

Expanding Alzheimer's Research at the University of Delaware and Beyond:

Proposed Delaware Center for Cognitive Aging Research (DECCAR)

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Alzheimer's disease (AD) is the leading cause of dementia in older adults and is among the fastest growing causes of morbidity and mortality in the United States.¹ The growing problem of AD and related dementias (ADRD) is likely to disproportionately impact the State of Delaware, which has one of the largest older adult populations in the United States due to its low cost of living and desirable retirement locations. Approximately 19,000 older adults have been formally diagnosed with AD in Delaware and this number is expected to rise to 23,000 by 2025.² These cases affect approximately 55 thousand caregivers who provide 63 million hours of unpaid care worth \$822 million.²

To address this issue, the Delaware Valley chapter of the Alzheimer's Association and the State's Division of Services for Aging and Adults with Physical Disabilities (DSAAPD) formed a joint task force in 2012 and published the "*Delaware State Plan to Address Alzheimer's Disease and Related Disorders.*" Among other things, this plan resulted in an online Alzheimer's Toolkit for patients, families, and health professionals (https://dhss.delaware.gov/dhss/dsaapd/alzheimers_toolkit.html). In line with other national and international AD initiatives,³ it also included a call to increase Delaware's capacity for AD-related research and increase training and professional development in ADRD to healthcare workers. In this article, we will provide an update on the current state of ADRD research at the University of Delaware (UD) and propose how a strategic investment in key infrastructure for cognitive aging research would make UD and partnering institutions well-positioned to contribute to the State's effort to address the growing problem of ADRD.

