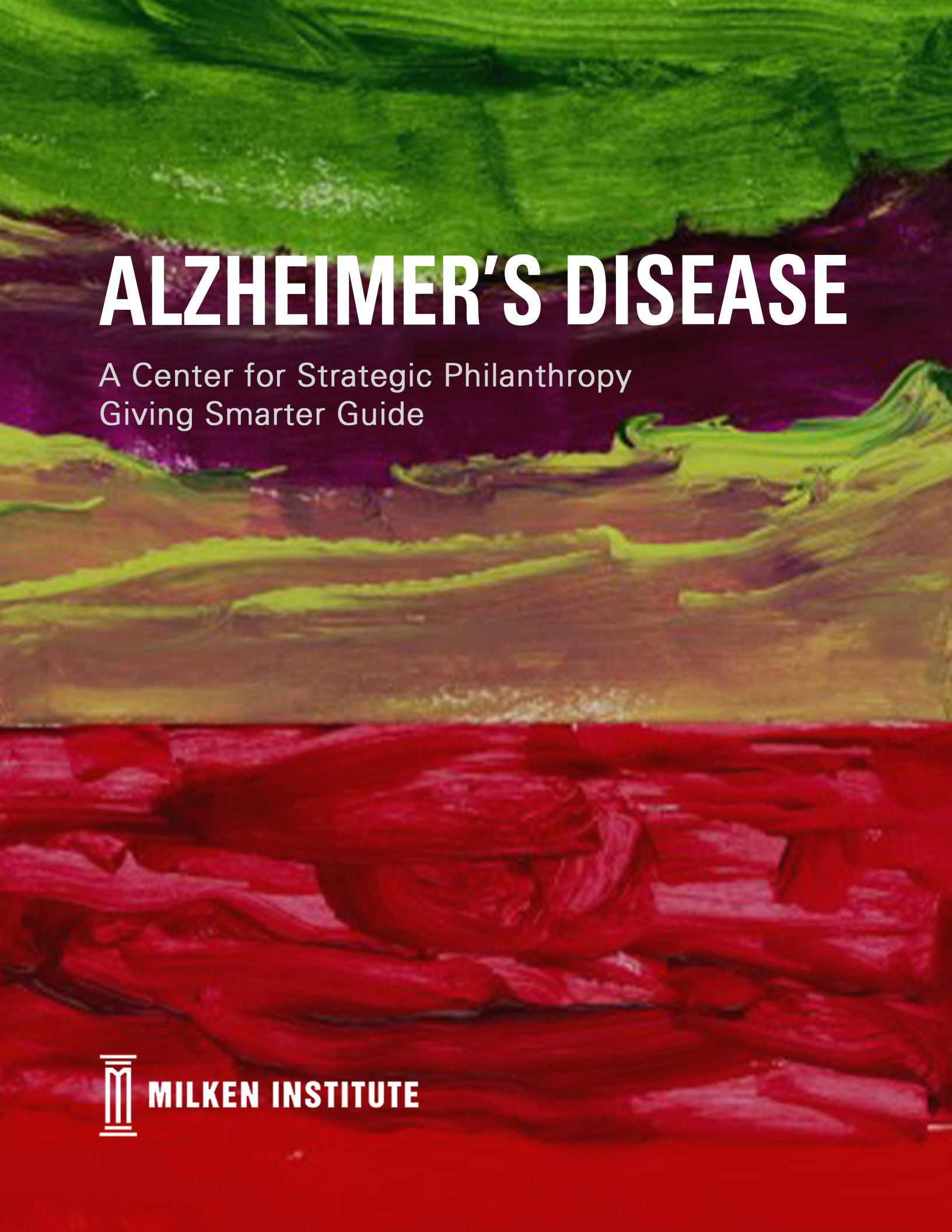

ALZHEIMER'S DISEASE

A Center for Strategic Philanthropy
Giving Smarter Guide

MILKEN INSTITUTE

ABOUT US

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ABOUT THE MILKEN INSTITUTE

The Milken Institute is a nonprofit, nonpartisan think tank determined to increase global prosperity by advancing collaborative solutions that widen access to capital, create jobs, and improve health. We do this through independent, data-driven research, action-oriented meetings, and meaningful policy initiatives.

ABOUT THE CENTER FOR STRATEGIC PHILANTHROPY

The Milken Institute Center for Strategic Philanthropy (CSP) designs smart giving strategies to accelerate philanthropic goals and progress. It is focused on maximizing the return on philanthropic investment by ensuring that innovation used to address one social issue is translated to another, best practices and metrics guide new and existing giving programs, and resources are invested to optimize outcomes. CSP provides comprehensive, digestible information that helps donors evaluate research efforts and funding opportunities in various areas of health and medical research. Expert advisory boards, in-depth due diligence, and an objective framework for evaluation shapes its analysis.

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Keeping Hope on the Horizon

Alzheimer's disease is increasingly in the spotlight after a number of high-profile clinical trial failures—an alarming trend as an estimated 5.5 million adult Americans live with this disease, which disproportionally affects the aged population. Because the over 65 population is projected to double by 2050, the number of new cases of Alzheimer's and related dementias is expected to soar. Consequently, Alzheimer's disease is projected to overwhelm the national health care system, affecting 16 million Americans and costing Medicare and Medicaid $1.1 trillion by 2050. Yet, the stark reality remains that no therapeutic has been approved to prevent, slow, or cure Alzheimer's disease. Not one.

As dire as these facts may appear, there is reason to remain hopeful. With the growing number of therapeutics in the pipeline, scientists appear to be close to a breakthrough. Therefore, we must use our precious time and resources judiciously to support their efforts. To that end, CSP worked closely with the S Family Foundation to determine strategic solutions that can impact our future. This Giving Smarter Guide is intended to inform those involved in the fight against Alzheimer's disease (AD), especially philanthropists.[1]

[1] *The Milken Institute published a Giving Smarter Guide for Alzheimer's disease in 2015.*

WHAT IS ALZHEIMER'S DISEASE?

The brain consists of billions of cells called neurons. Neurons communicate with each other through coordinated electrical and chemical signals, which are vital for proper functioning of the brain and the body. During the normal aging process, some neurons begin to die, causing some normal functions to decline. However, this process can accelerate because of disease or injury, a process called neurodegeneration, which occurs in diseases such as Alzheimer's and Parkinson's.

Notable biological differences underlie the neurodegenerative diseases and their accompanying symptoms. For example, Alzheimer's disease is characterized by the abnormal presence of two cellular proteins: amyloid and tau. In sporadic AD, an unknown process spurs an abundance of amyloid outside of the neuron, which eventually stick together to form a plaque. These plaques are thought to hinder communication between neurons, causing some of the symptoms. Over time, the protein tau also sticks together to form tangles inside of the neuron leading to dysfunction within the cell, and ultimately these neurons die. Although we know that amyloid and tau are part of the AD puzzle, we are still missing many pieces needed to understand the whole picture and to tackle this disease.

Over the past several years, efforts to understand and treat AD have been bolstered by increased investments by the National Institutes of Health (NIH) of the United States and through philanthropic partnerships. As the increased burden of disease is overwhelming to both the national budget and our aging families, we must double down our investment to solve the AD crisis—with all sectors using a focused strategy to employ capital where it is needed most.

Alzheimer's disease is projected to overwhelm the national health care system, affecting 16 million Americans and costing Medicare and Medicaid $1.1 trillion by 2050.

PHILANTHROPIC OPPORTUNITIES

Supported by the S Family Foundation, the Milken Institute CSP brought together 30 experts in AD earlier this year to assess the current state of the field and to identify concrete opportunities where philanthropic capital could make a real difference. The top five are listed below.

Support Collaborative Basic Science

Our understanding of the causes of AD and its contributing factors is limited. A historical, intensive focus on one protein, amyloid, may have stifled exploration into other dynamics, causing a lack of diversity in the clinical pipeline. *Directed investment into the complex interplay of the full range of biological players promoting neurodegeneration would fill in critical knowledge gaps—gaps that could be turned into new therapeutic targets.*

Focus on Biomarkers of the Disease

Currently, the only definitive diagnosis of AD is made after death. Current tools to provide interim diagnoses are expensive and invasive, including brain imaging tests or sample collections through a spinal tap. Additionally, cognitive tests used in the clinic are not sensitive enough to detect problems until the disease has progressed significantly. *Investment into novel tools that are more sensitive, less invasive, and less expensive to measure AD could help change the disease trajectory for scientists, clinicians, and patients.*

Enable Data Science

More data exists than ever before, and are growing exponentially with the expansion of biological techniques examining whole genomes, proteomes, and beyond. Many systems have emerged to fill immediate data needs; however, these systems rarely talk to one another, limiting the ability to share or combine datasets. With big data comes even bigger breakthroughs, but the ability to store, access, and analyze these data are paramount. *Philanthropists can help support the crosstalk between big data platforms to unify existing data and can sponsor the integration of data scientists into neuroscience.*

Untangle Risk Factors

The AD field is in the early days of understanding risk factors beyond certain genes. Complicating matters is the lack of diagnostic tools for AD, as well as the co-illnesses that coincide with AD. These issues challenge the ability to untangle AD risk factors from those of other dementias or diseases. Understanding what factors contribute to an individual's risk of AD is a first step to learning how to mitigate risk. *Philanthropists should support long-term efforts to proactively screen patients for disease biomarkers, as well as the studies to follow these individuals over time to assess risk factors.*

Reinforce the Clinical Pipeline

No therapeutic has been approved to prevent, slow, or cure AD. The complexity of the disease has made development of model systems to test novel therapeutics challenging, and the long timescale of disease progression has prompted industry to shave off time by skipping vital steps in the process. *Support by philanthropists to develop and expand model systems would benefit the early clinical pipeline. Additionally, investment into the development and implementation of a "trial-ready" cohort would allow for adaptable clinical trials that fully utilize their potential patient population.*

In this Giving Smarter Guide, we outline the key barriers to progress within the AD field and identify areas where philanthropic capital can be leveraged to generate an outsized impact. We hope to provide a roadmap for philanthropists and foundations alike to invest their funds strategically and make strides in the fight against AD.

