental Therapeutics Committee (1990-2008), the Cancer in the Elderly Committee (1995-present). His work also included the Scientific Advisory Board of the Geriatric Oncology Consortium, the Elderly Taskforce of the Gynecologic Oncology Group, Cancer and Aging Research Group and the NCCN Guidelines Taskforce for the treatment, Evaluation of Older Women with Breast Cancer, Editorial Board of the Journal of Geriatric Oncology, External Advisory Board of the University of Iowa Cancer Center, Governing Board Cancer and the Kidney International Network. He has been a member of ASCO since 1988 and have been an active participant by serving on the Clinical Practice Committee, Scientific Program Committee, Geriatric Oncology Special Interest Group, an invited speaker at Educational Sessions, ASCO University, ASCO Post and a faculty member of the ASCO/AACR Vail Clinical Trials workshop for five sessions on the topic of special populations.

LAUREL J. PRACHT represents the patient perspective as protocols evolve into research concepts through her membership in a nationwide cooperative group. As lead patient advocate for a cancer prevention clinical trial, she assisted with the accrual of participants and direct support of the trial. As a member of the National Cancer Institute Symptom Management and Health-Related Quality of Life Steering Committee, her goal in reviewing concepts is to include suggested shared decision-making materials and adverse events to ensure patient-centeredness is a central goal of research. As a PCORI Ambassador, Pracht participated in a site visit to the Zuni Nation in Zuni, New Mexico, for an ongoing clinical trial. There, she reviewed a paper that was later published in a scientific journal. She became a PCORI Ambassador after cycling off the inaugural Patient Engagement Advisory Panel and anticipates that she will remain involved in the Ambassador program. Pracht received her Bachelor of Science at the University of Nebraska. She has also received Research Advocacy Network Symposium advocate training, and the American Society of Clinical Oncology Patient Advocate Training.

JOHN POWERS, M.D., is the Senior Medical Scientist at Leidos Biomedical Research in support of the Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health and an Associate Clinical Professor of Medicine at George Washington University School of Medicine in Washington, D.C. Dr. Powers' research interests are in clinical trials in a variety of infectious diseases with a focus on research methodology and patient centered outcomes, and measuring the safety and effectiveness of medical interventions. Dr. Powers also has a research interest in antimicrobial resistance and appropriate antimicrobial use. He was the co-chair of the United States Inter-Agency Task Force on Antimicrobial Resistance and is a member of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance. He received medical training in Internal Medicine at Temple University School of Medicine and sub-specialty training in Infectious Diseases at the University of Virginia.

ERIKA RAMSDALE M.D., is a dual-trained and board-certified geriatrician and oncologist at the University of Rochester Wilmot Cancer Institute. Her research involves the development and implementation of care delivery interventions to decrease polypharmacy in older adults with cancer. She has authored multiple peer-reviewed articles about polypharmacy and association with adverse outcomes within this population, and she is currently studying the role of virtual, pharmacist-led “deprescribing” interventions for these patients. She also has interest and expertise in the role of information technology in the care of older adults with cancer, including the development of digital approaches to capturing patient-reported data remotely. She received her BS and MD from the University of Kansas; she completed residency and fellowships in Hematology/Oncology and Geriatric Medicine at the University of Chicago. She is a current graduate student at the Goergen Institute for Data Science at the University of Rochester.

STEVEN ROTHSCHILD, M.D., is a family physician, educator and researcher in the Departments of Preventive Medicine and Family Medicine at Rush University. In addition to a 30-year clinical career focused on providing primary medical care to the medically underserved, he is an established researcher focusing on health services research, chronic illness self-management, and community- and team-based approaches to addressing health disparities. As an expert in community based participatory research, he has been an invited faculty member for the NIH Summer Institute on Design and Conduct of Randomized Clinical Trials involving behavioral interventions, sponsored by the Office of Behavioral and Social Sciences Research. As a faculty member at Rush, he has been recognized by students for his teaching excellence and humanism. He is also the co-convener of Rush's interprofessionalism interest group, bringing together over 30 clinicians and faculty from across the Medical Center to improve team-based education, research and patient care. Rothschild serves on the Chicago Board of Health, the advisory committee for the Albert Schweitzer Fellowship Program, and the Health and Medicine Policy Research Group, where he is vice president.

HARPREET SINGH, M.D., is a medical oncologist at the U.S. Food and Drug Administration (FDA) with an emphasis on cancer in older adults. She continues to see patients in a prostate cancer multidisciplinary clinic at the National Cancer Institute. She is native of Los Angeles and graduated from the University of California, San Diego

before completing her medical degree at the University of Southern California Keck School of Medicine. She completed her internal medicine residency and geriatrics fellowship at the Los Angeles County + University of Southern California Medical Center. She then went on to the National Cancer Institute at the National Institutes of Health for a fellowship in medical oncology. She focused on tumor immunology and biology, including cancer vaccines and immunotherapy clinical trials. Dr. Singh joined the FDA as a medical officer in 2015, where she quickly established herself as a leader in geriatric oncology.

RAJESHWARI SRIDHARA PH.D., is director of the Division of Biometrics V in the Office of Biostatistics which supports the Office of Hematology Oncology Products in the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration (FDA). Dr. Sridhara has contributed to the understanding of statistical issues unique to the area of oncology disease such as evaluation and analysis of time to disease progression. Her research interests include evaluation of surrogate markers and design of clinical trials. She has organized, chaired and given invited presentations at several workshops, and has worked on regulatory guidance documents across multiple disciplines. She has published extensively in refereed journals and presented at national and international conferences. She is an elected fellow of the American Statistical Association. Prior to joining FDA, Dr. Sridhara was a project statistician for the AIDS vaccine evaluation group at EMMES Corporation, and was an assistant professor at the University of Maryland Cancer Center.

SUSAN STRONG, M.A., works with local organizations including CU, as an Entrepreneur in Residence; SAGE in Boulder and Fort Collins helping early stage companies connect with teams of expert advisors; mentoring women-led companies with MergeLane; and as an Innosphere program manager helping with startup and scaleup. Susan is the principal of The Strong Group, a high technology consulting firm focusing on business development, sales and marketing and market research. Susan served in marketing executive positions at public and private companies including Agilent Technologies, Dionex, Dharmacon, GeneData and Genomica. Susan advises the SJSU Masters in Biotechnology program. Her degrees are from Penn State (BS Chemistry) and University of North Carolina at Chapel Hill (MS Analytical Chemistry).

JONATHAN TOBIN, PH.D., FACE, FAHA, is the President/CEO of Clinical Directors Network Inc. (CDN) and Co-Director of Community Engaged Research at The Rockefeller University Center for Clinical and Translational Science, teaches the fundamentals of getting started in collaborative community-based research to a live audience of family health center clinicians. A board certified epidemiologist, Dr. Tobin leads the audience through the key concepts and importance of translational research, the basic epidemiological skills necessary for the development and understanding and interpretation of community-based research, and how epidemiological measures relate to clinical research and clinical practice. Topics covered include measures of morbidity and mortality (prevalence and incidence), causal inference, data collection methods, validity, reliability, and working with human subjects. He closes with a practical exercise that assists with conceptualizing and developing research aims and questions.

ERIC TOPOL, M.D.,is a professor in the Department of Molecular Medicine, is an executive vice president at Scripps Research and the founder and director of the Scripps Research Translational Institute (previously Scripps Translational Science Institute). His work melds genomics, big data, and both information technologies and digital health technologies to advance the promise of personalized medicine. In 2016, the National Institutes of Health awarded Dr. Topol a $207 million grant to lead a significant part of the *All of Us* Research Program, a long-term research endeavor aimed at understanding how a person's genetics, environment and lifestyle can guide approaches to preventing or treating disease. Topol has published over 1,100 peer-reviewed articles, and his more than 200,000 citations place him among the top 10 most cited researchers in medicine as measured by Thomson Reuters' Institute for Scientific Information. Widely viewed as one of the most influential physician leaders in the country, Topol is the author of two bestselling books on the future of medicine: *The Creative Destruction of Medicine* and *The Patient Will See You Now*. His next book, *Deep Medicine*, focused on artificial intelligence, will be published in 2019.
.

ABOUT THE FORUM

The Forum on Drug Discovery, Development, and Translation of the National Academies of Sciences, Engineering, and Medicine was created in 2005 by the Board on Health Sciences Policy to provide a unique platform for dialogue and collaboration among thought leaders and stakeholders in government, academia, industry, foundations, and patient advocacy with an interest in improving the system of drug discovery, development, and translation. The Forum brings together leaders from private sector sponsors of biomedical and clinical research, federal agencies sponsoring and regulating biomedical and clinical research, the academic community, and patients, and in doing so serves to educate the policy community about issues where science and policy intersect. The Forum convenes several times each year to identify, discuss, and act on key problems and strategies in the discovery, development, and translation of drugs. To supplement the perspectives and expertise of its members, the Forum also holds public workshops to engage a wide range of experts, members of the public, and the policy community. The Forum also fosters collaborations among its members and constituencies. The activities of the Forum are determined by its members, focusing on the major themes outlined below.

INNOVATION AND THE DRUG DEVELOPMENT ENTERPRISE

Despite exciting scientific advances, the pathway from basic science to new therapeutics faces challenges on many fronts. New paradigms for discovering and developing drugs are being sought to bridge the ever-widening gap between scientific discoveries and translation of those discoveries into life-changing medications. There is also increasing recognition of the need for new models and methods for drug development and translational science, and "precompetitive collaborations" and other partnerships, including public–private partnerships, are proliferating. The Forum offers a venue to discuss effective collaboration in the drug discovery and development enterprise and also hosts discussions that could help chart a course through the turbulent forces of disruptive innovation in the drug discovery and development "ecosystem."

Key gaps remain in our knowledge about science, technology, and methods needed to support drug discovery and development. Recent rapid advances in innovative drug development science present opportunity for revolution- ary developments of new scientific techniques, therapeu- tic products, and applications. The Forum provides a venue to focus ongoing attention and visibility to these important drug development needs and facilitates exploration of new approaches across the drug development lifecycle. The Forum has held workshops that have contributed to the defining and establishment of regulatory science and have helped inform aspects of drug regulatory evaluation.

CLINICAL TRIALS AND CLINICAL PRODUCT DEVELOPMENT

Clinical research is the critical link between bench and bedside in developing new therapeutics. Significant infrastructural, cultural, and regulatory impediments challenge efforts to integrate clinical trials into the health care delivery system. Collaborative, cross-sector approaches can help articulate and address these key challenges and foster systemic responses. The Forum has convened a multiyear initiative to examine the state of clinical trials in the United States, identify areas of strength and weakness in our current clinical trial enterprise, and consider transformative strategies for enhancing the ways in which clinical trials are organized and conducted. In addition to sponsoring multiple symposia and workshops, under this initiative, the Forum is fostering innovative, collaborative efforts to facilitate needed change in areas such as improvement of clinical trial site performance.

INFRASTRUCTURE AND WORKFORCE FOR DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Considerable opportunities remain for enhancement and improvement of the infrastructure that supports the drug development enterprise. That infrastructure, which includes the organizational structure, framework, systems, and resources that facilitate the conduct of biomedical science for drug development, faces significant challenges. The science of drug discovery and development, and its translation into clinical practice, is cross-cutting and multidisciplinary. Career paths can be opaque or lack incentives such as recognition, career advancement, or financial security. The Forum has considered workforce needs as foundational to the advancement of drug discovery, development, and translation. It has convened workshops examining these issues, including consideration of strategies for developing a discipline of innovative regulatory science through the development of a robust workforce. The Forum will also host an initiative that will address needs for a workforce across the translational science lifecycle.

Forum on Drug Discovery, Development, and Translation

Robert Califf (Co-Chair)
Verily Life Sciences and Google Health

Gregory Simon (Co-Chair)
Kaiser Permanente Washington Health Research Institute

Amy Abernethy
Office of the Commissioner, U.S. FDA

Christopher Austin
National Center for Advancing Translational Sciences, NIH

Linda Brady
National Institute of Mental Health, NIH

Barry Coller
The Rockefeller University

Thomas Curran
Children's Mercy, Kansas City

Richard Davey
National Institute of Allergy and Infectious Diseases, NIH

Katherine Dawson
Biogen

James Doroshow
National Cancer Institute, NIH

Jeffrey Drazen
New England Journal of Medicine

Steven Galson
Amgen Inc.

Carlos Garner
Eli Lilly and Company

Julie Gerberding
Merck & Co., Inc.

Anne Heatherington
Takeda Pharmaceuticals

Deborah Hung
Harvard Medical School

Esther Krofah
FasterCures/Milken Institute

Lisa LaVange
University of North Carolina Gillings School of Global Public Health

Ross McKinney Jr.
Association of American Medical Colleges

Joseph Menetski
Foundation for the NIH

Arti Rai
Duke University School of Law

Kelly Rose
Burroughs Wellcome Fund

Susan Schaeffer
The Patients' Academy for Research Advocacy

Joseph Scheeren
Critical Path Institute

Anantha Shekhar
University of Pittsburgh School of Medicine

Jay Siegel
Retired

Ellen Sigal
Friends of Cancer Research

Lana Skirboll
Sanofi

Amir Tamiz
National Institute of Neurological Disorders and Stroke, NIH

Ann Taylor
AstraZeneca

Pamela Tenaerts
Clinical Trials Transformation Initiative

Joanne Waldstreicher
Johnson & Johnson

Jonathan Watanabe
University of California Irvine Samueli College of Health Sciences

Carrie Wolinetz
Office of Science Policy, NIH

Alastair Wood
Vanderbilt University

Janet Woodcock
Center for Drug Evaluation and Research, U.S. FDA

Project Staff

Carolyn Shore, Ph.D.
Forum Director

Jennifer Hinners, M.D., M.P.H.
Program Officer

Amanda Wagner Gee, M.S.
Program Officer

Eeshan Khandekar, M.Sc.
Associate Program Officer

Melvin Joppy
Senior Program Assistant

For more information, please visit:

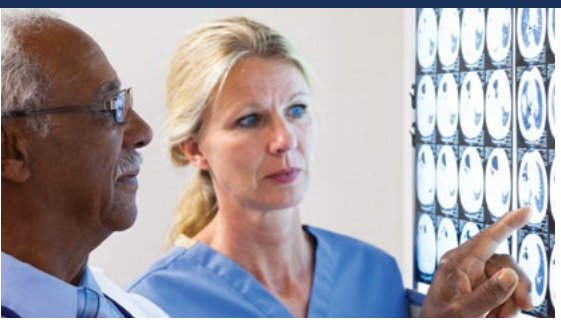
NATIONALACADEMIES.ORG/DRUGFORUM

Health and Medicine Division
Board on Health Sciences Policy

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

NATIONAL CANCER POLICY FORUM

ABOUT THE FORUM



The National Cancer Policy Forum serves as a trusted venue in which experts can identify emerging high-priority policy issues in cancer research and care and work collaboratively to examine those issues through convening activities focused on opportunities for action. The Forum provides a continual focus within the National Academies on cancer, addressing issues in science, clinical medicine, public health, and public policy that are relevant to the goal of reducing the cancer burden, through prevention and by improving the care and outcomes for those diagnosed with cancer. Forum activities inform stakeholders about critical policy issues through published reports and often inform consensus committee studies. The Forum has members with a broad range of expertise in cancer, including patient advocates, clinicians, and basic, translational, and clinical scientists. Members represent patients, federal agencies, academia, professional organizations, nonprofits, and industry.

The Forum has addressed a wide array of topics, including:

- enhancing collaborations to accelerate research and development;
- improving the quality and value of care for patients who have been diagnosed with or are at risk for cancer;
- developing tools and technologies to enhance cancer research and care; and
- examining factors that influence cancer incidence, mortality, and disparities.

Opportunities and Challenges for Using Digital Health Applications in Oncology

July 13-14, 2020

The National Cancer Policy Forum, in collaboration with the Forum on Cyber Resilience, is convening a workshop to examine the role of digital health applications in oncology research and care. Workshop speakers will discuss topics such as:

- Exemplars of novel digital health applications, including an emphasis on patient-facing technologies
- Regulatory priorities
- Ethical, security, governance, and payment considerations
- Opportunities to improve data availability and use in EHRs and large databases
- Participant reactions and recommendations for the path forward

Workshop website: https://www.nationalacademies.org/event/07-13-2020/opportunities-and-challenges-for-using-digital-health-applications-in-oncology-a-workshop

WORKSHOP SERIES ON OLDER ADULT POPULATIONS

Collaborative series convened by:
National Cancer Policy Forum
Forum on Drug Discovery, Development, and Translation
Forum on Aging, Disability, and Independence

Drug Research and Development for Adults Across the Older Age Span

August 5-6, 2020

There is a lack of evidence about the appropriate use of drugs in older adult populations, which hampers decision making about how to optimize care for older adults. A major contributor to this evidence gap is that older adults are vastly underrepresented in clinical trials. This workshop will convene stakeholders to discuss the challenges and opportunities in drug research and development for older adult populations, including the barriers that impede safety and efficacy studies in these populations. Workshop presentations and discussions will highlight opportunities to better engage older adults in clinical research and strategies to generate evidence-based prescribing information for older adult populations.

Workshop website: https://www.nationalacademies.org/event/08-05-2020/drug-research-and-development-for-older-adult-populations-a-workshop

Improving the Evidence Base for Treatment Decision Making for Older Adults with Cancer

Date TBD

Older adults represent the majority of patients diagnosed with cancer and the majority of cancer-related deaths. However, the evidence base to guide treatment decision making among older adults with cancer is sparse, primarily because older adults are underrepresented in clinical trials, and trials designed specifically for older adults are rare. This workshop will examine challenges and opportunities to improve the evidence base for treating older adults with cancer, including clinical trial design and analysis strategies, incorporation of geriatric assessments and patient reported outcomes in clinical trials, and the potential for real world data collection from clinical practice to fill evidence gaps.

Workshop website forthcoming

Addressing the Adverse Consequences of Cancer Treatment

November 9-10, 2020

Cancer care is associated with significant physical, mental, and socioeconomic consequences. This workshop will examine the array of short- and long-term toxicities and adverse effects that patients may experience as a result of cancer treatment and consider opportunities to improve quality of life for cancer survivors and their families. Workshop presentations and discussions will focus on topics such as:

- Strategies to better accrue data on short- and long-term effects of cancer and cancer treatment
- Opportunities to redesign cancer treatment to reduce short- and long-term toxicities without compromising treatment effectiveness
- Patient engagement in treatment decision-making and tools to facilitate understanding of risk/benefit tradeoffs
- System-level interventions and best practices for prevention, surveillance, and mitigation of the adverse effects of cancer treatment
- Opportunities to overcome the challenges that prevent uptake and dissemination of evidence-based approaches to address the adverse effects of cancer treatment.

Workshop website: https://www.nationalacademies.org/event/11-09-2020/addressing-the-adverse-consequences-of-cancer-treatment-a-workshop

Advancing Progress in the Development and Implementation of Effective, High-Quality Cancer Screening

Evidence-based screening approaches have contributed to improved patient outcomes, and research continues to develop and evaluate potential new strategies for early cancer detection. However, there are a number of challenges related to ensuring effective, high-quality screening. This workshop examined current issues in cancer screening, including principles and methods of cancer screening; key gaps in the evidence base for cancer screening, as well as statistical and methodologic challenges; validation and implementation of novel screening technologies; patient access to high-quality cancer screening and follow-up care; and shared decision making and communication in cancer screening.

Workshop videos and presentation files: https://www.nationalacademies.org/event/03-02-2020/advancing-progress-in-the-development-and-implementation-of-effective-high-quality-cancer-screening-a-workshop

Applying Big Data to Address the Social Determinants of Health in Oncology

This workshop, held in collaboration with the Committee on Applied and Theoretical Statistics, examined social determinants of health (SDOH) in the context of cancer and considered opportunities to effectively leverage big data to improve health equity and reduce disparities. Presentations and discussions highlighted the influence of SDOH on cancer risk and outcomes; novel data sources and methodologies; data policy and ethical considerations regarding the use of big data in SDOH research; opportunities for collaboration and data sharing; as well as avenues for future research.

Workshop videos and presentation files: https://www.nationalacademies.org/event/10-21-2019/applying-big-data-to-address-the-social-determinants-of-health-in-oncology-a-workshop

Health Literacy and Communication Strategies in Oncology

This workshop, held in collaboration with the Roundtable on Health Literacy, examined opportunities, methods, and strategies to improve the communication of cancer information in a clinic visit, across a health care organization, and among the broader community. Workshop presentations and discussion addressed procedures, policies, and programs to support health literacy needs of patients and families; best practices to improve communication about cancer prevention, detection, treatment, and survivorship; and communication strategies to build public trust and counter inaccurate information about cancer.

Workshop videos and presentation files: https://www.nationalacademies.org/event/07-15-2019/health-literacy-and-communication-strategies-in-oncology-a-workshop

Proceedings: http://www.nationalacademies.org/hmd/Reports/2020/health-literacy-and-communication-strategies-in-oncology-pw.aspx

Workshop Overview: https://www.nap.edu/resource/25664/interactive/

Workshop highlight videos are available at: www.youtube.com/watch?v=M1NjXeG_cgs and www.youtube.com/watch?v=9iyPsTZ7RNw

Developing and Sustaining an Effective and Resilient Oncology Careforce

Advances in cancer research, screening and diagnostic practices, and cancer treatment have led to improved outcomes for patients with cancer and a growing population of cancer survivors, but they have also increased the complexity of cancer care. Demographic trends, new payment models, growing emphasis on interprofessional practice, the widespread adoption of technologies in clinical practice, and a shift to the outpatient care delivery all have a profound effect on the cancer careforce. This workshop examined opportunities to better support the oncology careforce and improve the delivery of high-quality cancer care.

Workshop videos and presentation files: http://nationalacademies.org/hmd/Activities/Disease/NCPF/2019-FEB-11.aspx

Proceedings: https://www.nap.edu/catalog/25533/developing-and-sustaining-an-effective-and-resilient-oncology-careforce-proceedings

Workshop Overview: https://www.nap.edu/resource/25533/interactive/

FORUM SPONSORS

- Centers for Disease Control and Prevention
- National Institutes of Health/National Cancer Institute
- American Association for Cancer Research
- American Cancer Society
- American College of Radiology
- American Society of Clinical Oncology
- Association of American Cancer Institutes
- Association of Community Cancer Centers
- Bristol-Myers Squibb
- Cancer Support Community
- CEO Roundtable on Cancer
- Flatiron Health
- Merck
- National Comprehensive Cancer Network
- National Patient Advocate Foundation
- Novartis Oncology
- Oncology Nursing Society
- Pfizer Inc.
- Society for Immunotherapy of Cancer

MEMBERSHIP OF THE FORUM

Edward J. Benz, Jr., M.D. (Chair)
Dana-Farber Cancer Institute

Garnet Anderson, Ph.D.
Fred Hutchinson Cancer Research Center

Karen Basen-Engquist, Ph.D., M.P.H.
The University of Texas MD Anderson Cancer Center

Smita Bhatia, M.D., M.P.H.
University of Alabama at Birmingham

Linda Bohannon, R.N., B.S.N., MSM
Cancer Support Community

Chris Boshoff, M.D., Ph.D., F.MedSci.
Pfizer Inc.

Cathy Bradley, Ph.D.
University of Colorado Cancer Center

Otis W. Brawley, M.D.
Johns Hopkins University

Cynthia Brogdon, Ph.D., R.N.
Bristol-Myers Squibb

Robert W. Carlson, M.D.
National Comprehensive Cancer Network

Gwen Darien, B.A.
National Patient Advocate Foundation

Nancy E. Davidson, M.D.
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

George D. Demetri, M.D.
Dana-Farber Cancer Institute

James H. Doroshow, M.D.
National Cancer Institute

Nicole F. Dowling, Ph.D.
Centers for Disease Control and Prevention

Scot W. Ebbinghaus, M.D.
Merck

Kojo S.J. Elenitoba-Johnson, M.D.
Perelman School of Medicine, University of Pennsylvania

Stanton L. Gerson, M.D.
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center

Hedvig Hricak, M.D., Ph.D.
Memorial Sloan Kettering Cancer Center

Mimi Huizinga, M.D., M.P.H., FACP
Novartis Oncology

Roy A. Jensen, M.D.
The University of Kansas Cancer Center

Randy A. Jones, Ph.D., R.N., FAAN
University of Virginia School of Nursing

Beth Y. Karlan, M.D.
University of California, Los Angeles

Lisa Kennedy Sheldon, Ph.D., APRN-BC, AOCNP, FAAN
Oncology Nursing Society

Samir N. Khleif, M.D.
Georgetown University

Mia Levy, M.D., Ph.D.
Rush University Cancer Center

J. Leonard Lichtenfeld, M.D., MACP
American Cancer Society

Neal Meropol, M.D.
Flatiron Health

Martin J. Murphy, Ph.D., D.Med.Sc.
CEO Roundtable on Cancer

Randall Oyer, M.D.
Lancaster General Penn Medicine

Cleo A. Samuel, Ph.D.
University of North Carolina at Chapel Hill

Richard L. Schilsky, M.D., FASCO
American Society of Clinical Oncology

Julie Schneider, Ph.D.
Food and Drug Administration

Lawrence N. Shulman, M.D., FACP, FASCO
University of Pennsylvania Abramson Cancer Center

Lara Strawbridge, M.P.H.
Centers for Medicare and Medicaid Services

George J. Weiner, M.D.
University of Iowa Holden Comprehensive Cancer Center

Robert A. Winn, M.D.
Virginia Commonwealth University Massey Cancer Center

FORUM STAFF

Sharyl Nass, Ph.D.
Forum Director and Director, Board on Health Care Services

Erin Balogh, M.P.H.
Senior Program Officer

Emily Zevon, Sc.D.
Program Officer

Lori Benjamin Brenig, M.P.H.
Research Associate

Annalee Gonzales, B.A.
Administrative Assistant

Kate Hawthorne, B.A.
Senior Program Assistant

Micah Winograd, M.A.
Financial Officer

Health and Medicine Division
Board on Health Care Services

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

The nation turns to the National Academies of Sciences, Engineering, and Medicine for independent, objective advice on issues that affect people's lives worldwide.
www.nationalacademies.org

ABOUT THE FORUM

Forum on Aging, Disability, and Independence

The National Academies of Sciences, Engineering, and Medicine have formed the Forum on Aging, Disability, and Independence to foster dialogue and address issues of interest and concern related to aging and disability. This includes aging and the related disabling conditions that can occur, as well as aging with an existing disability. The Forum seeks to promote bridging of the research, policy, and practice interests of the aging and disability communities to accelerate the transfer of research to practice and identify levers that will effect change for the benefit of all. Of particular concern is promoting healthy aging, independence, and community living for older adults and people with disabilities.

PERSON-CENTERED/PARTICIPANT-DIRECTED MODEL

Underpinning all aspects of achieving health and community living goals is a holistic, well-coordinated, person-centered, and participant-directed planning and implementation process. As depicted in the model below, this process should be directed by the individual in need, or by someone who either the individual has chosen or has been appropriately designated to direct and coordinate the process. The main factors that need to be coordinated include home and community settings; services and support; workforce; and financing. All of these factors exist within an environment that includes several key elements: quality; technology; research and evaluation; and policy. The Forum is focused on improving the understanding of the relationships that exist among all of these factors and examining ways to improve policies and environments that will ultimately promote independence and quality of life for older adults and people who have disabling conditions.

COORDINATION

Many systems need to work together successfully to support healthy aging, independence, and community living for people with disabilities and older adults. While both medical and social services are key to keeping older adults and individuals with disabilities in the setting of their choice in the community, these two systems are not always well connected. Similarly, in many communities there is a divide between service systems for those who are under age 65 and those who are over age 65. A goal of the Forum is to improve system integration and access to person-centered supports and services that can improve quality of life for both populations. For some individuals, this could be in the form of a designated care coordinator, whereas for others it may mean ensuring that they have information about all available resources because they choose to be their own care coordinator.

HOME AND COMMUNITY SETTINGS

Being an active member of a community is a priority for many people. A primary goal of the Forum is to foster access to services and supports that allow people with disabilities and older adults to live safely in the setting of their choosing and have the supports they need in the workplace if they would like to continue working.

SERVICES AND SUPPORT

Having access to services and supports can be critical to improving quality of life, maximizing independence, and preventing hospital re-admission. Services and supports can include assistance with dressing or cooking, social engagement,

Model for Promoting Healthy Aging, Independence, and Community Living for People with Disabilities and Older Adults

or provision of medical care. It is important to ensure that potential beneficiaries are aware of available resources and take advantage of them as appropriate.

WORKFORCE

The nation faces a growing imbalance between the supply of and demand for its health care system as the number of older adults with complex health needs increasingly outpaces the number of workers with the knowledge and skills to adequately care for them. Similarly, health care professionals are often not well-informed about proper care for people with disabilities or the problems these individuals face as they age. Fundamental reforms are needed in the ways these populations receive care, including changes to workforce education and training so that the workforce can be utilized efficiently and effectively while also providing high-quality care.

FINANCING

Although there are various sources of financing to support healthy aging and independent living services, they can be insufficient and difficult to access. Financing sources range from federal and state programs to non-profit foundations and philanthropic organizations. In addition, the private sector offers insurance (medical and long-term), and many commercial companies provide programs that can offset costs for assistive products under specified conditions. However, the individual (or family members) often finances some or, in some cases, all services that are received. Innovations in financing are needed. Preventive services are underdeveloped and "under-offered," resulting in greater expense in the long run, even though some services have found ways to cut costs while maintaining or even improving quality. The Forum examines ways to increase use of prevention strategies and provide financing that is more transparent and usable by people desiring these services.

TECHNOLOGY

Technology products have improved functioning and quality of life for people with disabilities of all ages. They can range in complexity from a calendar to coordinate which days of the week different services will be provided to devices that facilitate mobility and beyond. This is an area with many possibilities to connect the needs of consumers, regulators, businesses, and product developers. It also involves assistance in a myriad of settings, such as home, transport vehicles, medical facilities, workplaces, and community venues.

POLICY

Numerous social inequities and other barriers prevent older adults and people with disabilities, particularly those with multiple chronic conditions, from realizing their full potential for social and economic participation. The Affordable Care Act offers new opportunities, both to improve the service delivery system and to provide coverage for workers who become disabled. Yet the need for policy improvements involving equitable financing for health care, access to affordable, person-centered long-term supports and services, and workplace accommodation still remains.

RESEARCH AND EVALUATION

As policy changes are made, new technologies are developed, and the workforce adapts, evaluation and research are needed to determine whether these changes are beneficial and to validate best practices and inform future directions. Given that there are limited resources, wise use of existing data and effective coordination of research by all sectors of the nation are essential.

QUALITY

Quality is a key characteristic that encompasses all elements of the Forum's model. It is needed in any system supporting healthy aging, independence, and community living. If the systems in place are not of good quality, then they could break down, coordination could be lost, or individuals may lose trust in the people, research, and devices that are intended to help them achieve personal goals.

FORUM GOVERNANCE AND ACTIVITIES

The Forum is self-governing. Thus, the Forum membership identifies the topics it wishes to address, and with assistance from staff, develops meeting agendas and identifies workshop topics. The Forum meets 2-3 times annually and also has working groups that plan workshops and other activities. Products include workshop proceedings; cooperative projects initiated by Forum members; independently authored articles concerning Forum topics; and derivative consensus studies.

SPONSORS

AARP
Administration for Community Living
The American Geriatrics Society
Archstone Foundation
Consumer Technology Association Foundation
Department of Veterans Affairs
The Gerontological Society of America
Health Resources and Services Administration
The John A. Hartford Foundation
LeadingAge
National Institute on Aging
National Institute on Disability, Independent Living, and Rehabilitation Research
PHI
Qualcomm
The SCAN Foundation

FORUM DIRECTOR

Tracy Lustig, DPM, MPH
202-334-2574
tlustig@nas.edu

Disparate Inclusion of Older Adults in Clinical Trials: Priorities and Opportunities for Policy and Practice Change

Angelica P. Herrera, DrPH, Shedra Amy Snipes, PhD, Denae W. King, PhD, Isabel Torres-Vigil, DrPH, Daniel S. Goldberg, PhD, and Armin D. Weinberg, PhD

Older adults are vastly underrepresented in clinical trials in spite of shouldering a disproportionate burden of disease and consumption of prescription drugs and therapies, restricting treatments' generalizability, efficacy, and safety. Eliminating Disparities in Clinical Trials, a national initiative comprising a stakeholder network of researchers, community advocates, policymakers, and federal representatives, undertook a critical analysis of older adults' structural barriers to clinical trial participation. We present practice and policy change recommendations emerging from this process and their rationale, which spanned multiple themes: (1) decision making with cognitively impaired patients; (2) pharmacokinetic differences and physiological age; (3) health literacy, communication, and aging; (4) geriatric training; (5) federal monitoring and accountability; (6) clinical trial costs; and (7) cumulative effects of aging and ethnicity. (*Am J Public Health.* 2010;100:S105–S112. doi:10.2105/AJPH.2009.162982)

In the past century, tremendous strides have been made in the effective management of chronic diseases through biomedical innovations, health promotion studies, and prevention trials, along with an improved understanding of pharmaceutical treatments and genetic determinants of health.[1] However, not every population benefits equally from these advancements, and disparities are perpetuated by the low clinical trial participation of vulnerable populations.[2–4] Exclusion of older adults as clinical trial participants is highly problematic, because older adults suffer the greatest health burden in the Western world, enduring disproportionately high rates of cancer,[5] cardiovascular disease,[6] dementia,[7] arthritis, and Parkinson's disease.[8] They spend 36% of total US personal health care dollars[9] and consume 42% of all prescription drugs.[10] Equitable participation in clinical trials on the basis of age, then, is vital, because it can advance medical knowledge and test the safety and efficacy of new treatments that are generalizable to aging populations.[11–13]

However, older adults continue to be underrepresented in clinical trials.[14] Although two thirds of cancer patients are older than 65 years, only about 25% of cancer trial enrollees have attained this age.[15] Further research indicates that older adults carry 60% of the national disease burden but represent only 32% of patients in phase II and III clinical trials.[16] Clinical trial participation of older adults is also low in research on Alzheimer's disease,[17] arthritis,[18] epilepsy,[19] incontinence,[20] and cardiovascular disease.[21] These failings may limit generalizability, provide insufficient data about positive or negative effects of treatment among specific populations,[3,13] and hinder much-needed access to new treatments.

The reasons for disparate inclusion of older adults in clinical trials are complex and challenging. Typically, older adults face a combination of obstacles, including comorbidities,[4] ageism,[4] economic constraints, underinsurance, lack of insurance,[22] communication issues (e.g., hearing difficulties that interfere with telephone interviews and impaired vision that affects written surveys),[9,23] and physical immobility that constrains transportation options.[24,25] The unethical treatment of African Americans in research, epitomized by the Tuskegee Syphilis Study,[26,27] may partly explain why older ethnic minorities may be reluctant to participate in today's clinical trials, despite achievements in human participant protections. For example, though individuals from racial/ethnic minority groups comprise about a quarter of the US population, fewer than 1 in 10 participants in cancer studies conducted between 1995 and 1999 were from racial/ethnic minority groups.[28] We recognize that for many older members of racial/ethnic minority groups, the cumulative effect of a lifetime of poverty, racial discrimination, segregation, migration histories, and ill health creates divergent world views in older age than Whites,[29] which may fuel their mistrust in medical establishments and research.

We identified policy gaps from a current and historical context, and pinpointed limitations in evidence-based knowledge and practice that may contribute to disparities in older adults' participation in clinical trials. We describe policy-oriented and practical recommendations that can be applied across all clinical trial phases and disease areas. These key areas point to several short- and long-term opportunities for recruiting and retaining older adults into clinical trials. Our findings ensued from a workgroup on aging and clinical trials under the auspices of a national initiative, Eliminating Disparities in Clinical Trials (EDICT).

EDICT OVERVIEW AND TIMELINE

In July 2005, the Chronic Disease Prevention and Control Research Center at Baylor College of Medicine, in collaboration with the Intercultural Cancer Council, began an initiative to identify methods for improving clinical trial recruitment and retention in underrepresented populations (e.g., based on geographical isolation, age, ethnicity, disability). The EDICT initiative (principal investigator: Armin Weinberg, PhD) brought together more than 300 stakeholders nationally across thematic workgroups that convened at 3 national meetings, and via monthly Web-based teleconferences and in-person meetings. Stakeholder teams encompassed policy experts, federal agencies, community advocates, and academic, clinical, and pharmaceutical researchers.

The first of these meetings was held in September 2006 in Houston, Texas, with the purpose of reviewing existing data and formulating a platform for effectively disseminating policy recommendations aimed at increasing the participation of underrepresented groups in clinical trials. Nine thematic workgroups, each comprising a representative group of stakeholders, emerged from this event to identify issues and refine proposed suggestions into policy recommendations. From October to December 2007, an internal stakeholder policy review was conducted; between January and February 2008, an external stakeholder policy review—including a public comment period—was completed. In March 2008, 33 finalized policy recommendations were presented on Capitol Hill. Although the EDICT initiative pursued a broader assessment of underrepresented groups, we present the findings from a workgroup that compiled the concerns and critiques focused on older adults that were noted across the 9 thematic teams.

EMERGING THEMES AND RECOMMENDATIONS

Our policy-oriented recommendations were analyzed according to the "Three Rs"[30]: ensuring equal enrollment (*recruitment*), minimizing drop-out rates (*retention*), and including a post-trial environment in which researchers, sponsors, and pharmaceutical companies interact with the community to provide accountability and tangible benefits (*return*). The workgroup considered the following questions: (1) What are the policy's strengths and weaknesses? (2) Which audiences should be targeted for behavioral change? (3) What are the policy's unintended consequences and social, political, ethical, and financial obstacles? (4) How might the policy be modified to be more effective? We present perspectives, observations, and rationales for each of the derived recommendations.

Develop Best Practices and Standardize Protocols

We recommend that the Department of Health and Human Services Office of Human Research Protections, which oversees the regulation of institutional review boards, and the Association for the Accreditation of Human Research Protection Programs (AAHRPP), should develop best practices and standardize informed consent processes for those with cognitive impairments. This would reduce ethical and legal concerns and promote equal representation in clinical trials. Specifically, we suggest that standard criteria be modified, ensuring that caregivers of cognitively impaired older adults are informed about their supporting roles in studies, and that the autonomy of cognitively impaired elders is protected. Clinical research staff must also receive ample training regarding such processes, including any Health Insurance Portability and Accountability Act implications and state, federal, and National Institutes of Health (NIH) regulations regarding the appropriate use and definition of a proxy.

According to the Alzheimer's Association, 1 in 8 persons aged older than 65 years is diagnosed with Alzheimer's disease or dementia.[31] Alzheimer's disease and dementia interfere with cognitive abilities and, thus, with informed consent processes. Cognitively impaired individuals have difficulty making informed, competent, and voluntary decisions about participating in clinical trials, introducing ethical and legal challenges.[32,33] However, tools exist to aid researchers in identifying eligible participants among those with cognitive impairment.[34,35] For instance, a 3-item questionnaire that could be easily integrated into the informed consent process has been successfully tested in persons with Alzheimer's disease and diabetes to determine their capacity to make informed decisions.[35]

The Health Insurance Portability and Accountability Act introduces privacy and legal concerns for patients, providers, and family members that affect the inclusion of older adults who require the consent of a proxy or caregiver.[36] Criteria are needed to help researchers designate the most appropriate proxies and caregivers, because caregivers' attitudes do not always reflect patients' interests or preferences[37] despite the fact that older adults often consult with family members before considering a clinical trial[38] and may refuse to sign any documents before discussing them with a family member.[39,40] However, the caregiver or surrogate may not be available, may not understand the protocol, may not desire the patient to be involved because of undue burden to the caregiver, or may act on their own misconceptions of clinical trials.[10] Factoring caregivers into the informed consent process is crucial, because the number of older adults depending on caregivers is likely to increase in the future.[41]

Establish and Reinforce Guidelines

We recommend that federal mandates require age-related pharmacokinetic disclosures on all labels for all medications (i.e., improved geriatric use labeling), without exception. Pharmacokinetic and age-based differences contribute to the risk of poorly designed clinical trials that do not evaluate an inclusive participant pool.[42] Stringent eligibility criteria may inadvertently limit enrollment of older adults with multiple morbidities, which is common in older adults.[43] Indeed, adults may face organ abnormalities or lower functional status with increasing age, particularly with respect to the instrumental activities of daily living and corresponding number of comorbidities.[15,39] Kidney function, for instance, may decline in older adults, impairing drug excretion and metabolic clearance of drugs.[44] In older type 2 diabetes patients, a higher prevalence of comorbidities, tolerance of adverse effects from medication, and changes in metabolic control requires a modified treatment approach.[45]

The Social Security Administration and Medicare are examples of entities that have long retained antiquated definitions of old age (e.g., ≥65 years) based on chronological age. Scientifically, however, these age thresholds are arbitrary and uninformative for the purpose of delineating constructive clinical guidance on treatment decisions. Even when clinical trials provide an adequate representation of chronologically older adults, they describe a disproportionately healthier group than the average older-age population. Clinical trials designed with physiological age in mind would certainly lead to more meaningful results. Admittedly, the science for determining physiological age is poorly defined and inexact. Investigators only recently identified potential biomarkers that are highly predictive of chronological and physiological age in worms; the science in humans remains unreliable and subjective at best.[46] Until we acquire and test more sophisticated measures of physiological aging, to minimize biases in clinical trials from healthier populations of older adults, we support the Food and Drug Administration's (FDA's)

recommendation that clinical researchers proactively include older adults aged 75 years and older, which the literature reports as suffering from a significantly higher rate of disease burden than younger older adults.

Phase I trials may not necessitate representation of older adults with high-risk complications. However, adequate enrollment of older adults in phase II and III clinical trials is essential, because of the goal of confirming dosage, safety, adverse effects, and effectiveness. Further, similar to successful pediatric-specific trials, future research in older adults may wish to investigate any advantages and disadvantages of geriatric-specific clinical trials to help elucidate the safety and effectiveness of drug and other therapies in this growing population.

Physiological age is also affected by comorbidities, quality of life, predicted life expectancy, and a patient's perceived benefits and discomfort, which may all become adversaries to treatment. Studies examining pharmacologic differences between "fit" and "frail" older adults are also needed. Fit elderly are defined as those who meet standard eligibility criteria and are capable of tolerating experimental treatment during clinical trials.[47] However, there is little discussion about "frail" elderly who are less likely to participate in clinical trials.[48] Frail elderly have reasonable functional status, with some degree of comorbidity. Clinical trial researchers must ensure the adequate representation of older persons with and without comorbidities to glean an accurate examination of a treatment's safety and efficacy.

Older adults are at high risk for adverse drug reactions because of the pharmacokinetic and pharmacodynamic changes associated with aging.[48,49] Data suggest that 19.6% of older veterans received at least 1 drug deemed inappropriate according to the 2006 criteria in the Health Plan Employer Data and Information Set.[50] To remedy this, the FDA issued its Guideline for Industry[51] to encourage the fair representation of elderly participants in clinical trials. The document emphasized the importance of considering common conditions related to aging, such as renal impairment, the significant inclusion of people aged older than 75 years in clinical trials, and the study of interactions with other commonly prescribed medications in older adults. Guidance for Industry[52] covers various drug classes believed to pose problems in geriatric patients, but it does not require manufacturers to include sufficient numbers of geriatric patients in clinical trials. The guidelines merely allow manufacturers to state in the package insert that insufficient numbers of geriatric patients were included in the trials preceding FDA approval.[53]

The FDA still fails to require continued clinical trials for older adults with comorbidities who use high-risk drugs. Nevertheless, the tone of their amendment represents a more aggressive stance on noncompliance, which may be an important step toward inclusivity and reducing disparities arising from poor study design. The FDA's guidelines for geriatric labeling have increased awareness of the need for more older adults in clinical trials and more information on common or hazardous adverse effects among older adults. In 1998, the FDA released draft guidelines that specified the content and format for geriatric labeling on medications.[53] The proposal stipulated that pharmaceutical manufacturers submitting new drug applications also include geriatric labeling supplements in package inserts, subject to FDA approval. However, agency approval is not required if insufficient data exist on whether older patients react to the drug differently from younger patients.[53]

The FDA's guidelines for geriatric labeling are problematic because of the insufficient numbers of elderly people in premarketing clinical trials. About half of all drugs marketed after 1998 contain information on use by older patients, but few describe specific problems encountered in this population.[54] In fact, only 28 of the top 50 oral medications prescribed to older adults had age-specific dosing information available, and only 8 of those included specific milligram recommendations.[55]

Employ Age-Friendly Methods of Communication

We recommend that clinical trial sponsors require that researchers use consent forms, promotional materials, and other study forms in age-appropriate formats and adjusted literacy levels. This includes large-print, third- to fifth-grade reading level materials, accompanying audiovisuals for the hearing- and vision-impaired, and other clinical teaching aids that are appropriate to culture and literacy level (e.g., videos, charts, and diagrams). Trials should procure or facilitate access to supportive services, such as a participant navigator trained in geriatrics, additional funding for transportation, and access to benefit eligibility counselors. With updates pertaining to older adults, the National Standards on Culturally and Linguistically Appropriate Services, developed by the Office of Minority Health, can be used as a starting point.

Physical health impairment and low health literacy are major barriers to clinical trial enrollment for older adults. Lee et al.[56] found that low health literacy (the ability to read and comprehend basic health-related materials[57]) was common among community-dwelling Medicare beneficiaries enrolled in a national managed care organization. Older adults have poor functional health literacy overall,[56] even after visual acuity and medical conditions are accounted for, and those with inadequate health literacy are likely to be older ethnic minorities with a lower annual income, fewer years of education, and a higher mortality rate.[58] African American and Hispanic patients have consistently lower rates of health literacy than non-Hispanic Whites, even after factors such as education are accounted for.[59] Those with low health literacy and chronic diseases also know less about their diseases and plausible treatment methods, and exhibit poorer self-management and health overall.[57,59] The National Standards on Culturally and Linguistically Appropriate Services provide principles of culturally competent care, issued by the US Department of Health and Human Services' Office of Minority Health.[60] These standards presently only address the language of materials and communications, and do not provide guidelines specific to older adults with low literacy levels or hearing and vision impairment.[61]

Support Geriatric Education and Training

We recommend that the Liaison Committee for Medical Education, which addresses education regarding clinical research, amend medical education requirements and curricula objectives to sensitize future practitioners to the special needs of older and ethnic minority adults. The Accrediting Council for Continuing Medical Education and the Accrediting Council for Graduate Medical Education should consider working with the American Geriatrics Society to adopt additional coursework and

continuing education concerning geriatrics, ageism, and the intersection of age and clinical trials. The AAHRPP should reinforce these criteria by requiring that all personnel involved in a clinical trial complete training in the recruitment and retention of a geriatric population.

Biases and ageism manifest as systemic barriers that impede minority elder enrollment in clinical trials.[62] Health care providers are less likely to refer older ethnic minorities for screening and treatment, including those provided by clinical trials.[63,64] A prevalent notion expressed by researchers is that older adults are less willing to participate in clinical trials than are younger adults.[64,65] However, studies indicate that many older people want to participate in trial research and describe such participation as a positive experience, even when studies have neutral or negative outcomes.[11,62,66,67]

In a 2006 survey of 89 national colleges and schools of pharmacy, 43% of schools reported having 2 full-time geriatrics faculty members, whereas the rest relied on part-time faculty.[68] Of 125 accredited medical schools, only 12 teach geriatrics as a separate required course, only 14 have mandatory geriatrics clerkships, and most mix geriatrics training into regular coursework.[68] Two major obstacles to sound geriatric medicine programs are lack of research faculty and meager monetary incentives.[69] The lack of specially trained providers to meet the needs of the aging population is expected to worsen unless we invest in geriatric education.[69] Meager preparation among clinicians and researchers can lead to care that is unsuitable for older adults, as well as lower rates of clinical trial participation in this population.[69] Compounding this problem, the AAHRPP, the accrediting body for institutional review boards, does not require training on the equitable participation of underrepresented groups in clinical trials, nor does it make accrediting decisions on the basis of institutional review boards' performance in this area.[70]

Improve Federal Monitoring and Accountability

We recommend that clinical trial sponsors require, and enforce, clinical researchers to report age by strata to document adequate representation of older adults in clinical trials. A promising policy aimed at addressing inclusion criteria in clinical trials is the NIH Revitalization Act of 1993, which mandated that women and minorities be included in NIH-funded studies involving human participants, and allowed for subset analysis by gender or race and ethnicity.[71] This legislation, however, does not include recommendations regarding older adults. To begin to adequately document representation of older adults' involvement in clinical trials and conduct analysis based on specific age strata, an additional inclusion policy that provides for oversight ensuring proper implementation (i.e., uniform reporting of inclusion of older adults for all studies) should be adopted.

