

Duke University Medical Center
Claude D. Pepper Older Americans Independence Center

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SECTION I. DESCRIPTION OF CENTER

The overall goal of the Duke Claude D. Pepper Older Americans Independence Center (Duke OAIC) is to support research and training that improves the independence of older Americans. Our primary focus: *To understand and optimize reserve and resilience*. Our approach is founded on the insight that independence in older adults is related to an individual's ability to withstand or recover from functional decline following acute or chronic health stressors. Our overall strategy for the OAIC is to serve as a sustained resource to our investigators through a broad range of training and research studies; the goal will be to address knowledge gaps in our focus with an emphasis on translational and interdisciplinary research. We recruit and develop early stage investigators in aging research related to our focus and utilize the substantial strengths of the Duke academic and health system environment to advance our focus.

The Duke Pepper Center has been at the forefront of geriatric research and training focused on the development of interventions to improve the functional status of older adults and the support of research that identifies risk factors predictive of functional decline. The Duke Pepper Center originally began its funding as a Geriatric Research and Training Center (GRTC) in 1991. The GRTC was originally funded with three research cores and support for junior faculty and pilot projects, which reflects the organization of the current OAIC structure. One year later, Duke was awarded a Pepper Center and, at the direction of the National Institute on Aging, the two programs were combined into one. Initial Pepper Center support focused on the development of promising interventions to promote the independence of older Americans and faculty development. Since then, the Duke OAIC has produced an impressive portfolio of relevant research and innovations in faculty development.

The specific goals of the Duke Pepper Center are:

- 1) To better understand and optimize reserve and resilience in older adults through an integrated research program.
- 2) To develop and evaluate new methods that advance the study of reserve and resilience.
- 3) To support pilot studies through the PESC that acquire information needed to select or design, more definitive research studies related to the Duke OAIC focus.
- 4) To identify and develop the next generation of researchers who will become leaders in aging and geriatrics research related to the Duke OAIC focus.

SECTION II. RESEARCH, RESOURCES, AND ACTIVITIES

A. CORES

Resource Cores

Molecular Measures Core (Resource Core 1)

Virginia B. Kraus, MD, PhD, Core Leader

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Molecular profiling can uniquely discover biomarkers, and predict and monitor traits and processes to understand and optimize reserve and resilience. The goal of the Molecular Measures Core is to promote an understanding of the means to optimize whole person reserve and resilience through analyses of molecular factors indicative of cellular and tissue level ability to withstand and recover from stressors. The Molecular Measures Core complements the whole person level analyses offered through the Physical Measures Core and is inter-dependent with the Analysis Core, which is responsible for statistical analysis and modeling of data generated by the Physical Measures Core and Molecular Measures Core. The Molecular Measures Core has extensive molecular profiling capabilities, including, among others: inflammatory, metabolic, tissue matrix, genetic and genomic analyses. The Molecular Measures Core has capabilities to expand and adapt existing core capabilities to facilitate the many needs of the novel investigator-initiated research projects affiliated with our Duke OAIC.

The specific aims of the Molecular Measures Core are to:

- 1) Perform molecular analyses to support and assist research projects of the Duke OAIC.
- 2) Develop new molecular profiling and testing capabilities to evaluate cellular, tissue, and organ resiliencies.
- 3) Perform systems pathway analyses to identify biological pathways indicative of resilient phenotypes.
- 4) Serve as a resource for research-oriented advice and training on principles and methods of molecular analyses.

Physical Measures Core (Resource Core 2)

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The Physical Measures Core serves as the central resource for Center investigators seeking advice, training, laboratory access, and equipment for valid, sensitive, and reliable physical/ no biological measures. A panel of 13 members, with complementary expertise in measurement across multiple domains, comprises the Core and provides highly integrated, customized support

to investigators supported by our Research Education Component, Pilot/Exploratory Studies Core, Externally Funded Projects, and the larger Duke Community engaged by the Duke OAIC. The PMC supports investigators by meeting regularly throughout the full spectrum of project development, from early phase planning, to final interpretation of findings, to subsequent grant preparations, to dissemination and/or implementation. These meetings concurrently involve members of the Analysis and Molecular Measures Cores to assure maximal synergy.

The specific aims of the Physical Measures Core are to:

- 1) Provide centralized expertise available for consultation on the measurement of reserve and resilience.
- 2) Develop measurement protocols and train personnel in administration and data collection.
- 3) Identify gaps in resiliency measures and develop or adapt innovative new measurement approaches across the adult lifespan for related outcomes.

Analysis Core (Resource Core 3)

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The Analysis Core provides specialized expertise in the design, collection, and management of data, and in analytic methodologies. The Analysis Core promotes novel lines of research by developing new methods specifically targeted to detect and measure reserve and resilience. Finally, the Analysis Core supports training objectives by developing fellow and faculty understanding of biostatistics and research methodology—critical areas of the research enterprise that are typically a knowledge gap in basic, translational, and clinical researchers.

The Analysis Core works closely with other components of the Duke OIAC to achieve shared goals. The Analysis Core collaborates with the two Resource Cores (Molecular Measures Core and Physical Measures Core) to manage data and perform analyses. The Analysis Core collaborates with OAIC investigators to direct study design and analysis, to insure studies are properly powered and address targeted research questions. Furthermore, the Analysis Core is uniquely positioned to expand studies to evaluate additional or emerging hypotheses, including those that support methodologic investigations in statistical science, a unique goal of this Core.

The specific aims of the Analysis Core are to:

- 1) Provide data management and analytic support to funded and proposed projects, pilots, and junior faculty and OAIC investigations to enable research and to address hypotheses within our theme.
- 2) Develop and disseminate analytic methodologies in biostatistics to advance the study of resilience and reserve.
- 3) Provide training and mentoring to the fellows and faculty in the Duke OAIC.

Other Cores

Pilot/ Exploratory Studies Core (PESC)

Heather Whitson, MD, MHS, Core Leader

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The Pilot/Exploratory Studies Core emphasizes physiological reserve at the cell/tissue/organ level, which we hypothesize is a key contributor to resilience at the whole person level. The PESC impacts public health by performing studies that develop knowledge to maintain or recover independence in older Americans, by promoting reserve and resilience in the face of chronic and acute stressors. We use small exploratory pilot monies as a rapid response mechanism to take advantage of cutting edge areas. The PESC solicits and selects high quality pilot studies from across Duke University Medical Center using a rigorous, multi-stage process that incorporates internal and external review. The PESC carefully monitors study progress and assists in the development of larger grant proposals from pilot study findings. The Duke PESC includes several highly innovative features: 1) the Pilot Grants Workshop, developed by OAIC Director Kenneth Schmader and frequently requested in national venues, 2) the inclusion of patient/community representatives on the Review Panel that selects pilots, 3) the Data Integration Working Group, which is a central hub for scientific development, oversight, and translation, and 4) mechanisms that support the science and careers of unfunded pilot study applicants.

The specific aims of the Pilot/ Exploratory Studies Core are to:

1. Advance top quality science related to late-life reserve and resilience.
2. Attract and nurture a diverse cadre of outstanding early investigators in aging research or established investigators pursuing promising new directions related to our theme.
3. Build and sustain relationships with critical stakeholders to maximize the impact and translation of the work conducted through this and future OAICs.

Research Education Component (REC)

Cathleen Colón-Emeric, MD, MHS, Core Leader

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The objective of the Research Education Component is to develop the next generation of researchers who will become leaders in integrating basic science and clinical insights into innovative interventions promoting reserve and resilience in late life.

Guided by educators in the Aging Center with nationally recognized expertise in curriculum development and evaluation, the REC measures the impact of OAIC programs on Scholars' career progression using innovative evaluation methods such as nominal group sessions. We

have established a close partnership with the Duke Clinical Translational Science Award Center (CTSA) KL2 program to enhance scholar recruitment and to share curriculum and resources; the Duke OAIC REC and CTSA share the same co-leader and project director to facilitate interactions. The School of Medicine offers excellent professional development programs, research leadership training, and grant-writing education and support services that are utilized by our scholars.

The specific aims of the Research Education Component are to:

1. Coordinate delivery of aging research curriculum to early investigators across the University.
2. Provide a structure for individualized aging and research mentorship at Duke.
3. Evaluate the effectiveness of aging research across the Duke OAIC.

Leadership and Administrative Core

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The Leadership and Administrative Core (LAC) provides the scientific leadership and administrative infrastructure to create a robust environment for aging and geriatrics research in our theme. The Leadership and Administrative Core promotes the development of early investigators with interests in aging and geriatrics research and ensures the coordination, integration, funding, and translation of research within the Duke OAIC, a mission that supports our ultimate goal of improving the independence of older adults.

The specific aims of the Leadership and Administrative Core are to:

- 1) To provide overall coordination, integration, and administration of the Duke OAIC.
- 2) To stimulate, assist, monitor and evaluate the progress of the OAIC towards achieving the research and education goals of the Duke OAIC.
- 3) To assess scientific opportunities for innovative research in our theme with an emphasis on translational and interdisciplinary research.
- 4) To utilize and develop resources effectively to meet the goals of the Duke Pepper OAIC.

