complexity & connectivity
decoding the process of aging
Conventional wisdom has long held that symptoms associated with old age are immutable. Muscles get weak, bones get brittle, balance worsens, and memory gets fuzzy—it’s just a matter of time before frailty sets in, impacting mobility and independence. At the Hinda and Arthur Marcus Institute for Aging Research (Marcus Institute) we are optimistic that by fully understanding the complex nature of age-related conditions, the potential for physical, emotional, and social vitality still exists as we grow older.

For more than 50 years, our faculty members have focused on clinical syndromes that profoundly impact older adults and their families but have often been overlooked by other scientists. We have learned that understanding the causes and finding ways to prevent or treat age-related diseases and disabilities require a holistic approach to research—one that looks at the totality of the aging experience.

To stay healthy and function normally, our bodies must effectively integrate elaborate networks and control systems, including feedback loops and other regulatory mechanisms that are organized at molecular, subcellular, cellular, and organ tissue levels. Observing and analyzing the dynamic interplay between all of these components are important to understanding what exactly keeps us strong, resilient, and vital, and conversely what causes frailty when things go awry. When the body can no longer compensate for challenges to its intricate physiological systems it becomes difficult to perform functions as basic as walking, digesting a meal, fighting infections, or dealing with challenging social stresses.

Decoding the process of aging so we can learn how to optimize quality of life as more and more of us live longer is certainly an ambitious project and will take time. For that reason, training the next generation of gerontological researchers remains an important part of the Marcus Institute’s long-term goals. I can proudly report that the Marcus Institute attracts some of the nation’s most talented young scientists who are growing their careers with us and staking their claim on expanding the frontiers of aging research. They are positing and exploring novel hypotheses that address some of the most vexing and confounding challenges associated with maintaining good health with age.

I invite you to meet our researchers in the following pages to learn what we do individually and together to envisage a new age in old age.

Lewis A. Lipsitz, M.D.
Director, Hinda and Arthur Marcus Institute for Aging Research
A slow gait, which is common among older adults, has a profound impact on mobility and independence. Slow gait predicts several adverse outcomes, including decreased mobility and falls.

Why gait slows with age is a complex puzzle. Mobility is not only dependent on the peripheral neuromuscular, skeletal, and cardiorespiratory systems, but also on numerous brain networks and cognitive functions. Studies in the Center for Translational Research in Mobility and Falls, led by Lewis Lipsitz, M.D., and Brad Manor, Ph.D., are investigating the complex relationship between the brain, balance, and mobility.

Studies supported by an NIA-funded project called the MOBILIZE (Maintenance of Balance, Independent Living, Intellect, and Zest) Boston Study have revealed relationships between abnormal blood flow to the brain and slow gait speed in older adults. Our observations have led us to hypothesize that alterations in the control of brain blood flow, associated with aging and cardiovascular risk factors, cause damage to white matter in the frontal cortex of the brain resulting in slowed gait, and cognitive impairment, along with their functional consequences, including falls.

Foot sole sensation also plays a role in balance and requires a complex system of sensory neurons and pathways that provide neural feedback to the brain about how the body is oriented with the ground and is essential for the control of gait and balance. Our investigators, led by Dr. Manor, are showing how very low levels of electrical current, called transcranial direct current stimulation (tDCS), applied non-invasively to the forehead can improve sensory feedback.

Walking is often performed while doing other tasks, such as reading street signs, talking, or using a cell phone. This is called “dual-tasking” and diverting attention from the act of walking can threaten gait and balance. Marcus Institute scientists are using tDCS to activate attention control networks in the frontal cortex of the brain, and showing that this simple painless intervention applied for 20 minutes every day for two weeks can improve walking while dual-tasking, as well as other measures of balance and cognitive function. They are now testing a tDCS device that can be used at home, and are developing a cell phone app that can be used anywhere to test gait and balance to help predict and ultimately reduce the risk of falls.
Americans fear developing dementia more than any other disease. There is no cure, but Marcus Institute researchers are searching for ways to prevent or slow disease progression.

Aging Brain Center Director Sharon Inouye, M.D., M.P.H., is well-known for her pioneering work on delirium. Often striking older patients who are hospitalized, delirium presents as an abrupt confusion or sudden change in cognitive abilities. Efforts to accurately diagnose delirium and develop and advocate for the use of preventive tools have become increasingly important as the Aging Brain Center team works to identify and describe the interface between delirium and dementias like Alzheimer’s disease (AD).