DRIVING SCIENCE THROUGH PHILANTHROPY

Historically, funding of the scientific enterprise often has been left to government bodies and commercial industries, especially in the United States. This trend tracks back to several drivers, the primary ones being the significant levels of capital investment and complex infrastructure required to support meaningful academic research and clinical development. Governments can often provide consistent, funding to a breadth of research topics, while industry can move new therapies from the benchtop to the population.

Nevertheless, problems can emerge when only government and industry distribute the wealth in science. For instance, government funds can be slow to respond, given bureaucracy and relentless election cycles. Additionally, government funders are usually risk averse, typically favoring more "accepted" research and thereby leaving little room for creativity or untested ideas. On the other side, commercial players—from pharmaceutical giants to emerging biotechnology firms—are beholden to their investors who can also be wary of uncertainty. Similarly, when the bottom line is not met on funded projects, private investors may divest regardless of how successful—or needed—the research itself may be. The combination of these two realities can lead to stagnation in scientific innovation, that is, an inability to react quickly to a changing climate and gaps in funding to address complex problems.

At the Milken Institute Center for Strategic Philanthropy, we have witnessed first-hand how philanthropic capital can fill the gaps where commercial and government funds cannot. Foundations and philanthropists alike can fund cutting-edge research and novel hypotheses, providing the seed that might spark a field-altering discovery or spawn a new branch of science. In addition, they can move quickly in response to immediate needs, whether because of defunding through other mechanisms or a crisis event.

DRIVING SCIENCE THROUGH PHILANTHROPY

An infusion of philanthropic funds can de-risk a sector and demonstrate a proof-of-concept. ***Philanthropy can act where other entities cannot—bridging sectors without consideration of partisanship, bottom lines, or policy stances and providing support where most needed.***

Philanthropy, however, has limitations as well. In the U.S., philanthropic capital represents a small percentage of overall scientific funding—just 2 to 4 percent depending on how it is counted. Therefore, this capital must be invested as wisely as possible to ensure that it reaps the desired dividends.

At CSP, we know that the most effective philanthropists are usually the best informed. Like any savvy investor, philanthropists need due diligence and market analysis to identify the key gaps, barriers to entry, and hidden leverage points that can accelerate discovery and development. Using a systems-based approach and a cross-sectoral vantage point, philanthropy can be used strategically to solve some of the most challenging problems in science and beyond.

In the pages that follow, and in all of our Giving Smarter Guides, CSP strives to provide deep scientific insight into the issues and to outline a concrete and actionable set of options for all philanthropists—no matter their size or location. We welcome all feedback regarding our findings, as well as partners in our quest to advance scientific knowledge through philanthropy. The stakes are high, and time is short. Let's work together to get this right.

ALZHEIMER'S DISEASE: AN OVERVIEW

Alzheimer's disease (AD) is a chronic disease characterized by slow, yet progressive damage and death of a certain type of brain cells called neurons. AD is the most common form of dementia and is responsible for from 60 to 80 percent of diagnosed dementia cases. Dementia is a group of syndromes that share one common trait: cognitive decline, which can include memory loss, personality changes, and difficulties with problem-solving. These symptoms result from the damage of neurons in certain regions of the brain responsible for cognitive function. Neuronal damage increases and spreads as symptoms progress, but the rate of progression varies among individuals. Once in the later stages of dementia, patients require assistance to perform basic tasks, such as eating or bathing, and around-the-clock care. Ultimately, AD is fatal, either indirectly through secondary conditions such as pneumonia, or directly, through extensive brain damage.

Although the syndromes under the umbrella term of dementia share similarities, each syndrome is associated with a distinct brain abnormality and/or symptom profile and is thus unique. As such, AD is characterized by two very specific molecular abnormalities occurring both outside and inside neurons. First, a cellular protein called beta-amyloid accumulates in the outer areas surrounding neurons. When this accumulation occurs, the protein sticks together to form plaques, which can block communication between neuronal cells. Second, another cellular protein called tau sticks to itself and tangles inside the cell. The exact mechanism behind why amyloid plaques and tau tangles cause damage and death to neuronal cells is unknown. While the average age of onset for cognitive symptoms is 65, protein accumulation begins decades prior, building plaques and spreading across different regions of the brain.

There is no definitive test to diagnose AD. However, doctors use a battery of tests to determine whether a patient likely has AD.

These tests include a basic neurological exam, labs tests to help rule out other potential causes of confusion, such as vitamin deficiency, and mental status tests to assess memory and the ability to think through problems. Additionally, brain imaging tools may be used to identify visible abnormalities in the brain or to visualize specific markers that correlate with disease, such as the presence of the amyloid or tau protein. However, this diagnosis can only be confirmed post-mortem when a microscopic examination of the brain can reveal characteristic signs of plaques and tangles. This inability to definitively diagnose leads to a number of misdiagnoses and challenges.

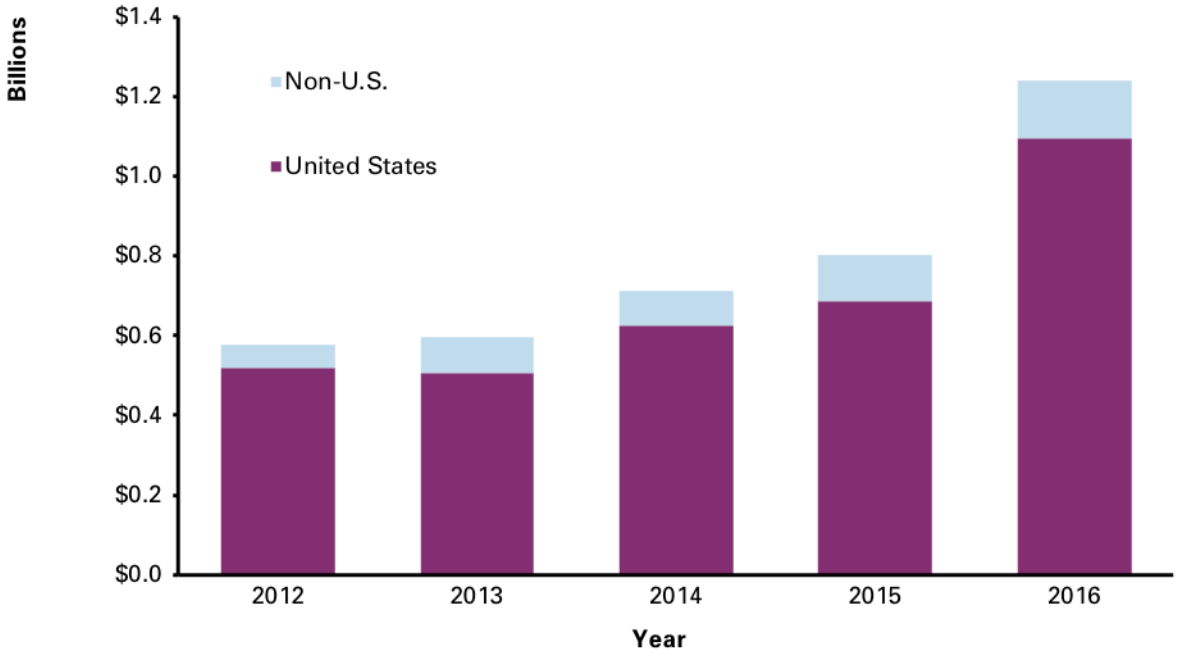
Additionally, ***there is no approved treatment to prevent, slow, or cure AD***. Therefore, increasing levels of care and support are necessary to combat the inevitable progression of the disease. Not only is this emotionally and financially taxing for caregivers and loved ones of AD patients, but also the expected impact on the national scale is extremely daunting. Without any treatment options, AD is expected to overwhelm the national health care system, affecting a projected 14 million Americans and costing Medicare and Medicaid $1.1 trillion by 2050. Despite this impending crisis, large pharmaceutical companies have begun to close their internal neuroscience programs due to the devastating billion-dollar failures in clinical trials. To combat this trend and thwart this crisis, increased investment from all sectors and sources—government, philanthropy, and private industry—is necessary.

In this Giving Smarter Guide, we outline key barriers within the AD research field that have hindered progress on finding viable therapeutics and identify issue areas in which philanthropic capital can be leveraged to generate an outsized impact. With this guide, we hope to provide a roadmap for philanthropists and foundations alike to invest their funds strategically and make strides in the fight against AD.

ALZHEIMER'S DISEASE RESEARCH FUNDING IN THE U.S. AND ABROAD

Over the past five fiscal years (2012-2016), global funding for AD research has increased significantly, from $580 million to more than $1.2 billion. As shown in Figure 1, the U.S. accounts for the majority of AD spending, funding more than $1 billion in 2016 alone.

Figure 1. Total Global Funding Dedicated to AD Research from FY 2012-2016



Note: Global funding has more than doubled over the past five fiscal years, driven by a $400M increase from the U.S. from FY 2015 to 2016.

Source: Milken Institute.

