

# ALZHEIMER'S DISEASE

A GIVING SMARTER GUIDE



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## EXECUTIVE SUMMARY

Alzheimer's disease (Alzheimer's, AD) is the sixth leading cause of death in the United States (U.S.), claiming the lives of more than 500,000 individuals each year. Today, approximately 5.3 million Americans are living with this disease. AD burdens the U.S. with a project economic cost of \$226 billion in 2015, and is on pace to cost \$1.1 trillion in 2050.

Although AD is widely recognized as an epidemic by individual nations as well as by the World Health Organization, progress in AD clinical research and integrated care has been modest at best. Key challenges to combating this disease include:

- Poor understanding of disease onset and progression
- Gaps in funding to support high-risk research efforts
- Insufficient research tools and companion resources
- Lack of disease-modifying treatments
- Limited public awareness of its societal impact

In order to avoid the economic and social catastrophes caused by AD, we must address these deficiencies. Strategic focus on funding high-impact research and critical infrastructure to support both AD research and patients are essential to achieving this goal.

The Milken Institute Philanthropy Advisory Service has developed this Giving Smarter Guide for Alzheimer's disease to help patients, supporters, and other stakeholders understand the state of the science and how they can help accelerate research progress. Although philanthropy accounts for only 3 percent of medical research funding, it can have an outsized impact if it is strategically focused. This guide will help to answer the following questions:

- *What are key facts about the disease?*
- *Why is it important to invest in AD research?*
- *What is the current state of care?*
- *What is the current state of research?*
- *What are major barriers to progress?*
- *How can philanthropy advance a cure for AD?*

## INTRODUCTION

Alzheimer's disease (Alzheimer's, AD) is a degenerative brain disease that severely impairs cognitive functions, including memory, language, problem-solving, and judgment. AD is the most common form of dementia, accounting for 60 to 80 percent of all cases. Although AD typically occurs in the elderly, it is not a normal part of aging.

Contrary to a common misconception, AD is a fatal disease. Patients experience gradual loss in both mental and physical functions as the disease progresses. Ultimately, their memory and coordination become severely compromised, and fatal complications such as pneumonia and malnutrition often ensue.

Although there are treatments that can temporarily alleviate symptoms and improve quality of life for patients and their caregivers, they do not stop the disease from worsening. At present, there are no disease-modifying agents for Alzheimer's disease. There is no cure.

## DISEASE BURDEN: SCOPE AND IMPACT

### POPULATION BURDEN

As of 2015, approximately 5.3 million individuals in the United States (U.S.) have Alzheimer's, representing more than 1.5 percent of the population. By 2050, that number is expected to triple to 16 million in the absence of significant medical breakthroughs to prevent, halt, or cure the disease.

The projected upsurge is driven mainly by the aging US population given that the prevalence of AD increases with age. As illustrated in Figure 1, 96 percent of AD patients in the United States are age 65 or older. One in nine individuals in this age group has Alzheimer's; and among those who are more than 84 years

old, one in three has the disease. As the size and proportion of these older populations continue to grow, the number of Americans with AD and other forms of dementia will rise.

Meanwhile, more deaths will become attributed to Alzheimer's. According to the Centers for Disease Control and Prevention, deaths due to AD increased by 71 percent between 2000 and 2013, while deaths from other major diseases such as cancer and heart disease decreased. AD is now the sixth leading cause of death for adults in the United States and the fifth leading cause of death for adults ages 64 years and older. Among the top 10 causes of death in the United States, AD is the only disease that cannot be prevented, slowed, or cured.

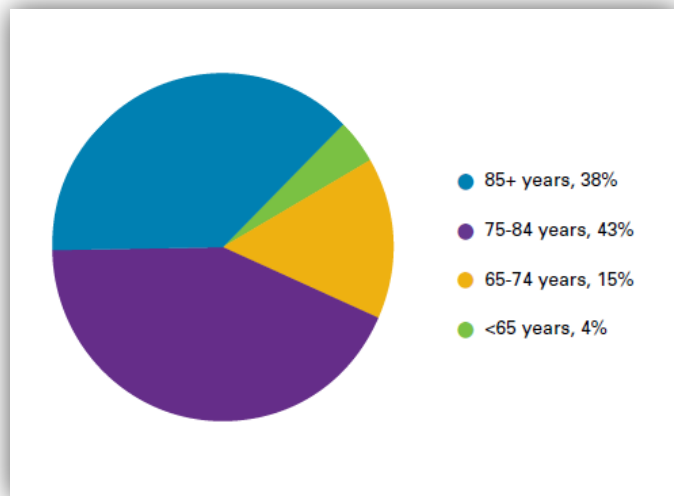


Figure 1: Ages of People with Alzheimer's Disease in the United States (2015).

Source: Alzheimer's Association, 2015 Alzheimer's Disease Facts and Figures.

In addition to causing more deaths, Alzheimer’s is generating more cases of poor health and disability in the United States. The average survival time upon diagnosis is between 8 and 10 years, although some individuals live as long as 25 years. This long period of illness before death represents a progressive deterioration of function that results in substantial disability and dependency. According to a public health study by the U.S. Burden of Disease Collaborators, AD rose from the 25th most burdensome disease in the United States to the 12th between 1990 and 2010, the largest increase by any disease. Thus the population burden of AD entails both increased mortality and morbidity.

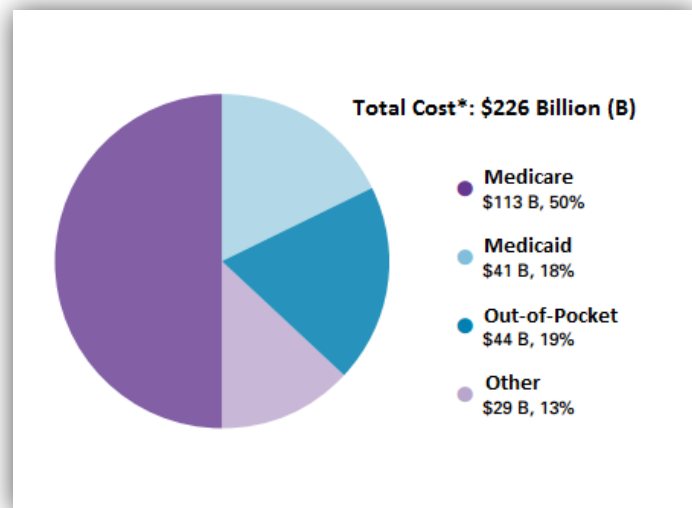
The burden of Alzheimer’s and other dementias spans the globe. In 2015, the number of individuals with dementia worldwide is estimated at 46.8 million and projected to surpass 131.5 million in 2050. The World Health Organization (WHO) recognizes dementia as a global epidemic because it presents the largest burden on healthcare systems around the world.

## ECONOMIC BURDEN

Alzheimer’s is one of the most costly diseases to society. The economic impact of the disease comprises large expenditures for chronic treatment and care as well as lost productivity by patients and their caregivers. At present, the total worldwide cost of AD and other types of dementia is estimated at \$818 billion per year, or approximately 1 percent of the global gross domestic product. In the United States, the estimated total for 2015 is \$226 billion; without disease-modifying interventions, the total annual cost is estimated to surge to \$1.1 trillion by 2050.

Given that Alzheimer’s and other dementias primarily affect the elderly, one-half of the total care costs in the United States is borne by Medicare (Figure 2). Nearly one-third of the Medicare beneficiaries with AD and other dementias also have Medicaid coverage. Thus, together, public insurance programs pay 68 percent of the total dementia care costs in the United States, which will amount to \$154 billion in 2015. By 2050, this government expense will increase five-fold.

Individuals with AD use a disproportionate amount of healthcare resources. According to the Alzheimer’s Association, the average per-person Medicare spending on beneficiaries with Alzheimer’s and other dementias is three times higher than that for beneficiaries without dementia. Moreover, the average per-person Medicaid spending for seniors with Alzheimer’s and other dementias is 19 times greater than that for seniors without



**Figure 2: Cost of Care by Payment Source for Americans Age 65 and Older with Alzheimer’s Disease and Other Dementias (2015).** Data are in 2015 dollars. “Other” payment sources include private insurance, health maintenance organizations, other managed care organizations and uncompensated care. \*Totals for payment sources may not add to total cost due to rounding.

**Source: Alzheimer’s Association, 2015 Alzheimer’s Disease Facts and Figures.**

dementia.

The burden of Alzheimer's, a care-intensive chronic disease, extends beyond individual patients, particularly to family members and friends who serve as caregivers. Given the physical, mental, and emotional stresses of caring for a person with AD, the health of caregivers often declines throughout the duration of care. In addition to physical illnesses, caregivers are more likely to experience depression and abuse substances. This impact on caregivers' health results in substantial additional healthcare costs, estimated at \$9.7 billion for the United States in 2014, and thus contributes significantly to the economic burden of AD.

Furthermore, because of the demanding nature of caring for dementia patients, caregiving often leads to disruptions in employment. The resulting financial harm is felt by not only the caregivers but also employees. In the United States, businesses lose more than \$61 billion each year as a result of costs related to caregiver absenteeism, employee replacement, employee assistance programs, and related productivity loss.

## PUBLIC POLICIES IN THE UNITED STATES

Alzheimer's disease is a national priority. To ensure that medical research and healthcare systems are adequately structured and funded to combat the looming AD crisis, the U.S. government has implemented several policy initiatives. These initiatives address core systemic issues that impede progress, including lack of research funding and care coordination as well as restrictive regulatory processes for drug development.

Considering the chronic and complex nature of the disease, legislators at both the state and national levels seek to coordinate and leverage existing AD-related efforts through strategic plans. As of 2015, 36 states and the District of Columbia have established their own State Government Alzheimer's Disease Plans. The federal initiatives include the National Alzheimer's Project Act and the Alzheimer's Accountability Act.

### NATIONAL ALZHEIMER'S PROJECT ACT

The **National Alzheimer's Project Act (NAPA)** was signed into law in January 2011 after unanimous passage by Congress. The Act mandated the creation of a national plan to accelerate research toward prevention and treatment of AD, and to improve care and services. Through outcome-driven objectives, recommendations, implementation steps, accountability, and engagement of the various stakeholders, this plan would provide a strategic framework to address the burden of the disease.

