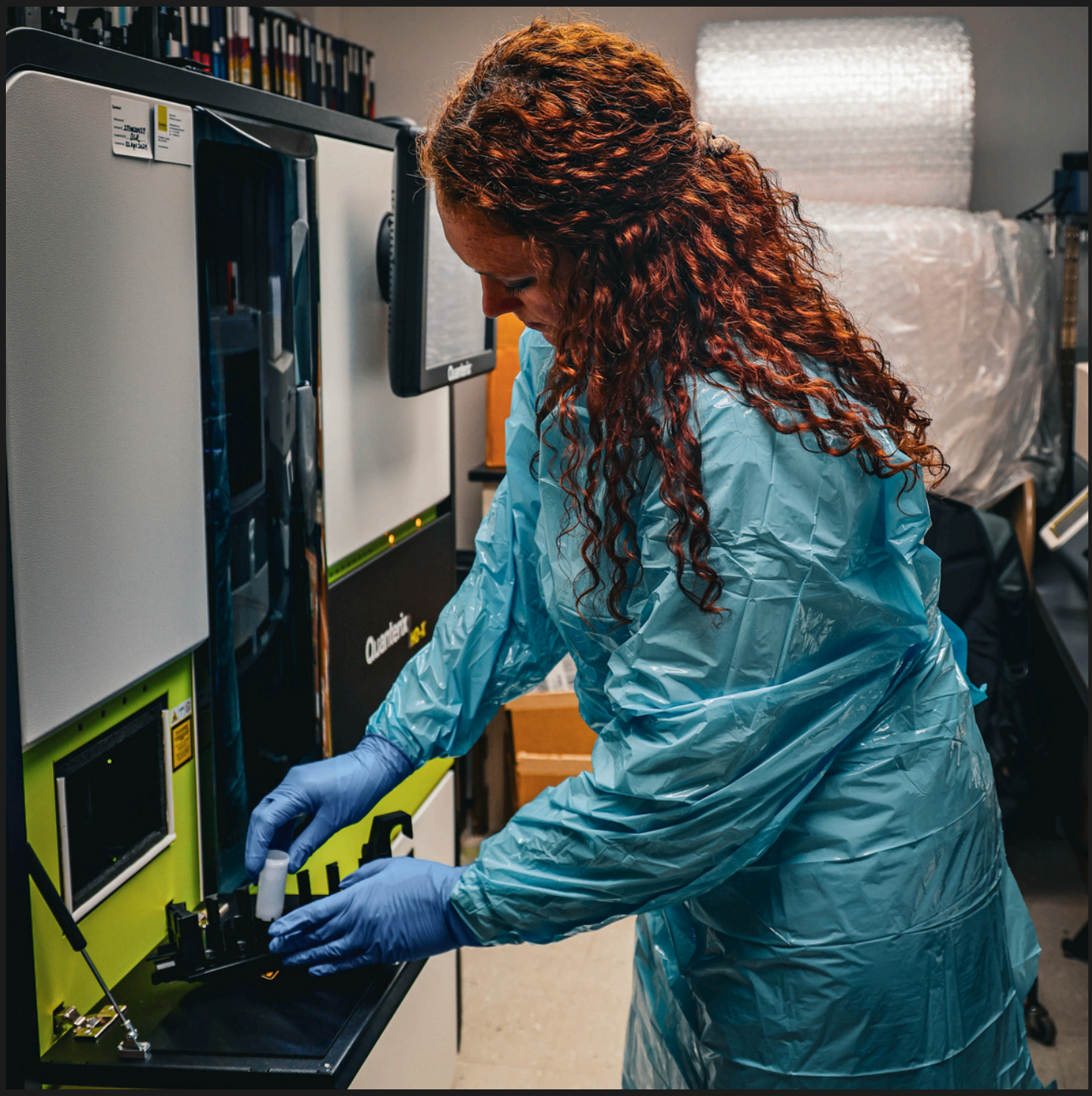
VANDERBILT UNIVERSITY MEDICAL CENTER | Vanderbilt Memory & Alzheimer's Center