The FDA provides some guidance on the reporting of clinical trial data by age.[72] The recommendations encourage drug sponsors to report the age of each clinical trial participant to allow for identification of differences in safety and effectiveness associated with age. The recommended age-reporting formats include average age, the ages of the youngest and oldest participant, and the number of participants who fall into specific age categories.[72] Additionally, clinical review summaries provided to the FDA contain safety and efficacy data reported by age, gender, and race/ethnicity.[72] These guidelines are easily transferable and can be adopted by clinical trial researchers.

Reduce Clinical Trial Costs

We recommend that changes be made to the cost coverage of clinical trial participation, particularly by the Centers for Medicare and Medicaid Services (CMS). The number of Medicare beneficiaries more than doubled between 1966 and 2000, and is expected to double again, to about 77 million, in 2030.[73] In most cases, clinical trial patients receive drugs and trial-specific care at no cost. However, they may be held responsible for some routine care associated with the trial and the cost of travel and initial screening visits. Further, because some health plans define clinical trials as experimental, health insurance coverage may not include the costs of routine patient care that is part of the trial.[74]

In 2000, an executive mandate from President Clinton created an amendment to Medicare policy that required the coverage of routine patient care costs associated with clinical trials. This policy change successfully increased clinical trial enrollment for older patients from 25% to 38% between 1993 and 2003. Most of this increase, however, may have occurred among Medicare beneficiaries with supplemental private insurance coverage and may not have included underrepresented groups.[75] CMS revisited the national clinical trial coverage decision in July 2006 to address issues associated with the policy, such as clarifying payment criteria for procedures associated with clinical research.[75] During the public comment phase, some urged CMS to add criteria for including underrepresented groups in clinical trials. Ultimately, CMS made no changes to its original 2000 clinical trials policy.[75] It noted that doing so without adequate time to fully scrutinize the new FDA Amendments Act might risk duplicating contingencies stipulated by Congress.

To alleviate out-of-pocket costs, a growing number of states have passed legislation that requires health plans to pay for the routine medical care of clinical trial patients. According to the National Cancer Institute, 20 states provide mandatory third-party reimbursement for clinical cancer treatment trials.[74] Unfortunately, only 8 states offer coverage through all 4 phases of the clinical trial process,[74] and of the states that provide clinical trial coverage, several stipulate specific requirements. In California, coverage only applies to routine patient care costs related to clinical cancer trials with a therapeutic purpose, as recommended by a treating physician. To be eligible for coverage in Connecticut, clinical trials for cancer prevention must include a phase III trial with therapeutic interventions conducted at multiple institutions and approved by a federal authority. Other states, such as Georgia, only require third-party coverage for routine patient care costs incurred in conjunction with children's clinical cancer trials.[74]

Respond to Effects of Race/Ethnicity and Age

We recommend that health care researchers address some of the damaging legacies of medical research among members of racial/ethnic minority groups to successfully recruit and retain them in clinical trials. Racial/ethnic minorities will make up the largest segment of the older adult population by the year 2050.[76] African Americans and Latinos, in particular, are disproportionately affected by chronic illness, disability, depression, poverty, and substandard quality of life.[76] Throughout time, members of racial/ethnic minority groups, children, prisoners, and poor people have been exploited for unethical medical research, without their consent

or knowledge. Thus, inherited beliefs about the hazards associated with research and the structured inequality of the medical establishment are common among ethnic minority elderly.[77] Racial/ethnic minority group members have historically been reluctant to participate in clinical trials. Older African Americans, in particular, are more likely than older Whites to be familiar with the negative legacies of clinical research, such as the Tuskegee Syphilis Study.[26,27] These past abuses of power leave many African Americans guarded against enrolling in clinical trials. In addition to distrust of the medical establishment, older members of racial/ethnic minority groups express concern that clinical researchers lack an understanding of their beliefs and values; they also express a lack of encouragement from their physicians, and fear adverse effects of medical experimentation.[27,78,79]

Compared with the general older-age population, older persons from racial/ethnic minority groups have lower health literacy rates,[56] higher poverty, and higher rates of morbidity[22] that serve as barriers to participation in clinical trials. In addition to limited access to health care, cultural and language barriers, a lack of financial incentives, and unawareness of clinical trials, racial/ethnic minority group members experience more chronic illness and disability than non-Hispanic Whites, which may disqualify them from clinical trials.[80–84] Some cultures see illness as more multidimensional—encompassing religion, spirituality, and environment—than the medical establishment does, which may further inhibit access to treatment.[85]

Increasing the pool of racial/ethnic minority physicians is an important and often-cited step toward creating a culturally competent health care workforce, but it is not always sufficient to overcome barriers to access. For instance, a cross-sectional study of 742 physicians' attitudes and practices regarding clinical trials found that Latino physicians were significantly less likely to refer patients to clinical trials or find scientific value in trials.[86] They reported fewer patients inquiring about clinical trials, and more who were deemed ineligible after referral. Similarly, simply having African American clinicians as the faces of a clinical trial may not produce the intended effects, if we recall that African American clinicians were responsible for executing the disastrous Tuskegee Syphilis Study protocol.

Cultural competency must encompass attention to differences in language, culture, and socioeconomic background. It also necessitates an awareness of historical context and relationships with the medical community that have consequently led to distrust of healthcare research by racial/ethnic groups. Opportunities for researchers to emulate best practices do exist. One prime example comes from the Resource Centers for Minority Aging Research (RCMAR), first funded by the National Institute on Aging in 1997, which have spearheaded studies leading to best practices in conducting research with older ethnic minorities. Their efforts have focused on developing trust among racial/ethnic minority older adults and providing possible solutions to recruiting and retaining older adults from racial/ethnic minority groups in clinical trials.[87] RCMARs have also increased the number of researchers who specialize in health of older adults from racial/ethnic minority groups, and enhanced diversity and cultural competency in the professional workforce by mentoring racial/ethnic minority academic researchers.

The Resource Centers for Minority Aging Research's focus on community-based participatory research brings in the vital perspective of community members and includes one-on-one advising, directed pilot research projects, and group feedback. This approach has proven to be effective in attracting individuals from racial/ethnic minority groups and older adults.[88] However, researchers have concluded that as beneficial as community-based participatory research can be in reaching underrepresented groups, it is also an arduous, long-term process that requires considerable commitment and buy-in from collaborators in the academic sector and the community at large.[89]

FUTURE DIRECTIONS AND PRACTICAL IMPLICATIONS

Strategies for increasing older adults' participation in clinical trials must consist of programmatic and study design changes.[7,90,91] Successful recruitment requires identifying and consulting individuals who are knowledgeable about and trusted by members of the aging community,[92,93] adhere to the principles of community-based participatory research,[26] engage the community as a partner,[92,93] recognize cultural perspectives,[94] and provide clear and adequate information regarding risks, benefits, costs, and time required to participate in trials.[6] Successful recruitment must also address issues of awareness, lack of resources, physical barriers, distrust of researchers, and ageism among researchers.[95,26] These strategies, however, must be backed by relevant policy at institutional and federal levels to achieve widespread and sustained impact.

Approximately 19.3% of Americans will be aged 65 years or older by 2030, a significant increase from 12.6% in 2007.[94] Additionally, because individuals from racial/ethnic minority groups will comprise the largest segment of the older-adult population by 2050[76] and are disproportionately affected by chronic illness, disability, poverty, and poor quality of life, it is imperative that policy makers, clinical researchers, federal regulatory agencies, funders, caregivers, and the general public be apprised of the importance of equal representation by age and race/ethnicity in clinical trials.

Our recommendations are not intended to address all aspects of this important issue but to invigorate a dialogue around policy-driven solutions. We are cognizant of the resistance to adopting unfunded mandates. However, we contend that when researchers and policy makers incorporate elements of these policies early in the design and development of research, higher costs can be averted. If one considers the legal and ethical ramifications of prescribing treatments on the basis of inaccurate evidence, cost should not be an excuse to avoid testing and enforcing these recommendations. Most drug therapy trials are funded by pharmaceutical companies, placing on them the larger burden of ensuring drug safety. Pharmaceutical companies face lawsuits for various reasons, from concealing crucial and sometimes detrimental study results to distributing drugs that cause adverse reactions or even death. This provides an incentive for ensuring that drug safety takes precedence and that the study population adequately reflects those who represent the consumers of such therapies.

Our recommendations, though not prescriptive, provide some guidance for developing a coordinated and comprehensive approach to reducing significant health disparities and highlight noteworthy areas for further

investigation. One of the many effects of an aging population is that more people will require safe, affordable treatments for longer periods of time. A multipronged policy approach will help us achieve this goal while improving the quality of life of thousands of Americans, saving great financial and human costs in the long run. ■

About the Authors

At the time of the study, Angelica P. Herrera, Shedra A. Snipes, Denae W. King, and Isabel Torres-Vigil were with The University of Texas M.D. Anderson Cancer Center, Houston. Daniel S. Goldberg and Armin D. Weinberg are with the Chronic Disease Prevention and Control Research Center, Department of Medicine, Baylor College of Medicine, Houston, TX.

Correspondence should be sent to Angelica P. Herrera, DrPH, Stein Institute for Research on Aging, University of California, San Diego, 9500 Gilman Dr, #0664, La Jolla, CA 92093-0664 (e-mail: apherrera@ucsd.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints/Eprints" link.

This article was accepted July 24, 2009.

Contributors

All authors contributed to the writing, development, conceptualization, and review of all drafts of this article. A.P. Herrera convened the workgroup on aging, coordinated planning and discussion groups, and led the development and review of policy issues and practice recommendations from stakeholders. S.A. Snipes and D.W. King assisted with literature review and analyses, and consolidated findings from workgroup discussions. I. Torres-Vigil and A.D. Goldberg provided insight and review on ethical implications of recommendations, and adherence to a systematic review and equitable participation of stakeholders. A. Weinberg was the principal investigator on the Eliminating Disparities in Clinical Trials (EDICT) project, was instrumental in bringing in external experts, and provided a critical review of the rationale behind each policy and the group's overall process.

Acknowledgments

We acknowledge funding support from the Kellogg Health Scholars Program (grant P0117943); Project EXPORT: Centers of Excellence, Excellence in Partnerships for Community Outreach, and Research on Disparities in Health and Training grant, provided by the National Center on Minority Health and Health Disparities, National Institutes of Health (5 P60 MD000503) for Herrera, King, and Snipes; SIP 16-04 Prevention Research Centers' Cancer Prevention and Control Research Network: Latinos in a Network for Cancer Control for Torres-Vigil; and Genentech Inc for Goldberg.

The authors graciously acknowledge the contribution of the EDICT project team and its project director, Cynthia Spiker. For their critical review, we thank Lodovico Balducci, professor of medicine and oncology at the University of South Florida College of Medicine, and program leader of the Senior Adult Oncology Program at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida; Robert B. Wallace, epidemiologist in aging at the College of Public Health, University of Iowa; and Larry E. Laufman, at the Baylor College of Medicine. For their assistance with editing, we thank Nirmala Nataraj, Rachel Shada, and Otila Martinez.

Human Participant Protection

This study was submitted for review by The University of Texas M.D. Anderson Cancer Center institutional review board and found to be exempt.

References

1. Smedley BD, Syme SL. *Promoting Health: Intervention Strategies From Social and Behavioral Research.* Washington, DC: National Academies Press; 2000.

2. Institutes of Medicine. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care.* Washington, DC: National Academies Press; 2000.

3. Haynes A, Smedley BD. *The Unequal Burden of Cancer: An Assessment of NIH Research and Programs for Ethnic Minorities and the Medically Underserved. Committee on Cancer Research Among Minorities and the Medically Underserved. Health Sciences Policy Program Health Sciences Section.* Washington, DC: National Academies Press; 1999.

4. Murthy VH, Krumholz H, Gross GP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA.* 2004;291(22):2720–2726.

5. Townsley CA, Pond GR, Oza AM, et al. Evaluation of adverse events experienced by older patients participating in studies of molecularly targeted agents alone or in combination. *Clin Cancer Res.* 2006;12(7 pt 1): 2141–2149.

6. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med.* 2002;162(15):1682–1688.

7. Arean PA, Alvidrez J, Nery R, Estes C, Linkins K. Recruitment and retention of older minorities in mental health services research. *Gerontologist.* 2003;43(1): 36–44.

8. Witham MD, McMurdo ME. How to get older people included in clinical studies. *Drugs Aging.* 2007;24(3):187–196.

9. DiBartolo MC, McCrone S. Recruitment of rural community-dwelling older adults: barriers, challenges, and strategies. *Aging Ment Health.* 2003;7(2):75–82.

10. Linnebur SA, O'Connell MB, Wessell AM, et al. Pharmacy practice, research, education, and advocacy for older adults. *Pharmacotherapy.* 2005;25(10): 1396–1430.

11. Siu LL. Clinical trials in the elderly—a concept comes of age. *N Engl J Med.* 2007;356(15):1575–1576.

12. Satcher D. Mental health: a report of the Surgeon General – executive summary. *Prof Psychol Res Pr.* 2000;31(1):5–13.

13. Yancey AK, Ortega AN, Kumanyika SK. Effective recruitment and retention of minority research participants. *Annu Rev Public Health.* 2006;27:1–28.

14. Projected State-Specific Increases in Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitations: United States, 2005–2030. Atlanta, GA: Centers for Disease Control and Prevention; 2007:608–610.

15. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol.* 2003;21(7):1383–1389.

16. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Under-representation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med.* 1999;341(27):2061–2067.

17. Cohen-Mansfield J. Recruitment rates in gerontological research: the situation for drug trials in dementia may be worse than previously reported. *Alzheimer Dis Assoc Disord.* 2002;16(4):279–282.

18. Elley CR, Robertson MC, Kerse NM, et al. Falls Assessment Clinical Trial (FACT): design, interventions, recruitment strategies and participant characteristics. *BMC Public Health.* 2007;7:185.

19. Leppik IE. Epilepsy in the elderly. *Epilepsia.* 2006;47(suppl 1):65–70.

20. Morse AN, Labin LC, Young SB, Aronson MP, Gurwitz JH. Exclusion of elderly women from published randomized trials of stress incontinence surgery. *Obstet Gynecol.* 2004;104(3):498–503.

21. Dhruva SS, Redberg RF. Variations between clinical trial participants and Medicare beneficiaries in evidence used for Medicare national coverage decisions. *Arch Intern Med.* 2008;168(2):136–140.

22. *Older Americans 2008: Key Indicators of Well-Being.* Washington, DC: Federal Interagency Forum on Aging-Related Statistics; 2008.

23. Moreno-John G, Gachie A, Fleming CM, et al. Ethnic minority older adults participating in clinical research: developing trust. *J Aging Health.* 2004;16(5 suppl): 93S–123S.

24. Leader MA, Neuwirth E. Clinical research and the noninstitutional elderly: a model for subject recruitment. *J Am Geriatr Soc.* 1978;26(1):27–31.

25. Applegate WB, Curb JD. Designing and executing randomized clinical trials involving elderly persons. *J Am Geriatr Soc.* 1990;38(8):943–950.

26. Dilworth-Anderson P, Williams SW. Recruitment and retention strategies for longitudinal African American caregiving research: The Family Caregiving Project. *J Aging Health.* 2004;16(5 suppl):137S–156S.

27. Shaya FT, Gbarayor CM, Yang HK, Agyeman-Duah M, Saunders E. A perspective on African American participation in clinical trials. *Contemp Clin Trials.* 2007; 28:213–217.

28. Quality of care for older adults with chronic obstructive pulmonary disease and asthma based on comparisons to practice guidelines and smoking status. *BMC Health Serv Res.* 2008;8:144.

29. Wykle M, Ford A, eds. *Serving Minority Elders in the 21st Century.* New York, NY: Springer Publishing Company; 1999.

30. Bustillos D. The "three Rs" of clinical trial participation: an organizing framework. 2006. Available at: http://www.bcm.edu/edict/PDF/The_Three_Rs.pdf. Accessed May 2, 2008.

31. Alzheimer's Association. 2009 Alzheimer's disease facts and figures. Available at: http://www.alz.org/national/documents/report_alzfactsfigures2009.pdf. Accessed November 24, 2009.

32. Kim SYH, Caine ED, Currier GW, Leibovici A, Ryan JM. Assessing the competence of persons with Alzheimer's disease in providing informed consent for

participation research. *Am J Psychiatry.* 2001;158(5): 712–717.

33. Karlawish JH, Knopman D, Clark CM, et al. Informed consent for Alzheimer's disease clinical trials: a survey of clinical investigators. *IRB.* 2002;24(5):1–5.

34. Jeste DV, Palmer BW, Applebaum PS, et al. A new brief instrument for assessing decisional capacity for clinical research. *Arch Gen Psychiatry.* 2007;64(8): 966–974.

35. Palmer BW, Dunn LB, Applebaum PS, et al. Assessment of capacity to consent to research among older persons with schizophrenia, Alzheimer's disease, or diabetes mellitus. *Arch Gen Psychiatry.* 2005;62(7):726–733.

36. Williams AM. Caregivers of persons with stroke: their physical and emotional well-being. *Qual Life Res.* 1993;2(3):213–220.

37. Levine C. HIPAA and talking with family caregivers: what does the law really say? *Am J Nurs.* 2006;106(8): 51–53.

38. Fried TR, Bradley EH, Towle VR. Valuing the outcomes of treatment: do patients and their caregivers agree? *Arch Intern Med.* 2003;163(17):2073–2078.

39. Gueldner SH, Hanner MB. Methodological issues related to gerontological nursing research. *Nurs Res.* 1989;38(3):183–185.

40. Townsley CA, Chan KK, Pond GR, et al. Understanding the attitudes of the elderly towards enrollment into cancer clinical trials. *BMC Cancer.* 2006;6:34.

41. Schumacher K, Beck CA, Marren JM. Family caregivers: caring for older adults, working with their families. *Am J Nurs.* 2006;106(8):40–49.

42. Brooks JD, King ML. Geneticizing disease: implications for racial health disparities. Washington, DC: Center for American Progress; 2008. Available at: http://www.americanprogress.org/issues/2008/01/geneticizing_disease.html. Accessed June 12, 2007.

43. Lee PG, Cigolle C, Blaum PG. The co-occurrence of chronic diseases and geriatric syndromes: the Health and Retirement Study. *J Am Geriatr Soc.* 2009;57(3):511–516.

44. Beglinger C. Ethics related to drug therapy in the elderly. *Dig Dis.* 2008;26(1):28–31.

45. Abbatecola AM, Maggi S, Paolisso G. New approaches to treating type 2 diabetes mellitus in the elderly: the role of incretin therapies. *Drugs Aging.* 2008;25(11):913–925.

46. Golden TR, Hubbard A, Dando C, Herren MA, Melov S. Age-related behaviors have distinct transcriptional profiles in Caenorhabditis elegans. *Aging Cell.* 2008;7(6):850–865.

47. Trimble EL. Concluding remarks: optimal treatment for women with ovarian cancer. *Semin Oncol.* 2006;33(6 suppl 12):S25–S26.

48. Bressler R, Bahl JJ. Principles of drug therapy for the elderly patient. *Mayo Clin Proc.* 2003;78(12): 1564–1577.

49. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol.* 2003;38(8):843–853.

50. Pugh MJ, Hanlon JT, Zeber JE, Bierman A, Cornell J, Berlowitz DR. Assessing potentially inappropriate prescribing in the elderly Veterans Affairs population using the HEDIS 2006 quality measure. *J Manag Care Pharm.* 2006;12(7):537–545.

51. US Food and Drug Administration. Guideline for industry. Studies in support of special populations: geriatrics. 1994. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129519.pdf. Accessed November 24, 2009.

52. US Food and Drug Administration. Guidance for industry. Content and format for geriatric labeling. 2001. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075062.pdf. Accessed November 24, 2009.

53. US Food and Drug Administration. *HR 3580.* Available at: http://www.fda.gov/oc/initiatives/hr3580.pdf. Accessed May 1, 2008.

54. Steinmetz KL, Coley KC, Pollock BG. Assessment of geriatric information on the drug label for commonly prescribed drugs in older people. *J Am Geriatr Soc.* 2005;53(5):891–894.

55. Rohan EA, Berkman B, Walker S, Holmes W. The geriatric oncology patient: ageism in social work practice. *J Gerontol Soc Work.* 1994;23(1/2):201–221.

56. Lee SD, Gazmararian JA, Arozullah AM. Health literacy and social support among elderly Medicare enrollees in a managed care plan. *J Appl Gerontol.* 2006;25(4):324–337.

57. Kutner M, Greenberg E, Jin Y, Paulsen C. *The Health Literacy of America's Adults: Results From the 2003 National Assessment of Adult Literacy.* Washington, DC: US Department of Education, National Center for Education Statistics; 2003. NCES 2006–483.

58. Baker DW, Gazmararian JA, Sudano J, Patterson M. The association between age and health literacy among elderly persons. *J Gerontol B Psychol Sci Soc Sci.* 2000;55(6):S368–S374.

59. Baker DW, Wolf MS, Feinglass J, Thompson JA, Gazmararian JA, Huang J. Health literacy and mortality among elderly persons. *Arch Intern Med.* 2007;167(14): 1503–1509.

60. US Department of Health and Human Services. *National Standards for Culturally and Linguistically Appropriate Services in Health Care: Executive Summary.* Washington, DC: Office of Minority Health; 2001. No. 282-99-0039. Available at: http://www.omhrc.gov/assets/pdf/checked/executive.pdf. Accessed September 20, 2007.

61. Chang DC, Bass RR, Cornwell EE, MacKenzie EJ. Undertriage of elderly trauma patients to state-designated trauma centers. *Arch Surg.* 2008;143:776–781.

62. Schron EB, Wassertheil-Smoller S, Pressel S. Clinical trial participant satisfaction: survey of SHEP enrollees. SHEP cooperative research group. Systolic Hypertension in the Elderly Program. *J Am Geriatr Soc.* 1997;45(8): 934–938.

63. *A Congressional Forum Sponsored by the Alliance for Aging Research: Redesigning Healthcare for an Aging Nation.* Washington, DC: Alliance for Aging Research; 2003. Available at: http://www.agingresearch.org/content/article/detail/701. Accessed November 3, 2007.

64. Herzog AR, Rodgers WL. Cognitive performance measures in survey research on older adults. In: Schwartz N, Park DC, Knauper B, Sudman S, eds. *Cognition, Aging, and Self-Reports.* Philadelphia, PA: Psychology Press; 1999:327–341.

65. Kelsey JE, Carroll BJ, Ereshefsky L, et al. The use of antidepressants in long-term care and the geriatric patient. Question-and-answer session. *Geriatr.* 1998;53: S34–S39.

66. Comis RL, Miller JD, Aldige CR, Krebs K, Stoval E. Public attitudes toward participation in cancer clinical trials. *J Clin Oncol.* 2003;21(5):830–835.

67. Peterson ED, Lytle BL, Biswas MS, et al. Willingness to participate in cardiac trials. *Am J Geriatr Cardiol.* 2004;13(1):11–15.

68. Delafuente JC. Reflections on geriatric pharmacy practice: the times they are a changin'. *Ann Pharmacother.* 2006;40(5):950–951.

69. Warshaw GA, Bragg EJ, Brewer DE, Megnathan K, Ho M. The development of academic geriatric medicine: progress toward preparing the nation's physicians to care for an aging population. *J Am Geriatr Soc.* 2007;55(12):2075–2082.

70. Accreditation of Human Research Protections Programs. AAHRPP accreditation standards. Updated May 10, 2004. Available at: http://www.aahrpp.org/Documents/D000067.PDF. Accessed September 1, 2008.

71. Freedman LS, Simon R, Foulkes MA, et al. Inclusion of women and minorities in clinical trials and the NIH Revitalization Act of 1993: the perspective of NIH clinical trials. *Control Clin Trials.* 1995;16(5):277–285.

72. Marroum PJ, Gobburu J. The product label: how pharmacokinetics and pharmacodynamics reach the prescriber. *Clin Pharmacokinet.* 2002;41(3):161–169.

73. Kaiser Family Foundation. Medicare elderly fact sheet. 2007. Available at: http://www.kff.org/medicare/elderly.cfm. Accessed July 26, 2007.

74. National Cancer Institute. States that require health plans to cover patient care costs in clinical trials. Available at: http://www.nci.nih.gov/clinicaltrials/developments/laws-about-clinical-trial-costs. Accessed June 22, 2007.

75. Centers for Medicare and Medicaid Services. Decision for clinical trial policy. 2007. Available at: https://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?from2=viewdecisionmemo.asp&id=1868. Accessed July 26, 2007.

76. *Older Americans 2008: Key Indicators of Well-Being.* Washington, DC: Federal Interagency Forum on Aging-Related Statistics; 2008.

77. Gallagher-Thompson D, Rabinowitz Y, Tang PCY, et al. Recruiting Chinese Americans for dementia caregiver intervention research: suggestions for success. *Am J Geriatr Psychiatry.* 2006;14(8):676–683.

78. Freimuth VS, Quinn SC, Thomas SB, Cole G, Zook E, Duncan T. African Americans' views on research and the Tuskegee Syphilis Study. *Soc Sci Med.* 2001;52(5): 797–808.

79. Corbie-Smith G, Thomas SB, Williams MV, Moody-Ayers S. Attitudes and beliefs of African American participation in medical research. *J Gen Intern Med.* 1999;14(9):537–546.

80. Long JA, Chang VW, Ibrahim SA, Asch DA. Update on the health disparities literature. *Ann Intern Med.* 2004;141(10):805–812.

81. Harris Y, Gorelick PB, Samuels P, Bempong I. Why African Americans may not be participating in clinical trials. *J Natl Med Assoc.* 1996;88(10):630–634.

82. Shavers VL, Lunch CF, Burmeister LF. Racial differences in factors that influence the willingness to

participate in medical research studies. *Ann Epidemiol.* 2002;12(4):248–256.

83. Centers for Disease Control and Prevention. Health disparities experienced by Hispanics: United States. *MMWR Morb Mortal Wkly Rep.* 2004;53(40):935–937.

84. Centers for Disease Control and Prevention. Health disparities experienced by black or African Americans: United States. *MMWR Morb Mortal Wkly Rep.* 2005; 54(1):1–3.

85. Mezzich JE, Caracci G. Issues in the assessment and diagnosis of culturally diverse individuals. In: *Cultural Formulation: A Reader for Psychiatric Diagnosis.* Lanham, MD: Jason Aronson Publishers; 2008:115–148.

86. Ramirez AG, Wildes K, Talavera G, Napoles-Springer A, Gallion K, Perez-Stable EJ. Clinical trial attitudes and practices of Latino physicians. *Contemp Clin Trials.* 2008;29(4):482–492.

87. Stahl SM, Vasquez L. Approaches to improving recruitment and retention of minority elders participating in research: examples from selected research groups including the National Institute on Aging's Resource Centers for Minority Aging Research. *J Aging Health.* 2004;16(5 suppl):9S–17S.

88. Carrasquillo O, Chadiha LA. Development of community-based partnerships in minority aging research. *Ethn Dis.* 2007;17(1 suppl):S3–S5.

89. Moreno-John G, Fleming C, Ford ME, et al. Mentoring in community-based participatory research: the RCMAR experience. *Ethn Dis.* 2007;17(1 suppl): S33–S43.

90. Souder JE. The consumer approach to recruitment of elder subjects. *Nurs Res.* 1992;41:314–316.

91. Levkoff S, Levy B, Weitzman PF. The role of religion and ethnicity in the help seeking of family caregivers of elders with Alzheimer's disease and related disorders. *J Cross Cult Gerontol.* 1999;14(4):335–356.

92. McNeely EA, Clements SD. Recruitment and retention of the older adult into research studies. *J Neurosci Nurs.* 1994;26(1):57–61.

93. Stahl SM, Hahn AA. The Resource Centers for Minority Aging Research (RCMAR): community/researcher interaction and relationships. *Ethn Dis.* 2007; 17(1 suppl):S1–S2.

94. Administration on Aging. A profile of older Americans: 2008. Available at: http://www.aoa.gov/AoARoot/Aging_Statistics/Profile/2008/docs/2008profile.pdf. Accessed November 24, 2009.

95. Thompson LW, Gallagher D, Nies G, Epstein D. Evaluation of the effectiveness of professionals and nonprofessionals as instructors of "coping with depression" classes for elders. *Gerontologist.* 1983;23(4): 390–396.

VIEWPOINT

Accelerated Drug Approval and Health Inequality

Alex John London, PhD
Department of Philosophy and Center for Ethics and Policy, Carnegie Mellon University, Pittsburgh, Pennsylvania.

Jonathan Kimmelman, PhD
Studies of Translation, Ethics and Medicine (STREAM), Biomedical Ethics Unit, McGill University, Montréal, Quebec, Canada.

Corresponding Author: Jonathan Kimmelman, PhD, Studies of Translation, Ethics and Medicine (STREAM), Biomedical Ethics Unit, McGill University, 3647 Peel St, Montréal, QC H3A 1X1, Canada (jonathan.kimmelman@mcgill.ca).

In the United States, there is considerable political momentum for accelerating access to novel medications. Faster access is often portrayed as increasing fairness by providing treatment options to patients who currently lack them. There has been scant attention, however, to the broader effects such proposals would have on equity within health care and research.

The most important product of the drug development process is the evidence base about how to use potential new medications. This evidence base also informs further research.[1] This information includes which patients to treat, at what dose, and with what other treatments. It also includes estimates of the benefits and risks of appropriate use of the drug. Approving medications with data from fewer patients or patient-years of exposure diminishes this information base and increases the remaining uncertainty about benefits, risks, and use of a new medication. The costs and burdens of this additional uncertainty are unequally distributed in 4 ways.

First, earlier drug approval directs the burdens of medical uncertainty toward groups of people who are often disadvantaged. The amount of research conducted on a new medication determines how much information is available to guide its use. The United States already provides the fastest approval for new drugs in the world,[2] with almost a quarter of drugs approved in 2015 receiving approval through either breakthrough or accelerated pathways. Even under current laws and regulations, licensing approval is often based on trials of modest size, or single pivotal studies.[3] Patients enrolled in many studies are selected based on strict eligibility criteria; for instance, they are often healthier than the patients in whom the drug will typically be used. As a result, the evidence base available for guiding the use of novel drugs for other groups of patients is already thin.

Earlier approvals would amplify these inequalities. In early phase trials, the elderly, disabled, or ethnically diverse persons; women; and patients taking multiple medications are especially underrepresented,[4] in part because drug developers seek to minimize comorbidities or drug interactions that might derail research programs. Under proposals for accelerated approval, such patients will confront increased uncertainty and risk compared with men, people who are middle aged, or patients who may be healthier. Ironically, in some cases such "underrepresented populations" constitute the majority of the intended treatment population. In cancer, for example, roughly 60% of new cases occur among people aged 65 years or older.[5] Some previous efforts to accelerate drug approval have been associated with black-box warnings for groups of patients, such as rituximab for patients with hepatitis B exposure.[6,7]

Some legislation that aims to accelerate drug approvals, such as the 21st Century Cures Act, proposes to improve the evidence base for treating groups of people who have traditionally been underrepresented by promoting their inclusion in trials. Increasing diversity within trials is an important goal that the US Food and Drug Administration (FDA) is taking steps to advance.[8] However, the aspirations of accelerated approval and increased diversity in preapproval studies conflict. Permitting approval on the basis of data from fewer patients or from fewer patient-years of exposure, reduces the power of studies to detect differences in risks and benefits in relevant subgroups. Similarly, relying on trials that exclude patients who are elderly, who take multiple medications, or who have comorbidities leads to studies that have limited statistical power to detect differential effects in these groups. To accelerate approval, studies involving underrepresented groups would have to be conducted after drugs are approved, an approach that is problematic.

Second, earlier drug approvals strain the capacity of the health care system to distribute health care resources fairly. For pharmaceutical manufacturers, market approval represents a shift from spending money to conduct trials to earning money from product sales. Because incentives to conduct additional trials are vastly diminished after licensure and regulatory enforcement is lacking, the pace of drug company follow-through with postapproval trial obligations is often glacial. For example, 18 years after the accelerated approval of midodrine hydrochloride for symptomatic orthostatic hypotension, postapproval efficacy studies mandated by the FDA had yet to be completed.[9]

After marketing approval, the costs of reducing uncertainty about the benefits and risks of drugs are typically borne by health care organizations and research funded by government organizations. Health systems, however, are designed to deliver care, not to generate reliable medical evidence. Practices like blinding, randomization, or standardized-event recording are more difficult to implement in systems that are oriented toward care. Health care systems represent inefficient environments in which to learn about differential effects of novel drugs.

Disparities in health information for different patient groups could persist for long periods and be difficult to eliminate. Health systems could attempt to address them, but this would require a substantial shift of resources from delivering therapies toward evidence generation (eg, training physicians to record outcomes in a standardized fashion), further straining the resources available for care. Alternatively, publicly funded research systems like the National Institutes of Health could fund research to reduce residual uncertainties. Although this approach is more likely to produce reliable evidence efficiently, government agencies have limited resources and competing funding

priorities, including sponsorship of research not normally supported by drug companies.

Third, accelerating approval for new drugs socializes more of the costs of uncertainty, while private entities profit from new drug development. Many of the costs of uncertainty shift at the point of licensure from developers to those purchasing new drugs. Whether through out-of-pocket expenses, the costs of health insurance, or tax dollars, consumers bear both the cost of purchasing new medications and a larger share of the costs of generating the information needed to maximize the clinical benefit of these drugs.

It might be argued that this shift in the distribution of drug development costs is justifiable as a means of encouraging companies to research treatments for difficult-to-treat or rare diseases. However, there is no assurance that companies would invest in such efforts instead of focusing on other research areas or merely returning profits to shareholders.

Fourth, accelerating the drug approval process would shift the burdens of uncertainty away from study participants who are provided with a relatively rigorous and comprehensive process of informed consent. In research, institutional review boards and other oversight bodies ensure that uncertainty is explicitly communicated to study subjects. This respects the autonomy of participants by giving them the opportunity to accept or decline risks in light of an adequate understanding of relevant information. Consent procedures for trials prior to the licensure of drugs are often especially rigorous. Although informed consent should be an important component of all medical care, disclosure is often less demanding in care settings and is not subject to prior review. Indeed, some proponents of mechanisms that integrate care and research, like "learning health care systems," have advocated more lenient consent processes.[10]

The ability of health systems to safely and effectively treat diverse groups of people is an important issue of public policy. So too is the ability to contain health care expenditures and allocate them efficiently. Marketing approval for new medications represents a turning point in which costs and burdens associated with medical uncertainty shift from sponsors and research subjects to health systems and treatment populations. Accelerating the point at which approval takes place reduces the quality and relevance of medical information in a way that has substantial implications for the productivity and efficiency of the research and health systems.

Without corrective measures, accelerating market approval for new drugs may make the process of reducing health care disparities more costly, more burdensome to patients, and more protracted. Further evidence collection is likely to occur in settings where patients are less well protected by rigorous informed consent processes. Debates about accelerated access have inadequately addressed these broader effects on equity in health care and research.

ARTICLE INFORMATION

Published Online: June 13, 2016. doi:10.1001/jamainternmed.2016.2534.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was funded by Canadian Institutes of Health Research (EOG 111391).

Role of the Funder/Sponsor: The funding institution had no role in the conception and creation of this article; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Kimmelman J, London AJ. The structure of clinical translation: efficiency, information, and ethics. *Hastings Cent Rep*. 2015;45(2):27-39.

2. Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. Regulatory review of novel therapeutics—comparison of three regulatory agencies. *N Engl J Med*. 2012;366(24):2284-2293.

3. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA*. 2014;311(4):368-377.

4. Seidenfeld J, Horstmann E, Emanuel EJ, Grady C. Participants in phase 1 oncology research trials: are they vulnerable? *Arch Intern Med*. 2008;168(1):16-20.

5. Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. *Cancer*. 1997;80(7):1273-1283.

6. Richey EA, Lyons EA, Nebeker JR, et al. Accelerated approval of cancer drugs: improved access to therapeutic breakthroughs or early release of unsafe and ineffective drugs? *J Clin Oncol*. 2009;27(26):4398-4405.

7. Frank C, Himmelstein DU, Woolhandler S, et al. Era of faster FDA drug approval has also seen increased black-box warnings and market withdrawals. *Health Aff (Millwood)*. 2014;33(8):1453-1459.

8. Califf R. 2016: The year of diversity in clinical trials. http://blogs.fda.gov/fdavoice/index.php/2016/01/2016-the-year-of-diversity-in-clinical-trials. Published January 27, 2016. Accessed May 9, 2016.

9. Mitka M. Trials to address efficacy of midodrine 18 years after it gains FDA approval. *JAMA*. 2012;307(11):1124-1127.

10. Menikoff J. The unbelievable rightness of being in clinical trials. Commentary. *Hastings Cent Rep*. 2013;43(spec no):S30-S31.

VIEWPOINT

Inclusion Across the Lifespan
NIH Policy for Clinical Research

Marie A. Bernard, MD
National Institute on Aging, National Institutes of Health, Bethesda, Maryland.

Janine A. Clayton, MD
Office of Research in Women's Health, National Institutes of Health, Bethesda, Maryland.

Michael S. Lauer, MD
Office of Extramural Research, National Institutes of Health, Bethesda, Maryland.

In 2005, a trial supported by the National Institutes of Health (NIH) that included patients with a mean age of 60 years demonstrated that implantable cardioverter-defibrillators had improved survival rates over amiodarone in patients with congestive heart failure.[1] This study and another that examined cardioverter-defibrillator therapy contributed to change in clinical practice.[2] However, 40% of patients who subsequently received cardioverter-defibrillators were older than 70 years and 10% to 20% were older than 80 years,[2] illustrating the importance of adequate inclusion of appropriate populations in clinical studies. In a review of 109 clinical trials, Zulman et al found inadequate inclusion of older adults to allow for informed decision making.[3] In a review of 338 phase 3 and phase 4 NIH-funded studies that were actively recruiting in ClinicalTrials.gov, Spong and Bianchi noted that 75.7% explicitly excluded children, contributing to problems with adequate information for pediatric dosing and other interventions.[4]

To help reduce inadequate inclusion of younger and older populations, the NIH's Inclusion Across the Lifespan (IAL) policy[5] will become effective for all grant applications submitted on or after January 25, 2019. This policy is the next step in a series of policies to facilitate the inclusion of scientifically appropriate and relevant populations for the many questions addressed by NIH-funded clinical researchers. In this Viewpoint, we summarize the policies and mandated activities that preceded the IAL policy and the provisions of the policy. The implementation of this policy will have implications for all clinical research supported by the NIH and should enhance transparency and support reproducibility of clinical study findings in broader populations.

> The implementation of this policy will have implications for all clinical research supported by the NIH and should enhance transparency and support reproducibility of clinical study findings in broader populations.

Inclusion Policy History

Following NIH guidance on inclusion of women in clinical studies in 1986, the NIH developed a policy responsive to legislation requiring inclusion of women and minorities in NIH-funded clinical research in 1994.[6] This policy included a requirement that phase 3 clinical trials subject to US Food and Drug Administration regulation be designed such that a valid analysis stratified by sex/gender and race/ethnicity could be performed. In 1998, the NIH issued a policy regarding the inclusion of children in clinical research and amended the policy in 2015 to clarify the definition of a child as someone younger than 18 years.[7]

With the passage of the 21st Century Cures Act in December 2016,[8] Congress required the NIH to collect data on the inclusion of participants in clinical trials by age. Congress also required the NIH to (1) convene within 180 days a workshop on age groupings and age exclusions in clinical research, (2) post workshop findings on an NIH website, (3) publish data on age of participants in NIH-funded clinical research, including pediatric subgroups, and (4) determine, within 180 days of the workshop, whether to revise inclusion guidelines on age.

IAL Workshop

The NIH convened the workshop in June 2017 to consider issues of the inclusion of infants, children, adolescents, and older adults in clinical studies. Experts in pediatrics, geriatrics, biostatistics, ethics, and scientific publication were assembled for the workshop. The NIH charged the group to consider opportunities for enhanced participation of these populations regardless of whether the research was funded by the NIH.

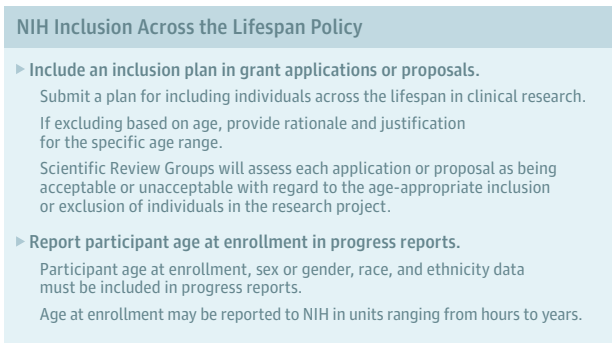
The participants of the workshop identified opportunities for enhancing the inclusion of pediatric and older populations.[9] Some suggested changes that could be implemented in the short-term included reviewing and revising NIH policies on the inclusion of pediatric and older adult populations to maximize inclusiveness; revising grant applications to ensure inclusion; reinforcing to reviewers that inclusion is part of the review criteria; and reporting by age and tracking inclusion of children and older adults in clinical studies.[9]

Subsequent Actions

Extensive discussion at the workshop focused on the need for more detailed information regarding the age of individuals participating in clinical research and the challenge of appropriately representing age. Age might be categorized in one way for one research question, and in another way for a different question. Given the choice, many researchers prefer using continuous rather than categorical data because more can be learned from analyses presented in different ways. For example, for a study participant who is 12 years old and another participant who is 8 years old, more granular information can be obtained from analyses that consider the participant's individual age, rather than from

Corresponding Author: Marie A. Bernard, MD, National Institute on Aging, National Institutes of Health, 5C35, Bethesda, MD 20892 (mbernard@nia.nih.gov).

Figure. Summary of the National Institutes of Health's (NIH's) Inclusion Across the Lifespan Policy



analyses that include the 12-year-old child in a group defined as "aged 12 to 18 years" and the 8-year-old child in a group defined as "aged 6 to 11 years." Therefore, the NIH will ask investigators to submit anonymized individual-level data on age and other demographics. These data will make it possible for the agency to answer questions such as "What are the sex-specific age distributions of men and women enrolled in NIH-funded studies of Paget disease of bone?" Going forward, this change will allow the NIH to respond to another provision of the 21st Century Cures Act that calls for reporting of demographics of participants of NIH-funded studies by disease category.

The IAL policy, summarized in the **Figure**, calls for researchers to justify a higher or lower age requirement for participation in clinical studies. The policy also calls for grant application reviewers to carefully consider the age groups proposed for studies to determine whether the projected population is appropriate for the scientific question being posed.

Challenges

Enrolling older patients in clinical trials invariably means patients with more comorbidities will be included in studies, meaning that the data will be "noisier." This inclusion of older patients and the identification of heterogeneity of treatment response among subgroups (eg, very old, very young) may, in some cases, impose the need for larger sample sizes. But, the inclusion of potentially more heterogeneous groups of older and younger patients also challenges investigators to identify more nimble, cost-effective approaches (eg, adaptive or Bayesian designs).[9] Researchers will need to consider better ways to collect data to efficiently facilitate the conduct of larger-scale trials at a reasonable cost, such as through randomized registry trials. In addition, there will be a need for a cultural challenge to make it acceptable to enroll more complex patients into trials.

Expected Outcomes

The IAL policy, and the review and reporting requirements associated with it, should help ensure that children and older adults are not inappropriately excluded from clinical studies. The policy also has the potential to provide a more robust understanding of the full spectrum of participants recruited into clinical studies. Insights garnered from this expanded inclusion approach could enhance reproducibility and generalizability of clinical study findings.

ARTICLE INFORMATION

Published Online: September 21, 2018. doi:10.1001/jama.2018.12368

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352(3):225-237. doi:10.1056/NEJMoa043399

2. Revenco D, Morgan JP, Tsao L. The dilemma of implantable cardioverter-defibrillator therapy in the geriatric population. *J Geriatr Cardiol*. 2011;8(3):195-200. doi:10.3724/SP.J.1263.2011.00195

3. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *J Gen Intern Med*. 2011;26(7):783-790. doi:10.1007/s11606-010-1629-x

4. Spong CY, Bianchi DW. Improving public health requires inclusion of underrepresented populations in research. *JAMA*. 2018;319(19):2045. doi:10.1001/jama.2018.4098

5. National Institutes of Health. *Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects*. Bethesda, MD: National Institutes of Health; 2017. Notice NOT-OD-18-116. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html. Accessed June 26, 2018.

6. National Institutes of Health. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. https://grants.nih.gov/grants/guide/notice-files/not94-100.html. Accessed June 26, 2018.

7. National Institutes of Health. Inclusion of children in clinical research: change in NIH definition. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html. Published October 13, 2015. Accessed June 26, 2018.

8. National Institutes of Health. 21st Century Cures Act. Pub L No. 114-255, 130 Stat 1033. https://www.nih.gov/research-training/medical-research-initiatives/cures. Accessed June 26, 2018.

9. National Institutes of Health. Inclusion Across the Lifespan: June 1–2, 2017 Workshop Summary. Bethesda, MD: National Institutes of Health; 2017. https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20_FINAL_508.pdf. Accessed June 26, 2018.

A Patient-Centered Approach to Comparative Effectiveness Research Focused on Older Adults: Lessons From the Patient-Centered Outcomes Research Institute

Noah R. Mason, BA, Harold C. Sox, MD, and Evelyn P. Whitlock, MD, MPH

ABSTRACT: The mission of the Patient-Centered Outcomes Research Institute (PCORI) is to fund the production of high-quality evidence that will enable patients and clinicians to make informed, personalized healthcare decisions. Since 2012, the PCORI has invested $177 million in patient-centered comparative effectiveness research (CER) that specifically targets the health needs of older adults, with additional relevant studies in its broader portfolio. Developing the PCORI's research portfolio has provided us with significant insights into what factors to consider when conducting CER in older adult populations. When comparing the net benefit of two or more interventions for older adults, investigators should consider the following: absolute risk difference, competing risks, life expectancy, the difference between chronologic and physiologic age, the importance of patient preferences, and other potential drivers of variable treatment effects. Investigators should also engage older adults and their caregivers as partners throughout the research process. Their input helps to identify key outcomes of interest and insights about the conduct of the research. As the PCORI continues to support research that addresses the healthcare decisions of the rapidly growing older adult population, it needs to partner with patients and researchers to identify the most important questions to address. **J Am Geriatr Soc 00:1–8, 2019.**

Key words: comparative effectiveness research; patient-centered outcomes research; geriatrics; older adults; treatment response heterogeneity

From the *Patient-Centered Outcomes Research Institute, Washington, District of Columbia.

Address correspondence to Harold C. Sox, MD, Patient-Centered Outcomes Research Institute, 1828 L St NW, Ste 900, Washington, DC 20036. E-mail: hsox@pcori.org

DOI: 10.1111/jgs.15655

INTRODUCTION

The theme of this article is framing patient-centered comparative effectiveness research (CER) on health problems of older people. By patient-centered research, we mean the generation of evidence that helps clinicians and patients to choose a test or treatment that is tailored to the patient's needs and preferences. Accordingly, the article focuses on research approaches that provide strong evidence to inform individualized healthcare choices by older people and their clinicians.

The article begins with an introduction to the Patient-Centered Outcomes Research Institute (PCORI) and its portfolio of geriatric research. The middle section focuses on patient-level factors that drive differing treatment effects, each discussed in the context of the needs of older persons. The last section is about choosing outcome measures that best suit the preferences of older persons and how the PCORI engages older stakeholders in designing research that meets their needs. To illustrate some of these points, we present examples from the PCORI's current portfolio.

The PCORI and Its Portfolio of Geriatrics Research

The PCORI is the first publicly supported funding organization whose primary mission is to fund clinical CER that examines clinical effectiveness, risks, and benefits of two or more medical treatments, services, or strategies used in diagnosis, treatment, management, and/or prevention of illness or injury.[1] The purposes of CER were articulated by the PCORI's legislative authorization[1] and by the Institute of Medicine (now the National Academy of Medicine).[2,3] The PCORI's Board of Governors focused the organization's mission on CER that is patient centered, and the PCORI has been a leader in the movement to involve patients and other stakeholders in developing its portfolio of CER.

The PCORI's research priorities, as established by its Board of Governors, address health disparities, improving health systems, communication and dissemination, methods, and interventions to assess, prevent, diagnose, and treat clinical conditions. Since 2012, the PCORI has funded $1.7 billion in research that addresses these

Journal of the American Geriatrics Society published by Wiley Periodicals, Inc. on behalf of The American Geriatrics Society. 0002-8614/18/$15.00

priorities, particularly patient-centered clinical CER and approaches to improve the delivery of patient-centered care.

The PCORI has positioned itself to support important research that addresses the needs of older adults. The PCORI already has substantial experience in funding geriatrics research, with $177 million (39 projects; 10% of $1.7 billion total funding) awarded to date in research clearly targeting common geriatric conditions (eg, falls) or focused on older adult and Medicare populations. The PCORI's diverse "geriatrics portfolio" targets cancer (six projects), musculoskeletal diseases (six projects), mental illness, neurological diseases, and multiple comorbid conditions (four projects each). Other disease categories have one or two projects, and seven projects do not target a specific disease, but address problems experienced with many diseases, such as care transitions (Appendix Table).

