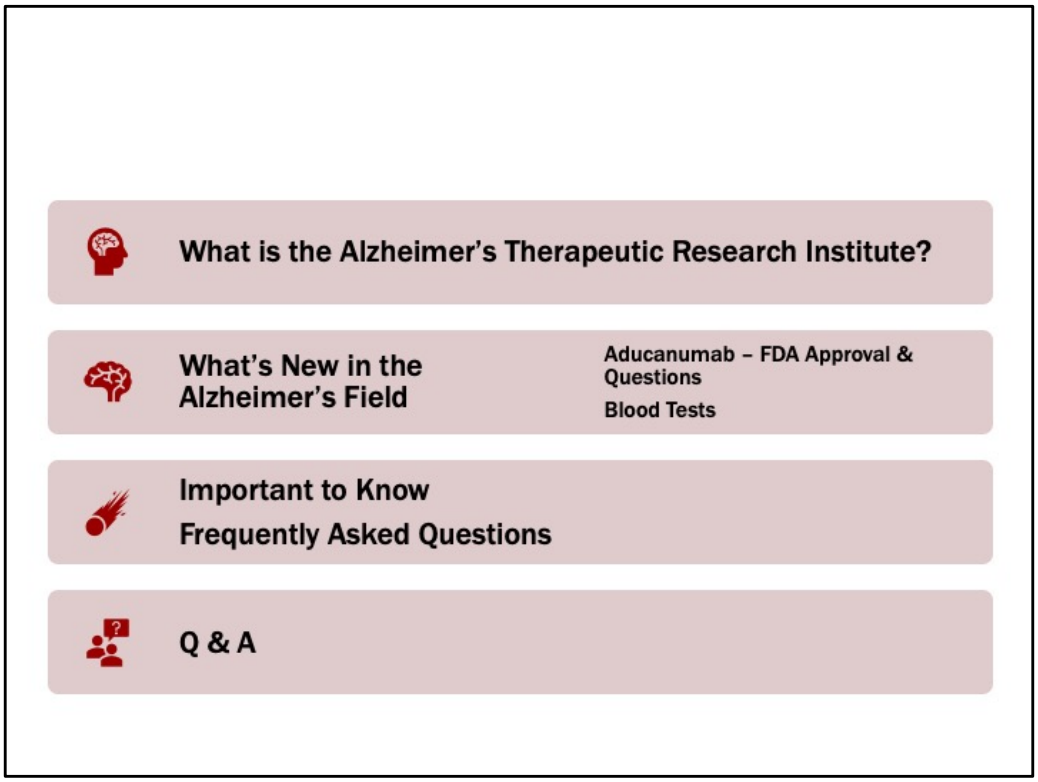
Dr. Mindy Lipson Aisen, MD has been a member of the USC Keck Department of Neurology since 2009. She currently supports the Alzheimer's Therapeutic Research Institute with Medical Safety.


What is the Alzheimer's Therapeutic Research Institute?
What's New in the Alzheimer's Field
Aducanumab – FDA Approval & Questions
Blood Tests
Important to Know
Frequently Asked Questions
Q & A

The Alzheimer's Therapeutic Research Institute is an academic research center for the most innovative design and coordination of Alzheimer's clinical trials. ATRI researchers are internationally recognized experts in the field. Since it's opening in 2015, ATRI has consistently accounted for 20% of all of Keck's NIA contracts and grants.

The mission of the ATRI is to rigorously test methods for early detection of and treatments for Alzheimer's disease (AD).

Led by Paul Aisen, MD, ATRI is comprised by a growing set of teams of highly skilled researchers with expertise in biostatistics, psychology, informatics, bench science, molecular neuroimaging, neuroscience and more.

ATRI is an integral part of the San Diego and USC communities, yet oversees and manages clinical trials and studies at major academic medical centers throughout the US and internationally.
As an academic institute, ATRI not only focuses on research; it offers educational programs for learners at multiple levels.

ATRI plays a leading role in the Alzheimer's Therapeutic Clinical Trials Consortium (ACTC) dedicated to the acceleration of therapeutic interventions for AD.

ATRI teams have designed and provided leadership to the Alzheimer's Disease Neuroimaging Initiative, (ADNI) which is considered to be the NIH/NIA's leading model for public domain research to facilitate the scientific evaluation of neuroimaging and other biomarkers for the onset and progression of MCI and Alzheimer's disease.

ATRI

- USC Institute in San Diego
- 7 faculty, 160 staff
- Mission: accelerate the development of effective treatments for AD

Infrastructure for therapeutic trials (ACTC, TRC-PAD)

Improve methods: trial designs, data analysis, biomarker use ..