Dr. Inouye and her team have collaborated with researchers from other institutions on studies that suggest delirium and AD share a complex relationship in that they can occur independently, concurrently, and interactively. They share a concern that delirium may promote onset of AD or accelerate progression of the disease. It also appears that severe delirium has the highest risk for negative outcomes on health and cognition.

According to Dr. Inouye, “Though delirium generally subsides after a period of time, it appears to have lasting effects and those effects are related to the severity of the delirium itself. Our studies show the need to target patients with high delirium severity for strategies to prevent progressive cognitive decline as they are at increased risk for dementia.”

Our vision is to reduce delirium and its complications for patients worldwide. This mission is realized through rigorous research studies and is supported by a dedicated staff, along with interdisciplinary collaborators and trainees in a supportive environment utilizing high-quality, innovative methods, and technology.
PALLIATIVE CARE RESEARCH CENTER

Caring for Older People with Advanced Illness: The Quality of Life Connection

Director of Palliative Care Research Susan Mitchell, M.D., M.P.H., has had a profound effect on the medical community’s appreciation of caring for older people living with late-stage Alzheimer’s disease and related dementia. Her studies show that patients with advanced dementia commonly experience uncomfortable or aggressive interventions that may not be of clinical benefit or consistent with comfort-focused care as preferred by the majority of these patients. Moreover, it is not unusual for patients with advanced dementia to experience distressing signs and symptoms that could have been addressed by palliative care.

Dr. Mitchell has conducted studies focused on educating clinicians and families on the progression of dementia and how to make decisions for care as the disease advances. A recent study published in *JAMA Internal Medicine* found AD patient proxies are a fairly accurate judge of the length of life left for their loved one. And, when proxies have judged that their loved one has less than six months to live, they are more likely to have discussed goals of care with the health care team, and less likely to agree to burdensome interventions.

Dr. Mitchell is also conducting large state-of-the-art rigorous clinical trials to study interventions that may improve the care of those living with advanced dementia. For example, a trial funded by the National Institutes of Aging (NIA) is currently being conducted in 28 Boston-area nursing homes testing whether a multi-component educational program can reduce the use of unnecessary and potentially harmful antibiotic use in these patients.

Corey Fehnel, M.D., M.P.H., a faculty member in the Palliative Care Research Center, is a critical care neurologist exploring how to improve care of older adults with life-threatening neurological conditions, such as stroke. He has been awarded a Grant for Early Medical/Surgical Specialists’ Transition to Aging Research (GEMSSTAR) from the NIA with which he will use large national databases to better understand how to promote the best outcomes and quality of life for older individuals with severe eating problems following a stroke. Hospital-level care can be traumatic and often not beneficial for people near the end of life. Using nationwide data, Ellen McCarthy, Ph.D., M.P.H, is studying how new national policies aimed at reducing unnecessary hospitalizations have impacted nursing home residents with advanced illness.

Social connections are vital to optimizing quality of life for patients with end-stage dementia. Families play a critical role.
Keeping Bones and Muscles Strong: The Nature/Nurture Connection

If the brain is command central, the musculoskeletal organs provide the body’s structural integrity and represent another vast system of complexity and connectivity. Loss of bone and muscle strength, along with pain associated with diseases of the musculoskeletal system, leads to falls and fractures that severely limit mobility for many older adults.

Scientists from the Musculoskeletal Research Center are leaving no stone unturned to understand what causes bones and muscles to weaken with age. They study the roles genes, exercise, nutrition, and disease play in determining bone and muscle strength. By understanding better how all these factors work alone, and in concert, they continue to develop effective strategies to prevent or slow progression of diseases like osteoporosis and sarcopenia (muscle loss), and offer effective treatments.

**Bones provide the scaffolding**

Starting with the skeleton, keeping bones strong is vital to preventing fractures. Research shows that older adults who sustain a fracture do not always meet the traditional bone density diagnostic criteria for osteoporosis, a disease characterized by bone loss. Bones become fragile not only due to low bone mineral density (BMD), but also deterioration in bone structure. Using high-resolution peripheral computed tomography (HR-pQCT) researchers are able to probe deeper into bone structure and have found that while BMD remains a useful tool, HR-pQCT allows clinicians to analyze a patient’s bone microarchitecture. The main structural determinants of bone mechanical strength include width and porosity in the cortical bone; and shape, width, connectivity, and anisotropy in the trabecular bone. Analyzing bone microarchitecture is an important step in identifying additional bone traits that predict fracture risk.