Approximately two thirds of the PCORI's $177 million investment addresses clinical comparative effectiveness questions (Appendix Table). Table 1 depicts two such in-process studies. In study 1-A, the PCORI together with the National Institute on Aging funded a $30 million randomized trial comparing a multifactorial strategy for reducing the risk of serious falls and fall-related injuries to enhanced usual care among 5300 older adults at increased risk for serious falls. Study 1-B compares the effectiveness of different medication strategies for treatment-resistant depression in older adults.

The other one third of the PCORI's geriatrics-focused funding are studies of methods for making the delivery and/or organization of clinical care for older adults more effective and more patient centered. Our premise is that enhancing care delivery should lead to better clinical outcomes. These projects address shared decision making, care coordination and transitions, navigating the patient care system, palliative care and advance care planning, and home-based care delivery. Table 1 depicts two such studies. Study 1-C compares strategies to improve care coordination and self-management support for older people with asthma. Study 1-D compares the use of community-based patient advocates to usual care for supporting chronically ill older adults' transition from the emergency department to home.

Additional studies in the PCORI portfolio also address problems that affect adults of all ages (searchable on the PCORI's website at https://www.pcori.org/research-results?f%5B0%5D=field_project_type%3A298[4]) and complement the specific geriatrics portfolio described herein. As with other PCORI awards, the topics in our geriatrics portfolio were driven by the interests of individual investigators and PCORI stakeholders. To maximize the PCORI's contribution, the field of geriatrics and the community it serves should continue to take advantage of the PCORI's open invitation to stakeholders to tell us their needs for additional CER.

Simply focusing on specific clinical issues associated with aging or including older adults in research is not sufficient for generating the evidence to support individualized care. Table 2 outlines major strategies for conducting patient-centered CER. The next section details patient factors that can lead to differing effects from the same treatment and how these factors affect both research and clinical considerations in older adults. The following section discusses outcomes from the perspective of older adults. The last section addresses a novel research strategy, one for which the PCORI has been a leader: involving patients and other stakeholders in the design and conduct of healthcare research.

Healthcare Decision Making for Older Adults: How Individual Characteristics and Preferences Drive Treatment Choices and Net Benefit

Clinicians, older patients and their caregivers, and policy makers regularly face decisions about health and healthcare. The backbone of decision making in medicine is an assessment of the expected benefits, harms, and, ultimately, net benefit of the interventions for the individual. This assessment of benefits and harms should include the patient's feelings about the future health states that he or she may experience. Clinicians intuitively grasp that patients will vary in their response to treatments (heterogeneity of treatment effect), but the search for the factors that drive response has only recently begun in earnest.[5] In the PCORI's legislative mandate, Congress stipulated that the PCORI shall produce evidence about differences in comparative effectiveness in subpopulations and individuals;[1] this mandate is particularly important for research addressing older adults, who are a highly varied population. In a large community-based sample of older patients with heart failure, for example, the presence of any functional limitations greatly increased risk for death and other major adverse outcomes, particularly in the presence of two or more noncardiovascular comorbidities; however, 25% of patients with heart failure had neither multimorbidity nor functional limitations.[6]

Patient-level sources of differing effects from the same treatments can be considered under four main areas: baseline risk, treatment responsiveness and harms, competing risks, and patient preferences for health states.[7] These factors are based on individual characteristics and vulnerabilities[8] that commonly differ between younger and older adults and among older adults. We cover these each in turn briefly, with illustrative examples in Table 2.

Baseline Risk

The baseline risk of a disease drives treatment choice. Baseline risk reflects the pretreatment risk of experiencing the outcome the treatment intends to prevent.[7] Baseline risk already informs common treatment choices, such as therapies to prevent cardiovascular disease,[9] in which age plus risk factors predict 10-year cardiovascular event rates ranging from less than 2.5% to 20.0% or greater;[10] baseline risk could better inform other treatment choices if more consistently considered and reported in research,[11] as recommended.[12]

- The benefit of an intervention is often expressed as the relative risk (the ratio of benefits for treatment A to the benefits for treatment B), but absolute risk difference is usually more informative.[8] For example, the absolute risk difference (the mortality rate after treatment A minus the mortality rate after treatment B) describes a tangible result: the percentage reduction in outcome rates. Even when relative treatment effects are consistent across subgroups (ie, there is no statistical heterogeneity of treatment effect,[13] absolute treatment effects will differ among subgroups with meaningful differences in their

Table 1. Selected PCORI Studies That Focus on the Needs of Older Adults

Variable	Falls Prevention	Depression	Asthma Care	Hospital Use
Study title (PI name)	Randomized Trial of a Multifactorial Fall Injury Prevention Strategy: A Joint Initiative of PCORI and the National Institute on Aging (Shalender Bhasin, MD)	Optimizing Outcomes in Treatment-Resistant Depression in Older Adults (Eric Lenze, MD)	Clinic-Based vs. Home-Based Support to Improve Care and Outcomes for Older Asthmatics (Alex Federman, MD, MPH)	An Emergency Department-to-Home Intervention to Improve Quality of Life and Reduce Hospital Use (Donna Carden, MD)
Study ID[a]	1-A	1-B	1-C	1-D
Study purpose	To compare a multifactorial fall injury prevention intervention with enhanced usual care for reducing the risk of serious fall injuries among noninstitutionalized older adults.	To compare the benefits and risks of different antidepressant strategies (augmentation and switching drugs) among older adults.	To compare a clinic-based asthma care coach with a home-based community health worker coach with usual care for improving asthma-related outcomes among older adults.	To compare use of trained community-based patient advocates with usual post-ED care for improving outcomes after ED discharge.
Study population	Community-living persons ≥75 y who are at increased risk for serious fall injuries	Adults ≥60 y with major depressive disorder resistant to two or more antidepressant trials	African American or Hispanic/Latino adults ≥60 y who have poorly controlled asthma	Medicare fee-for-service beneficiaries with one or more chronic conditions
Interventions	Multifactorial fall injury prevention intervention: risk assessments, individualized fall care plans that address identified risk factors, and ongoing monitoring. Enhanced usual care: patients discuss booklet on falls with primary care provider.	Step 1 strategies: ADM + aripiprazole (augmentation), ADM + bupropion (augmentation), or switch from ADM to bupropion. Participants resistant to step 1 will be randomized to step 2: augment with lithium or switch to nortriptyline.	Routine PCP care + a community health worker work to support and coordinate patient care in their home. Routine PCP care + an asthma care coach for patient care in clinic. Usual care: routine PCP care without any additional care coordination or support provided.	ED-to-home transition intervention: home visit and telephone calls with a trained, community-based patient advocate who will help patients to attend follow-up physician visits, respond to signs of worsening disease, address medication concerns, and communicate with healthcare providers.
Out comes	Serious falls, fall injuries, concerns about falling, physical function and disability, anxiety/ depressive symptoms, hospitalizations, nursing home admissions, and death	Psychological well-being, remission from depression, serious adverse events, falls and fall-related injuries, physical function, and social participation	Asthma control, quality of life, resource use, medication adherence, self-management behaviors, ability to conduct daily activities, and patient and caregiver satisfaction with care	Health-related quality of life (health status, satisfaction with care, physical function, and social and emotional health), ED visits, hospital admissions, ability of patients to make decisions about their health and healthcare

Abbreviations: ADM, antidepressant medication; ED, emergency department; ID, identification; PCORI, Patient-Centered Outcomes Research Institute; PCP, primary care provider; PI, principal investigator.

[a]The study ID is a code that appears next to text that refers to an example study described in a table. It enables the reader to find the detailed information to which the body of the text refers.

Study 1-A is available at https://www.pcori.org/research-results/2014/preventing-serious-falls-among-older-adults-project-supported-pcori-and; study 1-B is available at https://www.pcori.org/research-results/2016/comparing-treatments-older-adults-who-have-major-depression-does-not-respond; study 1-C is available at https://www.pcori.org/research-results/2013/comparing-two-ways-offering-treatment-older-adults-asthma-samba-study; and study 1-D is available at https://www.pcori.org/research-results/2013/emergency-department-home-intervention-improve-quality-life-and-reduce.

baseline outcome risk.[5] Recent meta-research suggests baseline outcome risk varies substantially in trials among selected candidates for pharmaceutical treatment.[14]

Risk for many diseases increases with age, and so absolute treatment benefit may also increase, and inform age-specific comparative effectiveness. For some years, cardiac surgery was deemed less effective in older people because survival rates after coronary revascularization were considerably lower in older people. However, because survival rates of comparable older people with medical therapy were even lower relative to younger people, the difference in mortality rates after treatment (absolute risk difference for surgery vs medical therapy) was larger after treatment of older people than younger people.[15] Although age is a prominent risk factor for cardiovascular disease, among older adults, other risk

Table 2. Strategies for Conducting Effective, Patient-Centered CER in Older Adult Patient Populations

Strategies	Study ID[a]	Examples From the PCORI's Geriatrics Portfolio
Focus on conditions and/or clinical dilemmas that disproportionately or exclusively affect older adults	N/A	The PCORI's geriatrics portfolio includes many projects studying conditions or health topics that affect the health of older adults, such as falls, frailty, cognitive impairment, multiple chronic/comorbid conditions, communication and medical decision making, and palliative care.
Effectively engage older adults throughout the research process: hypothesis generation, study design, conduct of the study, data analysis, and dissemination of results	N/A	Refer to example studies in Table 3.
Include and engage caregivers of older adults throughout the research process	2-C	Example study: Improving Communication for Chemotherapy: Addressing Concerns of Older Cancer Patients and Caregivers (Supriya Mohile, MD, MS): caregivers provided significant input at all stages of this study's preliminary work, including helping to develop the geriatric assessment intervention and choose outcomes for the study. Patients and caregivers were both part of the study population, and caregiver satisfaction and burden were among the secondary outcomes being assessed.
Effectively target interventions for older adults by considering the following: • Drivers of differing treatment effects (baseline risk, treatment responsiveness, treatment harm, and competing risks) • Importance of net benefit (ie, balance of benefits and harms) • Values and preferences of older adults • Difference between chronologic and biologic age	2-D	Example study: Patient Valued Comparative Effectiveness of Corticosteroids Versus Anti-TNF Alpha Therapy for Inflammatory Bowel Disease (James Lewis, MD)[2-D]: this study compared the benefit-harm profiles of anti-TNF agents and corticosteroids for the treatment of inflammatory bowel diseases. By measuring both the benefits (reduced need for bowel resection surgery) and harms (serious infections and short-term mortality risks) of each therapy and by using patient preference weights for each outcome, this study could compare each therapy's net benefit (J Lewis, unpublished data, https://clinicaltrials.gov/ct2/show/NCT02316678, 2012).
	2-E	Example study: Preparing Spanish-Speaking Older Adults for Advance Care Planning and Medical Decision Making (Rebecca Sudore, MD): this study was based on the key difference between chronologic and biologic age. The investigators chose to recruit older adult patients with a lower minimum age (55 y) than the traditional 65-y age limit because they recognized that adults in safety net settings (low socioeconomic status) experience accelerated aging, functional decline, and sequelae of chronic disease.[9,10]
Adapt study design to incorporate older adults' values and preferences, include broad, real-world older adult population and robust HTE analyses, and include longer length of follow-up (than typical trials) to adequately capture safety/adverse event outcomes	2-F	Example study: Comparative Effectiveness of Behavioral Interventions to Prevent or Delay Dementia (Glenn Smith, PhD): this study's broad inclusion criteria help to ensure a study population that represents a real-world population of patients with amnestic mild cognitive impairment. The investigators are planning to explore potential heterogeneity of treatment effects by assessing interactions between treatments and age, along with other baseline demographic variables.
Ensure study outcomes account for the importance of harms, baseline risk, both relative and absolute harms and benefits, provider-patient communication, and relevant patient-centered outcomes (eg, quality of life, functional ability, independence, and time at home)	2-G	Example study: A Practical Intervention to Improve Patient-Centered Outcomes After Hip Fractures Among Older Adults (REGAIN Trial) (Mark Neuman, MD, MS): the outcomes of this study include ability to walk (primary outcome), ability to live at home independently, overall health and disability, pain, mortality, and safety and tolerability outcomes (acute postoperative pain, satisfaction with care, and major adverse events during hospitalization).

Abbreviations: CER, comparative effectiveness research; HTE ; ID, identification; N/A, not applicable; PCORI, Patient-Centered Outcomes Research Institute; TNF, tumor necrosis factor.

[a]The study ID is a code that appears next to text that refers to an example study described in a table. It enables the reader to find the detailed information to which the body of the text refers.

Study 2-C is available at https://www.pcori.org/research-results/2013/improving-communication-chemotherapy-addressing-concerns-older-cancer-patients study 2-D is available at https://www.pcori.org/research-results/2013/anti-tnf-drugs-versus-long-term-steroid-use-patients-inflammatory-bowel study 2-E is available at https://www.pcori.org/research-results/2013/preparing-spanish-speaking-older-adults-advance-care-planning-and-medical study 2-F is available at https://www.pcori.org/research-results/2013/comparative-effectiveness-behavioral-interventions-prevent-or-delay-dementia; and study 2-G is available at https://www.pcori.org/research-results/2015/comparing-how-two-types-anesthesia-affect-recovery-hip-fracture-surgery-regain.

Table 3. The PCORI Geriatrics Portfolio: Engagement of Older Adults and Their Caregivers in CER[a]

Study	Group Exercise for Older Adults (3-A)	Navigating High-Risk Surgery (3-B)
Title	On the Move: Optimizing Participation in Group Exercise to Prevent Walking Difficulty in At-Risk Older Adults (Jennifer Brach, PhD)[28]	Navigating High Risk Surgery: Empowering Older Adults to Ask Questions That Inform Decisions About Surgical Treatment (Margaret Schwarze, MD, MPP)[29]
Study period	2013–2017	2015–2020
Engagement activities	Community-dwelling older adults and providers were involved throughout the research process, including preparation, execution, analysis, and dissemination phases.	A PFAC, surgeons, and community members met monthly and were involved in identifying the research question, developing the intervention, and executing the research project.
Impact on study design	• New aim examining the sustainability of the intervention was added thanks to providers' feedback. • Older adults' preferences influenced the randomization scheme. • Inclusion/exclusion criteria were made more inclusive thanks to providers' feedback. • Focus groups of adults helped develop the exercise intervention.	The PFAC identified the need for more information and decisional support during preoperative conversations. The PFAC stressed the importance of including family members as study participants. The PFAC, surgeons, and focus groups of community members helped design and revise the question prompt list intervention to specifically target the needs of patients considering high-risk surgery.
Impact on study outcomes	During focus groups, older adults identified maintaining independence as a key outcome. Investigators subsequently designated function, disability, and mobility as their three primary outcomes.	The PFAC helped identify impractical measures for patients to answer over the telephone, helped identify those outcomes that were relevant to patients and families, and stressed the need not to be "blindsided" by the outcomes of surgery. Outcomes included in the study were as follows: (1) patient engagement in decision making and (2) psychological well-being.

Abbreviations: CER, comparative effectiveness research; PCORI, Patient-Centered Outcomes Research Institute; PFAC, Patient and Family Advisory Council.
[a]The study ID is a code that appears next to text that refers to an example study described in a table. It enables the reader to find the detailed information to which the body of the text refers.
Study 3-A is available at https://www.pcori.org/research-results/2013/comparing-two-types-group-exercise-classes-help-older-adults-improve-walking; and study 3-B is available at https://www.pcori.org/research-results/2015/navigating-high-risk-surgery-empowering-older-adults-ask-questions-inform.

factors have stronger relative effects and thus the absolute risk for cardiovascular disease varies widely.[16] Another advantage of absolute risk difference for clinicians is its easy translation to a number that implies the effort or exposure needed to achieve an outcome (eg, number needed to treat or number needed to harm), because the reciprocal of the absolute risk difference is the number of people exposed to an intervention to produce one person's outcome.

Treatment Responsiveness and Vulnerability to Treatment Harms

Net treatment benefit (benefits minus harms) should drive decision making. Therefore, even with a larger absolute benefit based on greater pretreatment risk, the desirability of a treatment is also affected by its absolute harms. For example, risk of gastrointestinal tract bleeding, which varies widely based on age, sex, and medical history,[17] influences the desirability of chemoprevention with aspirin.[18] Treatment harms may be more likely in older adults because of comorbidities and common use of multiple medications. Similarly, the magnitude of benefit (also known as treatment responsiveness) may vary in older adults because of differences in body composition (percentage body water), in function (balance or strength), or in other physiological factors (frailty) whose effects may require direct evidence in older adults rather than extrapolation from evidence in younger individuals.[19,20] Study 2-D in Table 2 illustrates how investigators study benefits, harms, and net benefit from interventions.

Competing Risks

Competing risks may affect treatment choices. Competing risks from other disease processes can prevent an individual from experiencing the expected benefit from treatment. Screening for cancer illustrates this point; the mortality benefits of screening typically do not appear for several years after starting regular screening, during which time the patient may succumb from disease or injury.

Older individuals typically have more than one chronic disease, making competing risks important to factor into research and critical when choosing among comparative treatments.[7] The time horizon for achieving benefits or avoiding harms becomes important in treatment choices for older adults, so time-to-benefit analyses can be informative. Measuring the impact of common competing risks for a variety of decision dilemmas would be an important geriatrics research agenda.

Competing risks include considerations of life expectancy. Life expectancy (approximated by the inverse of the annual mortality rate) goes steadily down as a person gets older, but also shows wide variability among those of the same chronological age.[21] With advancing age, differences in life expectancy due to differences in health status become larger.[22] Therefore, expected net benefits (benefits minus

harms) of two interventions that differ based on post-intervention life expectancy are more prominent in comparative effectiveness decisions in older adults than in younger people. One way to compare the benefits of two interventions is to measure the life-years gained from the interventions. Comparing the likelihood that an older person will live long enough to benefit from the intervention (life expectancy after the intervention), while also considering the probability of experiencing adverse effects in the interim, can inform a decision between treatment choices for an individual patient.

In the future, one imagines that clinical practices and guidelines, such as those about when to stop screening, will become more nuanced and attuned to a person's life expectancy, which is longer for people in excellent health than for those in poor health, regardless of chronological age.[22] Study 2-E (Table 2) exemplifies how considering physiologic age instead of chronologic age led one investigator to lower the inclusion criteria for a study of vulnerable older people from 65 to 55 years.

Patients' Preferences for Future Health States

Although patients' preferences are important throughout all ages and healthcare choices, they are particularly important for older adults who seek to maintain their quality of life despite age-related deterioration. Life expectancy per se (a simple quantitative estimate of years of life remaining) does not reflect the value that people would place on the health states that they could experience in their remaining years. As a concrete example, prostate cancer screening trialists found that some patients' values for the adverse effects of prostate cancer treatment (sexual dysfunction, urinary incontinence, and bowel dysfunction) would decrease the expectation of life in good health after screening because screening led to health states that they especially wanted to avoid.[23,24] Health professionals participating in decision making with older adults and their caregivers must be sure that the conversation includes feelings about experiencing present and future health states (Table 3). Study 2-D in Table 2 illustrates how investigators integrate patient preferences into an assessment of net benefit from treatments with agents that have serious adverse effects.

These key considerations—baseline risk, the net benefit of treatment, competing risks, and patients' preferences for present and future health states—taken together with increasing life expectancy and healthy lifestyles in older people present funders with substantial opportunities. The PCORI and other funders can seize these opportunities by commissioning PCOR and CER that directly inform the healthcare decisions of older people—especially the rapidly growing group older than 80 years.[25] Accordingly, the PCORI's research framework includes a commitment to involving patients in the design and conduct of research, in addition to a requirement to test for treatment response heterogeneity.

Engaging Older Adults and Their Caregivers Throughout the Research Process

Engaging patients, caregivers, and other interested stakeholders throughout the research process is a core tenet of the PCORI's mission. Stakeholders do drive PCORI-funded research, from the identification and prioritization of research topics to the design and conduct of individual studies. We hope that meaningful stakeholder engagement in the research process will improve the relevance of research questions, increase the transparency of the research process, and accelerate the adoption of research findings into everyday practice.[26] In a recent example, community members helped ensure broad participation by older adults in research to determine barriers to help seeking, and these participants also suggested patient-centered strategies to overcome these barriers to safely support aging in place.[27] The PCORI believes that involving older adults and their caregivers in every phase of the research process is crucial to conducting CER that will ultimately lead to healthier older adults (Table 3). Caregivers and family members are an important target of PCORI-funded research in their roles as patient advocates, as support systems, and, at times, as surrogate decision makers for older adults with cognitive impairment.[8,28]

Active and methodical engagement of older adults in clinical research is especially important because they continue to be underrepresented in clinical trials despite their documented interest in participating in research.[29] Study 3-A (Table 3) is an example of meaningful engagement in the PCORI's portfolio. It compares a novel group exercise program vs a standard group exercise program on improving older adults' function, disability, and walking ability. Engaging older adults and their providers throughout this study led to several specific changes: the addition of a new aim examining the intervention's sustainability; a modified randomization scheme that incorporates older adults' preferences; broadened and more pragmatic inclusion criteria; and primary outcomes that align with older adults' wish to remain independent as they age.[30] Study 3-B (Table 3) compares usual care with a "question prompt list" intervention designed to empower older adult patients to participate more actively in decision making about high-risk surgery. This study established a Patient and Family Advisory Council that helped identify the research question, develop the intervention, and identify the most relevant outcomes for both patients and their family members.[31]

Choosing Outcomes and Study Design That Meet the Needs of Older Adults

Older people have several characteristics that can alter the choice of outcome measures. Their life expectancy is measured typically in years, not decades. They have seen suffering as friends and family contend with chronic disease and with the decline that precedes death. As a result, the first priority for many is to maintain the highest quality of life during the years left to them, rather than live for more years with a lower quality of life. Consequently, primary outcome measures often include measures of function, such as the 12-item survey of functional health (SF-12), avoidance of disability, and time spent at home. The PCORI awardees often relegate to secondary outcomes such end points as mortality and discrete clinical events, such as major adverse cardiac events (all-cause mortality, myocardial infarction, or coronary revascularization). Study 2-G (Table 2) illustrates the extensive use of patient-reported outcomes in older adults recovering from hip fracture.

Decision aids can facilitate discussions between an older person and a health professional. The PCORI has a large portfolio of research whose results will fill evidence gaps in our knowledge of the effectiveness of decision aids in promoting decisions that align with how patients value the outcomes they may experience. These include PCORI-funded randomized controlled trials in which the researchers tested the quality of decisions using a decision aid compared with decisions made without the aid; some of these studies are specific to decisions made by older people.

As health declines, many older people require help in navigating life because of cognitive, mental, or physical ill health. Caregivers provide essential support, especially for free-living older persons. Caregivers are typically relatives, a sibling, or a child. Learning to become an effective caregiver and to deal with its emotional stresses can result in better caregiver health, which can trickle down to the health state of the declining older person. One PCORI-funded study compared two leading programs to train caregivers on reducing caregiver burden and caregiver symptoms of depression.[32]

CONCLUSION AND FUTURE DIRECTIONS

In this article, we have provided an overview of the PCORI's CER portfolio on topics of interest to older adults and the research and clinical communities that serve them. The PCORI funds research on the factors that inform decision making by individual patients, especially expected net benefit, which varies widely in older adults. We have described the research considerations that influence net benefit. The PCORI wants to receive high-quality applications that reflect the needs and values of older adults. To that end, we have communicated our perspective on CER as applied to older adults.

Finally, we briefly describe how the geriatrics community can influence the PCORI's CER portfolio. Input from a wide variety of stakeholders, including patients and the research community, actively advocating for needed research through the PCORI's Advisory Panels and acting as applicants, merit reviewers, and peer reviewers of completed research, largely determines what we fund. In performing our board-directed theme of patient centeredness, the PCORI has become a leader in involving stakeholders, including patients and caregivers, in the research process at all levels. To continue to shape the PCORI's funding priorities in geriatrics research will take ongoing, committed effort by the stakeholder community.

ACKNOWLEDGMENTS

The views presented in this article are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its Board of Governors, or its Methodology Committee. We acknowledge the contribution of Emily Lazowick, MPH, in preparing the manuscript for publication.

Conflict of Interest: All three authors were employed by the Patient-Centered Outcomes Research Institute at the time of authorship.

Author Contributions: All three authors took an active role in drafting and revising the article.

Sponsor's Role: A member of the Patient-Centered Outcomes Research Institute's (PCORI's) leadership read the manuscript and approved it. Dr. Whitlock and Dr. Sox are employees of the PCORI.

REFERENCES

1. Compilation of Patient Protection and Affordable Care Act § 6301, Public Law 111-148, 111th Congress. Subtitle D of Title VI. Patient-Centered Outcomes Research. 2010
2. Institute of Medicine. Knowing What Works in Health Care: A Roadmap for the Nation. Washington, DC: National Academies Press, 2008.
3. Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. Washington, DC: National Academies Press, 2009.
4. Patient-Centered Outcomes Research Institute. Explore our portfolio of funded projects (online). Available at https://www.pcori.org/research-results?f%5B0%5D=field_project_type%3A298. Accessed 9 November 2018.
5. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients. JAMA 2007;298:1209–1212.
6. Manemann SM, Chamberlain AM, Roger VL et al. Multimorbidity and functional limitation in individuals with heart failure: A prospective community study. J Am Geriatr Soc 2018;66:1101–1107.
7. Segal JB, Weiss C, Varadhan R. Understanding heterogeneity of treatment effects in pragmatic trials with an example of a large, simple trial of a drug treatment for osteoporosis (online). 2011. Available at http://www.cmtpnet.org/docs/resources/Segal-Heterogeneity-in-Pragmatic-Trials.pdf. Accessed 9 November 2018.
8. Scott IA, Guyatt GH. Cautionary tales in the interpretation of clinical studies involving older persons. Arch Intern Med 2010;170:587–595.
9. U.S. Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: U.S. Preventive Services Task Force recommendation statement. JAMA 2016;316:1997–2007.
10. Goff DC, Lloyd-Jones DM, Bennett G et al. ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014 2013;129:S49–S73.
11. Kent DM, Rothwell PM, Ioannidis JP et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010;11.
12. Pocock SJ, Lubsen J. More on subgroup analyses in clinical trials. N Engl J Med 2008;358:2076–2077.
13. Wang R, Lagakos SW, Ware JH et al. Statistics in medicine: reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189–2194.
14. Kent DM, Nelson J, Dahabreh IJ et al. Risk and treatment effect heterogeneity: re-analysis of individual participant data from 32 large clinical trials. Int J Epidemiol 2016;45:2075–2088.
15. Graham MM, Ghali WA, Faris PD et al. Survival after coronary revascularization in the elderly. Circulation 2002;105:2378–2384.
16. Stam-Slob MC, Visseren FLJ, Jukema JW et al. Personalized absolute benefit of statin treatment for primary or secondary prevention of vascular disease in individual elderly patients. Clin Res Cardiol 2017;106:58–68.
17. Whitlock EP, Williams SB, Burda BU et al. U.S. preventive services task force evidence syntheses, formerly systematic evidence reviews. Aspirin Use in Adults: Cancer, All-Cause Mortality, and Harms: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality, 2015.
18. Bibbins-Domingo K, on behalf of the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Int Med 2016;164:836–845.
19. Kyle UG, Genton L, Hans D et al. Total body mass, fat mass, fat-free mass, and skeletal muscle in older people: cross-sectional differences in 60-year-old persons. J Am Geriatr Soc 2001;49:1633–1640.
20. Schoeller DA. Changes in total body water with age. Am J Clin Nutr 1989;50:1176–1181.
21. Arias E. United States Life Tables, 2008. Atlanta, GA: Centers for Disease Control and Prevention; 2012
22. Welch HG, Albertsen PC, Nease RF et al. Estimating treatment benefits for the elderly: the effect of competing risks. Ann Int Med 1996;124:577–584.
23. Heijnsdijk EA, Wever EM, Auvinen A et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012;367:595–605.
24. Sox HC. Quality of life and guidelines for PSA screening. N Engl J Med 2012;367:669–671.
25. Jacobsen LA, Kent M, Lee M et al. America's Aging Population. Population Reference Bureau, Washington, DC., USA, 2011.
26. Concannon TW, Fuster M, Saunders T et al. A systematic review of stakeholder engagement in comparative effectiveness and patient-centered outcomes research. J Gen Intern Med 2014;29:1692–1701.

27. Lindquist LA, Ramirez-Zohfeld V, Forcucci C et al. Overcoming reluctance to accept home-based support from an older adult perspective. J Am Geriatr Soc 2018;66:1796–1799.
28. Walter LC, Covinsky KE. Cancer screening in elderly patients: A framework for individualized decision making. JAMA 2001;285:2750–2756.
29. Townsley CA, Chan KK, Pond GR et al. Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. BMC Cancer 2006; 6:34.
30. Brach JS, Perera S, Gilmore S et al. Stakeholder involvement in the design of a patient-centered comparative effectiveness trial of the "On the Move" group exercise program in community-dwelling older adults. Contemp Clin Trials 2016;50:135–142.
31. Steffens NM, Tucholka JL, Nabozny MJ et al. Engaging patients, health care professionals, and community members to improve preoperative decision making for older adults facing high-risk surgery. JAMA Surg 2016;151:938–945.
32. Luchsinger JA, Burgio L, Mittelman M et al. Northern Manhattan Hispanic Caregiver Intervention Effectiveness Study: protocol of a pragmatic randomised trial comparing the effectiveness of two established interventions for informal caregivers of persons with dementia. BMJ Open 2016;6.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix Table 1. The PCORI's Geriatrics Portfolio by Primary Disease/Condition.

REVIEW ARTICLE

Pharmacotherapy in Older Adults with Cardiovascular Disease: Report from an American College of Cardiology, American Geriatrics Society, and National Institute on Aging Workshop

Janice B. Schwartz, MD, Kenneth E. Schmader, MD,[†‡] Joseph T. Hanlon, PharmD, MS,[§] Darrell R. Abernethy, MD, PhD,[¶†] Shelly Gray, PharmD, MS,[‖] Jacqueline Dunbar-Jacob, PhD, RN,** Holly M. Holmes, MD, MS,[††] Michael D. Murray, PharmD, MPH,[‡‡] Robert Roberts, MD,[§§] Michael Joyner, MD,[¶¶] Josh Peterson, MD, MPH,[‖‖] David Lindeman, PhD,[***] Ming Tai-Seale, PhD, MPH,[†††] Laura Downey, DVM, MSM,[‡‡‡§§§] and Michael W. Rich, MD[¶¶¶]*

OBJECTIVES: To identify the top priority areas for research to optimize pharmacotherapy in older adults with cardiovascular disease (CVD).

DESIGN: Consensus meeting.

SETTING: Multidisciplinary workshop supported by the National Institute on Aging, the American College of Cardiology, and the American Geriatrics Society, February 6–7, 2017.

PARTICIPANTS: Leaders in the Cardiology and Geriatrics communities, (officers in professional societies, journal editors, clinical trialists, Division chiefs), representatives from the NIA; National Heart, Lung, and Blood Institute; Food and Drug Administration; Centers for Medicare and Medicaid Services, Alliance for Academic Internal Medicine, Patient-Centered Outcomes Research Institute, Agency for Healthcare Research and Quality, pharmaceutical industry, and trainees and early career faculty with interests in geriatric cardiology.

MEASUREMENTS: Summary of workshop proceedings and recommendations.

RESULTS: To better align older adults' healthcare preferences with their care, research is needed to improve skills in patient engagement and communication. Similarly, to coordinate and meet the needs of older adults with multiple comorbidities encountering multiple healthcare providers and systems, systems and disciplines must be integrated. The lack of data from efficacy trials of CVD medications relevant to the majority of older adults creates uncertainty in determining the risks and benefits of many CVD therapies; thus, developing evidence-based guidelines for older adults with CVD is a top research priority. Polypharmacy and medication nonadherence lead to poor outcomes in older people, making research on appropriate prescribing and deprescribing to reduce polypharmacy and methods to improve adherence to beneficial therapies a priority.

CONCLUSION: The needs and circumstances of older adults with CVD differ from those that the current medical system has been designed to meet. Optimizing pharmacotherapy in older adults will require new data from traditional and pragmatic research to determine optimal CVD therapy, reduce polypharmacy, increase adherence, and meet person-centered goals. Better integration of the multiple systems and disciplines involved in the care of older adults will be essential to implement and disseminate best practices. **J Am Geriatr Soc 00:1–10, 2018.**

From the *Divisions of Geriatrics and Clinical Pharmacology, Departments of Medicine and Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, California; [†]Division of Geriatrics, Department of Medicine, Duke University Medical Center, Durham, North Carolina; [‡]Geriatric Research, Education, and Clinical Center, Durham Veterans Affairs Medical Center, Durham, North Carolina; [§]Division of Geriatrics, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; [¶]Office of Clinical Pharmacology, U.S. Food & Drug Administration, Silver Spings, Maryland; [‖]Department of Pharmacy, University of Washington, Seattle, Washington; **School of Nursing, University of Pittsburgh, Pittsburgh, Pennsylvania; [††]Geriatric and Palliative Medicine, Department of Medicine, McGovern Medical School, Houston, Texas; [‡‡]Department of Pharmacy Practice, Regenstrief Institute, Purdue University, West Lafayette, Indiana; [§§]Department of Medicine, College of Medicine, University of Arizona, Phoenix, Arizona; [¶¶]Departments of Anesthesiology and Perioperative Medicine and Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota; [‖‖]Departments of Biomedical Informatics and Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; [***]CITRIS and the Banatao Institute, University of California, Berkeley, California; [†††]Division of Health Policy, Department of Family Medicine and Public Health, University of California, San Diego, San Diego, California; [‡‡‡]Concordance Health Solutions, West Lafayette, Indiana; [§§§]Krannert School of Management, Purdue University, West Lafayette, Indiana; and the [¶¶¶]Cardiovascular Division, Department of Internal Medicine, Washington University, St. Louis, Missouri.

Address correspondence to Janice B. Schwartz, MD, 3333 California Street, Suite 430L, San Francisco, CA 94143-1265. E-mail: janice.schwartz@ucsf.edu

[†]Deceased

See related editorial by Forman et al.

DOI: 10.1111/jgs.15634

0002-8614/18/$15.00

Key words: cardiovascular medication; adverse effects; de-prescribing; polypharmacy; adherence

The pathogenesis and incidence of cardiovascular disease (CVD) are mechanistically linked to aging and to exposure to conventional cardiovascular disease risk factors.[1–3] A high prevalence of coronary heart disease, heart failure, valvular heart disease, arrhythmias, peripheral arterial disease, and other CVD processes will inevitably burden the expanding population of older adults, but multiple comorbid conditions and common geriatric syndromes that fundamentally alter the risk:benefit relationship for virtually all diagnostic procedures and therapeutic interventions, including medications proven to be effective in younger, healthier individuals, often complicate caring for older adults with CVD. The multiple healthcare providers involved in managing older adults with multiple conditions further complicates care. Optimal person-centered care for the growing population of older adults thus demands that these multiple complex interactions be better delineated and more fully integrated into routine clinical decision-making and drug prescribing for older adults with CVD.[4]

These issues were the impetus for a series of workshops supported by the National Institute on Aging (NIA), the American College of Cardiology (ACC), and the American Geriatrics Society (AGS) to identify critical knowledge gaps and research priorities for optimizing person-centered care and outcomes for older adults with CVD. The first workshop, in 2015, focused on multimorbidity in older adults with CVD and identified challenges to and opportunities for advancing principles of multimorbidity, identified research opportunities and resources for integration of multimorbidity into research and clinical care, and identified targets such as practice guidelines and methods to assess and record people's goals and priorities as part of a paradigm shift from disease-focused to person-centered care. A product of the conference was a comprehensive state-of-the-art review on multimorbidity in older adults with CVD targeted to the cardiology community.[5] The workshop also stimulated conceptualization of a rationale and vision for geriatric cardiology that would infuse cardiology practice with expanded proficiencies in diagnosis, risks, care coordination, communications, end-of-life, and other competencies required to best manage older adults with CVD. [6]

The second workshop, "Pharmacotherapy in Older Adults with CVD,", took place February 6 to 7, 2017, in Washington, District of Columbia. The main objective was to identify knowledge gaps and research priorities for optimizing pharmacotherapy in older adults with CVD within the areas of polypharmacy, adverse drug effects (ADEs), medication adherence, aligning therapy with individuals' goals, and novel approaches to drug prescribing. Drs. Joseph Hanlon, Kenneth Schmader, and Janice Schwartz co-chaired the workshop. Attendees included leaders from the cardiology and geriatrics communities (officers in professional societies, journal editors, clinical trialists, prominent division chiefs) and representatives from the NIA; National Heart, Lung, and Blood Institute; Food and Drug Administration (FDA); Centers for Medicare and Medicaid Services, Alliance for Academic Internal Medicine, Patient-Centered Outcomes Research Institute (PCORI), Agency for Healthcare Research and Quality, pharmaceutical companies, and selected trainees and junior faculty with interests in geriatric cardiology. This article briefly summarizes the conference proceedings, highlighting challenges to optimal outcomes of medical management related to knowledge gaps, too much medication (age-related changes in medication pharmacokinetics (PK) and pharmacodynamics (PD), multimorbidity, polypharmacy, ADEs), and too little medication (adherence, underprescribing). A discussion of the top priorities for research that workshop participants identified follows. Supplementary Appendix S1 details the topics and speakers, and the presentations are available at https://www.acc.org/membership/sections-and-councils/geriatric-cardiology-section/section-initiatives/workshops.

CVD PREVALENCE AND MEDICATION USAGE

CVD is the leading cause of death, a major cause of functional impairment and loss of independence, and the most common disease in older people in the United States. Prevalence of CVD, including hypertension, coronary heart disease, heart failure, and stroke, is 65% to 70% in persons aged 60 to 79 and 79% to 86% in those aged 80 and older.[7] Because of the high burden of CVD in older adults, cardiovascular drugs are the most commonly used therapeutic classes of drugs in older adults. In the National Social Life, Health and Aging Project home medication survey, 15 of the top 20 most frequently used medications in older adults were cardiovascular drugs. Estimated prevalence of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor use (statins) was 50.1%, of antiplatelet agents was 43.0%, of angiotensin converting enzyme inhibitors was 30.4%, of diuretics was 29.5%, of angiotensin II receptor blockings was 13.2%, of antihypertensive combinations was 12.4%, of calcium channel blockers was 10.5%, and of vitamin K antagonists was 6.4%.[8] The high rate of cardiovascular medication use also reflects benefits that research has demonstrated of pharmacological treatment of hypertension to reduce strokes and cardiac events, cholesterol reduction to prevent initial and recurrent coronary events and strokes, anticoagulation to prevent strokes in individuals with atrial fibrillation or mitral valve disease, renin-aldosterone system inhibition to reduce morbidity and mortality in individuals with reduced ejection fraction heart failure, aspirin to reduce myocardial infarctions, and antiplatelet drugs to reduce cardiac events after interventional revascularization procedures. Nevertheless, as noted previously, the applicability of the results of these studies to older adults with multiple chronic conditions, variable social circumstances, and highly individualized healthcare goals is largely unknown. Furthermore, age-related changes in organ function, PK, and PD fundamentally alter the balance between benefits and risks of drug therapy.

CHALLENGES TO OPTIMAL OUTCOMES AND MEDICATION MANAGEMENT

Benefitting from pharmacotherapy requires selecting the right medication at the right dose administered to the right

person at the right time for the right duration (5 R's of geriatric drug prescribing). To achieve this requires consideration of each medication in the holistic context of each person's psychosocial and healthcare milieu, with an understanding of and appreciation for the inherent effects of aging on organ function and drug metabolism.

Aging changes the PK and PD of medications.[9–11] Pharmacokinetic changes include reduction in renal and hepatic clearance and greater body fat, which lead to altered distribution, metabolism, and elimination of drugs, which increases the risk of ADEs in older adults, including cognitive impairment and falls. Age-related pharmacodynamic changes include altered end-organ responsiveness to drugs and reduced cardiac and baroreflex responses.[1–3] The FDA[12] and International Committee on Harmonization[13] recognized the need to consider potential age-related changes in PK and PD during drug development, but it is not required for premarketing drug evaluation or postmarketing surveillance. Large randomized double-blind studies to reduce cardiovascular morbidity and mortality have generally excluded very elderly adults (≥75) and older adults with multiple comorbid conditions or frailty and have enrolled fewer women than men and more Caucasians than other races.[14] The result is that clinicians often prescribe CVD drugs based on guidelines with limited information on benefits and risks in individuals routinely seen in clinical care (aged ≥75, with multimorbidity, women, functionally impaired or frail older persons). Current guidelines also assume that long-term use of cardiovascular drugs entails benefits and risks that remain constant over time. Current knowledge of and implementation gaps for CVD pharmacotherapy in older populations are summarized in Table 1.

Factors Resulting in Too Much Medication

CVD does not usually exist in isolation in older adults, the majority of whom have multiple comorbid conditions.[5,15,16] Multimorbidity leads to co-administration of multiple medications, and older adults often take vitamins and dietary supplements with pharmacological effects.[17,18] Polypharmacy is the term often used to describe use of multiple concomitant medications. Polypharmacy has varying definitions, but many define it as 5 or more co-administered drugs because there is a steep rise in the number of potential drug–drug interactions when 5 or more drugs are co-administered. Polypharmacy has increased dramatically in the U.S. older population—from 24% in 2000 to 39% in 2012. [19] The number of co-administered drugs has consistently been shown to be the strongest predictor of prescribing problems.[20–24] A phenomenon leading to an increase in medications in older adults has been termed the "prescribing cascade," which begins when an ADE caused by 1 medication is treated as a new condition, leading to another medication (e.g., hypertension due to a nonsteroidal antiinflammatory drug (NSAID) leading to prescription of an antihypertensive agent), an over-the-counter drug (e.g., acetaminophen or NSAID for statin myalgias), or a recommendation for a medical device to treat the initial ADE (e.g., pacemaker insertion for bradycardia related to cholinesterase inhibitor).[25,26] Drug–disease interactions (e.g., NSAID-induced worsening of heart failure) that might not be appreciated and shifting goals of care arising from the burden of increasing comorbidity and declining functional status further compound problems with polypharmacy, multimorbidity, and age-related changes in PK and PD.[27,28]

Deprescribing is defined as the process of stopping a medicine or reducing its dose to remedy polypharmacy, minimize risk of ADEs, and improve outcomes.[29,30] Initial targets for deprescribing to reduce ADEs nationally and internationally have largely focused on reducing use of single medications or classes of medications with the highest risk profiles in older adults, such as opioids, sedative hypnotics, and atypical antipsychotics[31] (e.g., Canadian Deprescribing Network, https://desprescribing.org/caden; Australian Deprescribing Network, http://w11.zetaboards.com/ADeN/index/), and have not targeted cardiovascular medications. Experience with deprescribing in older adults with CVD in the United States is limited. Recently, an expert panel developed criteria to define potentially unnecessary polypharmacy in individuals with limited life expectancy,[32] with the hope that eliminating some medications would improve care and quality of life. One randomized trial of statin discontinuation in individuals enrolled in palliative care programs demonstrated feasibility and participant and caregiver acceptance.[33]

Knowledge and Implementation Gaps for Interventions to Reduce ADEs

- Best and most efficient methods for detection and prevention of ADEs
- Prioritization of efforts to reduce ADEs
- Funding for drug safety research, education and dissemination, and implementation efforts

Factors Resulting in Too Little Medication

Medication adherence is required to achieve benefits of pharmacotherapy. The International Society for Pharmacoeconomic and Outcomes Research has standard terms to describe adherence: primary adherence (filling an initial prescription for a new medication), adherence persistence, and overadherence.[34,35] The principal methods for measuring adherence include self-report, pill counts, pharmacy refills, and electronic monitoring. Primary nonadherence is as high as 30% in primary care settings.[36] Nonadherence for chronic cardiac conditions increases over time and is as high as 60% by 3 years.[37,38] Nonadherence has been associated with poor quality of life, high medical costs, and mortality.[39,40] Older age is not a universally accepted independent risk factor for nonadherence, but factors that may affect adherence in older adults include sensory loss, dysphagia, physical or cognitive impairment, attitudes or beliefs about medications, and regimen cost or complexity. Data are sparse on accurate measurement of adherence in older adults with CVD and multiple chronic conditions.

Adherence interventions tested in heterogeneous populations have included patient and caregiver education; enhanced communication with patients, caregivers, and providers; electronic monitoring and reminders; telephone reminders; lottery-based rewards; and multidisciplinary team monitoring.[41] The more complex and multidimensional interventions

Table 1. Research Knowledge and Implementation Gaps and Top Priorities for Research

Knowledge and Implementation Gaps	Top Research Priorities
Benefits of Cardiovascular Pharmacotherapy in Older Populations	
• Pharmacokinetic and pharmacodynamic data for dosing of effective CVD therapies • Efficacy trials in elderly adults reflective of entire population • Data to determine appropriateness of use or underuse of cardiovascular drugs in multimorbid, frail, and very old adults	• Develop medication guidelines for older adults with CVD and multiple chronic conditions based on: a. Trial data (current and new), when available b. Consensus in absence of trial data • Determine best methods for dissemination and implementation of best prescribing and monitoring practices
Aligning prescribing with person-centered goals	
• Assessment of individual goals in older adults with CVD • Assess patient priorities related to health care • Patient perceived tradeoff of benefit vs risk regarding CVD therapy	• Develop training for goals-of-care communication skills • Develop and validate tools to determine patient preferences
Interventions to reduce ADEs from CVD pharmacotherapy	
• Best, most efficient methods for detection and prevention of ADEs • Prioritization of efforts to reduce ADEs • Funding for research, education and dissemination, and implementation efforts	• Perform clinical trials of deprescribing in patient subsets and medication classes (define benefits and potential harms; time to benefit or harm; behavioral, communication, and implementation methods) • Comparison of nonpharmacological strategies and pharmacological interventions
Optimizing adherence in older adults with CVD	
• Best, most efficient methods for detection of cardiovascular drug nonadherence • Best, most efficient methods for individualized multidimensional approaches to improve adherence to person-centered therapies for CVD • Incorporation of above techniques into clinical care • Interventions to improve adherence to appropriate cardiovascular medications in elderly adults	• Develop accurate, efficient methods to measure adherence • Determine underlying factors responsible for nonadherence • Determine best methods to optimize adherence
Approaches to care in older adults with CVD	
• Dosing models that include a broad range of personalization factors • Cognitive and interventional studies to learn how to best incorporate elements of precision medicine in routine clinical care of older adults with CVD • Evaluation of new technologies such as telemedicine to improve CVD pharmacotherapy in older adults • Effectiveness, cost-effectiveness, and implementation and integration of multidimensional and interdisciplinary care models to improve CVD pharmacotherapy in routine care • Practical methods to integrate health care, provide universal access to healthcare information and coordination of care programs	• Develop standardized medical review and management tools that can be individualized for individual characteristics and preferences • Develop methods to improve communication interoperability between electronic health record systems, prescribers, and pharmacies and between all systems to the point of care • Develop methods to achieve person-centered CVD care for older adults that involves multidisciplinary collaboration

ADE = adverse drug effect; CVD = cardiovascular disease.

tend to meet with more success.[42,43] A recent nationwide randomized trial in individuals with myocardial infarction that incorporated electronic pill bottles, lottery incentives, and social support without direct involvement of physicians or pharmacists did not improve medication adherence or reduce cardio vascular readmissions or costs.[44] In general, studies of adherence interventions in older adults have yielded mixed results, with some showing favorable effects on adherence rates and outcomes, some showing greater adherence rates with no effect on outcomes, and some showing no apparent benefit in adherence or outcomes.[45] Individuals with multiple chronic conditions are the least likely to show improvement despite multifaceted interventions.[41] In contrast, there is moderate-strength evidence that policy interventions that lower out-of-pocket expenses reduce but do not eliminate nonadherence to cardiovascular medications.[41] There is little information on behavioral or motivational aspects of adherence specific to older adults that recognize that they may place greater value on quality of life, ability to function independently, and avoidance of ADEs than on delayed potential benefits.

Knowledge and Implementation Gaps for Optimizing Adherence in Older Adults

- Best and most efficient methods for detection of nonadherence
- Best and most efficient methods for individualized multidimensional approaches to improve adherence to person-centered therapies (healthcare teams, individual and caregiver education and support, technology-based platforms)
- How to incorporate successful techniques into clinical care (implementation into systems, overcome financial and efficiency obstacles)

Underprescribing

Medications may also be underprescribed for older adults. Medication underuse, defined as the omission of potentially beneficial cardiovascular medication therapy or inadequate dose or duration, has been demonstrated for aspirin and beta-blockers after myocardial infarction, antihypertensive therapy for hypertension, angiotensin-converting enzyme inhibitors in heart failure, and anticoagulation to prevent strokes in individuals with atrial fibrillation,[46–49] but data are sparse on the effect of medication underuse on clinical outcomes.[50] A recent prospective population-based cohort study that assessed the prevalence, determinants, and outcomes of medication underuse based on the Screening Tool to Alert to Right Treatment (START)[51] found no association between medication underuse and cardiovascular events (fatal and nonfatal) but found a significant association between medication underuse and competing deaths from noncardiovascular causes.[52] Studies of outcomes in relation to "potential" undertreatment in older populations that have been underrepresented in CVD trials are needed.