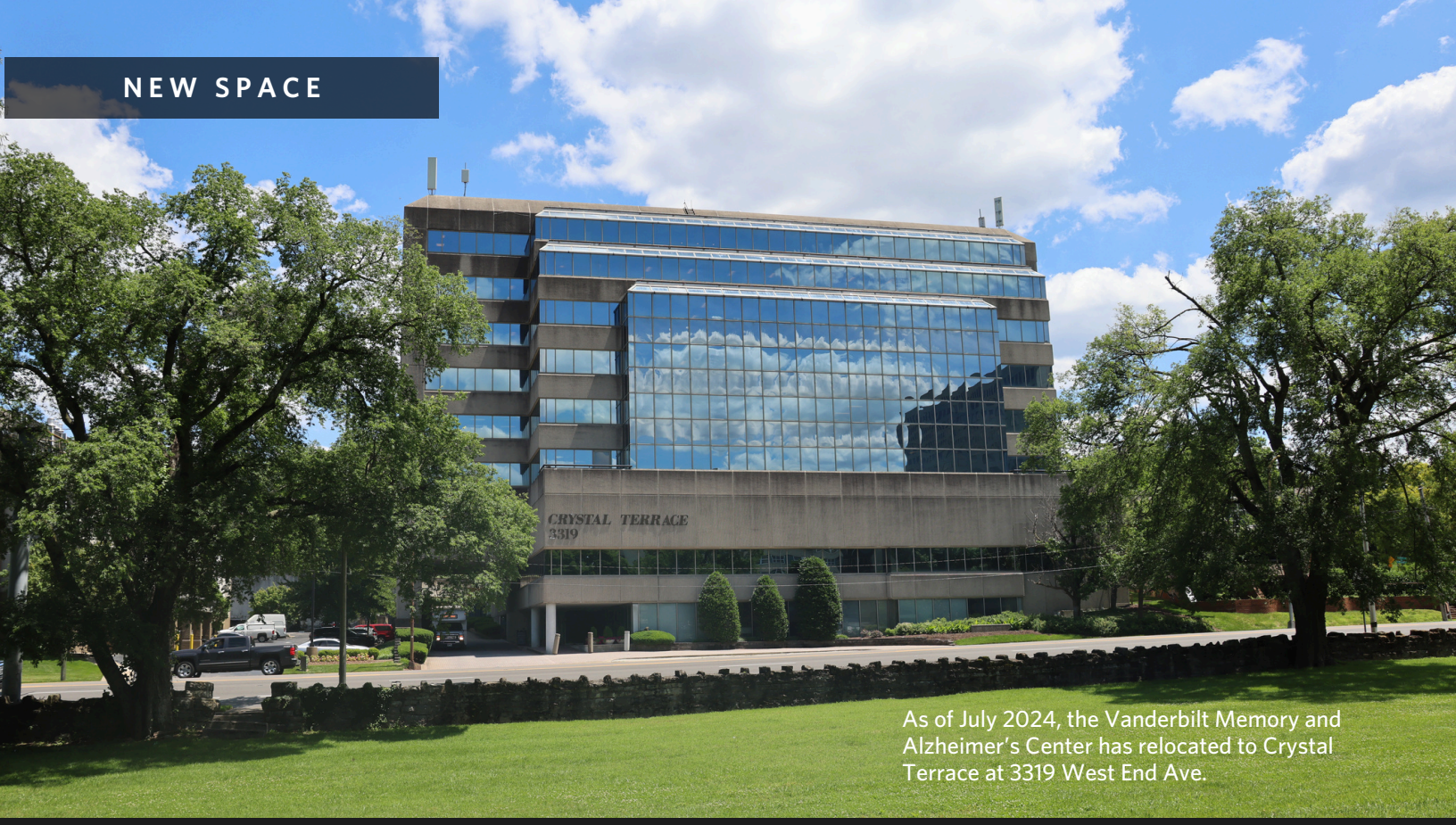


2023-2024

IMPACT REPORT

ADVANCING DISCOVERIES IN ALZHEIMER'S RESEARCH

NEW SPACE



As of July 2024, the Vanderbilt Memory and Alzheimer's Center has relocated to Crystal Terrace at 3319 West End Ave.

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LETTER FROM THE DIRECTOR

The 2023-2024 academic year has been a period of exceptional progress for the Vanderbilt Memory and Alzheimer's Center as we continue to make significant strides in the fight against Alzheimer's disease.

One of our most exciting advancements has been the implementation of a new biomarker discovery platform, which allows us to detect an Alzheimer's-related protein before symptoms begin using a simple blood test. This innovation has the potential to transform the way we diagnose and treat this devastating disease.

In the 2024 Impact Report, you will also read about advancements in our local research program, new developments in community outreach, and our ongoing commitment to training the next generation of clinicians and scientists.

I want to express my deepest gratitude to our participants, donors, and community partners, whose generous support makes our work possible. Together, we are paving the way for a future without Alzheimer's.