The **National Plan to Address Alzheimer's Disease** was released in May 2012 with the primary research goal of preventing or effectively treating Alzheimer's by 2025. It also focuses on enhancing care quality and efficiency, expanding supports for patients and caregivers, enhancing public awareness and engagement, and tracking progress. As directed by NAPA, the Plan is updated annually for review by Congress, presenting a recurring opportunity for stakeholders to assess the national effort in combating AD.

*"If we are to prevent Alzheimer's from becoming the defining disease of the next generation, it is imperative that we dramatically increase our investment in Alzheimer's disease research."*

—Senator Susan Collins (R-Maine), NAPA Co-Sponsor

To jumpstart the Plan, Congress allocated \$125 million in additional funding for AD research over the past two years. For fiscal year (FY) 2016, the Obama administration's budget proposal includes \$51 million in additional AD research funding. However, the NAPA strategic plan does not specify the level of resource commitment that will be necessary to support its outlined activities. The Advisory Council on Alzheimer's Research, Care and Services has recommended to Congress that the federal government provide at least \$2 billion a year for AD research in order to achieve the primary goal of the Plan. For FY 2015, federal funding for AD research is approximately \$586 million.

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## ALZHEIMER'S ACCOUNTABILITY ACT

Signed into law in December 2014 as part of the FY 2015 omnibus appropriations bill, the **Alzheimer's Accountability Act** builds on the coordinated goals of NAPA. The bipartisan legislation requires the **National Institutes of Health (NIH)** to submit an annual budget estimate directly to the President and Congress, specifying the resources needed to reach the Plan's goal of preventing or effectively treating AD by 2025. Although the Secretary of Health and Human Services and the Advisory Council on Alzheimer's Research, Care and Services have an opportunity to comment on the professional judgment budget, they cannot change the content. By employing the professional judgment budget approach, which bypasses the additional layers of bureaucracy that are a part of the standard budget review process, the Alzheimer's Accountability Act helps ensure that scientific judgment will guide government funding allocation for AD research each year until 2025.

In July 2015, the NIH released its first Alzheimer's bypass budget proposal, recommending an additional \$323 million above its estimated FY 2017 budget to continue progress toward preventing or treating AD by 2025. The document also provides specific milestones, lists research areas that are poised for future discoveries, and identifies the areas that would benefit the most from intensified investment in FY 2017.

To date, only two other areas of biomedical research have been granted this special budget approach: cancer and HIV/AIDS. This prioritization reflects the national urgency of addressing the public health, social, and economic challenges of AD.

## IMPERATIVE TO ADVANCE ALZHEIMER'S RESEARCH

The anticipated increase of Alzheimer's patients in the following decades makes development of effective treatments an urgent issue. The impact of a disease-modifying treatment would be huge: In the United States, delaying the onset of AD by five years starting in 2015 could reduce the number of cases by 5.9 million (43 percent) in 2050. Expressed monetarily, a five-year delay of onset could save \$447 billion of the total expected cost of \$1.1 trillion in the United States alone.

Yet, despite the growing burden of the disease in the absence of effective treatments, chronic underinvestment in AD research persists. Even with recent increases in public funding, the NIH is expected to spend only \$586 million on AD research in FY 2015. This means that for every \$26,000 that Medicare and Medicaid spend on AD care, the NIH spends only \$100 on AD research.

***In order to address the immense threat that AD poses to public health and the global economy, it is imperative to commit focused resources to raise awareness, support research, and encourage citizen participation in clinical research studies.***

## OVERVIEW OF ALZHEIMER'S DISEASE

Alzheimer's disease is the most common cause of **dementia**, contributing to 60 to 80 percent of all cases. Dementia describes a loss of cognitive function that is significant enough to interfere with independence in everyday activities. Depending on the cause of dementia, cognitive deficits may involve memory, language, visuospatial function, and executive function. Although AD and other forms of dementia typically develop in older adults, they are not a part of the normal aging process. Normal age-related cognitive decline is more gradual and associated with less disability; AD progresses at different rates and ends with severe brain damage.

Symptoms of AD vary among individuals and gradually worsen over time. In most cases, the disease first manifests as short-term memory loss and word-finding difficulties, then spreads to other brain functions such as reasoning, recognition, and judgment. Although memory loss is a key feature of AD, other symptoms include mood and personality changes, trouble organizing and expressing thoughts, repetitive questioning, confusion, and getting lost in familiar places. The disease ultimately leads to death.

## DISEASE BIOLOGY

The pathology of Alzheimer's disease involves the progressive damage and death of nerve cells, or **neurons**, in the brain. Human brain function depends on a network of approximately 100 billion neurons that transmit signals to each other via specialized connections called **synapses**. In Alzheimer's, brain function deteriorates with the loss of communication between injured neurons as well as the ultimate death of the cells. The neuronal damage initially appears in the hippocampus, the part of the brain involved with memory and learning, then spreads to other regions.

Barring certain genetic mutations that are found in approximately 1 percent of the patient population, the cause of Alzheimer's is mostly unknown. There are several competing hypotheses based on the following hallmark features of the disease:

- Amyloid plaques
- Neurofibrillary tangles
- Synaptic loss
- Acetylcholine deficiency
- Neuroinflammation

All of these abnormalities can lead to disruption in neuronal communication and/or neuronal death, which ultimately results in the clinical symptoms of Alzheimer's that impair cognitive abilities and interfere with independent living.

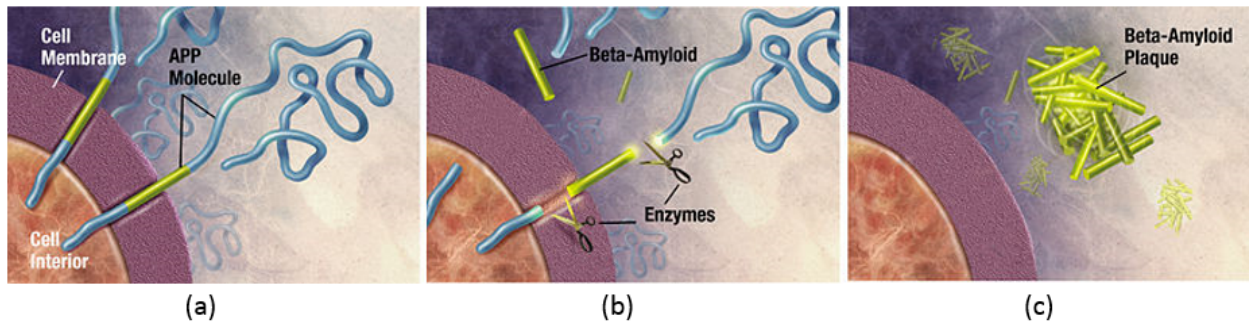
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### BETA-AMYLOID ACCUMULATION LEADS TO PLAQUES

**Beta-amyloid (A $\beta$ )** is a fragment of the **amyloid precursor protein (APP)**, which is located in synapses. The function of APP is unclear but possibly involves synapse formation and neuroplasticity. A $\beta$  is generated when two **enzymes**, beta-secretase and gamma-secretase, cleave APP (Figure 3). The fragments are released into the space outside the neurons, where they stick to each other in small, soluble aggregates called **oligomers**. Without sufficient clearance from the brain, these oligomers attract more A $\beta$  molecules and form fibrils, which then combine with other



proteins and cellular materials to form insoluble **amyloid plaques** (Figure 3). As more plaques develop, synapses deteriorate and neurons lose their ability to function and communicate with each other.

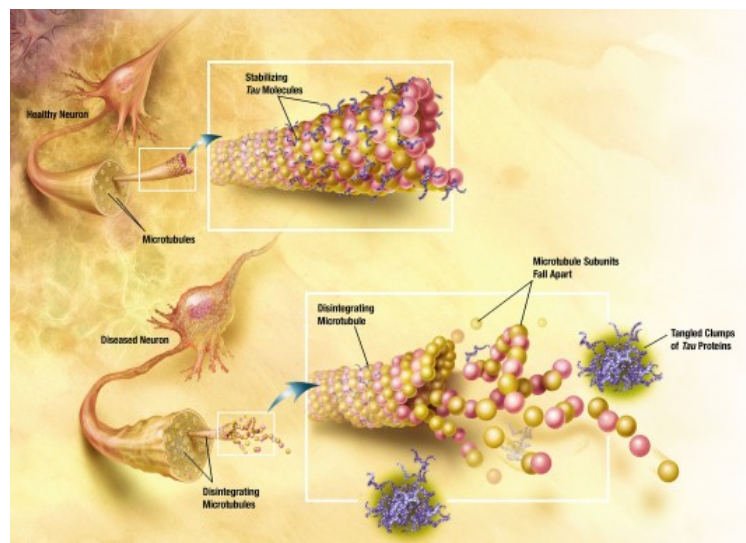


**Figure 3: Amyloid Plaque Formation.** APP (a) is snipped by enzymes to generate beta-amyloid fragments (b). These fragments aggregate outside the cell into oligomers and fibrils (not shown), which then combine with other cellular materials to form beta-amyloid plaques (c).  
*Source: National Institute on Aging, National Institutes of Health.*

Amyloid plaques are prevalent in particular regions of the AD brain and are a hallmark of the disease. However, it is unknown whether the amyloid plaques are a cause or consequence of AD. According to the **amyloid cascade hypothesis**, the accumulation of A $\beta$  initiates a series of events that culminates in AD neurodegeneration. The original hypothesis, which identifies A $\beta$  aggregates as the toxic species, was the basis for many early drug development work. However, all anti-amyloid drugs tested in clinical trials to date have failed to produce definite clinical benefit. Thus more recent variations of the hypothesis indicate aggregates of a different protein, tau, as the main cause of neuronal death.

## TAU ACCUMULATION LEADS TO TANGLES

Another hallmark of AD is the formation of **neurofibrillary tangles** inside neurons (Figure 4). These abnormal aggregates primarily consist of **tau**, a protein that stabilizes intracellular scaffolds called **microtubules**, which provide structural support as well as an internal transport network for nutrients and other cellular components. In AD, an abnormally large number of phosphate molecules becomes attached to tau in a process called **hyperphosphorylation**. The modified tau molecules disengage from microtubules and aggregate with one another, ultimately forming neurofibrillary tangles. These abnormal tau aggregates, including tangles, are toxic to neurons. Meanwhile, the destabilized microtubules disintegrate, leading to neuronal dysfunction and



**Figure 4: Tangle Formation and Microtubule Destabilization in AD.** Hyperphosphorylated tau disengages from the microtubule and forms neurofibrillary tangles. The microtubule disintegrates, leading to neuronal collapse.  
*Source: Alzheimer's Disease Education and Referral Center, National Institute on Aging, National Institutes of Health.*

contributing to cell death.