Observational studies to inform the field (ADNI, LEADS)

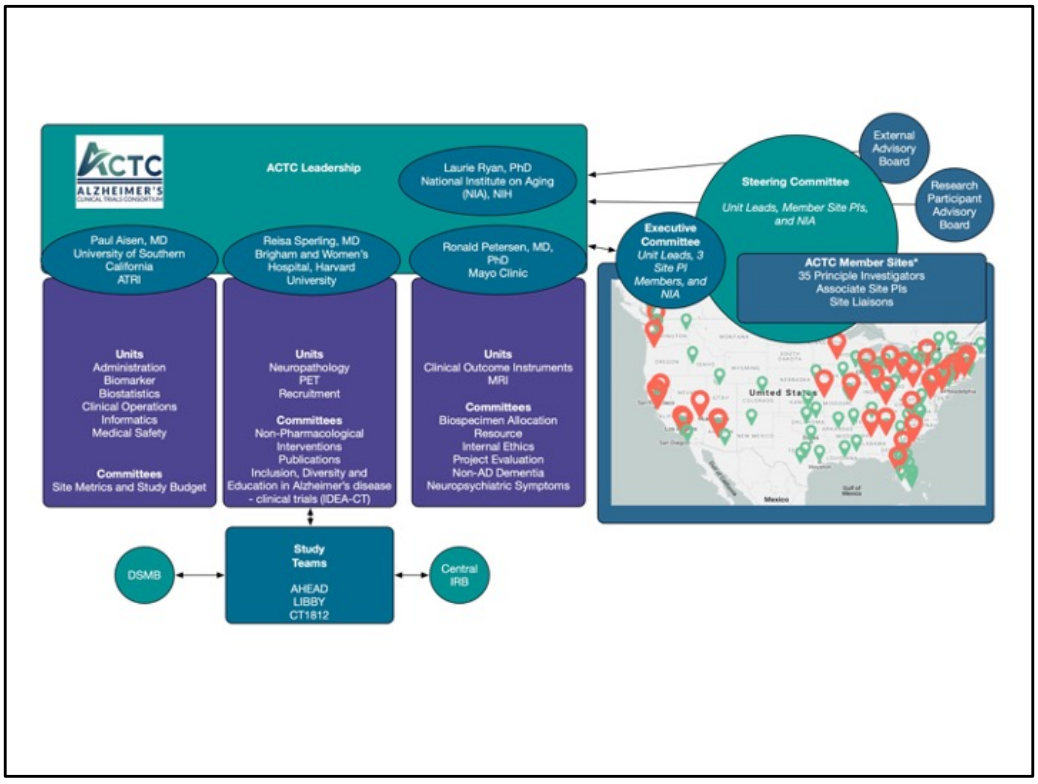
Conduct trials: academic, industry, public-private partnerships (eg, A4, AHEAD 3-45)

Down Syndrome: ACTC-DS, TRC-DS

Diversity and inclusion (faculty, staff, study participants)

Share methods and data

Education and training (IMPACT-AD



One of USC ATRI's Leadership Roles in the Field:

Alzheimer's Clinical Trials Consortium
To provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer's disease and related disorders.

NIA Press Release: https://www.nia.nih.gov/news/new-nih-consortium-award-enhance-clinical-trials-alzheimers-disease-related-dementias

In 2017 a new clinical trials consortium funded by the National Institutes of Health was established to accelerate and expand studies for therapies in Alzheimer's disease and related dementias.

The infrastructure of 35 sites across the United States – called the Alzheimer's Clinical Trial Consortium (ACTC) – will address the timeframe, complexity and expense of the recruitment process and site activation for Alzheimer's trials to find new and effective ways to treat or prevent these devastating disorders.

The ACTC will be led jointly by research teams from the University of Southern California Alzheimer's Therapeutic Research Institute (ATRI), San Diego, Harvard-affiliated Brigham and Women's Hospital and Massachusetts General Hospital,

Boston, and Mayo Clinic, Rochester, Minnesota. The funds were awarded by the National Institute on Aging (NIA) at NIH, which leads the federal effort in Alzheimer's research. NIA will also provide scientific input to the ACTC under the cooperative agreement.

The award for support of the consortium is expected to total nearly $70 million over five years, pending the availability of funds. Specific trials would be funded separately, under a process by which investigators can team up with the consortium to undertake research. Funding opportunity announcements for specific ACTC trials are expected to be released in early 2018 and will be open to all qualified investigators. It is anticipated that the ACTC will have the capacity to handle five to seven trials during the five-year award period.

Developing effective treatments for Alzheimer's and related dementias has proven extremely challenging. However, with recent advances in basic science and the identification of potential therapeutic targets, the number and types of possible therapies for testing have grown and are expected to increase significantly. Now, scientists are seeking to intervene as early as possible in disease development, before memory loss and other clinical signs of decline appear. Such early intervention and prevention studies require screening of thousands of volunteers to identify eligible participants, which can be time consuming and can result in delayed recruitment and under-enrollment. Other challenges facing Alzheimer's clinical trials include: development of more sensitive cognitive assessment and neuroimaging analyses, data management and bioethics considerations.