DR. ANGELA L. JEFFERSON

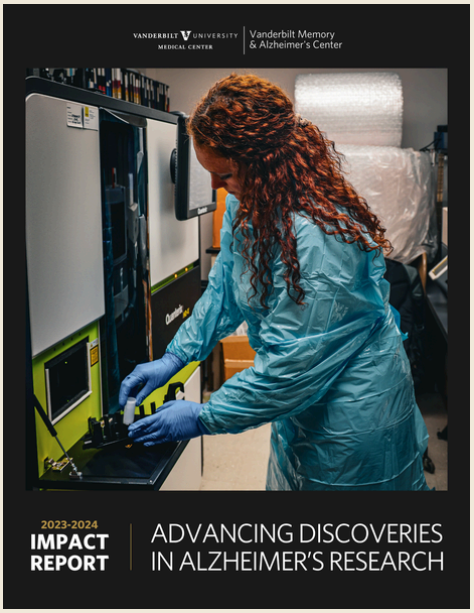
Herbert O. and Vineta Christopher Directorship in Alzheimer's Disease
Director, Vanderbilt Memory and Alzheimer's Center
Director, NIA Exploratory Vanderbilt Alzheimer's Disease Research Center
Vice Chair of Scientific Strategy and Innovation, Department of Neurology
Professor of Neurology

COVER STORY

VANDERBILT IMPLEMENTS INNOVATIVE BIOMARKER DISCOVERY PLATFORM

As we are entering a new era of Alzheimer's therapies, the ability to rapidly screen and detect the disease is more important than ever. New, ultra-sensitive technology can capture lower abundance proteins in the blood. With this technology, we can now use a blood test to detect phosphorylated tau, one of the primary protein abnormalities in Alzheimer's disease. Importantly, we can detect this protein well before symptom onset.

Last year, our Center purchased the Quanterix platform and installed it at Vanderbilt University Medical Center in collaboration with the Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center. We have initiated analyses of our blood and cerebrospinal fluid samples in both the Vanderbilt Memory and Aging Project and Tennessee Alzheimer's Project. The availability of a blood-based biomarker that can be used as an early identification tool has the potential to transform both Alzheimer's discovery and healthcare delivery.



VANDERBILT MEMORY AND AGING PROJECT

2012

LAUNCHED VMAP LEGACY COHORT

2013

LAUNCHED LUMBAR PUNCTURE PROTOCOL

2017

LAUNCHED 5-YEAR FOLLOW-UP VISITS

2020

$23M IN EXPANSION GRANTS AWARDED

2022

NBC TODAY SHOW FEATURE WITH MARIA SHRIVER

2022

RECEIVED FIRST BRAIN DONATION

2023

LAUNCHED AMYLOID + TAU PET PROTOCOLS

2024

LAUNCHED FLUID BIOMARKER DISCOVERY PLATFORM

VANDERBILT MEMORY AND AGING PROJECT CELEBRATES 12 YEARS OF DISCOVERY

In 2012, the Vanderbilt Memory and Aging Project (VMAP) was established to investigate the connection between vascular health and brain aging. By uncovering how vascular factors contribute to Alzheimer's disease, researchers aim to identify early intervention targets, offering the potential to delay or even prevent the onset of this devastating disease.

The original cohort of participants consisted of over 330 older adults with and without memory problems. These individuals completed a comprehensive range of study procedures, including neuropsychological assessment, brain and heart imaging, blood draw, and a lumbar puncture.

Several novel findings emerged from these data, including:

- Poor blood flow from the heart relates to reduced blood flow in brain regions where Alzheimer's first begins.
- In brain MRIs of older adults, fluid-filled spaces around small vessels in the brain are associated with worse cognition.
- Greater stiffness of the aorta, the body's main artery, is associated with lower blood flow to the brain and may play a role in cognitive decline.

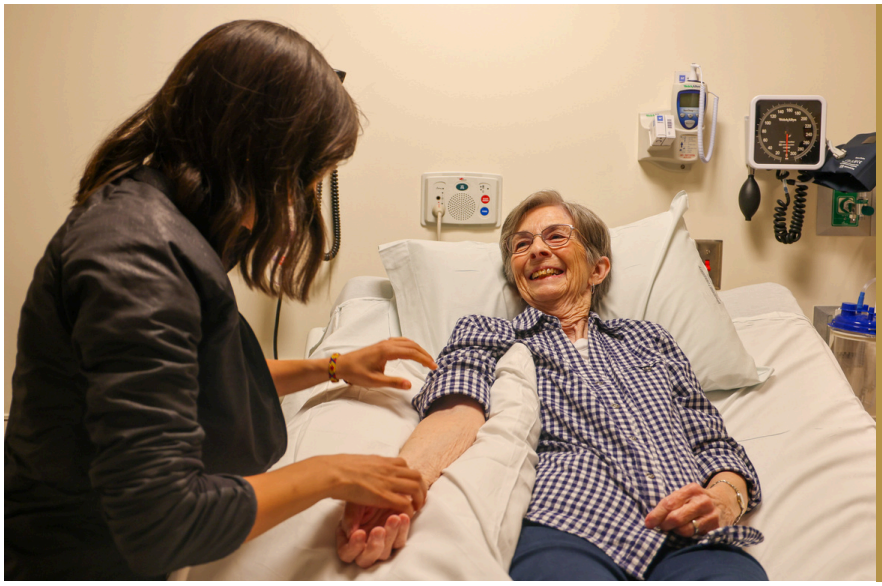
In 2020, the Vanderbilt Memory and Alzheimer's Center received two important grants from the National Institute on Aging to support a major expansion of the VMAP cohort. Part of that expansion was a commitment to recruiting at least 25% people of color to our new cohort who are disproportionately impacted by Alzheimer's disease yet historically underrepresented in research.