B. RESEARCH:

The Duke OAIC's research focus is **to understand and optimize reserve and resilience**. This work, supported by decades of basic, clinical, and translational research in our Center, posits that an older adult's long-term functional trajectory is deeply influenced by their response to acute and chronic stressors. The ability to resist or recover from functional decline following acute and/or chronic stressors is critical to independence. We have shifted in focus from '*decline*' to '*enhancement*' with an integrated research program that facilitates growth in our understanding of mechanistic, physiologic, psychosocial, and environmental contributors to improved health and well-being of both 'aging' and 'older' adults. Building on insights from our past work on "understanding and modifying multiple pathways of functional decline", we now focus on two ways to maximize independence: 1) optimizing physiological reserve – defined as the potential capacity of a cell, organ, tissue, or organ system to function beyond its basal level in response to alterations in physiologic demands; and 2) optimizing physical resilience – defined as an individual's ability to withstand or recover from functional decline following health stressors. An integrated approach examining the interplay between contributors to the constructs of reserve and resilience may elucidate why some seemingly frail individuals are resilient while some seemingly robust individuals are not, and allow us to develop appropriately targeted interventions.

Our OAIC developed a **Data Integration Working Group (DIWG)** to avoid research "silos" and connect researchers through our scientific meetings. The DIWG has long served as the mechanism through which center-wide research questions are developed and addressed, and the work of emerging Pepper Scholars is mentored and developed. It is an essential, permanent, and programmatic service for our center investigators. It integrates basic, translational, and clinical research across the OIAC by providing a biweekly venue for all ongoing science to be reviewed in a "lab meeting" setting. LAC members, Principal Investigators, investigative teams, REC Scholars, Pilot Awardees and Developmental Project PIs meet to confirm, generate, collate, integrate and interpret the significance of the data from molecular, physiologic and clinical research. It is within this venue, with the interface between basic, clinical and statistical researchers, that some of our best new translational approaches are developed. The DIWG provides a learning experience for trainees and enables OAIC research teams to generate new ideas and advances to provide a forum for collaborative research activities and accessible Core expertise. Our primary research efforts are twofold: 1) To support the investigations of our young Pepper Center Scholars and 2) To tackle overarching research questions. All REC and Pilot Study awardees are designated **Pepper Center Scholars** – a designation that extends beyond any particular funding period as we continue to develop and support our Scholars well beyond initial funding support.

The Ongoing REC Pepper Center Scholars and associated Research interests are:

Corey Simon, DPT, Assistant Professor, Department of Orthopaedic Surgery

Project period 6/2018-5/2020 (REC Study): *Physical Resilience to Pain with Activity Influences among Seniors (PRAISE) – Feasibility Study*. The long-term objective of my research is to develop tailored multi-factorial interventions that prevent disability among older adults with low back pain. Low back pain poses a major risk to senior health, as it is the global leader in years lived with disability and strongly associated with mobility disability. However, it is not clear why some older adults with low back pain succumb to mobility disability, while others do not. This aim of my REC study was to determine the feasibility of assessing three factors that may explain mobility disability among older adults with low back pain: pain with activity, fear of

movement, and dynamic inflammatory response to movement. Findings of this study will facilitate a vigorous research program to elucidate the extent to which these and other intrinsic factors predict downstream (i.e. 1-year) mobility disability; which in turn, will inform development of future tailored multi-factorial interventions for older adults with low back pain. I completed recruitment and data collection for 39 participants in my REC study, which exceeded my target goal (n=30). I am now working with my Pepper Center mentors to analyze data and prepare for scientific dissemination. In addition, my REC study provided important preliminary data for my K23 study application submitted to the NIA in June 2019 and I was recently awarded an NIA Loan Repayment Award.

Anthony Sung, MD, PhD, Assistant Professor, Department of Medicine, Division of Oncology
Project period 6/2018-5/2020 (REC Study): *High intensity interval training to improve pre- and peri-transplant function and outcomes.* Allogeneic hematopoietic stem cell transplant (HCT) has the potential to cure patients with hematologic malignancies. However, HCT is associated with significant treatment related mortality (TRM) ranging from 20-30%. TRM is particularly high in patients with advanced age (hazard ratio 1.84, age >60 years vs. <20) and decreased physical function (hazard ratio 2.94, bottom quartile vs. top quartile). There exists an opportunity to improve physical function during the 2-4 month window (median 101 days at Duke). The 2-4 month window of opportunity is between new patient evaluation and start of transplant with intervention programs such as high intensity interval training (HIIT). HIIT alternates short periods of intense anaerobic exercise with less intense recovery periods. Workouts typically last less than 30 min and are targeted to patients predicated maximum heart rate, allowing adjustment for age. While less intense exercise programs have failed to show an improvement in HCT outcomes, studies in the general population suggest that HIIT improves physical function and conditioning more than moderate intensity training programs. We hypothesize that in patients with advanced age, HIIT will improve pre-HCT physical function and post-HCT outcomes including TRM. We have been awarded NIA 1R21AG066388-01 on Evaluating Effects Of Age-Related Microbiota Modulations in Hematopoietic Stem Cell Transplant Patients.

Nazema Siddiqui, MD, MHS Associate Professor, Department of Obstetrics and Gynecology
Project period 6/2018-5/2020 (REC Study): *Effects of Aging and the Urinary Microbiome on Recurrent Urinary Tract Infections.* The urinary microbiome is a potential factor that could influence recurrent UTIs with aging. We now have significant evidence that a urinary microbiome exists, and that dysbiosis may be associated with disease. Studies show that lactobacilli are abundant in some urinary environments, but also that other heterogeneous genera are recovered from the urinary tracts of women without clinical UTI. Using this information, women can be grouped into "urotypes" based on the presence and predominance of different microbes. However, we have major gaps in our understanding of how these urotypes change with aging and whether specific urotypes are associated with recurrent UTI.

The objective of the proposed research is to improve our understanding of the microbes that occupy the urinary niche, how these microbes change with aging, and to determine whether particular urotypes are associated with postmenopausal recurrent UTI. Understanding how the urinary microbiome, and particularly how urinary lactobacilli change with aging and in the presence of estrogen is critical to this effort. Based on preliminary data from other studies in women, we *hypothesize* that urinary lactobacilli decrease after menopause, and that vaginal estrogen therapy facilitates recovery of lactobacillus abundance in urine. Furthermore, we hypothesize that there are urotypes that are associated with recurrent UTIs despite the presence of vaginal estrogen.

Physical Measurement Core Health Innovations and Technology Awards

Kevin Caves, ME, Departments of Medicine, Biomedical Engineering and Surgery Works in Progress (PMC Health Innovation project).

Project #1 (project period ending), “Integrating digital technology in the development of a new tool to measure mobility in older adults.” Project #1 Overview: Mr. Caves and his team developed the Gaitbox, a compact digital device that automatically records, stores, and displays walking speed. Mr. Caves has initiated new collaborations with Dr. Sandy Throckmorton, of Signal Analysis Solutions, LLC to pursue SBIR funding for the Gaitbox device. **Project #2**, “Developing a new activity monitoring device and analysis software to assess and analyze mobility in older adults in inpatient settings.” Project #2 Overview: Mr. Caves and his team have created a novel tool that uses two Inertial Measurement Units (IMUs) positioned on the body, and predictive analytic techniques and machine learning, to distinguish between lying, sitting, and standing body positions. They have also created an approachable user interface app (ImUP) that provides summative data and recommendations for patients and providers. Refinement work with clinical partners is ongoing. This project is in direct response to technology needs identified by Pepper investigators to detect and classify individual body positioning and mobility in the inpatient setting.

Jaime Hughes, PhD, Newly awarded work in progress (2019 Emerging Discovery/Health Innovation project). “Developing sensor-triggered ecological momentary assessment (EMA) diaries to monitor older adults’ sleep-activity behaviors.” Project Overview: This project involves developing a mobile app with a sensor based EMA system, which will analyze real-time activity data using machine trained algorithms. Sensor-based event prompts will query the participant about the physical and social surroundings, current type(s) of activity/inactivity, pain, and fatigue. Dr. Hughes will work closely with the PMC and Mr. Caves to develop this tool and evaluate feasibility and acceptability among older adults.

Ongoing Overarching Pepper Center Research/ Advances in Reserve and Resilience

UH2AG056925 on resilience (Drs. Colón-Emeric and Whitson)

Physical Resiliencies: Indicators and Mechanisms in the Elderly Collaborative

Physical resilience, defined as the ability to maintain or recover function following a stressor, is central to one’s ability to live long and well; however, the predictors and mechanisms of age-related changes in physical resilience remain undefined. Challenges to progress include a lack of standard definitions and validated measures. To fill this gap, we launched the PRIME Collaborative – Physical Resilience: Indicators and Mechanisms in the Elderly. The PRIME Collaborative is a multi-institutional collaboration organized into three working groups, each focusing on a specific type of resiliency. Our objectives are to characterize specific resiliency phenotypes, elucidate biological mechanisms, and validate clinically valuable tests of three resiliency domains: musculoskeletal resilience after hip replacement, cognitive resilience after elective surgery/anesthesia, and immunological resilience after infection. In its first two years, the PRIME Collaborative operationalized two approaches for quantifying the degree of resilience following health stressors. In one cohort, we identified a set of biomarkers that explain almost 40% of the variance in resilience after hip fracture. We identified a novel metric derived from

EEG data collected before and during surgery that predicted attention scores on Day 1 post-operatively. Two teams are evaluating whether transcriptomic profiles predict response to influenza vaccine or viral respiratory infections. This project is entering its second phase in which provocative tests, biomarkers and phenotypes identified will be validated in an elective knee replacement cohort.