We are also focused on which factors are essential to know in the one-year period before any fracture occurs, with an eye to providing the means to identify high-risk individuals. By directly studying factors contributing to falls in the nursing home population, Sarah Berry, M.D., M.P.H., has developed a screening tool that can predict fractures. She is implementing this tool for residents at Hebrew SeniorLife and in other facilities, showing how research can sometimes be quickly implemented to help older adults.
Geriomics program
Then there is the question: why are some people more disposed to age-related disease than others? Musculoskeletal disorders greatly impact quality of life across a spectrum of age groups. Yet despite their prevalence, relatively little is known about how genes work together with the environment to cause diseases of the musculoskeletal system. Common age-related conditions that are inherited, such as osteoporosis (bone loss), sarcopenia (loss of muscle), muscle weakness, foot disorders, and metabolic syndrome (insulin-related obesity) cause disability and frailty. Since these conditions are genetically determined, knowledge about their molecular underpinnings may yield important discoveries related to prevention and treatment.
Headed by Musculoskeletal Research Center Director Douglas P. Kiel, M.D., M.P.H., the Geriomics program is searching for genetic determinants of age-related diseases primarily of the musculoskeletal system. This program began as part of the Musculoskeletal Research Center and includes faculty and post-doctoral fellows appointed through Harvard Medical School. In collaboration with an international consortium of scientists, program faculty are already making important discoveries. Dr. Kiel took part in a groundbreaking study published in 2018 that succeeded in identifying 518 regions of the human genome that were significantly associated with bone density, many of which were not previously recognized. This raises the possibility of developing new treatment targets based on the genes involved.

Other parts of the anatomy, long neglected by research but critical to mobility, are the foot and the back. Musculoskeletal Research Center Co-director Marian T. Hannan, D.Sc., M.P.H., has also studied heritability of foot disorders and is finding that here too genes play a role. Foot pain is often underappreciated for the cascading effect it has on other joints, including knees and hips that culminate in immobility. Dr. Hannan and the Musculoskeletal group are providing seminal work on foot biomechanics and have inspired a new generation of scientists in this area of population research ranging from Australia to the U.K., including physicians, podiatrists, physical therapists, and translational scientists. Arthritis at knee and hip, as well as the foot remain key topics of concerns.
Similarly, Elizabeth J. Samelson, Ph.D., has been identifying factors that lead to spine degeneration and loss of mobility. And the key features of arthritis at the hip and knee are the focus for Michelle Yau, Ph.D., as she links bone lesions in the joints to onset or progression of the disease.
**Nutrition program**

We can’t choose our biological parents, but we can still make choices that compensate for genetic bad luck. Does dairy intake encourage good bone health and if so, what kind and how much? Does the vegetable-rich Mediterranean diet help stave off frailty? Do vitamin supplements make a difference in maintaining strong bones and muscle mass? These are the questions our researchers hope to answer, while at the same time keeping an eye on the interplay of nutrition with genes, disease, and the environment.

Nutrition has always played a central role in prevention and is important in maintaining optimal bone and muscle health. Work from the Musculoskeletal Research Center’s Nutrition program moves these ideas beyond the current boundaries with an aim to identify novel risk factors and pathways of age-related bone and muscle loss. This work has an overall theme of nutritional interventions at earlier phases of disease, as well as increased detection of people at high risk, with the overarching promise of strategies that will lead to development of effective interventions across the life span for adults.

Muscle mass and strength are equally important to mobility. In an ongoing study, Shivani Sahni, Ph.D., and faculty in the Musculoskeletal Research Center are examining the roles antioxidant intake, endothelial function, aortic stiffness, and mitochondrial dysfunction play in loss of muscle mass and strength, gait speed, and muscle quality in adults from the Framingham Offspring Study. A goal is to determine the combined effect of novel (antioxidants, vascular function, and mitochondrial DNA copy number) and established (protein intake, inflammation, and physical activity) risk factors on baseline measures of lean mass, upper extremity muscle quality, change in grip strength, and gait speed.