Today, VMAP is nearing its goal of enrolling 1,000 participants—17% of whom belong to underrepresented racial or ethnic groups. Some of these participants have been contributing to this vital research for over 11 years.

The advancements made in Alzheimer's research through VMAP would not have been possible without the generosity and dedication of our study participants. Their contributions are paving the way for a future where Alzheimer's disease can be better understood, treated, and ultimately prevented.

INTERESTED IN JOINING A STUDY?

PLEASE CONTACT OUR TEAM AT 615-875-3175 OR VMAC.RESEARCH@VUMC.ORG



I have been in the study since the very beginning. My mother-in-law had Alzheimer's and it is a really devastating disease. I am happy to do anything I can to help find a cure.

Judy Fox
VMAP Participant

Vanderbilt Memory and Alzheimer's Center Director Dr. Angela Jefferson with Jim and Trish Munro.

GENEROUS DONOR BEQUEST SUPPORTS INNOVATION IN ALZHEIMER'S RESEARCH

Jim and Trish Munro know firsthand the devastating reality of Alzheimer's, both experiencing the loss of their mothers who faced the disease. After Jim received life-saving care at Vanderbilt University Medical Center, he and Trish felt called to give back.

When considering their options, Jim and Trish decided that a bequest to the Vanderbilt Memory and Alzheimer's Center, as part of a will or trust, was the best choice.

"We decided to give back to the Vanderbilt Memory and Alzheimer's Center, a real force within the Vanderbilt medical system," said Jim Munro. "Through meetings with Dr. Jefferson, we began to understand what the Vanderbilt Memory and Alzheimer's Center is doing to get behind Alzheimer's identification before there are symptoms."

Jim and Trish Munro hope this gift will help accelerate Alzheimer's research advancements at the Vanderbilt Memory and Alzheimer's Center and support the Middle Tennessee community for years to come.

"Donations like this one give us the opportunity as scientists to really engage in high risk, high reward discoveries that push the needle in the diseases that we study," said Director of the Vanderbilt Memory and Alzheimer's Center Dr. Angela Jefferson. "When people are interested in creating a legacy and giving back to improve public health and their local community, this is a great way to do it."

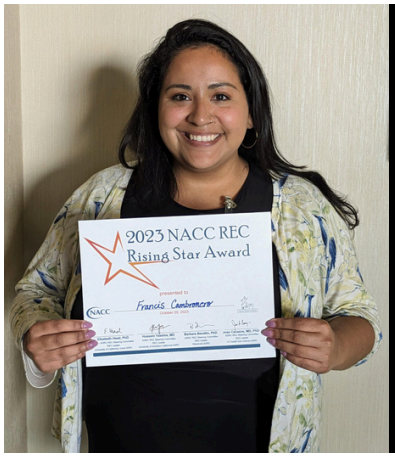
Scan the QR code with your smartphone camera for a video on Jim and Trish Munro's donation story