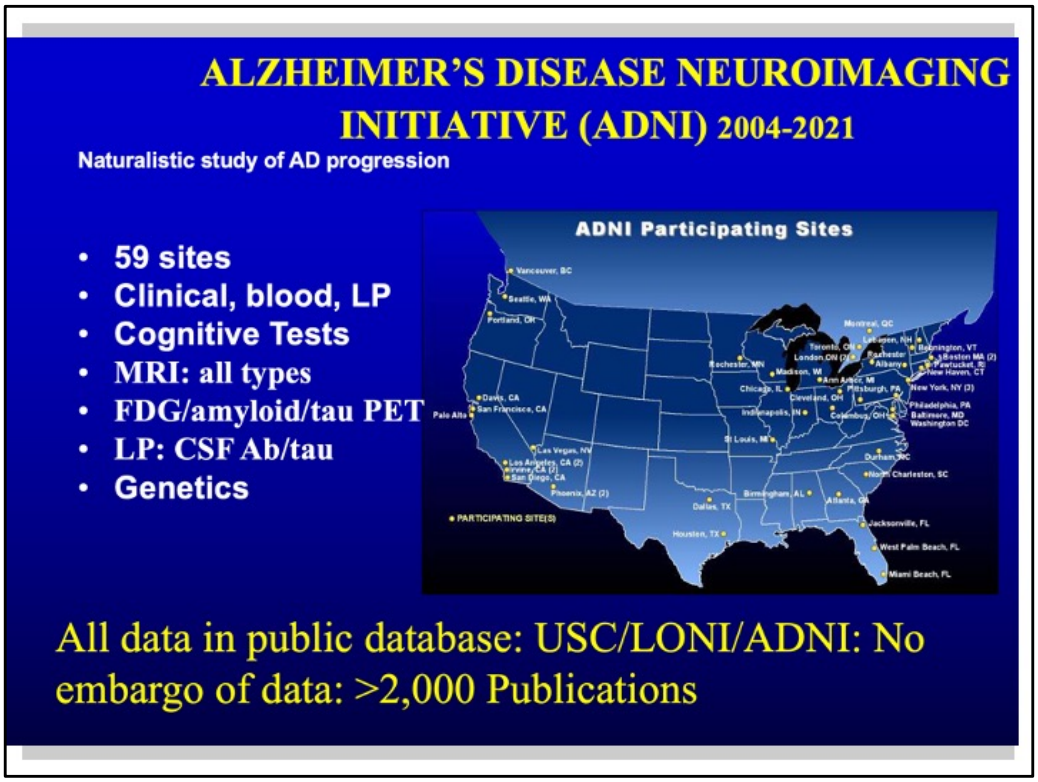
The ACTC experts and infrastructure will support the design and conduct of trials across the full spectrum of Alzheimer's and related dementias, from prevention initiatives to combination trials for advanced symptomatic stages. Specific objectives of the consortium include:

Creating infrastructure with expert leadership to streamline implementation of trials
Developing innovative trial design methods, outcomes and analysis strategies
Maintaining trial site quality standards during and between trials
Developing and implementing cutting-edge participant recruitment and retention strategies, especially in diverse populations
Using a centralized Institutional Review Board
Developing and running capture systems for data pertinent to the ACTC
Securing centralized tissue banking for specimens
Providing centralized imaging, biostatistics, bioinformatics and data management and analysis support
Facilitating and managing public-private partnerships

Trials would be conducted harnessing guidance from ACTC leaders, an executive committee and an external advisory board, which will include a patient advocate. The Principal Investigators for the project are:
Paul Stephen Aisen, M.D., director of the ATRI at the Keck School of Medicine of USC, San Diego
Reisa A. Sperling, M.D., director of the Center for Alzheimer Research and Treatment at the Brigham and Women's Hospital, professor of Neurology, Harvard Medical School, Boston
Ronald C. Petersen, M.D., Ph.D., director of the Mayo Clinic Alzheimer's Disease Research Center, professor of Neurology at Mayo Clinic College of Medicine and Science, Rochester, Minnesota
The ACTC consists of a coordinating center at ATRI and 10 units staffed with teams to manage areas such as biomarkers, biostatistics, clinical operations, informatics, magnetic resonance imaging, positron emission tomography, and recruitment. As part of its recruitment unit, the ACTC is establishing a new Minority Outreach and Recruitment Team, which will use innovations in recruitment to support both central and local partnerships with diverse communities.