Despite these seemingly large numbers, AD research has been historically underfunded during the past three decades, even though its importance in both health care and economics has increased. In 2015, an estimated 46.8 million people worldwide were living with dementia. This number is expected to double every 20 years. In the U.S., AD is the sixth leading cause of death and is projected to affect 16 percent of the population by 2050. Recently, the Alzheimer's Association published a report showing that AD-related deaths have increased by 123 percent over the past 15 years, while other leading causes of death, such as cardiovascular disease and prostate cancer,

have decreased significantly. It is thus surprising that AD research is so underfunded, especially when compared to the other top 10causes of death. Additionally, the percentage of the National Institutes of Health (NIH) budget earmarked for AD has remained mostly stagnant over the past 20 years, reaching only 3 percent of the total.

AD is the **6th** leading cause of death in the U.S.

The Alzheimer's Association estimates that the cost of AD for Medicare and Medicaid alone will grow from $186 billion in 2017 to $1.1 trillion in 2050; yet, the current research budget is less than 1 percent of the current total cost of disease. Thus, sustained increased investment in AD is warranted as the elderly population and the resultant burden on both the health care system and caregivers grow substantially.

$277B Total health-care cost of AD

SUMMARY OF AD RESEARCH FUNDING IN THE U.S. BY RESEARCH AREA

The national budget for AD research has increased, mainly driven by an expansion in the NIH budget for AD research following the bipartisan passage of the Alzheimer's Accountability Act, which was a part of the U.S. omnibus appropriations bill in 2015. After its passage, the Alzheimer's Bypass Budget received an additional $400 million for 2016 and 2017 and reached $1.8 billion in 2018. The U.S. is not alone in its efforts to accelerate AD research progress, as similar legislation and calls to actions have been issued in the United Kingdom, Canada, and Australia—emphasizing the gravity of the impending situation.

To understand how research dollars have been allocated in the U.S., we examined expenditure trends by research category to determine whether these trends mirror the state of the science. As overall funding increases, it will be important to understand these relationships to inform future money allocation.

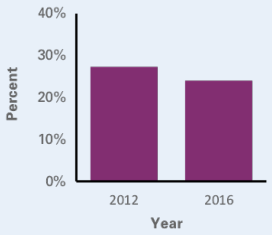
We completed an analysis of the global funding for AD research to understand the comparative scientific portfolios of multiple funders and to identify research areas with unmet needs that may require

philanthropic intervention. To this end, we collected publicly available information from 33 organizations across 10 countries for the past five fiscal years (2012-2016). When possible, we categorized funded research using the Common Alzheimer's Disease Research Ontology (CADRO) system, following a three-tiered system developed by the National Institute of Aging and the Alzheimer's Association.

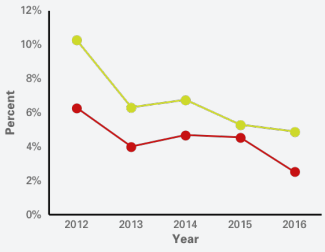
The U.S. funding focus has changed in five key ways over the past five fiscal years, as illustrated in Figure 2.

Figure 2. AD Funding Trends in the U.S., FY 2012-2016

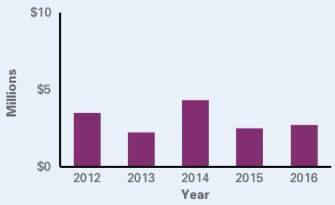
Basic disease biology experienced a modest decrease in funding allocation. Although the decrease is not extensive (from 30 percent to 24 percent of the overall budget for AD research from 2012 to 2016), it reflects the overall NIH trend of decreased funding for basic science, according to a study published by the National Institute of Neurological Diseases and Stroke (NINDS) in 2014. In a field such as AD, where major gaps exist in our understanding of key drivers of disease, this type of research is paramount.



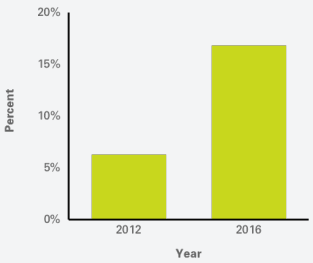
Funding of fluid biomarkers and behavioral, cognitive, and functional assessments experienced a significant decrease in funding. Fluid biomarkers, specifically blood and saliva, would be the most accessible in a clinical setting, as these are the least invasive and comparatively inexpensive. Additionally, the current measures of cognitive impairment are quite crude and cannot measure diminished cognition in pre-symptomatic patients. Therefore, this type of research is essential for the field.



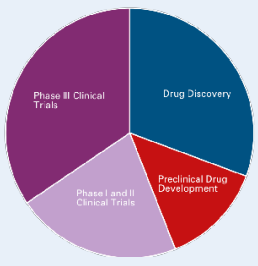
Funding for data analytics and storage tools is very low. Strikingly, funding for big data repositories and bioinformatics tools has not increased, despite the overall increased AD budget. In fact, the amount of funding dedicated to these resources has decreased—from $3.5 million in 2012 to $2.7 million in 2016. Because resource-building is necessary for large-scale data analytics, this represents a notable gap in funding.



A significant increase is observed in funding dedicated to epidemiology, which refers to the analysis of the incidence, distribution, and impact of diseases. Understanding the key factors that lead to AD, or confer a higher risk of AD, is an important step toward identifying a potential therapeutic target and/or developing strategies to enlist pre-symptomatic patients in clinical trials. Although funding has increased, this research area research remains in the early stages because of the previous lack of funding.



Clinical trial funding has shifted over the last 5 years. Currently, no treatments exist to prevent, slow the progression of, or reverse the disease. In 2016, late stage drug development (clinical phase III) received the most funding dollars. However, funding for phase II trials, which are crucial for testing early indications of drug effectiveness in smaller, controlled populations, has declined in percentage and has remained nearly stagnant in absolute dollars.



OVERVIEW OF CRITICAL BARRIERS IMPEDING AD

Using a systems-based approach, we identified and investigated various challenges that hinder progress in the AD research field. Emerging from this analysis, we determined five key barriers and promising solutions (see Figure 2):

1. Incomplete Understanding of Disease Biology

Understanding of the biological processes that cause and/or contribute to the onset or progression of AD is limited. This knowledge gap has contributed to the lack of diversity of therapeutic targets in the drug pipeline.

2. Lack of Biomarker Types and Tests

No biomarkers are available to accurately detect, diagnose, or track the progression of AD. Therefore, clinicians cannot appropriately segregate patients into the appropriate clinical trials or measure the effectiveness of a clinical intervention.

3. Limited Data Science Skills and Approaches

A lack of data sharing, inaccessibility to datasets, and a paucity of the skillsets needed to analyze large datasets hinder progress, either indirectly or directly at every stage of AD research.

4. Poor Understanding of Risk Factors

The field is in the early stages of identifying what drives the onset of AD beyond the currently known risk genes. To mitigate risk, a deeper understanding of the biological underpinnings of AD is necessary.

5. Suboptimal Clinical Trial Timing and Design

No therapeutic has been approved to slow, stop, or reverse the progress of AD. The focus on anti-amyloid therapeutics, the timing of clinical trials, and the current outcome measures have led to ineffective trials.

OVERVIEW OF CRITICAL AREAS IMPEDING AD

The following sections provide deeper context and background for each of the five barriers, and offer potential solutions and philanthropic opportunities to overcome these barriers.

Figure 3. Summary of Key Barriers and Related Solutions

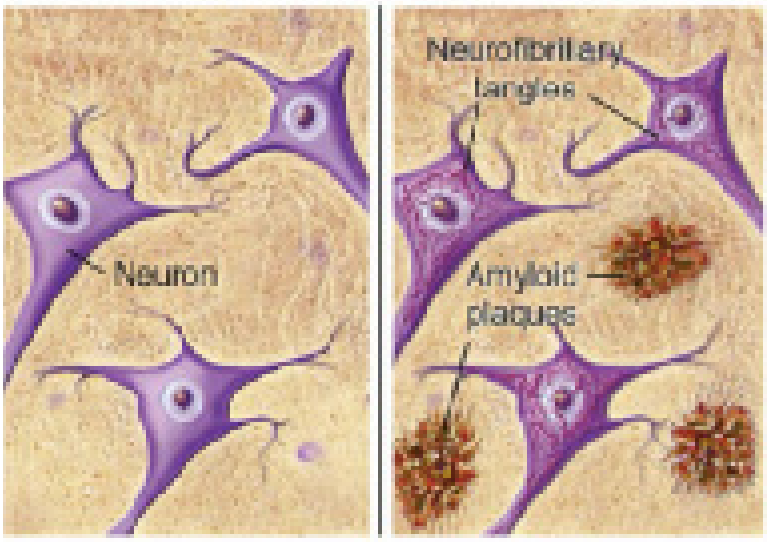
Barriers	Solutions		
Incomplete Understanding of Disease Biology	Multi-Disciplinary Teams	Prioritize Outstanding Questions	Next Generation of Scientists
Lack of Biomarker Types and Tests	Target Diversity	Early Detection	Alternate Modalities
Limited Data Science Skills and Approaches	Retention and Recruitment	Platform Synergy	Analytics and Tools
Poor Understanding of Risk Factors	Diversity and Inclusion	Longitudinal Studies	Risk Assessments
Suboptimal Clinical Trial Timing and Design	Preclinical Trials	Phase II Trials	Data Sharing

INCOMPLETE UNDERSTANDING OF DISEASE BIOLOGY

OVERVIEW OF BARRIER 1

The brain of an AD patient contains plaques comprised of different proteins located inside and outside the neuron. In earlier stages of the disease, these plaques consist of a single protein, beta-amyloid. As the disease progresses, another protein, known as tau, becomes tangled within neurons and generates plaques itself. In the presence of both types of plaques, neurons begin to die—a process known as neurodegeneration. Neuronal death ultimately drives cognitive decline and the malfunctioning of other important bodily processes, leading to deadly conditions such as organ failure.