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## ACETYLCHOLINE DEFICIENCY

**Acetylcholine** is a type of **neurotransmitter**, a chemical that transmits signals from one neuron to another. Another pathologic feature of AD involves the degeneration of cholinergic neurons and the associated loss of acetylcholine signaling to the cortex and hippocampus, which plays a key role in attention and memory. The **cholinergic hypothesis** states that deficiency in acetylcholine production and signaling initiates the progression of AD. Because initial drug development was based on this hypothesis, most of the currently available AD medications act by preserving acetylcholine. Although these medications help manage symptoms, they have not led to a cure. These results and other research findings suggest that acetylcholine deficiency may not be a direct cause of AD, but rather a result of widespread brain damage during disease.

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## CHRONIC NEUROINFLAMMATION

**Neuroinflammation** refers to an immune response that is primarily mediated by activated **microglia**, the resident immune cells of the central nervous system that normally respond to neuronal damage. However, in the context of various brain diseases, it is uncertain whether microglia play a beneficial or detrimental role. Although short-term microglial activity generally confers neuroprotection, long-term activation is implicated in the pathogenesis of neurodegenerative disorders, including AD. Chronic activation of microglial cells may cause further neuronal damage through the prolonged release of potentially neurotoxic agents such as pro-inflammatory cytokines and free radicals. In Alzheimer's, the deposition of amyloid plaques and neurofibrillary tangles as well as neuronal death are the primary sources of the inflammatory response. Because these stimuli are chronically present in the AD brain, chronic neuroinflammation ensues.

Whether the immunological changes are a cause or consequence of AD is not yet clear. It is also unknown which aspects of the inflammatory response contribute to the pathological process of AD, and which may be protective. However, targeting the inflammatory cascade to either attenuate harmful effects or promote clearance of toxic proteins is a potential therapeutic option. To date, clinical trials of aspirin and nonsteroidal anti-inflammatory drugs have yet to show definite benefits in AD. More research is necessary to determine whether treatments that modify AD neuroinflammation could have demonstrable benefits for patients.

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## GENETICS

Approximately 1 percent of all AD cases is caused by genetic mutations, which can exist in one of three genes: *amyloid precursor protein (APP)*, *presenilin-1 (PSEN1)*, and *presenilin-2 (PSEN2)*. Because the mutated genes are passed along from parent to child, this inherited form of AD is called **familial Alzheimer's disease (FAD)**. FAD mostly occurs before the age of 65, as early as 30, and is thus categorized as **early-onset Alzheimer's disease**. Other cases of early-onset AD, which account for about 5 percent of all AD cases, have no known genetic basis or cause.

The vast majority of AD patients have **late-onset Alzheimer's disease**, in which symptoms appear after the age of 65. Unlike FAD, this form of AD is not directly caused by particular genes. However, variation in the *apolipoprotein*

*E (APOE)* gene affects the likelihood of developing late-onset AD. There are three major variants, or **alleles**, of the *APOE* gene:  $\epsilon 2$ ,  $\epsilon 3$ ,  $\epsilon 4$ . Each person possesses two copies of *APOE* and, depending on the specific combination of alleles, carries a different level of risk for developing AD. In general, the  $\epsilon 2$  variant decreases the risk,  $\epsilon 3$  plays a neutral role, and  $\epsilon 4$  increases the risk. Notably, an individual with two copies of the  $\epsilon 4$  allele has up to 20 times the risk of developing AD and is also more likely to develop the disease before the age of 65. *APOE*  $\epsilon 4$  is thus a genetic risk factor because it significantly increases the chances of developing AD; it is not a determinant of the disease because some individuals with the  $\epsilon 4$  variant never develop AD.

The aforementioned genes are only a subset of those associated with the development of AD. Through the use of advanced mapping and sequencing techniques, researchers are continuously identifying new genes that may contribute to or protect against the disease.

## RISK FACTORS

Aside from the genetic mutations in FAD, the cause of the vast majority of AD cases is still unknown. As a complex chronic disease, the development of AD is likely influenced by a combination of factors that involve an individual's genes, environment, and lifestyle. The following risk factors increase a person's chances of developing AD.

### AGE

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The greatest known risk factor for AD is advancing age. Starting at age 65, the risk of developing the disease doubles every five years. However, AD is not a normal part of aging, and age alone is not sufficient to cause the disease.

### *APOE* $\epsilon 4$ GENE

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The *APOE*  $\epsilon 4$  gene is a genetic risk factor for late-onset AD. In addition to increasing a person's likelihood of developing the disease, the *APOE*  $\epsilon 4$  gene variant is also associated with an earlier age of onset. However, carrying the *APOE*  $\epsilon 4$  allele does not guarantee the development of AD.

### CARDIOVASCULAR DISEASE RISK FACTORS

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Cardiovascular health is essential for proper brain function because the heart and blood vessels continuously pump blood to the brain, delivering nutrients and removing toxic waste products. There is a strong association between dementia and cardiovascular disease in which there is a lack of blood reaching the brain. Thus factors that increase the risk of cardiovascular disease are also associated with a higher risk of AD and other dementias. These factors include smoking, high blood pressure, diabetes, high cholesterol, and obesity.

### FAMILY HISTORY

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A family history of AD increases a person's likelihood of developing the disease. The risk is even greater for those who have more than one first-degree relative with AD. This familial factor is not entirely based on the inheritance of *APOE*  $\epsilon 4$  and other risk genes, and it may also involve shared environmental and lifestyle factors.

### LOWER EDUCATIONAL ATTAINMENT

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Individuals with less formal education have a higher risk of developing AD and other dementias. However, the effective quantity and quality of education has yet to be determined.

## TRAUMATIC BRAIN INJURY (TBI)

Individuals who experience TBI are at increased risk of developing AD and other dementias. TBI is the disruption of normal brain function, usually caused by a forceful blow or jolt to the head. Moderate TBI can result in a state of unconsciousness or amnesia that lasts more than 30 minutes. Severe TBI involves more physical damage to the brain and can result in long-term complications, including loss of consciousness or posttraumatic amnesia that lasts more than 24 hours. While moderate TBI doubles the risk of developing dementia, severe TBI increases the risk by 4.5 times.

## STAGES OF DISEASE

AD is a progressive disease that typically develops slowly over several years. The course of disease is not the same for every patient, but symptoms develop over five general stages with progressive loss of functional independence (Figure 5). In the late stage of AD, individuals are unable to function independently in everyday activities and can experience serious complications that lead to death.

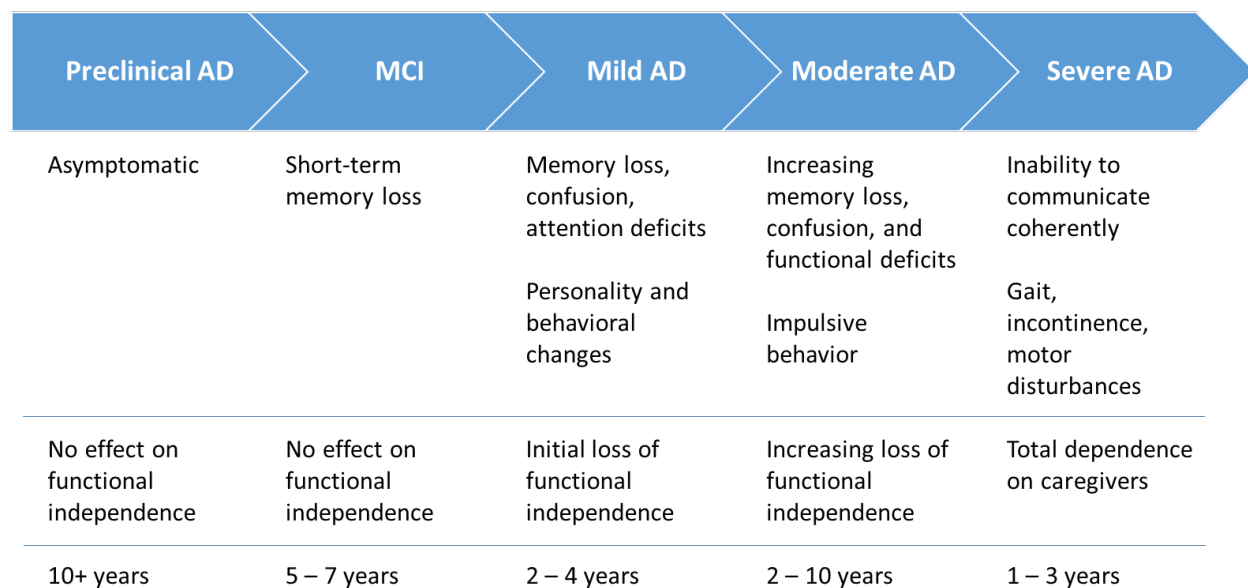


Figure 5: Stages of Alzheimer's Disease.

## PRECLINICAL AD

The development of AD involves brain changes that begin occurring a decade or more before clinical symptoms appear. Although what initiates the disease process is still largely unknown, the changes can go on for many years without symptoms. While current guidelines identify these preclinical changes as a stage of AD, they do not establish diagnostic criteria that physicians can use to categorize patients; instead these guidelines only apply in a

research setting. This stage of disease is also called *prodromal AD* because individuals have no AD-related symptoms.

## MILD COGNITIVE IMPAIRMENT (MCI)

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MCI involves a decline in cognitive abilities that is greater than expected for a person's age and level of education, but is not severe enough to compromise independent function. It is not specific to AD and may be caused by other types of dementia as well as various other medical conditions. Currently, it is not possible to definitively determine the underlying cause of MCI in a given patient.

Up to 15 percent of individuals with MCI develop Alzheimer's or other dementias, compared to 1 to 2 percent of the general population. Those whose MCI entails memory problems have a high probability of progressing to AD.

## MILD AD

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Symptoms of dementia become apparent in the mild AD stage. In this stage, cognitive impairments begin compromising a person's ability to function independently. Patients may experience short-term memory loss; difficulty planning or organizing; personality and behavioral changes; and getting lost or misplacing belongings. Most AD patients are diagnosed in this stage.