"When we announced the funding opportunity for a new publicly-supported clinical trials network, we envisioned a next-generation consortium, where shared expertise could enhance the ideas and approaches of individual investigators proposing and conducting trials," said Laurie Ryan, Ph.D., chief of the Dementias of Aging Branch in NIA's Division of Neuroscience, which leads NIH research on Alzheimer's. "I think we will have that now. I am particularly interested in how we can better engage diverse communities into research, so that trials can more effectively include and benefit everyone who is affected by Alzheimer's."
The consortium consists of 35 sites in 24 states and the District of Columbia. More sites may be added.

It is estimated that as many as 5.3 million people in the United States age 65 and older already show symptoms of Alzheimer's disease. Without effective intervention, those numbers are projected to rise to between 11 to 16 million by 2050.
Grant number: U24AG057437



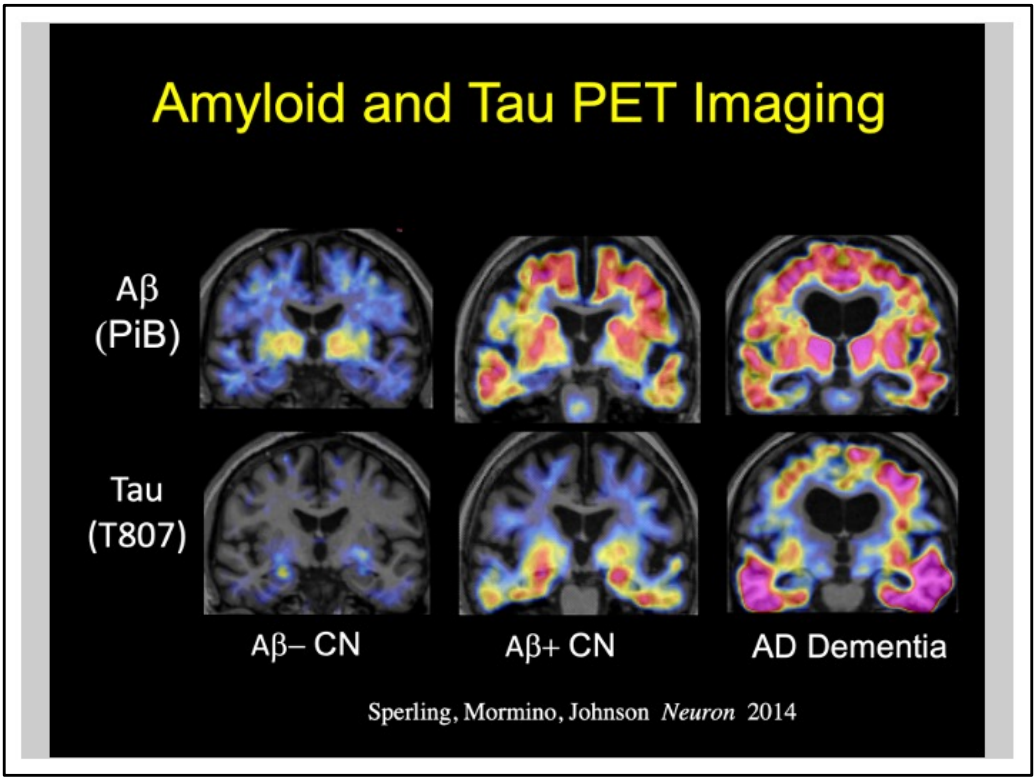
The [Alzheimer's Disease Neuroimaging Initiative (ADNI)], a landmark partnership and study that for years has profoundly influenced our understanding of Alzheimer's disease (AD), is identifying the earliest changes in brain structure and function that signal its onset and progression of AD. The study has been led by the National Institute on Aging (NIA) with support from the FNIH and more than 30 private-sector organizations since its launch in 2004. ADNI has gone through several peer-reviewed renewals since ADNI1, in 2014, with ADNI-GO and ADNI2. ADNI3 partnership and study was launched in 2016 and is expected to continue through 2022.

ADNI Contributions to the field

* Longitudinal Clinical/neuropsychological test data
* Enables clinical trial design/powering of trials
* Amyloid phenotyping: CSF AB, amyloid PET
* Tau phenotyping: CSF tau, tau PET
* Neurodegeneration phenotyping: structural, perfusion, diffusion, functional MRI
* Improved methodology: multisite harmonization
* Genetics; imaging/genetics, polygenic risk
* Pathology
* Plasma analytes

NIA content:

https://www.nia.nih.gov/research/dn/alzheimers-disease-neuroimaging-initiative-adni