SUPPORT ALZHEIMER'S RESEARCH EFFORTS HERE IN TENNESSEE
WWW. VUMC.ORG/VMAC/DONATE

VANDERBILT INTERDISCIPLINARY TRAINING PROGRAM IN ALZHEIMER'S DISEASE RENEWED

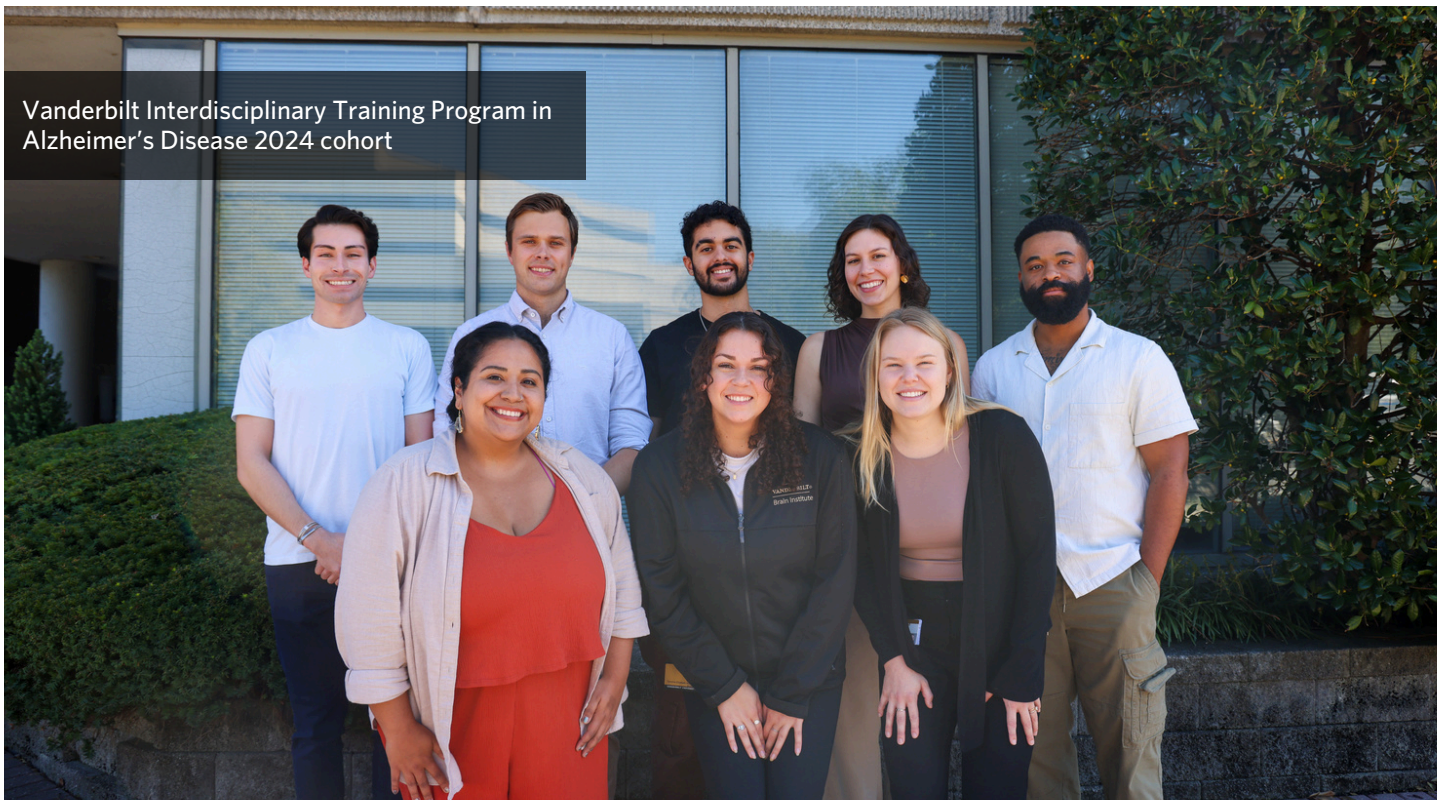
To ensure long-term sustainability and growth in Alzheimer's research and care, training the next generation of scientists and clinicians is a priority at the Vanderbilt Memory and Alzheimer's Center. In 2018, our Center received a National Institutes of Health grant to establish the Vanderbilt Interdisciplinary Training Program in Alzheimer's Disease. The program provides intensive training for talented PhD students and post-doctoral scientists.

To date, this robust program has nurtured the Alzheimer's intellectual neighborhood at Vanderbilt, supporting trainees from a variety of disciplines. Given its success, the training program was renewed in 2024 for five more years of funding. This past May, the Center proudly welcomed a cohort of five PhD students and 3 post-doctoral scientists representing multiple departments, including neuroscience, genetics, chemistry, and cell and developmental biology.



The Vanderbilt Interdisciplinary Training Program in Alzheimer's Disease offers the unique benefit of engaging with a truly interdisciplinary Alzheimer's research community. These interactions have enabled me to strengthen the translational nature of my own research, better identify opportunities for scientific collaboration, and expand my co-mentorship networks.

Francis Cambronero, PhD, Postdoctoral Fellow



Vanderbilt Interdisciplinary Training Program in Alzheimer's Disease 2024 cohort

NEW DISCOVERIES IN ALZHEIMER'S RESEARCH

GENETICS STUDY REVEALS LATE-LIFE MEMORY PERFORMANCE IS HIGHLY HERITABLE

To understand the role genetics plays in the development of Alzheimer's disease and related dementias, researchers conduct genome-wide association studies, commonly referred to as "GWAS."

During a GWAS, researchers analyze the genetic information of a large group of people to identify specific genetic variations that are more common in individuals with a particular trait or health condition compared to those without that trait or health condition.

Vanderbilt Memory and Alzheimer's Center researchers, including Assistant Professor of Neurology Dr. Derek Archer and Professor of Neurology Dr. Timothy J. Hohman recently led the largest cross-ancestry GWAS on memory performance and memory decline to date.

"We found several new genes associated with memory decline and found that the genetics of memory decline strongly resembles the genetics of Alzheimer's disease," said Dr. Derek Archer.