Advances in Molecular Profiling. In addition to providing molecular analyses to Pepper affiliated pilot projects, research scholars, and large external studies, the molecular measures core also provides training in molecular measures and is constantly developing and updating analytic capabilities. Some areas of particular interest and expertise relate to analysis of microRNA--master regulators of gene expression--and their change with age, resilience, and longevity. We are in the process of analyzing microRNA and their relationship with outcomes (such as insulin sensitivity, aerobic capacity and biological age) in large data sets including EPESE (focused on longevity), STRRIDE (exercise trials) and CALERIE (caloric restriction trial). We have also developed model systems and methodology to assess senescence phenotypes. In addition, we have expertise and interest in metabolism. One such study for which we provide ongoing support relates to metabolism of unintentional weight loss in elders. Unintentional weight loss in the elderly is associated with loss of resilience, and increased morbidity and mortality. The underlying pathophysiology is poorly understood. We have performed metabolomic analysis of serum from elders enrolled in the CHS All Stars study, comparing those with intentional and unintentional weight loss to matched, weight-stable controls. This study is a follow-up to the Cardiovascular Health Study (CHS), focusing on longitudinal observations of health outcomes in long-term survivors (the "All Stars"). Our collaborators are Drs. Stephen B. Kritchevsky and Mary Elizabeth Baugh at Wake Forest University and Dr. Anne B. Newman at the University of Pittsburgh. Data analysis is underway.

Other. We supported three new applications to advance the science of our thematic focus.

Intervention Development in Elderly Adults (IDEA) Workshop

The Overall Objective of the IDEA Workshop is to support Pepper Scholars and other early investigators in developing and testing effective complex interventions targeting older populations. Participants included 10 Pepper Scholars and other junior faculty at various stages of intervention development. Led by REC leader Colón-Emeric, Pepper faculty and other experts led semi-structured workshops with 7 sessions scheduled roughly bi-weekly, 1.5 hours. Objectives and background readings were provided prior to each session. Sessions were organized around the Medical Research Council framework for the development and evaluation of complex interventions to improve health. Faculty facilitators gave 20-30 min presentation reviewing key points, case study examples, providing materials/highlighting resources, identifying self-study materials. Remainder of time was discussion, small group work, problem-solving around the scholars' research area. This program has expanded to include not just Pepper Scholars, but REACH Equity Center Scholars, Duke CTSI KL2 Scholars, VA Quality Scholars, and Roybal Center Scholars, offering a new venue for collaborative relationships.

Pepper Shakers

In response to evaluations, we have initiated quarterly informal meetings for scholars to hear about each others' work and interact with Pepper faculty across the campus. Early evening meetings have offered networking opportunities, tours of relevant research buildings (e.g., Duke

Molecular Physiology Institute, Duke Diet and Fitness Center, K Lab), sharing research resources (e.g., Physical Measure Core website of performance measure SOPs), and reading hot new articles in the field.

Lifespan Studies of Physical Function, Reserve and Resilience

Externally Funded Lifespan Studies

Over our past funded research cycles we combined data from a series of cohort studies and clinical trials with common measures to represent a full adult life span. From these diverse studies, we developed analytic methods to reduce large numbers of biological markers and published papers describing the association between metabolic markers, age, and body mass index, and examined the impact of multiple inflammatory markers on physical function.

Molecular measures of inflammation and metabolism were also used to develop combined biomarker Indices of Robustness and Impairment using walking speed as a measure of fitness (X. Zuo et al JAGS 2018,66(7)1353-1359, PMID 29738072 DOI:10.1111/jgs.15393). Of interest while these indices contained some biomarkers in common, there were markers unique to the robustness index, and others unique to the impairment index suggesting that these are not simply opposite ends of the same biologic spectrum but may be mediated by somewhat different pathways.. We have begun analyses of these and other immunologic and metabolite measures in the PALS cohort to validate these indices and to explore new techniques for analysis. (See below).

Physical Performance Across the Lifespan (PALS) (Morey and Cohen, Co-PIs)

The PALS study, PIs Dr. Miriam Morey and Dr. Harvey Cohen, is a longitudinal cohort study created by the Duke OAIC (Pepper) Center during a prior funding cycle. The overall objective of the PALS study is to examine patterns of age and sex-related differences in biological markers, physical function, and physical activity across the adult lifespan, and to longitudinally characterize changes in biological markers and the association of these changes with functional aging. The design of PALS—in particular, the inclusion of young adults—was motivated by the recognition that biological aging occurs across the lifespan, not just among the aged. The recruitment phase for the PALS study was 2013-2016, and the 2-year follow-up data collection phase spans 2015-2018. Study assessments were completed in-person at baseline and at 2-years, with interim MURDOCK telephone surveys conducted yearly (and planned to continue indefinitely).

Study participants were drawn from the Measurement to Understand the Reclassification of Disease of Cabarrus/Kannapolis (MURDOCK) registry. Study participants were eligible if they were (a) at least 30 years of age; (b) residents of 20-Zip Code region that included Cabarrus and portions of surrounding Counties and the city of Kannapolis in North Carolina for at least 6 months; and (c) provided written informed consent. All potential participants were scheduled for an in-person baseline study visit, during which time informed consent, HIPAA authorization, and study measures were administered. Demographic variables (education, race, and ethnicity) are collected by self-report. Other measures include surveys of self-reported health and behaviors, physical performance measures, accelerometry, and blood samples in a non-fasting state that are stored for future investigations. Enrolled participants (N=1000) were stratified in equal numbers by decade of life with a target of 100 participants per decade divided equally between men and women from age 30 to 59, 200 per decade from age 60 to 79, and all interested participants over age 80. Six participants subsequently rescinded permission for use of data (Visit 1 working

n=994) with 692 participants completing assessments at Year 2. One manuscript, published this year, found that biological degradations occurred early in mid life and prior to noted impairments in physical function. (Parker D, Sloane R, Pieper CF, Hall KS, Kraus VB, Kraus WE, Huebner JL, Ilkayeva OR, Bain JR, Newby LK, Cohen HJ, Morey MC. Age-Related Adverse Inflammatory and Metabolic Changes Begin Early in Adulthood *J Gerontol A Biol Sci Med Sci*. 2019 Feb 15;74(3):283-289. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6376106/>). This finding coupled with a paper published last year by our team, which reported that physical function declined earlier in the lifespan than previously reported in the literature supports our lifespan approach for investigations in this area. Several manuscripts reporting longitudinal findings are underway.

Aging in 1000 Healthy Young Adults: The DUNEDIN Study

(NIA-R01AG032282-06, 2009-2020, Moffitt, T, PI) (NIA R01AG049789) “Neural signatures of healthy and unhealthy aging: The Dunedin Study, 2015-2020, Moffitt, T and Hariri, A, joint PIs)

The Dunedin Study is a longitudinal investigation of health and behavior in a representative birth cohort followed from birth to midlife. Participants (N=1,037; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand (NZ), who were eligible based on residence in the province at age 3 years. Assessments have been carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently at age 45 years, when 94.1% (N=938) of the 997 participants still alive took part (completed April 2019). The cohort represents the full range of socioeconomic status (SES) in the general population of NZ’s South Island, and as adults matches the NZ National Health and Nutrition Survey on key adult health indicators (e.g., body mass index (BMI), smoking, GP visits) and the NZ Census of citizens of the same age on educational attainment. Participants are primarily white (93%), matching South Island demographics. At age 45, each participant was brought to the research unit for a day and a half of interviews and examinations. Of 997 still-living cohort members, 875 (87.8%) completed MRI scanning in 2017-2019 during their age-45 assessment. MRI-scanned Study members did not differ from full cohort members on childhood IQ (M = 100 vs. M = 101) and family-of-origin socio-economic status (M = 3.76 vs. M = 3.75).

The inclusion of the Dunedin Study as part of our Duke OAIC provides a unique opportunity to gain insights into resilience in the context of an exceptionally well-phenotyped longitudinal cohort as it enters middle age. The OAIC provided a functional assessment battery for the age-45 assessments funded by the NIA. At present, we are conducting analysis of DNA methylation measured from blood samples taken when Dunedin Study members were aged 26 years and again when they were aged 38 years. the goal of these analyses is to establish DNA methylation-based measurements of biological aging that capture variation in the rate of biological aging occurring during the period spanning age 26, 32, 38 and 45. We also have a manuscript in review positing gait speed as a life long indicator of health as opposed to the current view of gait speed as a late-life indicator of health.

Advances in Statistical Methodology

Drs. Pieper and Pendergast, in collaboration with Mr. Bida Gu, a Biostatistics graduate student, completed a simulation study comparing the performance of latent class trajectory models and growth mixture models under a variety of settings and assumption violations. Capabilities and differences between two common software programs for implementing these types of analyses,

(Mplus and the SAS add-on TRAJ procedure) were highlighted in the simulation study. A manuscript describing the results of this study and importance of awareness of highlighted issues when using these methodologies has been submitted. Extensions of this work are being pursued with Dr. Megan Neely, an Asst. Professor in the Biostatistics department. .

C. PILOT PROJECTS

2018-2020 Pilot Projects and Pilot Pepper Scholar Interests are included:

Mihai Podgoreanu, MD Associate Professor of Anesthesiology (Pilot Study)
Metabolic Modifiers and Rehabilitation Phenotypes in Older Adults Subjected to Extracorporeal Support (METAMORPHOSES). The aims of this pilot study are: 1) to determine the feasibility of recruitment and data collection protocols needed to estimate functional trajectories among Duke extracorporeal membrane oxygenation (ECMO) patients receiving intensive care unit (ICU) rehabilitation and 2) to determine the feasibility of sample collection and processing protocols needed to quantify metabolic markers that may correlate to recovery phenotypes. In the first year of his funding, Dr. Podgoreanu and his team have obtained IRB approval for the physical measurements and sample collection in this vulnerable population. Staff have been hired and trained and recruitment began this month. The team plans to complete data collection and sample storage on 20 ECMO patients who are receiving ICU rehabilitation over the second year of funding.