Figure 4. Amyloid Hypothesis and AD



Note: The disease begins with an accumulation of amyloid outside of the neuron that forms plaques. Through an unclear mechanism, this triggers other abnormal processes, including the tangling of the protein tau inside the neuron. Ultimately, these neurons will die.

Source: BrightFocus.

From these observations, researchers hypothesized that amyloid accumulation initiates AD. Once the brain contains a critical amount of amyloid-based plaques, neuronal pathways within the brain begin to misfire leading to the accumulation and tangling of tau—and ultimately neurons die. This hypothesis, called the amyloid hypothesis (see Figure 4), drove the AD field for decades.

INCOMPLETE UNDERSTANDING OF DISEASE BIOLOGY

Historically, studies on amyloid or related concepts have received the majority of research funds, while industry has been hyper-focused on developing anti-amyloid therapeutics. Unfortunately, all anti-amyloid treatments have failed to prevent, slow, or cure AD in clinical trials.

Amplified by clinical trial failures, the amyloid hypothesis has come under intense criticism, requiring scientists to rethink their understanding of the disease and funders to reprioritize topic areas away from amyloid. This scrutiny has encouraged the entrance of new and exciting ideas into the field. For example, research on factors that contribute to the initiation or progression of AD have begun to yield interesting results, yet much remains unknown. These factors include, but are not limited to:

- Cerebrovascular system (the vascular system of the brain
- Misfolded proteins, in addition to amyloid and tau
- Immune response and inflammation
- Vulnerability and resilience (i.e., what makes some cells more or less susceptible to disease than others)

BIOLOGY REFRESHER

Proteins are large molecules within cells that perform a vast array of functions including metabolism, transport, and DNA replication. Proteins consist of molecules called amino acids that fit together based on their unique chemical makeup to form a fold. The folding of a protein determines its function. Misfolded proteins typically lose their functionality or gain spurious activity, which can be harmful to an organism.

PROBLEM: BASIC BIOLOGY OF AD IS STILL NOT FULLY UNDERSTOOD

A majority of scientists agree that the limited knowledge of the basic disease biology of AD has contributed to failures in the development of effective therapeutics. Given the daunting incidence and prevalence of this disease, there is an urgent need to fill these knowledge gaps by strategically prioritizing and addressing high-priority basic science questions about the factors driving AD. This type of focused and coordinated approach will accelerate progress and reveal potential avenues for therapeutic intervention.

To accomplish the goal of finding a successful therapeutic, we can learn from the field of cancer research, which also suffered from numerous clinical trial failures. To combat these failures, oncology researchers shifted their efforts away from the clinic and back to understanding the basic biology of cancer. These efforts paid off, and

the field subsequently has experienced incredible successes in developing life-saving treatments over the past decade.

Unfortunately, a decreased focus on basic science by various funding sources has left the research community with a resource gap (see Funding Landscape for more information). Potentially high-impact research projects are frequently underfunded due to perceived risk and the nascent stage of research.

SOLUTION: INVEST IN MULTIDISCIPLINARY BASIC SCIENCE TEAMS

It is clear that no single scientist or lab can answer the complex questions that remain within the AD field—a community approach is needed. Structured networks of scientists with varied expertise within and adjacent to the AD field are required to solve these substantial challenges and to provide the necessary data to bring forward new therapeutic targets. By defining the biology, identifying and understanding the contributing factors, and determining elements that protect against disease, a new range of potentially druggable targets could emerge. As the understanding of AD has moved beyond the amyloid hypothesis, it is imperative to fund topics outside of amyloid to learn more about factors that have been less studied but could lead to the identification of future targets for diagnostic, prognostic, or therapeutic development.

Corresponding Philanthropic Opportunities

Funding basic research to investigate the key contributors to AD development and progression beyond amyloid will require insight from diverse scientific disciplines. Key priority areas to consider are to:

- ***Decipher the link between misfolded proteins and neurodegeneration.*** The field does not understand, fundamentally, how a cell in an AD-affected brain is compromised by misfolded proteins. Addressing this basic question is essential to moving the field forward and priming the drug development pipeline with new targets.

- ***Understand selective vulnerability and resilience.*** The field does not understand why certain cell types are susceptible to disease while others are resilient. Experimental tools necessary to address this question require development, expertise, and coordination among different labs.

- ***Clarify the role of the immune system in AD.*** Although the specific role of the immune system is not yet deciphered, the genetics clearly point to its involvement. Funding a collaborative program among scientific labs will promote accelerated progress in discovering the role of the immune system, informed by the genetics and tested in model systems. A research roadmap with prioritized questions and defined roles for team members is necessary to complete the work.

SOLUTION: INVEST IN HUMAN CAPITAL

Incentivizing young researchers to join the AD field is challenging because of the perceived lack of progress stemming from clinical trial failures. Supporting young innovative investigators will advance the field by bringing in novel ideas and approaches.

Corresponding Philanthropic Opportunities

Bolster and expand current conferences and funding structures for young investigators studying AD. The Charleston Conference on Alzheimer's Disease is a philanthropically-sponsored event that gathers young investigators working on AD to develop and deliver research grants, with the assistance of established AD researchers who act as advisors. The meeting concludes with the funding of several of these research grants, which are chosen by the group. This program creates a community of young investigators supporting one another and allows them to develop and progress through their interaction with mentors in the field. This conference could be expanded to include more young investigators, more meetings, and more topic areas that are currently underexplored.

LACK OF BIOMARKER TYPES AND TESTS

OVERVIEW OF BARRIER 2

Biomarkers are measurable indicators of the state or condition of the human body and are used by researchers and clinicians to:

- Diagnose the presence or absence of disease
- Identify the risk of developing a disease
- Determine how a patient is responding to treatment

Additionally, researchers can use biomarkers to learn more about how a disease arises or progresses—providing invaluable information for the identification of new therapeutic targets.

Two biomarkers are currently used in clinical practice to diagnose and monitor. These two biomarkers indicate the presence of amyloid or tau proteins in the brain. While useful, sole dependence on these biomarkers is insufficient to move the field to where it should be to adequately diagnose AD and monitor treatment response. Some of the key challenges that the field is facing with respect to biomarkers and their corresponding solutions are outlined below.

BIOLOGY REFRESHER

Biomarker is short for biological marker. A biomarker is an objective, quantifiable characteristic of a biological process. A biomarker indicates the presence or absence of a disease or effectiveness of treatment. Biomarkers do not always correlate with a patient's experience or feelings of wellness. One commonly recognized example is cholesterol level serving as a biomarker for cardiovascular disease.

PROBLEM: LACK OF BIOMARKER DIVERSITY

As mentioned above, amyloid and tau are the only two validated biomarkers for AD—in large part because of the field's focus on the amyloid hypothesis. As the field continues to widen research paradigms to expand beyond that hypothesis, we are learning more about the biological underpinnings of AD. This new knowledge will ultimately help to uncover new biomarkers that could be more informative and effective in terms of specificity and sensitivity. Specifically, biomarkers with early diagnostic and prognostic capabilities would be impactful for the field.

LACK OF BIOMARKER TYPES AND TESTS

SOLUTION: CREATE AN ACCESSIBLE AND STANDARDIZED BIOMARKER TEST AND TOOL

The lack of diverse, reproducible, non-invasive biomarkers impedes research progress and clinical care. Therefore, the AD field should develop a diversified portfolio of accessible biomarkers (e.g., blood, urine, eye-monitoring), establish their test-retest reliability, and demonstrate their feasibility as clinical measures.

Providing accessible, standardized biomarkers may reduce the cost of clinical trials, thereby increasing the likelihood that all biomarkers can become a standard tool at all trial sites. Additionally, decreased costs open the door for identifying pre-symptomatic patients during normal wellness visits, paving the way for the potential use of health records as data points for longitudinal studies.

Corresponding Philanthropic Opportunities

Invest in standardized panels of biomarkers. Establishing a panel of fluid biomarkers as the gold standard for neuroscience studies could be an important step to generating comparable biomarker data across past, present, and future observational and therapeutic trials in AD. Funding initiatives aimed at supporting current efforts, such as the Neurotoolkit by Roche-Genentech or the Gates-ADDF sponsored Diagnostics Accelerator, could be considered.

PROBLEM: INVASIVE AND EXPENSIVE BIOMARKER TESTS

Amyloid and tau can be measured in two ways: brain imaging with positron emission topography (PET) or through cerebrospinal fluid (CSF), which is collected by a spinal tap. Both methods are expensive, because of the high costs of equipment, maintenance, and imaging agents, thereby inflating health care and clinical trial costs. Additionally, their invasive nature is difficult for patients to endure. The field should deepen exploration into other biomarkers that are less expensive and less invasive to collect as a solution to this problem.

LACK OF BIOMARKER TYPES AND TESTS

PROBLEM: OUTCOME MEASURES ARE NOT SENSITIVE ENOUGH TO DETECT EARLY STAGES OF DISEASE

Current measures of cognitive health cannot distinguish a healthy patient from a patient with pre-symptomatic AD who has brain plaques. Pre-symptomatic patients often display minor cognitive changes, but they are difficult to detect. If clinicians could detect these minor cognitive changes, they could more accurately identify pre-symptomatic patients, enroll them in clinical trials, and monitor treatment effects in significantly shorter time intervals. Currently, to determine treatment efficacy, clinicians must evaluate patients for large cognitive changes over long periods of time, which significantly drives up clinical trials costs. The implementation of new biomarker tests with more sensitive readouts would increase confidence that participants enrolled in clinical trials are in fact AD patients, and would reduce the average length and costs of clinical trials.

POWER SOLUTION: IMPROVE DIAGNOSTIC AND PROGNOSTIC CAPABILITIES FOR AD

The two current methods of detecting amyloid and tau are expensive, because of the high costs of equipment, maintenance, and imaging agents, thereby inflating health care and clinical trial costs. Additionally, their invasive nature is difficult for patients to endure. The field should deepen exploration into other biomarkers that are less expensive and less invasive to collect as a solution to this problem.