Additionally, researchers uncovered specific genes and pathways related to memory that act differently between the sexes. Incorporating larger sample sizes into future GWAS of memory may allow for the discovery of genes that could be targeted for developing Alzheimer's treatments.

ARTIFICIAL INTELLIGENCE AND ALZHEIMER'S DRUG REPURPOSING

Searching for new treatments for Alzheimer's disease, Vanderbilt Memory and Alzheimer's Center researchers led a study that examined the ability of artificial intelligence (AI) technologies to identify drug repurposing candidates for Alzheimer's disease.

Led by Associate Professor of Biomedical Informatics Dr. Wei-Qi Wei, researchers tasked ChatGPT with identifying any existing drugs used to treat other conditions that might help patients with Alzheimer's. ChatGPT is a cloud-based AI program based on a large language model. The research team prompted the chatbot to review the biomedical research literature and suggest 20 drugs for Alzheimer's disease, ranking them for potential effectiveness. With a second prompt they asked for confirmation of the initial 20 suggestions. This process was repeated 10 times.

Using the chatbot's 10 most frequently suggested drugs, the team analyzed medical records of patients aged 65 and older from the VUMC electronic health record and the All of Us Research Program. They looked at whether those patients exposed to any of the 10 drugs had lower rates of Alzheimer's disease.

Among the candidate drugs suggested by ChatGPT, the following drugs were associated with lower Alzheimer's risk:

- Losartan, used to treat high blood pressure and heart failure, was associated with 24% reduced risk.
- Metformin, used to treat Type 2 diabetes, was associated with 33% reduced risk.
- Simvastatin, used to treat high cholesterol and fat levels in the blood, was associated with 16% reduced risk.

These findings suggest AI technologies can incorporate scientific insights from an extensive Internet-based search space. This process can help prioritize drug repurposing candidates and facilitate the treatment of diseases.

"Large language models like ChatGPT speedily accomplish a form of extensive literature review, which has become infeasible for humans to perform alone." said Dr. Wei. "Our research indicates that it produces high-quality hypotheses for repurposing drugs.

ELEVATED PAR4 GENE EXPRESSION IN ALZHEIMER'S DISEASE PREDICTS COGNITIVE DECLINE

Professor of Pharmacology Dr. Heidi Hamm led a study to investigate the relationship between a specific gene, called PAR4, and cognitive performance in individuals with Alzheimer's disease. Researchers found that the levels of a molecule linked to this gene, known as F2RL3 mRNA, were higher in individuals with Alzheimer's disease.

The relationship between high F2RL3 levels and cognitive decline was particularly strong in individuals diagnosed with Alzheimer's, while it was less pronounced in those without cognitive impairment. Additionally, higher F2RL3 levels were linked to increased markers of inflammation, such as TNFα, IL-1β, NFκB, and fibrinogen.

Overall, these findings suggest that the PAR4 gene might play a significant role in the development of Alzheimer's disease and cognitive decline, indicating its potential as a target for new treatments or as a marker for predicting and monitoring the disease.

ALZHEIMER'S GENETIC RISK TRACKED ACROSS SEX AND RACE

A study led by Assistant Professor of Neurology Dr. Logan Dumitrescu examined how sex affects Alzheimer's genetic risk, and how those effects differ between races. This genetic association study is the largest known study of its kind, using harmonized data from more than 32,000 research participants aged 60 and older.

Apolipoprotein E (*APOE*), a gene involved in fat metabolism, is the strongest genetic risk factor for Alzheimer's disease. In humans, *APOE* comes in three variants. *APOE-e3*, the most common, is considered neutral with respect to Alzheimer's risk.

Though less common, *APOE-e4* is carried by half of people who develop Alzheimer's disease after age 65 and is known to increase risk. Past research has found that *APOE-e4* increases Alzheimer's risk more among women, but up until this study, it has been unclear whether this difference occurs across races.

APOE-e2, the least common variant, is considered to lower risk of cognitive impairment later in life. However, it has been unclear whether *APOE-e2* protection varies with sex or with race.

The study found that *APOE-e4* has stronger negative effects related to memory and language in females than in males and did not significantly differ among races. Surprisingly, the risk reduction from *APOE-e2* among men and women were similar overall. However, at the intersection of sex and race, *APOE-e2* showed a female-specific protective effect among White participants and a male-specific protective effect among Black participants when it comes to the ability to complete daily tasks.

"These findings are informative and somewhat surprising results," said Dr. Dumitrescu, "highlighting the fact that, while *APOE-e2* and *APOE-e4* have opposing effects on cognition and Alzheimer's disease risk, they are not simply two sides of the same coin. They are differently modified by sex and race, which has implications for precision medicine, clinical trial inclusion, and underlying biological etiology."

