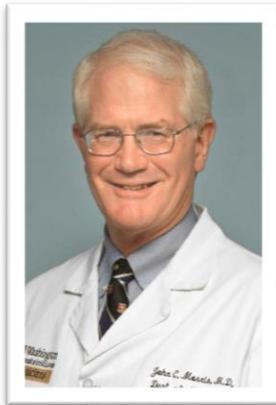


Knight Alzheimer's Disease Research Center
Knight ADRC
2020 Impact Report



A Message from Dr. John C. Morris



As I reflect upon our work over the past year, I want to share my sincere gratitude for all that we have been able to accomplish with the help of supporters, both those who are here in St. Louis and those elsewhere. To realize our vision of a world without Alzheimer's disease, we know that we must fully capitalize on interfaces between many scientific disciplines and develop innovative tools and approaches in pursuit of this aim. In this Impact Report, we describe just a few examples, such as a recently developed Alzheimer's Risk Calculator, advances at the intersection of genetics and neuroscience, and exploration of the role of physical activity and cardiorespiratory fitness in reducing the risk of neurodegeneration.

This year, the coronavirus pandemic has challenged us on many fronts, and I want to say how extremely grateful we are to our study participants and their families for the patience they have shown through this time. We are all eager to resume the full scope of our operations when it is safe to do so, and will be keeping everyone informed as we move forward. I hope you will have a chance to take a look at a short four-minute video that gives a look at how ongoing work is being managed, and expresses our heartfelt concern for and gratitude toward the participants in our studies. The video message is available on the Knight ADRC website: knightadrc@wustl.edu.

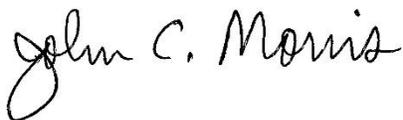
I want to take this opportunity to emphasize as well the foundational importance of equity in all that we do as a research center. The lack of equity in our health care system and in the system of medical science research is a problem that we have worked to overcome and will be doing more to address. At the Knight ADRC, we recognize that only if we carry out studies that are inclusive in terms of race, ethnicity and gender will we be able to make the benefits of future Alzheimer's disease treatments and interventions a reality for everyone. Important contributions are being made by the African-American Advisory Board, a critical component of the Knight ADRC since 2000, to improve the diversity of our study participants and of our clinical and research trainees.

Finally, I want to share an update about a new development that has relevance for all research at Washington University into conditions affecting the brain, as well as

for the midtown region of our city. Washington University broke ground on March 6, 2020, on a state-of-the-art neuroscience research building where ultimately 875 investigators from fields including neurology, neuroscience, neurosurgery, psychiatry, and anesthesiology will leverage synergies and chart new paths forward. Research teams in this 609,000-square-foot facility will benefit from its location near biotech startups in the Cortex Innovation Community in midtown St. Louis. The Cortex Innovation Community is one of the nation's fastest growing districts dedicated to innovation and entrepreneurship, and a critical component in the revitalization of midtown St. Louis. The neuroscience research building, scheduled to open in 2023, will bring additional momentum while serving the goal to move new discoveries out of the lab and into worldwide use.

The broad and collaborative effort we have sustained over the past year, and our willingness to address challenges, leave me with optimism about our future. In my many years as director of the Knight ADRC, I always am amazed and so appreciative of the commitment to excellence and integrity that is shown daily by our study participants, faculty, staff, and supporters and friends. I am confident that we will realize a future fully aligned with our values and with our vision to conquer Alzheimer's disease for all people for all time.

Gratefully,

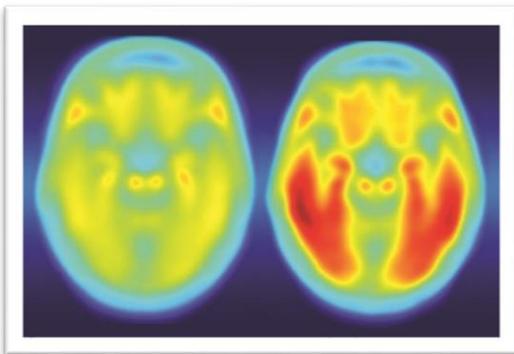
A handwritten signature in black ink that reads "John C. Morris". The signature is written in a cursive, flowing style.

John C. Morris, MD
Harvey A and Dorismae Hacker Friedman Distinguished Professor of Neurology
Professor of Pathology and Immunology
Professor of Physical Therapy
Professor of Occupational Therapy
Director, Knight ADRC
Head of Section of Aging & Dementia

Selected Highlights of Alzheimer's Research Progress

Assessing Individuals' Risk of Developing Alzheimer's Disease

Each year, hundreds of individuals who have no symptoms of Alzheimer's disease devote time and effort as participants in studies at the Knight ADRC. Their dedication, often over 10 or more years, makes it possible for us to collect data on healthy cognitive function in older adults, and to better understand the changes brought on by Alzheimer's disease. However, until now, these cognitively normal study participants had no access to their individual test results, or to informed interpretation of them. After a thorough evaluation of scientific, ethical and operational considerations, we are embarking on an effort to return test results of cognitively healthy study participants to them, and, importantly, to interpret these results as to their providing an individualized estimate of future increased or decreased risk of Alzheimer's disease.



