YALE UNIVERSITY
Claude D. Pepper Older Americans Independence Center

Thomas M. Gill, M.D. 203-688-9423 thomas.gill@yale.edu
Principal Investigator

Mary Geda 203-737-1800 mary.geda@yale.edu
Program Administrator

CENTER DESCRIPTION

The overarching mission of the Yale Older Americans Independence Center (OAIC), established in 1992, is to provide intellectual leadership and innovation for aging research that is directed at enhancing the independence of older persons. The unifying theme of the Yale OAIC is the investigation of multifactorial geriatric conditions, encompassing single conditions resulting from multiple contributing factors or affecting multiple outcome domains and multiple conditions occurring simultaneously.

The central Yale OAIC hypothesis is that geriatric conditions are determined by the co-occurrence of multiple predisposing and precipitating factors. These conditions and factors, in turn, affect a range of health outcomes. The predisposing factors may be at the genetic, molecular, physiologic, impairment, disease, or socio-demographic level, while the precipitating factors may be behavioral, environmental, social, medical, or psychological. The Yale OAIC theme requires designs and models (e.g. molecular, animal, and statistical) that inform the study of multiple, simultaneously interactive factors and outcomes. As a prominent subtheme, the Yale OAIC also aims to advance the science of clinical decision making in the face of trade-offs and multiple competing outcomes. This includes developing strategies to elicit older persons' health outcome priorities.

The Specific Aims of the Yale OAIC are to

1. Foster the career development of future academic leaders, from multiple disciplines, in aging research;
2. Train investigators, biostatisticians and other methodologists in the skills necessary to design, conduct, analyze, and disseminate findings from studies of multifactorial geriatric conditions;
3. Develop and disseminate design and analytic techniques for conducting studies of multifactorial geriatric conditions;
4. Develop strategies for recruiting into, and retaining, a broad spectrum of older persons, including minorities, into studies of multifactorial geriatric conditions;
5. Investigate the causative mechanisms of, and develop and test effective treatments for, geriatric conditions from a multifactorial research perspective;
6. Develop strategies to enhance clinical decision making in the setting of multiple competing outcomes;
7. Encourage and facilitate interdisciplinary research (basic, translational and clinical) that connects to our focus on multifactorial geriatric conditions; and further strengthen collaborations with other OAICs.

The Yale OAIC cores include: 1) Leadership and Administrative; 2) Research Education; 3) Pilot/Exploratory Studies; 4) Operations; and 5) Biostatistics.

CORES

Leadership and Administrative Core (LAC)

Leader 1:	Thomas M. Gill, MD	thomas.gill@yale.edu
Leader 2:	Terri Fried, MD	terri.fried@yale.edu
Leader 3:	Denise Acampora, MPH	denise.acampora@yale.edu
Leader 4:	Mary Geda, RN, BSN, MSN	mary.geda@yale.edu

The overarching objective of the Leadership and Administrative Core (LAC) is to advance the scientific knowledge base of multifactorial geriatric conditions. The LAC, which is led by two board-certified geriatric physician investigators with complementary expertise, is responsible for strategic planning, organization, administrative operations and evaluation of the OAIC research and training program. A special effort is devoted to ensuring the cohesion of the Center and maintenance of an interdisciplinary and translational research focus on the common research theme, which is "the investigation of multifactorial geriatric conditions". The key LAC tasks are achieved by the LAC leadership administrators, and three committees: the Executive Committee, the Internal Advisory Committee, and the External Advisory Committee.

Research Education Component (REC)

Leader 1:	Terri Fried, MD	terri.fried@yale.edu
Leader 2:	Albert Shaw, MD PhD	albert.shaw@yale.edu
Leader 3:	Denise Acampora, MPH	denise.acampora@yale.edu
Leader 4:	Andrew Cohen, MD, DPhil	andrew.b.cohen@yale.edu

The objective of the Research Education Core (REC) is to identify highly promising early-stage investigators and provide support to promote their development as independent investigators and leaders in aging research. The REC seeks to provide three groups of investigators, designated as Pepper Scholars, Small REC Awardees, and REC Affiliates, with the knowledge and skills to conduct biological, translational, and clinical studies of multifactorial geriatric conditions and to obtain subsequent funding from a broad range of sources. The outcomes and career advancement goals for the Pepper Scholars include: 1) publication of research results in high-impact journals; 2) success in obtaining independent funding, both to support further career development (e.g. K08 and K23 awards) and specific projects (e.g. R21 and R01 awards); and 3) development of leadership skills necessary to manage research teams and to become successful mentors themselves.

Pilot and Exploratory Studies Core (PESC)

Leader 1:	Albert Shaw, MD PhD	albert.shaw@yale.edu
Leader 2:	Terri Fried, MD	terri.fried@yale.edu
Leader 3:	Denise Acampora, MPH	denise.acampora@yale.edu

The primary goal of the Pilot/Exploratory Studies Core (PESC) is to facilitate the development of innovative and rigorous research studies that will enhance our understanding of the pathogenesis, etiology, diagnosis, prevention, and management of multifactorial geriatric conditions, leading ultimately to the development of efficacious and cost-effective interventions to increase or maintain the independence of older Americans.

Operations (RC1)

Leader 1: Katy Araujo, MPH katy.araujo@yale.edu
Leader 2: Mary Geda, RN, BSN, MSN mary.geda@yale.edu
Leader 3: Lauren Ferrante, M.D., M.H.S. lauren.ferrante@yale.edu

The Operations Core (OC) supports OAIC investigations of multifactorial geriatric conditions by recruiting and retaining diverse populations of older persons, seeking input from the local community in research, planning and dissemination, monitoring participant safety, ensuring regulatory compliance, developing surveys and instruments, designing Information Technology (IT) systems to implement research, collecting and preparing data for statistical analysis, and providing continuity and shared knowledge across projects. The overall goal of the OC is to ensure the successful implementation of research focused on multifactorial geriatric conditions. This goal will be accomplished by leading, managing, and coordinating the effective, efficient and innovative use of facilities, data, staff, resources, and space. There is a consistent demand for experienced personnel with the ability to quickly execute aging-focused research and an increasing need for informatics skills and technology to streamline work.

Biostatistical Design and Analysis Core (RC2)

Leader 1: Denise Esserman, PhD denise.esserman@yale.edu
Leader 2: Brent Vander Wyk, PhD brent.vanderwyk@yale.edu

The overarching goals of the Biostatistics Core (BC) are to provide design and analytical services to OAIC investigators conducting studies of multifactorial geriatric conditions; to develop and disseminate new design and analytical techniques for conducting studies with older persons; and to train a cadre of clinical investigators, biostatisticians, and epidemiologists in the skills necessary to design, conduct, and analyze gerontologic studies.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Minhee Sun 2023-2025 /
Instructor of Medicine (General Medicine) / Yale University 0 (total)
Opioid Use Disorder Management of Older Adults with Multimorbidity: a Delphi Study 0 (1st/Sr)

Specific Aim 1 to perform a scoping review of the existing literature to characterize the populations and outcomes studied. Part of the scoping review will also be to examine existing publicly available datasets of older adults to determine whether and how Opioid Use Disorder (OUD) was evaluated and its prevalence, in order to evaluate suitability for further epidemiologic studies of OUD among older persons. Specific Aim 2 will be to bring together the existing experts in aging and OUD in a Delphi panel to address several important clinical questions for which there are insufficient data to inform practice. These include: 1) should an older adult being treated with OUD who develops delirium with an acute illness remain on therapy? What factors, in terms of comorbid conditions and risks, should be considered in the decision?; 2) how should treatment for OUD in the older person be modified if the patient develops a geriatric syndrome such as cognitive impairment or falls? Key benchmarks for this project will be two manuscripts presenting the findings of each aim and preparation of an advanced VA CDA award.

