THE SPECTRUM OF BRAIN AGING:

BUILDING A FUTURE WITHOUT ALZHEIMER'S DISEASE

Cure Alzheimer's FUND

All of us are aging, but each of us ages differently. Despite being a universal experience, aging has long been poorly defined and understood scientifically. New discoveries teach us that brain aging increases Alzheimer's risk for some people but not for everyone. Supported by Cure Alzheimer's Fund, scientists are searching for drivers of resistance and resilience that can be harnessed to empower healthy brain aging for all of us.

AGING WITHOUT ALZHEIMER'S IS OUR GOAL

Alzheimer's is a disease of aging.

In 95% of Alzheimer's cases, cognitive symptoms emerge after the age of 65, and the likelihood of a diagnosis increases with each passing year. By age 85, about one in three individuals has the disease. Even people with early-onset familial Alzheimer's do not develop symptoms until middle age. Yet not everyone who ages experiences cognitive decline. Despite long-held beliefs that dementia is an inevitable part of aging, it isn't. The many examples around us of active, cognitively healthy people in their 80s, 90s and beyond offer hope that healthy aging can be available to all of us.

In Alzheimer's, brain changes begin decades before symptoms appear, and once symptoms emerge, irreversible brain damage already has taken place. Current treatments focus on the symptomatic stage and cannot reverse what's been lost. To shift towards prevention, we need to identify the earliest moment a brain deviates from healthy aging.

Imagine healthy brain aging as a straight line over time. The optimal intervention point for people at risk for dementia is the moment before they fall off that line and descend toward disease. However, before we can identify that point, we must define the baseline of healthy brain aging. This is challenging because brain aging exists as a spectrum. At one end are people with dementia, in the middle are those who are aging typically, and at the other end are superagers. Adding to this complexity are people with resistant or resilient brains, whose place on this spectrum remains unclear but whose study is essential to understanding the full range of brain aging.

To understand where resistant and resilient brains fit, we first need to look at how most brains age. The majority of people develop some degree of brain changes as they age, including plaques and tangles. For them, this buildup doesn't reach a level that triggers dementia. Resistant brains show little to no pathology no matter how long someone lives. Their resistant brains could reveal how to prevent Alzheimer's before it starts. Others accumulate extensive plaques and tangles yet remain cognitively healthy. These are resilient brains, and they prove that having pathology doesn't guarantee cognitive decline. Both groups can teach us something valuable: if some people's brains can avoid or withstand these changes, we might be able to help others do the same.

Superagers maintain sharp memory and thinking skills well into their 80s and beyond. While dementia is not part of healthy aging, subtle cognitive changes do happen over time, such as mild decreases in attention span, slower word recall times and difficulty multitasking. Superagers have the cognitive abilities of someone much younger. They represent the extreme positive end of healthy brain aging and may reveal strategies for maintaining cognitive sharpness throughout life.

Understanding the full spectrum of brain aging will help us identify intervention points and optimize brain aging for everyone, but it requires grappling with fundamental challenges in aging research itself. For too long, this area has been understudied. Dementia was thought to be an inevitable part of growing older, and scientists lacked both the tools and methods to study such a complex, lifelong process. But with populations aging globally and lifespans extending, defining what healthy brain aging looks like has become increasingly important.

STUDYING AGING IS MORE COMPLICATED THAN IT SOUNDS

Aging research might seem straightforward: simply study how people change as they get older. But it's not that simple. Aging is far more complex than it seems on the surface.

Everyone ages differently. We've all known people who look or seem younger (or older) than their actual age. This is due to the difference between chronological and biological age. Chronological age is the time since birth. Biological age measures how well cells and tissues age, and it varies wildly between individuals. Biological age is flexible, and it impacts our health and longevity. This flexibility means there's a personalized component to aging.

Aging also can differ within the same person because it is the sum of all the molecular and cellular changes happening simultaneously throughout the body. Research shows that our organs and systems, like the cardiovascular and immune systems, can age at different rates. Think of this as a car whose engine is still good, but the brake pads are wearing thin.

Making this even more complex, aging isn't just determined by genetics—it's heavily influenced by environment, behaviors and experiences. For decades, researchers thought DNA was the key to unlocking aging and disease. While genetics does play a role, researchers also have discovered epigenetics—how outside factors change which genes are expressed and how often, without altering the DNA itself. While this discovery provides hope because it means aging isn't predetermined, it is complicated by the fact that researchers must additionally understand how genes interact with countless environmental and experiential factors over time.