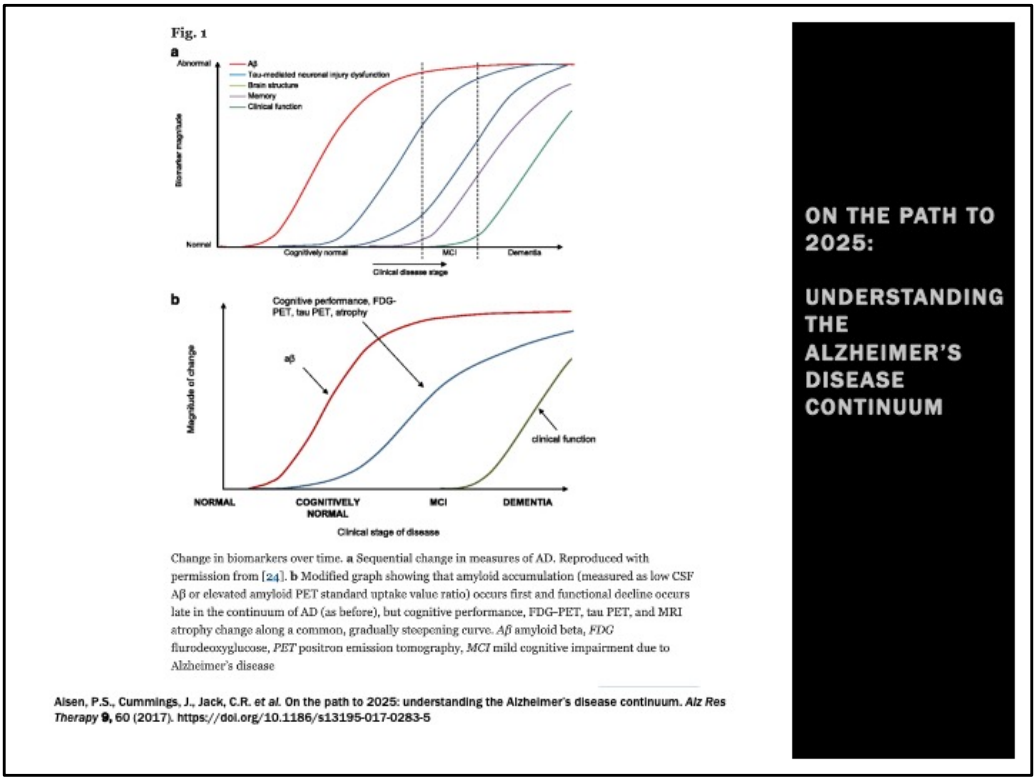


https://pubmed.ncbi.nlm.nih.gov/25442939/

Review Neuron. 2014 Nov 5;84(3):608-22.
doi: 10.1016/j.neuron.2014.10.038. Epub 2014 Nov 5.
The evolution of preclinical Alzheimer's disease: implications for prevention trials
Reisa Sperling [1], Elizabeth Mormino [2], Keith Johnson [3]
Affiliations
PMID: **25442939**
PMCID: PMC4285623
DOI: 10.1016/j.neuron.2014.10.038
Free PMC article
Abstract -

As the field begins to test the concept of a "preclinical" stage of neurodegenerative disease, when the pathophysiological process has begun in the brain, but clinical symptoms are not yet manifest, a number of intriguing questions have already arisen. In particular, in preclinical Alzheimer's disease (AD), the temporal relationship of amyloid markers to markers of neurodegeneration and their relative utility in the prediction of cognitive decline among clinically normal older individuals remains to be fully elucidated. Secondary prevention trials in AD have already begun in both genetic at-risk and amyloid at-risk cohorts, with several more trials in the planning stages, and should provide critical answers about whether intervention at this very

early stage of disease can truly bend the curve of clinical progression. This review will highlight recent progress in cognitive, imaging, and biomarker outcomes in the field of preclinical AD, and the remaining gaps in knowledge.



Basic research advances in recent years have furthered our understanding of the natural history of Alzheimer's disease (AD).

It is now recognized that pathophysiological changes (build up of amyloid and tau in the brain) begin many years prior to clinical manifestations of disease and the spectrum of AD spans from clinically asymptomatic to severely impaired.

Defining AD purely by its clinical presentation is thus artificial and efforts have been made to recognize the disease based on both clinical and biomarker findings.

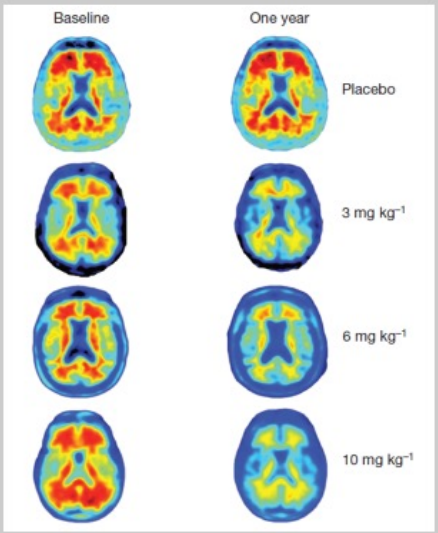
Advances with biomarkers have also prompted a shift in how the disease is considered as a clinico-pathophysiological entity, with an increasing appreciation that AD should not only be viewed with discrete and defined clinical stages, but as a multifaceted process moving along a seamless continuum.