The group also works to improve nutrition awareness for the Hebrew SeniorLife communities, as well as scientists and clinicians through the Nutrition Education and Community Outreach Series. This quarterly interdisciplinary series brings cutting-edge, clinical, and translational nutrition research to all the departments across HSL with strong attendance.
Research requires high-quality data collection and analysis to ensure that scientific results are valid and relevant for older populations. Marcus Institute projects require cutting-edge analytic tools to develop interventions that treat age-related disease and syndromes in our complex and sometimes high-risk populations.

For these reasons, in 2014, the Marcus Institute formed a core team of quantitative scientists under the direction of Thomas Travison, Ph.D. The Biostatistics and Data Sciences group collaborates with teams across the Marcus Institute using best contemporary scientific practices in data analysis. Its mission is to conduct cutting-edge studies in aging, in order to close the gap between research and the improvement of public health, using the combined expertise of the group in statistics, economics, genetics, epidemiology, clinical trials, big data, and aging itself. The team also has a significant focus on software development for research in aging, so that results and tool sets can be readily disseminated and shared with colleagues and the public worldwide.

Together the team has the technical and quantitative skills to solve complex visualization and data processing problems, and the passion and curiosity to do this work in the field of aging. The data science team works in concert with clinical and translational scientists driven to unravel the intricate mysteries underlying the most vexing age-related conditions. Together they envision a future where we all remain independent to the very end of life’s journey.
The Marcus Institute is distinguished from other institutions devoted to aging research by its location within an organization that provides communities and health care for seniors. Our researchers have access to geriatric care expertise within Hebrew SeniorLife and interface with the populations HSL serves.

As a result, Marcus Institute researchers are uniquely poised to design and conduct clinical trials that test cognitive, behavioral, functional, nutritional, technological, and multi-component interventions among vulnerable older individuals in various health care settings. These trials will directly inform clinical and policy decisions pertaining to the health of older adults.

In 2018, the Marcus Institute launched a new initiative—the Interventional Studies in Aging Center (ISAC). Under the direction of Susan Mitchell, M.D., M.P.H., and Thomas Travison Ph.D., ISAC stimulates the methodology and rigor of potentially high-impact clinical trials in aging, with particular focus on non-pharmacological interventions tested using cluster and/or pragmatic trial designs.

ISAC supports all types of trials with a particular focus on those that include diverse older patients with comorbid conditions, who are often excluded from more typical clinical trials. The trials take place in “real world” settings such as senior living communities or nursing homes, testing interventions in the settings where participants live, or are cared for, whether in assisted living, nursing homes, or the doctor’s office.

Studies supported by ISAC range from the effect of transcranial direct current stimulation on motor and cognitive functions in individuals with a history of unexplained falls to outcomes of Tai Chi among residents of senior housing to trials to reduce antimicrobial use in nursing home patients with Alzheimer’s and other dementias.
We face a critical shortage of clinical researchers across the board, and in aging research in particular. We simply don’t have enough people training in geriatric medicine and gerontology. This problem is compounded by the lack of role models to inspire young scientists to build careers in aging research. For this reason, the Marcus Institute has established support and mentorship of young faculty as a priority for its strategic growth plan.

Through generous philanthropic support, we’ve been able to attract talented young scientists and provide support that allows them to conduct studies that establish a track record, which in turn positions them to qualify for future grant awards.

But financial support is just part of the equation. The Marcus Institute is fortunate to include faculty who have been recognized for their exceptional roles as mentors. Senior faculty include brilliant and approachable scientists nurturing and cultivating the next generation of researchers. They are an invaluable asset to Hebrew SeniorLife, the rest of the medical community, and to the seniors with whom Marcus Institute researchers and Hebrew SeniorLife professionals work with every day.

Dr. Susan Mitchell mentors Corey Fehnel M.D., M.P.H., a researcher with the Palliative Care Research team. He is interested in patients who are critically ill in the intensive care unit and is concerned that clinicians do a lot to escalate care, but don’t know how to de-escalate care.
Aging Brain Center Director Sharon Inouye, M.D., M.P.H., Honored in 2018
Dr. Sharon Inouye received the Franz-Koehler Inflammation Award 2018 from the German Society of Anaesthesiology and Intensive Care Medicine and was made an Honorary Fellow of the American Academy of Nursing.

Marcus Institute Director Lewis Lipsitz, M.D., Received the Donald P. Kent Award
The Gerontological Society of America (GSA) chose Dr. Lewis Lipsitz as the 2018 recipient of the Donald P. Kent Award. This distinguished honor is given annually to a GSA member who best exemplifies the highest standards for professional leadership in gerontology through teaching, service, and interpretation of gerontology to the larger society. It was established in 1973 in memory of Donald P. Kent, Ph.D., for his outstanding leadership in translating research findings into practical use.