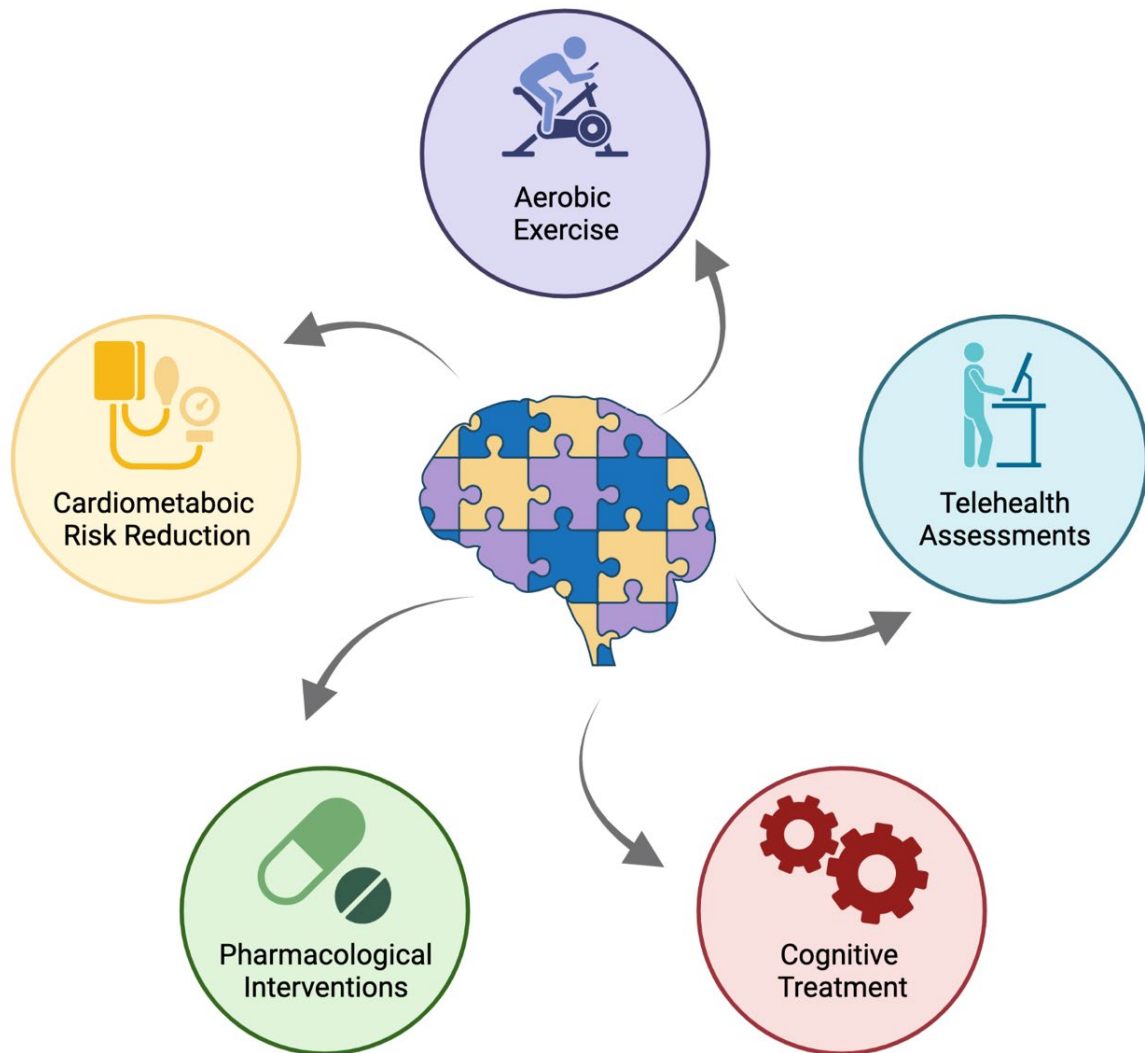
Focusing on Prevention

Because there are currently no curative or well-established disease-modifying drugs for AD, there is significant research interest in disease prevention and early intervention to preserve or slow the decline³ in cognitive function. This is a worthwhile enterprise given that an international body of experts recently asserted that up to 40% of ADRD cases could be significantly delayed or prevented by addressing twelve modifiable risk factors. In this pursuit, even small effects are highly significant. It has been estimated that delaying the transition to dementia *by even just a single year* could reduce the number of people with dementia by 9.2 million people globally,⁴ not to mention the profound benefit this would have for the individual, their family, and society.

As described elsewhere in this issue, there have been encouraging findings for behavioral preventive interventions to improve brain health. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study demonstrated that a 2-year intervention consisting of nutritional guidance, exercise, cognitive rehabilitation, and intensive monitoring and management of metabolic and vascular risk factors (e.g., diabetes, hypertension, hyperlipidemia) improved cognitive test scores more than a control group consisting of health education, counseling, and monitoring.⁵ This finding has inspired the creation of a “Worldwide FINGERS Network” that includes clinical trials in 25 countries to adapt the behavioral intervention framework for various cultural settings.⁶

Similar innovative work has been growing at UD over the past several years in the domains of prevention, early detection, and early intervention for ADRD (Figure 1). Our interdisciplinary team of investigators represents the fields of psychology, speech-language pathology, physiology, and biomedical engineering. Our current portfolio includes a clinical trial for improving memory and brain blood flow using a novel form of vitamin B3 (NCT03482167; PI: Martens), a 12-week aerobic exercise intervention for improving memory and brain tissue structure and integrity (NCT03855475; PI Johnson), and a third trial investigating a seven-week compensatory cognitive treatment set to begin in early 2022 (NCT04820335; PI: Lanzi). Furthermore, researchers from our group have a fourth trial preparing to start that examines the feasibility and acceptability of a telecare-based cognitive assessment and brain wellness program (PI: Cohen). Below is a brief description of these trials and readers are directed to clinicaltrials.gov for current information regarding the enrollment status and primary outcomes of these projects.

Figure 1. Overview of ongoing ADRD research at UD including behavioral, and pharmacological intervention strategies for improving cognitive function and novel approaches for the screening of older adults with MCI.



Cardiometabolic Risk Reduction

As noted by the FINGER trial, many of the underlying risk factors for ADRD are similar to cardiometabolic diseases including midlife hypertension, elevated blood lipids, and reduced vascular function.⁷⁻⁹ For example, there is mounting evidence supporting the role of blood pressure management as a key to preventing the development of mild cognitive impairment (MCI), the earliest symptomatic stage in the development of AD. In this regard, a recent ancillary study to the Systolic Blood Pressure Intervention Trial called SPRINT-MIND found that intensive pharmacological treatment of systolic blood pressure to below 120 mmHg reduced the incidence of MCI over an intervention period of about three years.¹⁰ Elevated blood pressure and other cardiometabolic risk factors are exacerbated by negative lifestyle behaviors including the consumption of an energy-dense Western style diet. As such, a major area of emphasis for our group at UD has been studying non-pharmacological strategies, including dietary and “nutraceutical” approaches to improve brain health in older adults with MCI by targeting elevated blood pressure and other cardiometabolic risk factors. To this end, we are currently exploring the potential efficacy of a novel form of vitamin B₃ called nicotinamide riboside (NR)