Michael Nanna 2023-2025 /
Assistant Professor of Internal Medicine (Cardiovascular Medicine) / Yale 9 (total)
Multimorbidity and Shared Decision Making for Treatment of Stable Coronary Artery Disease 3 (1st/Sr)

This work is predicated on several established findings: 1) there are no mortality differences between the two approaches; 2) each of the two approaches has a unique set of treatment burdens and potential for harm, and these are modified by patients' unique set of comorbid conditions; and 3) patients have unrealistic expectations regarding the treatment options. The goal of the tool is to help clinicians and patients consider these treatment options in the context of the individualized risks, preferences and priorities of the older person. The knowledge gap is a lack of understanding about how patients and clinicians factor these considerations into their decisions and the specific aspects of the therapies that matter to decision making. Specific Aim 1 will use qualitative methods to understand the concerns and priorities of older persons with cardiovascular disease related to the use of medical therapy and PCI, including views regarding relevant benefits and harms of each therapy and the importance of these to decision making. Specific Aim 2 will use consensus methods with a group of experts in geriatric cardiology to establish methods for identifying older adults with elevated likelihood of experiencing the outcomes elucidated in Specific Aim 1. Specific Aim 3 will involve the iterative design of a decision support tool with feedback from the participants in Aims 1 and 2 as well as general cardiologists

- HA-2021C3-24767

Guido Falcone 2017-2024 /
Assistant Professor of Medicine (Neurology) / Yale University 62 (total)
Multi-Phenotype Big Data Approach to Cerebral Small Vessel Disease Genomics 3 (1st/Sr)

- P30AG021342
- R03NS112859

Past Scholars

Xi Chen, Yale University (2016-2020)
Janice Hwang, Yale University (2018-2020)
Morgan Levine, Yale University (2018-2020)
Joan Monin, Yale University (2018-2020)
Brienne Miner, Yale University (2019-2021)
Maor Sauler, Yale University (2019-2021)
Gregory Ouellet, Yale University (2020-2022)
Zachary Levine, Yale University (2020-2022)
Edward Manning, Yale University (2021-2023)
Cameron Gettel, Yale University (2021-2023)

PILOT/EXPLORATORY PROJECTS (10 Pilot Projects Listed)

1. Project Title: Genetic Predisposition to Cardiovascular Disease and Risk of Death, Dementia and Disability in Older Persons: PESC (2021-2022) - carryover 2022-2024

Leader: Guido Falcone

Statins constitute a powerful treatment for hyperlipidemia, one of the most important risk factors for cardiovascular disease (CVD). While the benefit of statins in primary prevention has been clearly established for middle-aged persons, there is no definitive evidence supporting their use in older adults. The PREVENTABLE clinical trial will enroll 20,000 older adults to test the hypothesis that statins increase survival free of dementia or disability in persons aged >75 years without clinically-evident CVD. Through the support of this Yale Pepper Pilot Award, we will evaluate whether a higher genetic predisposition to CVD increases the risk of this composite outcome in this age group. The results from this pilot study will provide key preliminary data to support an R01 application for an ancillary genetic study to PREVENTABLE that will test the hypothesis that information on known genetic risk factors for CVD can identify persons aged >75 who may preferentially benefit from statin treatment. Genomic information is emerging as a powerful precision medicine tool to identify persons at highrisk of human disease. There are numerous genetic risk variants that contribute to the pathophysiological processes that lead to the endpoints evaluated by PREVENTABLE. These genetic variants constitute an excellent basis for developing precision medicine tools, as they remain constant throughout life and immune to confounding by post-natal exposures due to their random assignment during meiosis. While promising, the field still lacks evidence on whether these genetic risk factors retain their effect and predictive ability in older adults, a crucial prerequisite to explore genomic-based precision medicine strategies in this age group. We will address this knowledge gap by evaluating the role of genetic predisposition to CVD in determining the risk of death, dementia or disability in persons aged >75 years without clinically-evident CVD. We will harmonize, quality control and analyze clinical and genetic data from 95,541 persons aged >75 years enrolled in the Health and Retirement Study and the UK Biobank to pursue the following specific aims: (1) Determine whether a higher genetic predisposition to CVD is associated with higher composite risk of death, dementia and disability (primary PREVENTABLE endpoint) in persons aged >75 years without clinically-evident CV disease; and (2) determine whether a higher genetic predisposition to CVD is associated with a higher composite risk of acute myocardial infarction, stroke or death of any cause (secondary PREVENTABLE outcome) in persons aged >75 years without clinically-evident CVD. The proposed research will significantly advance our understanding of the role of high genetic predisposition to CVD in determining death, dementia, disability and acute vascular events in older adults without clinically-evident CVD.

2. Project Title: Aging of the Human Pulmonary Artery: Analyzing Gene Expression to Tissue: REC (2021-2023) Carryover 2023-2024

Leader: Edward Manning

There is a knowledge gap in the underlying mechanisms of how the pulmonary artery changes with age. Evidence from an aging mouse model shows that pulmonary arteries stiffen with an age. Pulmonary arterial stiffening in humans is associated with lung diseases including chronic obstructive pulmonary disease, pulmonary hypertension, and disease associated with dyspnea; dyspnea occurs in over 10 million Americans over the age of 65. Yet, the association between age and pulmonary arterial stiffening is poorly described. Dyspnea is associated with frailty and poor health in the older population, but the etiology of dyspnea in many of these older individuals is unexplained. Therefore, this study aims to identify an association between age and pulmonary arterial stiffness in the human pulmonary artery and investigate underlying mechanisms of human pulmonary arterial stiffening. These aims are based on findings from a mouse model of pulmonary arterial aging and will employ similar investigational techniques as those successfully used in the mouse model. The first aim is to characterize the association of material stiffness of the pulmonary artery with age by mechanically testing 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old. Material stiffness will be calculated from measurements of deformation of the pulmonary arteries, including diameter, pressure, and force, while mounted on cannulas and submerged in physiologic solution. An additional aim is to use 2-photon imaging of 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old to characterize the association of extracellular collagen fiber orientation with age. The orientation of collagen fibers will be calculated from using 2-photon imaging and fast fourier transform analysis. The final aim is to identify whether pulmonary arterial cell gene expression changes as a function of age by performing single cell RNA sequencing on 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old. This aim will be accomplished by performing single cell RNA sequencing, a unique tool to investigate cell populations in tissue with near complete genomic profile of individual cells. These cellular specific changes of genetic expression will identify multiple cellular pathways and mechanisms responsible for changes in the pulmonary artery as a function of age. This study will be the foundation for future clinical investigations to associate age-related pulmonary arterial stiffness and health outcomes. Additionally, a better understanding of underlying mechanisms related to increased pulmonary arterial stiffening will provide information to determine optimal non-invasive measurements of pulmonary arterial stiffening in clinical settings and potential therapeutic targets for slowing or reversing the aging process of the pulmonary artery in future studies.

3. Project Title: **Improving Hospital-Level Mortality Performance for Major Surgery in Older Adults: A Mixed Methods Study: small REC (2021-2022) carryover 2023-2024**

Leader: **Robert Becher**

Despite decades of efforts to improve care for patients undergoing major surgery, there remains substantial variation across hospitals in surgical mortality. For adult patients undergoing common general surgery operations, standardized mortality ratios range from an average of 1.7 at poor-performing hospitals to a mean of 0.5 at high-performing hospitals, more than a three-fold difference. For older persons, deficient surgical care is especially problematic. Major surgery is a common event in the lives of community-living older persons, with a 5-year cumulative incidence of 13.8%, representing nearly 5 million persons aged 65 years or older in the US. This value will increase substantially in the coming years based on the projected doubling of this age group to 98 million people by the year 2060. Therefore, despite the

importance of major surgery as a defining health issue for older persons, we know little about what distinguishes poor-performing from exceptionalperforming outlier hospitals with high- versus low-mortality. This lack of evidence about what accounts for hospital mortality variation for geriatric surgery is a critical gap in our current knowledge. To facilitate improvements and achieve truly optimal perioperative outcomes for older persons undergoing major surgery, quality improvement science espouses the concept that we must first accurately define the landscape of the quality problem. One novel approach to examining the variation in healthcare quality is called positive deviance. This mixed methods analytic strategy postulates that hospital structures, processes, and internal environments may influence clinical outcomes. While the positive deviance approach has proven instrumental in improving hospital-level quality for other fields of medicine, it has not previously been applied to surgery. Grounded in the tenets of positive deviance, we will employ both quantitative and qualitative research in a complementary fashion to: (1) evaluate hospital-level mortality performance for older persons undergoing major surgery; (2) compare the patient-, operation-, and hospital-level characteristics between the highmortality and low-mortality hospitals for older persons undergoing major surgery; and (3) develop the methods and processes necessary for a full-scale qualitative evaluation of the hospital-specific efforts that may explain hospital-level mortality performance at the high-mortality and low-mortality hospitals for older persons undergoing major surgery. By taking a mixed methods approach, the proposed Pepper Scholar project will provide information that is essential to understanding the hospital-level sources of variation in mortality for geriatric surgery. These results, coupled with a robust career development plan and experienced mentoring, are expected to lay the groundwork for a subsequent novel and innovative large-scale, mixed methods R01 grant, fully utilizing the positive deviance approach on a national level, to define, test, disseminate, and implement evidence-based, hospital-level efforts to elevate hospital performance for older persons having major surgery in the US.