Patient Engagement and Shared Decision-Making

Older adults with CVD may have goals that are different from outcomes measured in clinical trials of CVD therapies in younger adults. Concerns of older adults with CVD, especially those with multiple chronic conditions, tend to be about preservation of quality of life, daily function, and maintenance of independence and less about extension of life.[53] Most cardiology practitioners were not trained in the current era of person-centered care or in preparing for difficult medical decisions in advance of acute events. A special issue of *Health Affairs* in February 2013 reviewed emerging evidence suggesting that patient engagement and shared decision-making can help achieve goals of better quality of care, greater cost efficiency, and better population health, although the evidence base for improvement is limited, and even fewer data are available for what does and does not work in promoting patient engagement. It is likely that successful approaches to patient, family, and caregiver engagement will differ substantially between groups and individuals. Tools to assess a person's capacity for engagement will be critical, as well as tools for evaluating patient or caregiver preferences for level of engagement. Research should apply behavioral economic analyses to the supply (prescriber) and demand (consumer) sides of pharmaceuticals. Training will be needed for tools such as the Open Communication intervention,[54] which is being tested on a wide scale, and healthcare systems will need to promote patient engagement and provide the time and means to achieve it. Barriers to shared decision-making include overworked physicians, insufficient provider training, and clinical information systems incapable of prompting or tracking patients through the decision-making process.[55] Methods to improve shared decision-making included using automatic triggers for the distribution of decision aids and engaging team members other than physicians in the process. Substantial investments in provider training, information systems, and process reengineering may be necessary to implement shared decision-making successfully.[55]

Evolving Technologies and Models of Healthcare

Precision Medicine

Numerous academic medical centers and integrated health systems are evaluating implementation of precision medicine, often focusing on individualized dosing algorithms incorporating renal and hepatic drug clearance estimates, as well as considerations of drug interactions to provide person-specific information at the point of care.[56] For example, inpatient clinical decision support for geriatric prescribing has been associated with fewer falls in the hospital.[57] Pharmacogenomic clinical decision support pharmacogenomics to conventional drug selection and dosing models and has been used for tailoring warfarin and clopidogrel therapy in younger individuals,[58–60] with improved ischemic and bleeding outcomes,[61,62] but there has been limited evaluation of outcomes based on pharmacogenomics in older adults with CVD.[63]

Electronic tools that can be used for medication monitoring are rapidly being developed using digital technology. Passive devices that collect information without patient involvement are becoming more feasible and reliable. Electronic devices currently on the market include smart caps and organizer boxes, some of which collect data and upload it, and smart bottles, which measure capacitance or drug weight. Challenges with these devices involve reliability, cost, ease of use, and need for programming. As research tools, adherence monitoring devices can provide more reliable data on adherence and dosing. Reminder applications are low cost and simple to use but are not linked to specific medications and thus rely on active participation by the patient. Patient acceptance, burden, and privacy concerns are additional challenges. A combination of ingestible event marker sensors embedded into orally administered tablets has also recently entered the market but has limited applications at this time. Technologies that offer speech-level interactions with consumers are on the horizon.

Telemedicine provides an opportunity to integrate technology with relationship-building and team care to optimize pharmacotherapy and reach patients with mobility and transportation challenges. For example, the U.S. Department of Veterans Affairs telemedicine project, Geriatric Research, Education, and Clinical Center Connect, uses existing infrastructure and a geriatrics multidisciplinary approach to address appropriate prescribing, deprescribing, and polypharmacy. The potential effect of telemedicine on cardiovascular pharmacotherapy in older adults with CVD is unknown, and challenges to its use include reimbursement barriers, lack of standardized and integrated infrastructure, lack of reliable technology, and sustainability.

Models of Care

Innovative models of care may maximize benefit and minimize harms of pharmacotherapy in older adults with CVD.[50] In the outpatient setting, where primary care physicians treat many older adults with CVD, one site participating in the Million Hearts Initiative, a federally sponsored nationwide randomized controlled trial (http://millionhearts.hhs.gov/), is using shared medical appointments to discuss health habits, medications, and how they affect CVD risk. Participants are informed of their Atherosclerotic Cardiovascular Disease score (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/), participate in

individualized shared decision-making, and jointly plan follow-through with the primary care team. In models that included pharmacist-led interventions in hospital, hospital-to-home, outpatient, and community settings, often involving CVD drugs, ADEs were reduced by 35% in older adults.[64] In an early seminal study, a nurse-directed, multidisciplinary model of care improved quality of life, increased medication adherence, and reduced hospital use and medical costs for elderly adults with congestive heart failure.[65,66] The effect of better care coordination in improving CVD prescribing, care, and outcomes has been demonstrated in fully integrated healthcare systems but remains a challenge in the absence of a fully integrated health system or universal medical record access.

Knowledge and Implementation Gaps for Newer Approaches to Care in Older Adults with CVD

- Dosing models that include a broad range of personalization factors
- Cognitive and interventional studies to learn how best to incorporate elements of precision medicine in routine clinical care
- Evaluation of new technologies such as telemedicine and wearable devices to improve CVD therapy in older adults
- Effectiveness, cost-effectiveness, implementation, and integration of multidimensional and interdisciplinary care models in routine care
- Practical methods to integrate health care services, provide universal access to healthcare information, and optimize coordination of care programs

RESEARCH DISCUSSION AND KEY RECOMMENDATIONS

Workshop attendees were asked to identify the top research priorities for addressing challenges related to aligning medication prescribing with person-centered treatment goals in older adults with CVD, including tools that are needed to implement patient-aligned drug prescribing in clinical practice; polypharmacy and overuse of medications in older adults with CVD; medication adherence in older adults with CVD; and redesigning drug therapy using novel approaches to prescribing and monitoring in older adults with CVD. The top research priorities for pharmacotherapy in older adults with CVD are presented in Table 1. Discussion of the top research priorities according to theme follows.

Aligning Medication Prescribing with Person-Centered Treatment Goals

Aligning medications with person-centered goals is the foundation of optimal drug prescribing in older adults. To operationalize person-centered care, it is necessary to develop training for healthcare providers for goals-of-care discussions. Development and validation of tools to determine patient preferences and to involve caregivers in decision-making and monitoring are needed. Tools and decision aids for discussing risks and benefits of CVD drugs with patients (incorporating patient preferences) need to be developed and tested with meaningful engagement of patients and families. These discussions and decision-making processes must incorporate patient representatives and take advantage of the skills of specialties and entities committed to person-centered care, including primary care providers, nurses, pharmacists, large pharmacy benefits plans, palliative care, public policymakers, and healthcare administration.

Polypharmacy and Overuse of Medications in Older Adults with CVD

Guidelines for Optimal Prescribing

There is a need to develop medication guidelines for common comorbid conditions that include appropriateness and inappropriateness of prescribing. The guidelines should be based on data from high-quality research studies and interventions. It will be necessary to use traditional (randomized double-blind placebo-controlled trials, cohort studies, registries) and nontraditional study designs (adaptive and pragmatic trials, "big data") to generate the requisite data. It is also imperative that study outcomes include those relevant to older people, such as quality of life, physical and cognitive function in daily activities, and incidence of common side effects that may limit quality of life. Trials should enroll older adults with CVD and other chronic conditions that commonly occur in combination with CVD and not focus on the less common older adult with few or no comorbid conditions. Analysis and presentation of guidelines should consider the time to benefit and time to harm of therapy with respect to physical and psychosocial function and quality of life in addition to cardiovascular disease morbidity and mortality. Assessment of time to harm versus time to benefit is particularly germane to older adults, because medication ADEs often occur early in the course of therapy (e.g., statin myalgias), whereas potential benefits are often delayed, sometimes for many years. To achieve these goals, patients and caregivers should be included on trial design advisory committees (as PCORI and other organizations advocate), data safety and monitoring boards, and ultimately, guideline committees.

Deprescribing and Potential for Decreasing Medication Overuse and ADEs

Deprescribing has been suggested as an approach to address polypharmacy and ADEs in elderly adults, and research in the area of deprescribing was ranked as high priority. Barriers to widespread application of CVD deprescribing include lack of data on the appropriate duration of cardiovascular pharmacotherapy, including time to benefit and time to harm, and on the effectiveness of cardiovascular medications in older adults with multimorbidity. In addition, clinicians are not well trained in shared decision-making to incorporate patients' goals of care and functional status when considering complex cardiovascular medication regimens.[67–69]

Deprescribing trials are needed in multiple care settings, in diverse patient subsets to identify those most likely to benefit, and across the range of CVD medication classes.

Initial targets should be individuals aged 75 and older with CVD and trials could include patient-activated strategies. Important components would include determining barriers to implementation of deprescribing and optimal strategies to incorporate patient goals and preferences, as well as methods for monitoring and evaluating adverse withdrawal events and therapeutic failures with deprescribing. A by-product of this conference and one of the first steps to stimulate more work in this area is the recently announced NIA funding opportunity to create a collaborative network to advance deprescribing research for older adults with multiple chronic conditions (https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-19-005.html).

Although dietary and exercise interventions as alternatives to or in conjunction with drug therapy are underrepresented in the literature on treatment of CVD in elderly adults, they may provide benefits affecting other conditions than CVD. Comparisons of nonpharmacological and pharmacological interventions for common types of CVD in older persons should also be a high priority as a way to decrease the number of medications prescribed.

Once sufficient data have accumulated, studies are needed to develop, test, and identify the most effective methods of dissemination and implementation of best prescribing practices. To facilitate implementation, it will be necessary to develop standardized medication review and management tools to assess the status of therapy. This will require enhanced communication and interoperability between electronic health record (EHR) systems and between EHR systems and community pharmacies, as well as development of systems to facilitate instant, integrated, efficient communication between systems and between healthcare providers at the point of care. To engage patients in the implementation process, it is critical that communication tools be developed that can be customized to individual characteristics and incorporate individual preferences.

Medication Adherence in Older Adults with CVD

Accurate methods for measuring adherence in older adults are needed. Electronic prescribing has brought new opportunities and challenges. Methods will need to involve merging multiple sources of data from pharmacies, medical records in hospitals and clinics, and patients and caregivers. It is also necessary to determine ways to incorporate adherence measures into clinical care and the EHR.

Once adherence can be accurately assessed, nonadherence can also be identified, and it will be essential to develop methods to determine underlying reasons for nonadherence in older adults and to predict nonadherence. Behavioral drivers need to be determined, and strategies for behavioral change in older patents need to be evaluated. Incentives individualized for patients, clinicians, and healthcare systems should be considered. A priority should be determining the most effective and cost-effective methods and technologies to improve adherence. This will need to be determined for specific patient groups (disease, sex, race, health literacy), for specific care settings, and during care transitions. It will also be important to explore factors related to medication packaging, instructional content and method of messaging and delivery, person(s) providing instructional content, recipient of the education (patient, caregiver), and patient preferences for learning and medication management. In other words, adherence interventions must be person-specific, recognizing patients' needs, cultural backgrounds, and varying circumstances; healthcare professional, patient, and caregiver collaboration is essential; and time and reimbursement are needed for these efforts.

Redesigning Drug Therapy Using Novel Approaches to Drug Prescribing and Monitoring

The medical care system in the United States is undergoing change that could promote better CVD medication therapy in elderly adults. Most hospitals and healthcare systems have adopted patient-focused telemedicine, whereas telehealth that focuses on populations has been less uniformly adopted. These systems are neither standardized across domains within a system nor integrated across systems and do not use standard platforms. Major needs are coordination of care within and between healthcare sites and caregivers and development of tools (technological, paper, social networks) to facilitate communication and medication prescribing, review, and monitoring. Components for investigation include "medical homes" with clear designation of primary prescribers, provision of point-of-care real-time digital data, including pharmacogenomic information (drug clearance, risk related), over-the-counter medications and dietary supplements, care goals, and physical function and cognitive status to guide medication prescribing and evaluation. Efficient, easy-to-use interfaces for data need to be created. Care teams for follow-up and patient education that incorporate nurses, pharmacists, medical assistants, and peer groups, including healthcare navigators, should be evaluated. A largely unexplored area in this age group is the potential role for social media and digital medicine (e.g., cellphone or computer applications, wearable devices) in monitoring medication effects and improving medication use. For digital medicine to be used in many older persons, strategies to address health and computer literacy will be needed, along with device adaptations to accommodate age-related limitations related to arthritis, vision loss, decreased hearing, and mobility as well as lack of universal internet or computer accessibility.

SUMMARY

Drug prescribing in older adults with CVD is complex (Figure 1). Optimal prescribing requires an approach that addresses the whole person. Older adults with CVD often have multiple medical conditions, and treatment risks and benefits must be balanced across multiple diseases. The medication regimen and potential treatment benefits should be considered in the context of the person's life expectancy and healthcare preferences. Challenges are to acquire novel data on best ways to achieve these goals, to educate and disseminate the information, and to develop systems and funding mechanisms to implement optimal CVD medication management strategies. To accomplish these objectives, substantial involvement will be needed from prescribers, patients, healthcare systems, researchers, and entities providing infrastructure for these efforts.

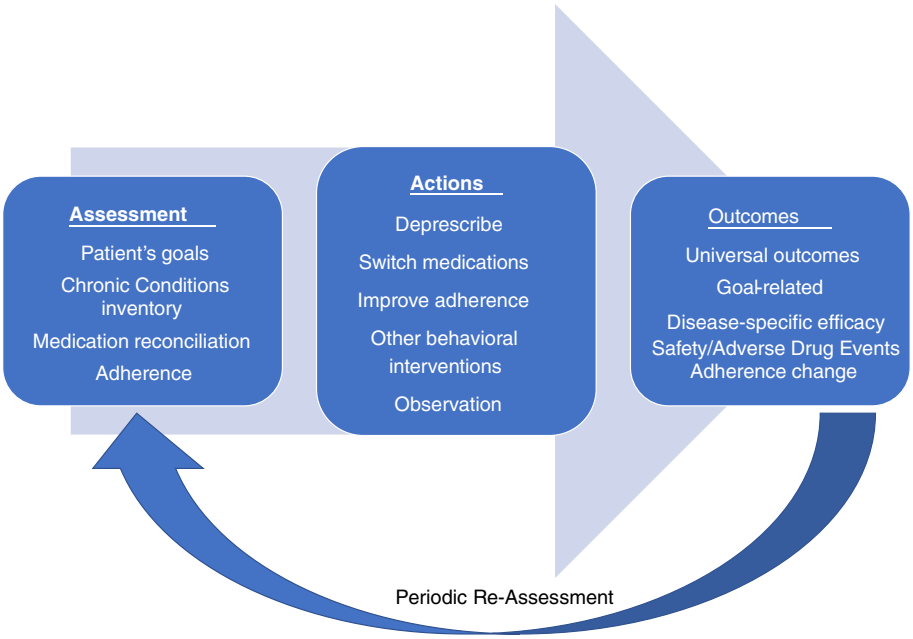


Figure 1. Steps in management of medications in older adults with cardiovascular disease.

ACKNOWLEDGMENTS

Funding for this conference was made possible in part by U13 AG 047008 from the National Institute on Aging (Michael W. Rich, MD, PI); by unrestricted grants from Amgen, Pfizer Inc., and Edwards LifeSciences, LLC; and by provision of conference facilities and staffing by the American College of Cardiology. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services or the National Institutes of Health, nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. government.

The authors gratefully acknowledge the assistance of Kelli Bohannon, Associate Director, Member Strategy, American College of Cardiology, who provided invaluable support in organizing the workshop; Frances McFarland, PhD, medical writer, who provided a detailed synopsis of the meeting; and Marcel Salive, MD, and Susan Zieman, MD, PhD, who provided valuable input in organizing the workshop.

Conflict of Interest: No authors report conflicts of interest.

Author Contributions: Janice B Schwartz, MD, Kenneth E Schmader, MD, and Joseph T Hanlon, PharmD, were conference co-chairs and were responsible for choosing and planning talks and editing summaries of all talks and the final manuscript in collaboration with Planning Committee members and Michael W. Rich, MD, Chair of the Planning Committee. Darrell Abernethy, MD, PhD, Shelly Gray, MS, PharmD, Jacqueline Dunbar-Jacob, PhD, RN, Holly M. Holmes, MD, MS, Michael D. Murray, PharmD, MPH, Robert Roberts, MD, Michael Joyner, MD, Josh Peterson, MD, MPH, David Lindeman, PhD, Ming Tai-Seale, PhD, MPH, Laura Downey, DVM, MSM spoke at the meeting and contributed to preparation of the manuscript.

Sponsor's Role: NIA representatives (Susan Zieman, MD, PhD, Marcel Salive, MD) participated in planning the workshop, as did representatives of the American College of Cardiology. The industry sponsors (Amgen, Inc., Pfizer Inc., Edwards LifeSciences, LLC) did not contribute to the conference content or manuscript preparation.

REFERENCES

1. Lakatta E, Levy D. Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises: Part I: Aging arteries a "set up" for vascular disease. Circulation 2003;107:139–146.
2. Lakatta E, Wang M, Najjar S. Arterial aging and subclinical arterial disease are fundamentally intertwined at macroscopic and molecular levels. Med Clin North Am 2009;93:583–604.
3. Lakatta E, Zhou Y, Xiao R et al. Aging of the cardiovascular system. In: Sperelakis N, Kurachi Y, Terzic A, Cohen M, eds. Heart Physiology and Pathophysiology, 4th Ed. Cambridge, Massachusetts: Elsevier, Academic Press, 2000, pp 737–760.
4. Forman DE, Rich MW, Alexander KP et al. Cardiac care for older adults. Time for a new paradigm. J Am Coll Cardiol 2011;57:1801–1810.
5. Forman DE, Maurer MS, Boyd C et al. Multimorbidity in older adults with cardiovascular disease. J Am Coll Cardiol 2018;71:2149–2161.
6. Bell SP, Orr NM, Dodson JA et al. What to expect from the evolving field of geriatric cardiology. J Am Coll Cardiol 2015;66:1286–1299.
7. Mozaffarian D, Benjamin EJ, Go AS et al. Heart disease and stroke statistics—2015 update: A report from the American Heart Association. Circulation 2015;131:e29–e322.
8. Qato DM, Wilder J, Schumm LP et al. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. JAMA Intern Med 2016;176:473–482.
9. Schwartz J, Abernethy D. Aging and medications: Past, present, future. Clin Pharmacol Ther 2009;85:3–10.
10. Sera LC, McPherson ML. Pharmacokinetics and pharmacodynamic changes associated with aging and implications for drug therapy. Clin Geriatr Med 2012;28:273–286.
11. Merck. Pharmacokinetics in the Elderly (online). Available at: https:/www.merckmanuals.com. Accessed June 19, 2018.
12. Guidelines for the Study of Drugs Likely to Be Used in the Elderly (Report HFD-100). Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research. Bethesda, MD; 1989.
13. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). E7 Studies in Support of Special Populations: Geriatrics. Questions and Answers 2012 (online). Available

at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM189544.pdf. Accessed June 19, 2018.
14. Rossello X, Pocock SJ, Julian DG. Long-term use of cardiovascular drugs: Challenges for research and for patient care. J Am Coll Cardiol 2015;66:1273–1285.
15. Moore K, Boscardin W, Steinman M et al. Patterns of chronic co-morbid medical conditions in older residents of U.S. Nursing Homes: Differences between the sexes and across the agespan. J Nutr Health Aging 2014;18:429–436.
16. Leroy L, Bayliss E, Domino M et al. The agency for healthcare research and quality multiple chronic conditions research network: Overview of research contributions and future priorities. Med Care 2014;52:S15–S22.
17. Kaufman DW, Kelly JP, Rosenberg L et al. Recent patterns of medication use in the ambulatory adult population of the United States. The Slone survey. JAMA 2002;287:337–344.
18. Nahin RL, Pecha M, Welmerink DB et al. Concomitant use of prescription drugs and dietary supplements in ambulatory elderly people. J Am Geriatr Soc 2009;57:1197–1205.
19. Kantor ED, Rehm CD, Haas JS et al. Trends in prescription drug use among adults in the United States from 1999–2012. JAMA 2015;314:1818–1830.
20. Denham MJ. Adverse drug-reactions. Br Med Bull 1990;46:53–62.
21. Nolan L, O'Malley K. The need for a more rational approach to drug prescribing for elderly people in nursing homes. Age Ageing 1989;18:52–56.
22. Spinewine A, Schmader KE, Barber N et al. Appropriate prescribing in elderly people: How well can it be measured and optimised? Lancet 2007;370:173–184.
23. Steinman MA, Handler SM, Gurwitz JH et al. Beyond the prescription: Medication monitoring and adverse drug events in older adults. J Am Geriatr Soc 2011;59:1513–1520.
24. Steinman MA, Miao Y, Boscardin W et al. Prescribing quality in older veterans: A multifocal approach. J Gen Intern Med 2014;29:1379–1386.
25. Gill SS, Anderson GM, Fischer HD et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: A population-based cohort study. Arch Intern Med 2009;169:867–873.
26. Rochon PA, Gurwitz JH. The prescribing cascade revisited. Lancet 2017;389:1778–1780.
27. Dorks M, Allers K, Schmiemann G et al. Inappropriate medication in non-hospitalized patients with renal insufficiency: A systematic review. J Am Geriatr Soc 2017;65:853–862.
28. Hanlon JT, Perera S, Newman AB et al. Potential drug-drug and drug-disease interactions in well-functioning community-dwelling older adults. J Clin Pharm Ther 2017;42:228–233.
29. Bain KT, Holmes HM, Beers MH et al. Discontinuing medications: A novel approach for revising the prescribing stage of the medication-use process. J Am Geriatr Soc 2008;56:1946–1952.
30. Scott IA, Hilmer SN, Reeve E et al. Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Intern Med 2015;175:827–834.
31. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. National Action Plan for Adverse Drug Event Prevention. Washington, DC. 2014 (online). Available at: https://health.gov/hcq/pdfs/ade-action-plan-508c.pdfNational. Accessed June 19, 2018.
32. Lavan AH, Gallagher P, Parsons C et al. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): Consensus validation. Age Ageing 2017;46:600–607.
33. Kutner JS, Blatchford PJ, Taylor DH, Jr et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: A randomized clinical trial. JAMA Intern Med 2015;175:691–700.
34. Hutchins DS, Zeber JE, Roberts CS et al. Initial medication adherence-review and recommendations for good practices in outcomes research: An ISPOR Medication Adherence and Persistence Special Interest Group report. Value Health 2015;18:690–699.
35. Abstracts of the ISPOR (International Society for Pharmacoeconomics and Outcomes Research). Eleventh Annual European Congress Abstractes. November 8-11 2008, Athens, Greece. Value Health 2008;11:A335–A659.
36. Tamblyn R, Eguale T, Huang A et al. The incidence and determinants of primary nonadherence with prescribed medication in primary care: A cohort study. Ann Intern Med 2014;160:441–450.
37. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: Its importance in cardiovascular outcomes. Circulation 2009;119:3028–3035.
38. Marcum ZA, Driessen J, Thorpe CT et al. Effect of multiple pharmacy use on medication adherence and drug-drug interactions in older adults with Medicare Part D. J Am Geriatr Soc 2014;62:244–252.
39. Madden JM, Graves AJ, Zhang F et al. Cost-related medication nonadherence and spending on basic needs following implementation of Medicare Part D. JAMA 2008;299:1922–1928.
40. Marcum ZA, Zheng Y, Perera S et al. Prevalence and correlates of self-reported medication non-adherence among older adults with coronary heart disease, diabetes mellitus, and/or hypertension. Res Social Adm Pharm 2013;9:817–827.
41. Viswanathan M, Golin CE, Jones CD et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: A systematic review. Ann Intern Med 2012;157:785–795.
42. Haynes RB, Ackloo E, Sahota N et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2008;2:CD000011.
43. Murray MD, Young J, Hoke S et al. Pharmacist intervention to improve medication adherence in heart failure: A randomized trial. Ann Intern Med 2007;146:714–725.
44. Volpp KG, Troxel AB, Mehta SJ et al. Effect of electronic reminders, financial incentives, and social support on outcomes after myocardial infarction: The heartstrong randomized clinical trial. JAMA Intern Med 2017;177:1093–1101.
45. Marcum ZA, Hanlon JT, Murray MD. Improving medication adherence and health outcomes in older adults: An evidence-based review of randomized controlled trials. Drugs Aging 2017;34:191–201.
46. Cherubini A, Corsonello A, Lattanzio F. Underprescription of beneficial medicines in older people: Causes, consequences and prevention. Drugs Aging 2012;29:463–475.
47. O'Mahony D, O'Sullivan D, Byrne S et al. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. Age Ageing 2015;44:213–218.
48. Steinman MA, Landefeld CS, Rosenthal GE et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 2006;54:1516–1523.
49. Wright RM, Sloane R, Pieper CF et al. Underuse of indicated medications among physically frail older US veterans at the time of hospital discharge: Results of a cross-sectional analysis of data from the Geriatric Evaluation and Management Drug Study. Am J Geriatr Pharmacother 2009;7:271–280.
50. Meid AD, Lampert A, Burnett A et al. The impact of pharmaceutical care interventions for medication underuse in older people: A systematic review and meta-analysis. Br J Clin Pharmacol 2015;80:768–776.
51. Barry PJ, Gallagher MP, Ryan C et al. START (screening tool to alert doctors to the right treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 2007;36:632–638.
52. Meid AD, Quinzler R, Freigofa J et al. Medication underuse in aging outpatients with cardiovascular disease: Prevalence, determinants, and outcomes in a prospective cohort study. PLoS One 2015;10:e136339.
53. Phelan EA, Anderson LA, LaCroix AZ et al. Older adults' views of "successful aging"—how do they compare with researchers' definitions? J Am Geriatr Soc 2004;52:211–216.
54. Tai-Seale M, Elwyn G, Wilson C et al. Enhancing shared decision making through carefully designed interventions that target patient and provider behavior. Health Aff (Millwood) 2016;35:605–612.
55. Friedberg MW, Van Busum K, Wexler R et al. A demonstration of shared decision making in primary care highlights barriers to adoption and potential remedies. Health Aff (Millwood) 2013;32:268–275.
56. Osheroff JA, Teich JM, Middleton B et al. A roadmap for national action on clinical decision support. J Am Med Inform Assoc 2007;14:141–145.
57. Peterson JF, Kuperman GJ, Shek C et al. Guided prescription of psychotropic medications for geriatric inpatients. Arch Intern Med 2005;165:802–807.
58. Cavallari L, Denny J, Lee C et al. Prospective Clinical Implementation of CYP2C19-Genotype Guided Antiplatelet Therapy After PCI: A Multi-Site Investigation of MACE Outcomes in a Real-World Setting. New Orleans, LA: American Heart Association, 2016.
59. Khan NA, Peterson JF. A surveillance tool to support quality assurance and research in personalized medicine. AMIA Annu Symp Proc 2011;2011:701–708.
60. Peterson JF, Field JR, Unertl KM et al. Physician response to implementation of genotype-tailored antiplatelet therapy. Clin Pharmacol Ther 2016;100:67–74.
61. Cavallari LH, Lee CR, Beitelshees AL et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. JACC Cardiovasc Interv 2018;11:181–191.
62. Lee CR, Sriramoju VB, Cervantes A et al. Clinical outcomes and sustainability of using CYP2C19 gentoype-guided antiplatelet therapy after percutaneous coronary intervention. Circ Genom Precis Med 2018;11:e002069.
63. Schwartz J, Kane L, Moore K et al. Failure of pharmacogenetic-based dosing algorithms to identify older patients requiring low daily doses of warfarin. J Am Med Dir Assoc 2011;12:633–638.
64. Gray SL, Hart LA, Perera S et al. Meta-analysis of interventions to reduce adverse drug reactions. J Am Geriatr Soc 2018;66:282–288.
65. Rich M, Beckham V, Wittenberg C et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med 1995;333:1190–1195.

66. Rich MW, Gray DB, Beckham V et al. Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure. Am J Med 1996;101:270–276.

67. Holmes H, Hayley D, Alexander G et al. Reconsidering medication appropriateness for patients late in life. Arch Intern Med 2006;166:605–609.

68. Holmes HM, Min LC, Yee M et al. Rationalizing prescribing for older patients with multimorbidity: Considering time to benefit. Drugs Aging 2013;30:655–666.

69. Tjia J, Briesacher BA, Peterson D et al. Use of medications of questionable benefit in advanced dementia. JAMA Intern Med 2014;174:1763–1771.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Appendix S1: Workshop Agenda for Pharmacotherapy in Older Adults with Cardiovascular Disease.

CLINICAL INVESTIGATION

American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults

*By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel**

The American Geriatrics Society (AGS) Beers Criteria® (AGS Beers Criteria®) for Potentially Inappropriate Medication (PIM) Use in Older Adults are widely used by clinicians, educators, researchers, healthcare administrators, and regulators. Since 2011, the AGS has been the steward of the criteria and has produced updates on a 3-year cycle. The AGS Beers Criteria® is an explicit list of PIMs that are typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions. For the 2019 update, an interdisciplinary expert panel reviewed the evidence published since the last update (2015) to determine if new criteria should be added or if existing criteria should be removed or undergo changes to their recommendation, rationale, level of evidence, or strength of recommendation. **J Am Geriatr Soc 00:1–21, 2019.**

Key words: medications; drugs; older adults; Beers list; Beers Criteria

The American Geriatrics Society (AGS) Beers Criteria® (AGS Beers Criteria®) for Potentially Inappropriate Medication (PIM) Use in Older Adults are widely used by clinicians, educators, researchers, healthcare administrators, and regulators. Since 2011, the AGS has been the steward of the criteria and has produced updates on a 3-year cycle that began in 2012.[1,2] The AGS Beers Criteria® are an explicit list of PIMs that are typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions.

From the *American Geriatrics Society, New York, New York.

Address correspondence to Mary Jordan Samuel, American Geriatrics Society, 40 Fulton St, 18th Floor, New York, NY 10038. E-mail: mjsamuel@americangeriatrics.org

See related editorial by Michael Steinman et al.

DOI: 10.1111/jgs.15767

For the 2019 update, an interdisciplinary expert panel reviewed the evidence published since the last update (2015) to determine if new criteria should be added or if existing criteria should be removed or undergo changes to their recommendation, rationale, level of evidence, or strength of recommendation. Each of the five types of criteria in the 2015 update were retained in this 2019 update: medications that are potentially inappropriate in most older adults, those that should typically be avoided in older adults with certain conditions, drugs to use with caution, drug-drug interactions, and drug dose adjustment based on kidney function.

OBJECTIVES

The specific aim was to update the 2015 AGS Beers Criteria® using a comprehensive, systematic review and grading of the evidence on drug-related problems and adverse events in older adults. The strategies to achieve this aim were to:

- Incorporate new evidence on PIMs included in the 2015 AGS Beers Criteria® and evidence regarding new criteria or modifications of existing criteria being considered for the 2019 update.
- Grade the strength and quality of each PIM statement based on the level of evidence and strength of recommendation.
- Convene an interdisciplinary panel of 13 experts in geriatric care and pharmacotherapy who would apply a modified Delphi method, informed by the systematic review and grading, to reach consensus on the 2019 update.
- Incorporate exceptions in the AGS Beers Criteria® that the panel deemed clinically appropriate. These exceptions would be designed to make the criteria more individualized to clinical practice and be more relevant across settings of care.

INTENT OF CRITERIA

The primary target audience for the AGS Beers Criteria® is practicing clinicians. The criteria are intended for use in adults 65 years and older in all ambulatory, acute, and institutionalized settings of care, except for the hospice and palliative care settings. Consumers, researchers, pharmacy benefits managers, regulators, and policymakers also widely use the AGS Beers Criteria®. The intention of the AGS Beers Criteria® is to improve medication selection;

0002-8614/18/$15.00

desired evidence). Special emphasis was placed on selecting systematic reviews and meta-analyses when available, because resource constraints precluded the panel from conducting these types of comprehensive analyses. In general, a study was considered relevant to older adults if the mean or median age of participants was older than 65 years, and especially relevant if most or all participants were older than this age threshold.

Articles comprising the best available evidence were abstracted by AGS staff into evidence tables. These tables summarized the design, population, and findings of each study, and identified markers of methodologic quality highlighted by the GRADE criteria for clinical trials and observational studies and by A MeaSurement Tool to Assess Systematic Reviews (AMSTAR).[6–8] Each work group then synthesized evidence for each criterion from the 2015 to 2017 literature reviews based on GRADE guidelines and the American College of Physicians' evidence grading framework (Table 1).[6,9]

Using evidence from the 2015 to 2017 literature review, evidence findings from previous updates in 2012 and 2015, and clinical judgment, each work group presented to the full panel its findings and suggestions for changes (or no change) to the criteria, with ensuing discussion. For most criteria, a consensus emerged, to leave an existing criterion from the 2015 update unchanged, to modify it, to remove it entirely, or to add a new criterion. Potential modifications included the drug(s) included in the criterion, the recommendation, the rationale, the quality of evidence, and the strength of recommendation. As noted in the GRADE guidelines, strength of recommendation ratings incorporate a variety of considerations, including expert opinion and clinical judgment and context, and thus do not always align with quality of evidence ratings.

After discussion of proposed changes, an anonymous Delphi process was used to ascertain panel consensus, using a five-point Likert scale with anchors of "strongly disagree" and "strongly agree." As a general rule, criteria receiving "agree" or strongly agree ratings from more than 90% of panelists were included. The remainder were brought back for group discussion, with final decisions resolved through consensus.

In addition to changes made on the basis of evidence, the panel decided on several modifications to improve clarity and usability of the AGS Beers Criteria®. These included removing a number of medications that are used only rarely. These removals should not be interpreted as condoning use of these medications but rather are intended to "declutter" the AGS Beers Criteria® and not distract from information on more commonly used medications. In selected cases, the panel changed the wording of certain criteria, recommendations, and rationale statements to improve clarity and avoid potential misinterpretations.

The final set of criteria was reviewed by the AGS Executive Committee and Clinical Practice and Models of Care Committee and subsequently released for public comment. Comments were solicited from the general public and sent to 39 organizations. Comments were accepted over a 3-week period from August 13, 2018, until September 4, 2018. A total of 244 comments were received from 47 individuals (79 comments), 6 pharmaceutical companies (10 comments), and 22 peer organizations (155 comments). All comments were reviewed and discussed by the panel cochairs. All comments along with proposed changes to the criteria were shared with the entire panel for final approval.

RESULTS

Noteworthy Changes to PIMs for Older Adults

Tables 2 through 6 show the 2019 criteria. Table 7 lists those drugs with strong anticholinergic properties that are sometimes referenced in Tables 2 through 6. Compared with the 2015 criteria, several drugs were removed from Table 2 (medications that are potentially inappropriate in most older adults), Table 3 (medications that are potentially inappropriate in older adults with certain conditions), and Table 4 (medications that should be used with caution). These removals are summarized in Table 8 and include removal of drugs no longer available in the United States (ticlopidine, oral pentazocine). In other cases, the recommendation was removed entirely because the panel decided the drug-related problem was not sufficiently unique to older adults (eg, using stimulating medications in patients with insomnia or avoiding medications that can lower the seizure threshold in patients with a seizure disorder). These removals do not imply that these medications are now considered safe for older adults; rather, they were made to help keep the AGS Beers Criteria® streamlined and focused on medications particularly problematic for older adults.

The H2-receptor antagonists were removed from the "avoid" list in patients with dementia or cognitive impairment. This is because evidence for adverse cognitive effects in these conditions is weak, and because the panel expressed concern that the intersection of this criterion with another criterion that discourages chronic use of proton-pump inhibitors in the absence of strong indications would overly restrict therapeutic options for older adults with dementia who have gastroesophageal reflux or similar issues. However, H2-receptor antagonists remain on the criteria as "avoid" in patients with delirium. In addition, wording of this criterion was modified to affirm that nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, the "Z drugs": zolpidem, eszopiclone, and zaleplon) should be avoided in older adults with delirium.

Two drugs with strong anticholinergic properties, pyrilamine and methscopolamine, were added to the list of anticholinergic drugs to avoid. Changes to criteria on cardiovascular drugs include minor updates to the rationale and a minor change to clarify the recommendation for avoiding digoxin as first-line therapy for atrial fibrillation and heart failure (Table 2). The rationale to avoid sliding-scale insulin has been revised to clarify its meaning and intent (Table 2). Glimepiride has been added to the list of sulfonylureas with a greater risk of severe prolonged hypoglycemia (Table 2). The duration of use of metoclopramide has been added to be consistent with US Food and Drug Administration labeling (Table 2).

The serotonin-norepinephrine reuptake inhibitors (SNRIs) have been added to the list of drugs to avoid in patients with a history of falls or fractures (Table 3). Following a principle that applies to all criteria, the panel recognizes there may be situations when SNRIs, other antidepressants, and other medications listed in this criterion may be appropriate for people with a history of falls

Table 2. 2019 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults[a]

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics[b]				
First-generation antihistamines Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Pyrilamine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate.	Avoid	Moderate	Strong
Antiparkinsonian agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention or treatment of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Antispasmodics Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Homatropine (excludes opthalmic) Hyoscyamine Methscopolamine Propantheline Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong
Antithrombotics				
Dipyridamole, oral short acting (does not apply to the extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Anti-infective				
Nitrofurantoin	Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression	Low	Strong
Cardiovascular				
Peripheral alpha-1 blockers for treatment of hypertension Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong

(Continued)

Table 2 (Contd.)

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Nortriptyline Paroxetine Protriptyline Trimipramine				
Antipsychotics, first (conventional) and second (atypical) generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible *and* the older adult is threatening substantial harm to self or others	Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy	Moderate	Strong
Barbiturates Amobarbital Butabarbital Butalbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines *Short and intermediate acting:* Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam *Long acting:* Chlordiazepoxide (alone or in combination with amitriptyline or clidinium) Clonazepam Clorazepate Diazepam Flurazepam Quazepam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia	Avoid	Moderate	Strong
Meprobamate	High rate of physical dependence; sedating	Avoid	Moderate	Strong
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") Eszopiclone Zaleplon Zolpidem	Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (ie, Z drugs) have adverse events similar to those of benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration	Avoid	Moderate	Strong
Ergoloid mesylates (dehydrogenated ergot alkaloids) Isoxsuprine	Lack of efficacy	Avoid	High	Strong

(Continued)

Table 2 (Contd.)

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Pain medications				
Meperidine	Oral analgesic not effective in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid	Moderate	Strong
Non–cyclooxygenase-selective NSAIDs, oral: Aspirin >325 mg/day Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those >75 years or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton-pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in ~1% of patients treated for 3-6 months and in ~2%-4% of patients treated for 1 year; these trends continue with longer duration of use. Also can increase blood pressure and induce kidney injury. Risks are dose related.	Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)	Moderate	Strong
Indomethacin Ketorolac, includes parenteral	Increased risk of gastrointestinal bleeding/peptic ulcer disease and acute kidney injury in older adults Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects.	Avoid	Moderate	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable	Avoid	Moderate	Strong
Genitourinary				
Desmopressin	High risk of hyponatremia; safer alternative treatments	Avoid for treatment of nocturia or nocturnal polyuria	Moderate	Strong

Abbreviations: CNS, central nervous system; HFrEF, heart failure with reduced ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
[a]The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.
[b]See also criterion on highly anticholinergic antidepressants.

Table 3 (Contd.)

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
	Zaleplon Zolpidem Antipsychotics, chronic and as-needed use[b]	others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.			
History of falls or fractures	Antiepileptics Antipsychotics[b] Benzodiazepines Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopiclone Zaleplon Zolpidem Antidepressants TCAs SSRIs SNRIs Opioids	May cause ataxia, impaired psychomotor function, syncope, additional falls; shorter-acting benzodiazepines are not safer than long-acting ones. If one of the drugs must be used, consider reducing use of other CNS-active medications that increase risk of falls and fractures (ie, antiepileptics, opioid-receptor agonists, antipsychotics, antidepressants, nonbenzodiazepine and benzodiazepine receptor agonist hypnotics, other sedatives/hypnotics) and implement other strategies to reduce fall risk. Data for antidepressants are mixed but no compelling evidence that certain antidepressants confer less fall risk than others.	Avoid unless safer alternatives are not available; avoid antiepileptics except for seizure and mood disorders Opioids: avoid except for pain management in the setting of severe acute pain (eg, recent fractures or joint replacement)	Opioids: moderate All others: high	Strong
Parkinson disease	Antiemetics Metoclopramide Prochlorperazine Promethazine All antipsychotics (except quetiapine, clozapine, pimavanserin)	Dopamine-receptor antagonists with potential to worsen parkinsonian symptoms Exceptions: Pimavanserin and clozapine appear to be less likely to precipitate worsening of Parkinson disease. Quetiapine has only been studied in low-quality clinical trials with efficacy comparable to that of placebo in five trials and to that of clozapine in two others.	Avoid	Moderate	Strong
Gastrointestinal					
History of gastric or duodenal ulcers	Aspirin >325 mg/day Non–COX-2–selective NSAIDs	May exacerbate existing ulcers or cause new/additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (ie, proton-pump inhibitor or misoprostol)	Moderate	Strong
Kidney/urinary tract					
Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	NSAIDs (non-COX and COX selective, oral and parenteral, nonacetylated salicylates)	May increase risk of acute kidney injury and further decline of renal function	Avoid	Moderate	Strong

(Continued)

Table 4. 2019 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medications: Drugs To Be Used With Caution in Older Adults[a]

Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Aspirin for primary prevention of cardiovascular disease and colorectal cancer	Risk of major bleeding from aspirin increases markedly in older age. Several studies suggest lack of net benefit when used for primary prevention in older adult with cardiovascular risk factors, but evidence is not conclusive. Aspirin is generally indicated for secondary prevention in older adults with established cardiovascular disease.	Use with caution in adults ≥70 years	Moderate	Strong
Dabigatran Rivaroxaban	Increased risk of gastrointestinal bleeding compared with warfarin and reported rates with other direct oral anticoagulants when used for long-term treatment of VTE or atrial fibrillation in adults ≥75 years.	Use with caution for treatment of VTE or atrial fibrillation in adults ≥75 years	Moderate	Strong
Prasugrel	Increased risk of bleeding in older adults; benefit in highest-risk older adults (eg, those with prior myocardial infarction or diabetes mellitus) may offset risk when used for its approved indication of acute coronary syndrome to be managed with percutaneous coronary intervention.	Use with caution in adults ≥75 years	Moderate	Weak
Antipsychotics Carbamazepine Diuretics Mirtazapine Oxcarbazepine SNRIs SSRIs TCAs Tramadol	May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Use with caution	Moderate	Strong
Dextromethorphan/quinidine	Limited efficacy in patients with behavioral symptoms of dementia (does not apply to treatment of PBA). May increase risk of falls and concerns with clinically significant drug interactions. Does not apply to treatment of pseudobulbar affect.	Use with caution	Moderate	Strong
Trimethoprim-sulfamethoxazole	Increased risk of hyperkalemia when used concurrently with an ACEI or ARB in presence of decreased creatinine clearance	Use with caution in patients on ACEI or ARB and decreased creatinine clearance	Low	Strong

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PBA, pseudobulbar affect; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VTE, venous thromboembolism.

[a]The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.

DISCUSSION

The 2019 AGS Beers Criteria® update contributes to the critically important evidence base and discussion of medications to avoid in older adults and the need to improve medication use in older adults. The 2019 AGS Beers Criteria® include 30 individual criteria of medications or medication classes to be avoided in older adults (Table 2) and 16 criteria specific to more than 40 medications or medication classes that should be used with caution or avoided in certain diseases or conditions (Tables 3 and 4). As in past updates, there were several changes to the 2019 AGS Beers Criteria®, including criteria that were modified or dropped, a few new criteria, and some changes in the level of evidence grading and clarifications in language and rationale (Tables 8–10).

The 2019 AGS Beers Criteria® is the third such update by the AGS and the fifth update of the AGS Beers Criteria® since their original release.[1,2,10–12] The criteria was first published almost 30 years ago in 1991, making them the longest running criteria for PIMs in older adults.

Table 5 (Contd.)

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Warfarin	Trimethoprim-sulfamethoxazole	Increased risk of bleeding	Avoid when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of bleeding	Avoid when possible; if used together, monitor closely for bleeding	High	Strong

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CNS, central nervous system; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin-angiotensin system; SNRI, serotonin- norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]CNS-active drugs: antiepileptics; antipsychotics; benzodiazepines; nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; TCAs; SSRIs; SNRIs; and opioids.

The 2019 update has a similar number of changes to the 2015 update but fewer changes than the 2012 update. This is likely because, with the support of the AGS and the expert panel, the criteria have been regularly updated about every 3 years since 2012. In 2019, 25 medications or medication classes to be avoided outright or in a disease condition were dropped from the AGS Beers Criteria® (Table 8). A few were also moved to a new table category or modified (Table 10). For medications to be removed from the AGS Beers Criteria®, the panel had to have new evidence or a strong rationale, for reasons such as the literature showed a change in evidence that cast new doubt on their "avoid" status. Finally, some drugs or drug-disease combinations were omitted because they are not disproportionately relevant to the older adult population; this included the criteria on drugs to avoid in adults with chronic seizures or epilepsy and in adults with insomnia.

Four new medications or medication classes were added to the list of drugs to be used with caution (Table 4; additions are also summarized in Table 9). Dextromethorphan/quinidine was added because of its limited efficacy, concerns for clinically significant drug interactions, and potentially increased risk of falls in older adults. TMP-SMX was placed in the "use with caution table" because of increased risk of hyperkalemia when used concurrently with an ACEI or ARB in the presence of decreased creatinine clearance.[13,14] Rivaroxaban was also added to the use with caution table for adults 75 years or older. Other important changes in the use with caution table included lowering the age threshold in the aspirin for primary prevention recommendation from 80 years or younger to 70 years or younger on the basis of emerging evidence of a major increase in the risk of bleeding at a lower age.[15] The Aspirin in Reducing Events in the Elderly (ASPREE) trial, which was published outside the window of our literature search, found that low-dose aspirin used for primary prevention in older adults did not confer a reduction in mortality, disability-free survival, or cardiovascular events.[16,17] In a few instances, the level of evidence was revised based on new literature and the improved modified grading method. For instance, H2-receptor antagonists were removed from the list of drugs to avoid in dementia, and the evidence level for H2-receptor antagonists was decreased to low (from moderate in 2015) for drugs to avoid in delirium.[18] Again in 2019, the panel clarified the language for sliding-scale insulin because this continued to be an area of confusion for clinicians.

Importantly, several drugs were added to the drug-disease and drug-drug interactions tables (Tables 3 and 5). Notably, SNRIs were added to the list of antidepressant drug classes to avoid in persons with a history of falls or fractures.[19,20] For this criterion, the level of evidence for opioids was changed to "moderate"; all other drugs remain at high. Two new drug-drug interactions involving opioids were added, reflecting evidence of substantial harms that can occur when opioids are used concurrently with benzodiazepines or gabapentinoids. Though these drug interactions involving opioids are problematic in all persons, they are growing increasingly common and may lead to greater harm in vulnerable older adults. These concerns need to be balanced with the need to treat chronic pain. A recent review of deaths from opioids concluded that the burden of opioid overdose in older adults requires special attention, noting the largest

Table 6 (Contd.)

Medication Class and Medication	Creatinine Clearance at Which Action Required, mL/min	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Hyperuricemia					
Colchicine	<30	Gastrointestinal, neuromuscular, bone marrow toxicity	Reduce dose; monitor for adverse effects	Moderate	Strong
Probenecid	<30	Loss of effectiveness	Avoid	Moderate	Strong

Abbreviations: CNS, central nervous system; CrCl, creatinine clearance; QTc, corrected QT interval; VTE, venous thromboembolism.