JJ Strouse, MD Associate Professor of Medicine and Pediatrics and **Charity Oyedeji, MD** Hematology Fellow (Pilot Study)
Focused Geriatric Assessment in Older Adults with Sickle Cell Disease. The aims of this pilot study are: 1) To evaluate the feasibility of focused geriatric assessment in twenty older adults (age 50 years or older) with sickle cell disease, 2) to assess the feasibility of a protocol to measure resilience of older adults with sickle cell disease after hospitalization, 3) to estimate the variability of biomarkers of inflammation, coagulation, and longevity in 20 older adults with sickle cell disease. Thus far, the team has completed collection of data and blood samples on 16 of 20 participants. Participants have tolerated the assessments and physical performance testing well, with no complications of sickle cell disease or other adverse events. The protocol calls for additional assessments after unplanned hospitalizations during the follow-up period and some hospitalizations have already occurred in the cohort, suggesting that the protocol will be a feasible means of capturing predictors of recovery patterns after unplanned hospitalizations in this population.

David Bartlett, PhD, Assistant Professor of Medicine (Pilot Study)
Exercise Training in Seniors with CLL: EMPHASIS Study The aims of this pilot study are: 1) To determine changes in physical reserve (aerobic capacity and strength) following 12-weeks of supervised exercise training in older adults with CLL and 2) To determine the relationships between changes in aerobic capacity and immunological mediators of improved resilience against CLL. In both non-exercise (n=10) and exercise (n=10) groups, Dr. Bartlett's team is assessing immunological reserve by changes in 1)lymphocyte doubling rate 2)neutrophil: lymphocyte and lymphocyte: monocyte ratios 3) NK-cell tumor cytotoxicity and 4) bacterial phagocytosis. The team has consented 14 of 20 participants and successfully randomized them

to the exercise and non-exercise study arms. Thus far, those who have completed the exercise intervention have had good adherence to the protocol. Recruitment and data collection are ongoing.

AnnaMae Diehl, MD Professor of Medicine (Exploratory Funds Recipient 2019)
Aging Effects on Hepatocyte Reprogramming and Liver Repair

The Diehl lab's studies on liver regeneration in young adult rodents reveal a signaling network that controls adult-to-fetal and fetal-to-adult reprogramming in hepatocytes. These findings extend work by others showing that the Hippo Kinase (HK) pathway and its downstream target, Yap1, critically regulate regenerative reprogramming in hepatocytes. Moreover, long-lived somatic cells of organs that are inherently less resilient than the liver can be coaxed to undergo the adult-to-fetal reprogramming process that occurs naturally in adult hepatocytes when they activate endogenous Yap1 during a regenerative stress. The Diehl lab seeks to advance knowledge that ultimately can be applied to promote more favorable response to stressors in a variety of aging tissues. The effect of age on the reprogramming signaling of hepatocytes, which is critical to their regenerative capacity, is unknown. The immediate objective is to evaluate young and old hepatocytes/livers pre- and post- regenerative challenges (e.g., partial hepatectomy) to identify aging-sensitive mechanisms that control endogenous HK signaling/Yap1 activity. Exploratory funding from the Pepper Center enables the Diehl lab to obtain aged mice from NIA and secure supplies and post-doctoral time to conduct the comparative experiment.

SECTION III. CAREER DEVELOPMENT (RECENT) AND SUBSEQUENT FUNDING

Recent RCDC Scholars

Richard Lee, MD

Medicine – Geriatrics/ Endocrinology
Duke University Medical Center
Durham, NC
RCD Supported (2013-2015)

Work in Progress: Two investigations to explore his hypothesis that increased functional impairment contributes significantly to the increased fracture risk in older patients with diabetes.

Subsequent funding

GEMSSTAR award 10/1/14-9/30/16: Aim: To identify potential novel biomarkers or pathways using metabolomics, associated with increased fracture risk, independent of bone mineral density, among older adults with diabetes.

American Diabetes Association 7/1/14-6/30/16

NIH Loan Repayment Program 7/1/14-6/30/16

NIA K23 award 6/1/18-5/31/24

Doris Duke Foundation Award, 7/1/19-6/30/20

Daniel Belsky, PhD

RCD Supported (2013-2015)

Work in Progress: To identify risk factors in early- to-midlife that can be ameliorated or reversed and also research to test effectiveness of these amelioration strategies.

Subsequent funding

1. 1R21AG054846-01 A pilot study to advance translation of molecular signatures of biological aging. Role: PI. March 15, 2017 – February 28, 2019
2. National Institutes of Health, Investigating increasing selectivity of low educational attainment across US birth cohorts in the 20th Century July 1, 2016 – June 30, 2017
3. R01AG032282-06 Aging in 1000 healthy young adults: The Dunedin Study. Role: Co-investigator
4. Jacobs Foundation Research Fellowship 2016–2018
Accepted faculty position in in the School of Public Health, Assistant Professor, Columbia University.

Rasheeda Hall, M.D., Pepper Center Diversity Supplement Awardee (2012-2013)

Medicine – Nephrology

Duke University Medical Center

Durham, NC

Subsequent funding

Research Award of Excellence: VA Institute of Medical Research

Doris Duke Charitable Foundation Fund to Retain Clinical Scientists Award –1/2018-12/2018 (awarded)

NIH Loan Repayment Award, 5/2018

NIH Beeson K76 award

Juliessa Pavon, MD, MHS

Medicine – Geriatrics

Duke University Medical Center

Durham, NC

Hartford COE Research Scholar Supported (2013-2015)

Duke Chair's Research Award Supported (2013-2014)

Work in Progress: Investigations to address hazards of hospitalization including high risk medication use and functional decline during hospitalization.

Subsequent funding

NIA GEMSSTAR award 2014-2016, Aim: To study adherence to venous thromboembolism prophylaxis guidelines in hospitalized older adults

T. Franklin Williams Scholar Award 2014-2016

AGS-SHM-AAIM Award 2014-2016

Hartford COE Collaborative Pilot Project Award, 2014-2016

NIH Loan Repayment Program, 2015-2017

NIA/Duke OAIC Pepper REC, 2016-2018 Aim: To study usability of mobile health technology to improve ambulatory activity of hospitalized older adults

NIA/Duke OAIC Pepper Physical Measures Health Innovation Technology Development Award, 2017-2018 Aim: to develop activity tracker and analysis software

NIA K23 award Aim: To study de-prescribing of psychoactive medications in hospitalized older adults

SECTION IV. DUKE PEPPER CENTER PUBLICATIONS –2018-2019

2018

Allen JD, Vanbruggen MD, Johannsen NM, Robbins JL, Credeur DP, Pieper CF, Sloane R, Earnest CP, Church TS, Ravussin E, Kraus WE, Welsch MA. PRIME: A Novel Low-Mass, High-Repetition Approach to Improve Function in Older Adults. *Medicine and science in sports and exercise*. 2018 May;50(5):1005-1014. PMID: PMC5899050.

Blay SL, Fillenbaum GG, Mello MF, Quintana MI, Mari JJ, Bressan RA, Andreoli SB. 12-month prevalence and concomitants of DSM-IV depression and anxiety disorders in two violence-prone cities in Brazil. *J affective disorders*. 2018 May;232:204-211. PMID: PMC6039111.

Cary MP Jr, Goode V, Crego N, Thornlow D, Colón-Emeric CS, Hoenig HM, Baba K, Fellingham S, Merwin EI. Hospital Readmission in Total Hip Replacement Patients in 2009 and 2014. *Arch Phys Med Rehabil*. 2018 Jun;99(6):1213-1216. PMID: PMC5970972.

Cary MP Jr, Hall RK, Anderson AL, Burd A, McConnell ES, Anderson RA, Colón-Emeric CS. Management Team Perceptions of Risks and Strategies for Preventing Falls Among Short-Stay Patients in Nursing Homes. *The health care manager*. 2018 January;37(1):76-85. PMID: PMC5777903.

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Collins AT, Hatcher CC, Kim SY, Ziemian SN, Spritzer CE, Guilak F, DeFrate LE, McNulty AL. Selective Enzymatic Digestion of Proteoglycans and Collagens Alters Cartilage T1rho and T2 Relaxation Times. *Ann Biomed Eng*. 2019 Jan;47(1):190-201. PMID: PMC6481190.

Colón-Emeric CS, Corazzini KN, McConnell ES, Pan W, Toles MP, Hall R, Batchelor-Murphy M, Yap TL, Anderson AL, Burd A, Amarasekara S, Anderson RA. Resident Vignettes for Assessing Care Quality in Nursing Homes. *J Am Med Dir Assoc*. 2018 May;19(5):405-410. PMID: PMC5924713.

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Domingue BW, Belsky DW, Fletcher JM, Conley D, Boardman JD, Harris KM. The social genome of friends and schoolmates in the National Longitudinal Study of Adolescent to Adult Health. *Proc Natl Acad Sci U S A*. 2018 Jan 23;115(4):702-707. PMID: PMC5789914.

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Furman BD, Kent CL, Huebner JL, Kraus VB, McNulty AL, Guilak F, Olson SA. CXCL10 is upregulated in synovium and cartilage following articular fracture. *J Orthop Res.* 2018 Apr;36(4):1220-1227. PMID: PMC5851826.