Fortunately, science is entering an era where these challenges are becoming surmountable. Longitudinal studies that began following individuals 20 to 30 years ago now have enough data for scientists to begin identifying aging patterns. As these participants continue to age, researchers will gain even more insights. Meanwhile, new laboratory models allow scientists to study aspects of human aging in the lab. These and other advances are finally providing scientists with the tools needed to tackle the complexity of aging.

BUILDING THE FOUNDATION FOR STUDYING THE SPECTRUM OF BRAIN AGING

In 2016, Cure Alzheimer's Fund (CureAlz) launched the Collaboration to Infer Regulatory Circuits and Uncover Innovative Therapeutic Strategies (CIRCUITS) consortium to explore how changes in the way our genes are read—our epigenetics—contribute to the risk of Alzheimer's disease as we age.

Our environment and behaviors influence these epigenetic modifications, which accumulate over time. Think of our DNA as an instruction manual for building and operating our bodies. Epigenetic changes don't rewrite the manual—they affect which pages get read and when. These changes can dramatically affect how our bodies function.

CIRCUITS Identified Critical Gaps In Aging Research

As CIRCUITS researchers worked to map these epigenetic changes, they confronted a limitation with a widely used laboratory model: induced pluripotent stem cells (iPSCs). iPSCs are created by reverting adult skin cells to a stem cell-like state, from which they can be transformed into brain cells or other cell types for study in the lab.

While this technology revolutionized disease research, the reversion step erases the epigenetic changes that accumulate over a person's lifetime. The CIRCUITS consortium's studies revealed just how severely this erasure impacted the field's work. To advance brain aging research further, the field needed a cell model that preserved aging-related changes.

Beyond the iPSC limitation, CIRCUITS findings also showed the need for a nuanced and comprehensive investigation of brain aging. CIRCUITS researchers discovered that different sections of the brain age at different rates and that aging involves many biological processes happening simultaneously. These insights made it clear that studying only epigenetics was too narrow a focus to explore the full story of what happens to a brain as it ages.

CIRCUITS Completes Its Mission

The invaluable datasets created by CIRCUITS, which are publicly available for the benefit of researchers worldwide, revealed the complex interplay between aging and disease. Through this work, CIRCUITS also illuminated what the field needed next: a cell model that preserved aging-related changes and a comprehensive approach that went beyond epigenetics alone. Having completed its research goals, CIRCUITS concluded in 2023, laying the groundwork for the next phase of discovery.

Aging Model Breakthrough

While CIRCUITS was mapping epigenetic changes, Dr. Andrew S. Yoo's team at the Washington University School of Medicine in St. Louis was tackling the iPSC limitations in aging studies head-on. The critical drawback of iPSCs is that the rewinding process erases all cellular history. All the molecular changes that might explain why the disease develops are wiped clean. Scientists are left studying brain cells that genetically match elderly patients but have the characteristics of young cells.

To truly study Alzheimer's—a disease driven primarily by aging—researchers needed cell models that preserved the molecular changes accumulated over a lifetime. Dr. Yoo's team set out to develop a model that could overcome this drawback by bypassing the iPSC process entirely.

"We need a system where we can actually study the process of how age, or neuronal aging, contributes to the onset of neurodegeneration," Dr. Yoo explains. "This allows us to go after the question of why aging is an important risk factor for Alzheimer's disease."

The development of this model was no easy feat. "The goal," says Dr. Yoo, "was to come up with a system where we can generate neurons from individuals that reflect the age of those individuals." In 2024, after eight years of CureAlz-supported hard work, they succeeded.

Rather than taking an indirect approach that involved the middle step of making cells young and malleable, the Yoo lab discovered how to reprogram a donor's skin cells directly into neuronal brain cells. They use small RNA molecules called microRNAs, which bind to specific genes and silence the signals that tell the cell it is a skin cell. Then, they activate signals that instruct the cell to become a neuron. Because the cell is directly reprogrammed from a skin cell to a neuron, it reflects the donor's age and all the changes that have happened over the donor's lifetime.

When placed in a 3D brain cell culture model called Alzheimer's in a Dish (developed by CureAlz Research Leadership Group Chair Dr. Rudy Tanzi and his colleague Dr. Doo Yeon Kim), the directly reprogrammed neurons from this process reproduced the key features of Alzheimer's.