*This solution addresses multiple problems to create an **outsized impact.***

LACK OF BIOMARKER TYPES AND TESTS

Corresponding Philanthropic Opportunities

Sponsor a challenge prize for digital biomarker tools. Sponsoring multi-stakeholder prize competitions would incentivize the development of digital biomarkers. In such competitions, individuals or teams compete for a prize, which is typically monetary. These competitions are particularly impactful because they increase awareness of an issue and drive competitors to find a solution in a specific timeframe. The prizes not only create a sense of urgency, but also reduce the risk to the sponsors because they are contingent on success—the competitors must clearly demonstrate a solution to win the prize. In addition, this type of philanthropic investment can provide leverage to attract additional support in the form of capital and/or additional team members.

- ***Early detection of cognitive decline.*** Efforts to develop tests that can detect early signs of cognitive decline would have an outsized impact on identifying patients for early stage clinical trials and on assessing treatment efficacy, thereby transforming the clinical development process.

- ***Creation of physiological and/or behavioral monitoring applications.*** Noncognitive indicators (e.g., pacing, wandering, sleep, mood) of AD are not yet clearly defined. Monitoring applications would help to (1) define and validate these indicators and (2) provide quantitative standards for disease progression. The use of these tools would greatly impact the AD field and the neuroscience community at large.

EXAMPLE

Academia, industry, and a nonprofit organization collaborated to create the digital "Sea Hero Quest" game to assess participants' spatial navigation ability, which declines early in AD patients. To date, this game has been played by millions of users around the world and has provided information to develop a baseline of spatial reasoning. The next steps are to see if AD patients have a measurable defect in their spatial reasoning as compared to baseline.

Fund a multi-lab consortium focused on immunology biomarkers related to neurodegeneration. One of the most striking developments in recent years has been the findings that brain inflammation is associated with AD progression. Yet, no reliable biomarkers exist to measure immune function in the brain. These findings must be translated into clinically useful and functionally relevant biomarkers. A multidisciplinary collaborative program that incorporates relevant

expertise, such as immunology and pharmacology, is needed.

Fund the start-up costs of a biobank for Down's syndrome patients. A large proportion of Down's syndrome patients will develop plaque pathology and young-onset AD. Development of a biobank to house tissue and fluid samples could assist researchers studying these cohorts. These samples have the potential to provide key insights, because disease progression is more predictable in this patient population and biomarkers may be more apparent.

PROBLEM: UNCLEAR RELATIONSHIP BETWEEN AMYLOID AND TAU BIOMARKERS AND COGNITIVE DECLINE

To fully understand this relationship, long-term studies that track the same patients over time and repeatedly measure both changes in cognition and biomarker signals are needed (i.e., longitudinal studies). These studies can be very expensive to conduct and thus are limited in number. However, if biomarkers were measured at regular intervals, their linkage to cognitive decline may become more apparent. Funding the more frequent measurement of biomarkers during longitudinal studies should be explored.

SOLUTION: ENRICH ONGOING CLINICAL TRIALS

Widespread support is needed to expand biomarker testing in clinical research settings. To increase rigor and reproducibility in preclinical and clinical trials, broader access to imaging reagents, equipment, and infrastructure is paramount. Unfortunately, there is a dearth in funding for infrastructure support, because many funders (government, nonprofits, and private philanthropists) tend to fund hypothesis-driven research. This solution provides an opportunity to leverage and enrich ongoing preclinical and clinical studies by enabling the increased use of additional investigational biomarkers and/or for collection of biomarker data at more frequent intervals.

LACK OF BIOMARKER TYPES AND TESTS

Corresponding Philanthropic Opportunities

Provide enrichment funding to existing studies to support biomarker usage and/or development. Many academic studies examining patient cohorts lack funding to perform adequate testing across longitudinal assessments and/or during postmortem follow-up. For example, the National Institute on Aging's AD Research Centers require researchers to submit a uniform dataset. However, this dataset does not include imaging biomarkers because adequate funding is not available at all sites to perform these measurements.

Fund equipment grants for institutions that lack PET/MRI imaging infrastructure. PET and magnetic resonance imaging (MRI) tools are used to detect signs of AD in living patients and are the most validated biomarker tools available. Unfortunately, PET and MRI machines are incredibly expensive to purchase and maintain. The NIH and private funding agencies often provide little to no support for lab equipment, despite their necessity for conducting certain experiments. Thus, for institutions with limited resources, PET/MRI biomarker testing is impossible without funding through a philanthropic source.

PROBLEM: GENDER, RACIAL, AND DEMOGRAPHIC DIVERSITY IS NOT CAPTURED IN CURRENT BIOMARKER STUDIES

Patients involved in clinical and biomarker trials are not representative of the entire population, limiting the demographic, gender, and racial diversity of the trial participant pool. As there are differences in disease prevalence and risk based on gender and racial background, potential contributing factors may be overlooked since these patients are not adequately studied.

SOLUTION: INCORPORATE DIVERSITY INTO RISK FACTOR STUDIES

The majority of studies have an overrepresentation of educated, white male populations, with the largest genetic studies occurring in Europe, which limits our potential insights. Other populations, such as African Americans and Hispanics, are known to have a higher risk of AD than whites, and women have a higher risk than men. Inclusion of populations with a known increased risk of AD is an important step in determining the relationship between risk factors, biomarkers and disease mechanism.

Corresponding Philanthropic Opportunities

Support an awareness and recruitment campaign in underrepresented communities. Engaging diverse populations in biomarker studies is necessary. Diversity across multiple factors, including education, race, socioeconomic status, and gender should be achieved. Small campaigns with local community leaders to promote awareness, trust, and understanding are a necessary step to recruiting underrepresented populations for biomarker studies and clinical trials.

LIMITED DATA SCIENCE SKILLS AND APPROACHES

OVERVIEW OF BARRIER 3

The AD community is slowed by barriers related to data sharing, accessibility, and analytics. Within the biomedical field, data are rapidly accumulating from various sources—including research studies, patient records, and clinical trials. This large influx presents significant challenges in how to structure, integrate, and interpret the data. Ultimately, these challenges hinder the ability of scientists to share and analyze their data.

Expanded data science skills and approaches could alter the state of the field and could promote discoveries in disease biology, biomarkers, and, ultimately, therapeutic targets. The following emphasizes a few of the key data-related barriers within the AD community and the corresponding solutions.

PROBLEM: INCOMPATIBLE DATASETS FOR CROSS-PLATFORM AND REPOSITORY

Every data repository and platform associates specific terms (ontologies) with data entry. Because the characterization of AD components varies, datasets cannot be easily integrated across all platforms. The creation of technologies that facilitate data integration could reveal previously unrecognized trends.

PROBLEM: INSUFFICIENT ANALYTICAL AND VISUALIZATION TOOLS AVAILABLE TO MINE DATASETS

User-friendly tools to quickly visualize large datasets and software to analyze data are not as effective or as accessible as needed. Additionally, institutions without software licenses or the funds to purchase analytical tools are often unable to analyze available datasets without developing their own tools.

LIMITED DATA SCIENCE SKILLS AND APPROACHES

POWER SOLUTION: PROMOTE DEVELOPMENT OF DATA INFRASTRUCTURE

Funding infrastructure development to make datasets interoperable and accessible would facilitate data sharing and analysis. The numerous data repositories, platforms, and sites are disconnected and often inaccessible (examples of such platforms are discussed in the Big Data Platforms section on page 23). Data entry can be onerous or expensive, and each platform requires different information with a unique categorization system. There is a need for more user-friendly interfaces and for publicly available data visualization and analysis tools.

This solution addresses multiple problems to create an ***outsized impact.***

Corresponding Philanthropic Opportunities

Engage software developers to develop front-end user interfaces. Funding short-term contracts with software developers to improve the user interface for various AD data platforms and repositories would help with overall usage and accessibility. Rigorous end-user testing should be employed to ensure product usability. Relationships with software developers could be leveraged for future development of other relevant tools.

Partner with technology firms to identify best practices for data collection and curation. Companies such as Google and Facebook are constantly innovating methods to handle the large amounts of data they encounter daily. Developing a core task force to perform a comprehensive analysis of current systems and tools and identifying best practices would inform efforts to clean up current systems, while laying a sustainable foundation for the future.

LIMITED DATA SCIENCE SKILLS AND APPROACHES

Develop a global linkage ontology to make datasets interoperable. The classification system among the various data repositories is not consistent. The development of a translation tool to connect the disparate systems would allow for the merging of multiple datasets from various sources and would improve the statistical power and depth of each individual study. However, all stakeholders must be engaged in the process to ensure adoption. A meeting series for AD big data platform leaders to define this ontology system (whether it is to adopt a previously generated system or to develop a new system) and an implementation plan are needed. Software developers should be engaged at an appropriate time to create a seamless front-end interface that shields the user from back-end data handling.

PROBLEM: LIMITED INCENTIVES TO SHARE DATA

Sharing data can be a time-consuming and expensive task for individual research labs. Furthermore, academic researchers are often reluctant to share data, which could jeopardize their publication record and career trajectory. Likewise, industry fears the loss of intellectual property rights and the associated revenue that may result from sharing data.

SOLUTION: ESTABLISH INCENTIVE STRUCTURES FOR DATA SHARING

Incentives for academics to share data must be created to promote data sharing. These incentives should include both financial motivations and a competitive edge to overcome the barriers that prevent sharing by academics. However, these incentives should become a universal initiative, thus creating a culture of sharing.