4. Project Title: Can Type 2 Acute Myocardial Infarction Be Classified as a Geriatric Syndrome? (PESC 2022-2023) Carryover 2023-2024

Leader: Alexandra Hajduk

While the archetype of acute myocardial infarction (AMI) is a disruption of plaque in a coronary artery leading to atherothrombosis (type 1 AMI), it is increasingly recognized that AMI does not always follow this definition. Type 2 AMI, which does not involve atherothrombosis in its pathogenesis but instead arises from supply-demand imbalance in myocardial oxygen secondary to other conditions (e.g., respiratory failure, anemia) is aprevalent AMI phenotype among older adults, particularly those with multiple comorbidities. Despite differences in pathogenesis, type 2 AMIs are often treated with the same diagnostic and treatment cascades as type 1 AMI, including angiography and secondary preventive medications. These treatments may be, at best, not helpful, and at worst, harmful, particularly to those with underlying vulnerabilities. A lack of tailored treatment strategies for type 2 AMI may explain, in part, the worse prognosis for mortality and morbidity for this AMI type when compared to type 1 AMI. Given the multiple etiologic factors, the increased incidence among older adults, and the poorly defined diagnostic and treatment pathways (with resulting poor outcomes), the primary aim of this work is to evaluate the appropriateness of characterizing type 2 AMI as a geriatric syndrome, i.e., a multifactorial health condition that occurs when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges. The objectives of this work align well with the unifying theme of the Yale Pepper Center, i.e., the investigation of multifactorial health conditions. This pilot project

will consist of a secondary analysis of data from the "ComprehenSIVe Evaluation of Older Patients with Acute Myocardial Infarction" (SILVER-AMI), a large cohort study of older adults with AMI that is unique in its collection of risk factors for geriatric syndromes at the time of AMI hospitalization. In aim 1, we will identify type 2 AMI cases via medical chart review using a hierarchical algorithm and a team-based adjudication process. We will not only discern type 2 AMI from type 1 AMI but will also examine the underlying condition(s) that precipitated type 2 AMI (e.g., arrhythmia, sepsis), thereby establishing a multifactorial pathogenesis. In aim 2, we will evaluate the appropriateness of characterization of type 2 AMI as a geriatric syndrome by associating it with a high prevalence of shared risk factors for geriatric syndromes: older age, functional impairment, mobility impairment, and cognitive impairment. To do this, we will evaluate the probability of type 1 vs. type 2 AMI, contingent on the presence of these shared risk factors. The findings from this pilot project will be used as preliminary data for an R21 proposal to the National Institute on Aging to evaluate differences in treatments and outcomes between types 1 and 2 AMI in older adults. The totality of this work will increase visibility of type 2 AMI as a condition that transcends traditional organ- and discipline-based boundaries, improve timeliness and accuracy of diagnosis, and facilitate development of appropriate treatment pathways, while reducing use of inappropriate treatments.

5. Project Title: Epigenetic Aging Clock, Metabolomic, and Health Profiles in Adulthood Following Early Life Adversities in Nonhuman Primates : PESC (2022-2023) Carryover 2023-2024

Leader: Amanda Dettmer

Societal and familial early life adversities (ELAs), including neglect, maltreatment, and low socioeconomic status (SES) are associated with adverse health outcomes in adulthood, yet it is unclear precisely how ELA "gets under the skin" to impact lifelong health. Given the high prevalence in the U.S. of childhood maltreatment and neglect (at least 15-20%), and that of children living in low-income families (38%), millions of children possess unique risks to healthy aging. Identifying biological mechanisms that link ELAs and age-related health outcomes is crucial for developing therapeutic treatments to ameliorate health disparities within the burgeoning population of older humans. Two promising mechanisms in associative studies in humans are dysregulated metabolism and epigenetic aging, both of which are correlated with chronological age and are associated with increases in obesity, diabetes, depression, and mortality. However, experimentally testing the hypothesis that ELA causes dysregulated metabolism and accelerated epigenetic aging in human cohorts is challenging. Children cannot be randomly assigned to adverse early experiences, and genetic and environmental confounds exist. Moreover, poor health in children may precede maltreatment or neglect. Finally, humans' long lifespan makes repeated sampling across the life course difficult and necessitates several decades for age-related health outcomes to emerge. Studying nonhuman primates (NHPs) as models of human health and aging has the potential to fill these critical gaps. NHPs possess striking biological, genetic, and behavioral similarities to humans, they have faster (~4x) developmental trajectories, and they can be randomly assigned to different early life experiences. We and others have previously shown that rhesus macaques (Macaca mulatta) randomly assigned to the ELA of nursery rearing (NR) in infancy, which models caregiver absence during critical developmental periods, have poorer health outcomes and acquire lower social ranks in adolescence and adulthood compared to mother-reared (MR) macaques. Additionally, macaques that are naturally born into low social ranks, a good proxy of low SES in humans, exhibit greater risk for adverse health outcomes. This pilot project will leverage the

macaque model to simultaneously examine whether experimentally-induced and naturally-occurring ELA is associated with differential likelihood of biological and health outcomes in adulthood. Capitalizing on our archive of over 30,000 biological samples and health data collected on macaques across the life course, we will examine whether NR and low social status differentially influence metabolism, epigenetic aging, and health outcomes in adulthood. Aim 1 will analyze plasma samples collected in adolescence and middle age from NR (n=12) and MR (n=12) macaques using global (untargeted) metabolomics, and white blood cells collected in middle age using epigenetic aging clock analysis; these measures will be correlated with occurrence of medical interventions, weight fluctuations and BMI, and adverse reproductive outcomes (stillbirths, spontaneous abortions, infant deaths, and C-sections) in middle age. Aim 2 will correlate epigenetic aging clock measures with the same health outcomes in a separate colony of high-ranking (n=10) and low-ranking (n=10) macaques. Results from this pilot study will be leveraged to pursue independent funding to expand this research into mechanistic evidence for the associations between ELA and adult health.

6. Project Title: Distressing Symptoms and Disability Among Older Adults Following Critical Illness: REC (2022-2024)

Leader: Snigdha Jain

The number of older adults who survive critical illness, estimated at about 1.4 million a decade ago, is increasing with the aging of the US population, advances in treatment for critical illness, and the current pandemic. Critical care medicine societies, nationally and internationally, are increasingly acknowledging challenges associated with critical illness survivorship, and multiple studies have described distressing symptoms across domains of physical, cognitive, and mental health among patients who survive hospitalization with a stay in the intensive care unit (ICU). However, these studies have enrolled patients at or after ICU hospitalization, precluding an evaluation of how symptoms change in the context of critical illness. Surviving hospitalization with a stay in the ICU is also accompanied by new or worsening disability for older persons. Whether distressing symptoms are associated with functional decline after critical illness has not been investigated. Furthermore, prior studies of distressing symptoms have not taken into account two particularly vulnerable populations - older persons with 1) multimorbidity, who are known to have greater symptom burden in later stages of life, and 2) individual and neighborhood socioeconomic disadvantage, who are at increased risk for functional decline after critical illness. I will utilize a unique longitudinal study of older persons, the Precipitating Events Project (PEP), that has prospectively collected information on distressing symptoms and disability for more than two decades, linked with Medicare claims, to evaluate the occurrence of distressing symptoms before and after hospitalization (Specific Aim 1) and to examine the association between distressing symptoms and the course of disability after critical illness survival (Specific Aim 2). In both aims, I will specifically examine these changes among older persons with multimorbidity as well as individual- and neighborhood-level socioeconomic disadvantage. The proposed work will move our knowledge from description of symptoms in the period after critical illness to an understanding of how distressing symptoms change in the context of critical illness hospitalization and their relationship with disability following critical illness survivorship. Furthermore, it will identify specific symptoms and population groups with the greatest increases in occurrence and the largest associations with disability. These findings will serve as the first step towards accomplishing my long-term objective, which is to integrate evaluation of evidence-based determinants of disability after critical illness into routine clinical practice, with the goal of

improving functional outcomes among older survivors of critical illness. Support from the award will also allow me to acquire advanced skills in geriatric epidemiology and biostatistics that will guide my future work in aging research.