Table 7. Drugs With Strong Anticholinergic Properties

Antiarrhythmic	Promethazine
Disopyramide	Pyrilamine
	Triprolidine
Antidepressants	
Amitriptyline	
Amoxapine	
Clomipramine	Antimuscarinics (urinary incontinence)
Desipramine	Darifenacin
Doxepin (>6 mg)	Fesoterodine
Imipramine	Flavoxate
Nortriptyline	Oxybutynin
Paroxetine	Solifenacin
Protriptyline	Tolterodine
Trimipramine	Trospium
Antiemetics	
Prochlorperazine	Antiparkinsonian agents
Promethazine	Benztropine
	Trihexyphenidyl
Antihistamines (first generation)	
Brompheniramine	Antipsychotics
Carbinoxamine	Chlorpromazine
Chlorpheniramine	Clozapine
Clemastine	Loxapine
Cyproheptadine	Olanzapine
Dexbrompheniramine	Perphenazine
Dexchlorpheniramine	Thioridazine
Dimenhydrinate	Trifluoperazine
Diphenhydramine (oral)	
Doxylamine	Antispasmodics
Hydroxyzine	Atropine (excludes ophthalmic)
Meclizine	Belladonna alkaloids
Clidinium-chlordiazepoxide	Scopolamine (excludes ophthalmic)
Dicyclomine	
Homatropine (excludes ophthalmic)	Skeletal muscle relaxants
Hyoscyamine	Cyclobenzaprine
Methscopolamine	Orphenadrine
Propantheline	

relative increase in opioids occurred in persons 55 to 64 (754% increase from 0.2% to 1.7%) and 65 years and older and the absolute number of deaths in this group is moderate.[21,22]

Several drug-drug interactions involving antimicrobial agents were also added to Table 5, and the recommendation to avoid concurrent use of three or more CNS-active medications was reformatted to clarify and bring further attention to the increased risk of falls and other harms that can occur when multiple CNS-active medications are combined.[23]

PIM use continues to be a serious problem in older adults and especially in vulnerable older adults with multiple chronic conditions. Thus, the AGS Beers Criteria® continue to be useful and necessary as a clinical tool, as an educational tool at the bedside, and as a public health tool to improve medication safety in older adults. The AGS Beers Criteria® can increase awareness of polypharmacy and aid decision making when choosing drugs to avoid in older adults. In a 2017 study using medical expenditure data (n = 16,588) in adults 65 years and older, poor health status was associated with increased PIM use. In another study, the use of PIMs, as measured by the 2015 criteria, in persons with dementia was 11% higher after diagnosis than in the year of diagnosis.[24,25] Benzodiazepine use remains common in older adults, especially in older women, despite the fact that older adults are highly vulnerable to harms associated with use of these drugs.[26] The challenge of decreasing PIM use and improving the overall quality of medication prescribing in older adults remains, and the AGS Beers Criteria® are one part of the solution.

The AGS Beers Criteria® are an essential evidence-based tool that should be used as a guide for drugs to avoid in older adults. However, they are not meant to supplant clinical judgment or an individual patient's preferences, values, care goals, and needs, nor should they be used punitively or to excessively restrict access to medications. These criteria were developed to be used in conjunction with a person-centered team approach (physicians, nurses, pharmacists, other clinicians, the older adult, family, and others) to prescribing and monitoring adverse effects.[27] A companion article published to the 2015 updated AGS Beers Criteria®, entitled "How to Use the Beers Criteria: A Guide for Patients, Clinicians, Health Systems, and Payors," remains an important guide for using the AGS Beers Criteria®. It reminds clinicians that medications listed in the Criteria are potentially inappropriate, rather than definitely inappropriate for all older adults, and encourages users to read the rationale and recommendation statements for each medication to avoid because these statements provide important guidance.[3] Moreover, the criteria should not be interpreted as giving license to steer patients away from PIMs to even worse choices. For example, the recommendation to avoid chronic, regular use of NSAIDs should not be

Table 10. Medications/Criterion Modified Since 2015 American Geriatrics Society Beers Criteria®

Medication/Criterion	Modification
Independent of Diagnosis or Condition (Table 2)	
Peripheral α-1 blockers	For treatment of hypertension
Digoxin for atrial fibrillation and heart failure	Added wording to Drug column; modified rationale; QE for atrial fibrillation changed to Low
Estrogen with or without progestin	Added "recurrent" urinary tract infections
Sliding-scale insulin	Clarified definition of sliding-scale insulin
Metoclopramide	Added duration of use to recommendation
Meperidine	Removed caveat from recommendation
Considering Disease and Syndrome Interactions (Table 3)	
Heart failure	Reorganized recommendations; separated COX-2 inhibitors from other NSAIDs; added QE and SR for COX-2 inhibitors; changed recommendation for NSAIDs, COX-2 inhibitors, and thiazolidinediones to use with caution in asymptomatic heart failure and to avoid in symptomatic heart failure; modified rationale
Syncope	Specified "nonselective peripheral α-1 blockers"; separated rationales, QE, and SR for AChEIs and nonselective peripheral alpha-1 blockers; modified QE for ACHEIs and antipsychotics
Delirium	Changed "Sedative/hypnotics" to Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; changed QE of H2-receptor antagonists to low
History of fractures and falls	Changed SR of opioids to strong
Parkinson disease	Added rationale for quetiapine, clozapine, and pimavanserin
Chronic kidney disease and NSAIDs	Changed wording (minor) of criterion title
Use With Caution (Table 4)	
Aspirin as primary prevention	Modified age, indication, rationale, and QE
Dabigatran	Modified rationale and recommendation
Prasugrel	Modified rationale
Clinically Important Drug-Drug Interactions (Table 5)	
The table title	Dropped "Non–anti-infective"
ACEIs/ARBs and hyperkalemia	Changed to renin-angiotensin system inhibitors
Combination of three or more CNS agents (antidepressants, antiepileptics, antipsychotics, benzodiazepines, and opioids)	Replaced individual criteria with a single criterion
Medications That Should Be Avoided or Have Their Dosage Reduced With Decreased Kidney Function (Table 6)	
Apixaban, dabigatran, edoxaban, and rivaroxaban	Revised CrCl at which action is required, rationale and recommendations to reflect current labeling, and CrCl exclusion parameters in clinical trials

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AChEI, acetylcholinesterase inhibitor; ARB, angiotensin receptor blocker; CNS, central nervous system; COX, cyclooxygenase; CrCl, creatinine clearance; NSAID, nonsteroidal anti-inflammatory drug; QE, quality of evidence; SR, strength of recommendation.

deprescribing resources for many medications included in the 2019 AGS Beers Criteria® is https://deprescribing.org.

Of particular note is the potential role for nonpharmacological approaches to manage common conditions in older adults. The evidence base for specific nonpharmacological approaches with a person-centered approach to care is small but growing.[29–32] One example of the growing evidence for nondrug alternatives is in the area of care for persons with dementia and delirium. Scales and colleagues published a 2019 comprehensive review of evidence-based nonpharmacological approaches for behavioral and psychological symptoms of dementia. They evaluated 197 articles that included sensory practices (eg, massage, light therapy), psychosocial practices (eg, music, pet therapy, reminiscence), and structured care protocols (eg, mouth care, bathing). Though they had recommendations for improving the evidence base, they concluded most practices were acceptable to patients, had no harmful effects, and required minimal to moderate investment.[33] Online resources for some of these approaches can be found at www.nursinghometoolkit.com and www.hospitalelderlifeprogram.org.

While the AGS Beers Criteria® can be a valuable tool, it should be viewed within the larger context of tools and strategies for improving pharmacological care for older adults. Specifically, the AGS Beers Criteria® is one component of what should be a comprehensive approach to medication use in older adults, and it should be used in conjunction with other tools and management strategies for improving medication safety and effectiveness. Moreover, other explicit criteria for evaluating PIMs in older adults, including the screening tool of older people's prescriptions and screening tool to alert to right treatment criteria (STOPP/START criteria) can also be valuable resources for improving medication therapy.[34]

Finally, the 2019 AGS Beers Criteria® have several limitations. Evidence for the benefits and harms of medications in older adults is often limited, particularly from randomized

Veterans Affairs Medical Center, San Francisco, CA (cochair); Judith Beizer, PharmD, BCGP, FASCP, AGSF, St Johns University, Queens, NY; Nicole Brandt, PharmD, MBA, BCPP, BCGP, FASCP, University of Maryland, Baltimore, MD; Robert Dombrowski, PharmD, Centers for Medicare and Medicaid Services, Baltimore, MD (nonvoting member); Catherine E. DuBeau, MD, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Lynn Pezzullo, RPh, CPEHR, Pharmacy Quality Alliance, Alexandria, VA (nonvoting member); Jerome J. Epplin, MD, AGSF, Litchfield Family Practice Center, Litchfield, IL; Nina Flanagan, PhD, GNP-BC, APHM-BC, Decker School of Nursing, Binghamton University, Dunmore, PA; Emily Morden, MSW, National Committee for Quality Assurance, Washington, DC (nonvoting member); Joseph Hanlon, PharmD, MS, BCPS, FASHP, FASCP, FGSA, AGSF, Department of Medicine (Geriatric Medicine) School of Medicine, University of Pittsburgh and Geriatric Research, Education and Clinical Center, Veterans Affairs Healthcare System, Pittsburgh, PA; Peter Hollmann, MD, AGSF, Brown Medicine, Providence, RI; Rosemary Laird, MD, MHSA, AGSF, Geriatric Medical Leader for Florida Hospital, Winter Park, FL; Sunny Linnebur, PharmD, FCCP, BCPS, BCGP, FASCP, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO; Satinderpal Sandhu, MD, SUNY Upstate Medical University and Syracuse Veterans Affairs Medical Center, Syracuse, NY.

REFERENCES

1. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616-631.
2. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227-2246.
3. Steinman MA, Beizer JL, DuBeau CE, et al. How to use the American Geriatrics Society 2015 Beers Criteria: a guide for patients, clinicians, health systems, and payors. J Am Geriatr Soc. 2015;63(12):e1-e7.
4. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines, 1: introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394.
5. Institute of Medicine (U.S.). Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher M, Wolman DM, et al., eds. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.
6. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines, 3: rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-406.
7. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines, 4: rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407-415.
8. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
9. Qaseem A, Snow V, Owens DK, Shekelle P, Clinical Guidelines Committee of the American College of Physicians. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010;153(3):194-199.
10. Beers MH, Ouslander JG, Rollingher I, et al. Explicit criteria for determining inappropriate medication use in nursing home residents. Arch Intern Med. 1991;151(9):1825-1832.
11. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. Arch Intern Med. 1997;157(14):1531-1536.
12. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163(22):2716-2724.
13. Chan WY, Clark AB, Wilson AM, et al. The effect of co-trimoxazole on serum potassium concentration: safety evaluation of a randomized controlled trial. Br J Clin Pharmacol. 2017;83(8):1808-1814.
14. Higashioka K, Niiro H, Yoshida K, et al. Renal insufficiency in concert with renin-angiotensin-aldosterone inhibition is a major risk factor for hyperkalemia associated with low-dose trimethoprim-sulfamethoxazole in adults. Intern Med. 2016;55(5):467-471.
15. Whitlock EP, Burdu BU, Williams SB, et al. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(12):826-835.
16. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509-1518.
17. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med. 2018;379(16):1499-1508.
18. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing. 2011;40(1):23-29.
19. Marcum ZA, Perera S, Thorpe JM, et al. Antidepressant use and recurrent falls in community-dwelling older adults: findings from the health ABC study. Ann Pharmacother. 2016;50(7):525-533.
20. Torvinen-Kiiskinen S, Tolppanen AM, Koponen M, et al. Antidepressant use and risk of hip fractures among community-dwelling persons with and without Alzheimer's disease. Int J Geriatr Psychiatry. 2017;32(12):e107-e115.
21. Gomes T, Tadrous M, Muhammad M, et al. The burden of opioid-related mortality in the United States. JAMA Network Open. 2018;1(2):1–6.
22. Samet JH, Kertesz SG. Suggested paths to fixing the opioid crisis: directions and misdirections. JAMA Network Open. 2018;1(2):1–22.
23. Hanlon JT, Boudreau RM, Roumani YF, et al. Number and dosage of central nervous system medications on recurrent falls in community elders: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2009;64(4):492-498.
24. Miller GE, Sarpong EM, Davidoff AJ, et al. Determinants of potentially inappropriate medication use among community-dwelling older adults. Health Serv Res. 2017;52(4):1534-1549.
25. Gnjidic D, Agogo GO, Ramsey CM, et al. The impact of dementia diagnosis on patterns of potentially inappropriate medication use among older adults. J Gerontol A Biol Sci Med Sci. 2018 [Epub ahead of print];73:1410-1417. https://doi.org/10.1093/gerona/gly078.
26. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiat. 2015;72(2):136-142.
27. The American Geriatrics Society Expert Panel on Person-Centered Care. Person-centered care: a definition and essential elements. J Am Geriatr Soc. 2016;64:15-18. Available at https://onlinelibrary.wiley.com/doi/10.1111/jgs.13866.
28. Fick DM, Resnick B. 2012 Beers criteria update: how should practicing nurses use the criteria? J Gerontol Nurs. 2012;38(6):3-5.
29. Livingston G, Kelly L, Lewis-Holmes E, et al. Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. Br J Psychiatry. 2014;205:436-442.
30. Resnick B, Kolanowski AM, Van Haitsma K. Promoting positive behavioral health: a nonpharmacological toolkit for senior living communities. J Gerontol Nurs. 2014;40:2-3.
31. Fick DM, DiMeglio B, McDowell JA, et al. Do you know your patient? knowing individuals with dementia combined with evidence-based care promotes function and satisfaction in hospitalized older adults. J Gerontol Nurs. 2013;39:2-4.
32. Molony SL, Kolanowski A, Van Haitsma K, et al. Person-centered assessment and care planning. Gerontologist. 2018;58(suppl_1):S32-S47.
33. Scales K, Zimmerman S, Miller SJ. Evidence-based nonpharmacological practices to address behavioral and psychological symptoms of dementia. Gerontologist. 2018;58(suppl_1):S88-S102.
34. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213-218.
35. Neyarapally GA, Hammad TA, Pinheiro SP, et al. Review of quality assessment tools for the evaluation of pharmacoepidemiological safety studies. BMJ Open. 2012;2:e001362.
36. Hilmer SN, Gnjidic D, Abernethy DR. Pharmacoepidemiology in the postmarketing assessment of the safety and efficacy of drugs in older adults. J Gerontol Ser A: Biomed Sci Med Sci. 2012;67A:181-188.

Medication Overload: America's Other Drug Problem

How the drive to prescribe is harming older adults

EXECUTIVE SUMMARY

April 2019

LOWN INSTITUTE

Introduction: An Epidemic of Too Much Medication

In the last year, older adults in the U.S. sought medical care nearly 5 million times due to serious side effects from one or more medications. More than a quarter million of these visits resulted in hospitalizations, at a cost of $3.8 billion (see Appendix A in the full report).

These numbers point to a rapidly growing epidemic of medication overload among older Americans. Over the last decade, adults age 65 and older have been hospitalized for serious drug side effects, called adverse drug events (ADEs), about 2 million times. To put this in context, older adults are hospitalized for adverse drug events at a greater rate than the general population is hospitalized for opioids.[1]

The trend of increasing ADEs is not propelled by drug abuse, but by the rising number of medications prescribed to older adults (called "polypharmacy" in the scientific literature). More than 40 percent of older adults take five or more prescription medications a day, a three-fold increase over the past two decades.[2,3] The greater the number of medications—most of which are prescribed for legitimate reasons—the greater the risk for serious adverse reactions in older patients.

Medication overload is causing widespread yet unseen harm to our parents and our grandparents. It is every bit as serious as the opioid crisis, yet its scope remains invisible to many patients and health care professionals. While some clinicians are trying to reduce the burden of medications on their individual patients, no professional group, public organization, or government agency to date has formally assumed responsibility for addressing this national problem.

If current trends continue, we estimate that medication overload will be responsible for at least 4.6 million hospitalizations between 2020 and 2030. It will cost taxpayers, patients and families an estimated $62 billion. Over the next decade, medication overload is expected to cause the premature death of 150,000 older Americans.

In this report, the Lown Institute calls for the development of a national strategy to address medication overload and help older people avoid its devastating effects on the quality and length of their lives. A subsequent National Action Plan for Addressing Medication Overload will lay out a national strategy to address the epidemic of prescribing and ensure the safety of millions of older adults who are now at risk of preventable harm and premature death.

Polypharmacy

A term used in the scientific literature to describe the condition of taking multiple medications. Usually the threshold for polypharmacy is five or more medications, although the cutoff varies because there is not a single agreed upon definition. Polypharmacy can be helpful or harmful, depending on the patient's conditions and the specific medications.

Medication Overload

The use of multiple medications for which the harm to the patient outweighs the benefit. There is no strict cutoff for when the number of medications becomes harmful, but the greater number of medications a person is taking, the greater their likelihood of experiencing harm, including serious adverse drug events

Scope of the Epidemic

Researchers generally define polypharmacy as taking five or more drugs. Not every person on five or more drugs will suffer a serious side effect—people with multiple chronic conditions may require multiple medications. However, the more medications a person takes, the greater their risk of debilitating, sometimes even deadly side effects.

Polypharmacy has become alarmingly common, especially among older people. Nearly 20 million older adults in the U.S. are taking five or more prescription medications. Including over-the-counter medications and supplements, 67 percent of older adults take five or more drugs.[2,5]

The cumulative effect of so many drugs can be devastating. Serious drug reactions include internal bleeding, heart attacks, strokes, and even death. Older people are particularly vulnerable to confusion, dizziness, insomnia, and incontinence, and even a mild reaction can have serious consequences. For example, taking four or more medications significantly increases the risk of falling.[6] Falls can result in a head injury or broken hip, which in turn may cause of premature death.

Older adults taking five or more medications are at least 88 percent more likely to seek medical attention for an ADE compared to those taking one or two medications.[7] As the rate of polypharmacy rises, so has the rate of polypharmacy-related harm. The rate of ADEs among older adults in the U.S. has more than doubled since 2000, with an estimated one in five experiencing an ADE in 2018.

The potential ill effects of excessive prescribing go beyond ADEs and hospitalization. People can be confused and overwhelmed by having to keep track of numerous medications—when they should be taken, how they should be taken, what they're for, reducing the quality of their lives and increasing the risk for ADEs.

Impact of Adverse Drug Events in Older Adults, 2018

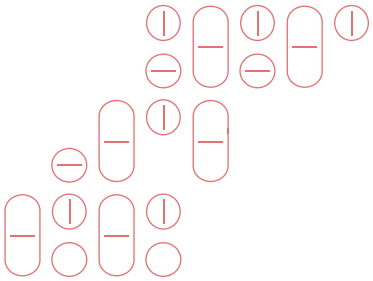
10 million experiences of adverse drug events

4.8 million outpatient visits

660,000 Emergency Department visits

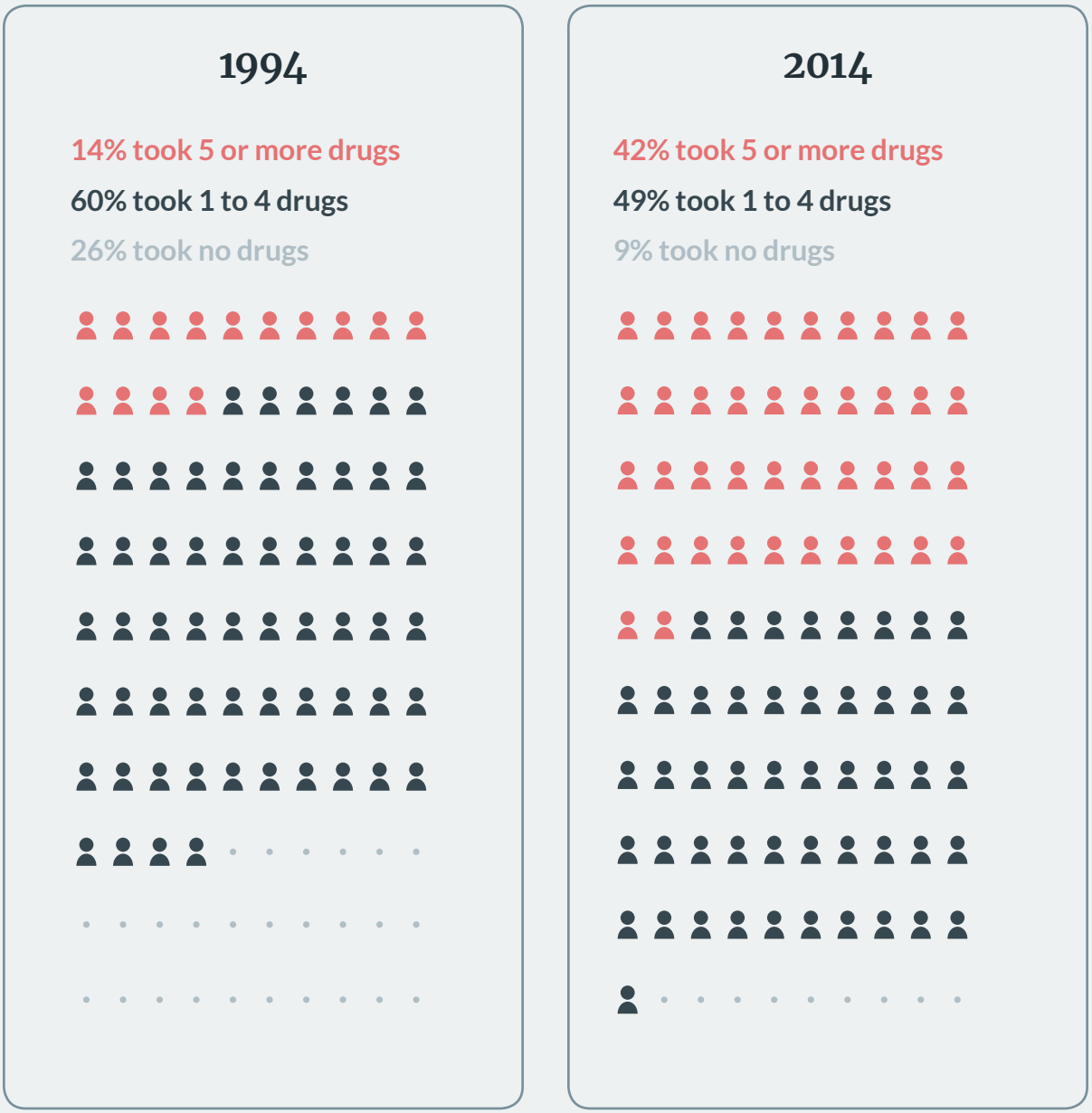
280,000 hospitalizations

9000 deaths



The Increasing Prevalence of Polypharmacy

From 1994 to 2014, the proportion of older adults taking five or more drugs tripled, from 13.8 percent to 42.4 percent. [2,4]



Drivers of Medication Overload

No single cause explains the dramatic rise in the number of medications older people are taking. Rather, a broad array of forces is at work, with three overarching aspects of our health care system contributing to the epidemic of medication overload:

Culture of Prescribing

Twenty years of advertisements linking prescription medications to happiness and health, the increased medicalization of normal human aging and experiences, the hurried pace of medical care, and a desire on the part of both health care professionals and patients and their families to "do something" have together fostered a shared expectation that there is a "pill for every ill." Both patients and clinicians have been oversold on the benefits of medications, to the point where a prescription is seen as caring, and withdrawal of medication connotes giving up on the patient.

Information & Knowledge Gaps

Clinicians and patients lack critical information and skills they need to appraise the evidence and make informed decisions regarding medications. From professional school to continuing education, nowhere is learning about the dangers of excessive prescribing a mandated, formal part of the curriculum for clinicians. Moreover, clinical guidelines, which doctors and other prescribers rely on in making decisions about medications, offer little information about how to adjust doses for older patients with multiple chronic conditions or how to stop a drug.

Fragmentation of Care

American health care suffers from a pervasive lack of coordination, or communication among a patient's various providers. In care transitions — between hospitals, rehab units, and long-term care facilities — additional medications may be prescribed with little information about the patient's current prescriptions. Often, more prescriptions are written to treat what appears to be a new condition, when in reality prescribers are treating a side effect of another drug. This "prescribing cascade" can lead to a cycle of debilitation and even death. EMRs have proved to be a poor solution to the overall lack of coordination across the system.

Numerous barriers stop clinicians from reducing or eliminating medications from a patient's regimen (a process called "deprescribing"). Patients may resist going off a drug they believe is keeping them healthy. Clinicians may fear a bad outcome from stopping a drug more than they fear a bad outcome from starting one. They often hesitate to take a patient off a drug that was prescribed by another clinician. Even clinicians who want to deprescribe do not know how to stop or taper drugs safely.

"At the end of his life, Joe was taking over 20 medications and 31 pills a day, but not one physician saw this as a problem worth addressing."

Patient Story

Killed by a Prescription Cascade

How did Joe Esposito go from a man in remarkable health, effortlessly running half marathons in his 50s, to being debilitated and incapacitated, struggling at death's door, in just a few years? When Joe sought treatment for his mild to moderate Crohn's disease, his list of medications cascaded from one to six to twenty, as each new medication brought on a new side effect.

The steroids he was prescribed to treat Crohn's led to bone loss and anal fistulas. He was given antibiotics for the fistulas, which caused peripheral neuropathy in his feet. He couldn't sleep from the pain so he was prescribed benzodiazepines and Ambien for sleep, Lyrica for the nerve damage, and Tramadol for the pain. Several of the drugs gave him severe diarrhea. To treat his diarrhea, he was given opium drops, and other medications. Additional drugs weakened his kidneys, which in turn raised his blood pressure, so he was put on four blood pressure medications. And an experimental anti-inflammatory drug led to Joe contracting pericardial tuberculosis, which almost killed him.

At the end of his life, Joe was taking over 20 medications and 31 pills a day, but not one physician saw this as a problem worth addressing or even considered that his symptoms were caused by the drugs and not the Crohn's disease.

Story originally told by Joe's wife, Gayle Esposito

Interventions to Avoid Medication Overload

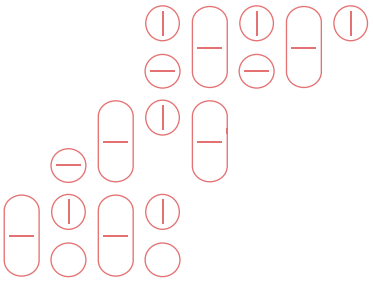
The medication overload afflicting millions of older adults is a complex problem, with many causes and agents and no easy fix. Addressing it will require a holistic, multi-pronged set of policies, regulations, and payment models, as well as changes in both the training and practice habits of health care professionals. A comprehensive set of solutions must include interventions to help prevent excessive prescribing as well as interventions to promote judicious discontinuation of medications that are inappropriate, potentially harmful, or no longer necessary.

As shown on the following page, solutions must address the three main drivers described previously: the culture of prescribing, information and knowledge gaps, and our fragmented health care system.

There is a critical need to increase awareness of medication overload among the public and providers alike, which will require public campaigns and targeted outreach. Awareness however, is only the first step. We need better information, better education for clinicians, and tighter regulations that would reduce the influence of the pharmaceutical industry on the public and the practice of medicine. Perhaps most importantly, we need to continue health care reforms that support the role of the primary care provider as the hub of the wheel in a fully coordinated care system.

The U.S. has had limited success with a handful of policies related to medication overload, but we continue to lag behind other high-income countries. Canada and Australia, for example, have established "deprescribing networks," made up of a diverse group of stakeholders who have come together to share information, draft strategies, and disseminate proven interventions to address this problem.

To catalyze action on this critical issue, the Lown Institute and a working group of expert clinicians, pharmacists, researchers, health policy advocates, and patients have undertaken a year-long effort to draft a National Action Plan for Addressing Medication Overload. This plan will focus on the most urgent actions needed to combat this epidemic and the paths to implementing them.



Impact and Feasibility of Interventions

Culture of Prescribing	Impact	Feasibility
Launch public service campaigns for both health professionals and non-professionals to increase awareness of medication overload	2	3
Empower patients and families by promoting the use of patient decision aids and shared decision making	3	2
Reduce pharmaceutical industry influence by limiting industry marketing to health professionals and direct-to-consumer advertising	3	1

Information and Knowledge Gaps	Impact	Feasibility
Ensure that clinical guidelines take into account patient age and comorbidities, and whenever possible, include recommendations for stopping medications	3	2
Further develop & disseminate deprescribing guidelines to help clinicians and pharmacists know how to deprescribe safely	2	2
Include training on appropriate prescribing and deprescribing for all students/trainees, as well as continuing medical education training for health professionals	3	1
Continue research on medication overload and deprescribing to fill research gaps	1	3

Fragmentation of Care	Impact	Feasibility
Implement team-based care models in hospitals and clinics, incorporating pharmacists into care teams when possible	2	1
Give primary care providers adequate time and information to do prescription checkups	3	1
Make electronic medical records more user-friendly and fully interoperable, so patients and providers can easily access a full list of patients' medications	2	1
Implement patient-centered prescription checkups periodically and during care transitions	3	2

Conclusion

The United States is in the grips of an unseen epidemic of harm from the excessive prescribing of medications. If nothing is done to change current practices, medication overload will lead to the premature deaths of 150,000 older Americans over the next decade and reduce the quality of life for millions more.

This report should serve as a clarion call to policymakers, regulators and legislators, along with health care providers and patient advocates, to come together to adopt a national strategy for addressing medication overload. Such a strategy can build on the recommendations in the National Action Plan for Addressing Medication Overload to create a thoughtful and inclusive framework for systemic change that will produce measurable and meaningful results.

Focusing on reducing inappropriate or unnecessary medications could save as much as $62 billion over the next decade in unnecessary hospitalization for older adults alone. As a nation, we would also save billions more on the cost of unnecessary drugs and visits to the emergency room and outpatient clinics. More important even than the associated costs, successfully tackling medication overload holds the promise of lessening disability, cognitive decline, and time in the hospital for patients. That translates into better lives for millions of people.

References

1. HCUP Fast Stats. Healthcare Cost and Utilization Project (HCUP). . 2018. www.hcup-us.ahrq.gov/faststats/opioid/opioiduse.jsp?radio3=on&location1=US&characteristic1=01&setting1=ED&location2=US&characteristic2=01&setting2=IP&expansionInfoState=hide&dataTablesState=hide&definitionsState=hide&exportState=hide (accessed November, 14, 2018 2018).
2. Statistics NCfH. Health, United States, 2016: With Chartbook on Long-term Trends in Health. In: Statistics NCfH, editor.; 2017.
3. Shehab N, Lovegrove MC, Geller A. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA 2016; 316(20): 2115-25.
4. Mitchell AA, Kaufman DW, Rosenberg L. Patterns of Medication Use in the United States. Boston, MA: The Sloane Epidemiology Center at Boston University, 2007.
5. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA Intern Med 2016; 176(4): 473-82.
6. Zia A, Kamaruzzaman S, Tan M. Polypharmacy and falls in older people: Balancing evidence-based medicine against falls risk. Postgraduate Medicine 2014; 127(3).
7. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. Pharmacoepidemiology and drug safety 2010; 19(9): 901-10.

21 Longwood Avenue
Brookline, MA 02446-5239 www.lowninstitute.org info@lowninstitute.org 617-992-9322

How Clinical Trials From Home Can Increase Access to Life-Changing Treatments

nextavenue.org/clinical-trials-from-home

October 3, 2019

By Beth BakerOctober 3, 2019

Credit: Adobe Stock

Some 85% of people over 60 use prescription drugs, according to the National Center for Health Statistics (NCHS). Yet, older people are not well represented in clinical trials, the gold standard for testing the safety and efficacy of medications, the NCHS says.

The Food and Drug Administration's 2018 Drug Trials Snapshot Summary Report found that for 59 new drugs, only 15% of the 44,000 patients who participated in clinical trials were 65 or older. For neurology drug trials, only 3% were older adults.

An effort is underway, however, to make it easier for people to join some clinical trials. Rather than travel to a research center, patients participate from home.

"The overwhelming majority of research studies are not done at the convenience of a participant," says Adrian Hernandez, vice dean for clinical research at Duke University

School of Medicine, who studies ways to increase patient engagement in clinical trials. “They’re done at the convenience of an investigator. People come in and are donating their time, their efforts, their blood, their data.”

> “The overwhelming majority of research studies are not done at the convenience of a participant.”

Hernandez and colleagues are launching a trial for people 75 and older to examine whether statins can help prevent cardiovascular disease and dementia. Participants will be recruited through their health care systems and the study will take place in their homes.

“For older people, getting involved in a trial can be difficult — navigating the system, going from the parking lot to the clinic, and then being able to interact with whatever tools or technologies that we have sometimes is not as friendly for older people,” Hernandez says.

Why It Matters

Until recently, researchers frequently excluded older participants, who often are on multiple medications or have several medical conditions. The fear was that the results would be inconsistent or not apply to a general population.

But that rationale does not make sense, says Steven Cummings, director of the San Francisco Coordinating Center, a nonprofit academic research organization.

“If your drug only works in the small portion of older people who don’t have any other problems or medications, then it will be irrelevant to the vast majority of older people,” Cummings says. The pharmaceutical industry has excluded older people “without any reason or evidence that this would be a problem,” and only by having older people in clinical trials can physicians know the drug’s real-world effects, he adds.

Researchers have recognized this problem of excluding older adults for years and are trying to address it. But even so, there are barriers, including the difficulty of travel for older adults.

Seventy percent of potential clinical trial participants (of all ages) live more than two hours from a trial center, according to the Deloitte Center for Health Solutions.

Reducing Patient Burden

Donna Cryer, 49, of Washington, D.C., CEO of the nonprofit advocacy organization the Global Liver Institute, has had a liver transplant and has other serious medical conditions. Having participated in several clinical trials, she strongly supports making them available to people at home.

“It’s hard to get out of the house as it is, and now you’re being asked to come out multiple times,” she says. “You’re just worn out. If we’re moving to create a culture of participation in clinical research, we have to focus on reducing the patient burden.”

Cryer was among the patient representatives and researchers at a 2018 National Academies of Science workshop that explored the pros and cons of so-called virtual or site-free clinical trials, meaning that patients could participate without going to a research center.

Cummings and other researchers at the workshop said that site-free trials would be cheaper and simpler, potentially yielding valuable medical advances more quickly.

New Home-Based Parkinson’s Drug Trial

Will McIntyre, 52, diagnosed with Parkinson’s Disease in 2013, has participated in a clinical trial to test a drug for symptom relief. He didn’t like the hassles. He works for a technology company in New Jersey and hated missing work to travel to Philadelphia to a research center. Plus, “oftentimes it will cost you,” he says. “It’s a forty-five or fifty-minute drive; tolls, parking can be twenty five dollars or thirty dollars. Some clinical trials are good about refunding expenses, but that can take months.”

McIntyre’s case is mild, he stresses, but in the advanced stages there can be many more barriers to participation. For one, the symptoms can make it hard to drive or take public transit. “The more you have difficulty with the disease, anything you can do to virtualize the experience would be extraordinarily valuable,” he says.

To address these concerns, Cummings is launching a new drug trial for Parkinson’s that would give older patients a way to participate in the research without having to travel.

“Patients with Parkinson’s have a very high risk of breaking a bone because they fall a lot,” he says. Very few get treatment to prevent fractures, because “there’s no evidence they would benefit,” he says.

Cummings’ new study, dubbed TOPAZ (Trial of Parkinson’s And Zoledronic Acid), will determine whether a treatment used for osteoporosis, Zoledronate, would help prevent fractures in Parkinson’s patients. The treatment is administered once intravenously and lasts two years. “If it works, it’s extremely convenient,” he says.

He has found from previous studies that making enrollment easy for patients is crucial to their willingness to participate. With TOPAZ, patients will be identified through their health system, the Parkinson’s Foundation or other trusted sources.

“We’re making it really simple,” he says. “They go to a website and if they qualify, a nurse will come to their home and give them an infusion of either the drug or a placebo. That’s it.”

Lower Cost, Less Time

Cummings' team aims to recruit more than 3,500 Parkinson's patients 65 and older, making it the largest study done on people with the disease, he says. "It doesn't matter where you live, you'll be able to join the study," he says. Recruitment will be rolled out by region, beginning with the Carolinas.

Had the trial been done the traditional way, Cummings says, it would likely involve 100 clinics to recruit 3,500 participants, each staffed by nurses, technicians and research assistants, and taking far longer.

"From conversations with colleagues in Pharma (the pharmaceutical industry), they roughly estimated [drug trials cost] thirty five thousand dollars to fifty thousand dollars per participant for five years, not including employees who support trial functions," Cummings says. "TOPAZ costs nine thousand one hundred and fifty dollars per participant, including all coordinating center staff support." The National Institute on Aging awarded TOPAZ researchers a $32.6 million, five-year grant for the study.

One Size Does Not Fit All

However, researchers caution that there's no one best approach to clinical trials. Some participants may actually prefer to go to a research site. Hernandez notes that patients may not remain as engaged if they are participating from home.

"With an in-person trial, there's a strong relationship with the study team, and retention is higher than virtual studies, at least so far," he says.

As an example, Hernandez points to his father, 80, who is participating in two trials related to healthy aging. "He likes coming in for an in-person visit because it's a social thing," Hernandez says. "Each person is different."

His mother, 72, is unwilling to participate, because she doesn't want to take the time and has privacy concerns about sharing health information over the internet, as would likely be done with most home-based clinical trials.

"Patient identification protection is a real concern for many people," says Cryer. "But that should not dissuade us from moving forward and using all the opportunities for sharing data."

At the same time, patients should not be asked to sign away their data "for any purpose and for whatever profit," Cryer says. Instead, they should be able to say whom they're willing to share their data with and for what purpose.

Technology Considerations

There are also equity concerns regarding technology that may be needed for home-based trials. Although 81% of U.S. adults own smartphones, just 53% of people 65 and older do, according to the Pew Research Center. Older people are also less likely to use the internet, according to the National Academies of Science workshop.

Researchers shouldn't assume that adequate bandwidth is universally available and affordable, says Silas Buchanan, CEO of eHealth Equity, a for-profit company connecting underserved groups with health information.

"Those are real obstacles, and that leads us into a conversation about social determinants of health, where people live, work, play and pray, age and die, and whether or not they are in a position to participate, even though they may want to," Buchanan says.

Buchanan's company works with faith groups to build bridges with the medical community. For example, he initiated a "Know Your Numbers" campaign in New York City with 10 churches to communicate with their members, many of them older adults, about monitoring their blood pressure. More than 500 church members participated.

McIntyre believes that patients have an important role to play in research. "We have to consider ourselves a fount of information for researchers," he says. "If we want a cure, we should be serious about opening the faucet. Every time we're offered the opportunity [to be in a trial] and we can afford to be there, I think we should do everything we can to participate."

By Beth Baker

Beth Baker is a longtime journalist whose articles have appeared in the Washington Post, AARP Bulletin, and Ms. Magazine. She is the author of *With a Little Help from Our Friends — Creating Community as We Grow Older* and of *Old Age in a New Age — The Promise of Transformative Nursing Homes*.

Next Avenue Editors Also Recommend:

Make a Donation

Sponsored

CLINICAL TRIAL PORTFOLIOS

A CRITICAL OVERSIGHT IN HUMAN RESEARCH ETHICS, DRUG REGULATION, AND POLICY

BY ALEX JOHN LONDON AND JONATHAN KIMMELMAN

Clinical trials cannot be reviewed in isolation from each other. Trial portfolios—series of trials interrelated by a common set of objectives—must be considered. The acceptability of a trial can change depending on the characteristics of the portfolio in which it is embedded. And different ways of structuring trial portfolios have different risks, benefits, and prospects for generating socially valuable information.

Evidence generated from clinical trials is critical to a wide range of stakeholders in making decisions and fulfilling their moral obligations. Regulators rely on clinical trials for drug approval and labeling decisions. Health systems, medical societies, and expert committees rely on the evidence from trials to determine treatment and utilization policy or to set treatment guidelines. Clinicians use this evidence to support treatment recommendations, and patients rely on it to decide which courses of care to undertake. Many of these stakeholders presume that the careful review of individual studies is enough to address the ethical and scientific questions and problems that arise in clinical trials. For example, new cancer drugs are routinely granted regulatory approval on the basis of a single trial showing large effects. Nowhere is this presumption more apparent than in the current system of research ethics and oversight.

The fields of research ethics and oversight presume that nearly all relevant ethical issues in research involving human participants can be identified and dealt with by the careful review of individual study protocols or their components. Its core institution, the institutional review board, and its central documents—such as the U.S. Common Rule (the federal regulations governing research with human subjects), *The Belmont Report*, the Declaration of

Alex John London and Jonathan Kimmelman, "Clinical Trial Portfolios: A Critical Oversight in Human Research Ethics, Drug Regulation, and Policy," *Hastings Center Report* 49, no. 4 (2019): 31-41. DOI: 10.1002/hast.1034

Helsinki, and Council for International Organizations of Medical Sciences guidelines—provide moral standards for evaluating individual study protocols. With rare exceptions,[1] ethical and policy debates focus on moral dimensions of individual research procedures (such as sham surgery[2] or research biopsy[3]), particular study designs (such as cluster randomized trials[4]), and the ethics of particular contested trials (such as the Surfactant Positive Airway Pressure and Pulse Oximetry Trial [SUPPORT][5]). Focusing ethical analysis and oversight on individual trials presumes that information reported in individual trial protocols is sufficient to render a sound ethical assessment of a trial or its results and that, if each study protocol meets an ethically acceptable standard, then the entire enterprise of human research will meet that standard as well. The problem, however, is that both of these presumptions are false.

In what follows, we demonstrate that explicit consideration of trial portfolios—series of trials that are interrelated by a common set of objectives—is crucial for two distinct but related reasons. First, the ethical acceptability and evidentiary probity of individual trials can change depending on the characteristics of the portfolios in which they are embedded. Second, how trial portfolios are composed, how well they are coordinated, and how efficiently they use information determines the balance of risks and benefits they present as well as their different prospects for generating socially valuable information; these three factors also raise distinct questions of justice.

Our analysis has implications for many stakeholders in research. We show that a set of what are currently treated as private decisions of study sponsors raise ethical questions that require explicit justification and that make them legitimate targets for policies that encourage fairer and more efficient portfolios. Oversight and regulatory bodies may need to adjust how they evaluate research claims. Clinicians, health systems, policy-makers, and other consumers of research information may need to broaden the scope of information they use to evaluate treatments and services. And bioethics and research ethics need to better facilitate discussions about the fairness and economy with which the costs and burdens of medical uncertainty are distributed across health care and research systems.

The Concept of the Drug Trial Portfolio

One of the main goals of clinical translation is to identify clinically useful interventions (from now on, we will refer to these simply as "drugs") and to generate sufficient evidence to warrant or discourage an intervention's clinical use. Establishing the clinical utility of a drug for a particular indication requires a sequence of studies. We call the sequence of studies in which a drug is tested in a particular indication a "research trajectory."

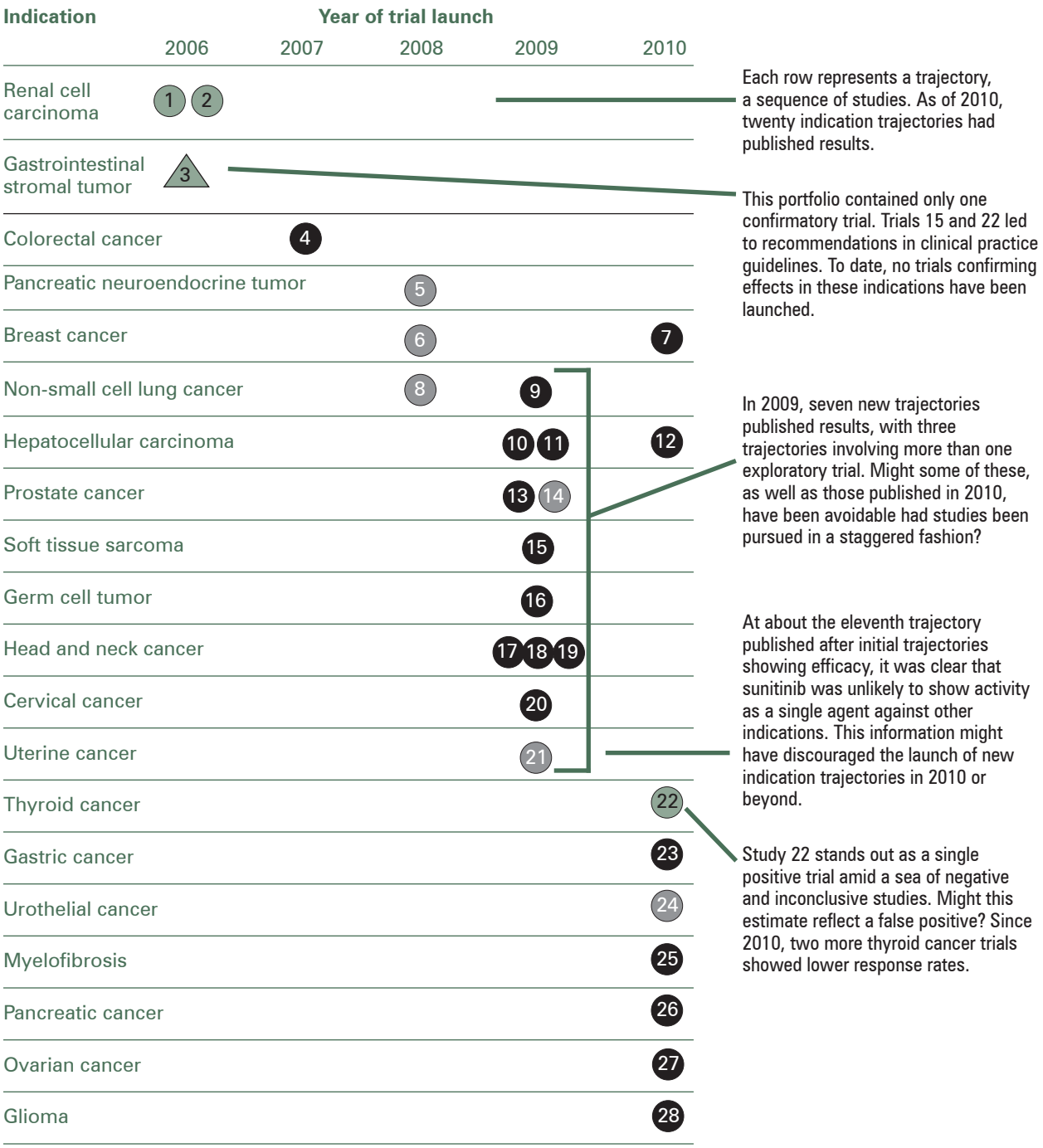
Research trajectories involve a division of labor between different types of studies. Typically, a research trajectory begins with a hypothesis that a drug may have clinical utility in a particular indication. Early studies aim to explore hypotheses about how features of the drug's use—such as dose, schedule, co-interventions, and so on—might modulate its clinical effects. The goal of these exploratory trials is to identify the ensemble of practices[6] most likely to result in clinical utility. Once this has been identified, late-phase, confirmatory trials subject the deployment of a drug within that package of practices to testing that provides a more reliable estimate of treatment effects.

For example, the trajectory of development of sunitinib as a treatment for renal cell carcinoma began when patients with this malignancy showed promising responses to it in a phase I trial.[7] The hypothesis that sunitinib could be effective for renal cell carcinoma was then tested directly in a single-armed phase II study.[8] After this study was positive, researchers conducted a phase III study aimed at testing a more defined hypothesis, namely, that sunitinib could be effective as first-line therapy if patients who were at a higher risk for serious side effects due to the drug's cardiotoxicity were excluded.

A drug trial portfolio consists of the set of trials in various research trajectories in which the same drug is tested against a range of indications. These studies are linked by a network of evidentiary connections such as assumptions about the mechanism of action of a drug and the pathophysiology of disease. The development of sunitinib for renal cell carcinoma thus represents one research trajectory within the larger portfolio of sunitinib research. While researchers were pursuing the sunitinib-renal cell carcinoma trajectory, other researchers were pursuing trajectories testing sunitinib for gastrointestinal stromal tumor, breast cancer, and lung cancer.[9] In cancer, these distinct research trajectories often develop out of common exploratory studies that test the same drug in multiple indications looking for signals of promise. What we are calling drug trial portfolios are distinct from "indication trial portfolios"—trial portfolios in which a range of drugs are tested against the same indication.[10] The figure in this article graphically represents the completed drug trial portfolio for sunitinib monotherapy as of 2010, as well as moral dynamics that we will discuss below.