Corresponding Philanthropic Opportunities

Form an alliance of private organizations to impose strict sharing requirements. Private research funders within the AD community could induce a cultural shift around data sharing by making it a condition of a grant award. Relevant funders could develop a

common data sharing policy, specifically addressing timing, sample deposition, and requirements for specific data types (e.g., genomic vs. lead optimization data).

PROBLEM: ABSENCE OF INDIVIDUALS WITH SKILLSETS NECESSARY TO NAVIGATE, ANALYZE, AND/OR CURATE BIG DATASETS

There is more data than ever before. However, the technical ability needed to fully mine and analyze these datasets is lacking. Training opportunities for neuroscientists in computational or data science are rare, and financial incentives for data scientists to enter neuroscience are scarce.

SOLUTION: INVEST IN HUMAN CAPITAL FOR DATA SCIENCE

Investment in human capital development and recruitment of data and computational scientists into the neuroscience field would transform AD research. The promising insights that could be gained from big data will remain elusive without the analytical skills necessary to make sense of the data. Data and computational scientists should be offered competitive compensation. Additionally, young neuroscientists should be afforded training opportunities in big data analytics to facilitate communication and collaboration with data scientists.

Corresponding Philanthropic Opportunities

Fund high-value fellowships for data or computational scientists entering into neuroscience. Data and computational scientists are paid at a premium in the technology industry. To attract these individuals into the neuroscience field, they should be offered a targeted high-value postdoctoral fellowship after graduate school. The fellowship would provide an industry-competitive salary and would allow the individual to be unencumbered with submitting grant proposals in an unfamiliar field.

LIMITED DATA SCIENCE SKILLS AND APPROACHES

Pilot a program to introduce a core team of data scientists to a network of AD neuroscientists. Projects for data scientists may be limited in duration, which may not be appealing for those seeking stability. A program that makes data services a core institutional functionality would ensure a more consistent work load and could increase project momentum and communication. This would also enable cost sharing across labs to provide market rate compensation.

Establish an internship program for students studying neurodegeneration to gain experience with technology firms or data science labs. Young neuroscientists do not have sufficient exposure to data science and programming within their graduate programs or their labs. Funding a short-term "sabbatical"-like experience at a technology company or a data science program would allow these neuroscientists to develop computational skills, while promoting future collaborations among these disciplines. Partnerships with technology firms would need to be developed and incentivized.

PROBLEM: DATA FROM FAILED CLINICAL TRIALS OFTEN NOT SHARED

After a failure, pharmaceutical companies are not incentivized to share data, often citing time and concerns over patient consent. Although the majority of patients are comfortable with sharing their data when informed, they are rarely asked. As such, patient data are highly protected and stored in a unique repository for each trial. When de-identified raw data are uploaded to open access databases, the process to gain access is not always effective or efficient.

SOLUTION: PUBLICIZE THE NEED FOR SHARING OF PATIENT DATA

Patient data should be available for researchers to learn from and to avoid repeating mistakes or experiments. However, companies and researchers are hesitant to share data—often citing patient protection as justification. Campaigns to urge data sharing could prompt these groups to rethink their sharing practices.

Corresponding Philanthropic Opportunities

Generate a public campaign for sharing of failed clinical trial results. Public outrage can incite change. Clinical researchers shared with us that several of their patients were angered to learn that their data was not shared openly after clinical trials. Public campaigns to highlight this issue would bring awareness and could motivate pharmaceutical companies to provide failed trial data. Additionally, efforts to address this issue, such as the Critical Path Initiative, could be expanded to cover a larger swath of industry companies sharing data from unsuccessful trials.

POOR UNDERSTANDING OF RISK FACTORS

OVERVIEW OF BARRIER 4

A risk factor is a variable that increases the likelihood of developing a disease. Some risk factors are modifiable (such as smoking) or treatable (such as high blood pressure), while others are inherent (such as genetics). Risk factors not only tell scientists and clinicians about potential means for intervention, but also can provide valuable insight into basic disease biology and progression.

The inability to separate AD patients from patients suffering from other types of dementia presents a major challenge to identifying specific risk factors for AD. As discussed previously, AD is difficult to diagnose because of the lack of biomarkers and additionally, because of symptom overlap with other neurodegenerative diseases.

BIOLOGY REFRESHER

Genes are a heritable unit passed from parents to offspring. Genes encode for molecules that define characteristics of offspring. A gene can be thought of as recipe for a cellular protein. They provide information about the unique shape and size of the resulting protein. Genes can be modified by other molecules to make more or less of their encoded protein.

There are several outstanding issues which, if addressed, could have an outsized impact on the understanding of risk factors for AD as well as disease biology and progression. Five key issues that remain unanswered and the associated opportunities are described below.

PROBLEM: DIFFERENCES IN RISK FACTORS ARE NOT DEFINED BETWEEN AD AND OTHER DEMENTIAS

The current risk profiles for AD are confounded by the lack of biomarker data from patients. This means that these patients may not have AD, but another form of dementia, which complicates the results. A diverse study pool with validated biomarkers of disease and clinical diagnoses are necessary to develop a robust dataset to distinguish the risk factors for AD in the global population, in exclusion of other dementias.

SOLUTION: BIOMARKERS ARE NOT INCORPORATED INTO RISK FACTOR STUDIES

One challenge to identifying risk factors for AD stems from the inability to accurately separate AD from other dementias. Previous risk factor studies relied upon participants self-reporting their AD diagnosis,

which may be inaccurate. Biomarkers, such as PET imaging of amyloid and tau plaques, would help to stratify dementia patients so that it is easier to distinguish AD patients from other dementia patients. In turn, a more accurate population would be available to effectively assess risk factors.

Corresponding Philanthropic Opportunities

Invest in observational studies with biomarker validation. To untangle AD from other dementias, biomarker screening and/or genetic testing prior to enrolling a patient in a risk factor study is necessary. Funding studies with this added step would inform understanding of which factors actually contribute to AD versus another type of dementia. Additionally, leveraging existing resources by retrospectively testing cohorts from previous studies is another option to better stratify patients in existing datasets.

PROBLEM: THE EFFECT OF COGNITIVE RESERVE ON THE RISK AND PROGRESSION OF AD IS NOT WELL UNDERSTOOD

Cognitive reserve can be thought of as the brain's ability to improvise and find alternative ways of achieving tasks. Researchers suspect that cognitive reserve may play a role in reducing the risk for AD, but this field is still very nascent and requires more investigation.

PROBLEM: THE RELATIONSHIP BETWEEN GENETIC AND EPIGENETIC RISK FACTORS IS LARGELY UNSTUDIED

Although researchers have focused on genetic risk factors for AD, the vast majority of AD cases are likely a consequence of non-genetic factors. Epigenetic markers are molecular modifications of genes that can influence how much a certain gene is expressed by a cell; however, little is known about how epigenetics modifies risk. These markers may be a missing link to understanding non-genetic risk.

POWER SOLUTION: INVEST IN BASIC BIOLOGY APPROACHES

The role of risk factors in disease pathology or progression remains largely not understood, yet these data could be vital in identifying

potential drug targets or in utilizing non-drug-based interventions. Investing in basic biology to understand risk is vital to understanding this avenue of science.

*This solution addresses multiple problems to create an **outsized impact.***

Corresponding Philanthropic Opportunities

Fund a collaborative study on cognitive reserve. Cognitive reserve is a unique phenomenon that allows for a significant delay of symptoms in patients who have amyloid plaques in their brain. The amyloid plague burden in these patients would typically be coupled with severe cognitive decline, but they have no noticeable symptoms. However, this period of asymptomatic plaque burden is followed by a subsequent rapid decline and death. Understanding cognitive reserve and its contributing factors would provide relevant insight into AD disease biology and potential mechanisms to delay symptom onset.

Develop a mouse model hub for genetic modifier screens. Genetic modifiers can alter the function of a gene, by acting as a suppressor (reducing expression or activity) or as an enhancer (increasing expression or activity). A mouse cohort using genetic engineering techniques could be developed to look at genetic modifiers in the various genetic mouse models of AD. This would enable researchers to ask about the influence of genetic modifiers on risk.

PROBLEM: BESIDES APOE2, LITTLE IS KNOWN ABOUT RISK FACTORS THAT ACCOUNT FOR RESILIENCE TO AD

Some people, despite being at high risk for AD, never develop the disease—they seem protected or resilient. One gene, APOE2, is known to be important for this protection, but only in part. Additional factors likely play a role and could be a key to finding ways to slow or prevent AD.

POOR UNDERSTANDING OF RISK FACTORS

SOLUTION: SUPPORT CURATION OF LONGITUDINAL DATASETS

Unmined datasets from a variety of previous longitudinal cohorts provide a trove of potential information about risk factors for disease initiation and for variable disease progression. These longitudinal cohorts are particularly informative because they provide information over the disease course, sometimes from pre-symptomatic through death (which means there is a confirmed diagnosis of patient).

Corresponding Philanthropic Opportunities

Fund a targeted project to mine large datasets for treatments that demonstrate a protective effect. A wealth of data exists about patients who have used various therapeutics to treat other chronic health conditions such as high-blood pressure, heart disease, and depression (e.g., a cholesterol-blockers, anti-coagulants). Mining this data for treatments with a potential protective effect could inform understanding of factors that contribute to both AD risk and resilience, while providing a possible therapeutic intervention.

Fund the development of a global ID system for AD brain banks. A comprehensive strategy is needed to more efficiently utilize brain tissue samples. Currently no standard method exists to track and link samples to the comprehensive clinical history of the donor. Researchers have raised the need for a universal identification tracking system that allows access to more comprehensive clinical patient data, so that they can conduct more robust and efficient research on this limited resource. With this approach, each donor would be assigned a unique identification code to use in all subsequent analysis. The subsequent collected data could be aggregated across completed studies, thus improving statistical power through more data points. Additionally, relationships between clinical history and future studies would become possible, because the retrospective clinical data attached to the brain identification code would be readily accessible.