## MODERATE AD

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During the moderate stage of AD, damage spreads to areas of the brain that control language, reasoning, and conscious thought. Individuals become more forgetful and confused and begin to need help with daily activities. This is typically the longest stage of AD, and, as the disease progresses, the patient requires a greater level of care. Patients may show increasingly poor judgment and deepening confusion; experience even greater memory loss and the inability to learn new things; exhibit impulsive behavior; and have trouble controlling bladder and bowels.

## SEVERE AD

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Individuals with severe AD cannot communicate coherently and experience significant declines in movement and physical abilities. They are completely dependent on others for their care. Near the end, a patient may be in bed most or all of the time as the body shuts down.

## DEATH

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Contrary to a common misconception, AD is a fatal disease. In late-stage AD, the loss of coordination and mobility contributes to fatal complications such as pneumonia and malnutrition. The majority of AD-related deaths are due to pneumonia because impaired swallowing allows food or beverages to enter the lungs, in which an infection ensues. Other common causes of death include complications from urinary tract infections and falls. In addition, poor judgment and high-risk behaviors, such as wandering into dangerous situations, can lead to fatal incidents.

## DIAGNOSIS AND PROGNOSIS

The diagnosis of AD entails a comprehensive assessment of an individual’s mental and physical functions. In the clinic, the most commonly utilized tool for cognitive assessment is the Mini Mental State Examination (MMSE), which tests an individual’s problem-solving skills, attention span, counting skills, and memory. In addition to helping diagnose AD, the MMSE and related tests of mental function can be administered recurrently throughout a patient’s life to monitor disease progression. However, these tests are relatively insensitive to the early cognitive symptoms of AD and are thus inadequate for detecting MCI and mild AD alone. General laboratory tests, neurological exams, and brain scans are also performed to dismiss other possible causes of decreased cognitive function. Nevertheless, a definite diagnosis is only possible after death, by examining the patient’s brain tissue under the microscope for specific hallmarks of the disease.

Today, only about one-half of individuals with AD are diagnosed. Among those who have been clinically diagnosed, only 33 percent are informed of their diagnosis. Upon a clinical diagnosis, individuals with AD live an average of 8 to 10 years, while some survive as long as 25 years. The rate at which AD progresses varies widely across patients, depending partly on age at diagnosis and the presence of other health conditions. In particular, this large variability in disease progression presents a major challenge for evaluating and developing treatments for AD. Today, without any disease-modifying treatments, the outlook for individuals with AD is poor; there is nothing that can effectively slow, stop, or reverse the brain degeneration.

Research is under way to develop simple, reliable, and inexpensive tests that could be used for AD diagnosis and prognosis. One promising approach is the use of **biomarkers**, biological indicators of disease that are typically measured in brain images, blood, cerebrospinal fluid (CSF), or urine. For instance, studies indicate that A $\beta$  and tau proteins in CSF may serve as biomarkers of AD. The ideal diagnostic biomarker would enable early identification of AD-associated changes in the brains of individuals with preclinical AD or MCI due to AD, and thus make it possible to intervene at earlier stages of disease, before the degenerative process causes irreversible damage to the lives of patients and their caregivers.

## CURRENT TREATMENTS

At present, five drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer’s (Table 1). The primary goals of treatment are to preserve the patient’s independence and maintain quality of life by slowing the worsening of symptoms. However, these pharmacologic treatments only provide short-term alleviation of symptoms (6 to 18 months) and, most importantly, do not affect the pathology of the disease.

Table 1: FDA-approved Treatments for Alzheimer’s Disease in 2015

Drug Name	Mechanism of Action	Stage of Disease Treated		
		Mild	Moderate	Severe
Donepezil	Cholinesterase Inhibitor	X	X	X
Galantamine	Cholinesterase Inhibitor	X	X	
Rivastigmine	Cholinesterase Inhibitor	X	X	

Memantine	Glutamate Inhibitor	X	X
Namzaric™ (Donepezil + Memantine)	Cholinesterase Inhibitor + Glutamate Inhibitor	X	X

Three of the currently available drugs are **cholinesterase inhibitors**, which block the enzyme that breaks down acetylcholine. Because AD is associated with low levels of acetylcholine, inhibiting the degradation of the neurotransmitter may help improve brain function. While cholinesterase inhibitors may mitigate symptoms for up to 1 year, they lose their efficacy as more neurons become damaged and die. Furthermore, benefits for these medications typically occur at higher doses, which increase the likelihood of side effects.

Another class of drug that is currently used to treat AD works by regulating the activity of **glutamate**, a neurotransmitter in the brain that is involved in learning and memory. As part of its signaling mechanism, glutamate binds to and activates specific proteins on the surface of neurons called NMDA receptors, which in turn allow calcium ions to enter the cells. In AD, damaged neurons release excess glutamate. This results in chronic activation of NMDA receptors and overexposure to calcium, which can speed up neuronal damage and death. Memantine helps prevent this detrimental glutamatergic effect by blocking the NMDA receptors.

In December 2014, the FDA approved Namzaric™ for the treatment of moderate to severe AD. This treatment is a combination of two previously approved drugs, a cholinesterase inhibitor (donepezil) and a glutamate inhibitor (memantine). Because the two components work via different mechanisms, they can be prescribed in combination.

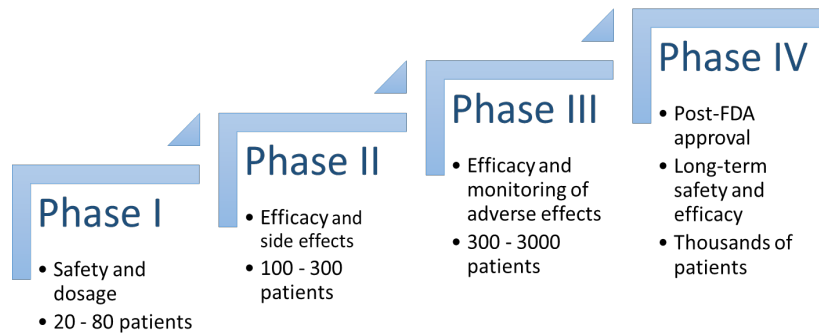
The efficacy and benefit of all the current treatment options are marginal at best. These drugs solely treat the symptoms of AD; none of them provides a cure. Thus a breakthrough AD treatment would treat the underlying disease and stop or delay its progression.

## THERAPEUTIC DEVELOPMENT LANDSCAPE

### CLINICAL TRIALS

**Clinical trials** are research studies with human subjects that evaluate the safety and efficacy of potential interventions, including drugs, vaccines, and medical devices. In order to obtain FDA approval for use in human patients, a new treatment must undergo a series of clinical trials from a small-scale Phase I study on safety and dosage to a large-scale Phase III study on efficacy and adverse effects (Figure 6).

A crucial step in the therapeutic development process, clinical trials require substantial resources. On average, it takes \$37 million and 5 to 7 years to complete the first three phases of clinical trials. Typical sponsors include pharmaceutical, biotechnology, and medical device companies as well as governmental organizations.



As of October 2015, 182 active clinical trials are evaluating

Figure 6: Phases of Clinical Trials.

symptomatic or disease-modifying treatments for AD. The potential interventions include small molecule drugs, antibodies, stem cells, gene therapy, medical devices, and nutraceuticals. Behavioral interventions, such as exercise, diet, and occupational therapy, are not included in the analysis.

Despite decades of AD research and drug development, the available treatment options are relatively few in number. Less than 1 percent of therapeutics investigated in clinical trials for AD have successfully completed the entire process and received FDA approval. Among drugs that are now on the market (Table 1, page 13), none modifies the progression of the disease.

### INVESTIGATIONAL THERAPIES

As of October 2015, 113 therapeutic products are in clinical trials for AD. Figure 7 illustrates the distribution of the investigational therapies by phase of clinical development.

Unlike the present AD treatments, these therapies represent a variety of therapeutic approaches for alleviating symptoms as well as for slowing or stopping disease progression. The key therapeutic strategies

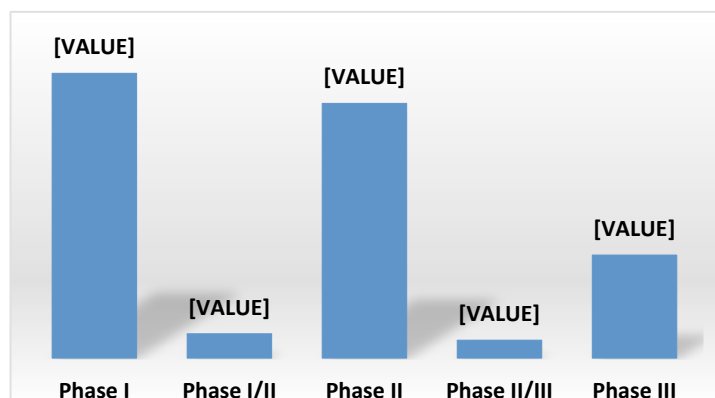


Figure 7: Therapeutic Products in Clinical Development for AD (October 2015). Created from data from BioCentury Online Intelligence.



currently being evaluated in AD clinical trials include those described below.

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#### AMYLOID-RELATED THERAPY

Since the inception of the amyloid cascade hypothesis more than 20 years ago, most AD therapeutic development efforts have focused on addressing the pathological accumulation of A $\beta$  in the brain. Nearly 90 percent of the disease-modifying treatments that are currently in clinical development are related to A $\beta$ . Amyloid-related therapies aim to modify AD progression by one or more of the following mechanisms:

- Inhibition of A $\beta$  production
- Inhibition of A $\beta$  aggregation
- Dissolution of existing A $\beta$  plaques
- Clearance of A $\beta$

The inhibition of A $\beta$  production entails targeting the three enzymes that cleave APP: beta-secretase, gamma-secretase, and alpha-secretase. APP cleavage by beta-secretase and gamma-secretase generates A $\beta$ , whereas cleavage by alpha-secretase circumvents generation of the pathological protein fragment. Therefore, drugs that inhibit beta-secretase (*BACE1 inhibitors*) or gamma-secretase (*GSI* and *GSM*), as well as drugs that activate alpha-secretase have been investigated as potential disease-modifying treatments for AD. To date, these types of drugs have been largely ineffective in clinical trials and have been associated with adverse side effects. At present, several *BACE1 inhibitors*, *GSI*, and *GSM* are in various stages of clinical development.