For many drugs, trial portfolios consist of a small number of trials and trajectories. But for drugs that are considered breakthroughs, trial portfolios can be enormous. For the "silver bullet" anticancer drug imatinib, the first ten years of testing resulted in a portfolio consisting of thirty-seven trajectories and 128 trials.[11] For sorafenib, one of the first multityrosine kinase inhibitors, the first thirteen years of testing resulted in a portfolio consisting of twenty-six trajectories and 203 trials. The

Sunitinib Monotherapy Trial Portfolio, 2006-2010



Each numbered node represents one trial, color coded based on whether the results were positive (green with a black number), nonpositive (black), or inconclusive (gray with a white number). Triangles indicate trials that are confirmatory and phase III, and circles indicate exploratory and phase II trials. This graph does not include trials pursued in a trajectory after a given indication received FDA approval. The data in this figure derive from B. Carlisle et al., "Benefit, Risk, and Outcomes in Drug Development: A Systematic Review of Sunitinib," *Journal of the National Cancer Institute* 108, no. 1 (2016): doi:10.1093/jnci/djv292. (Graphical representation of trial portfolios is described further in S. P. Hey, C. M. Heilig, and C. Weijer, "Accumulating Evidence and Research Organization [AERO] Model: A New Tool for Representing, Analyzing, and Planning a Translational Research Program," *Trials* 14 [2013]: doi:10.1186/1745-6215-14-159.)

trial portfolio for the blockbuster antiseizure drug pregabalin produced a portfolio of twenty-four trajectories and seventy-three trials.[12] Checkpoint inhibitors have rapidly transformed cancer care in the last five years. According to one report, there are 803 open trials testing checkpoint inhibitors for treatment of cancer, with over 166,000 patient slots.[13]

Many institutions concerned with clinical research—such as institutional review boards, funding bodies, and regulatory agencies—view clinical trials as the primary mechanism for generating knowledge about treatments. The methods and design of clinical trials are scrutinized for a variety of scientific characteristics, including the steps taken to guard against various forms of bias or confounding (for example, a difference between groups of participants within a study with respect to characteristics that affect the association between the study intervention and the outcome measures). How a trial is designed and executed and how well information is used within that trial affect the risks to which participants are exposed, the prospect that those risks are offset by direct medical benefit to participants, and the prospect that those risks are offset by the production of medical information that has scientific and social value.

Trial portfolios raise two sets of related but distinct challenges for ethics, policy, and decision-making. First, the ethical acceptability of individual trials and the strength of the evidence they produce, considered in isolation, can change when considered in the larger context of a trial portfolio.[14] As a result, the assessment of individual studies is incomplete if not carried out at least partly with consideration of the context of the trial portfolio to which those studies belong. Second, trial portfolios themselves can present a more or less optimal balance of risks and benefits, present different prospects for generating socially valuable information, and raise distinct questions of justice depending on what trials they contain and how well trials within them are coordinated with each other. Decisions and policies that affect trial portfolio properties and composition therefore warrant explicit ethical and policy consideration.

Portfolio Composition, Risk, and Expected Benefits

Currently, the assessment of risk in research involves balancing the burdens and potential harms within individual studies against the likelihood of direct benefit to participants and against the value of the information that the investigations are expected to produce. Because trial portfolios are interrelated sets of studies, the composition of a portfolio can affect both the merits of individual studies in that set and the overall risk-benefit associated with the portfolio.

The composition of trials in a portfolio matters because of the aforementioned division of scientific labor between studies in a research trajectory. Exploratory studies (typically, phase I and II trials) use surrogate end points in small samples of participants over relatively short periods to identify and define the ensemble of practices most likely to result in clinical utility. Confirmatory trials (typically, phase III trials) test whether a drug, delivered according to this ensemble of practices, has clinical value by enrolling larger populations of patients and often targeting clinical end points. As a result, these trials require more time and resources to complete. In the absence of confirmatory trials, the results of exploratory studies have asymmetric value. When these studies are negative (in other words, they fail to support the hypothesis around which the trial was designed), they generate information that is valuable to a range of stakeholders: drug developers, clinicians, policy-makers, and patients learn that this drug is unlikely to have a beneficial effect when delivered as tested. However, the information from positive exploratory trials is often unreliable. Because they lack specificity for detecting clinical promise, treatment effects on surrogate end points in small studies conducted over a short time might not translate into beneficial effects in the clinical setting. As a result, the information from such studies is most useful to researchers who can subject such findings to confirmatory trials.

To appreciate the ethical consequences of different compositions of studies in alternate trial portfolios, consider a drug development portfolio in which a prior trajectory has resulted in regulatory approval for the use of the drug in a first indication. Knowledge of the drug's pharmacology, preclinical evidence, and an understanding of disease mechanism suggest strong promise in two indications, although there is a range of other indications that might respond to the drug as well. For simplicity, now imagine two alternative strategies for expanding this portfolio, each potentially involving a thousand patients.

The first strategy expands the portfolio by adding two small trials (a and b) enrolling one hundred patients each, exploring a drug's activity in the two indications of promise. If either of these studies shows a signal of promise, a large confirmatory trial involving eight hundred participants is carried out. The second strategy expands the portfolio by initiating ten small trials in ten new trajectories (trials a and b plus eight other exploratory trials), each enrolling one hundred patients, aimed at exploring the potential of the drug against ten different indications.[15]

The composition of a trial portfolio affects the merits of the individual studies in it. Trials a and b have greater social value in the context of the first way of expanding the portfolio because the expected value of an exploratory study depends, in part, on whether it is a member of a trial portfolio in which signals of promise are likely to be subject to confirmatory testing. In this portfolio, trials a and b perform the task to which they are best suited—supplying information to researchers that can be subjected to

confirmatory testing. In the second way of expanding the portfolio, these studies have less value because their results, on their own, are unreliable and unsuited to guiding clinical practice. Positive findings from exploratory studies that are not followed by confirmatory testing can entice patients and providers to consider off-label use of the drug for the promising indication. These stakeholders, along with health systems, policy-makers, and third-party payers, are left without sufficient evidence to warrant using that intervention in the relevant patient population. The result is that potentially large populations of patients are exposed to drugs that are possibly ineffective or harmful.[16]

Ethical review practices do not usually consider the composition of studies in a trial portfolio when evaluating individual protocols. Nor do they necessarily contemplate the prospect of follow-up trials that would be necessary to redeem the burdens and social investments for an exploratory trial. As a result, ethical review practices often involve tacit assumptions that exploratory studies, if positive, are likely to feed into confirmatory testing.[17] At the very least, such considerations should be placed in the foreground and made the subject of explicit ethical assessment, if not regulatory evaluation.

Trial portfolios also have properties that should be subject to ethical assessment in their own right. In the choice between alternative trial designs, if all else is equal, an approach that reduces the number of people harmed without detracting significantly from the quality of the evidence produced is ethically preferable to one that results in a larger number of people harmed for roughly the same gain in information. This principle applies at the level of trial portfolios as well.

If we consider the likelihood that risks from study participation in any given trial will be justifiable in light of the prospect of direct benefit to participants, then the first portfolio is ethically preferable. That portfolio concentrates on indications in which there is prior signal of promise and enrolls additional patients only if those signals are borne out in subsequent studies. The second portfolio allocates patients to a range of trajectories for which evidence of promise is weak, increasing the proportion of study participants unlikely to receive direct medical benefit.

If we consider the value of the information that these portfolios are expected to produce, we also see that the first portfolio, as a whole, is ethically preferable to the second. The first portfolio has the prospect of producing evidence sufficient for guiding clinical practice because any signal of promise will be followed up with confirmatory testing. Moreover, the second portfolio is less able to guide clinical practice because it does not subject any positive results that emerge from exploratory trials to confirmatory testing.

The composition of studies included in a drug trial portfolio thus affects the value of the individual trials included in that portfolio, the number of people placed at risk in a group of studies, the extent to which those harms are likely to be offset by direct benefits to participants, and the expected value of the information resulting from the series of tests.

Evidentiary Linkages and Efficient Knowledge Production

In a trial portfolio, trials in different trajectories pursue hypotheses that are related to each other. A drug trial portfolio features a drug that is tested in different indications, generally because some aspect or aspects of its activity might be useful against some set of pathophysiological mechanisms shared by different diseases. As a consequence, evidence from trials testing a drug against one disease is relevant to the probability that a different but related disease might respond to the drug. The pacing and coordination of studies in a portfolio determines the extent to which these evidentiary linkages are exploited to reduce the burdens necessary to generate reliable medical evidence.

"Pacing" refers to the timing with which new trials and trajectories are initiated. When trajectories are launched simultaneously, lessons learned in one trajectory about toxicities, optimal dosing, scheduling, and response that affect the window of clinical utility cannot be applied in other trajectories.[18] There are no opportunities to absorb emerging insights into the planning and design of new trajectories so that hazards can be avoided and inquiries can be concentrated on promising avenues.

"Coordination" refers to the degree to which information from studies in a portfolio is incorporated into or influences the conduct of other studies in the portfolio. Recently, trial designs have been proposed that evaluate a larger portion of a trial portfolio under a uniform statistical and methodological framework. Basket, umbrella, platform, and some expansion cohort trials[19] represent an effort to subsume many trials within a unified design that integrates evidence across studies, allowing unpromising

As portfolios expand—as additional trials are added—it becomes more difficult to avoid false positives or inaccurate estimates of treatment effects.

trajectories to be quickly identified and terminated so that resources can be shifted to more promising indications. Trial designs that efficiently use evidentiary linkages between studies of a drug in different indications can generate reliable medical information using fewer participants.[20]

Our aim is not to advocate for specific trial designs, but to use these examples to illustrate two points about research ethics. First, both pacing and coordination can alter the balance of risks and benefits in individual trials. Whether unnecessary risks and burdens have been eliminated from individual studies cannot be determined unless researchers or other stakeholders consider how information from other studies in the portfolio could be used to increase the efficiency of the study design. Second, whether portfolios make efficient use of evidentiary connections affects the number of patients that are burdened or harmed in the process of generating the same medical evidence. Because rapidly paced and poorly coordinated portfolios make an inefficient use of resources and generate risks and burdens that can be eliminated within alternative portfolios, their risks and burdens are not necessary to generate reliable medical evidence. The same moral principles that support eliminating unnecessary risks and burdens within individual trials support an ethical preference for trial portfolios that make a more efficient use of evidentiary linkages between trials in a portfolio. Nevertheless, decisions about how studies in a drug trial portfolio are paced and coordinated are not the focus of explicit policy, oversight, or review. Even though these decisions affect the health and welfare of study participants and the use of scarce resources, they are left to the discretion of private parties pursuing their own interests.

Portfolio Expansion and Inferential Power

Given the linkages between trials in a portfolio, the evidentiary value of any of its individual studies cannot be evaluated without considering the other studies conducted in the portfolio. There is another way in which studies in a trial portfolio are interlinked even when they explore radically different hypotheses. Adding new trials to a portfolio expends a portion of that portfolio's ability to detect true treatment effects. The more trials are added to a portfolio, the more resources are needed to estimate the efficacy of a treatment accurately. This effect derives from two features of trial portfolios that become increasingly important as portfolios grow in size: random variation in measured effects and heterogeneity in populations or diseases tested.

When testing a hypothesis in a randomized trial, researchers power their studies based on a prespecified tolerance for declaring differences between a treatment and comparator to be "real" even though they are due to chance alone (the value of this tolerance is called an "alpha"). For many clinical trials, researchers use an alpha of 0.05, meaning that they are willing to tolerate a 1 in 20 chance that, because of random variation, they will wrongly accept the hypothesis that a drug has a bigger or smaller treatment effect than the comparator in a randomized trial. Often, however, data monitors wish to probe whether treatment effects are emerging early on so that, if a study is futile or if it is showing a huge treatment effect, the trial can be stopped early. Yet, unless the alpha in a trial is adjusted, the statistical testing of an additional hypothesis increases the probability of a false positive.[21] Researchers therefore often adjust their alpha so that their overall tolerance for a false positive is still 1 in 20. They might do this by using a very small alpha for interim analysis (say, 0.01) and then a slightly adjusted alpha for the overall trial (such as 0.04 instead of 0.05). This adjustment is called an "alpha spending function."[22] Effective trial conduct requires stewarding a tolerance for false-positive results by testing as few hypotheses as possible, thus minimizing the spending of a trial's alpha.

What is true about false positivity and spending within trials is also true for trial portfolios. The more trials in a trial portfolio that test an intervention in different settings, populations, or subgroups, the greater the odds that some trials will produce false positive results. Because there is random variation across multiple trials within a portfolio, estimates of treatment effect from any one trial must be adjusted in light of effects observed in other trials within the portfolio. Imagine that a drug that has no effect on any disease is tested in a trial prespecifying a tolerance for false-positive results of 5 percent. If that drug is tested in a portfolio consisting of only one trial, then the probability that the portfolio will produce a false-positive result favoring the drug is 2.5 percent (assuming a two-tailed test is used). Now imagine that the same drug is tested in a portfolio consisting of twenty trials. The probability that the portfolio will produce at least one false positive result is more than 40 percent. If the portfolio had forty trials, this probability would jump to 87 percent. As this example makes clear, the greater the number of trials in a portfolio, the greater the probability of erroneously concluding that drug works against a disease for which it is tested.

Additionally, trials within portfolios show variability in treatment effects due to underlying heterogeneity in populations or diseases tested. As a consequence of this heterogeneity, outcomes in each trial in a portfolio also vary randomly around a central effect, the "portfolio mean." Because the variability in treatment effects that are estimated in trials exceed the true variability, trials that show unusually large effects are likely to overestimate efficacy unless they are adjusted downward toward the portfolio mean using a statistical technique known as "shrinking."[23] Similarly, trials showing unusually small effects should be "shrunk" upward toward a portfolio mean. The idea that estimates from

one trial should be adjusted in light of estimates from another trial testing a different disease is highly counterintuitive and hence called "Stein's paradox."[24] Problems of overestimation are compounded if outcomes of trials within portfolios correlate with each other (for example, when outcomes in breast cancer trials provide information on the probability of detecting efficacy in lung cancer).

Therefore, as portfolios expand—as additional trials are added—it becomes more difficult to avoid false positives or inaccurate estimates of treatment effects. As a result, more resources are needed to avoid these errors, including larger numbers of participants who must be exposed to the burdens and inconveniences of clinical investigation to test a given claim of clinical efficacy. A corollary of this observation is that the risk-benefit ratio for a trial under review is potentially diminished by the launch of other new trials pursuing different hypotheses within the trial portfolio. To accurately assess the inferential power of a trial and whether it is sufficient to offset risks to participants that are not offset by the prospect of direct benefit, individual trials have to be evaluated in light of all other trials in the drug trial portfolio.

Expanding trial portfolios has significant implications for the value of the evidence produced by individual studies and for the number of participants who must be exposed to research risk in order to generate reliable medical evidence. Adding exploratory trials that are not supported by a strong signal of promise increases the probability of spurious positive results. If these results are not subject to confirmatory testing or to correcting in light of the entire portfolio of research, they can mislead a range of stakeholders into undertaking treatments or dedicating resources to interventions that lack clinical utility. These defects in the value of information undermine the justification for exposing study participants to the associated risks from these added exploratory trials. Adding studies to a portfolio requires using larger numbers of participants in subsequent trials, thereby increasing the number of participants exposed to research risks. However, these problems cannot be identified, let alone addressed, if the fields of research ethics and regulatory oversight limit their attention to the assessment of individual study protocols.

These properties of trial portfolios also have important implications for decision-making in policy and regulation. When companies submit trial results to regulatory agencies like the U.S. Food and Drug Administration for approval, they select among the drug-indication pairings that show the greatest efficacy. As noted above, these trials are likely to have overestimated treatment effects and are at elevated risk of generating false positives. Unless the FDA (or guideline developers) adjusts effects observed in trials based on the risk of false positives and by shrinkage, the trial results used in regulatory decisions (or clinical practice guidelines) are likely to be biased—especially when trial portfolios are large.

> Decisions about how to pace and coordinate studies in a drug trial portfolio affect the health and welfare of study participants, yet they are left to the discretion of private parties pursuing their own interests.

Portfolios, Medical Uncertainty, and Justice

Part of the scientific and social value of individual studies resides in the prospect that their successful completion will reduce medical uncertainty and contribute to improvements in clinical practice.[25] The gatekeeping function of regulators involves establishing evidentiary thresholds for safety and efficacy that balance the need for timely access to medical innovation with the importance of ensuring a sound evidence base for the many stakeholders who rely on medical evidence in their decision-making.[26] Together, the considerations addressed above influence whether studies in a trial portfolio are likely to reduce or amplify medical uncertainty, where that uncertainty is addressed, and who bears the cost of dealing with such uncertainties.

For example, drug developers cannot earn revenue from a novel drug until regulators grant a license based on positive confirmatory trials. This provides strong incentive to construct drug portfolios that concentrate on indications with prior signals of promise and that include confirmatory trials. Once a drug is approved, however, companies and academic researchers often expand portfolios by launching many small exploratory studies.[27] The incentives for drug companies to run large and expensive confirmatory trials are attenuated when physicians are free to use a drug off label, and many clinical practice guidelines offer recommendations based on exploratory trial evidence.[28] Public funding is far more limited for academic researchers wishing to conduct expensive confirmatory trials. As a result, the threshold for initiating exploratory

trials is low, while revenue can be earned (or careers advanced) simply by showing a signal of promise in small, and less reliable, exploratory trials. This creates an incentive for companies and academic researchers to explore a wide range of indications, and even to explore indications where the evidence base for success is dubious but the potential market revenues from a positive signal are sufficiently high.[29]

Promising but incomplete research trajectories shift the burden of evidence generation from drug developers to patients, clinics, hospitals, and health systems. When these parties use drugs off label, they expend resources to purchase and implement interventions of unproven value and then shoulder the costs of investigating their clinical merits—if such investigations are even carried out. In such cases, drug developers potentially reap a double windfall—they enjoy revenues from expanded sales of drugs without having to cover the costs of validating their efficacy. Taxpayers also pay a double burden, because they foot the bill for publicly funded research while also paying for the reimbursement of off-label medical interventions that are motivated by exploratory but inconclusive studies. Because this windfall comes at the cost of information that patients, providers, policy-makers and others rely on to make momentous decisions, it raises questions about the justice of the system of incentives currently used to align the interests of stakeholders with the production of medical evidence.

Even when developers plan to pursue promising results with large-scale confirmatory trials, they frequently face choices about study pacing and coordination. To maximize the duration of their exclusive right to sell a drug, developers launch multiple studies in parallel. This decision effectively trades an increase in speed and profit against an increase in the number of participants likely to be harmed or burdened in the process. Similarly, sponsors may be reluctant to include their drug in study designs that maximize the comparability of results from testing different drugs against common indications if this involves disclosing comparative effectiveness information earlier in the life cycle of development. For example, I-SPY 2 is a phase II breast cancer drug trial designed to compare multiple investigational drugs to a common control and to one another.[30] Although six drugs have "graduated" from the trial and others are still being evaluated, no direct comparisons of investigational drugs to other investigational drugs have been reported to date. Decisions about how to use the full range of information available in a drug trial portfolio can pit the interests of health care systems, clinicians, and patients in having access to compendious evidence about the relative clinical merits of available treatments against the parochial interests of drug developers.

Similarly, the decision to expand portfolios by running many exploratory studies that are not supported by strong prior evidence of promise expends inferential capital in a way that increases the likelihood of obtaining false-positive results. When such results are not subject to confirmatory testing, spurious findings can drive the decision-making of patients, providers, and policy-makers, increasing costs without improving patient outcomes or health system efficiency. Portfolios containing positive exploratory trials without confirmatory testing therefore have questionable social value at best and, because they can distort the decision-making of many stakeholders, potentially have negative social value.

Because decisions about portfolio expansion and composition take place outside the frame of individual trial protocols, they are not subjected to scrutiny within research ethics or regulatory review. This means that there is frequently no public accountability for these decisions. Their rationale is not known, and how they balance important ethical values like reducing risk, ensuring social value, and promoting clinical utility over private considerations, such as companies' financial goals or researchers' professional interests, remains largely outside the scope of oversight. Treating such decisions as purely private matters for firms or academic investigators fails to account for the social implications of such decisions. The current narrow focus on protocol-level evaluations permits a range of morally relevant inefficiencies without public debate, let alone oversight.

Policy Implications and Possible Responses

The analysis presented here has implications for many stakeholders in the research enterprise. First, if the scientific and ethical merits of an individual trial cannot be reliably assessed in isolation from the larger portfolio of studies to which it is connected, then current practice within research ethics, oversight, and regulation is inadequate. Within the research enterprise, the assessment of the reasonableness of research risks, the distribution of research costs and burdens, and the value of information likely to be produced by individual trials will have to be made with reference to a much larger base of information. Outside of research, stakeholders who rely on evidence generated from individual clinical trials will have to evaluate findings in light of a similarly broadened information base. This includes a reassessment of the adequacy of regulatory procedures for approving new drugs and additional indications.

Second, this analysis suggests that traditional values of research ethics related to risk assessment, the social value of studies, and the justice of the way benefits and burdens of research are distributed should be applied at the level of trial portfolios. Because decisions that are traditionally seen as the private prerogatives of study sponsors or investigators can impinge on each of these values,

these decisions are legitimate targets for ethical assessment and policy-making. In particular, this analysis highlights the ethical issues involved in decisions about how studies are paced and whether to employ comprehensive study designs that more efficiently capture and use information generated from clinical studies. Additionally, some of these decisions involve other important values, such as respecting intellectual property, fostering innovation, enabling freedom of inquiry, and promoting competition in appropriate areas of drug development.

To address the issues we raise here, research ethics, policy, and regulation require mechanisms to evaluate trials or influence their planning in light of the larger portfolios in which they are embedded. The goal of these mechanisms should be to encourage portfolio composition, coordination, and pacing in a manner that minimizes risk, makes efficient use of medical information, promotes social value and facilitates an equitable distribution of the costs and burdens of research.

Many institutions charged with human protections, research policy, and drug approval have limited traction on various aspects of trial portfolios. Institutional review boards (IRBs) and data monitoring committees, for example, are authorized to consider only individual protocols. Funding bodies and drug companies might have control over some—but not all—trials in a portfolio. Drug regulators typically oversee individual trials, and ultimately evaluate single trajectories when making regulatory decisions. As a result, addressing the challenges presented here may require alterations to the current approaches to research ethics, oversight, drug regulation, and health care policy.

Research ethicists and policy-makers need to consider how oversight practices, public funding, drug approval, health care reimbursement, and perhaps other policy instruments like tax law or drug pricing can be altered to be more sensitive to the issues we have raised here. In the immediate term, IRBs and regulatory authorities can use their existing power to influence the organization of portfolios or to leverage the information contained in them by requiring researchers and funding agencies to submit comprehensive assessments of prior and ongoing studies along with individual protocol submissions.

Permissive ethical approval of clinical trials enables some of the problematic coordination and inefficiencies in trial portfolios. IRBs can play a role in promoting portfolios that reduce patient burden by requiring sponsors to submit information about the portfolio in which a trial is embedded, alongside supporting evidence in a trial brochure. For drugs that are not yet approved, this information would specify the composition of studies planned in a drug development trajectory and outline methods being employed to coordinate studies to increase efficient use of evidentiary linkages and reduce unnecessary risk and burden to study participants. For trials being added to trial portfolios involving an already approved drug, IRBs can ask sponsors to present information from public trial registries like ClinicalTrials.gov to show how many other exploratory trajectories within a portfolio have been launched. This can be supplemented with information on how many trajectories have led to results that are clinically actionable. If a large number of poorly coordinated trials have been launched, IRBs can withhold approval to encourage at least a more staggered pacing of portfolio expansion.

IRBs can also use information on the number of unsuccessful trajectories launched to assess the probability that a new trajectory will lead to clinically actionable evidence. If dozens of trajectories have been launched without leading to the discovery of new responding indications that are well on their way toward confirmation, IRBs should demand especially compelling evidence before approving a new trajectory. Data safety monitoring bodies should be similarly apprised of parallel trajectories within a portfolio and should use more stopping rules when a trial is testing hypotheses that will be partly addressed in parallel investigations.

IRBs can play a role in promoting portfolios that reduce patient burden by requiring sponsors to submit information about the portfolio in which a trial is embedded, alongside supporting evidence.

Regulatory authorities like the FDA can ask drug companies submitting applications for regulatory approval to also describe all launched trajectories, as well as estimates from completed trials, within a trial portfolio. If regulators state that they will shrink estimates and adjust inferential tests based on portfolio size, drug companies will have incentives to limit testing only to indications supported by a higher level of evidence. Such a proposal is less radical than it sounds, since the pharmaco-epidemiology division of FDA already collects and analyzes safety information for a drug across many different drug development trajectories.

We do not for a moment underestimate the policy challenges of addressing research inefficiencies and inequities that emerge from poor trial portfolio management. For example, it may be difficult for companies and academic researchers to anticipate the way portfolios might grow. Pressures like intellectual property issues will continue to influence the willingness of developers to exploit the full range of emerging information in trial portfolios. Another challenge concerns the illiquidity of research resources: an academic's decision to forgo an exploratory trial does not entail that the resources she might have expended will now be used for a confirmatory trial. Ultimately, new institutions—like portfolio-level data safety monitoring boards—might be needed to encourage better planning, coordination, and use of information generated in trial portfolios. For now, however, our point is a simple one: current systems of research ethics, drug regulation, and evidence synthesis cannot fulfill their mandates without considering how trial portfolios shape a broad range of scientific and ethical aspects of clinical research.

Acknowledgment

We thank Benjamin Carlisle, Carole Federico, Spencer Hey, Adelaide Doussau, and Mithat Gönem for ongoing discussions about the concept of trial portfolios, and the participants in the 2018 Carnegie Mellon Center for Ethics and Policy Workshop on Philosophical Issues in Research Ethics for their helpful feedback.

Notes

1. L. Gelinas et al., "When Clinical Trials Compete: Prioritising Study Recruitment," *Journal of Medical Ethics* 43, no. 12 (2017): 803-9; L. Pierson and J. Millum, "Health Research Priority Setting: The Duties of Individual Funders," *American Journal of Bioethics* 18, no. 11 (2018): 6-17.

2. W. R. Galpern et al., "Sham Neurosurgical Procedures in Clinical Trials for Neurodegenerative Diseases: Scientific and Ethical Considerations," *Lancet Neurology* 11, no. 7 (2012): 643-50; A. J. London and J. B. Kadane, "Placebos That Harm: Sham Surgery Controls in Clinical Trials," *Statistical Methods in Medical Research* 11, no. 5 (2002): 413-27.

3. J. Kimmelman et al., "Burdensome Research Procedures in Trials: Why Less Is More," *Journal of the National Cancer Institute* 109, no. 4 (2017): doi:10.1093/jnci/djw315.

4. C. Weijer et al., "Ethical Issues Posed by Cluster Randomized Trials in Health Research," *Trials* 12 (2011): doi:10.1186/1745-6215-12-100.

5. J. D. Lantos and C. Feudtner, "SUPPORT and the Ethics of Study Implementation: Lessons for Comparative Effectiveness Research from the Trial of Oxygen Therapy for Premature Babies," *Hastings Center Report* 45, no. 1 (2015): 30-40.

6. J. Kimmelman, "A Theoretical Framework for Early Human Studies: Uncertainty, Intervention Ensembles, and Boundaries," *Trials* 13, no. 1 (2012): article 173; J. Kimmelman and A. J. London, "The Structure of Clinical Translation: Efficiency, Information, and Ethics," *Hastings Center Report* 45, no. 2 (2015): 27-39.

7. S. Faivre et al., "Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients with Cancer," *Journal of Clinical Oncology* 24, no. 1 (2006): 25-35.

8. R. J. Motzer et al., "Sunitinib in Patients with Metastatic Renal Cell Carcinoma," *Journal of the American Medical Association* 295, no. 21 (2006): 2516-24.

9. B. Carlisle et al., "Benefit, Risk, and Outcomes in Drug Development: A Systematic Review of Sunitinib," *Journal of the National Cancer Institute* 108, no. 1 (2016): doi:10.1093/jnci/djv292.

10. Although we focus on drug trial portfolios here, we recognize that it may be possible to distinguish other types of portfolios organized around different considerations. An indication portfolio, for example, includes all the drugs tested on a particular indication. Portfolios might be organized around populations or other variables. The limits and implications of our ability to identify portfolios is the subject of further work.

Our use of the concept of a portfolio differs from the way drug companies use the term "portfolio" in several respects. First, drug companies often use this term to refer to the collection of different molecules in their development pipeline. We use this term to refer to the collection of studies testing a particular drug in different indications. Second, whereas drug companies use the term to mark out their intellectual property and their research plans, our use of the term does not presuppose that all of the studies within a portfolio are managed, sponsored, or conducted by a single entity. As we use the term here, portfolios reflect the sum of research activities involving a particular drug, regardless of sponsorship. Third, "portfolio" is often used to denote a synchronic process of culling drugs that are flagging and of investing in trials of drugs that show promise. Our use of the word "portfolio" is meant to capture diachronicity as well. Trials involving a drug that were completed long ago remain within its "drug development" portfolio.

11. J. Kimmelman, T. Zheng, and B. Carlisle, "Cancer Precision Medicine Drug Development Is Often Empirical: The Case of BCR-ABL Inhibitors," unpublished dataset, 2017.

12. C. A. Federico et al., "Assessment of Pregabalin Postapproval Trials and the Suggestion of Efficacy for New Indications: A Systematic Review," *JAMA Internal Medicine* 179, no. 1 (2019): 90-97.

13. L. Brawley, "With 20 Agents, 803 Trials, and 166,736 Patient Slots, Is Pharma Investing Too Heavily in PD-1 Drug Development?," *Cancer Letter* 42, no. 37 (October 7, 2016), https://cancerletter.com/articles/20161007_1/.

14. We show that studies that appear to be acceptable when viewed in isolation may be problematic when viewed in the larger context of their drug portfolio. Might it also be the case that studies that are viewed as ethically problematic in isolation could be seen as ethically acceptable in this larger context? Although this might be possible, conceptually, the reality of the incentives that stakeholders face to clearly elaborate the ethical merits of individual trials makes this less likely. For example, researchers proposing a drug trial in indication A will often direct reviewers to consider a positive trial result in indication B. Rarely will they direct reviewers to consider negative trials in indications C, D, and E.

15. With surprising frequency, detection of activity in positive exploratory trials is not followed up on with confirmatory trials. For example, in one study of the anticancer drug sorafenib, 11 percent of phase 2 trials produced a positive result on their primary end points but were not followed up with confirmatory clinical trials (see J. Mattina et al., "Inefficiencies and Patient Burdens in the Development of the Targeted Cancer Drug Sorafenib: A Systematic Review," *PLoS Biology* 15, no. 2 (2017): e2000487).

16. B. Carlisle, C. A. Federico, and J. Kimmelman, "Trials That Say 'Maybe': The Disconnect between Exploratory and Confirmatory Testing after Drug Approval," *BMJ* 360 (2018): doi:10.1136/bmj.k959.

17. Federico et al., "Assessment of Pregabalin Postapproval Trials."

18. Kimmelman and London, "The Structure of Clinical Translation."

19. L. A. Renfro and D. J. Sargent, "Statistical Controversies in Clinical Research: Basket Trials, Umbrella Trials, and Other Master Protocols: A Review and Examples,"

Annals of Oncology: Official Journal of the European Society for Medical Oncology 28, no. 1 (2017): 34-43.

20. S. M. Berry et al., "Bayesian Hierarchical Modeling of Patient Subpopulations: Efficient Designs of Phase II Oncology Clinical Trials," *Clinical Trials* 10 (2013): 720-34.

21. T. V. Pereira and J. P. A. Ioannidis, "Statistically Significant Meta-analyses of Clinical Trials Have Modest Credibility and Inflated Effects," *Journal of Clinical Epidemiology* 64, no. 10 (2011): 1060-69.

22. D. L. Demets and K. K. G. Lan, "Interim Analysis: The Alpha Spending Function Approach," *Statistics in Medicine* 13, no. 13-14 (1994): 1341-52.

23. J. Kimmelman, B. Carlisle, and M. Gonen, "Drug Development at the Portfolio Level Is Important for Policy, Care Decisions and Human Protections," *Journal of the American Medical Association* 318, no. 11 (2017): 1003-4; A. M. Lipsky et al., "The Importance of 'Shrinkage' in Subgroup Analyses," *Annals of Emergency Medicine* 55, no. 6 (2010): 544-552.e3; S. J. Kathman and M. D. Hale, "Combining Estimates from Multiple Early Studies to Obtain Estimates of Response: Using Shrinkage Estimates to Obtain Estimates of Response," *Pharmaceutical Statistics* 6, no. 4 (2007): 297-306.

24. B. Efron and C. Morris, "Stein's Paradox in Statistics," *Scientific American* 236 (1977): 119-27.

25. A. J. London, "Learning Health Systems, Clinical Equipoise and the Ethics of Response Adaptive Randomisation," *Journal of Medical Ethics* 44, no. 6 (2018): 409-15.

26. A. J. London, "A Non-paternalistic Model of Research Ethics and Oversight: Assessing the Benefits of Prospective Review," *Journal of Law, Medicine & Ethics* 40, no. 4 (2012): 930-44.

27. Carlisle et al., "Benefit, Risk, and Outcomes in Drug Development"; Federico et al., "Assessment of Pregabalin Postapproval Trials"; Mattina et al., "Inefficiencies and Patient Burdens in the Development of the Targeted Cancer Drug Sorafenib."

28. Many recommendations in influential clinical practice guidelines are based on low-level evidence—in some cases coming from exploratory trials and, in other cases, coming from subgroup analyses within exploratory trials, observational evidence, or even case reports. Consider the National Comprehensive Cancer Center guidelines—one of five compendia that are used to determine Medicare reimbursement in the United States (A. K. Green, W. A. Wood, and E. M. Basch, "Time to Reassess the Cancer Compendia for Off-Label Drug Coverage in Oncology," *Journal of the American Medical Association* 316 (2016): 1541-42). In one analysis, 94 percent of recommendations were based on lower-level evidence (T. K. Poonacha and R. S. Go, "Level of Scientific Evidence Underlying Recommendations Arising from the National Comprehensive Cancer Network Clinical Practice Guidelines," *Journal of Clinical Oncology* 29, no. 2 [2011]: 186-91).

29. Carlisle et al., "Benefit, Risk, and Outcomes in Drug Development"; Federico et al., "Assessment of Pregabalin Postapproval Trials and the Suggestion of Efficacy for New Indications"; Mattina et al., "Inefficiencies and Patient Burdens in the Development of the Targeted Cancer Drug Sorafenib."

30. S. Das and A. W. Lo, "Re-inventing Drug Development: A Case Study of the I-SPY 2 Breast Cancer Clinical Trials Program," *Contemporary Clinical Trials* 62 (2017): 168-74.

4. Gullón A, Formiga F, Díez-Manglano J, et al. NONAVASC study group. Vascular Risk Group of the Spanish Society of Internal Medicine. Influence of frailty on anticoagulant prescription and clinical outcomes after 1-year follow-up in hospitalised older patients with atrial fibrillation. Intern Emerg Med 2019;14:59–69.
5. Gullón A, Suárez C, Díez-Manglano J, et al. Antithrombotic treatment and characteristics of elderly patients with non-valvular atrial fibrillation hospitalized at internal medicine departments. NONAVASC registry. Med Clin (Barc) 2017;148:204–210.
6. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012; 16:601–608.
7. Alegre O, Formiga F, López-Palop R. LONGEVO-SCA registry investigators. An easy assessment of frailty at baseline independently predicts prognosis in very elderly patients with acute coronary syndromes. J Am Med Dir Assoc 2018;19: 296–303.
8. Rodriguez-Pascual C. Oral anticoagulants in frail patients with atrial fibrillation: Moving in the uncertainty of daily clinical practice. Rev Esp Geriatr Gerontol 2018;53:311–331.
9. Formiga F, Ferrer A, Mimbrera D, et al. High rate of anticoagulation therapy in oldest old subjects with atrial fibrillation: The Octabaix study. J Am Med Dir Assoc 2012;13:8–10.
10. Rodríguez-Pascual C, Torres-Torres I, Gómez-Quintanilla A, et al. Safety of direct oral anticoagulants and vitamin K antagonists in oldest old patients: A prospective study. J Am Med Dir Assoc 2018;19:936–941.

Francesc Formiga, MD, PhD
Internal Medicine Service
Hospital Universitari de Bellvitge
IDIBELL L'Hospitalet de Llobregat
Barcelona, Spain

Alejandra Gullón, MD
Carmen Suárez-Fernández, MD, PhD
Internal Medicine Department
University Hospital of La Princesa
Institute for Biomedical Research IIS-Princesa
Madrid, Spain

https://doi.org/10.1016/j.jamda.2019.02.016

Pharmacotherapy Research Priorities in Older Adults With Cardiovascular Disease in Nursing Homes, Assisted Living, and Home Care: Report From a Satellite Symposium of the ACC, AGS, NIA Workshop

Long-term care (LTC) services include a broad range of health, personal care, and supportive services provided at home (health agencies, hospice, or community providers) (HC), assisted living (AL) communities, and nursing facilities (NF).[1] Although the population of adults >85 years is increasing, the number of NF residents (1.4 million) will remain flat. In the future, a significant proportion of LTC for older adults will be HC. Evidence regarding strategies to optimize pharmacotherapeutic outcomes and medication safety across the LTC spectrum is scarce, creating a strong research need. To drive this research agenda, we identified a set of setting-specific pharmacotherapy research needs identified as part of a satellite symposium focused on pharmacotherapy across the LTC spectrum.

Methods

Under a U13 National Institutes of Health (NIH) grant (http://grantome.com/grant/NIH/U13-AG047008-05), the National Institute on Aging (NIA), the American College of Cardiology (ACC), and the American Geriatrics Society (AGS) sponsored a series of biennial workshops to identify critical knowledge gaps and research priorities for optimizing patient-centered care and outcomes in older adults with cardiovascular (CV) disease. A satellite symposium addressing pharmacotherapy in long-term care settings (LTC) was convened as part of the second workshop in February 2017 to specifically focus on information gaps and research priorities.[2] Participants had diverse backgrounds, including nursing, pharmacy, medicine, and administrative. Using a nominal group technique, participants identified barriers to conducting research, unique environmental characteristics, and primary gaps in knowledge related to pharmacotherapy across the 3 LTC settings (NF, AL, HC). The information gathered is summarized and a set of research priorities presented.

Research Challenges by LTC Setting

Most research has traditionally focused on NF. However, NF have evolved significantly over the past several decades, now having widely divergent resident populations. This has resulted in highly variable care processes necessary to address this heterogeneity.[3] Goal-directed care for those admitted to NF for post-acute care who will be rehabilitated and discharged differs compared to that for long-stay residents or those present for end-of-life care. On average, NF residents receive >8 medications per day, with CV medications accounting for >25% of prescriptions.[4] Concerns about polypharmacy, adverse drug events, drug interactions, and medication errors are high in this population.[5] Electronically available data are focused on daily care needs, identifying sentinel problems, and often do not include the detail, standardization, or measurement accuracy needed for research. In prior decades, NIH-sponsored Teaching Nursing Homes provided infrastructure for research at a number of academic centers. Unfortunately, these programs no longer exist.

AL is focused on aging in place and de-emphasizing medical services in relationship to providing a homelike nurturing environment.[6] Many AL residents have a high burden of chronic illnesses, disability, and frailty, and exhibit polypharmacy.[6–8] The social model of care, heterogeneity among residents and sites, and variable state regulations predispose to substantial diversity in care models, quality of care, and availability of assistive personnel. There are few data sources and limited market penetration of EHRs; manual research data collection is usually necessary. Conducting research in AL settings is thus more difficult than in NF, and few if any research consortiums exist.

The role of HC is increasing over other sites of LTC because of patient preferences and in an attempt to decrease health care costs. Medication oversight is limited in HC. High rates of multimorbidity and associated increased health care utilization make HC a particularly difficult setting in which to conduct clinical research.[9] Barriers to HC research result from few with HC research expertise, lack of organized data and patient access, and limited funding opportunities. The Palliative Care Research Cooperative is the first cooperative in the United States focused on palliative and end-of-life care research and serves as a potential model for HC-based research.[10]

Funding for this conference was made possible, in part by U13 AG 047008 from the National Institute on Aging. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government. Support as facilities and administrative was provided by the American College of Cardiology (ACC).
The authors declare no conflicts of interest.

Table 1
Pharmacotherapy Research Priorities in Older Adults With Cardiovascular (CV) Disease, by Long-term Care (LTC) Setting

Priority	Area	Desired Characteristics
Nursing facilities (NFs)		
1	Identify how to best measure quality	• Person centered, goal directed • Range of potentially relevant outcomes • Reflect different stakeholders' views • Quality interventions that cross morbidity lines, ie, multimorbidity, geriatric syndromes
2	Optimize prescribing	• Linked to person-centered, goal-directed outcomes • Address over- and undertreatment • Evaluate effectiveness and outcomes of deprescribing interventions • Reduce medication burden • Improve medication safety through pharmacokinetic and pharmacodynamic analysis of "high-risk" CV drugs in NF adults • Optimize methods to reduce drug-drug and drug-disease interactions
3	Study models of care • Claude Pepper Older Americans Independence Centers • Teaching LTC facilities	• Apply implementation science to identify the best methods and needed resources to make meaningful improvements in care for short- and long-stay residents • Evaluate best practices for improving care during care transitions • Identify models of care that optimize a culture of safety while maximizing the resident's independence • Address knowledge gaps in how to care for those with the greatest functional impairment • Encourage research on health problems prominent in NF • Develop strategies on current and new therapies and health maintenance
Assisted living and residential care communities (AL)		
1	Evaluate epidemiology	• Survey the AL landscape; define common elements of AL
2	Define data elements	• Consistent data elements are needed to compare interventions across care settings and geographical landscapes • Determine which data can be extracted from public files
3	Evaluate then optimize prescribing	• Determine state-level differences in prescribing • Characterize key indicators, such as adverse drug events to high risk medications • Longitudinal data are needed to describe persistence of drug use
Home care (HC)—research sites of the future		
1	Evaluate epidemiology of older adults living at home	• Develop standard definitions and vocabulary • Determine prevalence and patterns of in-home support
2	Define and differentiate between short- and long-term home-based care and caregiver needs	• Identify/define short-term needs for Medicare HC • Study outcomes, implementation, advantages, and disadvantages or informal caregiver support compared to paid caregiver support
3	Evaluate specific needs of HC adults in CV care and CV medications	• Comparison to the other most predominate conditions and drug therapy • Evaluate ways to decrease polypharmacy, including the efficacy of deprescribing medications
4	Define caregivers' medication support needs	• Determine needs and methods of delivery of education and support of informal caregivers in order to optimize medication administration, adherence, and monitoring
5	Medications at home	• Determine the impact of the home setting on medication choices, doses, and usage • Define optimum care for medication administration in the home setting

Research Priorities by Setting

Table 1 identifies a set of CV pharmacotherapy research priorities by setting. Research priorities in NF should center on how to best measure quality, optimize prescribing, and evaluate best practices for improving care for short- and long-stay residents. Person-centered, goal-directed quality interventions that cross morbidity lines are needed. In particular, research for reduction of the medication burden through deprescribing can improve medication safety, may reduce drug-drug interactions, and address overtreatment.

Given that less is known about CV pharmacotherapy in AL, research should survey the landscape and define data elements that can be used to compare care environments across care settings and geographic areas. Information on prescribing characteristics, medication persistence, and safety indicators like adverse drug events is needed.

Research priorities in HC begin with the fundamental necessity of developing standard vocabulary for the widely disparate patterns of in-home support. Differences between short- and long-term home-based care necessitate the study of outcomes and implementation, as well as the advantages and disadvantages of informal caregiver support compared to paid caregiver support. Environmental studies are needed to evaluate the specific pharmacotherapy needs of HC adults, including deprescribing and other ways to decrease polypharmacy. It is important to define caregiver's medication support needs in order to optimize medication administration, adherence, and monitoring. Researchers should

learn how the impact of the home setting affects medication choice, route of administration, and usage while defining optimum care for medication administration in the home.

Implications for Research Policy

A need exists to close the pharmacotherapeutic knowledge gap for older adults residing at home and in and NF environments to enable safe and effective care and appropriate use of medications. Despite the challenges, investigators can undertake the top research priorities while organizing networks to address more sophisticated research questions. To do so will require extensive coordination, access to necessary funding, patient/family/caregiver involvement, and leadership from professional organizations.

Acknowledgments

The authors also wish to acknowledge Kelli Bohannon, ACC, for her contributions in organization and logistical support for the meeting and the speakers Joseph Ouslander, MD, Colleen Maxwell, PhD, Christine Ritchie, MD, MSPH, and Jean Kutner, MD, at the conference, and Kate Lapane, PhD and Janice B. Schwartz, MD as co-chairs of the conference.

References

1. Harris-Kojetin L, Sengupta M, Park-Lee E, et al. Long-term care providers and services users in the United States: Data from the National Study of Long-term Care Providers, 2013-2014. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. Vital Health Stat 2016;3:1–118.
2. Schwartz JB, Schmader KE, Hanlon JT, et al. Pharmacotherapy in older adults with cardiovascular disease: Report from an ACC, AGS, NIA Workshop. J Am Geriatr Soc 2019;67:371–380.
3. Unroe KT, Ouslander JG, Saliba D. Nursing home regulations redefined: Implications for providers. J Am Geriatr Soc 2018;66:191–194.
4. Moore KL, Patel K, Boscardin WJ, et al. Medication burden attributable to chronic co-morbid conditions in the very old and vulnerable. PLoS One 2018;13:e0196109.
5. Simmons SF, Schnelle JF, Sathe NA, et al. Defining safety in the nursing home setting: Implications for future research. J Am Med Dir Assoc 2016;17:473–481.
6. Katz PR, Kronhaus A, Fuller S. The role of physicians practicing in assisted living: Time for change. J Am Med Dir Assoc 2018;19:102–103.
7. van den Brink AMA, Gerritsen DL, Oude Voshaar RC, et al. Residents with mental-physical multimorbidity living in long-term care facilities: Prevalence and characteristics. A systematic review. Internat Psychogeriatr 2013;25:531–548.
8. Resnick B, Galik E, Boltz M, et al. Polypharmacy in assisted living and impact on clinical outcomes. Consult Pharm 2018;33:321–330.
9. Abernethy AP, Aziz NM, Basch E, et al. A strategy to advance the evidence base in palliative medicine: Formation of a palliative care research cooperative group. J Palliat Med 2010;13:1–7.
10. Mondor L, Maxwell CJ, Hogan DB, et al. Multimorbidity and healthcare utilization among home care clients with dementia in Ontario, Canada: A retrospective analysis of a population-based cohort. PLoS Med 2017;14:e1002249.

Barbara J. Zarowitz, PharmD, FCCP, BCPS, BCGP, FASCP
The Peter Lamy Center on Drug Therapy and Aging
University of Maryland School of Pharmacy
Baltimore, MD

David A. Nace, MD, MPH
Division of Geriatric Medicine
University of Pittsburgh and Chief of Medical Affairs
UPMC Senior Communities
Pittsburgh, PA

Nicole Brandt, PharmD, MBA, BCGP, BCPP, FASCP
The Peter Lamy Center on Drug Therapy and Aging
University of Maryland School of Pharmacy
Baltimore, MD

Janice B. Schwartz, MD, AGSF, FACC, FAHA
Bioengineering & Therapeutic Sciences
University of California in San Francisco and Visiting Research Scientist
San Francisco, CA

https://doi.org/10.1016/j.jamda.2019.02.009

Pain Management in the Last 6 Months of Life: Predictors of Opioid and Non-Opioid Use

When it comes to pain, nursing home care falls short. The experience of pain negatively impacts life quality and function, especially for residents with multiple chronic comorbidities. The proportion of residents with pain is high, with estimates ranging from 45%[1] to 65%.[2] Because the experience of pain is primarily subjective, clinicians rely on patients' self-report to direct pain management strategies. Yet, in a nursing home, many residents have dementia and are unable to communicate pain. It is not surprising that pain in the nursing home is both high and underrecognized. In order to treat pain, it must be assessed. Pain rating scales, considered the gold standard of assessment, are used for persons with intact cognitive status who can self-report. For persons with dementia (PWD), the identification of pain and its treatment needs greater attention as we cannot always rely on self-report. Research shows an association between pain and disruptive behaviors in PWD in the nursing home, considered the consequence of untreated pain.[3] Tools developed to evaluate pain in PWD who cannot communicate focus on the identification of behavioral disturbances. For example, in the Pain in Advanced Dementia Scale,[4] vocalization, facial expression, and body language are cues to indicate pain. Despite the advancements toward designing pain assessment protocols, pain treatment lags behind. Nonpharmacologic techniques can be used to enhance comfort, particularly for PWD who cannot communicate their pain verbally.[5] Empirical evidence for the effectiveness of these techniques for pain treatment is lacking,[5] although there are some encouraging findings.[6] Regarding pharmacologic techniques, the World Health Organization[7] suggests a stepped approach to treat pain beginning with nonopioids, with increasing doses of opioids if needed. Some research has shown that pain for PWD was mostly treated with nonopioids, and only changed to opioids when end of life was near.[8] Hospice in the nursing home is also significantly associated with higher use of opioid pain medications.[9] Clinicians prefer to avoid opioids in this population because of concern about polypharmacy and issues around metabolism and excretion of medications.[3]

We conducted a cross-sectional examination of nursing home decedents over a 1-year period, with a 6-month look-back period using retrospective medical record data to examine and compare the predictors of pain treatment using nonopioids and opioids. We examined the following predictors of pain treatment: diagnoses associated with pain in residents (arthritis, cancer, coronary artery disease, and diabetes), level of cognitive impairment, pain, and

This research was supported by the Patrick and Catherine Weldon Donaghue Medical Research Foundation award to the second author.
The authors declare no conflicts of interest.