PET shows tau protein in the brain to track cognitive decline due to Alzheimer's disease.

This work is led by Associate Professor of Psychiatry Sarah Hartz, MD, PhD, and Assistant Professor of Medicine Jessica Mozersky, PhD. The analytical tool that they developed – the Alzheimer Risk Calculator – takes into account age, family history, and a genetic risk factor known as the APOE genotype, as well as findings from a participant's most recent MRI brain scan and amyloid PET scan. Using the Alzheimer Risk Calculator, Drs. Hartz and Mozersky will be able to determine whether a

study participant's risk for developing Alzheimer dementia is increased, and, if so, by how much, or decreased, and, if so, by how much.

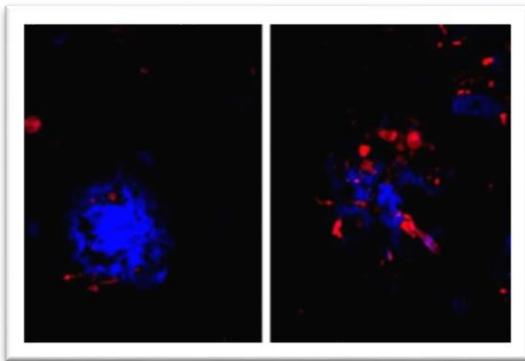
Drs. Hartz and Mozersky are in the process of copyrighting the Alzheimer Dementia Risk Calculator, and hope that in time it will become widely available. It is not yet public, but to see a preliminary version of the Alzheimer Dementia Risk Calculator, click here: [WashU Alzheimer Dementia Risk Calculator](#).

As we strive to bring forth treatment and prevention strategies for Alzheimer's disease, being able to identify and closely monitor individuals at higher risk will be critical. Our vision is that risk analysis tools like those being developed by

Drs. Hartz and Mozersky will help health care providers around the world one day deliver therapeutic intervention on a broad scale well before Alzheimer's symptoms would otherwise appear.

Expanding our Capacity to Conduct Clinical Trials

Through extraordinary philanthropic support, the Knight Alzheimer's Disease Research Center was able to realize a long-held goal, to establish the Knight ADRC Clinical Trials Unit. This unit will evaluate new drugs and other new therapeutic and diagnostic approaches. This means that we now have in St. Louis not only a top tier



In Alzheimer's, amyloid clumps (blue) develop first in the brain, followed by tangles of the protein tau (red). Tau is associated with memory loss and confusion.

research team investigating Alzheimer's disease, but also the ability to take the discoveries of science and test and fine tune them to ultimately achieve the goal of disease-modifying therapies or prevention strategies. The Knight ADRC Clinical Trials Unit is being led by Professor of Neurology B. Joy Snider, MD, PhD. The resources to launch this important expansion of our work were generously provided by Rodger and Paula Riney.

The Critical Intersection of Genomics and Neuroscience

In pursuit of a treatment or prevention strategy for Alzheimer's disease, it is critically important to clarify the genetic underpinnings of the disease process. At Washington University, we are able to build on a robust neurology and neuroscience environment as well as a remarkable history of accomplishment in genetics, including a leadership role in the mapping of the human genome in the early 2000s. Today, a Knight ADRC-affiliated lab is identifying genetic factors that can raise, or lower, the risk of developing Alzheimer's disease. Led by Professor Carlos Cruchaga, PhD, this work involves scanning the genomes of some 4,000 people – some of whom have Alzheimer's and others who don't – and comparing observed genetic variations with known molecular signs of Alzheimer's disease.

Dr. Cruchaga's research is not only looking at genomes, but also at other "omic" data such as transcriptomics and proteomics, to better understand the expression of information in RNA transcripts as well as protein structure and function within cells. We know that all human genes are part of one or more biological pathways, and points on a pathway can be potential targets for drug therapies aimed at influencing the disease process. As specific genes and pathways become better understood, the number of potential drug targets increases. Evidence suggests that there may be drugs already available which could target pathways of importance in Alzheimer's disease.

Exploring the Role of Cardiorespiratory Fitness

Work at the Knight ADRC and elsewhere has shed light on several aspects of the aging process and cognitive function. In assessing the overall risk of neurodegeneration, there is evidence that cardiovascular health and cardiorespiratory fitness play important roles. At the Knight ADRC, we are launching a project to evaluate the role of physical activity and cardiorespiratory fitness as mechanisms to reduce the risk of neurodegeneration, as measured by regional brain volumes seen on the brain scans of our study participants.