Investigational therapies for blocking A $\beta$  aggregation or dissolving existing plaques include anti-aggregation drugs, metal complexing agents, and immunotherapy. A $\beta$  clearance is also being pursued via immunotherapy, which is described in a separate section (page 17).

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#### TAU-RELATED THERAPY

Recently, AD drug development has been directed at tau pathology, which correlates more directly with the cognitive status of patients, compared to A $\beta$  pathology. Tau-related therapies aim to modify AD progression via one or more of the following mechanisms:

- Inhibition of abnormal tau production
- Inhibition of tau aggregation
- Dissolution of existing tau aggregates
- Compensation for lost tau function
- Clearance of abnormal tau

Inhibiting abnormal tau production involves targeting **kinases**, enzymes that hyperphosphorylate tau. Numerous types of kinases exist, many of which play redundant roles in phosphorylating specific proteins, and all of which play a central role in regulating cell function. The development of tau-related therapies based on kinase inhibition

90 percent  
of disease-modifying treatments  
in clinical trials address A $\beta$ .

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Alzheimer's Drug Discovery Foundation,  
2015

is thus challenging because an effective drug must target multiple types of kinases and because inhibition of these ubiquitous enzymes invariably disrupts normal cellular functions throughout the body. To date, all kinase inhibitors tested in AD clinical trials have yielded poor efficacy or severe adverse effects.

Another tau-related therapeutic approach is to prevent tau aggregation or dissolve existing aggregates. At present, a tau aggregation inhibitor called *methylene blue* is being evaluated for the treatment of mild to moderate AD in two Phase III clinical trials. In addition, drugs that stabilize microtubules can compensate for the loss of tau function in affected neurons as well as preclude formation of tau aggregates. Three microtubule-stabilizing agents are currently in various stages of clinical development.

Clearance of pathological tau species in the brain is currently being pursued via immunotherapy, which is described in the following section.

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## IMMUNOTHERAPY

AD immunotherapeutic strategies seek to remove pathologic A $\beta$  and tau species from the brain. **Active immunotherapy** involves the administration of drugs that stimulate the patient's immune system to generate antibodies against A $\beta$  or tau. In **passive immunotherapy**, antibodies against A $\beta$  and tau are produced by other means, outside of the patient's body, and administered as the drug themselves.

### ANTI-AMYLOID IMMUNOTHERAPY

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Although a number of immunotherapy drugs targeting A $\beta$  have been evaluated in AD clinical trials, there is no clear indication that these drugs can improve the clinical symptoms of the disease. Post-mortem analysis of patients who had received immunization showed significant clearance of A $\beta$ ; however, there was no therapeutic effect with respect to cognitive decline and long-term survival. The lack of clinical efficacy in previous anti-A $\beta$  immunotherapy trials may indicate that the treatments were administered too late in the disease process. Alternatively, the failures suggest that other pathological species must be targeted, separately or in conjunction with anti-A $\beta$  drugs.

In addition, this class of drugs has raised significant safety concerns regarding excess fluid accumulation or microhemorrhages in the brain, particularly in patients with high levels of amyloid plaques. Researchers hypothesize that during the clearance process, anti-A $\beta$  agents compromise the integrity of blood vessels by mobilizing A $\beta$  from plaques in the brain across the blood vessel walls.

As of October 2015, 15 active and passive immunotherapy agents against A $\beta$  are being evaluated in clinical trials. Few agents that previously failed to show clinical benefit are now being re-evaluated in new studies with differently defined cohorts of patients, including those in earlier stages of AD.

### ANTI-TAU IMMUNOTHERAPY

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Given that tau pathology correlates better with the degree of dementia than do A $\beta$  plaques, clearance of tau aggregates may be more efficacious in halting the progression of Alzheimer's, and thus preventing associated cognitive decline. Anti-tau immunotherapy is a newer therapeutic approach for AD with one passive and two active drugs currently in Phase I clinical trials.

The biggest challenge in the development of tau-based immunotherapy is identifying which forms of tau are neurotoxic. Although neurofibrillary tangles are an established hallmark of AD, recent studies suggest that the smaller, soluble tau species may be the harmful tau species. Additionally, as learned from the first generation of anti-A $\beta$  immunotherapy trials, researchers must determine at which stages of the disease these treatments will likely be effective to successfully design clinical trials.

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## NEUROTRANSMITTER-RELATED THERAPY

Acetylcholine depletion and synaptic dysfunction, two classic features of AD, have served as the basis for many early AD drug development efforts, which have generated the currently available treatments, acetylcholine inhibitors and NMDA receptor antagonists. Although drugs that regulate the production, release, or recycling of brain neurotransmitters cannot stop the progression of AD, researchers continue to pursue novel therapeutics to more effectively treat the symptoms of the disease. In October 2015, there are more than 25 neurotransmitter-related drugs in all stages of clinical development. These drugs directly modulate the brain level and signaling of acetylcholine as well as that of other neurotransmitters such as glutamate and **serotonin**.

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## NEUROINFLAMMATION-RELATED THERAPY

Chronic neuroinflammation is a hallmark trait of AD that contributes to its pathogenesis through numerous mechanisms. This immune response is primarily mediated by chronically activated microglia that subsequently release pro-inflammatory signals. Although these microglia normally engulf and destroy pathogens in the brain, recent evidence suggests that in AD they also attack neurons. Thus one therapeutic approach is to stimulate the microglia to favor attack on pathogens rather than bystander neurons and reduce pro-inflammatory signals in the brain. To date, clinical trials of aspirin and nonsteroidal anti-inflammatory drugs have yet to show definite benefits in AD. More research is necessary to determine whether treatments that modify AD neuroinflammation could have demonstrable benefits for patients. Phase I and II clinical trials are currently under way for a few anti-inflammatory agents.

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## NUTRACEUTICALS

Nutraceuticals are natural substances that are nutritional in nature and have purported therapeutic value. Researchers have identified several nutraceuticals that may exhibit protective properties against neurodegenerative disorders such as AD; however, evidence supporting the use of these substances to prevent or delay AD remains inconclusive. At present, approximately 20 clinical trials are investigating the effects of nutraceutical intervention on the progression of AD. Key nutraceuticals under evaluation include:

- **Flavonoids** are a group of compounds commonly found in fruits, vegetables, tea, cocoa, and wine. These compounds have been shown to modulate several neurological processes involved in neuronal function and survival. They also induce changes in cerebral blood flow, increase antioxidants at synapses, and inhibit pathological processes in brain regions that are typically affected in AD.
- **Resveratrol** is a compound found in seeds and the skin of many fruits. Preclinical studies have shown that resveratrol can increase serotonin activity, reduce inflammation, and protect neurons from death.
- **Curcumin** is the most active element of turmeric and has antioxidant and anti-inflammatory properties. It has been shown to reduce A $\beta$  pathology in AD mouse models.

- **Omega-3 fatty acids** are concentrated in fish, vegetable oils, nuts, and leafy vegetables. They are an integral part of cell membranes throughout the body, especially at neuronal synapses, and have been shown to exhibit anti-inflammatory properties.

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#### COMBINATION THERAPY

Because of the complexity and multifactorial nature of AD, an effective therapy to halt the disease may entail treatments with more than one drug. A combination therapy may employ various therapeutic strategies to target multiple molecules or pathways, such as anti-tau immunotherapy and anti-neuroinflammation. It may also combine different therapeutic agents within a given strategy, such as tau antibodies that target different tau species.

## STRATEGIC PHILANTHROPIC OPPORTUNITIES

In January 2015, the Milken Institute Philanthropy Advisory Service convened 12 world-renowned Alzheimer's experts to discuss the state-of-the-science of AD and the barriers to research progress. The goal of the retreat was to identify high-impact opportunities for strategic philanthropic investment. The experts prioritized the following challenges impeding AD research:

- Lack of reliable biomarkers
- Inadequate preclinical models
- Identification of new therapeutic targets
- AD research is conducted in silos

This section outlines each of the key challenges along with potential solutions and corresponding philanthropic opportunities to address the issue and accelerate AD research progress. *The opportunities presented below are high-level representations and should be considered carefully with respect to your philanthropic goals and discussed in detail with a philanthropic advisor.*

### LACK OF RELIABLE BIOMARKERS

#### THE PROBLEM

Biomarkers are valuable in both clinical and research settings. Reliable biomarkers for AD would enable:

- Conclusive and early diagnosis, including in presently asymptomatic individuals
- Standardized measurement of disease progression
- Accurate assessment of drug activity
- Complete monitoring of treatment responses

At this time there is no single biomarker that can be used confidently for these purposes.

Current methods used to track AD pathology, primarily imaging along with A $\beta$  and tau biomarkers found in CSF, are riddled with variability.

These challenges significantly impede both standard of care and clinical development in that we do not have a reliable way to track disease progression in patients, nor do we have the necessary tools to effectively evaluate behavior and performance of drug candidates in preclinical models. The inherent limitations of the preclinical data due to lack of biomarkers has partially led to the large number of failed clinical trials.

#### POTENTIAL SOLUTIONS

- *Standardization and validation of existing biomarkers*—A concerted effort to standardize and validate current imaging and CSF biomarkers would help mitigate variability and increase their utility.
- *Identification of new biomarkers*—A strategic clinical program could incentivize the collection of patient fluid samples (e.g., blood, CSF, saliva, urine) as a standard and thus allow researchers to rationally explore

various protocols that may unveil not only new biomarkers, but also new ways to quantify current biomarkers.

- *Studies correlating genotype, phenotype, and biomarkers*—Large-scale collection of the various types of fluids mentioned above would enable an integrated research program to find correlations between an individual's genes (genotype), clinical symptoms (phenotype), disease stage, and various biomarkers. These studies will help unveil biomarkers that can be used to diagnose, monitor progression, and/or evaluate treatment response. For example, evaluating a combination of biomarkers may help distinguish subtypes of AD patients that respond differently to a given drug and thus must be placed on distinct therapeutic regimens.