POOR UNDERSTANDING OF RISK FACTORS

PROBLEM: ESTABLISH TO WHAT EXTENT DIFFERENT RISK FACTORS ACCOUNT OR COMPENSATE FOR AD

The disease stages and their links to specific risk factors are relatively unknown, including the relationship between amyloid plaque accumulation and cognitive decline. Because AD can occur alongside other health conditions, untangling these multiple effectors will be a key, yet challenging, endeavor.

SOLUTION: INVEST IN NEW TECHNOLOGIES TO MEASURE RISK

Currently, most measures of risk beyond genetics and gender are self-reported and qualitative, such as activity level. Technologies that can provide quantitative data on lifestyle factors, such as exercise, exposure to environment, and sleep, could be linked with measurements of disease progression to understand how these two factors are linked.

Corresponding Philanthropic Opportunities

Partner with an app company to develop a monitoring program to inform risk studies. Companies such as Fitbit, Facebook, and MyFitnessPal collect billions of data points on activity, diet, and social activity. Developing research methods that utilize their technology and link the collected data from the app with current metrics of disease progression would accelerate understanding of risk, as well as the effects of various lifestyle choices on AD risk.

SUBOPTIMAL CLINICAL TRIAL TIMING AND DESIGN

OVERVIEW OF BARRIER 5

There is not a single approved therapeutic to slow, stop, or reverse the progress of AD. Yet, pharmaceutical companies are pulling resources out of neurodegenerative disease programs because of failures in billion-dollar trials. The drivers behind these clinical trial failures are numerous and are examined below. Associated opportunities are also listed below.

REFRESHER

Clinical trials are research studies that determine the effectiveness of new medical approaches in humans. Each phase has a unique purpose.

Preclinical - Toxicity

Phase I - Safety and dosage

Phase II - Effectiveness and side effects

Phase III - Effectiveness and monitoring adverse reactions

PROBLEM: CURRENT MODEL SYSTEMS USED TO TEST DRUG CANDIDATES NOT PREDICTIVE OF AD

Clinical trials for AD are risky investments, and development of a full early pipeline of rigorously tested therapeutics is needed. A predictive model of disease to rapidly test therapeutics is a prerequisite for a strong pipeline of candidates. Unfortunately, the current models used in most labs are not predictive of disease and do not replicate the pathologies observed in humans. Efforts to develop and adopt more robust model systems would make early stage screening more effective and potentially more predictive of future therapeutic success.

SOLUTION: SUPPORT DEVELOPMENT OF PREDICTIVE MODELS OF DISEASE

Drug pipelines rely heavily on high throughput screening of candidate therapeutic compounds that were initially tested in various model systems (cell lines, animals, or organoids that mimic the human system). Although some models demonstrate certain aspects of AD pathology, such as plaques or tangles, no models are actually predictive of AD. The use of these models has led to inappropriate candidate selection for human trials; thus, a new approach to adequately screen drug candidates prior to clinical trials is needed.

SUBOPTIMAL CLINICAL TRIAL TIMING AND DESIGN

Corresponding Philanthropic Opportunities

Support an effort to develop and expand model systems that are predictive of diseases. Current animal models that are modified to accumulate amyloid or tau do not show cognitive symptoms like their human counterparts. Other model systems, such as human induced pluripotent stem cells (iPSCs) and 3-D organoids, currently exist within research settings, but are not utilized in candidate screening en masse. Their full utility has not been demonstrated because they are not completely characterized and broadly used. An emphasis on predictive models is essential to creating a new screening tool to perform assessments of efficacy and promise across various drug candidates. Such systems could be developed through partnerships with academia and industry and offered as a resource through partnerships such as the F-NIH's Accelerating Medicines Partnerships for AD (AMP-AD) or other repositories (see Current Initiatives, Partnerships, and Funds section on page 27 for more detail).

PROBLEM: LACK OF RIGOROUS VETTING OF THERAPEUTICS ENTERING PHASE III CLINICAL TRIALS

Therapeutics in current and past clinical trials moved from phase I to phase III, often skipping phase II, with little to no indication of efficacy. As a result, drugs with critical flaws, such as not crossing the blood-brain barrier or not binding the intended target, can advance through the pipeline. Often, nonprofits support preclinical to phase I trials, while large pharmaceutical companies support phase III trials. Support of phase II trials is a gap that needs to be filled to ensure that drugs that are not efficacious fail earlier in the process, thereby saving both time and money.

SOLUTION: STREAMLINE TRANSITION TO PHASE II CLINICAL TRIALS TO RIGOROUS TEST THERAPEUTICS

Each stage of a clinical trial tests specific aspects of a new therapeutic in a certain group of participants, all of which are critical to the process. Phase I trials primarily focus on determining the safety of a drug at various dosages and on monitoring participants for any adverse drug interactions. This phase occurs in healthy volunteers. Phase II trials determine the effective dosage and also monitor side effects of the therapeutic, which are tested in a small number of patients with disease. Because of the critical need for AD therapeutics combined with the lengthy time required to test therapeutics at each clinical trial phase in AD patients, companies are skipping phase II and moving directly to phase III. Drug failure in phase III is costly, because this phase involves a large patient population and price tag in the hundreds of millions. To combat this issue, targeted investment in phase II trials by all stakeholders is important, along with education and support for clinical investigators on how to efficiently move a drug from phase I to phase II.

Corresponding Philanthropic Opportunities

Support phase II clinical trials. As a critical component that provides data on the safety, dosage, and efficacy of a drug in a small population, phase II clinical trials are necessary to fail drugs earlier and cheaper. The success of a drug in a phase II trial can inform the optimal design of phase III trials. Partnering with nonprofits that already fund preclinical and phase I clinical trials to also fund phase II would provide the financial support and stability needed to incentivize the completion of a phase II trial. Additionally, support services—for example, to develop and submit the materials required by the Food and Drug Administration (FDA) to gain approval for a phase II clinical trial—could be a valuable addition to a grant program to help streamline the transition from one phase to the next.

SUBOPTIMAL CLINICAL TRIAL TIMING AND DESIGN

PROBLEM: UNABLE TO DEVELOP A "TRIAL-READY" COHORT

Clinical trial enrollment is challenging for many disease areas. However, it is especially difficult in AD research because the patient population is cognitively impaired. This impairment can exacerbate issues related to access to trials and participant compliance once enrolled. In addition, patients who are screened for a clinical trial but turned away because they do not meet all of the requirements are not always referred to another clinical trial that might be a better match. Collectively this is a lost opportunity for the field. Tracking of these pre-screened "trial ready" patients in a universal database could lead to faster and more efficient trial enrollment because the database would allow sites to easily identify and target patients that meet their specific enrollment criteria.

SOLUTION: DEVELOP AND IMPLEMENT A MASTER CLINICAL TRIAL PROTOCOL

A master clinical trial protocol allows multiple trials to be run under a single umbrella. The cancer field reported more success after the introduction of this trial format. The key advantages to a master trial versus a standard trial are multi-faceted. First, these trials allow for sharing of control patients among the various trial arms, which decreases the number of participants needed overall. Additionally, this protocol utilizes a master consent agreement, which allows patients to move to different trial arms depending on biomarker status and treatment response. This type of trial also allows for the simultaneous testing of multiple drug candidates all within the same trial protocol, thereby standardizing data collection (including biomarker samples) to produce more robust datasets. This trial feature gives rise to the commonly used descriptor of an "adaptive clinical trial." In addition, this type of trial is well suited to leverage "trial-ready" cohorts.

Corresponding Philanthropic Opportunities

Development of a master clinical trial protocol. Developing a master protocol for AD clinical trials would require pre-competitive collaboration among pharmaceutical companies, in addition to a willingness of these companies to work closely with academic researchers and patient groups. Initial steps could include convening a clinical trial group, such as the Alzheimer's Clinical Trial Consortium, to assess the field's desire to incorporate standardization and collaboration to develop a master clinical trial protocol. Innovating in this way could dramatically increase patient enrollment rates, improve trial efficiency, and reduce overall costs.

KEY STAKEHOLDERS IN ALZHEIMER'S RESEARCH

RESEARCH GRANT-MAKING ORGANIZATIONS

The following section provides information about nonprofit organizations that fund basic, translational, and clinical research of AD. Organizations that fund patient services, advocacy, or awareness are not included. Additionally, any organization that has not actively funded AD research after 2014 or has funded less than $2 million per year toward their philanthropic mission was excluded. Table 1 lists the organizations and their location, with information regarding their mission and organizational overview following.

Table 1. Funding Agencies and Country Affiliation

Funding Agency	Country
Alzheimer's Association	United States
Alzheimer's Drug Discovery Foundation	United States
Alzheimer Nederland	The Netherlands
Alzheimer's Research UK	United Kingdom
Alzheimer Society of Canada	Canada
Alzheimer's Society UK	United Kingdom
BrightFocus Foundation	United States
Cure Alzheimer's Fund	United States
Geoffrey Beene Foundation	United States
Foundation of the NIH	United States
UsAgainstAlzheimer's	United States

KEY STAKEHOLDERS IN ALZHEIMER'S RESEARCH

Alzheimer's Association

The Alzheimer's Association supports the dementia community through three major arms: care and support, research, and advocacy. It is the largest nonprofit funder of Alzheimer's research, awarding more than $410 million to scientific investigators since its inception in 1982. It supports a wide breadth of research topics from basic biology to prevention, as well as provides services to assist in matching healthy volunteers, patients, and caregivers with ongoing clinical trials through its TrialMatch® technology. Additionally, it promotes collaboration and knowledge sharing by hosting the annual Alzheimer's Association International Conference (AAIC) and through development of the Global Alzheimer's Association International Network (GAAIN) online database and analytics center.