for improving memory in older adults with MCI. Our previous work with this compound suggests that it may lower systolic blood pressure and reduce arterial stiffness in otherwise healthy middle-aged and older adults.¹¹ NR works by raising blood levels of nicotinamide adenine dinucleotide (NAD⁺), a ubiquitous molecule that is involved in processes ranging from cellular energy production to DNA damage repair. Aside from our primary vascular end points, there is also strong evidence from animal studies suggesting that NR supplementation may improve cognitive function through direct neuroprotective benefits including reduced neuroinflammation, accelerated brain amyloid clearance, increased neurogenesis, and improved brain energy metabolism.^{12–14} To test this, we are conducting a 12-week, randomized, double-blind, placebo controlled clinical trial in older adults with amnesic MCI to determine if NR supplementation improves memory and markers of cardiovascular function and brain health including blood pressure, arterial stiffness, and cerebral blood flow. Our study is funded by a grant from the National Institute on Aging and is actively enrolling participants with a targeted completion date of spring 2023.

Aerobic Exercise and Brain Integrity

Exercise training interventions are among the most successful in improving cognitive function in older adults, with studies consistently reporting positive relationships with fitness and changes with training despite differences in intervention type and length.^{15–17} Rodent studies have identified that exercise training results in increased neuroplasticity, particularly through enhanced neurogenesis in the hippocampus,¹⁸ which is a neural structure that strongly supports memory process, and improvement in hippocampal size and memory performance is one of the most salient effects of exercise in humans.¹⁹ Physical activity and exercise training have also shown promise for rehabilitating cognitive function and brain health in persons with MCI,²⁰ though with conflicting evidence on their effectiveness.²¹ Part of this uncertainty stems from a general lack of large, comprehensive, Phase III clinical trials, though examples of these are underway including the Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE) trial.²² However, understanding the links between exercise, brain health, and cognitive function are impacted by the lack of methods for sensitively evaluating neural tissue integrity.

At UD we seek to overcome this limitation through the use of a novel imaging technique called magnetic resonance elastography (MRE) that measures the mechanical properties of neural tissue.^{23,24} These mechanical properties, such as stiffness and viscosity, can noninvasively inform us about the underlying tissue microstructure and health, which in turn are affected by aging and neurodegenerative disorders including ADRD.²⁵ Notably, our group has found that these mechanical properties are strongly related to memory performance and cognitive function,^{26,27} more so than other traditional neuroimaging methods, which suggests they may be valuable in assessing the response of the brain to exercise. We have previously shown that hippocampal viscosity mediates the relationship between fitness and memory in young adults,²⁸ and in a pilot study of exercise training in adults with multiple sclerosis showed improvement in hippocampal properties and concomitant improvements in memory function.²⁹ Based on these data, we are studying exercise in older adults through the highly sensitive measures of brain integrity from MRE. To that end, we are conducting a 12-week randomized controlled trial in older adults with amnesic MCI to determine how aerobic exercise affects the brain and cognition, with primary outcomes being the mechanical properties of the hippocampus and a range of memory tasks. Our

study is funded by a grant from the National Institute on Aging and is actively enrolling participants with a targeted completion date of spring 2023.

Cognitive Rehabilitation

Another area of behavioral interventional research at UD is cognitive rehabilitation. Broadly speaking, cognitive rehabilitation approaches can be categorized as either restorative or compensatory³⁰ in philosophy. The goal of restorative cognitive rehabilitation is to “fix” impaired cognitive substrates (e.g., memory) through rote repetition of tasks. Although previous research suggests restorative treatment improves performance on trained tasks,^{31–33} there is less evidence for generalization to everyday tasks.^{34,35} Thus, there is growing interest in the field to examine compensatory cognitive treatments that teach strategies and tools (e.g., calendar systems) to help participants compensate for their cognitive weakness during everyday tasks.³⁶ The focus of compensatory cognitive rehabilitation is not to repair weak cognitive skills but rather to compensate for them, thus maintaining functional independence and delaying the transition to dementia.