## STRATEGIC PHILANTHROPIC OPPORTUNITIES

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- Support initiatives that focus on standardizing imaging parameters and CSF biomarkers.
- Support researchers that are willing to validate old and new biomarkers, by attempting to replicate the original data and publishing the results whether they are positive or negative. The gift should fully support the validation work; however, to incentivize researchers to participate, a separate portion of the gift should go toward other relevant projects under way in the researcher's lab.
- Support a team of researchers that propose the best plan for conducting a large-scale genotype-biomarker-phenotype correlation study in various patient populations, stratified by stage of disease, using fluid and imaging samples.

## INADEQUATE PRECLINICAL MODELS

### THE PROBLEM

Developing preclinical models of AD is particularly challenging given the complexity of the brain as well as the disease. Current cellular and animal models do not adequately recapitulate human AD pathology and thus provide poor predictive value in testing potential therapeutics. As a result, drugs that seemingly modify the disease in animals or conventional cell lines do not have the same effect in humans; this issue contributes to the large number of drugs that fail in clinical trials.

### POTENTIAL SOLUTIONS

*Humanized cells as an alternative to animal models*—In this approach, induced pluripotent stems (iPS) cells are made from patient skin cells then reprogrammed to become neurons. These neurons can be used to study genetic variants of AD that are specific to individual patients. These patient- and disease-specific human iPS cells can be used as a drug discovery platform that will ultimately enable a personalized medicine approach for AD and potentially shave years off of the drug development timeline. Although this approach is exciting and considered to be a major breakthrough, more research is required to validate the generated cells as a representative model of human tissue in AD.

## STRATEGIC PHILANTHROPIC OPPORTUNITIES

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- Support studies that validate iPS cells as models of in vivo human cells by comparing the transcriptional profile (the pattern by which the cells make DNA) of cells from human tissue samples with that of differentiated iPS cell transcriptional profiles.
- Support a personalized medicine study using iPS cells from an individual patient, in which researchers recreate the patient's specific disease pathology in a petri dish to test the efficacy of various drugs.

## IDENTIFICATION OF NEW THERAPEUTIC TARGETS

### THE PROBLEM

Historically, AD drug development has primarily focused on acetylcholine and A $\beta$ . In 2015, four of the five currently available treatments involve acetylcholine and nearly 90 percent of disease-modifying treatments in clinical trials address A $\beta$ . Although there is evidence that drugs targeting A $\beta$  can successfully engage the A $\beta$  aggregates, they have demonstrated, at best, modest efficacy in mitigating the clinical symptoms of AD. Their continuous failure in clinical trials warrants the investigation of other therapeutic targets.

### POTENTIAL SOLUTIONS

Rather than focusing on the same avenues that have led to no treatment breakthroughs, more research should be conducted on other biological processes involved in AD pathology in order to identify novel therapeutic targets. These processes include but are not limited to neuroinflammation, vascular and synaptic changes in the brain, and genetic mutations that protect against AD. Increased focus on new therapeutic targets would diversify the AD therapeutic development pipeline and thus enhance the prospects for finding effective treatments.

## STRATEGIC PHILANTHROPIC OPPORTUNITIES

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- Support studies of synaptic biology in healthy and AD brains using optogenetics (a biological technique that involves the use of light to control cells in living tissue) and other cutting-edge technologies.
- Support studies that explore the role of vascular changes on AD onset and progression, including the identification of genes relevant to AD that affect vascular function.
- Support studies that explore the role of the immune system by studying the communication between the peripheral and central immune systems and how this communication relates to AD susceptibility.
- Support genotyping of individuals at high risk for the development of AD but have maintained normal cognition into old age. These studies can potentially identify mutational variants that can protect against AD.
- Support longitudinal studies focused on deepening understanding of the physiology of healthy brain aging with the purpose of comparing results to the physiological changes of AD brains and potentially identifying physiological processes and/or genes that protect against AD.

### THE PROBLEM

Alzheimer's research is currently conducted in silos, meaning that knowledge on different aspects of the disease are not efficiently connected together. For example, a researcher studying tau pathology may not regularly communicate with a researcher studying vascular system changes in AD patients. This fragmentation of the research community and AD intelligence is a significant impediment to research progress and drug development.

These silos also facilitate duplication of efforts. For example, drugs that are highly similar or the same are often developed at multiple institutions because there is no efficient way of knowing which molecules have been created and tested if the results were not published. This generates an enormous waste of resources and time, particularly if the drugs had already failed testing and the data had not been shared. Oftentimes, researchers are only able to build on the work of others once that work has been published or shared pre-publication through a collaborative agreement between researchers.

### POTENTIAL SOLUTIONS

The silos that are currently hindering AD research progress could be dissolved by:

- Providing more in-person opportunities to communicate and share ideas among experts working in areas of the field that are currently not well connected.
- Providing additional centralized infrastructures to support sharing of ideas and data among researchers.
- Developing and using a systems-based infrastructure that can be populated with all published information on AD research with the aim of creating a knowledge network that will enable the assembly of a more complete picture of the etiology, pathology, and progression patterns of AD.

### STRATEGIC PHILANTHROPIC OPPORTUNITIES

- Support interactive workshops for AD experts working in diverse fields, as well as outside experts working in related fields, e.g., immunologists and data scientists, to come together to present their work, discuss research roadblocks, identify ways to address these roadblocks, and potentially build collaborations.
- Support initiatives that incentivize sharing of medicinal chemistry data, which can serve as key starting points for motivated stakeholders in the AD community to develop new chemical entities and ultimately diverse drug classes. Consider funding projects that will:
  - Provide an infrastructure for academic centers to catalog agents being developed in their labs and incentivize the use of such resource
  - Incentivize drug development companies to share structural safety databases
- Support the development of a "Bloomberg-like" data infrastructure that can be populated with all published information on AD research and used to create a knowledge network that will enable rational



testing of drug candidates based on human AD pathology and molecular pharmacology. This will attenuate the AD community's current dependence on preclinical animal models, which are generally poor predictors of treatment efficacy in humans.

## KEY STAKEHOLDERS IN THE ALZHEIMER'S COMMUNITY

### RESEARCH GRANTMAKING ORGANIZATIONS

This section provides a brief overview of the nonprofit organizations involved in AD research. Their involvement can be through directly funding research or supporting research, for example, by charting the research roadmap for the disease or collecting tissue samples. This section only includes U.S.-based AD organizations with a research focus. Organizations that are solely involved in patient support, advocacy, awareness, or whose mission is to fund one specific research center are excluded.

Table 2: Top Nonprofit Organizations Funding AD Research in FY 2014

Organization	Research Grants (\$)	% of Total Expenditure
Alzheimer's Association	15,602,000	12.3
Alzheimer's Drug Discovery Foundation	9,189,031	68.0
BrightFocus Foundation Alzheimer's Research Program	5,211,638	46.6
Cure Alzheimer's Fund	5,351,659	73.2

Table 2 displays the top four nonprofit funders of AD research. Each organization is described below.

#### ALZHEIMER'S ASSOCIATION

The Alzheimer's Association is a voluntary health organization in AD care, support, and research. Incorporated in 1980, it now operates through a network of 80 chapters across the United States and a national office in Chicago. In FY 2014, research grants accounted for \$15.6 million, or 12.3 percent of the Association's total expenditure. In addition to directly funding research, the organization also focuses on building collaborations and leveraging resources for AD research advancement. It currently sponsors the Global Alzheimer's Association Interactive Network, which is a Big Data community that enables data sharing and collaboration among AD researchers around the world. The Association also includes various programs to strengthen the AD research community, including an annual international research conference, three journals, and a professional society. In addition, the Association is active in providing patient support, increasing public awareness on AD, providing information for healthcare professionals, and conducting advocacy and legislation efforts through its public policy groups.

#### ALZHEIMER'S DRUG DISCOVERY FOUNDATION

Founded in 1998 and based in New York City, the Alzheimer's Drug Discovery Foundation (ADDF) funds preclinical drug development and early-stage clinical trials, involving new drug targets that may not be far enough along in the pipeline to receive financial support from the pharmaceutical industry or other partners. By bridging the gap between basic research and drug development, the Foundation enables scientists to pursue innovative and novel therapies that might otherwise go unexplored. In 2014, grants amounted to \$9.2 million, or 68.0 percent of its total expenditure. After receiving initial seed funding from ADDF, research grantees have received follow-on commitments of more than \$1.6 billion from government, pharmaceutical companies, and venture capital firms to further their breakthrough drug research. ADDF operates through a venture philanthropy model; from more than \$15.7 million invested in biotech programs, the Foundation has received \$3.6 million in returns, which were reinvested in drug discovery and development programs.

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## BRIGHTFOCUS FOUNDATION

Founded in 1973, the BrightFocus Foundation is based in Clarksburg, Maryland. It supports research and public education for brain and eye diseases with programs in AD, macular degeneration, and glaucoma. The AD research program was formed in 1985 and currently supports 74 research projects around the world. In FY 2014, the Foundation provided more than \$5.2 million in AD research grants, or 46.6 percent of the AD research program's total expenses. The research program focuses on advancing early-stage, investigator-initiated AD research by providing initial funding for highly innovative or experimental ideas. Thus approximately 60 percent of the Foundation's grants are for basic science research, and 35 percent are for translational research.

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## CURE ALZHEIMER'S FUND

Founded in 2004, Cure Alzheimer's Fund is a venture-based AD research fund designed to dramatically accelerate research, make bold bets, and focus exclusively on finding a cure. Instead of funding investigator-initiated project proposals, the Fund's Research Consortium selects the researchers who are aligned with its research agenda and solicits proposals directly. The Fund's research approach is to identify all genes associated with late-onset AD, use those genes to reveal underlying disease mechanisms, and pursue potential therapies based on the gained knowledge. In 2014, the Fund provided more than \$5.3 million in research grants, or 73.2 percent of its total expenses. All funds raised by the organization go directly to research; the Board of Directors covers all overhead expenses.

## OTHER KEY ORGANIZATIONS

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### ACCELERATING MEDICINES PARTNERSHIP

The Accelerating Medicines Partnership (AMP), formerly the Target Validation Consortium, is a precompetitive collaboration among government, academia, and industry, convened to harness collective capabilities and scale resources toward improving current efforts to develop new therapies for complex, heterogeneous diseases. The current programs are in AD, type 2 diabetes, and autoimmune disorders of rheumatoid arthritis and lupus. The AMP-AD program is a precompetitive partnership among the NIH, pharmaceutical companies, and nonprofit organizations that focuses on discovering novel therapeutic targets for AD and on developing biomarkers to help validate existing therapeutic targets. This multi-sector partnership is managed by the Foundation for the NIH. The combined funding support for this 5-year endeavor is \$92.5 million (\$69.6 million from the NIH, \$21.9 million from industry, and \$1.0 million from nonprofit organizations).