7. Project Title: Multimorbidity and Shared Decision Making for Treatment of Stable Coronary Artery Disease: small REC (2022-2023)

Leader: Michael Nanna

Older adults living with multiple chronic conditions and chronic coronary disease experience significant morbidity, disability, and mortality. Treatment options in patients with chronic coronary disease are varied and can include a variety of potential medical and invasive therapies, all of which carry unique risks and benefits. In older adults with multiple chronic conditions, these treatment decisions are particularly complex, with highly variable patient priorities, multifactorial symptoms, and interactions between other chronic conditions and treatments for chronic coronary disease. Clinicians are often forced to presuppose the individual importance and likelihood of these outcomes, while simultaneously navigating how best to incorporate the impact of non-cardiac conditions that modify the effect of these treatments on the outcomes that matter most to their patient. In the face of this uncertainty, the development of a dedicated decision support tool to help clinicians align treatment decisions for chronic coronary disease with their older patients' goals of care within the context of their multiple chronic conditions is a crucial step in improving the overall care of these individuals. Given the uncertainty surrounding treatment decisions for older adults with chronic coronary disease and MCCs, it is important to engage both clinicians and patients in identifying the information that should inform patient-specific decision-making. A necessary initial step is identifying, from both clinician and patient-care giver perspectives, what information should inform treatment decisions. The process should include input from including both clinicians who offer their judgement on treatments and patients who establish the full range of domains that matter most to them. Importantly, patient stakeholders must serve a central role in informing the most pressing priorities and preferences of older patients with chronic coronary disease. Thus, our Specific Aims are 1) To generate a summary of the factors influencing the treatment of older adults with MCCs with chronic coronary disease through a robust process including multiple stakeholders; and 2) To develop and test a shared decision-making tool to apply to older adults with multiple chronic conditions presenting for the treatment of chronic coronary disease. The study design will include an initial needs assessment, literature review, and a consortium of both patients and clinicians to conduct both participant-specific and multi-stakeholder groupings, in order to identify the factors influencing person-centered decisions in this population (Aim 1). We will then apply a user-centered design approach and established decision support frameworks, including the Ottawa Decision Support Framework (ODSF) and International Patient Decision Aid Standards (IPDAS), to develop a chronic coronary disease decision support tool tailored to the unique and complex needs of the older adult populations with MCCs (Aim 2). Beta testing and initial pilot feasibility testing of the decision aid will be measured by reported successful completion by both patient and clinician, along with additional measures of feasibility, acceptability, and appropriateness, and qualitative feedback from patient and clinician stakeholders. Ultimately, the pilot-tested decision-support tool generated from this project will serve as the groundwork for a future proposal to more broadly test and implement

8. Project Title: **Opioid Use Disorder Management of Older Adults with Multimorbidity: a Delphi Study: small REC (2023-2024)**

Leader: **Minhee Sun**

Among older adults, opioid use disorder (OUD) diagnoses have increased three-fold from 2013 to 20181,2 and is expected to rise substantially higher due to the aging Baby Boomer generation who have higher rates of substance use compared to previous generations.1,3 Much attention has been paid to expanding the initiation of medications for opioid use disorder (MOUD) for individuals with OUD, effective treatments for curbing opioid overdose deaths and OUD-related hospital visits.4 As a result, a growing number of individuals prescribed MOUD, including buprenorphine and methadone, are approaching older age.5,6 However, limited attention has been paid to understand how to optimize long-term MOUD treatment among older adults. There have been increasing calls to address this knowledge gap due to a growing appreciation of the complexities and trade-offs of reducing OUD-related harms by continuing MOUD indefinitely.7 Tradeoffs include adverse effects of MOUD including somnolence and cognitive impairment,5,7-10 which may lead to falls and fractures, highly morbid events for older adults.11 Lifelong MOUD use may also contribute to polypharmacy which is associated with frailty among other harms.12,13 Furthermore common causes for medication nonadherence among older adults, such as cognitive impairment and lack of caregiver support,14 may make it difficult to continue lifelong MOUD. To further inform decision making, certain MOUD such as buprenorphine provide the added benefit of analgesia due to its partial opioid agonist effects,15 which may be desired in older adults as chronic pain is prevalent and causes functional impairment.16 Buprenorphine has been the primary treatment used to expand MOUD access to treat OUD recently due to its office-based availability.17 Therefore, our objective is to gain a comprehensive understanding of factors that impact the use of buprenorphine long-term among older adults with OUD using sequential mixed methods18 by achieving the following Specific Aims: 1) to identify factors that impact the continuation/discontinuation of buprenorphine long-term among older adults with OUD by conducting a qualitative study of older Veterans with current/past receipt of buprenorphine for ³1 year for OUD and buprenorphine-prescribing clinicians and 2) to quantify the geriatric conditions and experiences of older individuals with OUD prescribed long-term buprenorphine by conducting a cross-sectional survey among Veterans on long-term buprenorphine. I am well-positioned to conduct this proposal as a buprenorphine-prescribing Internal Medicine physician with imminent Addiction Medicine certification who treats and studies OUD in older adults and has experience with qualitative/quantitative methods.19,20 I have been appointed to Instructor in the Yale Program in Addiction Medicine through a Veterans Health Administration (VHA) career development award to conduct this proposal. My mentors are experts in Addiction Medicine, aging, and mixed methods. Generating innovative knowledge on factors impacting OUD treatment among older adults through this proposal is timely and highly relevant with potential for long-term impact given the worsening opioid epidemic and growing cohort of individuals aging with OUD. Completion of my aims will lay the necessary foundation for me to build a prospective cohort to conduct longitudinal then intervention studies, leading me to become an independent clinical investigator focused on optimizing OUD care among older adults.

9. Project Title: **Exploring Novel Environmental and Climatological Determinants of Health for Aging Populations: small REC (2022-2023) Carryover 2023-2024**

Leader: **Natalia Festa**

Older adults are differentially susceptible to adverse environmental exposures, while those with age-related disability require intensive healthcare and custodial supportive services. Nonetheless, there is scarce information regarding the relationship between environmental exposures and aging outcomes. Because disabled older persons are often reliant upon local aging infrastructure, such as nursing homes and home and community-based services (HCBS), understanding the potential of environmental factors—ranging from climatological hazards to rurality—to affect access to these resources is vital. The interdependence of older persons and aging infrastructure renders environmental and climate adaptation more complex for this enlarging demographic group and has made appropriate modifications of aging infrastructure a national priority in the United States.1 The specific aims outlined in this small grant application are designed to evaluate novel environmental determinants of health for aging populations. Because our planned research focuses on nursing home residents and recipients of home and community-based services, our findings will have direct implications for older adults with multiple chronic conditions and disabilities. Each specific aim focuses on an area in which there are knowledge gaps in environmental gerontology, using three categories of environmental exposures. First, we will quantify potential changes in the relative risk of mortality due to cold temperature exposure during the 2022-2023 winter, adjusting for home heating oil prices as an effect modifier in the context of current energy shortages. Second, we will evaluate the geographic access of nursing homes to hospital care as a potential determinant of rehospitalizations and mortality. Because driving time to healthcare facilities and rurality have emerged as important environmental determinants of health for multiple conditions, we will evaluate these exposures and their interaction in relation to nursing home resident outcomes. Third, we will evaluate the magnitude and statistical significance of the association between administrative emergency preparedness and outcomes among nursing home residents exposed to Hurricane Matthew in 2016.

10. Project Title: **Senescence-Associated Endosomes and Vascular Healthspan: Translational Geroscience (2023-2024)**

Leader: **Dan Jane-wit**

Age-related vascular conditions have had a devastating negative impact on the morbidity and mortality of elderly patients. In the U.S. alone, the aged population >65 years old encompasses ~56 million individuals, and this large cohort shows disproportionately increased risk for vascular disease. Improved understanding of the molecular underpinnings of vascular aging is urgently warranted to inform new anti-senolytic therapies for these at-risk individuals. Our extramurally-funded research lab uses patient-centered approaches to study how endothelial cells (ECs), cells that line blood vessels, contribute to the longevity of tissue allografts. Using humanized models and patient specimens, we discovered a new molecule in ECs called ZFYVE21. ZFYVE21 is an ancient protein whose functions are virtually unknown. We found that ZFYVE21 was expressed on intracellular vesicles called Rab5 endosomes. ZFYVE21 was capable of modifying the protein constituency of Rab5 endosomes to elicit inflammatory signaling, a process causal for vascular senescence, a key mediator of healthspan. To explore ZFYVE21 in vascular senescence, we generated ZFYE21 EC-/- mice using gene targeting technology. Mice lacking ZFYVE21 in ECs developed vascular dysfunction and sequelae of age-related vascular disease including failure to thrive, renal insufficiency, hepatic insufficiency, and HFpEF. Multi-system organ dysfunction in ZFYVE21 EC-/- mice