Gray SL, Marcum ZA, Schmader KE, Hanlon JT. Update on Medication Use Quality and Safety in Older Adults, 2017. *J Am Geriatr Soc.* 2018 Dec;66(12):2254-2258. PMID: PMC6421859.

Gray SL, Hart LA, Perera S, Semla TP, Schmader KE, Hanlon JT. Meta-analysis of Interventions to Reduce Adverse Drug Reactions in Older Adults. *J Am Geriatr Soc.* 2018 Feb;66(2):282-288. PMID: PMC5809283.

Hall KS, Morey MC, Beckham JC, Bosworth HB, Pebole MM, Pieper CF, Sloane R. The Warrior Wellness Study: A Randomized Controlled Exercise Trial for Older Veterans with PTSD. *Transl J Am Coll Sports Med.* 2018 Mar 15;3(6):43-51. PMID: PMC5889111.

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Huang Z, Huang C, Xie J, Ma J, Cao G, Huang Q, Shen B, Byers Kraus V, Pei F. Analysis of a large data set to identify predictors of blood transfusion in primary total hip and knee arthroplasty. *Transfusion.* 2018 Aug;58(8):1855-1862. PMID: PMC6131039.

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Morey MC, Lee CC, Castle S, Valencia WM, Katzel L, Giffuni J, Kopp T, Cammarata H, McDonald M, Oursler KA, Wamsley T, Jain C, Bettger JP, Pearson M, Manning KM, Intrator O, Veazie P, Sloane R, Li J, Parker DC. Should Structured Exercise Be Promoted As a Model of Care? Dissemination of the Department of Veterans Affairs Gerofit Program. *J Am Geriatr Soc*. 2018 May;66(5):1009-1016. PMID: PMC5992009.

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2019

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DeFrate LE, Kim-Wang SY, Englander ZA, McNulty AL. Osteoarthritis year in review 2018: mechanics. *Osteoarthritis and cartilage*. 2019 March;27(3):392-400. PMID: PMC6489451.

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SECTION V. EXTERNAL ADVISORY BOARD MEMBERS

Karen Bandeen-Roche, Ph.D., Johns Hopkins
Chair of Duke External Advisory Board,
Years of service: 9

George A Kuchel, MD., University of Connecticut
Years of Service: 3

Neil Alexander, MD. University of Michigan
Years of Service: 3

Duke OAIC Recognition and Awards
2018-2019

James Bain, PhD:

- Distinguished Nominee, Michelle P. Winn Inclusive Excellence Award, Inclusion Council, Office of Diversity and Inclusion, Duke University School of Medicine, June 30th, 2017. “In recognition of excellence, innovation, and leadership in diversity and inclusion.”
- 2018 Chandler Award, nonprofit North Carolina Fossil Club. “In recognition of significant contributions in education and outreach.”

David Bartlett, PhD

- Outstanding Poster Award 2019 Annual Pepper Center Meeting

Avshalom Caspi, PhD:

- 2018 Feature article in Science, about research program of Terrie Moffitt and **Avshalom Caspi**: <http://www.sciencemag.org/news/2018/02/two-psychologists-followed-1000-new-zealanders-decades-here-s-what-they-found-about-how>

Kevin Caves, ATP, MEM, RET:

- 2019 Faculty Recipient of the Betsy Alden Outstanding Service-Learning Award <https://servicelearning.duke.edu/news/kevin-caves-2019-faculty-recipient-betsy-alde-outstanding-service-learning-award>

Katherine Hall, PhD

- Promoted to Associate Professor of Medicine in the Division of Geriatrics
- Elected as Co-Chair of the Military and Veterans Health Special Interest Group, Society of Behavioral Medicine

Rasheeda Hall MD, MBA, MHS

- 2019 received the American Geriatric Society New Investigator Award
- 2019 invited speaker to the 56th European Renal Association-European Dialysis Transplant Association Congress. Talk title: “Addressing Potentially Inappropriate Medications in Older Adults with Kidney Disease”

Susan Hastings, MD

- Joseph C. Greenfield Jr Research Mentorship Award, 2019
- Inaugural invited guest at Regenstrief Institute External Speaker Series “Accelerating Innovation in the Care of Older Adults: the Case of STRIDE”. Indianapolis, IN. November, 2018
- Visiting Scholar, Aurora Health System, Milwaukee, WI. November, 2018

- Keynote Address. 19th Annual Safe Patient Handling and Mobility Conference. “Promoting Mobility in the Hospital: the Case of STRIDE”. Orlando, FL. March 5, 2019

Helen Hoenig:

- Fellow, American Congress of Rehabilitation Medicine

Virginia Kraus, MD, PhD:

- Aug 2018 honorary PhD from University of Tampere
- 2019 elected to American Association of Physicians
- 2019 received Lifetime Achievement Award from the osteoarthritis research society international

Amy McNulty, PhD:

- 1st Place in the 2019 ORS Scientific Photo Competition
- 1st Runner-up in the 2019 Duke Department of Orthopaedic Surgery Photo Competition
- Promoted to Associate Professor in Orthopaedic Surgery and Pathology
- Elected as Chair Elect for the Meniscus Section of the Orthopaedic Research Society
- Selected to serve on the Orthopaedic Research Society Program Committee
- Invited Speaker to the American Academy of Orthopaedic Surgeons. Talk title: The Biology of Meniscal Injury and Treatment
- Press release (<https://corporate.dukehealth.org/news-listing/scaffold-helps-cells-repair-torn-meniscus-lab-tests?h=nl>) on our recent publication in Scientific Reports (<https://rdcu.be/bG924>) on our work to generate and test a meniscus-derived matrix scaffold to promote meniscus tissue repair

Terrie Moffitt, PhD:

- 2018 Elected to the National Academy of Medicine (Moffitt). <http://www.nationalacademies.org/>; <https://nam.edu/national-academy-of-medicine-elects-85-new-members/>
- 2018 Feature article in Science, about research program of **Terrie Moffitt** and Avshalom Caspi: <http://www.sciencemag.org/news/2018/02/two-psychologists-followed-1000-new-zealanders-decades-here-s-what-they-found-about-how>

Miriam Morey, Ph.D

- 2018 Gold Status Fellow, VHA Diffusion of Excellence, for Gerofit Program

Charity Oyedeji, PhD

- Outstanding Poster Award 2019 Annual Pepper Center Meeting

Daniel Parker, MD

- Outstanding Poster Award 2019 Annual Pepper Center Meeting

Juliessa Pavon, MD, MHS:

- Society of Hospital Medicine, elected to Research Committee
- Society of Hospital Medicine HM 19 meeting, 2019 Clinical Updates, "Things we do for no reason", paper recognition
- Epic national Geriatrics Steering Board, elected as member

Kenneth Schmader, M.D.

- Named as an Editor for the 8th edition of Hazzard's Textbook of Geriatric Medicine and Gerontology

Corey Simon, PhD

- Outstanding Poster Award 2019 Annual Pepper Center Meeting

James White, PhD

- 2019 NIA/U13 Osteoporosis & Soft Tissue Disorders Workshop: Rising Star Award
- Invited Speaker to the 2019 Barshop Conference on Aging "Resilience in Aging and Age-Related Disease." Presentation: "Chronic exposure to youthful circulation improves resilience in old mice"
- Nathan Shock Center (UTSA) Pilot Awardee: Project title: Chronic exposure to youthful circulation improves longevity and healthspan in old mice.

Heather Whitson, MD, MPH:

- UCSF Geriatrics & Gerontology Visiting Scholar (2019), UCSF Medical Center
- Richard Grohl Visiting Scientist Award (2018), Radboud Institute for Health Sciences, Nijmegen, the Netherlands
- Appointment as Director, Duke Center for the Study of Aging and Human Development

**Minority Research
The Duke University Pepper Center
2018 - 2019**

General Brief Description of Minority Activities:

Special Projects

**HOSPICE and PALLIATIVE CARE
Kimberly Johnson, MD – Ongoing**

Practices Among Hospice Providers to Increase Service to African Americans

African Americans use hospice at lower rates than Whites. The overall goal of this work is to identify best practices among hospice providers in reaching African Americans. The study includes a national sample of hospice providers. Participants provide information about their community education and outreach practices, admission practices beyond those required in Medicare Hospice Benefit, cultural sensitive training, goals and strategies to increase service to African Americans, and identify barriers and facilitators of these efforts. The overall goal is to identify best practices among hospice providers in reaching older African Americans.

To-date, we have enrolled 204 hospices across the United States. The vast majority of hospices were not-for-profit (79.4%), freestanding (70.1%), and located in the South (52.9%). Nearly 70% offered cultural competency training and 52% participated in community education and outreach to increase service to African Americans, most commonly involving churches, social service agencies, and healthcare providers. Participating hospices reported that the most successful strategies included partnerships with churches and community physicians with large numbers of African Americans. The least successful strategies to reach African Americans included the use of printed material or other advertising. We are involved in ongoing analyses which will lead to specific recommendations for hospice providers to increase service to African Americans in their communities.