BRAIN BLOOD VESSEL CHANGES AND GENETIC RISK

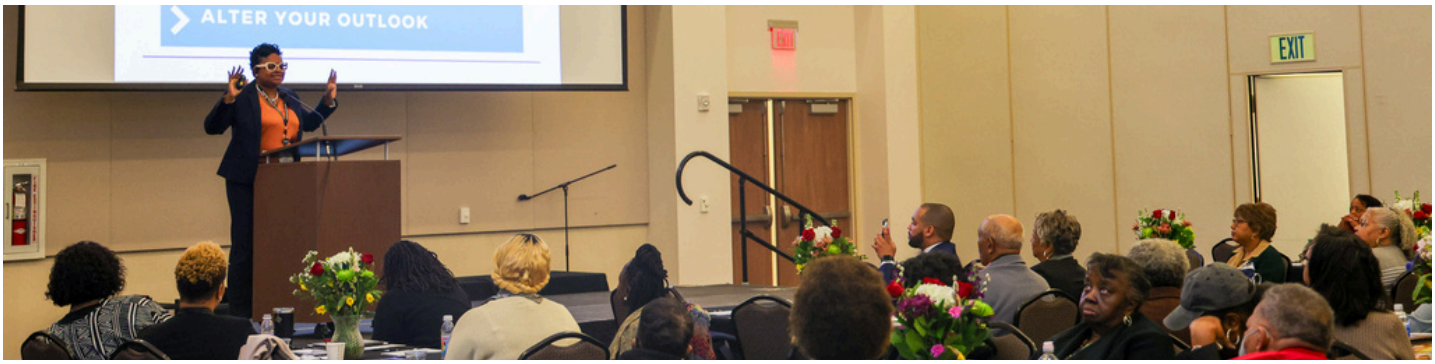
Using Vanderbilt Memory and Aging Project data, researchers conducted a study to determine how large spaces around blood vessels in the brain, called enlarged perivascular spaces (ePVS), interact with *APOE-e4*, the largest genetic risk factor for Alzheimer's disease, in older adults without dementia.

The study led by Center Director Dr. Angela Jefferson found that having more ePVS was linked to poorer cognitive abilities in both people with and without the *APOE-e4* allele, however the effect was stronger in individuals with the *APOE-e4* allele.

When researchers looked at changes over time, the link between more ePVS and worse cognition seemed stronger in individuals without the *APOE-e4* allele. These results could be due to the allele's negative effects on cognition throughout life leading into late adulthood.

Overall, the study findings suggest that *APOE-e4* status influences how small blood vessel problems in the brain affect memory and thinking abilities as we age. Understanding the interplay between ePVS and genetic risk can help in developing more targeted interventions for prevention or early detection of Alzheimer's disease.

CONNECTING OUR COMMUNITY



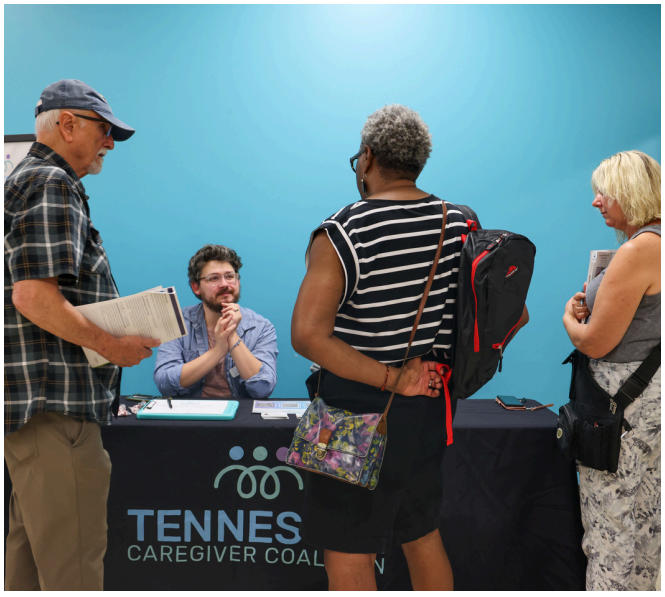
CREATING DEMENTIA-FRIENDLY CONGREGATIONS

In February 2024, the Vanderbilt Memory and Alzheimer's Center and Meharry-Vanderbilt Alliance hosted the second annual Finding God in Alzheimer's event. We were fortunate to bring together 80 attendees, including clergy, researchers, clinicians, and community health experts, to discuss how we can create more dementia-friendly congregations by supporting our faith communities.

The event's keynote speaker was Dr. Fayron Epps, the Karen and Ronald Hermann Distinguished Chair in Caregiver Research at The University of Texas Health Science Center San Antonio School of Nursing. Dr. Epps shared information about Alter Dementia, a program she started to inspire and equip faith-based communities in creating dementia-friendly congregations, which now supports over 80 churches across the country. Following the keynote presentation, we held small group discussions and a community panelist discussion for attendees.