developed by 8-12 wks of age, equivalent to 20-30 yrs of age in humans, and occurred in association with increased markers of cellular senescence. Rab5 endosomes isolated from ZFYVE21 EC-/- mice showed dramatically reduced levels of various anti-senolytic proteins including pENOS. pENOS is an EC-specific enzyme that catalyzes the formation of nitric oxide (NO), a bioactive gas well known to support EC health by upregulating genes promoting growth and tissue repair. ZFYVE21 EC-/- mice showed systemic deficits in NO generation, and NO supplementation using isosorbide improved renal insufficiency. Our data showed that an altered cohort of endosomes which we call senescence-associated endosomes (SAEs) were unable to support the stability of anti-senolytic molecules including pENOS, resulting in accelerated aging and decreased healthspan. NO-modifying drugs including isosorbide and sildenafil are used in clinical practice to treat vascular conditions including heart failure and pulmonary hypertension, respectively. Our findings open the possibility that these FDA-approved therapies could be repositioned to support vascular healthspan in aged individuals by blocking the negative systemic effects of SAEs. Based on our studies we explore the hypothesis that SAEs regulate vascular senescence. In Specific Aim 1 we will characterize changes in SAEs in aged ZFYVE21 EC-/- mice which developed clinically relevant vascular disease. Informed by these studies, in Specific Aim 2, we will examine frequencies of SAEs isolated from patient tissues from solid organ transplant recipients, and we will calculate correlations of these molecules with patient parameters including use of NO-modifying therapies. My lab has had long-standing, multi-disciplinary collaborations with Dr. George Tellides in the Dept of Cardiovascular Surgery, Dr. Jordan Pober in the Dept of Pathology, Dr. Arnar Geirsson in the Dept of Surgery, and Dr. Sanjay Kulkarni in the Dept of Transplant Surgery. My lab has numerous publications and co-PI funding awards with all these investigators who are included in this proposal. Our proposal carries important implications for age-related vascular conditions and reflects a significant divergence from our current projects. By analyzing SAEs in patient specimens and focusing on new anti-senoltyic molecules amenable to drug manipulation, our application addresses vascular senescence, a problem relevant to translational geroscience.

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. **Project Title:** **NOSI YES3 Software (2021-2023)**
   Leader: **Cynthia Brandt**
   Core(s):

   This year, we secured a supplemental NOSI grant funded by the Office of Data Science Strategy (ODSS). With the award, we are refactoring and refining high-utility software that has been used to support our most successful studies including DCare, STRIDE, SILVER-AMI, and VALIANT. The NOSI award consists of a Web Portal EM and Dashboard EM. The YES3 Web Portal EM provides researchers with an intranet platform to deliver customized group communications, study documents, announcements, and real-time performance reports. The YES3 Dashboard EM (see Diagram 1) provides a feature-rich control panel used to manage workflow; view, filter, and manage participant status; track visit windows; communicate with study staff, and monitor outcomes. The YES3 Dashboard provides the research team with an organized, real-time view into study activities and the necessary tools to manage the study protocol effectively. In turn, this can position the study to on-time data collection metrics and study milestones, improved data quality, and more efficient staff management. The code can be modified and repurposed by any REDCap software developer to allow future innovation. We will disseminate these EMs through the REDCap EM Repository and plan to feature our work within the National OAIC network and NIA Research Centers Collaborative Network (RCCN).

2. **Project Title:** **Multilevel Cosinor Analysis (2022-2023)**
   Leader: **Margaret Doyle**
   Core(s):

   This DP will extend Ms. Doyle's work with the cosinor model36,37 to allow for mul-tilevel modeling and will develop a SAS macro for implementation that will be disseminated through GRASP. This work will directly impact the analysis of the association between ambient light levels in the ICU and sleep disruption as captured by actigraphy and/or heart rate acrophase (EP-24).

3. **Project Title:** **YES3 Report Card- Ops (2022-2023)**
   Leader: **Mary Geda**
   Core(s):

   Yale Study Support Suite (YES3): Dashboard and Web Portal Software Supporting Research Workflow through integrated, customizable REDCap External Modules Specific Aim 1: To refactor, refine and repackage high utility Yale Study Support Suite (YES3) External Modules: (1.) Web Portal and (2.) Dashboard External Modules and disseminate them through the REDCap EM Repository and feature within the National OAIC network and RCCN. Specific Aim 2: Ensure the access, dissemination, and evolution of the YES3 software by (1.) establishing an opensource integrated developer workflow process that incorporates the security and validation practices published by the EM community within the REDCap Consortium (2.) by developing the required detailed technical documentation (e.g. source code documentation, UX and UI design considerations, testing documents. This work is complemented by a

supplemental NOSI award which comprises a generalizable Web Portal and Dashboard EM whose software will be interoperable with the Exporter EM. The Biostatistics Core also has a Development Project to build software for data visualization. We are maximizing resources by implementing multiple simultaneous initiatives with the intent of creating high-utility software to support research operations and analysis.

RESEARCH (0 Projects Listed)

PUBLICATIONS

2024

2023

1. **Polygenic Susceptibility to Hypertension and Blood Pressure Control in Stroke Survivors.**
   Acosta JN, Both CP, Demarais ZS, Conlon CJ, Leasure AC, Torres-Lopez VM, de Havenon A, Petersen NH, Gill TM, Sansing LH, Sheth KN, Falcone GJ
   Neurology, 2023 Apr 11, 100(15): e1587-e1597
   https://doi.org/10.1212/WNL.0000000000206763 | PMID: 36690452 | PMCID: PMC10103110
   Citations: 2 | AltScore: 9.4
2. **A multivariate joint model to adjust for random measurement error while handling skewness and correlation in dietary data in an epidemiologic study of mortality.**
   Agogo GO, Muchene L, Orindi B, Murphy TE, Mwambi H, Allore HG
   Ann Epidemiol, 2023 Jun, 82: 15-Aug
   https://doi.org/10.1016/j.annepidem.2023.03.007 | PMID: 36972757 | PMCID: PMC10239394
   Citations: NA | AltScore: NA
3. **Prior cycles of anti-CD20 antibodies affect antibody responses after repeated SARS-CoV-2 mRNA vaccination.**
   Asashima H, Kim D, Wang K, Lele N, Buitrago-Pocasangre NC, Lutz R, Cruz I, Raddassi K, Ruff WE, Racke MK, Wilson JE, Givens TS, Grifoni A, Weiskopf D, Sette A, Kleinstein SH, Montgomery RR, Shaw AC, Li F, Fan R, Hafler DA, Tomayko MM, Longbrake EE
   JCI Insight, 2023 Aug 22, 8(16):
   https://doi.org/10.1172/jci.insight.168102 | PMID: 37606046 | PMCID: PMC10543713
   Citations: NA | AltScore: NA
4. **Better but Not Well: Disability, Frailty, and Cognitive Impairment One Year after COVID-19 Critical Illness.**
   Auriemma CL, Ferrante LE
   Ann Am Thorac Soc, 2023 Feb, 20(2): 202-203
   https://doi.org/10.1513/AnnalsATS.202211-929ED | PMID: 36723478 | PMCID: PMC9989858
   Citations: NA | AltScore: NA
5. **Comparisons Between GPS-based and Self-reported Life-space Mobility in Older Adults.**
   Bai C, Zapata R, Karnati Y, Smail E, Hajduk AM, Gill TM, Ranka S, Manini TM, Mardini MT
   AMIA Annu Symp Proc, 2022, 2022: 212-220
   PMID: 37128363 | PMCID: PMC10148377
   Citations: NA | AltScore: NA
6. **Racial, Ethnic, and Rural Disparities in US Veteran COVID-19 Vaccine Rates.**
   Bernstein E, DeRycke EC, Han L, Farmer MM, Bastian LA, Bean-Mayberry B, Bade B, Brandt C, Crothers K, Skanderson M, Ruser C, Spelman J, Bazan IS, Justice AC, Rentsch CT, Akg?n KM
   AJPM Focus, 2023 Mar 24, 2(3): 100094

https://doi.org/10.1016/j.focus.2023.100094 | PMID: 37362395 | PMCID: PMC10038675
Citations: NA | AltScore: 0.5