Acknowledging this concept is critical to understanding the development process for disease-modifying therapies, and for initiating effective diagnostic and disease management options. In this article, we discuss the concept of a disease continuum from pathophysiological, biomarker, and clinical perspectives, and highlight the importance of considering AD as a continuum rather than discrete stages.

While the pathophysiology of AD has still not been elucidated completely, there is

ample evidence to support researchers and clinicians embracing the view of a disease continuum in their study, diagnosis, and management of the disease.

ADUCANUMAB AMYLOID REDUCTION (PHASE 1B)



Among the first trials to enroll "early AD" patients: MCI or mild dementia with positive amyloid PET scan

N=165, 5 arms (4 doses plus placebo)

Primary aim: safety and tolerability

Highest dose arm (30mg/kg) dropped because of ARIA risk

Accelerated approval

- Basis of amyloid plaque removal
- Additional trial required to confirm clinical benefit given inconsistent clinical findings across two Phase 3 trials (plus Phase 1b)

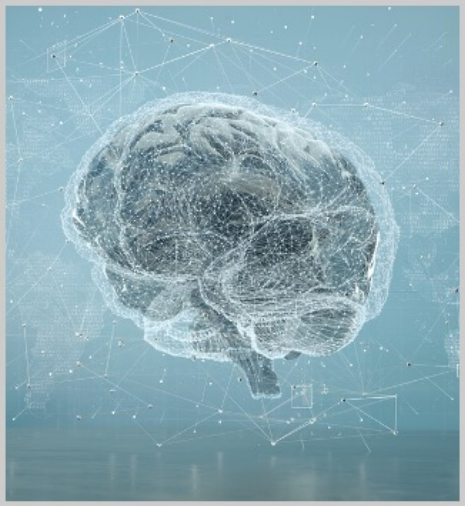
Indication is broad – "For the treatment of Alzheimer's disease"

- Clinical trials conducted in symptomatic patients (MCI and mild AD dementia) who had evidence of amyloid pathology on screening PET

Unclear what eligibility will be required by insurance

FDA ADVISORY MEETING

- FDA clinical summary strongly supportive of approval
- FDA statistical summary highly skeptical
- Advisory committee voted against approval



Accelerated approval

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- Unclear what eligibility will be required by insurance

Some Questions:

Should clinicians prescribe aducanumab?

For whom should aducanumab be recommended?

FDA is vague; should be restricted to biomarker-confirmed early AD

Will Medicare and private insurers pay for aducanumab?

I suspect the answer is yes, but restricting use based on population studied (early AD)

Many Alzheimer's Experts Say Use of Aduhelm Should Be Sharply Limited

Even those who supported the F.D.A.'s approval of the controversial new drug said authorizing it for anyone with Alzheimer's disease was much too broad.

"It will be important to have comprehensive discussions with patients and families about 'how to weigh the inconvenience and cost and risk against the possible benefit,' Dr. Aisen said."

By Pam Belluck
Published June 21, 2021Updated June 22

Dr. Aisen clarifies that he did not suggest FDA approval, rather is pleased that they addressed the amyloid hypothesis.

Detect Alzheimer's disease with a simple blood test before symptoms appear

We want to find a safe and affordable test to diagnose AD even in those without symptoms, ultimately allowing us to treat AD earlier, before memory loss occurs.

Kernls Project:

Through a program we've created to build a trial-ready cohort, we have recruited 40,000 people interested in getting involved in clinical trials aimed at discovering treatments that will reduce the risk of AD. These people, all age 50 and older, have been screened and are members of the general population.

We want to invite 2,000 of these people for blood sample analysis every other year for the next 6 years. Our goal is to work with these people to find a blood test that accurately and reliably detects AD before any symptoms of memory loss occurs.

If found, this test will make it easier for people at risk to get involved in AD research and, ultimately, help us find a treatment or cure for AD faster.
This project is focused on raising funds for the first round of blood tests.

If you are 50 years of age or older, now is the time to join the Alzheimer Prevention TrialsWebstudy (APT Webstudy) and help fight the fight against Alzheimer's. The APT Webstudy, which is being conducted through the USC Alzheimer's Therapeutic Research Institute (USC ATRI),isan online memory and thinking research studyaiming to accelerateenrollment into Alzheimer's clinical trials.

What should you expect?
Participants will have their memory assessed every 3 months and will be tracked over time, all online. If it is found that you are at increased risk for developing Alzheimer's, you may beinvited for an in-person evaluation thatmay include additional memory tests, brain scans and blood tests. If eligible, you willthen be provided the opportunity to enroll in a clinical trial aimed at preventing the cognitive decline associated with Alzheimer's. Who can participate?