2023-2024 OUTREACH HIGLIGHTS

39	175	47	11
COMMUNITY EVENTS ATTENDED	MEMORY SCREENINGS	BLOOD PRESSURE SCREENINGS	LUNCH AND LEARN PRESENTATIONS

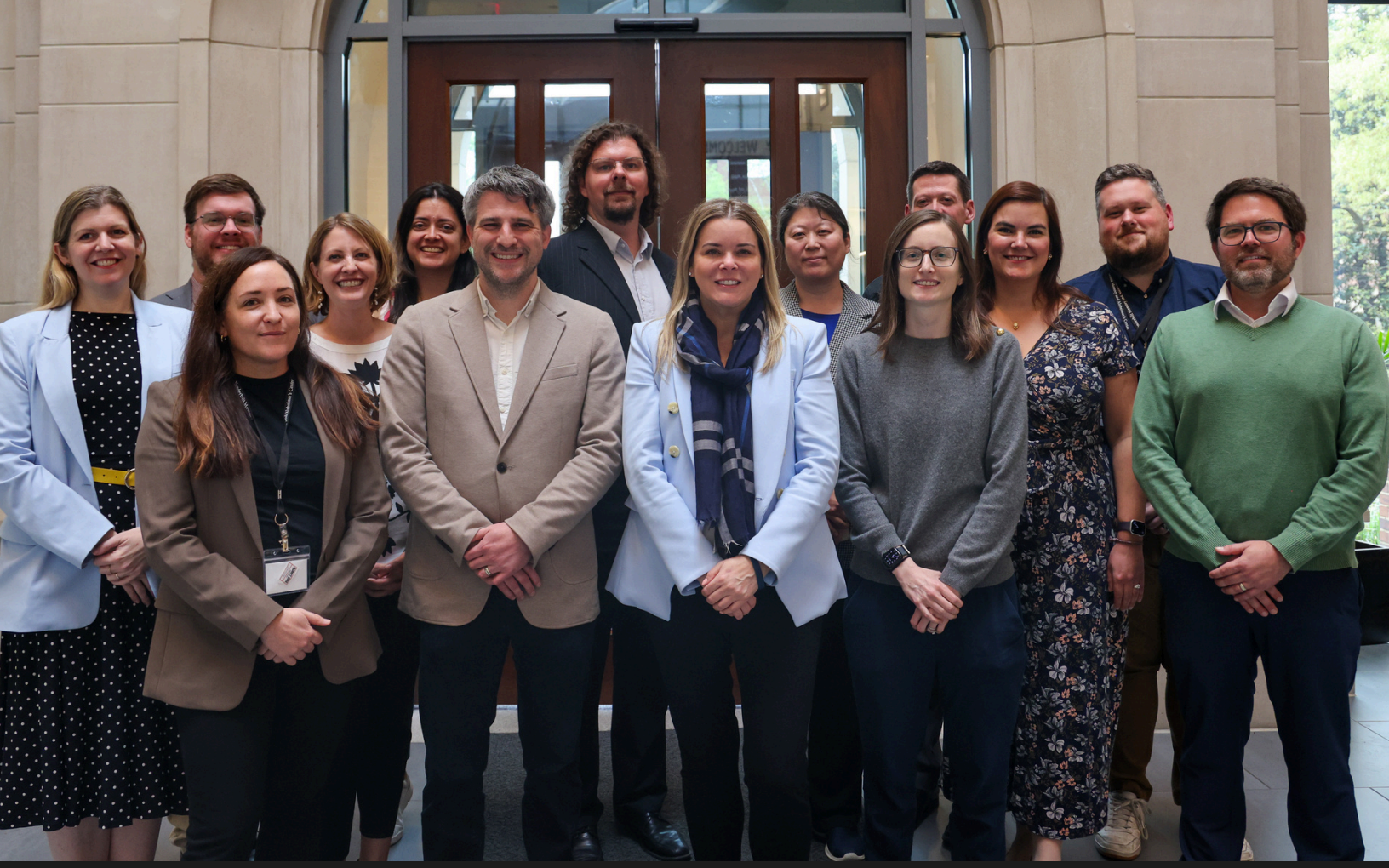


ALZHEIMER'S DISEASE RESOURCE FAIR

In July 2024, the Vanderbilt Memory and Alzheimer's Center hosted more than 100 community members at the Alzheimer's Caregiver and Family Resource Fair in partnership with engAGING Communities Tennessee.

We are grateful to the 20+ local organizations who came out to share support resources for families and caregivers facing Alzheimer's disease and dementia in Middle Tennessee.

Scan the QR code with your smartphone camera for local Alzheimer's support resources



THANK YOU FOR YOUR SUPPORT

From participation in research studies to financial donations, we want to thank you for the continued support of our Center. Without your generosity, our advancements in Alzheimer's research would not be possible.

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