7. **Sex Differences in Symptom Complexity and Door-to-Balloon Time in Patients With ST-Elevation Myocardial Infarction.**
Brush JE Jr, Chaudhry SI, Dreyer RP, D'Onofrio G, Greene EJ, Hajduk AM, Lu Y, Krumholz HM
Am J Cardiol, 2023 Jun 15, 197: 101-107
https://doi.org/10.1016/j.amjcard.2023.03.009 | PMID: 37062667 | PMCID: PMC10198892
Citations: 1 | AltScore: NA
8. **Effect of Exercise on Chemotherapy-Induced Peripheral Neuropathy Among Patients Treated for Ovarian Cancer: A Secondary Analysis of a Randomized Clinical Trial.**
Cao A, Cartmel B, Li FY, Gottlieb LT, Harrigan M, Ligibel JA, Gogoi R, Schwartz PE, Esserman DA, Irwin ML, Ferrucci LM
JAMA Netw Open, 2023 Aug 1, 6(8): e2326463
https://doi.org/10.1001/jamanetworkopen.2023.26463 | PMID: 37526937 | PMCID: PMC10394582
Citations: NA | AltScore: 232.63
9. **Associations Between Frailty and the Increased Risk of Adverse Outcomes Among 38,950 UK Biobank Participants With Prediabetes: Prospective Cohort Study.**
Cao X, Li X, Zhang J, Sun X, Yang G, Zhao Y, Li S, Hoogendijk EO, Wang X, Zhu Y, Allore H, Gill TM, Liu Z
JMIR Public Health Surveill, 2023 May 18, 9: e45502
https://doi.org/10.2196/45502 | PMID: 37200070 | PMCID: PMC10236284
Citations: NA | AltScore: 4.2
10. **Association of frailty with the incidence risk of cardiovascular disease and type 2 diabetes mellitus in long-term cancer survivors: a prospective cohort study.**
Cao X, Yang Z, Li X, Chen C, Hoogendijk EO, Zhang J, Yao NA, Ma L, Zhang Y, Zhu Y, Zhang X, Du Y, Wang X, Wu X, Gill TM, Liu Z
BMC Med, 2023 Feb 24, 21(1): 74
https://doi.org/10.1186/s12916-023-02774-1 | PMID: 36829175 | PMCID: PMC9951842
Citations: 3 | AltScore: 6.2
11. **Rationale, Design, and Characteristics of the VALIANT (COVID-19 in Older Adults: A Longitudinal Assessment) Cohort.**
Cohen AB, McAvay GJ, Geda M, Chattopadhyay S, Lee S, Acampora D, Araujo K, Charpentier P, Gill TM, Hajduk AM, Ferrante LE
J Am Geriatr Soc, 2023 Mar, 71(3): 832-844
https://doi.org/10.1111/jgs.18146 | PMID: 36544250 | PMCID: PMC9877652
Citations: NA | AltScore: 3.25
12. **Antibiotic therapy is associated with adverse drug events among older adults with advanced cancer: A cohort study.**
Datta R, Han L, Doyle M, Allore H, Sanft T, Quagliarello V, Juthani-Mehta M
Palliat Med, 2023 May, 37(5): 793-798
https://doi.org/10.1177/02692163231162889 | PMID: 36999898
Citations: NA | AltScore: 10.25
13. **Antimicrobial resistance in Escherichia coli and Klebsiella pneumoniae urine isolates from a national sample of home-based primary care patients with dementia.**
Datta R, Pirruccio G, Fried TR, O'Leary JR, Zullo AR, Cohen A
Infect Control Hosp Epidemiol, 2023 May 22 4-Jan

https://doi.org/10.1017/ice.2023.98 | PMID: 37211919
Citations: NA | AltScore: NA

14. **Mental Health Diagnoses are Not Associated With Indicators of Lower Quality Pain Care in Electronic Health Records of a National Sample of Veterans Treated in Veterans Health Administration Primary Care Settings.**
Dobscha SK, Luther SL, Kerns RD, Finch DK, Goulet JL, Brandt CA, Skanderson M, Bathulapalli H, Fodeh SJ, Hahm B, Bouayad L, Lee A, Han L
J Pain, 2023 Feb, 24(2): 273-281
https://doi.org/10.1016/j.jpain.2022.08.009 | PMID: 36167230 | PMCID: PMC9898089
Citations: NA | AltScore: 1.75
15. **Development and validation of a prediction model for persistent functional impairment among older ICU survivors.**
Ferrante LE, Murphy TE, Leo-Summers LS, O'Leary JR, Vander Wyk B, Pisani MA, Gill TM
J Am Geriatr Soc, 2023 Jan, 71(1): 188-197
https://doi.org/10.1111/jgs.18075 | PMID: 36196998 | PMCID: PMC9870848
Citations: NA | AltScore: 35.85
16. **Assessment of Regional Nursing Home Preparedness for and Regulatory Responsiveness to Wildfire Risk in the Western US.**
Festa N, Throgmorton KF, Davis-Plourde K, Dosa DM, Chen K, Zang E, Kelly J, Gill TM
JAMA Netw Open, 2023 Jun 1, 6(6): e2320207
https://doi.org/10.1001/jamanetworkopen.2023.20207 | PMID: 37358851 | PMCID: PMC10293909
Citations: NA | AltScore: 7.95
17. **Association of Nursing Home Exposure to Hurricane-Related Inundation With Emergency Preparedness.**
Festa N, Throgmorton KF, Heaphy N, Canavan M, Gill TM
JAMA Netw Open, 2023 Jan 3, 6(1): e2249937
https://doi.org/10.1001/jamanetworkopen.2022.49937 | PMID: 36607635 | PMCID: PMC9856665
Citations: 1 | AltScore: 35.6
18. **Emergency Department-to-Community Transitions of Care: Best Practices for the Older Adult Population.**
Gettel CJ, Hastings SN, Biese KJ, Goldberg EM
Clin Geriatr Med, 2023 Nov, 39(4): 659-672
https://doi.org/10.1016/j.cger.2023.05.009 | PMID: 37798071
Citations: NA | AltScore: NA
19. **Care transition outcome measures of importance after emergency care: Do emergency clinicians and older adults agree?**
Gettel CJ, Hwang U, Rising KL, Goldberg EM, Feder SL, Uzamere I, Venkatesh AK
Acad Emerg Med, 2023 Apr 4, 30(10): 1061-1064
https://doi.org/10.1111/acem.14732 | PMID: 37014286 | PMCID: PMC10548356
Citations: NA | AltScore: NA
20. **Distressing symptoms after major surgery among community-living older persons.**
Gill TM, Han L, Murphy TE, Feder SL, Gahbauer EA, Leo-Summers L, Becher RD
J Am Geriatr Soc, 2023 Apr 3, 71(8): 2430-2440
https://doi.org/10.1111/jgs.18357 | PMID: 37010784 | PMCID: PMC10524276
Citations: NA | AltScore: NA
21. **Stable Coronary Artery Disease in the Age of Geriatric Cardiology.**

Goyal P, Nanna MG
J Am Coll Cardiol, 2023 May 2, 81(17): 1710-1713
https://doi.org/10.1016/j.jacc.2023.03.378 | PMID: 37100487 | PMCID: PMC10395647
Citations: NA | AltScore: NA

22. **Radiomic markers of intracerebral hemorrhage expansion on non-contrast CT: independent validation and comparison with visual markers.**
Haider SP, Qureshi AI, Jain A, Tharmaseelan H, Berson ER, Zeevi T, Werring DJ, Gross M, Mak A, Malhotra A, Sansing LH, Falcone GJ, Sheth KN, Payabvash S
Front Neurosci, 2023, 17: 1225342
https://doi.org/10.3389/fnins.2023.1225342 | PMID: 37655013 | PMCID: PMC10467422
Citations: NA | AltScore: NA
23. **High Levels of Detection of Nonpneumococcal Species of Streptococcus in Saliva from Adults in the United States.**
Hislop MS, Allicock OM, Thammavongsa DA, Mbodj S, Nelson A, Shaw AC, Weinberger DM, Wyllie AL
Microbiol Spectr, 2023 Jun 15, 11(3): e0520722
https://doi.org/10.1128/spectrum.05207-22 | PMID: 37067447 | PMCID: PMC10269540
Citations: 1 | AltScore: NA
24. **Understanding multimorbidity requires sign-disease networks and higher-order interactions, a perspective.**
Hourican C, Peeters G, Melis R, Gill TM, Rikkert MO, Quax R
Front Syst Biol, 2023, 3:
pii: 1155599. https://doi.org/10.3389/fsysb.2023.1155599 | PMID: 37810371 | PMCID: PMC10557993
Citations: NA | AltScore: NA
25. **Preexisting Care Needs and Long-Term Outcomes After Mechanical Ventilation: Are We Any Closer to Informing Treatment Choices for Older Adults?**
Jain S
Crit Care Med, 2023 May 1, 51(5): 683-685
https://doi.org/10.1097/CCM.0000000000005827 | PMID: 37052439
Citations: NA | AltScore: 4.85
26. **The Plasma Cell Infiltrate Populating the Muscle Tissue of Patients with Inclusion Body Myositis Features Distinct B Cell Receptor Repertoire Properties.**
Jiang R, Roy B, Wu Q, Mohanty S, Nowak RJ, Shaw AC, Kleinstein SH, O'Connor KC
Immunohorizons, 2023 May 1, 7(5): 310-322
https://doi.org/10.4049/immunohorizons.2200078 | PMID: 37171806
Citations: NA | AltScore: 1
27. **Projecting Long-Term Care Costs for Home and Community-Based Services in China from 2005 to 2050.**
Jin H, Su Y, Ping Y, Pickersgill S, Chen X, Liu X, Watkins D, Li Y, Liu H, Wu C
J Am Med Dir Assoc, 2023 Feb, 24(2): 228-234
https://doi.org/10.1016/j.jamda.2022.11.005 | PMID: 36502859 | PMCID: PMC10134410
Citations: NA | AltScore: NA
28. **Association of Body Mass Index and Waist Circumference With Imaging Metrics of Brain Integrity and Functional Connectivity in Children Aged 9 to 10 Years in the US, 2016-2018.**
Kaltenhauser S, Weber CF, Lin H, Mozayan A, Malhotra A, Constable RT, Acosta JN, Falcone GJ, Taylor SN, Ment LR, Sheth KN, Payabvash S