Hospice Staff Cultural Competence Training: National Hospice Survey Findings

Compared to whites, racial/ethnic minorities are less likely to enroll in hospice and if they enroll, more likely to experience poor quality care. Building cultural competence (CC) among hospice staff is a strategy that may reduce these disparities. We analyzed data on CC practices of hospices from the national survey of hospices providers (described above). A total of 197 hospices provided data on CC training; most were not-for-profit (80%) with an average daily census over 100 (53%); 73% offered staff cultural competence training (CCT). There were no differences in characteristics of hospices who offered CCT and those that did not. Of hospices offering CCT, 54% held it annually. Most trainings were one hour (60%); content was delivered via web (58%) and/or lecture (57%). While over 90% of staff (i.e., nurses, social workers, and chaplains) completed CCT, a smaller proportion of medical directors (63%), senior leaders (70%) and board members (23%) did so. Most common (>70%) topics were: cross-cultural communication, death and illness beliefs, and spirituality's role, and healthcare disparities. The majority focused on African-Americans (83%), Hispanics (76%), and Asians (61%)—the most common U.S. minority groups. Almost 30% reported no assessment of effectiveness of CCT

while 45% reported a quiz at the end. In this study, most hospices offered some CCT. CCT has been shown to improve healthcare providers' knowledge and skills in caring for diverse patients and is associated with increased patient satisfaction. Future research should evaluate effectiveness of CCT in improving the ability of hospices to deliver high quality end-of-life care to diverse groups of older adults. Accepted as a paper Presentation. "Cultural Competence Training for Hospice Staff: Findings from a National Hospice Survey. The Gerontological Society of America's 71st Annual Scientific Meeting, Austin, Texas, November 2019.

Social Supports and Services Provided by Hospice

Basic social supports and services not routinely covered by insurers may be needed by terminally ill patients and their families. This may be especially true for those with low incomes and African Americans who report greater need for hospice services. Little is known about hospices' provision of such social supports and services. In the national survey of hospice providers (described above) we asked hospices about their support of patients' basic social needs. Over 80% (n = 203) reported using internal funds to cover services not reimbursed by insurers. Hospices used internal funds for food (81.7%), shelter (57.8%), utility bills (73.5%), and funeral costs (50%). Hospices referred patients/families to community organizations to obtain a similar range of services, including transportation, clothing, linens/towels, furniture/appliances, home repairs, and caregiver supports. In conclusion, hospices are using internal resources and accessing community resources to provide patients with basic social needs not routinely covered by insurance.

Access to Hospice for Undocumented Immigrants

The 11.2 million undocumented immigrants living in the United States are not covered by the Medicare Hospice Benefit and most are uninsured. Aging of undocumented patients in the United States is likely to increase hospice demand. Clinicians have reported challenges in obtaining hospice for undocumented immigrants. This study examined hospice agency practices and access for undocumented immigrants using data from the national survey of hospice providers (described above). Of 179 hospice agencies, 121 (67.6%) offered unrestricted enrollment to undocumented immigrants and 58 (32.4%) either limited the number enrolled or did not enroll undocumented patients. Not-for-profit hospices and larger hospices were more likely to enroll undocumented immigrants without restrictions. Sixty hospices reported receiving referrals to enroll undocumented immigrants in the last year with an average of 2 requests per agency. Approximately ¾ of those referred were enrolled. This study suggests that while some cities and states are expanding healthcare for undocumented immigrants, for many, healthcare access remains limited throughout the healthcare continuum, including at the end-of-life. Policies are needed to reduce barriers to hospice care for this population. |

Advance Care Planning

Reducing Disparities in the Quality of Palliative Care for Older African Americans through Improved Advance Care Planning (EQUAL ACP) (The study is funded by the Patient-Centered Outcomes Research Institute, 2017)

Patients who are seriously ill may benefit from advance care planning. In advance care planning, patients make decisions about care they would want to receive if they become unable to speak for themselves. Planning can help patients make sure that the care they receive at the end of life reflects their wishes. For example, patients may think about who should make medical decisions

on their behalf, what medical treatment they want or don't want, and cultural beliefs that may affect their decisions.

Blacks are less likely than whites to take part in advance care planning. Compared with whites, blacks are more likely to receive costly, poor-quality care that doesn't reflect their wishes at the end of life. Blacks are also less likely to use hospice care, more likely to have preventable hospital stays, and more likely to have poor communication with doctors than whites. Researchers don't know if these differences relate to differences in patients' cultural beliefs, knowledge, or access to advance care planning.

EQUAL ACP is a multisite study which will compare the effectiveness of two different approaches to advance care planning. Over the next 4 years, our research team will work with 10 clinics at 5 medical centers in the southern United States. We will enroll 800 adults age 65 or older who are seriously ill. Patients in the study will be at high risk of losing the ability to do daily tasks, having a hospital stay, or dying. Half the patients will be black and half will be white. In one advance care planning approach, called Respecting Choices First Steps, trained community members who don't work in health care will help patients and families with advance care planning. The community members will help patients choose a person to make healthcare decisions, talk about beliefs that may affect future medical decisions, talk about preferences for care if a serious illness or injury occurs, and create a written care plan. In the other approach, clinics will give patients the Five Wishes document, which is easy to use and written in language that is easy to understand. Five Wishes helps patients think about who can make medical decisions on their behalf, what medical treatments they want or don't want, how they want others to treat them, and what they want family members to know. The document helps patients talk about their wishes with family, friends, and doctors, and put those wishes in writing.

EQUAL ACP aims to determine which approach to advance care planning is more effective at increasing advance care planning overall and for different racial groups. The study will also determine the extent to which advance care planning reduces differences between blacks and whites in the quality of end-of-life care. A manuscript describing this work is in press. Ejem D, Barrett N, Rhodes, R, Olsen M, Bakitas M, Durant R, Elk R, Steinhauer K, Quest T, Johnson KS. Reducing disparities in the quality of palliative care for older African Americans through improved advance care planning: study design and protocol. *J Palliat Med*. In press.

Barriers to and Facilitators of Advance Care Planning:

We collaborated with other investigators to identify barriers to and facilitators of advance care planning (ACP) among African Americans. For this qualitative study we interviewed health disparities experts, community members, seriously ill African Americans and caregivers. We identified seven factors that influence ACP for African Americans: religion and spirituality; trust and mistrust; family relationships and experiences; patient-clinician relationships; prognostic communication, care preferences, and preparation and control. These findings suggest that respectful, rapport-building communication may facilitate ACP for older African Americans. Sanders JJ, **Johnson KS**, Cannady K, Paladino J, Ford DW, Block SD, Sterba KR. From barriers to assets: Rethinking factors impacting advance care planning for African Americans. *Palliat Support Care* 2019;17:306-313.

Goal Concordant Care and Advance Care Planning

Goal-concordant care (GCC) is care that aligns with a patient's known goals, values, and preferences. African Americans are less likely to receive GCC. In this study we examined which factors were associated with whether patients received goal-concordant care. The study used the Health and Retirement Study, which is a nationally representative, longitudinal cohort of adults over age 50. We included decedents whose family completed the 2014 post-death interview. Of 1175 respondents, 76% reported that the decedent "usually" or "always" received GCC. Patients who were older, had 3 or more chronic medical problems, and had a written advance care plan were more likely to receive GCC. African Americans who were able to participate in decision-making about the care that they wanted at the end-of-life were also more likely to receive GCC. This suggests that bringing the patient's voice into EOL care discussions through early advance care planning with those who will likely be involved in making medical decision may improve the likelihood that African Americans receive the care that they want. Haines L, Rahman O, Sanders J, **Johnson KS**, Kelley A. Factors that impact family perception of goal-concordant care at the end of life. *J Palliat Med* 2019;22:927-932.

Older Veterans Health and PTSD

Katherine Hall PhD (2017- Ongoing)

1) Exercise as a novel treatment option to address health disparities in older military veterans with posttraumatic stress disorder (PTSD).

Dr. Katherine Hall recently completed a randomized controlled pilot study of supervised exercise for older veterans with PTSD, a population at high risk for obesity, metabolic dysfunction, accelerated functional decline, and cardiovascular disease. Few studies targeting the prevention and management of chronic disease and disability in PTSD patients have been done, and have focused predominantly on White populations. Vietnam-era veterans make up the majority of the older (65+ years) veteran population, and among this cohort, both Hispanic and African American veterans have higher rates of PTSD compared to White veterans. We had great success recruiting minority patients to participate (83% African American). Results from this pilot study demonstrated improvements in PTSD symptoms, physical performance, metabolic syndrome risk indicators, and health-related quality of life in this population with significant comorbidities. We also learned important lessons around future implementation considerations, and tailoring for other minority sub-groups in this population, namely older female veterans. Dr. Hall is currently leading a project exploring preferences for content and delivery of health promotion programs among female veterans with mental health conditions.

Hall KS, Morey MC, Bosworth HB, Beckham JC, Pebole MM, Sloane R., Pieper CF. Pilot randomized controlled trial of exercise training for older veterans with PTSD. *J Behav Med*. 2019 Jul 1. doi: 10.1007/s10865-019-00073-w. PMID: 31264055.

Pebole MM & Hall KS*. Physical activity promotion in women with PTSD: What we need for progress. (2019). *Psychology of Sport and Exercise*, 41, 127-129.

Pebole MM & Hall KS*. Insights following implementation of an exercise intervention in older veterans with PTSD. (2019). *International Journal of Environmental Research and Public Health*, 16, 2630. doi:10.3390/ijerph16142630

*indicate senior author

Retrospective Cohort Analyses of Epidemiological Data in Brazil **Gerda Fillenbaum, PhD, Co-Investigator. (2007 – Ongoing)**

Dr. Fillenbaum has collaborated with colleagues from the Federal University of São Paulo in Brazil for a decade on analyses of a cross-sectional community survey, “The Elderly of Rio Grande do Sul”, conducted by the State of São Paulo Council on Aging.