The Structured External Memory Aid Treatment (SEMAT) is a novel compensatory treatment for adults with MCI designed by researchers at UD. The SEMAT improves upon previous compensatory treatments by using a scalable and person-centered approach to teaching various strategies and aids like use of calendar and note taking systems. The treatment uses a structured three-step approach³⁷ to teach these strategies, and unlike in previous approaches, the interventionist and participant work together to design the strategies and tools to meet the individual’s everyday needs and unique preferences. Our preliminary data suggests that the SEMAT is feasible and that adults with MCI can learn how to use the strategies and improve performance on everyday tasks for at least 3 months,^{1–3} however, more research is needed with larger-scale clinical trials to determine the efficacy and effectiveness of the treatment. To that end, our research group recently received a grant from the National Institute on Aging to conduct a pilot randomized controlled trial to evaluate the efficacy of the seven-week SEMAT for improving functional performance on everyday tasks. We expect to begin enrolling participants in this trial in early 2022. Successful completion of this research will result in data used to inform a future randomized controlled trial investigating the efficacy-effectiveness of the SEMAT in community settings.

Prevention and Early Detection

Finally, UD researchers are actively involved in research on the prevention and early detection of cognitive impairment using novel telecare-based approaches. A program called Memory Ambassadors was implemented in 2017 by clinicians within the Swank Center for Memory Care and Geriatric Consultation at ChristianaCare and grew to include collaborators from our team at UD,³⁸ as described elsewhere in this issue. This organization visits senior centers and senior living communities to provide brain wellness education and free screenings of nutrition, balance, hearing, and memory to older adults throughout the State of Delaware. Screening results, and recommended follow up steps are shared with attendees, as well as with their primary care clinician if desired.

While the Memory Ambassadors program was successful and growing in scope, the COVID-19 pandemic necessitated the adaptation of the program for online implementation. In fact, this proved to be beneficial because it permitted more frequent and efficient participation of faculty,

clinicians, and trainees, as well as the ability to reach older adults who could not or would not travel to an in-person event. There were barriers to this form of implementation as well, including participant access to and comfort with technology and the effectiveness of adapted screening and intervention approaches, which need to be addressed to maximize the efficacy and reach of such a program. To this end, researchers from UD and ChristianaCare are preparing to begin a study to develop and optimize the feasibility and acceptability of telecare-based brain wellness education, feedback about modifiable risk factors, screenings, and brief intervention. One innovative aspect of this project is its utilization of speech-language pathologists (SLPs), who constitute a large and underutilized workforce in brain wellness education, screening, and intervention.³⁸ This project is anticipated to begin in early 2022.

Memory Screenings

All of the above-mentioned clinical trials are focused on risk factor reduction and strategies for the prevention of dementia in older adults with MCI, which likely represents the most opportune treatment window for delaying clinical dementia from AD. Because these studies share similar inclusion criteria and because the recruitment of older adults with MCI is inherently challenging, we have established a collaborative protocol to coordinate the recruitment, memory screening, and enrollment of older adults with MCI into our respective trials. Our process includes a robust advertisement campaign targeting community-dwelling older adults with subjective cognitive complaints using digital and print marketing strategies, a brief telephone-based cognitive screening, and then a longer cognitive assessment battery that includes an interview with the participant and an informant and multiple tests of memory performance. In the end, participants in the registry meet multiple operational definitions of MCI, including the joint definition of the National Institute on Aging and Alzheimer's Association,³⁹ Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and the so-called "Petersen criteria."⁴⁰ In just two years, we have screened over 300 older adults within northern Delaware, Maryland, and parts of southeastern Pennsylvania and we have successfully identified approximately 50 individuals with amnesic MCI. To learn more about our memory screening process and for information on how to participate in one of our research studies visit sites.udel.edu/memoryresearch.