JAMA Netw Open, 2023 May 1, 6(5): e2314193
https://doi.org/10.1001/jamanetworkopen.2023.14193 | PMID: 37200030 | PMCID: PMC10196880
Citations: NA | AltScore: 12.6

29. **VISTA (PD-1H) Is a Crucial Immune Regulator to Limit Pulmonary Fibrosis.**
Kim SH, Adams TS, Hu Q, Shin HJ, Chae G, Lee SE, Sharma L, Kwon HK, Lee FY, Park HJ, Huh WJ, Manning E, Kaminski N, Sauler M, Chen L, Song JW, Kim TK, Kang MJ
Am J Respir Cell Mol Biol, 2023 Jul, 69(1): 22-33
https://doi.org/10.1165/rcmb.2022-0219OC | PMID: 36450109 | PMCID: PMC10324045
Citations: 2 | AltScore: 3.85
30. **Socioeconomic and racial disparities in source-apportioned PM(2.5) levels across urban areas in the contiguous US, 2010.**
Knobel P, Hwang I, Castro E, Sheffield P, Holaday L, Shi L, Amini H, Schwartz J, Sade MY
Atmos Environ (1994), 2023 Jun 15, 303:
pii: 119753. https://doi.org/10.1016/j.atmosenv.2023.119753 | PMID: 37215166 | PMCID: PMC10194033
Citations: NA | AltScore: NA
31. **Platelet response to influenza vaccination reflects effects of aging.**
Konstorum A, Mohanty S, Zhao Y, Melillo A, Vander Wyk B, Nelson A, Tsang S, Blevins TP, Belshe RB, Chawla DG, Rondina MT, Gill TM, Montgomery RR, Allore HG, Kleinstein SH, Shaw AC
Aging Cell, 2023 Jan 19, 22(2): e13749
https://doi.org/10.1111/acel.13749 | PMID: 36656789 | PMCID: PMC9924941
Citations: 1 | AltScore: 12.3
32. **Dectin-1 stimulation promotes a distinct inflammatory signature in the setting of HIV-infection and aging.**
Kumar A, Wang J, Esterly A, Radcliffe C, Zhou H, Wyk BV, Allore HG, Tsang S, Barakat L, Mohanty S, Zhao H, Shaw AC, Zapata HJ
Aging (Albany NY), 2023 Aug 21, 15(16): 7866-7908
https://doi.org/10.18632/aging.204927 | PMID: 37606991 | PMCID: PMC10497004
Citations: NA | AltScore: 71.51
33. **Life's Essential 8: Optimizing Health in Older Adults.**
Kumar M, Orkaby A, Tighe C, Villareal DT, Billingsley H, Nanna MG, Kwak MJ, Rohant N, Patel S, Goyal P, Hummel S, Al-Malouf C, Kolimas A, Krishnaswami A, Rich MW, Kirkpatrick J, Damluji AA, Kuchel GA, Forman DE, Alexander KP
JACC Adv, 2023 Sep, 2(7):
pii: 100560. https://doi.org/10.1016/j.jacadv.2023.100560 | PMID: 37664644 | PMCID: PMC10470487
Citations: NA | AltScore: 120.45
34. **Accelerated aging mediates the associations of unhealthy lifestyles with cardiovascular disease, cancer, and mortality.**
Li X, Cao X, Zhang J, Fu J, Mohedaner M, Danzengzhuoga, Sun X, Yang G, Yang Z, Kuo CL, Chen X, Cohen AA, Liu Z
J Am Geriatr Soc, 2023 Oct 4
https://doi.org/10.1111/jgs.18611 | PMID: 37789775
Citations: NA | AltScore: NA
35. **Self-perceived memory is negatively associated with chronic disease awareness: Evidence from blood biomarker data.**

Lin Z, Fu M, Chen X
SSM Popul Health, 2023 Jun, 22: 101361
https://doi.org/10.1016/j.ssmph.2023.101361 | PMID: 36852376 | PMCID: PMC9958050
Citations: NA | AltScore: NA

36. **Racial/ethnic disparities in PM(2.5)-attributable cardiovascular mortality burden in the United States.**
Ma Y, Zang E, Opara I, Lu Y, Krumholz HM, Chen K
Nat Hum Behav, 2023 Aug 31
https://doi.org/10.1038/s41562-023-01694-7 | PMID: 37653149
Citations: NA | AltScore: NA
37. **Simulating time-to-event data subject to competing risks and clustering: A review and synthesis.**
Meng C, Esserman D, Li F, Zhao Y, Blaha O, Lu W, Wang Y, Peduzzi P, Greene EJ
Stat Methods Med Res, 2023 Feb, 32(2): 305-333
https://doi.org/10.1177/09622802221136067 | PMID: 36412111
Citations: NA | AltScore: 7.25
38. **Associations between dementia staging, neuropsychiatric behavioral symptoms, and divorce or separation in late life: A case control study.**
Monin JK, McAvay G, Zang E, Vander Wyk B, Carri?n CI, Allore H
PLoS One, 2023, 18(8): e0289311
https://doi.org/10.1371/journal.pone.0289311 | PMID: 37585365 | PMCID: PMC10431668
Citations: NA | AltScore: NA
39. **A Genomic Risk Score Identifies Individuals at High Risk for Intracerebral Hemorrhage.**
Myserlis EP, Georgakis MK, Demel SL, Sekar P, Chung J, Malik R, Hyacinth HI, Comeau ME, Falcone GJ, Langefeld CD, Rosand J, Woo D, Anderson CD
Stroke, 2023 Apr, 54(4): 973-982
https://doi.org/10.1161/STROKEAHA.122.041701 | PMID: 36799223 | PMCID: PMC10050100
Citations: 1 | AltScore: 18.6
40. **Management of Stable Angina in the Older Adult Population.**
Nanna MG, Wang SY, Damluji AA
Circ Cardiovasc Interv, 2023 Apr, 16(4): e012438
https://doi.org/10.1161/CIRCINTERVENTIONS.122.012438 | PMID: 36916288 | PMCID: PMC10121835
Citations: 1 | AltScore: NA
41. **Principal component analysis of synaptic density measured with [(11)C]UCB-J PET in early Alzheimer's disease.**
O'Dell RS, Higgins-Chen A, Gupta D, Chen MK, Naganawa M, Toyonaga T, Lu Y, Ni G, Chupak A, Zhao W, Salardini E, Nabulsi NB, Huang Y, Arnsten AFT, Carson RE, van Dyck CH, Mecca AP
Neuroimage Clin, 2023, 39: 103457
https://doi.org/10.1016/j.nicl.2023.103457 | PMID: 37422964 | PMCID: PMC10338149
Citations: NA | AltScore: 9.5
42. **A digital biomarker for aortic stenosis development and progression using deep learning for two-dimensional echocardiography.**
Oikonomou EK, Holste G, Yuan N, Coppi A, McNamara RL, Haynes N, Vora AN, Velazquez EJ, Li F, Menon V, Kapadia SR, Gill TM, Nadkarni GN, Krumholz HM, Wang Z,

Ouyang D, Khera R
medRxiv, 2023 Sep 29
pii: 2023.09.28.23296234. https://doi.org/10.1101/2023.09.28.23296234 | PMID: 37808685 | PMCID: PMC10557799
Citations: NA | AltScore: NA