Cells from both early-onset familial and late-onset (the more common form of Alzheimer's) patients quickly developed amyloid plaques and tau tangles, followed by inflammation and cell death. Cells from healthy older individuals showed small amounts of amyloid, indicating that the model captures normal aging processes while distinguishing between disease and healthy aging.

The CureAlz-funded researcher community recognized this extraordinary breakthrough by awarding Dr. Yoo and his postdoctoral colleague, Dr. Zhao Sun, the second annual Cure Alzheimer's Fund Jeffrey L. Morby Prize in 2025.

This groundbreaking model gives scientists something they've never had before: a way to study brain aging—healthy and diseased—in the lab using human cells that reflect the donor's actual age. Combining the Yoo lab's directly reprogrammed neurons with clinical and genetic data, researchers can examine how normal aging affects the brain and investigate why the complex mix of aging, lifestyle and genetics leads to late-onset Alzheimer's in some people but not others. They also can explore why certain individuals stay mentally sharp despite having brain changes that cause dementia in others and, most importantly, they can test treatments specifically designed to help brain cells stay healthy as we age.

The CureAlz Brain Aging Consortium

By 2025, the pieces to comprehensively study brain aging were in place: Dr. Yoo's aging model was validated, CIRCUITS datasets were available and powerful new technologies allowed scientists to study thousands of molecules in a single sample alongside rich human data collected over many years. With these critical tools assembled, CureAlz launched the Brain Aging Consortium to identify the precise biological changes that, over time, determine whether a brain becomes susceptible to Alzheimer's disease.

While CureAlz continues to support high-risk, high-potential individual projects, recent advances called for an expanded approach: bringing multiple laboratories together to tackle specific challenges in Alzheimer's research through collaboration. The Brain Aging Consortium unites six world-renowned Alzheimer's researchers and their teams, each approaching aging and Alzheimer's from unique but complementary perspectives. Their diverse expertise in aging biology, genetics, neuroscience and Alzheimer's research creates a tightly integrated environment where insights from one group accelerate progress in another.

The consortium is tackling three major questions: How do biological changes during aging contribute to Alzheimer's risk? What biological markers reveal signs of disease before symptoms appear? Is brain aging accelerated in Alzheimer's, and what distinguishes those who remain cognitively sharp from those who develop the disease? Answering these questions could unlock strategies to promote healthy brain aging and prevent Alzheimer's disease.

To do so, the Brain Aging Consortium is focusing on three strategies:

1. Comparing Groups Across the Aging Spectrum:

Consortium laboratories are studying brain aging at multiple time points in unique cohorts. At one end are individuals carrying rare gene variants causing early-onset Alzheimer's who develop symptoms in middle age, before most changes associated with brain aging. At the other end are centenarians who remain cognitively sharp despite living to age 100 and longer. These individuals have

either resisted the development of amyloid plaques and tau tangles or stayed cognitively resilient despite them, even when carrying the APOE4 risk gene. In the middle are those individuals across the adult lifespan whose brain aging follows the typical straight line. The approach provides a powerful opportunity to study Alzheimer's disease independently of brain aging and exceptional brain aging independently of disease, by focusing on unique populations that do not follow the typical line of aging.

2. Tracking Cellular Changes:

Using leading-edge tools, consortium researchers are profiling proteins, lipids, gene activity and epigenetics at the single-cell level across different brain regions, including the choroid plexus, and cell types. Beyond brain tissue, they are measuring changes in blood and cerebrospinal fluid. They also are using the aging model developed by Dr. Yoo's lab to watch how aging unfolds in the laboratory.

3. Uncovering Patterns Through Big Data:

The consortium is generating incredibly rich datasets that capture the wide range of biological molecules and processes across its studies. Aligning these diverse types of data between laboratories opens new possibilities to uncover previously unrecognized patterns and relationships—revealing where disease deviates from the line of healthy aging and pointing to novel therapeutic targets.

Having launched their partnership, the groups meet regularly to discuss data, share progress and actively collaborate across projects, leveraging each other's insights to tackle the complex interplay between aging and Alzheimer's. By integrating their findings, the consortium teams are building the most comprehensive picture yet of how aging shapes brain health and are positioned to accomplish what no individual researcher, laboratory or institution can achieve alone: uncover how biological aging drives Alzheimer's risk to identify the earliest, most effective points for intervention.