Growing ADRD Research at UD

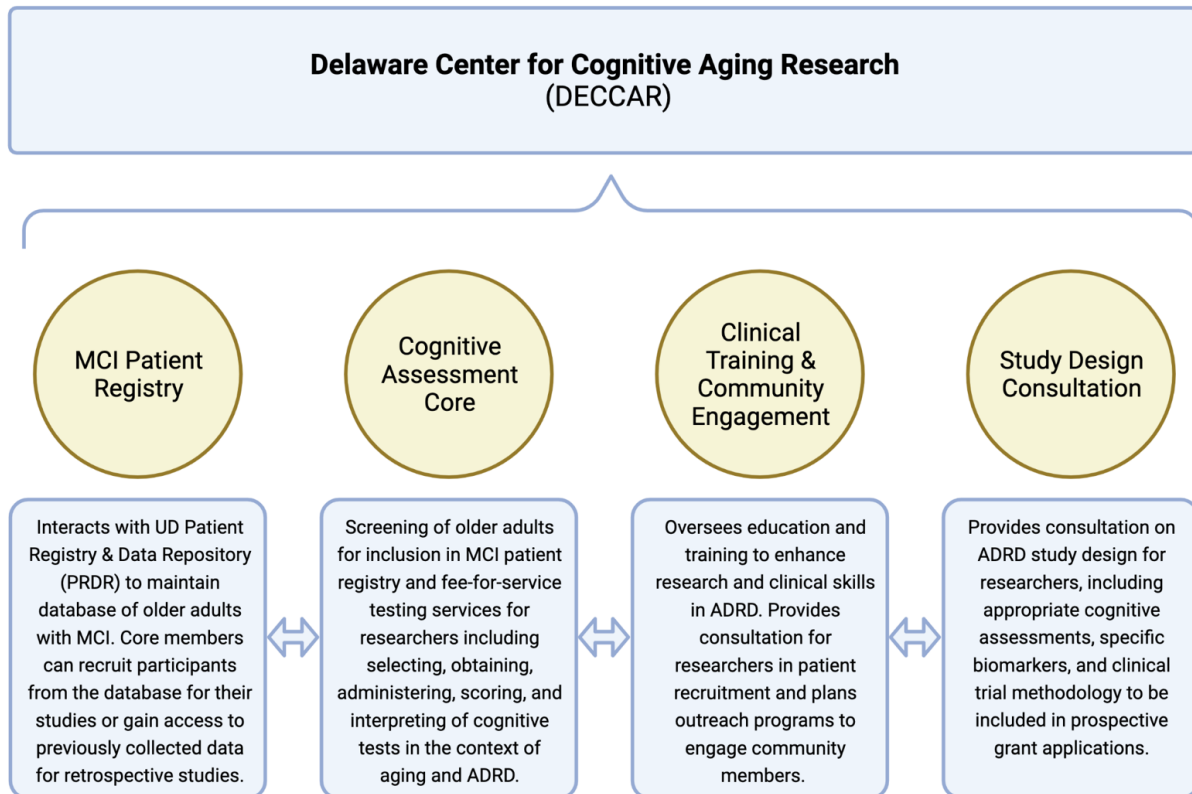
Establishing our memory screening protocol and running our clinical trials has made our collaborative group a visible presence in the Delaware research community and has attracted the interest of other UD researchers wanting to study ADRD. In this regard, we recently helped two UD faculty members receive supplemental funding to add an ADRD component to their existing grants funded by the NIH; however, we do not yet have the personnel or resources necessary to recruit and enroll enough participants to meet all research needs. In addition to the immediate public health need for ADRD research, the time has never been better to conduct this research from a financial standpoint. In 2015, Congress approved a bypass budget allocating additional funding to NIH for ADRD research and this federal allocation has grown annually with a current total contribution of over \$3 billion. The payline for ADRD research has also increased dramatically and is currently nearing the 30th percentile, making success rates for ADRD proposals almost three times higher than other areas of biomedical research. In contrast, less than 2% of UD's roughly \$50 million annual NIH-funded research portfolio is devoted to ADRD, emphasizing a critical need to invest in ADRD research infrastructure in order for UD to secure additional external funding and become a leader in cognitive aging research.

Investing in New Infrastructure

To develop the infrastructure needed to support our growing cadre of cognitive aging researchers at UD, and to expand our ability to interact with other state and local parties invested in the fight against ADRD, we have recently proposed the establishment of a new “**Delaware Center for Cognitive Aging Research**” (DECCAR). Our goal is to advance research, education, and clinical training in ADRD by supporting UD researchers in conducting clinical and translational research that improves the timeliness and accuracy of diagnosis, identifies new and effective interventions, and improves person-centered clinical care and quality of life for older adults and their families. Although our focus is on ADRD, we are committed to supporting research that improves brain health for all older adults across the continuum from typical aging to dementia.