This survey focused on adults aged 60 years and older who lived in private households in the state of Rio Grande do Sul, Brazil and was based on a cross-sectional study of non-institutionalized persons on a multistage stratified random sample.

Analyses have examined relationships of race and other demographic variables to use of health services, functional status, levels of physical activity, alcohol abuse and dependence, prevalence and severity of arthritis, and health burden associated with comorbid depression in older Brazilians with diabetes.

Additional studies examining the impact of living in a violence-prone area found that, while the prevalence of anxiety and depression was high, and associated with living in a violence-prone area, use of mental health services was lower among persons with higher resilience, even after demographic characteristics, anxiety, depression, and area homicide rate had been taken into account.

Blay SL, Fillenbaum GG, Mello MF, Quintana MI, Mari JJ, Bressan RA, Andreoli SB. 12-month prevalence and concomitants of DSM-IV depression and anxiety disorders in two violence-prone cities in Brazil. *J Affect Disord*. 2018 May;232:204-211. doi: 10.1016/j.jad.2018.02.023. Epub 2018 Feb 17. PMID:29499502. PMCID: [PMC6039111](https://pubmed.ncbi.nlm.nih.gov/6039111/)

Fillenbaum GG, Blay SL, Mello MF, Quintana MI, Mari MJ, Bressan RA, Andreoli SB. Use of mental health services by community-resident adults with DSM-IV anxiety and mood disorders in a violence-prone area: São Paulo, Brazil. *Journal of Affective Disorders*, 2019; First published version available online: 5-MAR-2019 DOI information: 10.1016/j.jad.2019.03.010

Race differences in change in physical functioning status in older African American and White male veterans with HIV

Gerda Fillenbaum, PhD, Co-Investigator, and Mehri McKellar, MD – (Pepper Scholar)

Ten years of data on African American and White male veterans age 50 years and over participating in the Veterans Aging Cohort Study Survey, showed that while physical functioning was lower than expected for age, was associated with multiple health conditions, and

in particular with depression, physical functioning scores (PCS score on SF-12) were (unexpectedly) stable through age 75. Throughout the study, PCS score was not associated with race or with interactions among age, race, and HIV status. Increased attention should be paid to comorbid conditions.

McKellar MS, Kuchibhatla MN, Oursler KK, Crystal S, Akgün KM, Crothers K, Gibert CL, Nieves-Lugo K, Womack J, Tate JP, Fillenbaum GG. Race differences in change in physical functioning in older male veterans with HIV. *AIDS Research and Human Retroviruses*. 2019 Jun 18. doi: 10.1089/AID.2018.0296. [Epub ahead of print] PMID: 30963773 Accepted 2019

Pepper REC Scholar 2016-2018 (*Duke Minority Supplement Awardee 2012-2014*)
Rasheeda K. Hall, MD, MHS, MBA

Dr. Rasheeda Hall is an Instructor in Nephrology with an interest in exploring solutions to health system problems for vulnerable populations, such as low-income, elderly, and uninsured patients with chronic kidney disease (CKD) that rely on Medicare and Medicaid for healthcare coverage. She completed a diversity supplement to develop a deep understanding of the health system problems that impact the vulnerable population of nursing home (NH) residents with CKD. She is currently completing a Pepper-supported pilot study of physical resilience in dialysis patients described below.

2. CANDIDATE'S PROPOSED RESEARCH PLAN for 2016-ongoing

Resilience in Older Dialysis Patients. Adults over age 65 are the most rapidly growing population initiating dialysis; however, 2/3 experience functional decline within six months.¹⁶ Before interventions to promote resilience after dialysis initiation can be developed, we need a better understanding of how to measure it. Resilience can be described as recovery after each dialysis session (day-to-day resilience), and as maintenance of functional status after development of end-stage renal disease (long-term resilience, figure). Long-term resilience is influenced by the chronic inflammatory state of end-stage renal disease that is manifested by protein-energy wasting and frailty. Day-to-day resilience is influenced by the acute intermittent stress of hemodialysis, when the cardiovascular system is exposed to rapid hemodynamic shifts, and the dialysis membrane's foreign material promoting inflammation. Interventions such as multifactorial geriatric assessment may improve both day-to-day and long-term measures of resilience.

Aim 1. Identify feasible, reliable, sensitive measures of day-to-day resilience for older dialysis patients.

1a. Determine the range and within-subject variability in physical activity (PA) using step activity monitors and a self-reported fatigue score over 14 days and in relation to timing of dialysis.

1b. Determine the correlation between within-subject trajectories of fatigue score and PA and between a self-reported, validated measure of recovery time and an objective measure of recovery time from PA data.

Aim 2. Identify feasible, reliable, sensitive measures of long-term resilience for older dialysis patients.

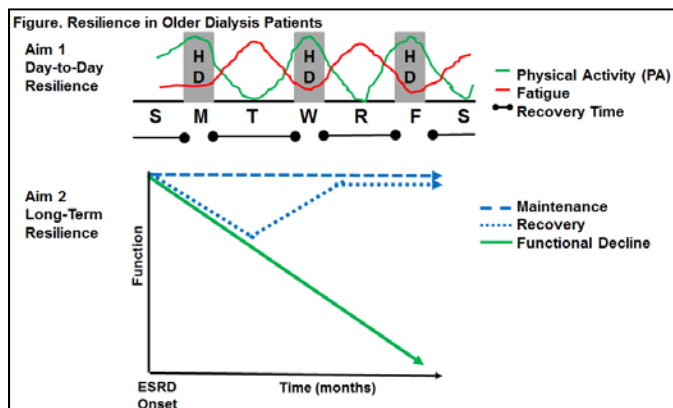
2a. Describe the change in function [short physical performance battery (SPPB), handgrip, and activities of daily living (ADLs)] over the first six months of dialysis (administered on a mid-

week dialysis day at baseline, 3 months, and 6 months) and between dialysis and non-dialysis days (administered twice over a 48-hour period).

2b. Determine the correlation between within-subject performance in the Functional Independence Measure (FIM), physical performance measures (SPPB, handgrip) and ADLs.

Significance: Completion of these aims will identify optimal measures of resilience in an older dialysis population and provide Dr. Hall with feasibility and measurement pilot data supporting an intervention development grant application.

Approach. A sample of 30 subjects ≥ 65 years who initiated hemodialysis within the past 30 days will be recruited. Exclusions include non-ambulatory status, dependence in all ADLs, advanced dementia, non-English speaking, and hospice enrollees. Subject screening, recruitment and consent will occur at dialysis units within 15 miles of Duke; in this area, there are 250 prevalent hemodialysis patients aged ≥ 65 years



and 15 new patients/month. Clinical characteristics (co-morbidities, intradialytic weight gain, hemodialysis access, hemoglobin, dialysis adequacy, and albumin) will be obtained from medical records. Subjects will undergo home PA monitoring with accelerometers for 14 days. During this time, study personnel will call subjects each weekday to ask subjects to report their fatigue score at that moment on a numeric rating scale (0-10). A validated measure of recovery time will be obtained at baseline. Functional measures will be tested in the dialysis unit before dialysis on a mid-week dialysis at baseline, 3, and 6 months (SPPB, handgrip strength, Lawton ADLs, and Katz ADLs). During the same week, these measures will be repeated on a non-dialysis day in each subject's home. Simultaneously, a physical therapist will conduct a home assessment involving the Functional Independence Measure (FIM).

Aim 1 analysis will calculate the proportion of subjects who complete the study protocol, the distribution of self-reported recovery time and within-subject changes in fatigue score and PA counts. Bivariate associations will test whether mean fatigue scores and PA counts are similar on dialysis and non-dialysis days. Associations of clinical characteristics with longitudinal changes in fatigue score and PA counts will be assessed using a mixed model with repeated measures logistic regression. Within-subject trajectories of fatigue score and PA counts will assess correlation between the two measures. Kaplan-Meier survival analysis will estimate time to recovery after dialysis using within-person changes in fatigue score and PA counts. The cut-points that will define time to recovery will be determined from the distribution of fatigue scores and PA counts. Mixed models to estimate the average within-person correlation between self-reported recovery time and recovery time derived from survival analyses. A sample size of 30 will provide power to detect correlations with moderate to large effect sizes ($r > .3$) with a confidence interval of 0.1, but is not large enough for modeling with covariate adjustment.

Aim 2 analysis will examine the distribution of individual and group means of physical performance and ADLs over time. Mixed models with repeated measures design will evaluate within-subject and between-subject variability at each time-point (baseline, 3 months, and 6 months) and include a home-clinic factor to measure slopes for each functional measure. This model will also identify the change score in each dyad. The correlation coefficient will be used

to evaluate the relationships between each functional measure and FIM and the relationships between SPPB and handgrip (objective measures) and ADL scores (subjective measures) using the mixed model approach. **Interaction with Duke OAIC Cores:** Both aims will be supported by the Dr. K. Hall in the Physical Measures Core and Dr. Pieper of the Analysis Core, who have developed data management and analysis protocols for dealing with the complex accelerometer data generated by this project. In addition, Dr. V. Kraus of the Molecular Measures Core will work with this scholar to explore the relationship of IL-6, CRP, s-VCAM, miRNA, and LPS to functional measures of resilience as a mentored basic science integration experience.

Cary, M. P., Hall, R., Anderson, A., Burd, B., McConnell, E., Anderson, R., & Colon-Emeric, C. Management perceptions of fall prevention among short-stay patients in nursing homes. *Health Care Manag.* 2018 Jan/Mar;37(1):76-85.