Harnessing wearable device data to improve state-level real-time surveillance of influenza-like illness in the USA: a population-based study

Jennifer M Radin, Nathan E Wineinger, Eric J Topol, Steven R Steinhubl

Summary

Background Acute infections can cause an individual to have an elevated resting heart rate (RHR) and change their routine daily activities due to the physiological response to the inflammatory insult. Consequently, we aimed to evaluate if population trends of seasonal respiratory infections, such as influenza, could be identified through wearable sensors that collect RHR and sleep data.

Methods We obtained de-identified sensor data from 200 000 individuals who used a Fitbit wearable device from March 1, 2016, to March 1, 2018, in the USA. We included users who wore a Fitbit for at least 60 days and used the same wearable throughout the entire period, and focused on the top five states with the most Fitbit users in the dataset: California, Texas, New York, Illinois, and Pennsylvania. Inclusion criteria included having a self-reported birth year between 1930 and 2004, height greater than 1 m, and weight greater than 20 kg. We excluded daily measurements with missing RHR, missing wear time, and wear time less than 1000 min per day. We compared sensor data with weekly estimates of influenza-like illness (ILI) rates at the state level, as reported by the US Centers for Disease Control and Prevention (CDC), by identifying weeks in which Fitbit users displayed elevated RHRs and increased sleep levels. For each state, we modelled ILI case counts with a negative binomial model that included 3-week lagged CDC ILI rate data (null model) and the proportion of weekly Fitbit users with elevated RHR and increased sleep duration above a specified threshold (full model). We also evaluated weekly change in ILI rate by linear regression using change in proportion of elevated Fitbit data. Pearson correlation was used to compare predicted versus CDC reported ILI rates.

Findings We identified 47 249 users in the top five states who wore a Fitbit consistently during the study period, including more than 13·3 million total RHR and sleep measures. We found the Fitbit data significantly improved ILI predictions in all five states, with an average increase in Pearson correlation of 0·12 (SD 0·07) over baseline models, corresponding to an improvement of 6·3–32·9%. Correlations of the final models with the CDC ILI rates ranged from 0·84 to 0·97. Week-to-week changes in the proportion of Fitbit users with abnormal data were associated with week-to-week changes in ILI rates in most cases.

Interpretation Activity and physiological trackers are increasingly used in the USA and globally to monitor individual health. By accessing these data, it could be possible to improve real-time and geographically refined influenza surveillance. This information could be vital to enact timely outbreak response measures to prevent further transmission of influenza cases during outbreaks.

Funding Partly supported by the US National Institutes of Health National Center for Advancing Translational Sciences.

Lancet Digital Health 2020; 2: e85–93

Published Online January 16, 2020 https://doi.org/10.1016/S2589-7500(19)30222-5

See Comment page e54

Translational Institute, Scripps Research, La Jolla, CA, USA (J M Radin PhD, N E Wineinger PhD, Prof E J Topol MD, S R Steinhubl MD)

Correspondence to: Dr Jennifer M Radin, Translational Institute, Scripps Research, La Jolla, CA 92037, USA **jmradin@scripps.edu**

Introduction

In the USA, approximately 7% of working adults and 20% of children younger than 5 years of age get influenza annually.[1] Traditional influenza surveillance relies largely on a combination of virologic and syndromic influenza-like illness (ILI) surveillance to estimate influenza trends.[2] However, ILI surveillance has a 1–3 week reporting lag and is often revised weeks later by the US Centers for Disease Control and Prevention (CDC).[3]

Several groups have attempted to use rapid influenza tests,[4] data on internet search terms (eg, Google Flu Trends),[5] and social media outlets such as Twitter[6] to provide real-time influenza surveillance. However, despite some success, Google Flu Trends was found to miss early waves of the 2009 H1N1 pandemic influenza[7] and over-estimate activity during outbreaks.[7,8] Although Twitter could improve traditional ILI surveillance, it had variable success on its own.[6,9] The challenge with using these methods is distinguishing between activity related to an individual's own illness and those related to media or heightened awareness and interest about influenza during the influenza season. Consequently, there is a great need

Research in context

Evidence before this study

Influenza results in up to 650 000 deaths worldwide each year. Traditional influenza surveillance reporting in the USA and globally is often delayed by 1–3 weeks, if not more, and revised months later. This delay can allow outbreaks to go unnoticed, quickly spreading to new susceptible populations and geographical regions. We searched PubMed from Jan 1, 1990, to July 20, 2019, using combinations of words or terms that included "influenza" OR "influenza-like illness" AND "predictions" OR "modeling" OR "nowcasting". Previous studies have attempted to use crowd-sourced data, such as Google Flu Trends and Twitter, to provide real-time influenza surveillance information—a method known as nowcasting. However, these methods typically overestimate rates during epidemic periods and have variable success on their own, especially at the state level.

Added value of this study

To our knowledge, this is the first study to evaluate and show that objective data collected from wearables significantly improved nowcasting of influenza-like illness. This result held in all five states that we examined, with an average increase in Pearson correlation of 0·12 over baseline, resulting in correlations ranging from 0·84 to 0·97 in the final models. These associations remained consistent when correcting for first-order autocorrelation in time-matched or 1-week-lagged models.

Implications of all the available evidence

In the future, wearables could include additional sensors to prospectively track blood pressure, temperature, electrocardiogram, and cough analysis, which could be used to further characterise an individual's baseline and identify abnormalities. Future prospective studies will help to differentiate deviations from an individual's normal levels resulting from infectious versus non-infectious causes, and might even be able to identify infections before symptom onset. Capturing physiological and behavioural data from a growing number of wearable device users globally could greatly improve timeliness and precision of public health responses and even inform individual clinical care. It could also fill major gaps in regions where influenza surveillance data are not available.

to enhance traditional ILI surveillance with new objective data streams that can provide real-time information on influenza activity.

A 2016 study estimated that 12% of US consumers owned a fitness band or smartwatch[10] and this number continues to grow. Wearable sensors that continuously track an individual's physiological measurements, such as resting heart rate (RHR), activity, and sleep, might be able to identify abnormal fluctuations indicting perturbations in one's health, such as an acute infection. It is a normal physiological response to have an elevated RHR as a result of infection, especially when it is accompanied by a fever.[11] Sleep and activity are also likely to differ from the norm when someone does not feel well. The purpose of our study was to evaluate whether wearable sensor data could improve influenza surveillance at the state level—so-called nowcasting. Enhanced ILI surveillance would improve the ability to enact quick outbreak response measures to prevent further spread of new influenza strains.

Methods

Data collection

Through a research collaboration between Scripps Research Translational Institute and Fitbit, we obtained de-identified data from a convenience sample of 200 000 consistent users who wore a Fitbit device from March 1, 2016, until March 1, 2018. These users wore their Fitbit for at least 60 days during this study time and had only one Fitbit tracker for the whole period. Inclusion criteria included having a self-reported birth year between 1930 and 2004, height greater than 1 m, and weight greater than 20 kg. User location (ie, state) was only collected for measurements after Dec 1, 2016, and was inferred for the previous period on the basis of the most frequent state reported. To sufficiently measure changes at a population level, we only evaluated users from the top five states with the most Fitbit users in our dataset: California, Texas, New York, Illinois, and Pennsylvania. De-identified Fitbit data were used for this study, which was determined by the Scripps institutional review board to be exempt from institutional review board review. All Fitbit users, including those whose data are used in this study, are notified that their de-identified data could potentially be used for research in the Fitbit Privacy Policy.

The dataset included daily measurements of RHR, sleep minutes from main sleep (ie, the longest sleep of the day), and wear time. Daily measurements with missing RHR, missing wear time, and wear time less than 1000 min per day were excluded from the study dataset. We also excluded data obtained in the first 2 weeks of March, 2016, because Fitbit implemented a change in their RHR algorithm at that time. Daily activity data were not available.

We obtained final end-of-season unweighted ILI rates from the CDC's FluView database.[12] CDC ILI rates are calculated as the weekly percentage of outpatient office visits for ILI, which is defined as fever (temperature >37·8°C) and a cough or sore throat without a known cause other than influenza, and are collected from sentinel surveillance clinics.[2]

Calculation of the RHR

According to Fitbit, RHR is calculated as follows: periods of still activity during the day are identified by looking at the accelerometer signal provided by the device. If

inactivity is observed for a sufficiently long time (eg, 5 min), then it is assumed that the person is in a resting state, and their heart rate at that time is used to estimate their RHR. If the user wears the device to sleep at night, their sleeping heart rate is also used to improve this estimate. Note that the lowest heart rate during sleep can be lower than the RHR since the RHR is intended to capture the heart rate when a user is awake and at rest.[13]

The manufacturer has found that the estimated RHR based on this algorithm closely matches the value reported by the Fitbit device when measured by users in a supine position immediately after waking.[13] The manufacturer has also verified the accuracy of the device in measuring heart rate during still periods by direct comparison with an electrocardiogram (ECG) reference and found a mean average error of less than 1 beat per min (bpm).[13] Fitbit devices have shown good agreement with polysomnography and ECGs in measuring sleep and heart rate during sleep, with average heart rate less than 1 bpm lower than that recorded by ECG.[14,15]

Data analysis

For each user, overall mean (SD) of RHR and sleep duration during the entire study period were calculated. Any users with fewer than 100 RHR measures were excluded. Each user's weekly RHR and sleep averages were also calculated to align with CDC ILI surveillance data reported on a weekly basis. Users with fewer than four RHR measures during a given week were omitted from downstream analyses pertaining to that week.

We hypothesised that elevated RHR and increased sleep duration compared with an individual's average might be indicative of ILI. During each week, a user's data were identified as abnormal if their weekly average exceeded a given threshold: a sleep time that was longer than 0·5 SD below their overall average and an RHR that was either 0·5 SD (model 1) or 1·0 SD (model 2) above their overall average. Additionally, thresholds that included a constant value higher than average were also evaluated. Users were stratified by state, and the proportion of users meeting these thresholds each week was calculated. Thus, for a given state k, the proportion of users with abnormal data for week j is defined as $x_{j,k,l}$ where l represents the 0·5 SD (model 1) or 1·0 SD (model 2) thresholds above average.

The number of CDC-reported ILI cases $y_{j,k}$ among the number of outpatient office visits $n_{j,k}$ during each week over the observation period across each state k was likewise collected. To simplify analytic issues dealing with 0 case counts in a given week, 1 was added to both measures. The proportion of cases in each state (ie, $y_{j,k}/n_{j,k}$) is defined as $p_{j,k}$.

Various state-stratified models were considered to evaluate the relationships between ILI rates and Fitbit data. The first naive model, m_{naive}, simply modelled the CDC ILI case count as a function of the proportion $x_{j,k,l}$ of Fitbit users with abnormal data in a given week using a negative binomial model with offset $n_{j,k}$. Because CDC ILI data are often delayed by several weeks and later revised, a 3-week lagged autoregressive term $p_{j-3,k}$ was added to the m_{naive} model to create the m_{abs} model. This model was similar, but more conservative, to the autoregressive AR(3) model used by Yang and colleagues[3] to evaluate the predictive power of Google Flu Trends using CDC ILI rates from up to 3 weeks before, and models the absolute ILI count $y_{j,k}$ in each week j. Formally:

$$m_{abs,H1}: \log(y_{j,k}) = \beta_0 + \beta_{p,k} \cdot p_{j-3,k} + \beta_{x,k} \cdot x_{j,k,l} + \log(n_{j,k})$$

where m_{abs} is a negative binomial model with offset term $\log(n_{j,k})$. The H_1 model shown assumes the ILI case count $y_{j,k}$ is affected by the proportion of users with abnormal data, whereas the baseline model $m_{abs,H0}$ omits $x_{j,k,l}$ such that the null hypothesis is $H_0: \beta_x = 0$ for each state k. Decisions to stratify by state were based on modifications of the m_{abs} model; the modified model combined data across states and included a state main effect and state-by-$x_{j,k,l}$ interaction term:

$$\log(y_{j,k}) = \beta_0 + \beta_{p,k} \cdot p_{j-3,k} + \beta_{x,k} \cdot x_{j,k,l} + \log(n_{j,k}) + \sum_k \beta_k \cdot 1(k) + \sum_k \beta_{x*k} [x_{j,k,l} \cdot 1(k)]$$

where $1(k)$ represents an indicator variable for state k, β_k is the coefficient for the main effect, and β_{x*k} is the coefficient for the interaction term. The presence of significant interactions indicated that the effect of the Fitbit variable might differ by state, and thus we opted for a stratified approach.

Finally, we created a linear regression model to predict change in ILI rate from week to week. For each state k, change in ILI rate is given by $p_{j,k*} = p_{j,k} - p_{j-1,k}$ and change in the proportion of users with abnormal data is given by $x_{j,k,l*} = x_{j,k,l} - x_{j-1,k,l}$, and the resulting m_{change} model more appropriately accounts for autocorrelation that remains present in m_{abs}:

$$m_{change}: p_{j,k*} = \beta_0 + \beta_x \cdot x_{j,k,l*}$$

This change is evaluated by linear regression for each state k with elevated sleep and RHR thresholds l. In the first instance, parameters corresponding to the change in proportion $x_{j,k,l}$ of elevated RHR and sleep were of main interest, and compared with models omitting this term. Cross-correlation was used to evaluate 1-week lead ($x_{j-1,k,l}$) and 1-week lag ($x_{j+1,k,l}$) of the Fitbit data—ie, whether changes in Fitbit data occurred before or after corresponding changes in ILI rates. Pearson correlation (r) was used to compare predicted rates with CDC-reported ILI rates for time-matched, 1-week-lag, and 1-week-lead time periods. Additionally, we assessed correlation using only influenza-season data (week 40 up to week 20 the following year).

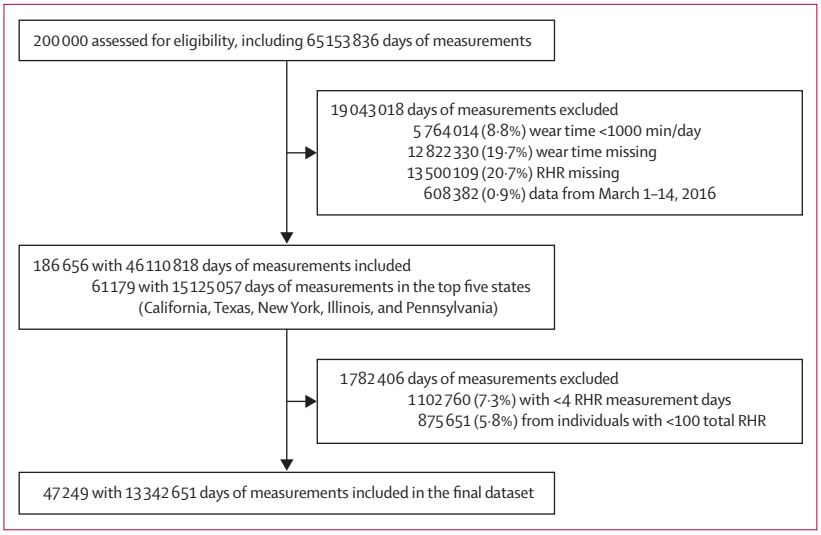


Figure 1: **Study profile**
RHR=resting heart rate.

Model validation

We did a validation analysis, in which we used data from the first season (season 1: 2016 [week 11]–2017 [week 10]) for model training and data from the second season (season 2: 2017 [week 11]–2018 [week 9]) for model validation. Our validation analysis showed the addition of the Fitbit variable improved the correlations in all states except New York when using just one season of data. When season 2 data were used to predict ILI rates using the model fit with season 1 data, the Fitbit variable also improved correlations in all states except New York (appendix p 10).

See Online for appendix

We were limited to 2 years of Fitbit data, and therefore only had one season each for training and validation. Consequently, we found that New York, for which ILI cases were not reported during summer weeks in 2017 (season 1), had the lowest correlations for the $m_{abs,H0}$ and $m_{abs,H1}$ models compared with the other states (appendix p 10). Additionally, since influenza can peak at different times from season to season, and it had much higher activity in the second season, especially in California and Illinois, the $m_{abs,H0}$ model had lower Pearson correlations in season 2 than in season 1 in those states. However, overall correlations showed improvements with the addition of the Fitbit variable, and reduced error terms (root mean squared error and mean absolute percentage error), indicating a better overall fit when the Fitbit variable was added to the models (appendix p 9).

Role of the funding source

The funder did not play any role in data collection, analysis, interpretation, writing of the manuscript, or decision to submit. JMR had access to all the data and was responsible for the decision to submit the manuscript. The US National Institutes of Health National Center for Advancing Translational Sciences grant UL1TR002550 supported part of the salary for SRS and EJT. Fitbit pulled the data with input from Scripps Research Translational Institute.

Results

We originally obtained more than 65 million measurements from 200 000 Fitbit users (figure 1). Among those, 47 249 users totalling 13 342 651 daily measurements from five of the most populous states met inclusion criteria (figure 1). The mean age of included individuals was 42·7 years (SD 14·6) and 28 465 (60·2%) were female (table 1). The number of Fitbit users grew during the study period, especially around January, 2017 (figure 2).

On average, users in the full dataset had an RHR of 65·6 bpm (SD 8·4), slept 6·6 h (SD 1·9) per night, and wore their device for 22·5 h (1·6) daily (table 2). RHR and sleep and wear time among users in the final dataset did not vary substantially by state (table 2). SDs for RHR (range 0·2–18·3 bpm) and sleep time (24–336 min) varied considerably from individual to individual.

We tested varying levels of data abnormality depending on different RHR and sleep measurements. Our model 1 threshold definitions classified 531 648 (24·3%) of 2 186 559 weekly measurements as abnormal, whereas our model 2 definitions classified 245 060 (11·2%) measurements as abnormal. We found the highest correlation with CDC-reported ILI rates when using the model 1 thresholds—ie, defining abnormal Fitbit data as 0·5 SD above a user's average RHR combined with sleep more than 0·5 SD below the user's average—and made it our final model (table 3). We also found that the addition of the sleep threshold improved our models slightly over ones that only incorporated RHR. We found that using an individual's RHR SD from the entire study period, rather than using a constant value higher than their average, resulted in higher correlations. We also found that the proportion of participants with Fitbit data above the threshold was higher during the 2017–18 influenza season compared with the 2016–17 influenza season (figure 2).

In all states, the $m_{abs,H1}$ models had significantly higher correlations with ILI rates than the baseline $m_{abs,H0}$ models, with improvements in Pearson correlations ranging from 6·3% (New York, model 1) to 32·9% (California, model 1), indicating that the Fitbit variable was a significant predictor of ILI (table 3, figure 3). The average increase in Pearson correlation was 0·12 (SD 0·07) over baseline. In general, prediction levels from the full $m_{abs,H1}$ model were high, although more consistently for model 1, with California having the highest correlation (r=0·97; p<0·0001) and New York the lowest (r=0·89; p<0·0001; table 2). We found a significant interaction between the state variable and the Fitbit variable (p<0·0001) in our modified m_{abs} model, indicating that the role of the Fitbit variable varied by state. We also tested the correlation for the same model but restricted to data from the influenza seasons only (ie, week 40 up to week 20 in the following year) and found similar correlations (table 4).

	Top five states (n=47 249)	California (n=13 632)	Texas (n=12 399)	New York (n=7872)	Illinois (n=7132)	Pennsylvania (n=6214)
Gender						
Female	28 465 (60·2%)	8126 (60·0%)	7139 (57·6%)	4860 (61·7%)	4444 (62·3%)	3896 (62·7%)
Male	18 594 (39·4%)	5457 (40·0%)	5205 (42·0%)	3977 (37·8%)	2658 (37·3%)	2297 (37·0%)
Unknown	190 (0·4%)	49 (0·4%)	55 (0·4%)	35 (0·4%)	30 (0·4%)	21 (0·3%)
Age (years)	42·7 (14·6)	43·5 (14·9)	41·9 (14·1)	42·6 (14·8)	42·6 (14·6)	42·7 (14·8)
BMI						
Underweight (<18·5 kg/m²)	585 (1·2%)	175 (1·3%)	144 (1·2%)	90 (1·1%)	98 (1·4%)	78 (1·3%)
Normal (18·5–24·9 kg/m²)	12 751 (27·0%)	4034 (29·6%)	3158 (25·5%)	2137 (27·2%)	1822 (25·6%)	1600 (25·8%)
Overweight (25·0–29·9 kg/m²)	17 064 (36·1%)	5010 (36·8%)	4500 (36·3%)	2890 (36·7%)	2481 (34·8%)	2183 (35·1%)
Obese (≥30·0 kg/m²)	16 849 (35·7%)	4413 (32·4%)	4597 (36·3%)	2755 (35·0%)	2731 (38·3%)	2353 (37·9%)

Data are n (%) or mean (SD). BMI=body-mass index.

Table 1: **Frequency of self-reported participant characteristics by state from March 15, 2016, to March 1, 2018 (n=47 249)**

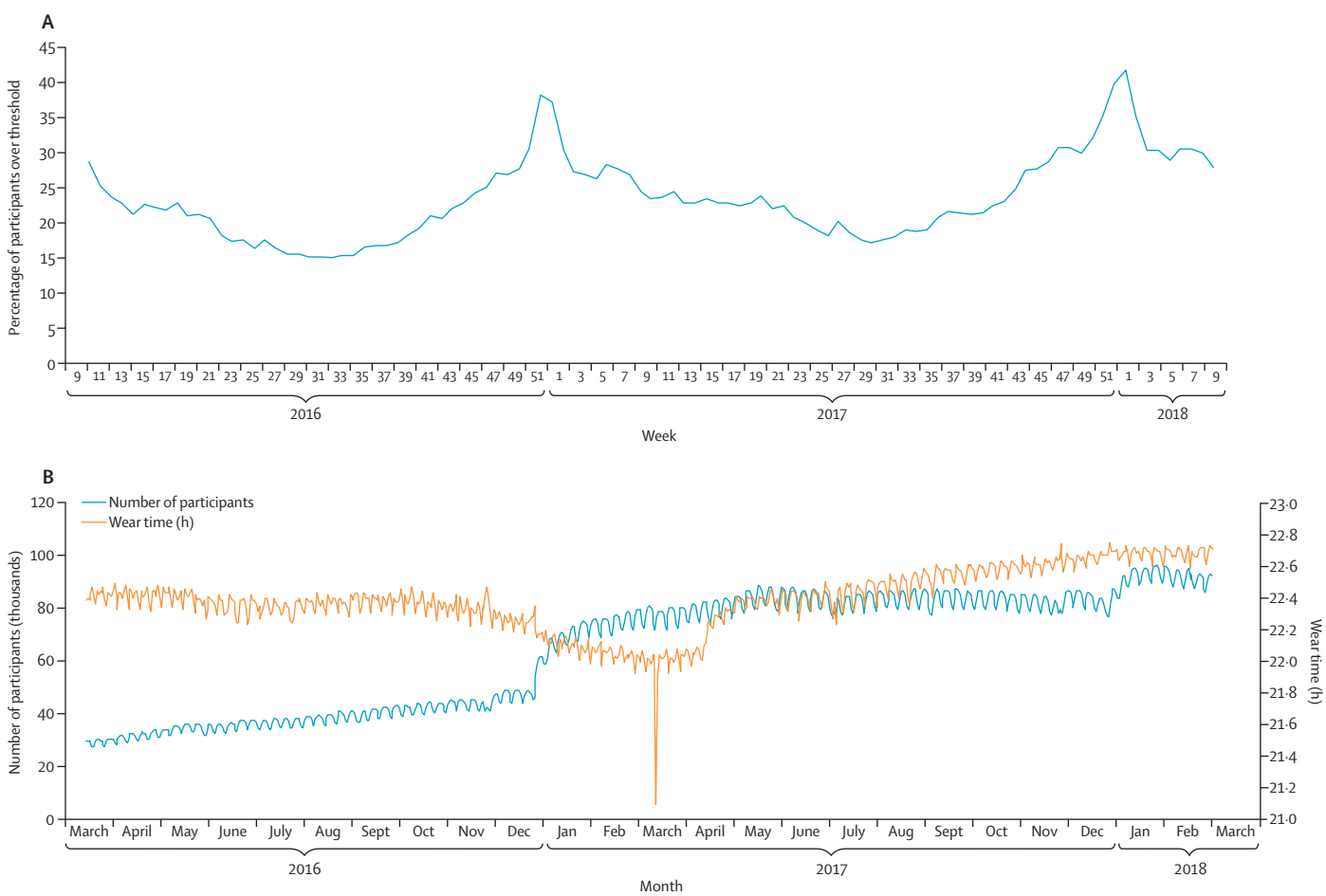


Figure 2: **Percentage of participants with weekly data above threshold of the m_{naive} model (A) and average daily wear time against number of users (B)**
Data are from March 15, 2016, to March 1, 2018. (A) Measurements from 144 360 users from all states were included. Measurements with missing wear time, wear time less than 1000 min/day or missing RHR were excluded, as well as weeks with fewer than four RHR measurements and users with less than 100 total RHR measurements. Model 1 thresholds were used: participants were over the threshold for any given week if they had a sleep time that was greater than 0·5 SD below their overall average and an RHR that was 0·5 SD above their overall average. (B) Measurements from 186 656 users from all states were included. Measurements with missing wear time, wear time less than 1000 min/day, and missing RHR were excluded for this analysis. The sharp downwards spike in wear time in March, 2017, is the result of daylight saving time. RHR=resting heart rate.

	Users	Total measurements	Mean resting heart rate, bpm	Mean sleep time, h	Mean wear time, h
USA*	200 000	46 110 818	65·6 (8·4)	6·6 (1·9)	22·5 (1·6)
California	13 632	616 646	65·3 (7·6)	6·5 (0·9)	22·4 (0·7)
Texas	12 399	591 431	65·9 (7·8)	6·6 (0·8)	22·4 (0·6)
New York	7872	351 768	65·5 (7·7)	6·6 (0·9)	22·4 (0·7)
Illinois	7132	340 347	66·1 (7·8)	6·6 (0·9)	22·5 (0·6)
Pennsylvania	6214	286 257	66·0 (7·9)	6·6 (0·9)	22·4 (0·7)

Data are n or mean (SD). State data show population averages of individuals' mean resting heart rate, sleep time, and wear time during entire study period, using data from the final dataset. bpm=beats per min. *Full dataset (before exclusions). Measurements taken from March 15, 2016, to March 1, 2018.

Table 2: **Number of measurements and average resting heart rate, sleep time, and wear time for full dataset and top five states**

	Negative binomial model predicting ILI case counts				Linear regression model predicting weekly change in ILI rates		
	m_{naive}	$m_{abs,H0}$	$m_{abs,H1}$	p value*	m_{change}	m_{change} (1-week lag)	m_{change} (1-week lead)
Model 1 (lower RHR threshold)							
California	0·92	0·73	0·97	<0·0001	0·62†	0·31†	0·32†
Texas	0·77	0·84	0·92	<0·0001	0·24†	0·22†	0·10
New York	0·33	0·79	0·84	<0·0001	0·15	0·20†	−0·05
Illinois	0·72	0·80	0·92	<0·0001	0·35†	0·34†	0·16
Pennsylvania	0·48	0·78	0·89	<0·0001	0·27†	0·16	−0·11
Model 2 (higher RHR threshold)							
California	0·90	0·73	0·96	<0·0001	0·66†	0·36†	0·28†
Texas	0·73	0·84	0·90	<0·0001	0·19	0·24†	0·04
New York	0·30	0·79	0·82	<0·0001	0·11	0·19†	−0·06
Illinois	0·70	0·80	0·90	<0·0001	0·35†	0·42†	0·08
Pennsylvania	0·42	0·78	0·88	<0·0001	0·23†	0·24†	−0·14

Individuals were classified as having a week with abnormal Fitbit data if their weekly average exceeded a given threshold: a sleep time that was longer than 0·5 SD below their overall average and an RHR that was either 0·5 SD (model 1) or 1·0 SD (model 2) above their overall average. Naive models included just Fitbit data. H_0 models assumed the ILI case count was not affected by the proportion of users with abnormal Fitbit data, whereas H_1 models assumed that it was. CDC=US Centers for Disease Control and Prevention. ILI=influenza-like illness.RHR=resting heart rate. *p value comparing H_0 to H_1 models. †Pearson correlations were significant (p<0·05).

Table 3: **Pearson correlations comparing CDC ILI rates with predicted rates in naive, null, and full negative binomial models and comparing change in CDC ILI rates with change in Fitbit data with a 1-week lag and a 1-week lead**

When modelling the change in ILI rates from one week to the next, the m_{change} models mostly showed statistical association with proportions of elevated weekly RHR and abnormal sleep across all states, for either the time-matched or lagged data, at either RHR threshold (table 3). Inspection of the cross-correlation between fitted and observed models showed the Fitbit data generally did not lead the ILI rate data—that is, changes in Fitbit data were not observed before changes in ILI rate data. Instead, it was more common that Fitbit changes occurred in the week of changes in ILI rates (time matched) or in the following week (1-week lag). This implies that the changes in Fitbit data occur during or after the changes in ILI rates, and are therefore less predictive at forecasting future ILI events.

Discussion

Improved characterisation of an individual's average values through wearable sensors will allow us to better identify deviations that could indicate the incidence of acute disease states, such as cold and influenza infections. To our knowledge, this is the first study to evaluate the use of RHR and sleep data in a large population to predict real-time ILI rates at the state level. We saw significant improvements in our ability to predict influenza when incorporating the proportion of users with abnormal sleep and RHR values in our full $m_{abs,H1}$ model and in our m_{change} model, as well as reduced prediction errors (appendix p 9). Currently, CDC ILI data are typically reported 1–3 weeks late and reported numbers are often revised months later. The ability to harness wearable device data at a large scale might help to improve objective, real-time estimates of ILI rates at a more local level, giving public health responders the ability to act quickly and precisely on suspected outbreaks.

When someone is unwell, their RHR increases, their total sleep is likely to increase, and their activity is likely to decline. However, an elevated amount of sleep or elevated RHR for one person might be a normal level for someone else. Consequently, tracking an individual's physiological changes over time and comparing their values over time to their individual norm or average could be a means of identifying assaults to their health. Our findings also supported the benefit of using individual health metrics: in our models, we found higher correlations from our predicted values with CDC ILI rates when we used an individual's SD above normal to identify abnormal values instead of using the same value above average across the entire population.

The impact of infections on an individual's RHR has been documented in several studies. One study found ill participants had RHRs that were elevated by 2·02–4·66 SD above their normal measurements.[16] A study that examined 27 young men with acute febrile infections found that heart rates increased by 8·5 bpm per every 1°C increase in temperature.[11] Similarly, a study among children with acute infections found that heart rate rose by 9·9–14·1 bpm for every 1°C increase in temperature, with higher increases in younger children.[17] These studies indicate that infections can increase heart rate, probably due to increased body temperature and inflammatory responses as the body fights off an infection.

Our m_{change} models were better at predicting change with a 1-week lag compared with a 1-week lead. It is possible that an ILI infection results in an elevated RHR for several weeks after initial infection. Previous studies have also indicated that an elevated heart rate can occur before symptom onset.[16] Since influenza has an incubation period of 1–4 days, there is only a short opportunity to identify infections before symptom onset. However, since individuals with febrile respiratory illness typically seek care 3–8 days after symptom onset,[18] it is conceivable that ILI cases could be identified via sensor

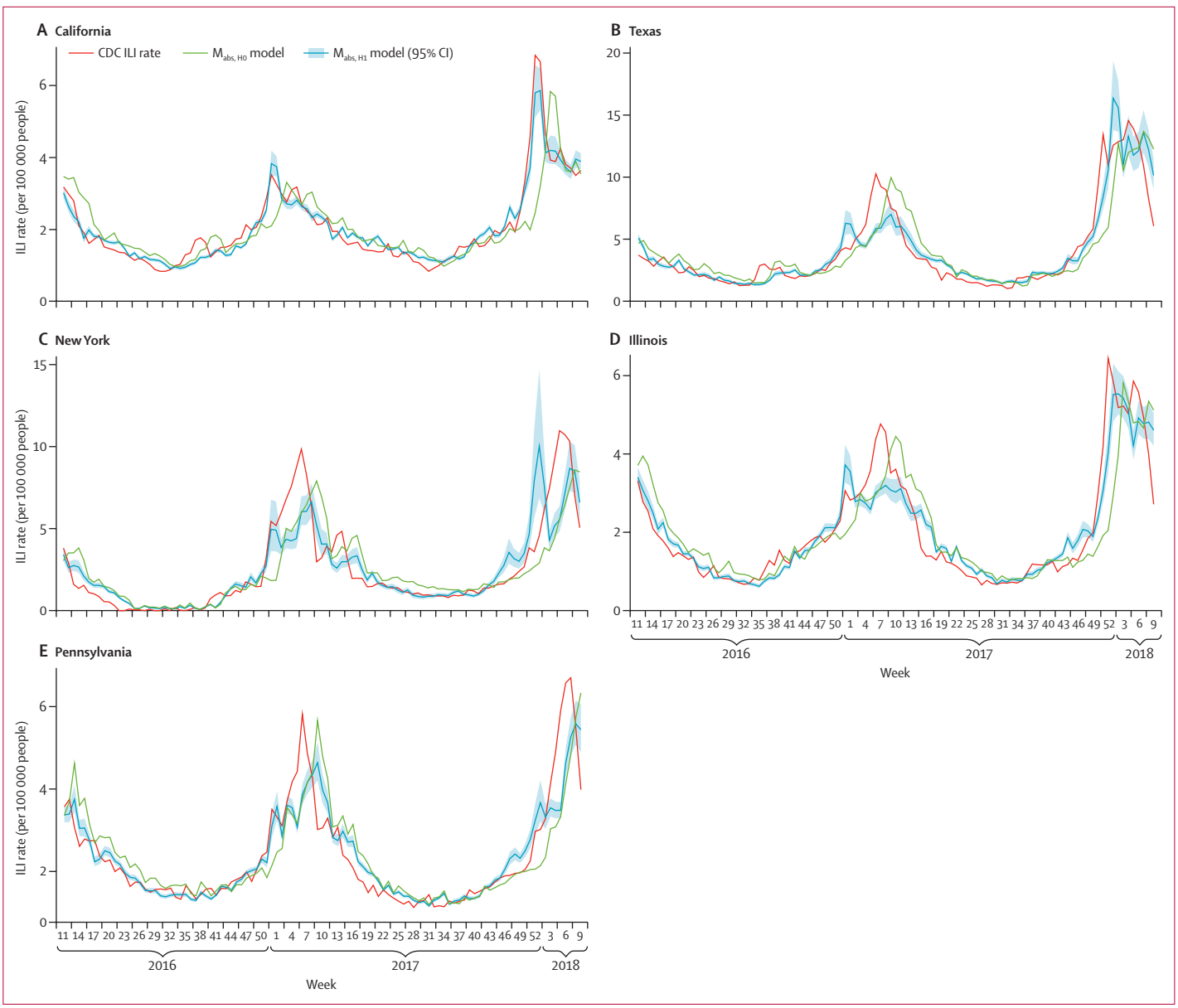


Figure 3: **Weekly CDC ILI rates, predicted ILI rates from the baseline $m_{abs,H0}$ model, and predicted rates and 95% CIs for the $m_{abs,H1}$ model, by state**
Model 1 is used, with the lower heart rate cutoff. Data are from March 16, 2016, to March 1, 2018. CDC=Centers for Disease Control and Prevention. ILI=influenza-like illness.

data earlier than through traditional, clinic-based ILI surveillance. Early identification via our method might be more likely if rates were predicted at a daily, rather than weekly, rate.

Lack of sleep can be a marker of stress, which can also raise RHR. In our study, users were considered to have normal sleep values if their weekly sleep average was less than 0·5 SD below their overall sleep average, as nights of short sleep duration have been shown to result in elevated heart rate the following day.[19,20] We found that our correlations improved slightly when we classified people as displaying normal values when they had low sleep. In the future, improved measurements of stress by wearable devices, either by detection of voice changes or galvanic skin response, could further improve our ability to identify other non-infectious causes of elevated RHR.

Previous models to predict ILI rates have mainly used International Classification of Diseases codes,[21] ILInet (CDC's influenza database), Twitter, Google Flu Trends, Wikipedia, weather, crowd-sourced data, and school vacation schedule data.[22] However, Twitter, Google Flu Trends, Wikipedia, and self-reported crowd-sourced data—and even ILInet—are all affected by outside factors

	Negative binomial model predicting ILI case counts				Linear regression model predicting weekly change in ILI rates		
	m_{naive}	$m_{abs,H0}$	$m_{abs,H1}$	p value*	m_{change}	m_{change} (1-week lag)	m_{change} (1-week lead)
California	0·91	0·61	0·97	<0·0001	0·71†	0·32†	0·33†
Texas	0·72	0·79	0·89	<0·0001	0·27†	0·20	0·11
New York	0·31	0·71	0·79	<0·0001	0·15	0·21	−0·07
Illinois	0·61	0·71	0·88	<0·0001	0·42†	0·37†	0·13
Pennsylvania	0·34	0·71	0·85	<0·0001	0·29†	0·16	−0·11

Influenza season is defined as week 40 to week 20 in the following year. Individuals were classified as having a week with abnormal Fitbit data if their weekly average exceeded a given threshold: a sleep time that was longer than 0·5 SD below their overall average and an RHR that was 0·5 SD (model 1) above their overall average. Naive models included just Fitbit data. H_0 models assumed the ILI case count was not affected by the proportion of users with abnormal Fitbit data, whereas H_1 models assumed that it was. CDC=US Centers for Disease Control and Prevention. ILI=influenza-like illness. RHR=resting heart rate. *p value comparing H_0 to H_1 models. †Pearson correlations were significant (p<0·05).

Table 4: **Pearson correlations from model 1 restricted to influenza season only comparing CDC ILI rates with predicted rates in naive, null, and full negative binomial models and comparing change in CDC ILI rates with change in Fitbit data with a 1-week lag and a 1-week lead**

such as media coverage of the influenza, with more of the so-called worried well seeking care or searching for information about influenza during epidemic periods. Use of sensor-based data would offer the first objective and real-time measurement of illness in a population that could potentially reduce the effect of overestimation during epidemics

By incorporating Fitbit data, we were able to improve ILI predictions at the state level. The predicted values from our m_{naive} model that just used the Fitbit variable with no lag indicate that this sensor-based method could potentially be useful on its own in local regions where ILI surveillance data might not be available. With greater volumes of data to analyse, this sensor-based surveillance method could be applied to more geographically refined areas in the future, such as county-level or city-level data.

Variation in individual characteristics can affect illness risk and physiological response to illness. In general, owners of wearable devices are usually wealthier than the general population, potentially making them less likely to have comorbidities that could make them more susceptible to severe infections. Additionally, these users might be more likely to get influenza vaccines or receive antivirals or other medications if they do get sick, which could reduce disease severity. A study that administered intravenous acetaminophen to critically ill febrile patients found that it significantly reduced their heart rate after 2 h.[23] Individuals with comorbidities, as well as young children and people older than 65 years, typically have more severe responses to influenza infections[24,25] and could have higher heart rate responses. In the future, understanding the role of individual characteristics such as age, comorbidities, obesity, and sex on abnormal values will be important for improving ILI prediction using this method.

It is likely that non-influenza or even non-respiratory infections are also captured by our Fitbit variable, which predominately relies on elevated RHR. It is possible that different infections, or even different influenza strains, could result in different physiological responses, with varying changes of heart rate or length of elevation. For example, H3N2 typically causes more severe illness[24,25] than other strains. Like the CDC, which identified higher rates of ILI for 2017–18, we also saw higher peaks of the proportion of users with elevated Fitbit data during this influenza season compared with the previous year. It is also possible that our algorithm could pick up less severe infections that would not necessarily be captured by traditional ILI surveillance, which requires a visit to a health-care provider. Future work to better understand typical heart rate responses to specific viral or bacterial infections or even different influenza subtypes could improve our ability to track infections.

Additionally, there are external factors, other than illness, that could influence a person's RHR and sleep. It is possible that our model is capturing some seasonal trends in RHR from changes in activity, holidays, or weather, rather than changes that result from just influenza or cold infections. Winter holidays have been associated with changes in weight gain,[26] social mixing, increases in health-care seeking, differences in surveillance reporting,[27] and potentially changes in alcohol consumption and stress. These factors could increase susceptibility to infection and can also affect ILI surveillance. A study found that RHR is higher at very cold or hot temperatures[28] and heart rate can also be elevated when someone is dehydrated, which could be more likely to happen during certain seasons. Additionally, people might be less active during colder, winter months, resulting in deconditioning and increased heart rate. Future prospective studies should attempt to measure and adjust for these external variables and link individual Fitbit data to reported symptoms or laboratory influenza confirmation.

Our data had several limitations, including no activity data, which is typically collected by Fitbit devices. An activity variable could have improved the predictive ability of our models by allowing us to control for seasonal fitness changes or more short-term activity changes that could result from an illness. Another limitation is that our weekly RHR averages might include both days when an individual is sick and days when they are not sick, and therefore might be calculated using both normal and abnormal RHR and sleep measurements. Consequently, this could result in underestimation of illness by lowering the weekly averages. Additionally, sleep measuring devices have been found to have low accuracy.[29] However, accuracy of devices will continue to improve as technology evolves.

Every year, up to 650 000 people die from influenza, globally.[30] Quick detection of increases in ILI, indicating potential influenza epidemics, is key to early initiation of important non-pharmaceutical (eg, staying home when sick or handwashing) and pharmaceutical interventions (deploying antivirals and vaccines) that can help to prevent

further spread and infection in the most susceptible populations. This study shows that using RHR and other metrics from wearables has the potential to improve real-time ILI surveillance. New wearables that include continuous sensors for temperature, blood pressure, pulse oximetry, ECG, or even cough recognition[31,32] are likely to further improve our ability to identify population and even individual-level influenza activity. In the future, with access to real-time data from these devices, it might be possible to identify ILI rates on a daily, instead of weekly, basis, providing even more timely surveillance. As these devices become more ubiquitous, this sensor-based surveillance technique could even be applied at a more global level where surveillance sites and laboratories are not always available.

Contributors

JMR did the literature search, conceived the study design, and did the data analysis, data interpretation, figure creation, and writing of the manuscript. NEW contributed to the study design, data analysis, data interpretation, and writing of the manuscript. EJT and SRS revised the manuscript and provided scientific input. All authors edited and approved the final draft.

Declaration of interests

We declare no competing interests.

Data sharing

Programming code can be requested by contacting the corresponding author. Data were made available by Fitbit according to appropriate security control and research agreements. For more on Fitbit's work with the research community, please see the Fitbit Research Pledge.

Acknowledgments

This study was supported in part by the US National Institutes of Health National Center for Advancing Translational Sciences grant UL1TR001114.

References

1 Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007; **25:** 5086–96.
2 Centers for Disease Control and Prevention. Influenza (flu): overview of influenza surveillance in the United States. Oct 15, 2019. https://www.cdc.gov/flu/weekly/overview.htm (accessed Jan 7, 2020).
3 Yang S, Santillana M, Kou SC. Accurate estimation of influenza epidemics using Google search data via ARGO. *Proc Natl Acad Sci USA* 2015; **112:** 14473–78.
4 Gren LH, Porucznik CA, Joy EA, Lyon JL, Staes CJ, Alder SC. Point-of-care testing as an influenza surveillance tool: methodology and lessons learned from implementation. *Influenza Res Treat* 2013; **2013:** 242970.
5 Ginsberg J, Mohebbi MH, Patel RS, Brammer L, Smolinski MS, Brilliant L. Detecting influenza epidemics using search engine query data. *Nature* 2009; **457:** 1012–14.
6 Paul MJ, Dredze M, Broniatowski D. Twitter improves influenza forecasting. *PLoS Curr* 2014; **6:** ecurrents.outbreaks.90b9ed0f59bae4ccaa683a39865d9117.
7 Olson DR, Konty KJ, Paladini M, Viboud C, Simonsen L. Reassessing Google Flu Trends data for detection of seasonal and pandemic influenza: a comparative epidemiological study at three geographic scales. *PLoS Comput Biol* 2013; **9:** e1003256.
8 Butler D. When Google got flu wrong. *Nature* 2013; **494:** 155–56.
9 Nagel AC, Tsou MH, Spitzberg BH, et al. The complex relationship of realspace events and messages in cyberspace: case study of influenza and pertussis using tweets. *J Med Internet Res* 2013; **15:** e237.
10 Pai A. Study: 12 percent of US consumers own a fitness band or smartwatch. mobihealthnews. May 5, 2016. http://www.mobihealthnews.com/content/study-12-percent-us-consumers-own-fitness-band-or-smartwatch (accessed Jan 7, 2020).
11 Karjalainen J, Viitasalo M. Fever and cardiac rhythm. *Arch Intern Med* 1986; **146:** 1169–71.
12 Centers for Disease Control and Prevention. FluView: national, regional, and state level outpatient illness and virus surveillance. Dec 15, 2017. https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html (accessed Jan 7, 2020).
13 Heneghan C, Venkatraman S, Russell A. Investigation of an estimate of daily resting heart rate using a consumer wearable device. *medRxiv* 2019; published online Oct 18. DOI:10.1101/19008771 (preprint).
14 de Zambotti M, Baker FC, Willoughby AR, et al. Measures of sleep and cardiac functioning during sleep using a multi-sensory commercially-available wristband in adolescents. *Physiol Behav* 2016; **158:** 143–49.
15 Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR. Accuracy of PurePulse photoplethysmography technology of Fitbit Charge 2 for assessment of heart rate during sleep. *Chronobiol Int* 2019; **36:** 927–33.
16 Li X, Dunn J, Salins D, et al. Digital health: tracking physiomes and activity using wearable biosensors reveals useful health-related information. *PLoS Biol* 2017; **15:** e2001402.
17 Thompson M, Harnden A, Perera R, et al. Deriving temperature and age appropriate heart rate centiles for children with acute infections. *Arch Dis Child* 2009; **94:** 361–65.
18 Radin JM, Hawksworth AW, Kammerer PE, et al. Epidemiology of pathogen-specific respiratory infections among three US populations. *PLoS One* 2014; **9:** e114871.
19 Antunes BM, Campos EZ, Parmezzani SS, Santos RV, Franchini E, Lira FS. Sleep quality and duration are associated with performance in maximal incremental test. *Physiol Behav* 2017; **177:** 252–56.
20 Kuetting DLR, Feisst A, Sprinkart AM, et al. Effects of a 24-hr-shift-related short-term sleep deprivation on cardiac function: a cardiac magnetic resonance-based study. *J Sleep Res* 2019; **28:** e12665.
21 Gog JR, Ballesteros S, Viboud C, et al. Spatial transmission of 2009 pandemic influenza in the US. *PLoS Comput Biol* 2014; **10:** e1003635.
22 McGowan CJ, Biggerstaff M, Johansson M, et al. Collaborative efforts to forecast seasonal influenza in the United States, 2015–2016. *Sci Rep* 2019; **9:** 683.
23 Schell-Chaple HM, Liu KD, Matthay MA, Sessler DI, Puntillo KA. Effects of IV acetaminophen on core body temperature and hemodynamic responses in febrile critically ill adults: a randomized controlled trial. *Crit Care Med* 2017; **45:** 1199–207.
24 Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004; **292:** 1333–40.
25 Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003; **289:** 179–86.
26 Helander EE, Wansink B, Chieh A. Weight gain over the holidays in three countries. *N Engl J Med* 2016; **375:** 1200–02.
27 Gao H, Wong KK, Zheteyeva Y, Shi J, Uzicanin A, Rainey JJ. Comparing observed with predicted weekly influenza-like illness rates during the winter holiday break, United States, 2004–2013. *PLoS One* 2015; **10:** e0143791.
28 Madaniyazi L, Zhou Y, Li S, et al. Outdoor temperature, heart rate and blood pressure in Chinese adults: effect modification by individual characteristics. *Sci Rep* 2016; **6:** 21003.
29 Lee J, Finkelstein J. Consumer sleep tracking devices: a critical review. *Stud Health Technol Inform* 2015; **210:** 458–60.
30 WHO. Up to 650 000 people die of respiratory diseases linked to seasonal flu each year. Dec 14, 2017. https://www.who.int/en/news-room/detail/14-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu-each-year (accessed Jan 7, 2020).
31 Abeyratne UR, Swarnkar V, Setyati A, Triasih R. Cough sound analysis can rapidly diagnose childhood pneumonia. *Ann Biomed Eng* 2013; **41:** 2448–62.
32 Amrulloh YA, Abeyratne UR, Swarnkar V, Triasih R, Setyati A. Automatic cough segmentation from non-contact sound recordings in pediatric wards. *Biomed Signal Proces* 2015; **21:** 126–36.