To find out more visit: *https://bit.ly/curealzbac*


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The Researchers Leading the Brain Aging Consortium

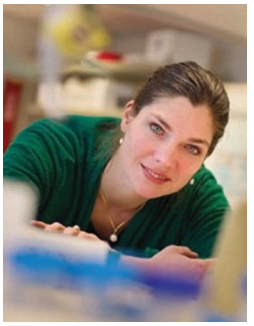
DECODING BRAIN AGING TO PREDICT ALZHEIMER'S

Randall J. Bateman, M.D.,
Chair of the Brain Aging Consortium

Washington University School of Medicine in St. Louis

"Brain aging research is the foundation of understanding neurodegenerative diseases, because age is the single greatest risk factor for all forms of Alzheimer's disease. We can now measure thousands to millions of different biomolecules at molecular scales in the brain and analyze with deep artificial intelligence to discover fundamental processes of brain aging with the goal of identifying targets to prevent brain aging and neurodegeneration, such as Alzheimer's disease."

UNLOCKING THE SECRETS OF LIFELONG BRAIN HEALTH



Henne Holstege, Ph.D.

VIB-KU Leuven, Belgium

"By mapping the molecular constellation of brain tissue from people who stayed cognitively sharp beyond 100 years, we aim to unlock the secrets of lifelong brain health. Aging reshapes the brain—we're finding out how to keep it healthy."

UNCOVERING THE DIVERSE PATHS OF BRAIN AGING

Miranda Orr, Ph.D.

Washington University School of Medicine in St. Louis

"Five years ago, we couldn't study cells in their native environment at this level of detail. Advances in spatial proteogenomics now allow us to analyze the entire transcriptome alongside thousands of proteins within intact tissue at single-cell resolution. This lets us gain insights into how individual neurons, glia, immune cells, vasculature and disease-related pathologies emerge, interact, and change across the brain during aging and disease."

UNCOVERING LIPID SIGNATURES OF AGING AND ALZHEIMER'S DISEASE

Li-Huei Tsai, Ph.D.

Massachusetts Institute of Technology and the Broad Institute

"We have the perfect tools to study how certain molecules, including proteins and lipid species, change during aging. These and the health data from the cohorts can help us understand how aging affects cognitive function and other disease phenotypes."

CHOROID PLEXUS AGING AND ALZHEIMER'S DISEASE

Tony Wyss-Coray, Ph.D.