Anyone age 50 and older is invited to join the APT Webstudy –it's simpleand free, and there are no other eligibility criteria. And because it's done all online, you can do this from anywhere at any time!All you need is an Internet-connected device and have an interest in participating in Alzheimer's research studies.

Why should I join?Access to secure, personalized, web-based tools to assess and track your memory and thinkingperformanceYou may have the opportunity to

participate in FREE comprehensive memory evaluations at one of our nationwide clinical sites You could be matched with the opportunity to participate in Alzheimer’s prevention clinical trials
It’s easy and free

You could help prevent and put an end to Alzheimer’s disease

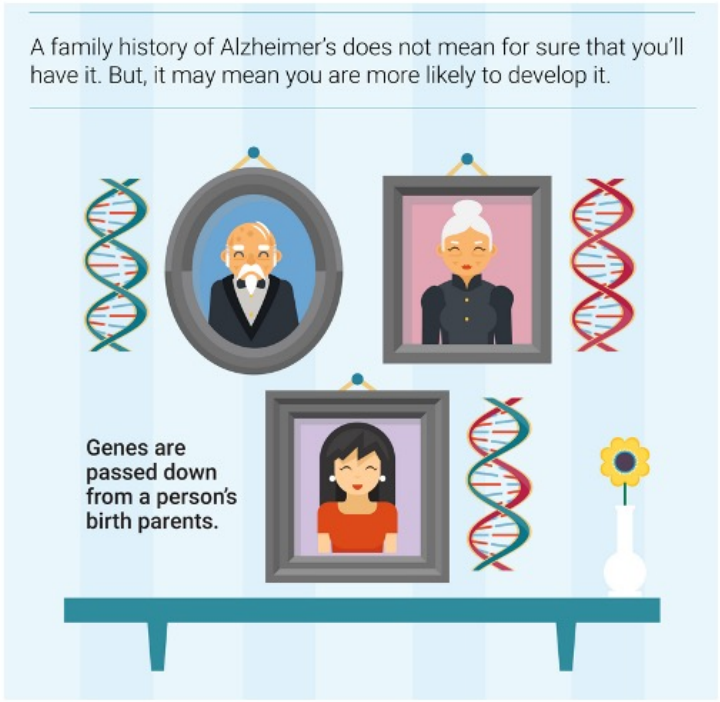
Participants will receive the latest Alzheimer's news and research findings
We need your help!

Did you know the majority of research studies are delayed because they can't recruit enough people at the start? We hope you will consider joining the APT Webstudy!

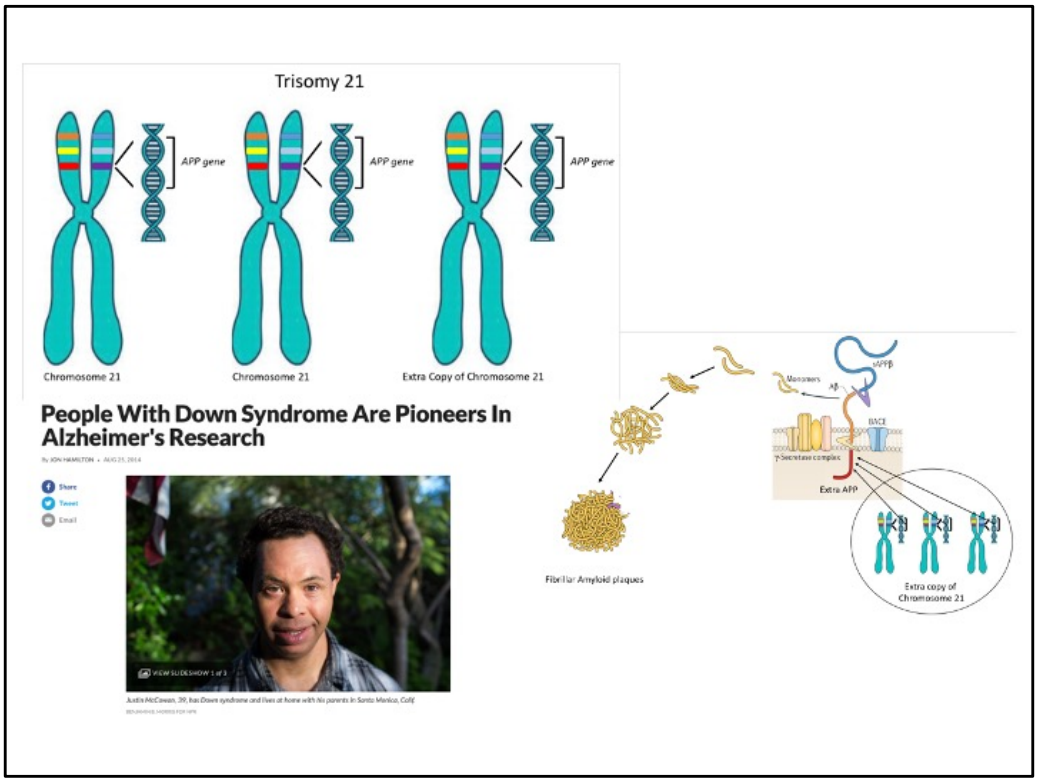
https://www.nia.nih.gov/health/infographics/national-institute-aging-transforming-aging-through-research