For more on the **Fitbit Research Pledge** see https://healthsolutions.fitbit.com/research-pledge

Passive Monitoring of Physiological Data and Self-reported Symptoms to Detect Clusters of People with COVID-19

Giorgio Quer[1,*], Jennifer M. Radin[1,*], Matteo Gadaleta[1,*], Katie Baca-Motes[1], Lauren Ariniello[1], Edward Ramos[1,2], Vik Kheterpal[2], Eric J. Topol[1], Steven R Steinhubl[1]

[1] Scripps Research Translational Institute, 3344 N Torrey Pines Ct Plaza Level, La Jolla, California 92037 USA

[2] CareEvolution, 625 N Main St, Ann Arbor, Michigan 48104 USA

*Authors G. Quer, J. Radin and M. Gadaleta equally contributed to the analysis of the data, the discussion and the preparation of the manuscript.

Correspondence to: Giorgio Quer Scripps Research Translational Institute, 3344 N Torrey Pines Ct Plaza Level, La Jolla CA 92037 USA; gquer@scripps.edu.

ABSTRACT

Traditional screening for COVID-19 typically includes survey questions about symptoms, travel history, and sometimes temperature measurements. We explored whether longitudinal, personal sensor data can help identify subtle changes which may indicate an infection, such as COVID-19. To do this we developed an app that collects smartwatch and activity tracker data, as well as self-reported symptoms and diagnostic testing results from participants living in the US. We assessed whether symptoms and sensor data could differentiate COVID-19 positive versus negative cases in symptomatic individuals. Between March 25 and June 7, 2020, we enrolled 30,529 participants, of whom 3,811 reported symptoms, 54 reported testing positive for COVID-19, and 279 negative. We found that a combination of symptom and sensor data resulted in an AUC=0.80 [0.73 – 0.86] which was significantly better ($p < 0.01$) than a model which just considered symptoms alone (AUC=0.71 [0.63 – 0.79]) in the discrimination between symptomatic individuals positive or negative for COVID-19. Such orthogonal, continuous, passively captured data may be complementary to virus testing that is generally a one-off, or infrequent, sampling assay.

INTRODUCTION

Due to the current lack of fast and reliable testing, one of the greatest challenges for preventing transmission of SARS-CoV-2 is the ability to quickly identify, trace, and isolate cases before they can further spread the infection to susceptible individuals. As regions across the U.S. start implementing measures to reopen businesses, schools, and other activities, many rely on current screening practices for COVID-19, which typically include a combination of symptom and travel-related survey questions and temperature measurements. However, this method is likely to miss pre-symptomatic or asymptomatic cases, which make up approximately 40% to 45% of those infected with SARS-CoV-2, and who can still be infectious.[1,2] An elevated temperature (>100 degrees Fahrenheit) is not as common as frequently believed, being present in only 12% of individuals who tested positive for COVID-19,[3] and just 31% of hospitalized COVID-19 patients at the time of admission.[4]

Smartwatches and activity trackers, which are now worn by 1 in 5 Americans,[5] can improve our ability to objectively characterize each individual's unique baseline for resting heart rate,[6] sleep,[7] and activity and therefore can be used to identify subtle changes in that users data which may indicate that they are coming down with a viral illness. Previous research from our group has shown that this method, when aggregated at the population level, can significantly improve real-time predictions for influenza-like illness.[8] Consequently, we created a prospective app-based research platform, called DETECT (Digital Engagement & Tracking for Early Control, & Treatment), where individuals can share their sensor data, self-reported symptoms, diagnoses, and electronic health record data with the aim of improving our ability to identify and track individual and population level viral illnesses, including COVID-19.

A previously reported study that captured symptom data in over 18,000 SARS-CoV-2 tested individuals via a smartphone-based app found that symptoms were able to help distinguish between individuals with and without COVID-19.[2] The aim of this study is to investigate if the addition of individual changes in sensor data to symptom data can be used to improve our ability to identify COVID-19 positive versus COVID-19 negative cases among participants who self-reported symptoms.

METHODS

Study population

Any person living in the United States over the age of 18 years old is eligible to participate in the DETECT study by downloading the iOS or Android research app, MyDataHelps. After consenting into the study, participants are asked to share their personal device data (including historical data collected prior to enrollment), report symptoms and diagnostic test results, and connect their electronic health records. Participants can opt to share as much or as little data as they would like. Data can be pulled in via direct API with Fitbit devices, and any device connected through Apple HealthKit or GoogleFit data aggregators. Participants were recruited via the study website (www.detectstudy.org), media reports, and outreach from our partners at Fitbit, Walgreens, CVS/Aetna, and others.

Between March 25, 2020 and June 7, 2020, our research study enrolled 30,529 individuals with representation from every state in the United States. Among the consented individuals, 62.0% are female and 12.8% are 65 or more years old. 78.4% of participants connected their Fitbit device to the study-app, 31.2% connected the data from Apple Health Kit while 8.1% connected data from Google Fit (note that one individual can connect to multiple platforms). In addition, 3,811

reported at least one symptom (12.5%), and of those 54 also reported testing positive for COVID-19, and 279 reported testing negative for COVID-19. The number of days per different data types and data aggregator system is presented in Table 1, while the symptoms distribution for symptomatic individuals tested for COVID-19, or not tested is shown in Figure 1.

Ethical Considerations

The protocol for this study was reviewed and approved by the Scripps Office for the Protection of Research Subjects. All individuals participating in the study provided informed consent electronically.

Statistical Analysis

Only participants with self-reported symptoms and COVID-19 test results were considered in this analysis. For each participant, two sets of data were extracted: the *baseline data*, which included signals spanning from 21 to 7 days before the reported start date of symptoms, and the *test data*, which included signals beginning the first date of symptoms to 7 days after symptoms. Three types of data were considered from personal sensors: daily resting heart rate (*DailyRHR*), sleep duration in minutes (*DailySleep*) and activity based on daily total step count (*DailyActivity*). The daily resting heart rate is calculated by the specific device.[35] The total amount of sleep for a given day was based on the total period of sleep between 12 noon of the current day to 12 noon of the next day. When multiple devices from the same individual provide the same information, Fitbit device data was prioritized for consistency. Overlapping data were combined minute by minute, before aggregating for the whole day.

A single baseline value per individual was extracted for each data type by considering the median value over the individual's baseline data. This value is representative of a participant's

"normal" before the reported symptoms. The baseline value was compared to the test data as follows:

$$RHRMetric = \frac{max(DailyRHR[test\ data]) - median(DailyRHR[baseline\ data])}{4.00}$$

$$SleepMetric = \frac{mean(DailySleep[test\ data]) - median(DailySleep[baseline\ data])}{56.06}$$

$$ActivityMetric = \frac{mean(DailyActivity[test\ data]) - median(DailyActivity[baseline\ data])}{2489.85}$$

Values were normalized to have a unitary interquartile range using normalization parameters calculated on all data recorded. For all these metrics, values close to zero indicate small variations from baseline values.

For the metric based on symptoms only, we adapted the results from the study by Menni et al.[2] to our available data:

$$SymptomMetric = -1.32 - (0.01 * age) + \big(0.44 * gender\ (male = 1; female = 0)\big) + (1.75 * DecreaseInTasteSmell) + (0.31 * Cough) + (0.49 * Fatigue)$$

A simple manual metric aggregation strategy without optimization was used to enable a clear understanding of the benefits provided when data from multiple sources were considered together. The aggregated metrics were:

$$SensorMetric = RHRMetric\ /\ 10 + SleepMetric - ActivityMetric$$

$$OverallMetric = SensorMetric + SymptomMetric$$

The main outcomes are receiver operating characteristic (ROC) curves for each of the proposed metrics. The curves are obtained by considering a binary classification task between participants self-reported as COVID-19 positive and negative. Confidence intervals, reported with a confidence level of 95%, are estimated using bootstrap method by repeatedly sampling the

dataset with replacement. The sampling is performed in a stratified manner, i.e., the balance of the classes is maintained over all experiments. Values for sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) were also calculated (Figure 2). These values are based on the point in the ROC with the optimal trade-off between sensitivity and specificity, which may vary depending on the shape of the curve. For each metric analyzed, we applied the Mann-Whitney U test to investigate the statistical difference among positive and negative class values and we reported the p-value. The comparison metric to assess the overall performance was the area under curve (AUC) of the ROC.

RESULTS

The symptoms distribution for symptomatic individuals tested for COVID-19, or not tested is shown in Figure 1.

Sensor Data

A minority of symptomatic participants (30.3%) who tested for COVID-19 had an RHR greater than 2 standard deviations above the average baseline value during symptoms. Change in RHR on its own (Table 1) did not allow for significant discrimination between COVID-19 positive and negative subjects using the RHRMetric (AUC of 0.52 [0.41 – 0.64]). (Figure 2a)

Sleep and activity did show a significant difference among the two groups, (Table 1) with an AUC of 0.68 [0.57 – 0.79] for the SleepMetric (Figure 2.b) and 0.69 [0.61 – 0.77] for the ActivityMetric (Figure 2.c), supporting that the sleep and activity of COVID-19 positive participants were impacted significantly more than COVID-19 negative participants. Sleep and activity are slightly correlated, with a negative correlation coefficient of -0.28, p-value < 0.01.

To evaluate the contribution of all the data type commonly available through personal devices, we combined the RHR, sleep, and activity metrics in a single metric (SensorMetric, Figure 2.d). This improved the overall performance from the three sensor metrics to an AUC of 0.72 [0.64 – 0.80].

Symptom Data

We also considered a model only based on self-reported symptoms (SymptomMetric, Figure 2.e), along with age and sex. With respect to the previously published model,[2] we measure a slightly lower AUC of 0.71 [0.63 – 0.79].

Combined Symptoms & Sensor Data

When participant-reported symptoms and sensor metrics are jointly considered in the analysis (OverallMetric, Figure 2.f), the achieved performance was significantly improved ($p < 0.01$), relative to either alone, with an AUC of 0.80 [0.73 – 0.86].

DISCUSSION

Our results show that individual changes in physiologic measures captured by most smartwatches and activity trackers are able to significantly improve the distinction between symptomatic individuals with and without a diagnosis of COVID-19 beyond just symptoms alone. While encouraging, these results are based on a relatively small sample of participants.

This work builds on our earlier retrospective analysis demonstrating the potential for consumer sensors to identify individuals with influenza-like illness, which has subsequently been replicated in a similar analysis of over 1.3 million wearable users in China for predicting COVID-19.[8,9] In response to the COVID-19 pandemic a number of prospective studies, led by device

manufacturers and/or academic institutions, including DETECT, accelerated deployment to allow interested individuals to voluntarily share their sensor and clinical data to help address the global crisis.[10-14] The largest of these efforts, Corona-Datenspende, was developed by the Robert Koch Institut in Germany and has enrolled over 500,000 volunteers.[15]

As different individuals experience a wide range of symptomatic and biologic responses to infection with SARS-CoV-2, it is likely that their measurable physiologic changes will also vary.[16-18] For that reason, it is possible that biometric changes may be more valuable in identifying those at highest risk for decompensation rather than just a dichotomous distinction in infection status. Due to limited testing in the United States, especially early in the spread of the COVID-19 pandemic, individuals with more severe symptoms may have been more likely to be tested. Consequently, the ability to differentiate between COVID-19 positive and negative cases based on symptoms and sensor data may change over time as testing increases, and as other upper respiratory illnesses such as seasonal influenza increase this fall.

The early identification of symptomatic and pre-symptomatic infected individuals would be especially valuable as transmission is common and people may potentially be even more infectious during this period.[19-21] Even when individuals have no symptoms, there is evidence that the majority have lung injury by CT scan, and a large number have abnormalities in inflammatory markers, blood cell counts and liver enzymes.[18,22-24] As the depth and diversity of data types from personal sensors continues to expand—such as heart rate variability (HRV), respiratory rate, temperature, oxygen saturation, and even continuous blood pressure, cardiac output and systemic vascular resistance—the ability to detect subtle individual changes in response to early infectious insults will potentially improve and enable the identification of individuals without symptoms.

In the past, the normality of a specific biometric parameter, such as resting heart rate, duration of nightly sleep, and daily activity, was based on population norms. For example, a normal RHR is generally considered anything between ~60-100 BPM. However, recent work looking at individual daily RHRs over two years found that each person has a relatively consistent RHR, for them, that fluctuates by a median of only 3 BPM weekly.[6] On the other hand, what would be considered normal RHR for an individual can vary by as much as 70 BPM (between 40 and 109 BPM) between individuals. The potential value in identifying important changes in an individual's RHR as an early marker for COVID-19 infection is suggested by the description of 5,700 hospitalized COVID-19 patients.[4] At the time of admission, a greater percentage of individuals had a heart rate of >100 BPM (43.1%) than had a fever (30.7%). Similarly, work in primate models of other viral and bacterial infections found that a significant increase in heart rate can be detected ~2 days prior to a fever. [25]

Just as individuals have heart rate patterns that are unique to them, the same is true for sleep patterns. While population norms for sleep duration have been defined by one-time survey data,[26] longitudinal analysis of daily sleep over several years support much greater variation in what is normal for a specific individual.[7] Recognizing what is normal for an individual enables much earlier detection of deviations from that normal.

A strategy of test, trace and isolate has played a central role in helping control the spread of COVID-19. However, testing comes with many challenges including the enormous logistical and cost hurdles of recurrently testing asymptomatic individuals. In addition, testing in a population with very low prevalence can lead to a high proportion of false positive cases. A refined predictive model, based on personal sensors, could potentially enable an early, individualized testing strategy to improve performance and lower costs. Early testing may make

the use of a contact tracing app more effective by identifying positive cases in advance and allowing for early isolation.

DETECT, and similar studies, also represents the transitioning of research from a dependence on brick and mortar research centers to a remote, direct-to-participant approach now possible through a range of digital technologies, including an ever-expanding collection of sensors, applications of machine learning to massive data sets, and the ubiquitous connectivity that enables rapid 2-way communications 24/7.[27,28] The promise of digital technologies is that their evolution will continue to bring us closer to identifying the best combination of measures and associated algorithms that identify infection with SARS-CoV-2 or other pathogens. However, it is equally critical to develop and continuously improve on an engaging digital platform that provides value to participants and researchers. This has proven to be extremely challenging with a recent analysis of 8 different digital research programs involving 100,000 participants have a median duration of retention of only 5.5 days.[29] Digital trials such as DETECT also do come with unique challenges to assure privacy and security, which can only be dealt with by effectively informing participants before consent, storing the data with the needed level of security and providing access to the data only for research purposes.[30] App-based contact tracing, which is not part of DETECT, is an especially sensitive and ethically complicated use of digital technology that can be used to address the pandemic.[31]

Limitations

Our analyses are dependent entirely on participant-reported symptoms and testing results, as well as the biometric data from their personal devices. Although this is not consistent with the historically more common direct collection of information in a controlled lab setting or via electronic health records, previous work has confirmed their value and their accuracy beyond

data routinely captured during routine care.[32-34] Additionally, individuals owning a smartwatch or activity tracker and having access to COVID-19 diagnostic testing may not be fully representative of the general population. Finally, in the early version of the DETECT app we were not able to track the duration or trajectory of individual symptoms, care received and eventual outcomes.

Conclusion

These preliminary results suggest that sensor data can incrementally improve symptom-only based models to differentiate between COVID-19 positive and negative symptomatic individuals, which has the potential to enhance our ability to identify a cluster before more spread occurs. Such orthogonal, continuous, passively captured data may be complementary to virus testing that is generally a one-off, or infrequent, sampling assay.

AUTHORS CONTRIBUTIONS

G.Q, J.M.R., K.B., V.K., E.J.T., and S.R.S. made substantial contributions to the study conception and design. K.B., L.A., E.R., V.K., S.R.S. made substantial contributions to the acquisition of data. G.Q. and M.G. conducted statistical analysis. G.Q, J.M.R., M.G. and S.R.S. made substantial contributions to the interpretation of data. G.Q., J.M. R. and S.R.S. drafted the first version of the manuscript. G.Q, J.M.R., M.G., K.B., L.A., E.R., V.K., E.J.T., and S.R.S. contributed to critical revisions and approved the final version of the manuscript. G.Q., J.M.R., and S.R.S. take responsibility for the integrity of the work.

COMPETING INTERESTS

S.R.S. reports grants from Janssen and personal fees from Otsuka and Livongo, outside the submitted work. G.Q., J.M.R., M.G., K.B., L.A., E.R., V.K. and E.J.T. report no competing interests.

	Total	Any symptom	COVID-19 positive	COVID-19 negative	P-value
Demographic Data					
Number of participants	30529	3811	54	279	-
Female [%]	62.0%	74.2%	79.6%	71.3%	0.65
Over 65 [%]	12.8%	5.7%	1.9%	7.5%	0.22
Fitbit Users [%]	78.4%	86.7%	85.2%	84.9%	1.00
Apple Users [%]	31.2%	32.0%	38.9%	33.7%	0.66
Sensor Data					
Available days (IQR)					
RHR	322 (131-387)	325 (153-396)	312 (98-377)	300 (119-392)	0.70
Sleep	249 (48-373)	273 (105-383)	283 (52-362)	246 (70-375)	0.56
Activity	394 (370-412)	407 (379-415)	404 (375-410)	401 (374-413)	0.57
Mean Change (SD)					
RHR (bpm)	~ 0 (2.84)	0.40 (3.18)	1.15 (4.83)	0.61 (3.68)	0.33
Sleep (min)	~ 0 (54)	3 (59)	57 (92)	4 (68)	< 0.01
Activity (steps)	52 (2659)	-323 (2771)	-3533 (4418)	-208 (3086)	< 0.01

Table 1: Participants characteristics and device usage

Summary of the collected data and demographic information about the cohort. Available days are specified for each data type, with median and interquartile range (IQR) values. Changes in RHR, Steps, and Sleep from baseline (-21 to 7 days) to symptomatic period (0-7 days) are reported, where for individuals with no symptoms we consider March 6, 2020 as the day 0. p-values are evaluated comparing COVID-19 positive and negative groups.

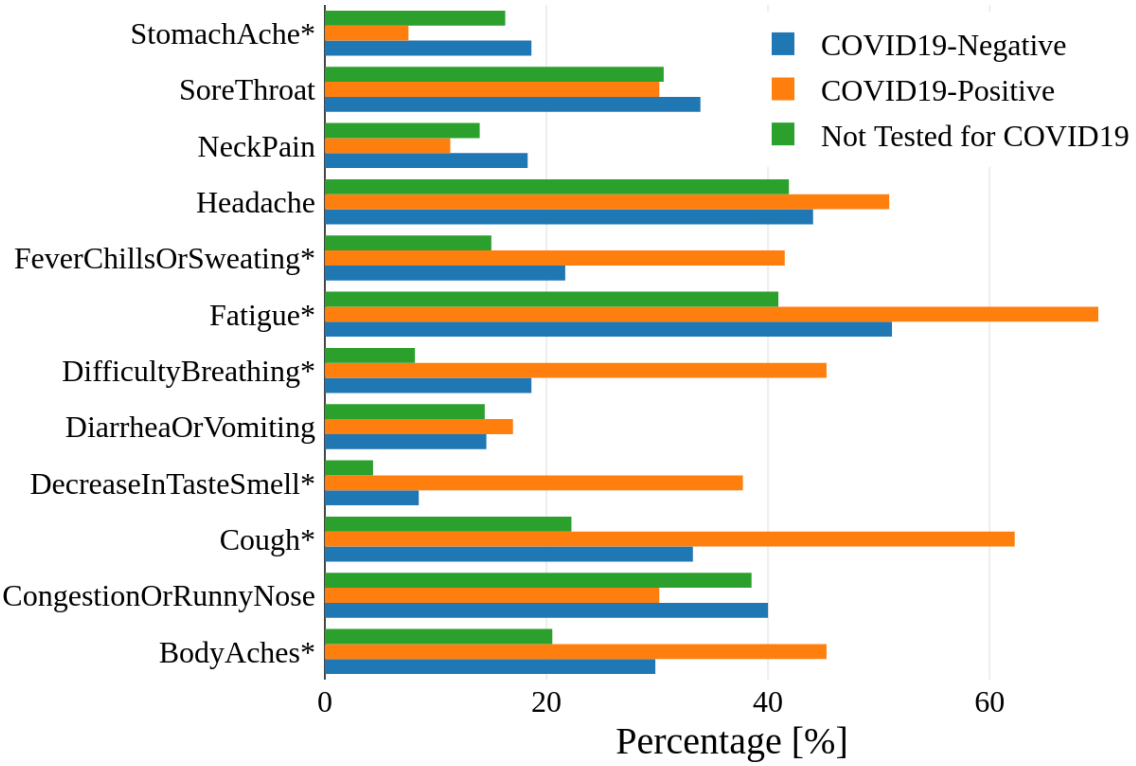


Figure 1: Frequency of symptoms among participants.

Participants who reported at least one symptom have been divided into 3 cohorts: participants negative and positive to a COVID-19 test, and participants who did not undergo a test for COVID-19. The frequency of each specific symptom is reported in the figures for the three cohorts. Symptoms with significant difference between COVID-19 positive and negative participants (p-value < 0.05 of Fisher's exact test) are marked with an asterisk in the figure.

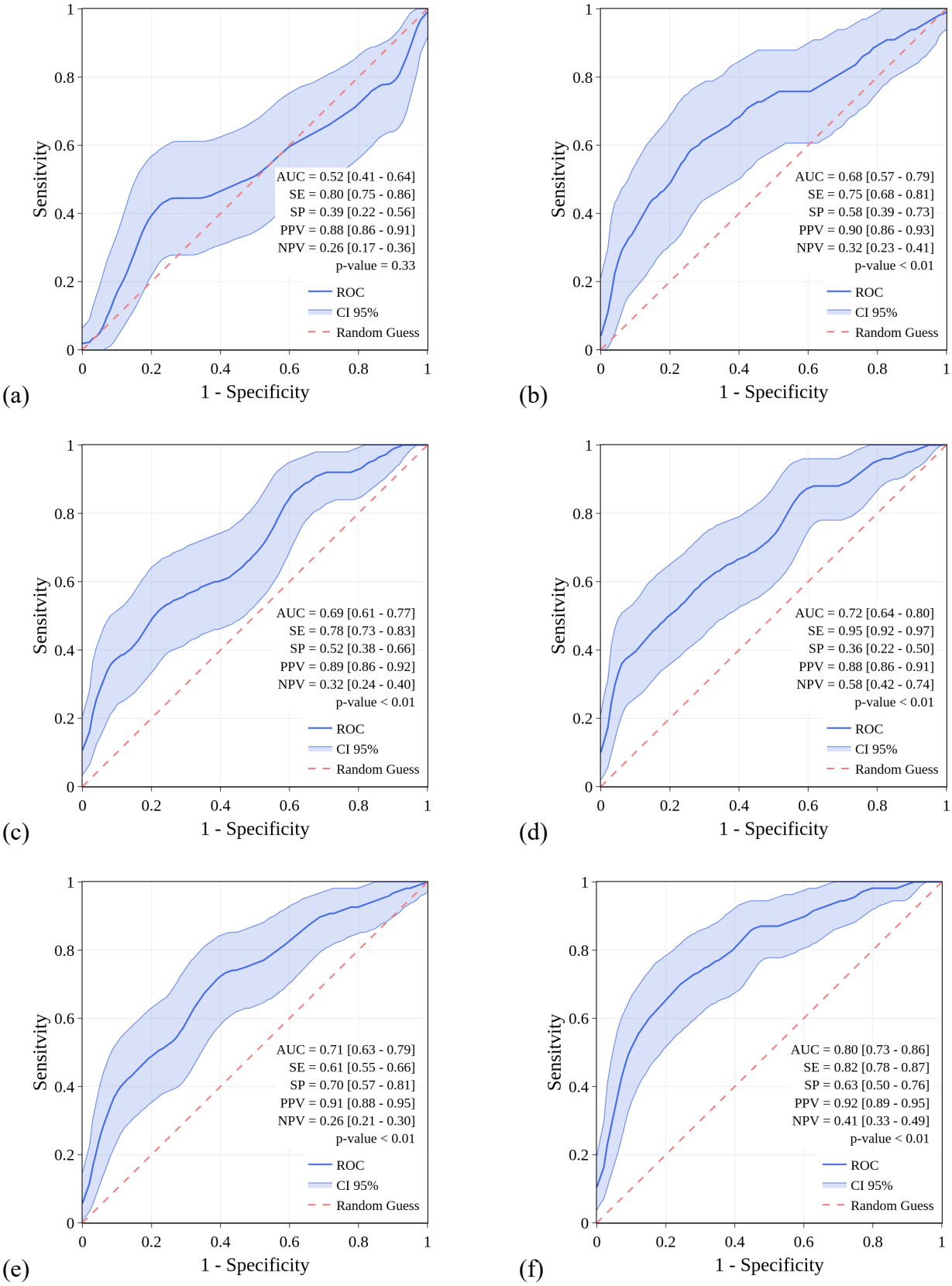


Figure 2: Prediction of COVID-19 from self-reported symptoms and sensor data.

ROC for the discrimination between COVID-19 positive and COVID-19 negative based on the available data: resting heart rate data (a); sleep data (b); activity data (c); all available sensor data (d); symptoms only (e); and symptoms with sensor data (f).

REFERENCES

1. Oran, D.P. & Topol, E.J. Prevalence of Asymptomatic SARS-CoV-2 Infection. *Annals of Internal Medicine* (2020).
2. Menni, C.*, et al.* Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nature Medicine* (2020).
3. Color Genomics, New COVID-19 Test Data, https://www.color.com/new-covid-19-test-data-majority-of-people-who-test-positive-for-covid-19-have-mild-symptoms-or-are-asymptomatic. (2020).
4. Richardson, S.*, et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama* (2020).
5. Vogels, E.A. About one-in-five Americans use a smart watch or fitness tracker. Vol. 2020 (ed. Center, P.R.) (2020).
6. Quer, G., Gouda, P., Galarnyk, M., Topol, E.J. & Steinhubl, S.R. Inter- and intraindividual variability in daily resting heart rate and its associations with age, sex, sleep, BMI, and time of year: Retrospective, longitudinal cohort study of 92,457 adults. *PLoS One* **15**, e0227709 (2020).
7. Jaiswal, S.J.*, et al.* Association of sleep duration and variability with body mass index: Sleep measurements in the US from a large population of wearable users. *JAMA Internal Medicine* **Accepted**(2020).
8. Radin, J.M., Wineinger, N.E., Topol, E.J. & Steinhubl, S.R. Harnessing wearable device data to improve state-level real-time surveillance of influenza-like illness in the USA: a population-based study. *The Lancet Digital Health* **2**, e85-e93 (2020).
9. Zhu, G.*, et al.* Learning from Large-Scale Wearable Device Data for Predicting Epidemics Trend of COVID-19. *Discrete Dynamics in Nature and Society* **2020**, 6152041 (2020).
10. Evidation Health and BARDA Partner on Early Warning System for COVID-19, https://evidation.com/news/evidationhealthandbardapartner/. (2020).
11. New Study from Fitbit Seeks to Advance COVID-19 and Flu Research with Early Detection, https://blog.fitbit.com/covid-19-study/. (2020).
12. Tempredict Study, Oura and UCSF, https://ouraring.com/ucsf-tempredict-study (2020).
13. Covidentify, Duke, https://covidentify.covid19.duke.edu/. (2020).
14. COVID-19 Wearable Study, Stanford, https://innovations.stanford.edu/wearables (2020).
15. Corona Datenspende, Robert Koch-Institut, https://corona-datenspende.de/science/. (2020).
16. Shen, B.*, et al.* Proteomic and Metabolomic Characterization of COVID-19 Patient Sera. *Cell* (2020).
17. Sharma, R., Agarwal, M., Gupta, M., Somendra, S. & Saxena, S.K. Clinical Characteristics and Differential Clinical Diagnosis of Novel Coronavirus Disease 2019 (COVID-19). *Coronavirus Disease 2019 (COVID-19)*, 55-70 (2020).
18. Tabata, S.*, et al.* Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis. *The Lancet. Infectious diseases*, S1473-3099(1420)30482-30485 (2020).

19. Ferretti, L., *et al.* Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science* (2020).
20. Chau, N.V.V., *et al.* The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. *medRxiv* (2020).
21. Jing, Q.L., *et al.* Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. *Lancet Infect Dis* (2020).
22. Meng, H., *et al.* CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan, China. *J Infect* **81**, e33-e39 (2020).
23. Inui, S., *et al.* Chest CT Findings in Cases from the Cruise Ship "Diamond Princess" with Coronavirus Disease 2019 (COVID-19). *Radiol Cardiothorac Imaging* **2**, e200110 (2020).
24. Long, Q.X., *et al.* Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nature medicine* (2020).
25. Milechin, L., *et al.* Detecting pathogen exposure during the non-symptomatic incubation period using physiological data. *bioRxiv*, 218818 (2017).
26. Sleep and Sleep Disorders. Center for Disease Control and Prevention, https://www.cdc.gov/sleep/data_statistics.html. (2020).
27. Steinhubl, S.R., Wolff-Hughes, D.L., Nilsen, W., Iturriaga, E. & Califf, R.M. Digital clinical trials: creating a vision for the future. *npj Digital Medicine* **2**, 126 (2019).
28. Steinhubl, S.R., McGovern, P., Dylan, J. & Topol, E.J. The digitised clinical trial. *The Lancet* **390**, 2135 (2017).
29. Pratap, A., *et al.* Indicators of retention in remote digital health studies: a cross-study evaluation of 100,000 participants. *npj Digital Medicine* **3**, 21 (2020).
30. Coravos, A., *et al.* Modernizing and designing evaluation frameworks for connected sensor technologies in medicine. *npj Digital Medicine* **3**, 37 (2020).
31. Bradford, L.R., Aboy, M. & Liddell, K. COVID-19 Contact Tracing Apps: A Stress Test for Privacy, the GDPR and Data Protection Regimes. *Journal of Law and the Biosciences* (2020).
32. Rivera, S.C., *et al.* The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis. *Health and Quality of Life Outcomes* **17**, 156 (2019).
33. Basch, E., *et al.* Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *Jama* **318**, 197-198 (2017).
34. Bell, S.K., *et al.* Frequency and Types of Patient-Reported Errors in Electronic Health Record Ambulatory Care Notes. *JAMA Network Open* **3**, e205867-e205867 (2020).
35. Heneghan, C., Venkatraman, S. & Russell, A. Investigation of an estimate of daily resting heart rate using a consumer wearable device. *medRxiv*, 19008771 (2019).

PERSPECTIVE

Geriatrics 2030: Developing Drugs to Care for Older Persons—A Neglected and Growing Population

S.W. Johnny Lau[1,*], Jan-Frederik Schlender[2], Patricia W. Slattum[3], Donald L. Heald[4] and Robin O'Connor-Semmes[5]

The global population aged 60 years or above numbered 962 million in 2017, more than double that as in 1980. The number of older persons is expected to double again by 2050. There are pressing needs to develop more patient-centric pharmacotherapy for these older persons. In this commentary, we discuss the application of clinical pharmacology principles to care, regulatory considerations in drug development, and quantitative approaches to streamline pharmacotherapy for this age group.

BACKGROUND

Many factors contribute to the population health outcomes of length and quality of life. Medications are one intervention to improve health outcomes. We are increasingly applying medication interventions to a growing aging population worldwide (**Figure 1**).[1] Three-quarters of Americans aged 65 years and above have multiple chronic health conditions,[2] which often leads to polypharmacy, increased risk of adverse drug events, and functional decline. To put a face on the challenges of providing optimal drug therapy for older persons, consider the case of Ms. S (**Figure 2a**).

APPLYING CLINICAL PHARMACOLOGY PRINCIPLES TO IMPROVE CARE FOR OLDER PERSONS

In the current clinical pharmacology paradigm framing optimal dosing around understanding sources of variability in pharmacokinetics and pharmacodynamics, aging is operationalized as chronological age. We study chronological age independent of chronic disease by studying the healthiest aging individuals. "Older person" has traditionally been defined as a person aged 65 years and above. Increasing chronological age is a risk factor for multimorbidity, functional impairment, frailty, and mortality. Thus, older ages may be more appropriate as inclusion criteria in clinical trials to represent a vulnerable age-defined cohort. A high degree of heterogeneity exists in the aging process, which has led to the idea of considering a biological or physiological age rather than a chronological age to quantify or describe aging. However, to date, no ideal biomarker has emerged.

Information on age-related differences in pharmacokinetics has been incorporated into product labeling to improve prescribing for older adults. Less is known about differences in exposure–response relationships with aging and the interactions among aging, multimorbidity, functional decline, frailty, and polypharmacy. Prescribers are charged with assessing potential risks and benefits of adding medications to the older person's regimen when there is often sparse evidence to support these decisions. Tools, such as the American Geriatrics Society Beers Criteria, help improve medication safety for older persons considering comorbidity, renal function, and drug interactions.[3] However, these evidence-based recommendations are not always available in product labeling. Holmes described a theoretical framework for prescribing in patients with reduced life expectancy that considers remaining life expectancy, patient's goals of care, and whether these factors are aligned with the treatment target as well as time-until-benefit for the medication.[4] To identify medications that should be started (at certain doses) or discontinued requires treatment-specific information, including likelihood of benefit, the time needed to achieve benefit, and the risk of harm in older persons with multimorbidity and/or functional decline. Risk

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [2]Systems Pharmacology and Medicine, Bayer AG, Leverkusen, Germany; [3]Department of Pharmacotherapy and Outcomes Science, Virginia Commonwealth University, Richmond, Virginia, USA; [4]Discovery Translational Research, Biologics Development Sciences, Janssen Biotherapeutics, Spring House, Pennsylvania, USA; [5]Quantitative Clinical Development, Parexel International, Durham, North Carolina, USA.
*Correspondence: S.W. Johnny Lau (sze.lau@fda.hhs.gov)

Received August 7, 2019; accepted September 17, 2019. doi:10.1002/cpt.1663

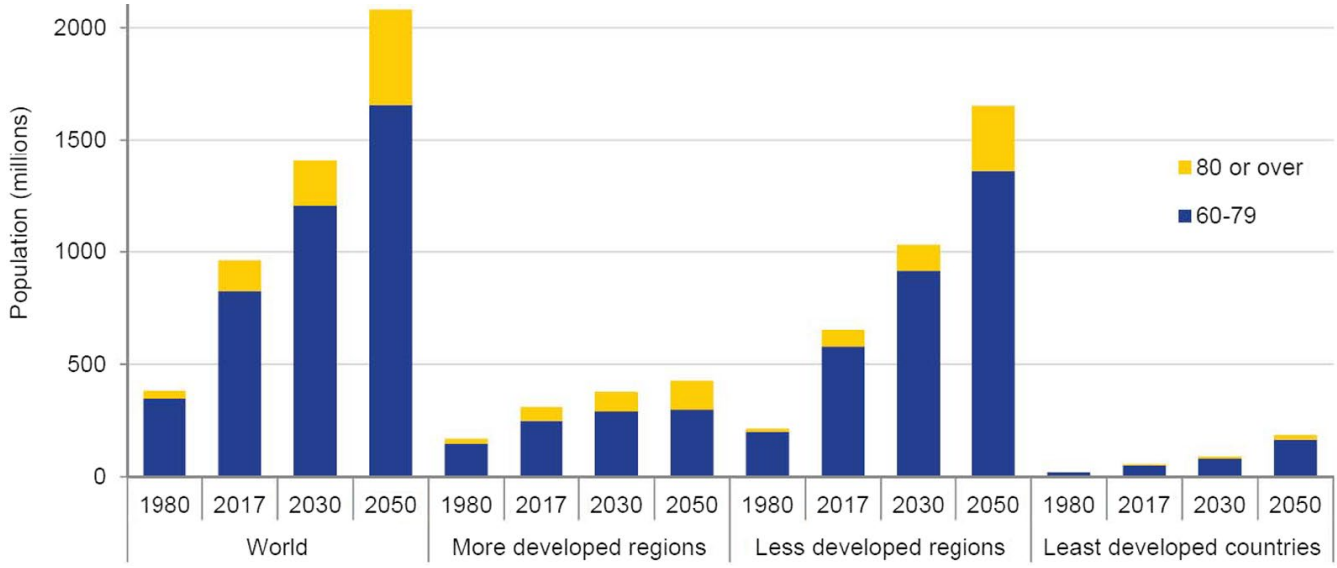


Figure 1 Number of persons aged 60–79 years and aged 80 years or over for the world and development groups, 1980, 2017, 2030, and 2050. From World Population Ageing 2017, by Department of Economic and Social Affairs, Population Division, (2017) United Nations. Reprinted with the permission of the United Nations.

(a)

	Ms. S
Chronological age	78 years
Living conditions	Lives independently in a senior affordable housing apartment.
Diagnoses	Chronic pain of the knee and hip, schizophrenia, hypertension, anxiety, depression, gastroesophageal reflux disease, and urinary incontinence
Health care providers	Sees a behavioral health case manager, pain specialist, psychiatrist, and primary care provider.
Clinical conditions	Experiences difficulty doing laundry and preparing meals. Uses a wheelchair to navigate outside of her apartment. Wears adult incontinence briefs everyday but is having trouble affording them. Had fallen and visited an emergency department (ED) the evening before her primary care clinic visit and received a new prescription for short-term opioid analgesics at the ED.
Prescription and over-the-counter medications	Trazodone 50 mg QHS, lurasidone 80 mg QHS, perphenazine 4 mg BID, bupropion 100 mg BID, hydroxyzine 50 mg TID, losartan 100 mg QD, atorvastatin 40 mg QHS, aspirin 81 mg QD, clonidine 0.2 mg TID, hydralazine 50 mg TID, omeprazole 50 mg QD, diclofenac gel as needed, gabapentin 800 mg TID, acetaminophen/diphenhydramine QHS, ibuprofen 800 mg BID, linaclotide 290 mcg QD, sennosides 8.6 mg 4 tablets as needed and acetaminophen/oxycodone 325mg/7.5 mg TID as needed for one week
Assessments	Ms. S's situation is quite complex. She is experiencing falls. Her medications and the interactions among them are likely p laying a role in her functional decline and falls.
Challenges	Her primary care provider is faced with evaluating the risks and benefits of each medication and deciding how to proceed with any plan to stop or reduce the dose of one or more medications.

(b)

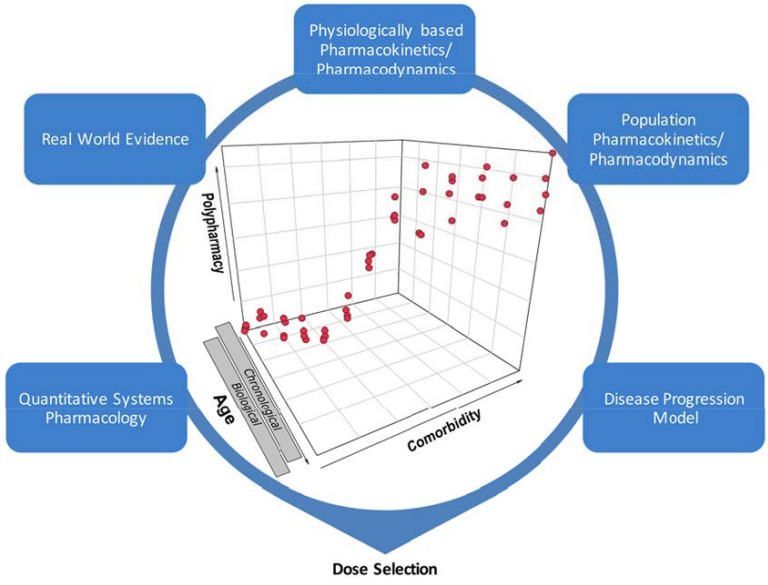


Figure 2 A case study illustrating the complexity of prescribing, optimal dosing, and deprescribing in older individuals with multimorbidity (**a**) and (**b**) quantitative methods to aid dose selection among the complex interplay of factors for older person's pharmacotherapy.

for medication harms, such as drug-induced cognitive impairment and falls that are particularly relevant to the quality of life of older persons, should be more formally assessed and considered for inclusion in product labels. Evidence on when and how to initiate deprescribing of unnecessary and harmful medications is often absent or inadequate to reduce adverse events associated with medication withdrawal.[5] Recent advances in geroscience suggest the possibility of developing interventions to modify the underlying biological processes of aging, thus opening the opportunity to develop a single intervention to influence the onset or progression of multiple underlying age-related health conditions. Our current drug development approach focuses on a specific target associated with a specific disease, but this approach may be ineffective in developing interventions addressing multimorbidity driven by major mechanisms underlying the aging process. Developing such interventions will require new clinical trial frameworks, biomarker discovery, and validation to demonstrate safety and efficacy.[6]

Dosage form development and evaluation of drug products is another important drug development issue affecting the care of older persons. The ability to swallow may be affected by aging and multimorbidity. Most medications are designed for self-administration, whereas older persons, especially those with disabilities, may need caregivers' assistance to administer their medications. Thus, a universal product design approach that considers the need of both patients and caregivers will be helpful to care for older persons. Flexibilities of drug dosage forms and strengths are important for an older population who may require more personalized dosing and administration.

REGULATORY CONSIDERATIONS ON DRUG DEVELOPMENT FOR OLDER PERSONS IN THE UNITED STATES

The US Food and Drug Administration's (FDA) "Guideline for the Study of Drugs Likely to Be Used in the Elderly" initially guided the inclusion of older persons in clinical trials of drugs for registration in the United States since 1989.[7] This guideline proposes that drugs should be studied in all age groups, including older persons, for which they will have significant utility. In 1994, the regulatory bodies of European Union, Japan, and the United States jointly published the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E7 guideline "Studies in Support of Special Populations: Geriatrics." The ICH E7 guideline noted the characteristics of the older patients that need specific attention, such as the frequent occurrence of concomitant illnesses and medications. In 2001, the FDA published guidance on the labeling of Geriatric Use subsection for human prescription drugs to include more complete information on the use of a drug or biological product in persons aged 65 years and above.[7] The ICH E7 guideline was updated in 2010 because of the rapidly changing worldwide demographics and patterns of drug use.[7] Particularly, people older than 75 years of age are the fastest growing population in many countries, and they have the high likelihood of comorbidities. There are preliminary data (2015 and 2014 vs. 2013) of increased participation of persons 65 years of age and above in clinical trials that may be due to the ICH E7 update.

Older persons continue to be under represented in clinical trials in relation to their diseases and likely exposure to the drug after drug registration. In Section 907 of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), Congress directed the FDA to develop a report on the inclusion of demographic subgroups in clinical trials and data analysis in applications for drugs, biologics, and devices within 1 year. In August 2013, the FDA released a report describing demographics and subset analyses included in 72 applications for drugs, biologics, and medical devices approved in 2011. Overall, the findings showed that the percentage of older persons participating in clinical trials varied by indication and tended to reflect the prevalence of the diseases in their population. Section 907 of the FDASIA also directed the publication "FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data" in August 2014, which includes the following three overarching priorities:[7]

- Improve the completeness and quality of demographic subgroup data collection, reporting, and analysis.
- Identify barriers to subgroup enrollment in clinical trials and strategies to encourage greater participation.
- Make demographic subgroup data more available and transparent.

Some action items can be accomplished quickly, whereas others will take longer to achieve and require additional resources. For example, the FDA implemented the Drug Trials Snapshots (DTS) to provide public information on participants in clinical trials that support new drug registrations. DTS also highlights potential differences in the benefits and side effects among age, sex, and race subgroups. DTS is part of an overall FDA effort to make demographic data more available and transparent.

QUANTITATIVE APPROACHES TO STREAMLINE PHARMACOTHERAPY IN OLDER PERSONS

Pharmacometrics and systems pharmacology have evolved and are already established for many scenarios during drug development especially toward new drug applications. Age is routinely assessed as a covariate in population pharmacokinetic and pharmacodynamic analyses. However, its impact is rarely considered in semimechanistic or disease progression approaches. The latter can serve as a powerful tool for clinical trial simulations or indicate whether a treatment has a beneficial impact on a longer timescale. Unfortunately, only a few simulators considered aging for their parameterization to date.

Beyond this classical and descriptive approach, routine study sequences during clinical drug development for specific populations, such as organ-impaired or pediatric patients, are routinely accompanied by physiologically-based pharmacokinetic (PBPK) modeling efforts. Although PBPK predictions for these scenarios are improving and gaining more acceptance, PBPK modeling for older persons is still in its infancy. This observation is mainly due to the complexity of age-related changes of system parameters and their interplay, which is barely analyzed in older persons on a whole-body level. Only recently has this model component been comprehensively and systematically evaluated in reduced and whole-body PBPK

approaches for older persons.[8,9] Besides routine pharmacokinetic evaluation for older persons, the newly developed PBPK approaches are applicable for additional purposes. Age-related pathophysiological alterations should be considered during the base PBPK model building because subsequent scaling to, for example, the pediatric age range will have different pathophysiological starting points.

Pharmacodynamics is an important driver for efficacy and safety of medications. A still understudied phenomenon of older persons is the deviation from the exposure–response relationships when compared with that of younger adults or the pharmacodynamic heterogeneity in older adult patients. A PBPK approach for older persons could serve as the starting point to investigate altered cellular exposure and indicating age-impacted target modification. This can also be evaluated through a more mechanistic pharmacodynamic approach, such as systems pharmacology. Similar to PBPK modeling, only a few system pharmacology models consider adjusting parameters to account for advanced age.

Although 25% of new drug application approvals lack explicit dosing recommendations for older persons,[10] pharmacometrics and systems pharmacology have the potential to meet this need. Model-informed conversion of theoretical concept into quantitative predictions by understanding the pathophysiological linkages gains confidence in the final dose selection (**Figure 2b**). The impact of comorbidity and polypharmacy are inevitably future challenges for these quantitative approaches.

A CALL TO ACTION

How do we improve drug development to care for our growing aging population? The following ideas may help:

- Recognize the imperative for increased attention to the needs of older persons.
- Continue to explore the development of biomarkers for biological aging and frailty to expand our understanding beyond chronologic age.
- Develop the evidence for likelihood of benefit/harm and time to benefit/harm of drugs for older persons by including more older persons and a population more representative of anticipated actual clinical use (multimorbidity and polypharmacy) in clinical trials.
- Investigate deprescribing of medications as part of drug development to reduce withdrawal-associated harms and include this information in product labels.
- Establish frameworks for studying the safety and efficacy of interventions directed at underlying biological aging processes and associated multimorbidity to encourage drug development in this area.
- Assess drug dosage forms for the ease of use and appropriateness in older populations and their caregivers.
- Apply quantitative approaches for model-informed drug development to convert theoretical concept to quantitative predictions and thereby support optimal dosing for older persons and those with multimorbidity.
- Align resources and incentives in the regulatory drug development process, as has been successfully implemented with other patient populations, such as pediatrics, to accelerate innovation.

DEDICATION

Darrell R. Abernethy.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Supplementary Reading

ACKNOWLEDGMENTS

Figure 1 is reproduced with permission from the United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Ageing 2017 (ST/ESA/SER.A/408), p. 11. We thank Ms. Annika Schneider of Systems Pharmacology and Medicine, Bayer AG, 51373 Leverkusen, Germany, for her assistance in generating **Figure 2**.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

DISCLAIMER

The contents of this article reflect the views of the authors and should not be construed to represent the US Food and Drug Administration (FDA)'s views or policies. No official support or endorsement by the FDA is intended or should be inferred.

1. United Nations, Department of Economic and Social Affairs, Population Division. World Population Ageing 2017 (ST/ESA/SER.A/408) <https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Report.pdf> (2017). Accessed September 16, 2019.
2. Gerteis, J. *et al*. Multiple Chronic Conditions Chartbook. AHRQ Publications No. Q14-0038 (Agency for Healthcare Research and Quality, Rockville, MD, 2014) <https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/prevention-chronic-care/decision/mcc/mccchartbook.pdf>. Accessed September 16, 2019.
3. American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc.* **67**, 674–694 (2019).
4. Holmes, H.M. Rational prescribing for patients with a reduced life expectancy. *Clin. Pharmacol. Ther.* **85**, 103–107 (2009).
5. Bruyère Research Institute. What is deprescribing? <https://deprescribing.org/what-is-deprescribing/>. Accessed September 16, 2019.
6. Ford, G.A., Lord, J.M., Ferguson, M.A., Bountra, C. & Le Couteur, D.G. Organizational innovation for developing new medicines that target aging and age-related conditions. *J. Gerontol. A Biol. Sci. Med. Sci.* https://doi.org/10.1093/gerona/glz062. [e-pub ahead of print].
7. De Spiegeleer, B. *et al*. Regulatory development of geriatric medicines: to GIP or not to GIP? *Ageing Res. Rev.* **27**, 23–36 (2016).
8. Chetty, M., Johnson, T.N., Polak, S., Salem, F., Doki, K. & Rostami-Hodjegan, A. Physiologically based pharmacokinetic modelling to guide drug delivery in older people. *Adv. Drug Deliv. Rev.* **135**, 85–96 (2018).
9. Schlender, J.F. *et al*. Development of a whole-body physiologically based pharmacokinetic approach to assess the pharmacokinetics of drugs in elderly individuals. *Clin. Pharmacokinet.* **55**, 1573–1589 (2016).
10. Jadhav, P.R. *et al*. A proposal for scientific framework enabling specific population drug dosing recommendations. *J. Clin. Pharmacol.* **55**, 1073–1078 (2015).