Stanford University

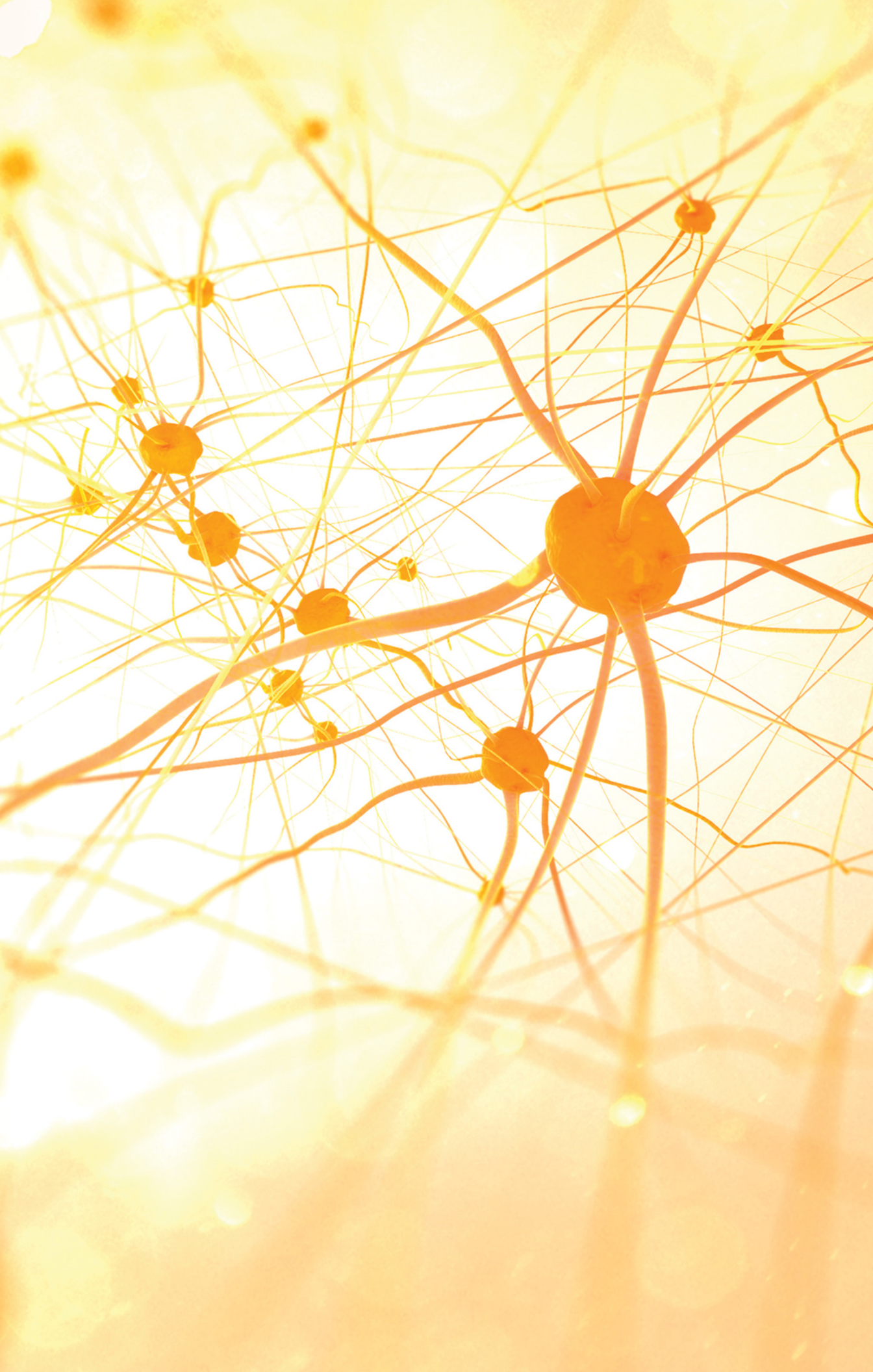
"We are particularly excited about new methods to track the production of cerebrospinal fluid proteins—critical for nourishing and protecting the brain—and study how this system changes with age and disease. We believe these approaches open new opportunities to improve brain health and develop strategies to preserve cognitive function with age."

RECREATING THE AGING BRAIN IN THE LAB TO UNDERSTAND ALZHEIMER'S DISEASE

Andrew S. Yoo, Ph.D.

Washington University School of Medicine in St. Louis

"Being able to generate human neurons that mirror the age of elderly individuals gives us a powerful way to test genes and pathways that might slow neuronal aging. We're excited about the possibility of uncovering new ways to target aging itself as a risk factor for neurodegeneration in Alzheimer's disease."



Ways to Donate

Cure Alzheimer's Fund is grateful to the thousands of donors who make contributions of all sizes to support our mission. Each and every donor is vital to accelerating an end to Alzheimer's disease. Here are some of the ways you can make an impact with your charitable contribution:

MAKE A ONE-TIME or RECURRING GIFT ONLINE

Make a secure gift online by credit card, PayPal, Venmo or cryptocurrency at *give.curealz.org/AnnualAppeal*

MAIL

Make your check payable to Cure Alzheimer's Fund and send to Cure Alzheimer's Fund, 34 Washington St., Suite 230, Wellesley Hills, MA 02481.

DONOR-ADVISED FUND (DAF)

Recommend a contribution to Cure Alzheimer's Fund through your donor-advised fund.

SECURITIES AND WIRE TRANSFER

Stock and other appreciated assets can support our mission and may reduce your taxes. For stock and wire transfer instructions contact Laurel Lyle at *LLyle@CureAlz.org*

TELEPHONE

To donate by telephone, or if you have questions about donating, please call us at 781-237-3800.

PLANNED GIVING

Planned gifts, including annuities, trusts, retirement assets or life insurance policies may be contributed. You may also include CureAlz in your will. Learn more by emailing us at *Legacy@CureAlz.org*

To explore these and other ways to give, please contact us at *info@CureAlz.org*

Cure Alzheimer's Fund is a nonprofit organization dedicated to funding research with the highest probability of preventing, slowing or reversing Alzheimer's disease.

100% of all general donations go to support our research program.

Cure Alzheimer's FUND

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