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### ALZHEIMER'S DISEASE INTERNATIONAL

Alzheimer's Disease International (ADI) is the international federation of more than 80 Alzheimer associations throughout the world. The organization works to focus attention on the AD epidemic and campaign for policy change from national governments and the World Health Organization. The group runs a series of workshops through Alzheimer's University, which focuses on helping Alzheimer's associations strengthen their organizations. ADI also hosts the longest-running annual conference on dementia, the Annual International Conference of ADI, and supports a research network that aims to redress the imbalance between population-based research in high-income and low- and middle-income nations.

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## ALZHEIMER'S IMPACT MOVEMENT

The Alzheimer's Impact Movement (AIM), the sister organization of the Alzheimer's Association, is a nonpartisan, nonprofit advocacy organization. Working as strategic partners, AIM and the Alzheimer's Association developed and advanced the Alzheimer's Accountability Act. With the help of its members, AIM is driving Congress to make AD a national priority. Its current priorities include increasing the commitment to AD research and improving access to diagnosis and care planning.

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## DEMENTIA DISCOVERY FUND

The Dementia Discovery Fund is a \$100 million global venture capital fund that is exclusively dedicated to research on AD and other dementias. Announced in March 2015, initial financing has been committed by the British government, Alzheimer's Research UK, and five major pharmaceutical companies (Johnson & Johnson, Eli Lilly, Pfizer, Biogen Idec, and GlaxoSmithKline). The Fund will support preclinical research in academia and small biotech firms to develop new drug targets. Research projects that secure funding will also gain mentored guidance from industry partners throughout the funding cycle. Once a project matures, individual pharmaceutical companies will have an opportunity to bid on the rights to commercially develop the technology. The money raised from the bidding process will be reinvested in the fund.

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## GLOBAL ALZHEIMER'S AND DEMENTIA ACTION ALLIANCE

In May 2014, ADI, the Alzheimer's Society (England, Wales, and Northern Ireland), and the Department of Health in England announced the formation of the Global Alzheimer's and Dementia Action Alliance (GADAA). This alliance was formed in response to a call for action during the 2013 G8 Summit on Dementia, which called for research funding increases, improved infrastructure to support dementia care, and community programs to change societal attitude toward dementia. GADAA aims to foster global collaboration among international nongovernmental organizations, professional associations, governments, and international statutory bodies in order to coordinate efforts and raise global awareness of AD and other dementias.

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## GLOBAL CEO INITIATIVE ON ALZHEIMER'S DISEASE

The Global CEO Initiative on Alzheimer's Disease (CEOi) is an organization of private-sector leaders providing business leadership in the fight against AD. CEOi partners with political leaders as well as non-governmental organizations in effort to identify and pursue research, therapy development, financing, and public awareness projects of the highest priority. CEOi has formed four Working Groups around developing a prioritized AD research agenda; compressing the time, cost, and risk in developing AD therapies; developing a robust patient registry to improve clinical trial enrollment; and raising awareness and reducing stigma. Each Working Group is co-led by a corporate member of the organization and a leading nongovernmental partner. Additionally, CEOi is developing the Global Alzheimer's Platform, which will be a global network of clinical trial sites, functioning under a globally convergent and synchronized regulatory body with alignment on key issues related to clinical trial design. The vision of this effort is to create a global infrastructure in which clinical trial sites can quickly and efficiently recruit participants, with the aim of reducing redundancy, expense, and time. This platform will also support data sharing to advance basic discovery and translational research.

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## NATIONAL INSTITUTE ON AGING

The National Institute on Aging (NIA) is one of the 27 Institutes and Centers of the NIH. It was established by law in 1974 to provide leadership in aging research, training, health information dissemination, and other programs relevant to aging and older people. Subsequent amendments to the legislation designated the NIA as the primary federal agency on AD research.

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## US AGAINST ALZHEIMER'S

USAgainstAlzheimer's (USA2) is a nonprofit organization devoted to mobilizing American political, business, and civic leaders to devote the necessary resources to AD research and to reform the drug development systems that currently impede promising treatments. It is an advocacy campaign to mobilize millions of Americans to contact Congress in support of AD research and to support candidates for federal office who are committed to combating the disease. Key milestone successes highlighted by the organization include helping to secure more than \$200 million in additional public funding for AD research over the past few years, driving global efforts that have resulted in the collaboration of G7 world leaders to embrace the goal of curing Alzheimer's by 2025, forging collaborations to improve efficiencies for expedited drug discovery and approval for AD, and inspiring clearer research milestones to measure progress of the National Alzheimer's Project Act.

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## WORLD DEMENTIA COUNCIL

The World Dementia Council (WDC) was formed in 2014 as a result of a commitment declared during the G8 Dementia Summit in December 2013. By providing independent, nongovernmental advocacy and global leadership, the primary goals of the council are to stimulate innovative development and commercialization of effective treatments and care for people with dementia, or at risk of dementia, within a generation. Led by World Dementia Envoy Dennis Gillings, WDC's initial focus was on finance, global integrated development, and open science and data. Over its first year, this has widened to include two additional priorities, care and risk reduction, to take a more holistic approach to improving dementia prevention, diagnosis, treatment, and care.

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## CONSORTIA

Consortia are temporary associations of stakeholders from various sectors—academia, industry, government, clinical care, nonprofits, and philanthropy—that share resources in order to achieve a common goal. According to *FasterCures'* Consortia-pedia, a database of biomedical research consortia, there are currently 60 consortia for AD. Described below are select consortia that are under way for AD research and therapeutic development. For a full list, please visit [www.consortiapedia.fastercures.org](http://www.consortiapedia.fastercures.org).

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## ALZHEIMER'S ASSOCIATION RESEARCH ROUNDTABLE

The Alzheimer's Association Research Roundtable (AARR) is a consortium of scientists from the pharmaceutical, biotechnology, diagnostics, imaging, and cognitive testing industries, and senior staff and advisors from the Alzheimer's Association. AARR members seek to facilitate the development and implementation of new treatments for AD by collectively addressing obstacles to research and development, clinical care, and public health education. Begun in 2003 with four sponsors, AARR now includes more than 26 corporate sponsors that

support research and clinical trials worldwide. Each company sends several senior scientists to AARR to benefit from state-of-the-field scientific presentations, collegial interactions, and networking opportunities. To help address these obstacles, the dialogue and presentations also include investigators from academia and government organizations such as the FDA, NIH, and the European Medicines Agency.

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#### ALZHEIMER'S DISEASE COOPERATIVE STUDY

The Alzheimer's Disease Cooperative Study (ADCS) was formed in 1991 as a cooperative agreement between the **National Institute on Aging (NIA)** and the University of California, San Diego. It is a government initiative for AD clinical studies, addressing treatments for both cognitive and behavioral symptoms. The organization specifically focuses on developing drugs for AD that might not be developed by industry, including agents that lack patent protection, are under patent protection but are already marked for other indications, and novel compounds developed by individuals, academic institutions, and drug discovery units. Made up of more than 76 research sites in the United States and Canada, ADCS investigates interventions that may benefit people across the disease spectrum, from the detection of AD-related brain changes in asymptomatic study participants to the treatment of agitation in people with Alzheimer's. To date, ADCS has conducted 30 studies (23 drug trials and 7 instrument development studies). It also provides infrastructure support to other NIA-funded clinical efforts, such as the Alzheimer's Disease Neuroimaging Initiative and Dominantly Inherited Alzheimer Network.

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#### ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a public-private research partnership tasked to identify diagnostic biomarkers for AD. The overall goal of ADNI is to validate biomarkers from blood and CSF tests, positron emission tomography (PET), magnetic resonance imaging (MRI), as well as others for use in AD clinical trials and diagnosis. The study includes scientists at 55 research centers in the U.S. and Canada and involves more than 800 study participants at different stages of AD, including those with subtle memory problems, MCI due to AD, and mild to moderate dementia due to AD. To date the ADNI study has helped to develop a diagnostic test that can help diagnose the beginning stages of AD sooner and more accurately by measuring tau and A $\beta$  in CSF.

Now in its third phase, ADNI 2, the research focuses on the rate of change of cognition, function, brain structure, and biomarkers in 150 elderly controls, 450 subjects with MCI, 150 with mild to moderate AD, and a new group of 100 people with significant, yet subtle, memory complaints, referred to as the significant memory concern cohort.

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#### ALZHEIMER'S PREVENTION INITIATIVE

Led by Banner Alzheimer's Institute, the Alzheimer's Prevention Initiative (API) is an international collaborative for AD prevention research that aims to evaluate the most promising therapies in cognitively normal people who, based on their age and genetic background, are at the highest imminent risk of developing AD. The group consists of scientists, physicians, and industry and regulatory agency representatives and focuses on prevention and treatment trials, biomarker studies, and a patient registry. Its cornerstone study is evaluating an experimental anti-amyloid antibody treatment called crenezumab in a large extended Columbian family, in which members share a rare genetic mutation that typically triggers AD symptoms around age 45.

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## COHORTS FOR ALZHEIMER'S PREVENTION ACTION

Created by ADDF in 2014, Cohorts for Alzheimer's Prevention Action (CAPA) focuses on optimizing the use of existing observational data to support AD prevention research. The consortium enables large-scale studies by providing datasets from different groups of people to identify lifestyle and risk patterns associated with the development of AD. It currently consists of 40 cohorts representing more than 180,000 people. CAPA funds analyses powered by data gathered from at least five of these observational cohorts that will address pivotal questions about potential treatments to prevent AD, related dementias, and cognitive decline.

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## COLLABORATION FOR ALZHEIMER'S PREVENTION

The Collaboration for Alzheimer's Prevention (CAP) was formed in 2011 to help researchers learn from and support each other's work; share data; harmonize data gathering and trial outcomes to allow for comparability across studies; hold open, informal dialogue with regulators; and chart new territories in Alzheimer's prevention. The purpose of this collaborative group is thus to accelerate the development of preventative therapies for AD. CAP aims for researchers to provide assistance to each other in the development of trial outcomes (cognitive and clinical endpoints, and biomarkers), standardization of sample and data collection (clinical and cognitive data, imaging, and biofluids), and recruitment and retention of study participants (registry development and risk disclosure). It consists of representatives from the Alzheimer's Association, FDA, NIA, Fidelity Biosciences Research Initiative, as well as the major ongoing AD prevention studies—Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4), Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), Alzheimer's Prevention Initiative (API), and TOMORROW.