To provide structured research support for new ADRD projects, we plan to develop the following “core” services that will work collaboratively to meet the needs of individual investigators (Figure 2). First, we plan to establish a new **MCI Patient Registry and Data Repository** that will enable longitudinal tracking of participants’ brain health over time. Patients entering the registry will complete our comprehensive screening assessment including extensive cognitive phenotyping for determination of MCI status. We also hope to offer assessment of genetic and blood-based biomarkers of ADRD risk. The intention of creating this registry is for UD investigators to be able to recruit eligible and interested participants for clinical trials or to perform retrospective analyses using previously collected data. The registry will be supported by a **Cognitive Assessment Core**, which will also provide consultation and full-service testing for UD researchers related to selecting, obtaining, administering, scoring, and interpreting cognitive tests in the context of aging and ADRD on a fee-for-service basis. A major goal of the increased NIH funding for ADRD research is to attract new investigators to the field.⁴¹ Thus, to draw in new users to our services and help them become competitive for extramural funding for ADRD research, we will also offer **Study Design Consulting** services, including assistance with study timepoints and statistical analyses, selection of cognitive assessments, and specific biomarkers or neuroimaging protocols to include in prospective grant applications, with the goal of increasing success for extramural grant applications related to ADRD. Eventually, we hope to also be able to award competitive pilot grants each year to support research expenses and registry fees for investigators to establish new ADRD research programs by generating the preliminary data needed to secure extramural funding for projects related to ADRD. Finally, we envision establishing a **Clinical Training and Community Engagement Core** that will oversee the education and training of students and clinicians to enhance their research and clinical skills in ADRD and create outreach programs that engage community members in the activities of the center. Through our memory screening protocol, we have already established a comprehensive training program in cognitive testing and other advanced geriatric assessment practices that helps SLP graduate students at UD obtain essential clinical hours and gain important skills that are currently lacking among many healthcare workers in the United States.

Figure 2. Proposed vision for a new Delaware Center for Cognitive Aging Research (DECCAR) at the UD which would serve as a central resource providing infrastructure for research and training in ADRD.



Our ultimate vision in establishing a new research center is to address several gaps in the existing framework for cognitive aging research and training at UD, stimulate new NIH-funded research, and grow the number of ADRD researchers at UD by engaging existing faculty and attracting new talent to the University. We also envision the proposed center as a platform for facilitating cross-institutional collaboration with other research and clinical institutions throughout the State of Delaware. Such research has the potential to lead to much-needed intervention strategies for slowing or even stopping the progression of MCI to clinical dementia, impacting the lives of Delawareans and their families. Leveraging our existing strengths within UD's College of Health Sciences and the ChristianaCare Swank Center for Memory Care and Geriatric Consultation, our focus on interventions for the *prevention* of cognitive decline through healthy lifestyle behaviors is unique relative to major Mid-Atlantic medical centers, which have historically focused more on pharmaceutical strategies for later-stage dementia, and positions UD to become a leader in healthy cognitive aging. Those interested in learning more about our efforts and engaging with ongoing research at UD are encouraged to visit our website at <https://sites.udel.edu/memory-research/>.

Conclusions and Future Directions

In summary, clinical ADRD research is expanding at UD and the broader research community in DE. In just the past several years, we have grown from a few like-minded investigators interested in cognitive aging research, to a growing body of faculty, students, and staff supporting the recruitment and enrollment needs of multiple clinical trials while training the next generation of researchers and clinicians. This work has laid the foundation for what we hope will become a new Delaware Center for Cognitive Aging Research and provide resources to others at UD

looking to join in our efforts to prevent ADRD. Through this new venture, we hope to also expand our existing partnership with the Swank Center for Memory Care and Geriatric Consultation at ChristianaCare and build new relationships with other providers, caregivers, patient advocacy groups, and policy-makers within the State of Delaware. Such partnerships would enable bi-directional access for patients to cutting-edge research and high-quality clinical care. Over the next several years, we aim to expand the number of clinical investigators at UD focused on ADRD research and increase our competitiveness for extramural funding from NIH for research grants and institutional training programs, attracting high quality students, postdoctoral fellows, and faculty to our institution. Our long-term vision is to serve as a central hub for research and innovation in ADRD research within the state of Delaware and a model for peer institutions looking to help in the early detection and prevention of ADRD.

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