Susan L. Mitchell, M.D., M.P.H., Honored by Beth Israel Deaconess Medical Center’s Special Thorndike Lecture Series
Dr. Mitchell was the 2018 Honoree of the Beth Israel Deaconess Medical Center’s Special Thorndike Lecture Series, which started several years ago to honor the contributions of impressive researchers with connections to BIDMC. The lectures have largely been overviews of honorees’ research contributions, as well as their career paths—including the personal aspects, what attracted them to science and research, how they trained and got started, and what the ups and downs of their paths were. These lectures have been incredibly inspirational to BIDMC residents. Dr. Mitchell received this honor for her mentorship of trainees at BIDMC and across the broader Harvard community, and to acknowledge her important scientific contributions.

Elizabeth J. Samelson, Ph.D., and Douglas P. Kiel, M.D., M.P.H., Selected as Fellows of the American Society for Bone and Mineral Research
Drs. Samelson and Kiel were recognized for being long-term members who have made outstanding contributions to the field of bone and mineral science. They were recognized at the ASBMR Annual Meeting, September 29-October 1, 2018 in Montréal, Québec, Canada.

2018 Faculty Recruitments
Dae Kim, M.D., M.P.H., is an Assistant Scientist II reporting to Dr. Lipsitz. He is also a staff geriatrician in the Division of Gerontology at Beth Israel Deaconess Medical Center and assistant professor of medicine at Harvard Medical School. As a geriatrician and clinical investigator, Dr. Kim’s research focuses on developing practical algorithms to facilitate personalized clinical decision-making in older adults, and using functional outcomes and disability as main measures of treatment effectiveness in older adults with advanced cardiovascular disease.

Ellen P. McCarthy, Ph.D., M.P.H., joined the Palliative Care Research Center as an associate scientist. Dr. McCarthy is associate professor of medicine and epidemiology at Harvard Medical School and Harvard T.H. Chan School of Public Health. Dr. McCarthy is an epidemiologist with more than 20 years experience leading and managing interdisciplinary research aimed at improving the care of older patients with advanced illness, and reducing disparities in end-of-life care. She is also an accomplished mentor.
Hinda and Arthur Marcus are recognized for their long-time support of research at Hebrew SeniorLife

The most impactful milestone in 2018 was the renaming of the Institute for Aging Research to acknowledge a transformative gift from Hinda and Arthur Marcus. Hinda Marcus, a Hebrew SeniorLife Board member and former Board Chair, has long been a champion, advocate, and supporter of Hebrew SeniorLife and its commitment to aging research.

Hinda and her husband Arthur hold a bedrock belief that the best way to improve the health and well-being of seniors both near and far is to increase the Marcus Institute’s capacity so its research and scientific collaborations will grow and its discoveries will be disseminated even more widely.

The Marcuses’ generosity will be instrumental in helping the Marcus Institute pursue its strategic plan for growth, and particularly to sustain the clinical trials program that they helped initiate. They recognized this is the time to redefine aging, and seized the opportunity to make a difference in the lives of seniors and their families for generations to come.

selected publications


2. Loizeau AJ, Shaffer ML, Habtemariam DA, Hanson LC, Volandes AE, Mitchell SL


   Frailty in Elderly Patients Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. J Am Coll Cardiol. 2017; 70: 689-700. PMID: 28693934

5. Park Y, Bateman BT, Kim DH, Hernandez-Diaz S, Patorno E, Glynn RJ, Mogun H, Huybrechts KF
   Use of Haloperidol versus Atypical Antipsychotics and Risk of In-Hospital Death in Patients with Acute Myocardial Infarction: Cohort Study. BMJ 2018; 360: k1218. PMID: 29592958; PMCID: PMC5871903.


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2018

Financials
Total Sponsored Award portfolio represents 90 sponsored awards with a total portfolio of $63,079,265.

Operating Revenue
- Endowment Interest and Philanthropy $1,289,282
- Sponsored Awards Facilities and Administrative (F&A) and fringe Revenue 3,417,393
- Sponsored Award Direct Revenue 6,591,527

$11,298,202

Sponsored Award Direct Revenue
- Federal Awards $5,133,851
- Industry Awards 263,561
- Foundation and Other Awards 101,700

$5,499,112