This work is being led by Denise Head, PhD, Professor of Psychological & Brain Sciences, Affiliated Faculty the Knight Alzheimer's Disease Research Center.

The Power of Philanthropy

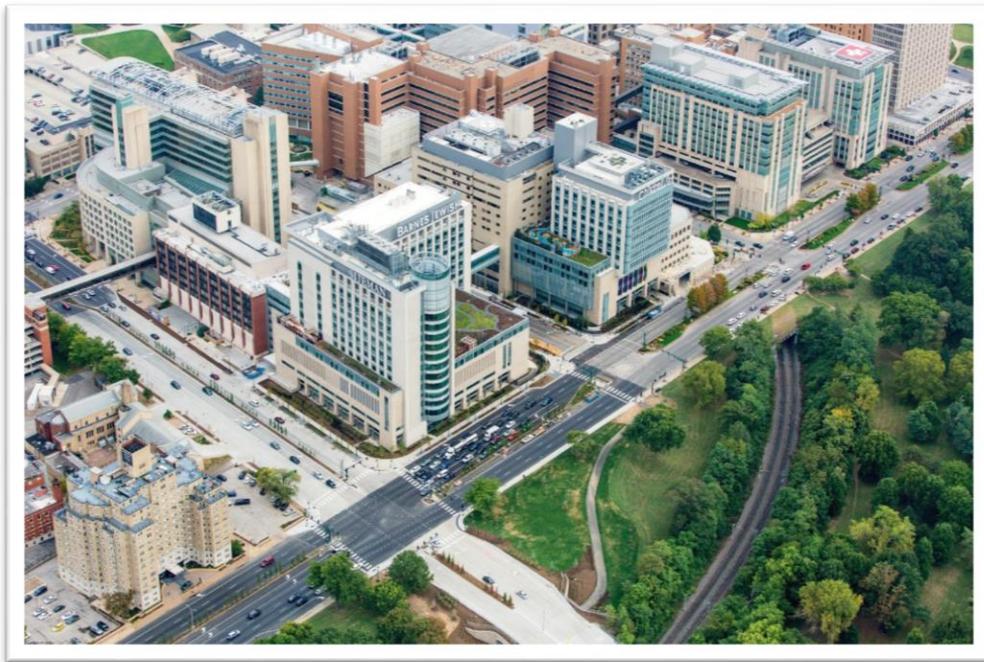


At the Knight ADRC, our multi-disciplinary, cutting-edge work has merited sustained support from federal funders such as the National Institute on Aging (NIA). In fact, the Knight ADRC has been continuously funded by the NIA since 1985. Yet our ability to successfully compete for federal agency support is absolutely dependent upon the vision and generosity of philanthropic

partners who make it possible for us to do foundational and proof of concept work necessary to secure such grants.

In other instances, we are doing work on drug development that pharmaceutical companies are unwilling to carry out. Typically this is because the lengthy periods of testing can exceed the life of the patent on the drug, making testing unprofitable as a business investment. In the complex field of Alzheimer’s drug development, philanthropic support is vital to the process of bringing medically viable solutions forward.

Given the urgency of the Alzheimer’s disease problem – and the tremendous potential for progress – we remain grateful to our philanthropic partners and dedicated to turning their support into a better future for individuals and families.



Medical Campus, Washington University in St. Louis

Propelling Discovery

Selected publications and talks by Knight ADRC-affiliated faculty.

“A harmonized longitudinal biomarkers and cognition database for assessing the natural history of preclinical Alzheimer’s disease from young adulthood and for designing prevention trials.”

– Alzheimer’s & Dementia, January 2019

“A naturalistic study of driving behavior in older adults and preclinical Alzheimer disease: a pilot study.”

– Journal of Applied Gerontology, February 2019

“Assessment of racial disparities in biomarkers for Alzheimer disease.”

– JAMA Neurology, March 2019

“Modeling functional connectivity changes in late onset Alzheimer’s disease using deep learning.”

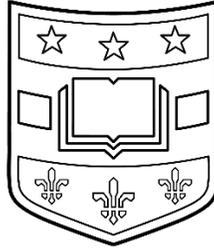
– Alzheimer's & Dementia, July 2019

“High-precision Plasma β -amyloid 42/40 Predicts Current and Future Brain Amyloidosis.”

– Neurology, August 2019

Lecture given by Dr. John C. Morris. American Neurological Association Presidential Symposium, St. Louis, Missouri, October 13, 2019

Lecture given by Dr. John C. Morris. World Congress of Neurology, Dubai, United Arab Emirates, October 25-29, 2019



For more information, please contact:

Alexandra Carr, Senior Director
Medical Advancement
CB 1247
7425 Forsyth Blvd.
St. Louis, MO 63105
Office: (314) 935-3498
Cell: (571) 229-2171
alex_carr@wustl.edu