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## DOMINANTLY INHERITED ALZHEIMER NETWORK

The Dominantly Inherited Alzheimer Network (DIAN) is an international partnership of leading scientists that was formed by the NIA to study rare, genetic forms of AD. DIAN research participants are members of families in which AD is dominantly inherited, meaning that about 50 percent of the individuals in each generation of a family develop the disease. DIAN studies the preclinical brain changes in people who carry an AD mutation to determine how the disease process develops before there are any clinical symptoms. The research goal is to identify physical and mental changes that would serve as prognostic biomarkers of future AD development. Another goal of DIAN is to establish a research database and tissue repository to support AD research by other investigators around the world. Additionally, the DIAN Trials Unit (DIAN-TU) at Washington University is conducting the first prevention clinical trial for families with dominantly inherited AD.

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## GLOBAL ALZHEIMER'S ASSOCIATION INTERACTIVE NETWORK

Sponsored and managed by the Alzheimer's Association, the Global Alzheimer's Association Interactive Network (GAAIN) is a virtual data-sharing community that brings together AD consortia, research studies, and clinics as data partners. It provides a global infrastructure for cooperative research by linking data repositories that have collected information from thousands of individuals who have been diagnosed with AD as well as those at risk of developing the disease. Researchers can graphically explore data from research studies around the world and view correlations and trends in aggregated datasets. The network also enables researchers to find specified cohorts for future studies as well as establish new collaborations with existing research studies.

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## GLOBAL BIOMARKER STANDARDIZATION CONSORTIUM

Established by the Alzheimer's Association, the Global Consortium for Biomarker Standardization (GCBS) aims to achieve consensus on the best ways to standardize and validate AD biomarker tests for use in clinical practices around the world. It includes researchers, clinicians, industry, regulatory, and government leaders in AD. Current projects of the Consortium aim to standardize (1) the extraction, handling, and storage of CSF for biomarker measurement and (2) brain imaging (hippocampal volumetry) protocols for AD diagnosis.

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## INTERNATIONAL ALZHEIMER'S DISEASE RESEARCH PORTFOLIO

The International Alzheimer's Disease Research Portfolio (IADRP), developed by the NIA and the Alzheimer's Association, is a database created to capture the full spectrum of current AD research investments and resources worldwide. Its ultimate goal is to support funding agencies in analyzing the changing landscape of AD research, identify opportunities for coordination of resources and support, and identify funding gaps as well as areas of overlap within and across agencies. At present, more than 30 funding organizations have shared their funding profiles and grants. Hosted and maintained by the NIA, this resource also helps track and implement research goals of the U.S. National Plan to Address Alzheimer's Disease (NAPA).

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## WORLD WIDE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

The World Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI) is a collaborative effort of scientists from around the world and is the umbrella organization for neuroimaging initiatives being carried out through the North American ADNI, European ADNI, Japanese ADNI, Australian ADNI, Taiwan ADNI, and two new initiatives in Brazil and India. Its overall goals are to help define the rate of progression of MCI and AD and to develop improved methods for identifying the appropriate patient populations to participate in clinical trials. WW-ADNI also aims to standardize the methods used for conducting imaging scans and gathering and testing fluid samples so that data from all sites can be easily combined and understood by researchers. The purpose of the Initiative is to better understand the physical changes that occur in healthy individuals compared with individuals with subjective memory complaints, MCI, and AD. WW-ADNI focuses both on changes in the brain that can be identified with imaging tools such as PET and MRI, and changes in fluids such as blood and CSF.



## GLOSSARY

**Acetylcholine:** a neurotransmitter that plays an important role in many neurological functions, including learning and memory.

**Active immunotherapy:** administration of a drug vaccine into the body to induce an immune response leading to the natural production of antibodies against a target.

**Alzheimer's Accountability Act:** bipartisan U.S. legislation that requires the NIH to submit an annual budget estimate directly to the President and Congress, specifying the resources needed to achieve the goal of the **National Plan to Address Alzheimer's Disease** of preventing or effectively treating AD by 2025. Although the Secretary of Health and Human Services and the Advisory Council on Alzheimer's Research, Care and Services have an opportunity to comment on the professional judgment budget, they cannot change the content. The Act was signed into law in December 2014 as part of the FY 2015 omnibus appropriations bill.

**Amyloid plaques:** insoluble deposits in the space between brain cells that primarily consist of beta-amyloid. They are one of the two anatomical hallmarks that define Alzheimer's; the other hallmark is **neurofibrillary tangles**.

**Amyloid precursor protein (APP):** a transmembrane protein found in neuronal synapses from which beta-amyloid protein is derived.

**Axon:** the appendage of a neuron that transmits impulses away from the cell body.

**Beta-amyloid (A $\beta$ ):** a protein that is derived from amyloid precursor protein and is the primary component of plaques characteristic of Alzheimer's.

**Biomarker:** a distinct biochemical, genetic, or molecular characteristic that is objectively measured and evaluated as an indicator of a particular biological condition or process.

**Blood-brain barrier:** a layer of cells lining the inner surface of brain capillaries. It protects the brain from infectious agents and toxic compounds by letting nutrients and oxygen in and waste products out. Because the barrier strictly regulates the passage of larger molecules and often prevents drug molecules from entering the brain, it has long posed one of the most difficult challenges in developing treatments for brain disorders.

**Cerebrospinal fluid (CSF):** clear, colorless body fluid that bathes the brain and spinal cord. Although the primary function of CSF is to cushion the brain within the skull and serve as a shock absorber for the central nervous system, CSF also circulates nutrients and chemicals filtered from the blood and removes waste products from the brain.

**Cholinergic hypothesis:** deficiency in acetylcholine production and signaling initiates the progression of Alzheimer's.

**Cholinesterase inhibitors:** a class of drugs that blocks the activity of cholinesterase. Most of the currently available treatments for Alzheimer's are cholinesterase inhibitors.

**Cholinesterase:** an enzyme that catalyzes the hydrolysis of acetylcholine, breaking it into acetic acid and choline.

**Clinical trials:** research studies on human subjects that are designed to evaluate the safety and efficacy of potential interventions, including drugs, vaccines, and medical devices.

**Dementia:** the loss of cognitive functioning such as thinking, remembering, and reasoning to an extent that it interferes with everyday activities. Types of dementia include Alzheimer's, vascular dementia, Lewy body dementia, and frontotemporal disorders.

**Early-onset Alzheimer's disease:** a form of AD that occurs before the age of 65, as early as 30. Approximately 5 to 10 percent of all AD cases are early-onset AD. Some are caused by inherited genetic mutations (familial early-onset AD) while others have no known genetic basis or cause.

**Enzyme:** a protein originating from living cells that catalyzes a specific biochemical reaction.

**Familial Alzheimer's disease (FAD):** a rare, inherited form of AD that is caused by a mutation in one of three genes: *amyloid precursor protein (APP)*, *presenilin-1 (PSEN1)*, and *presenilin-2 (PSEN2)*. FAD mostly occurs before the age of 65, as early as 30, and thus is also categorized as **early-onset Alzheimer's**.

**Glutamate:** a neurotransmitter that controls communication among neurons by regulating intracellular calcium ion levels. It is involved in learning and memory.

**Hyperphosphorylation:** a process in which an abnormally large amount of phosphate molecules become attached to a protein.

**Kinase:** an enzyme that catalyzes the addition of phosphorous and oxygen groups to a protein.

**Late-onset Alzheimer's disease:** a form of AD that occurs after the age of 65. The vast majority of AD patients have late-onset AD.

**Microglia:** the resident immune cells of the central nervous system that respond to and remove damaged neurons.

**Microtubule:** a hollow cylindrical protein structure in neurons that holds the cell in its proper shape and also helps transport nutrients within the cell.

**National Alzheimer's Project Act (NAPA):** Signed into law in January 2011 with unanimous passage by Congress, the Act mandated the creation of a U.S. national plan to accelerate research toward prevention and treatment of AD, and to improve care and services. Through outcomes-driven objectives, recommendations, implementation steps, accountability, and engagement of the various stakeholders, the plan would provide a strategic national framework to address the burden of the disease.

**National Institute on Aging (NIA):** an institute of the NIH that was established by law in 1974 to provide leadership in aging research, training, health information dissemination, and other programs relevant to aging and older people. It is the primary federal agency designated to AD research.

**National Institutes of Health (NIH):** primary agency of the U.S. government responsible for biomedical and health-related research. The NIH comprises 27 separate Institutes and Centers that conduct research in different disciplines of biomedical science.

**National Plan to Address Alzheimer's Disease:** Mandated by NAPA, this U.S. national plan was released in May 2012 with the primary research goal of preventing or effectively treating Alzheimer's by 2025. It also focuses on

enhancing care quality and efficiency, expanding supports for patients and caregivers, enhancing public awareness and engagement, and tracking progress.

**Neurofibrillary tangles:** collections of twisted protein threads found inside diseased neurons, composing primarily of abnormally modified tau protein. They are one of the two anatomical hallmarks that define Alzheimer's disease; the other hallmark is amyloid plaques.

**Neuroinflammation:** an innate immune response in the central nervous system that involves the accumulation of activated immune cells to a site of injury or foreign substances.

**Neuron:** a type of cell found in the nervous system that processes and transmits information to other cells through electrical and chemical signals; also called nerve cell.

**Neurotransmitter:** a chemical that transmits signals across a synapse from one neuron to another cell.

**Oligomer:** a molecular complex that consists of a few monomer units.

**Parasympathetic nervous system:** the part of the nervous system that regulates activities such as salivation, urination, digestion, defecation, and tear generation.

**Passive immunotherapy:** administration of antibodies or other immune system components that are made outside of the body.

**Serotonin:** a neurotransmitter that is involved in sleep, depression, memory, and other neurological processes.

**Synapse:** specialized connections between neurons where information is transmitted.

**Tau protein:** a protein that binds to and regulates the assembly and stability of neuronal microtubules; found in an abnormal form in Alzheimer's.

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