Hall R., Pieper C., Sloane R., Lyles K., Van Houtven C., Adler R., Colon-Emeric C. Competing Risks of Fracture and Death in Older Adults with Chronic Kidney Disease. *J Am Geriatr Soc.* 2018 Jan 10. doi: 10.1111/jgs.15256. [Epub ahead of print]

Hall RK, Luciano A, Pieper C, Colón-Emeric CS. Psychometric Evaluation of the Kidney Disease Quality of Life (KDQOL-36): A Comparison between Older and Younger Adults receiving Dialysis” in press, *Journal of Nephrology Social Work (JNSW)*, 2018.

Hall RK, Luciano A, Pieper C, Colón-Emeric CS. Association of Kidney Disease Quality of Life (KDQOL-36) with Mortality and Hospitalization in Older Adults receiving Hemodialysis, 2018 January 15;19(1):11. PMID: PMC5769495.

Research abstracts from this project between July 2018 and June 2019:

1. **Hall RK**, Luciano A, Pendergast J, Colón-Emeric C. Functional Decline and Associated Risk Factors in a Survivor Cohort of Older Dialysis Patients. American Society of Nephrology Kidney Week, San Diego, CA [poster]. October 2018.
2. **Hall RK**, Luciano A, Rutledge J, Colón-Emeric C. Racial Difference in Resilience among Older Dialysis Patients. Gerontological Society of America Annual Conference, Boston, MA [oral presentation]. November 2018.
3. **Hall RK**, Rutledge J, Luciano A, Hall K, Pieper C, Colón-Emeric C. Measuring Resilience in Older Dialysis Patients: A Pilot Study. American Geriatrics Society Annual Meeting, Portland, OR [poster] May 2019.

New Funding Since Pepper Support

Dr. Hall received funding from the HCSRN-OAICs AGING Initiative for a study “Development of a CKD Discordance Index to Identify High Healthcare Utilization”. *Researchers:* Kristi Reynolds, PhD (KPSC); Barrett Bowling, MD, MPSH (Duke); **Rasheeda Hall, MD (Duke)**. She also received a NIH Loan Repayment award and a Doris Duke “Fund to Retain Clinical Researcher” award. She received Paul B. Beeson Emerging Leaders Career Development Award in Aging K76 award and the American Society of Nephrology Harold Amos Medical Faculty Development Program award.

Other Pepper Center Scholars Mentored Minority Trainees

Michael Cary, RN, PhD (*Mentor*: Cathleen Colón-Emeric, MD, MHS)

Dr. Cary is conducting big data research on the impact of clusters of co-morbidities on functional recovery after hip fracture. He has developed machine learning algorithms for implementation in the electronic medical record that can identify high risk patients who require additional personalized interventions to maximize recovery trajectories.

Dr. Cary's prior research with retrospective cohort studies of Medicare data examines variables related to hip fracture and rehabilitation outcomes. This research will assist health policymakers in the identification of those who most need and are most likely to benefit from inpatient rehabilitation. This research also highlights subgroups in need of greater intervention to achieve better outcomes. Further examination of racial/ethnic and gender differences in rehabilitation outcomes is needed to better understand underlying causes of these disparities and develop interventions to reduce barriers to, and improve mediators of, equitable health care for all.

Cary, M. P., Hall, R., Anderson, A., Burd, B., McConnell, E., Anderson, R., & Colon-Emeric, C. Management perceptions of fall prevention among short-stay patients in nursing homes. *Health Care Manag.* 2018 Jan/Mar;37(1):76-85.

Cary MP Jr, Goode V, Crego N, Thornlow D, **Colón-Emeric CS**, Hoenig HM, Baba K, Fellingham S, Merwin EI. Hospital Readmission in Total Hip Replacement Patients in 2009 and 2014. *Arch Phys Med Rehabil.* 2018 Jun;99(6):1213-1216. doi: 10.1016/j.apmr.2017.12.031. Epub 2018 Jan 31.

Candace Brown, PhD, (*Mentors*: Miriam Morey, PhD, Deborah Gold, PhD)

Dr. Brown recently completed an Aging Center post-doctoral fellowship. She has a primary interest in examining how exercise can mitigate health disparities among at risk populations. She completed three-year service as Chair with the Emerging Scholar and Professional Organization of the GSA and was appointed as the Health Science Representative to the Minority Interest Group Committee of GSA. She completed several investigations exploring extrinsic motives among aging Black women triathletes (2 manuscripts in review) and has initiated novel investigations pertaining to motivations for long-term exercise among older Veterans. She completed the Butler Williams summer Scholars Program in 2018 and accepted a faculty position as and accepted a position as an Assistant Professor of Gerontology in the Department of Public Health Sciences at the University of North Carolina in Charlottesville, NC.

Publications Pertaining to Minority Research:

2018

Cary, M. P., Hall, R., Anderson, A., Burd, B., McConnell, E., Anderson, R., & Colon-Emeric, C. Management perceptions of fall prevention among short-stay patients in nursing homes. *Health Care Manag.* 2018 Jan/Mar;37(1):76-85.

Colon-Emeric CS, Corazzini K, McConnell E, Pan W, Toles M, Hall R, Batchelor-Murphy M, Yap T, Anderson A, Burd A, Amarasekar S, Anderson RA. Resident Vignettes for Assessing Care Quality in Nursing Homes. *J Am Med Dir Assoc.* 2017 Nov 21. pii: S1525-8610(17)30600-X. doi: 10.1016/j.jamda.2017.10.018. [Epub ahead of print]

Hall R., Pieper C., Sloane R., Lyles K., Van Houtven C., Adler R., Colon-Emeric C. Competing Risks of Fracture and Death in Older Adults with Chronic Kidney Disease. *J Am Geriatr Soc.* 2018 Jan 10. doi: 10.1111/jgs.15256. [Epub ahead of print]

Hall RK, Luciano A, Pieper C, Colón-Emeric CS. Psychometric Evaluation of the Kidney Disease Quality of Life (KDQOL-36): A Comparison between Older and Younger Adults receiving Dialysis” in press, *Journal of Nephrology Social Work (JNSW)*, 2018.

Hall RK, Luciano A, Pieper C, Colón-Emeric CS. Association of Kidney Disease Quality of Life (KDQOL-36) with Mortality and Hospitalization in Older Adults receiving Hemodialysis, in press, *BMC Nephrology*, 2018.

Hall RK, Myers ER, Rosas SE, O'Hare AM, Colón-Emeric CS. Choice of Hemodialysis Access in Older Adults: A Cost-Effectiveness Analysis. *Clin J Am Soc Nephrol.* 2017 Jun 7;12(6):947-954. doi: 10.2215/CJN.11631116. Epub 2017 May 18. PubMed PMID: 28522655; PubMed Central PMCID: PMC5460715.

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Cary M, Colon-Emeric C et al. Hospital Readmissions among Total Hip Replacement Patients in 2009 and 2014. *Archives of Physical Medicine and Rehabilitation*, in press 2018

Hall KS, Morey MC, Beckham JC, Bosworth HB, Pebole MM, Pieper CF, Sloane R. The Warrior Wellness Study: A Randomized Controlled Exercise Trial for Older Veterans with PTSD. *Transl J Am Coll Sports Med.* 2018 Mar 15;3(6):43-51. doi: 10.1249/TJX.000000000000056. PMID: 29632895; PMCID: PMC5889111.

2019

Sanders JJ, **Johnson KS**, Cannady K, Paladino J, Ford DW, Block SD, Sterba KR. From barriers to assets: Rethinking factors impacting advance care planning for African Americans. *Palliat Support Care* 2019;17:306-313.

Ejem D, Barrett N, Rhodes, R, Olsen M, Bakitas M, Durant R, Elk R, Steinhauser K, Quest T, Johnson KS. Reducing disparities in the quality of palliative care for older African Americans through improved advance care planning: study design and protocol. *J Palliat Med*. In press.

Haines L, Rahman O, Sanders J, **Johnson KS**, Kelley A. Factors that impact family perception of goal-concordant care at the end of life. *J Palliat Med* 2019;22:927-932.

McKellar MS, Kuchibhatla MN, Oursler KK, Crystal S, Akgün KM, Crothers K, Gibert CL, Nieves-Lugo K, Womack J, Tate JP, Fillenbaum GG. Race differences in change in physical functioning in older male veterans with HIV. *AIDS Research and Human Retroviruses*. 2019 Jun 18. doi: 10.1089/AID.2018.0296. [Epub ahead of print] PMID: 30963773 Accepted 2019

Fillenbaum GG, Blay SL, Mello MF, Quintana MI, Mari MJ, Bressan RA, Andreoli SB. Use of mental health services by community-resident adults with DSM-IV anxiety and mood disorders in a violence-prone area: São Paulo, Brazil. *Journal of Affective Disorders*, 2019; First published version available online: 5-MAR-2019 DOI information: 10.1016/j.jad.2019.03.010

Hall KS, Morey MC, Bosworth HB, Beckham JC, Pebole MM, Sloane R., Pieper CF. Pilot randomized controlled trial of exercise training for older veterans with PTSD. *J Behav Med*. 2019 Jul 1. doi: 10.1007/s10865-019-00073-w. PMID: 31264055.

Pebole MM & Hall KS*. Physical activity promotion in women with PTSD: What we need for progress. (2019). *Psychology of Sport and Exercise*, 41, 127-129.

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