Alzheimer's Drug Discovery Foundation (ADDF)

The ADDF exclusively focuses its funding on translating basic science discoveries into therapeutics for AD. To date, it has funded more than $100 million in research and clinical trials for drug discovery. In fact, the ADDF supports nearly 20 percent of drugs in clinical development. Currently, it concentrates on four core areas (drug discovery, clinical trials, biomarkers, and prevention) while taking an agnostic approach to therapeutic modality.

Alzheimer Nederland

Alzheimer Nederland is the major nonprofit for dementia in the Netherlands. It provides patient services, including basic information on the disease and support. Additionally, it funds research, working with academics, companies, and nonprofits. It enables research into causes, diagnosis, prevention, and treatment of dementia. Additionally, it has established Alzheimer's Centers for research, treatment, and counseling.

Alzheimer's Research UK

Alzheimer's Research UK (ARUK) is the leading dementia research nonprofit organization in the U.K. It works in four key areas: understanding of the disease, early and accurate diagnoses, reduced

risk, and effective treatments. ARUK's approach to research is to promote innovative research, translate these findings through big initiatives, and develop partnerships and collaborations with all sectors. In addition to funding, ARUK also works with policymakers and organizers to campaign for improved quality of life for patients with AD and their caregivers.

Alzheimer's Society of Canada

Alzheimer's Society of Canada (ASC) is the national nonprofit organization for AD and AD-related dementias (ADRDs) in Canada, providing support to all of the Societies for each province. ASC provides information, support, and education programs for people with dementia and for their families. It funds research to find a cure and to improve the care of people with dementia. Furthermore, it takes an active role in increasing public awareness of the social and personal implications of AD and ADRDs.

Alzheimer's Society UK

Alzheimer's Society UK (ASUK) is a leading nonprofit organization in the U.K. focused on dementia. ASUK developed a strategy with three key elements: support, society, and research. For support, it strives to support every individual who has been diagnosed with dementia in the U.K. For society, it has started a national movement to bring dementia into the mainstream and to ensure that people with dementia have equal rights. Finally, its research agenda is primarily focused on supporting U.K.'s dedicated Dementia Research Institute.

BrightFocus Foundation

The BrightFocus Foundation funds three areas of research: AD, macular degeneration, and glaucoma. Its research is focused primarily on basic science and preclinical work, funding innovative ideas to seed novel projects and avenues that may be otherwise unsupported. The Alzheimer's Disease Research program (ADR) has awarded nearly $110 million in grants since its inception in 1985.

Geoffrey Beene Foundation

The Geoffrey Beene Foundation was founded to support a variety of major causes, from cancer research to education. The Alzheimer's Initiative was developed in 2007 with the goal to enhance awareness programs and support next generation research in early diagnostics. It is particularly focused on the use of big data approaches and digital applications, with collaborations with inventors and researchers on real-world systems. It has donated $4.8 million toward fulfillment of its mission.

Foundation for the NIH (FNIH)

The Foundation for the National Institutes of Health (FNIH) manages alliances and funding between public and private institutions, while supporting the mission of the NIH. The FNIH is tasked with finding additional private-sector funding and resources to address significant health issues. The FNIH administers research programs, supports training and education, and develops health-related challenge prizes. Additionally, the FNIH supports the Biomarkers Consortium, which unites sectors to identify, develop, and qualify high-impact biomarkers.

UsAgainstAlzheimer's

UsAgainstAlzheimer's was founded to disrupt and diversify the movement to cure AD. It advances its mission by focusing on six key areas, primarily through policy and collaboration. Through its work, it has made efforts to improve brain health and early diagnosis and has worked to increase the diversity, speed, and efficiency of clinical trials. Additionally, it has helped to advance care goals and policies in support of individuals living with AD and their families. Through the entire program, it strives to include the patient and caregiver voice and to mobilize Americans to demand a cure and improvements to quality of life.

CURRENT INITIATIVES, PARTNERSHIPS, AND FUNDS

Alzheimer's Disease Neuroimaging Initiative (ADNI)

ADNI is longitudinal study with the aim of developing clinical, genetic, and biochemical biomarkers for early detection and tracking of AD. The three main goals are early detection and progression monitoring through biomarkers, support advances in AD intervention, prevention, and treatment through new diagnostic methods, and continue to provide all data to scientists across the world. The current study, ADNI-3, combines federal, industry, and foundation funding to study the use of tau PET and functional imaging techniques in clinical trials. Results of all trials are shared through the USC Laboratory of Neuro Imaging's Image and Data Archive (IDA).

Accelerating Medical Partnerships – Alzheimer's Disease (AMP-AD)

The AMP-AD program is a precompetitive partnership between the U.S. government, 12 biopharmaceutical companies, and several nonprofit organizations. The primary focus is the development of biomarkers to confirm existing therapeutic targets and to discover and validate novel targets. AMP-AD has received more than $225 million in funding (including $40 million in kind contributions). One major component is that all AMP-AD data will be publicly available for all researchers.

Critical Path for Alzheimer's Disease (CPAD)

CPAD is a public-private partnership developed to facilitate the creation of new tools and methodologies to accelerate the development of AD treatments. Its areas of focus include (1) qualification of biomarkers, (2) development of common data standards, (3) creation of an integrated database for clinical trials, and (4) development of quantitative tools for drug development.

Dementia Discovery Fund

The Dementia Discovery Fund is a specialist venture capital fund focused on seeding basic science to create novel therapeutics, while providing an attractive return on investment. It has raised more than £350 million for the development of therapies for all types of dementia. Its investment ranges from £0.1 million in hypothesis-specific projects to £10 million in companies—currently, it supports nine individual companies.

Cure Alzheimer's Fund

The Cure Alzheimer's Fund (CureAlz) is a venture philanthropy fund designed to accelerate research by focusing exclusively on finding a cure. CureAlz operates through a consortium model, supporting an invited group of established investigators in advancing innovative projects. The Board of Directors supports all administrative costs, allocating 100 percent of funds to research. To date, CureAlz has contributed $67.3 million to research since its founding in 2004. The foundational work of CureAlz is focused on identifying all the genes and gene mutations linked to AD, determining function, and designing therapeutics targeted to these projects. It provides grants in nine major areas of study, including the Alzheimer's Genome Project and the Genes to Therapies program.

BIG DATA PLATFORMS

BRAIN Commons

The Brain Research and Innovation Network (BRAIN Commons) will be an open, cloud-based resource for collaborative data storage and sharing in brain disease research. Additionally, this resource is designed to support analysis of multiple data modalities across neurological disorders. The platform is being developed through a partnership with Cohen Veterans Bioscience, the Open Commons Consortium, and the University of Chicago Center for Data Intensive Science.

Critical Path Institute Online Data Repository (CODR)

CODR developed a database of patient-level placebo arm data from 6,500 patients from clinical trials for AD and MCI. The data was remapped to a common data standard to allow for interoperability and cross-study analysis. It is openly available to researchers within the CPAD network. The database includes demographic information, APOE4 genotype, medications, and cognitive scales, but does not include biomarker data, test drug candidate information, or background therapies.

Dementias Platform UK (DPUK)

DPUK is a public-private partnership funded by the U.K.'s Medical Council to facilitate and accelerate the discovery of understanding, diagnosing, and treating dementia. The platform is a single, secure data repository that provides access to the health records of more than 2 million individuals. DPUK has engaged in partnerships and collaborative initiatives with U.K.-based universities to enable discovery and development from this large dataset. Currently, DPUK supports three technology networks: informatics, imaging, and stem cell. Additionally, it uses its platform to enable better recruitment of patients to dementia trials, through the Clinical Studies Register.

Global Alzheimer's Association International Network (GAAIN)

GAAIN is an online platform developed through a partnership with the Laboratory of Neuro Imagine (LONI) and the Alzheimer's Association. The goal of GAAIN is to provide a gateway for scientists to access dementia research data, while providing support through analytical tools and computational resources. This resource aims to provide the network and infrastructure necessary to allow for the various datasets and repositories to become interoperable, thereby accelerating research progress.

Global Alzheimer's Platform Foundation (GAP)

GAP was launched in 2015 through a partnership with UsAgainstAlzheimer's and the Global CEO Initiative on AD (CEOi). The goal is to create an integrated resource that links ongoing and recruiting clinical trials to reduce the time, cost, and risk of AD clinical trials. Additionally, GAP has a network of 60 leading academic and private research centers to serve as a platform to improve the speed of clinical trial recruitment and initiation.

Image and Data Archive (IDA)

IDA is a secure online repository and resource designed for sharing, visualizing, and exploring neuroscience data and is built from the LONI platform from the University of Southern California. IDA provides tools to aide in de-identification, integration, searching, visualizing, and sharing neuroscience data for individual labs. Currently, it houses over 117 studies and data on more than 41,500 subjects.

National Alzheimer's Coordinating Center (NACC)

The NACC is a program established by the National Institute on Aging that houses data collected from the Alzheimer's disease Research Centers (ADRCs) across the U.S. The NACC houses both clinical and neuropathological research data that has been standardized through a uniform dataset to allow for direct comparisons. This resource is free and openly available for the entire research community, and is one of the largest and most comprehensive datasets of its type in the world.

National Institute on Aging Genetics of Alzheimer's Disease Data Storage (NIAGADS)

NIAGADS is a national repository for genetics data that was developed by the National Institute on Aging to support access and analysis of genomic data from late-onset AD research. It currently houses 37 unique datasets with more than 37,890 samples. In addition, the platform provides free software, databases, and other tools to assist with data analysis and visualization.

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