43. **Association of Sociodemographic Characteristics With 1-Year Hospital Readmission Among Adults Aged 18 to 55 Years With Acute Myocardial Infarction.**
Okafor CM, Zhu C, Raparelli V, Murphy TE, Arakaki A, D'Onofrio G, Tsang SW, Smith MN, Lichtman JH, Spertus JA, Pilote L, Dreyer RP
JAMA Netw Open, 2023 Feb 1, 6(2): e2255843
https://doi.org/10.1001/jamanetworkopen.2022.55843 | PMID: 36787140 | PMCID: PMC9929697
Citations: 1 | AltScore: NA
44. **A qualitative study of coaching patient priorities-aligned decision-making through virtual case-based discussions.**
Ouellet JA, Kiwak E, Tinetti ME, Hashmi A, Ng H, Esterson J, Davenport C
J Am Geriatr Soc, 2023 Oct 3
https://doi.org/10.1111/jgs.18609 | PMID: 37787061
Citations: NA | AltScore: NA
45. **Association Between Daily Average of Mobility Achieved During Physical Therapy Sessions and Hospital-Acquired or Ventilator-Associated Pneumonia among Critically Ill Patients.**
Qi W, Murphy TE, Doyle MM, Ferrante LE
J Intensive Care Med, 2023 May, 38(5): 418-424
https://doi.org/10.1177/08850666221133318 | PMID: 36278257 | PMCID: PMC10065937
Citations: 1 | AltScore: 25.38
46. **Higher Hospital Frailty Risk Score Is Associated With Increased Risk of Stroke: Observational and Genetic Analyses.**
Renedo D, Acosta JN, Koo AB, Rivier C, Sujijantarat N, de Havenon A, Sharma R, Gill TM, Sheth KN, Falcone GJ, Matouk CC
Stroke, 2023 Jun, 54(6): 1538-1547
https://doi.org/10.1161/STROKEAHA.122.041891 | PMID: 37216451 | PMCID: PMC10212531
Citations: NA | AltScore: 9.65
47. **Polygenic Susceptibility to Hypertension and Cognitive Performance in Middle-aged Persons Without Stroke or Dementia.**
Rivier CA, Szejko N, Renedo D, Noche RB, Acosta JN, Both CP, Sharma R, Torres-Lopez VM, Payabvash S, de Havenon A, Sheth KN, Gill TM, Falcone GJ
Neurology, 2023 Aug 1, 101(5): e512-e521
https://doi.org/10.1212/WNL.0000000000207427 | PMID: 37295956 | PMCID: PMC10401683
Citations: NA | AltScore: 11.05
48. **Characteristics Associated with Spirometry Guideline Adherence in VA Patients Hospitalized with Chronic Obstructive Pulmonary Disease.**
Rodwin BA, DeRycke EC, Han L, Bade BC, Brandt CA, Bastian LA, Akg?n KM
J Gen Intern Med, 2023 Feb, 38(3): 619-626
https://doi.org/10.1007/s11606-022-07826-5 | PMID: 36241942 | PMCID: PMC9971396
Citations: NA | AltScore: 1

49. **Alveolar Vascular Remodeling in Nonspecific Interstitial Pneumonia: Replacement of Normal Lung Capillaries with COL15A1-Positive Endothelial Cells.**
Schupp JC, Manning EP, Chioccioli M, Kamp JC, Christian L, Ryu C, Herzog E, K?hnel MP, Prasse A, Kaminski N, Jonigk DD, Homer RJ, Yale-MHH-MGH Study Group
Am J Respir Crit Care Med, 2023 Oct 1, 208(7): 819-822
https://doi.org/10.1164/rccm.202303-0544LE | PMID: 37552025 | PMCID: PMC10563189
Citations: NA | AltScore: NA
50. **Feasibility of a Smartwatch Platform to Assess Ecological Mobility: Real-Time Online Assessment and Mobility?Monitor.**
Smail EJ, Alpert JM, Mardini MT, Kaufmann CN, Bai C, Gill TM, Fillingim RB, Cenko E, Zapata R, Karnati Y, Marsiske M, Ranka S, Manini TM
J Gerontol A Biol Sci Med Sci, 2023 May 11, 78(5): 821-830
https://doi.org/10.1093/gerona/glad046 | PMID: 36744611 | PMCID: PMC10172974
Citations: 1 | AltScore: NA
51. **Acute hospital use in older adults following the 2015 Dutch reform of long-term care: an interrupted time series analysis.**
Wammes JD, Bakx P, Wouterse B, Buurman BM, Murphy TE, MacNeil Vroomen JL
Lancet Healthy Longev, 2023 Jun, 4(6): e257-e264
https://doi.org/10.1016/S2666-7568(23)00064-8 | PMID: 37269863 | PMCID: PMC10316520
Citations: 1 | AltScore: NA
52. **Assessing the contributions of modifiable risk factors to serious falls and fragility fractures among older persons living with HIV.**
Womack JA, Murphy TE, Leo-Summers L, Bates J, Jarad S, Gill TM, Hsieh E, Rodriguez-Barradas MC, Tien PC, Yin MT, Brandt CA, Justice AC
J Am Geriatr Soc, 2023 Mar 13, 71(6): 1891-1901
https://doi.org/10.1111/jgs.18304 | PMID: 36912153 | PMCID: PMC10258163
Citations: NA | AltScore: 1
53. **Performance of a modified fracture risk assessment tool for fragility fracture prediction among older veterans living with HIV.**
Womack JA, Murphy TE, Leo-Summers L, Kidwai-Khan F, Skanderson M, Gill TM, Gulanski B, Rodriguez-Barradas MC, Tien PC, Yin MT, Hsieh E
AIDS, 2023 Jul 15, 37(9): 1399-1407
https://doi.org/10.1097/QAD.0000000000003566 | PMID: 37070536 | PMCID: PMC10329997
Citations: 1 | AltScore: NA
54. **Dog ownership may promote cardiometabolic health in U.S. military veterans.**
Woodward SH, Baldassarri SR, Pietrzak RH
Sci Rep, 2023 Jul 8, 13(1): 11075
https://doi.org/10.1038/s41598-023-38038-4 | PMID: 37422586 | PMCID: PMC10329684
Citations: NA | AltScore: NA
55. **Whole-Exome Sequencing Analyses Support a Role of Vitamin D Metabolism in Ischemic Stroke.**
Xie Y, Acosta JN, Ye Y, Demarais ZS, Conlon CJ, Chen M, Zhao H, Falcone GJ
Stroke, 2023 Mar, 54(3): 800-809
https://doi.org/10.1161/STROKEAHA.122.040883 | PMID: 36762557 | PMCID: PMC10467223
Citations: NA | AltScore: NA
56. **Association of childhood adversity with frailty and the mediating role of unhealthy**

lifestyle: Findings from the UK biobank.
Yang G, Cao X, Yu J, Li X, Zhang L, Zhang J, Ma C, Zhang N, Lu Q, Wu C, Chen X, Hoogendijk EO, Gill TM, Liu Z
medRxiv, 2023 Feb 10
pii: 2023.02.08.23285634. https://doi.org/10.1101/2023.02.08.23285634 | PMID: 36798168 | PMCID: PMC9934802
Citations: NA | AltScore: NA

57. **A genome-wide association study of frailty identifies significant genetic correlation with neuropsychiatric, cardiovascular, and inflammation pathways.**
Ye Y, Noche RB, Szejko N, Both CP, Acosta JN, Leasure AC, Brown SC, Sheth KN, Gill TM, Zhao H, Falcone GJ
Geroscience, 2023 Mar 16
https://doi.org/10.1007/s11357-023-00771-z | PMID: 36928559
Citations: 4 | AltScore: 10.55
58. **Long-term air pollution exposure and diabetes risk in American older adults: A national secondary data-based cohort study.**
Yitshak Sade M, Shi L, Colicino E, Amini H, Schwartz JD, Di Q, Wright RO
Environ Pollut, 2023 Mar 1, 320: 121056
https://doi.org/10.1016/j.envpol.2023.121056 | PMID: 36634862 | PMCID: PMC9905312
Citations: 1 | AltScore: 13.15
59. **Explaining obesity disparities by urbanicity, 2006 to 2016: A decomposition analysis.**
Zang E, Flores Morales J, Luo L, Baid D
Obesity (Silver Spring), 2023 Feb, 31(2): 487-495
https://doi.org/10.1002/oby.23608 | PMID: 36621926 | PMCID: PMC9877136
Citations: NA | AltScore: NA
60. **The mobility effects hypothesis: Methods and applications.**
Zang E, Sobel ME, Luo L
Soc Sci Res, 2023 Feb, 110: 102818
https://doi.org/10.1016/j.ssresearch.2022.102818 | PMID: 36796994 | PMCID: PMC9936082
Citations: 1 | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

Heather Whitson, MD
Duke University School of Medicine & Durham VA Medical Center
Serving since 2016 (8 years)

Neil Alexander, M.D., M.S.
University of Michigan
Serving since 2016 (8 years)

George Kuchel
University of Connecticut
Serving since 2023 (1 years)

Sara Espinoza
University of Texas Health Science Center
Serving since 2023 (1 years)

RECOGNITION AND AWARDS (2023-2024)

Recognition and Awards not specified.

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Lauren Ferrante, Assistant Professor of Medicine (Pulmonary); Director, Operations Core, Yale Claude D. Pepper Older Americans Independence Center
  Lauren Ferrante, MD, MHS, assistant professor of medicine (pulmonary, critical care, & sleep medicine), is the Director of the Operations Core and serves as a member of the Yale OAIC Executive Committee, which meets bimonthly.

No minority grant information specified.