Dr. Aisen notes that Mediterranean diet does not prevent Alzheimer's disease yet healthy eating can keep you healthy and active for longer… it can prevent compounding effects of aging.

https://www.nia.nih.gov/health/healthy-eating



https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet



People with Down syndrome are living healthier, longer and more independent lives than ever before. With this increased lifespan, we are finding that there is an increased risk for developing Alzheimer's disease. There is an urgent need to find therapies that treat or prevent AD in people with Down syndrome. ACTC-DS aims to bring the latest and most innovative AD therapies to the DS population.

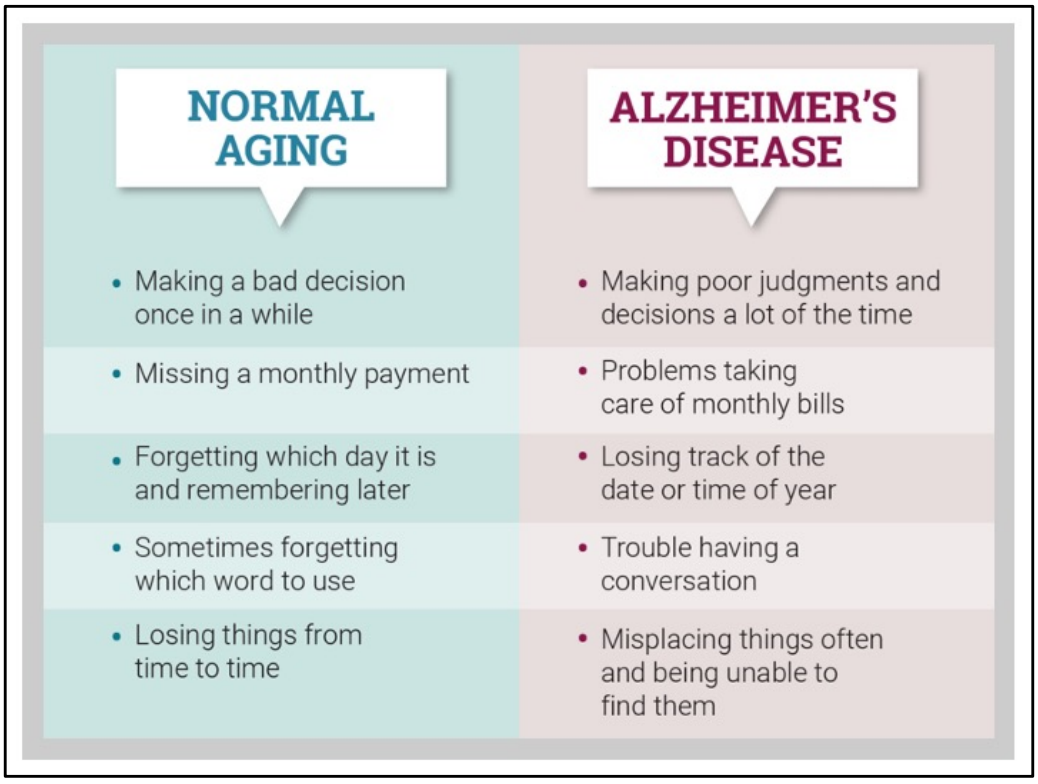
KPCW Article link:
https://www.kpcw.org/post/people-down-syndrome-are-pioneers-alzheimers-research#stream/0

https://www.actc-ds.org/

https://www.nia.nih.gov/health/do-memory-problems-always-mean-alzheimers-disease

Symptoms and Diagnosis of Alzheimer's Disease **Do Memory Problems Always Mean Alzheimer's Disease?**
Many people worry about becoming forgetful. They think forgetfulness is the first sign of Alzheimer's disease. But not all people with memory problems have Alzheimer's.
Share this infographic and help spread the word about what memory problems are normal and not. Other causes for memory problems can include aging, medical conditions, emotional problems, mild cognitive impairment, or another type of dementia.

Age-Related Memory Changes
Forgetfulness can be a normal part of aging. As people get older, changes occur in all parts of the body, including the brain. As a result, some people may notice that it takes longer to learn new things, they don't remember information as well as they did, or they lose things like their glasses. These usually are signs of mild forgetfulness, not serious memory problems, like Alzheimer's disease



View Dr. Paul Aisen's discussion of these symptoms during our Talk to Me event with journalist Dean Nelson:

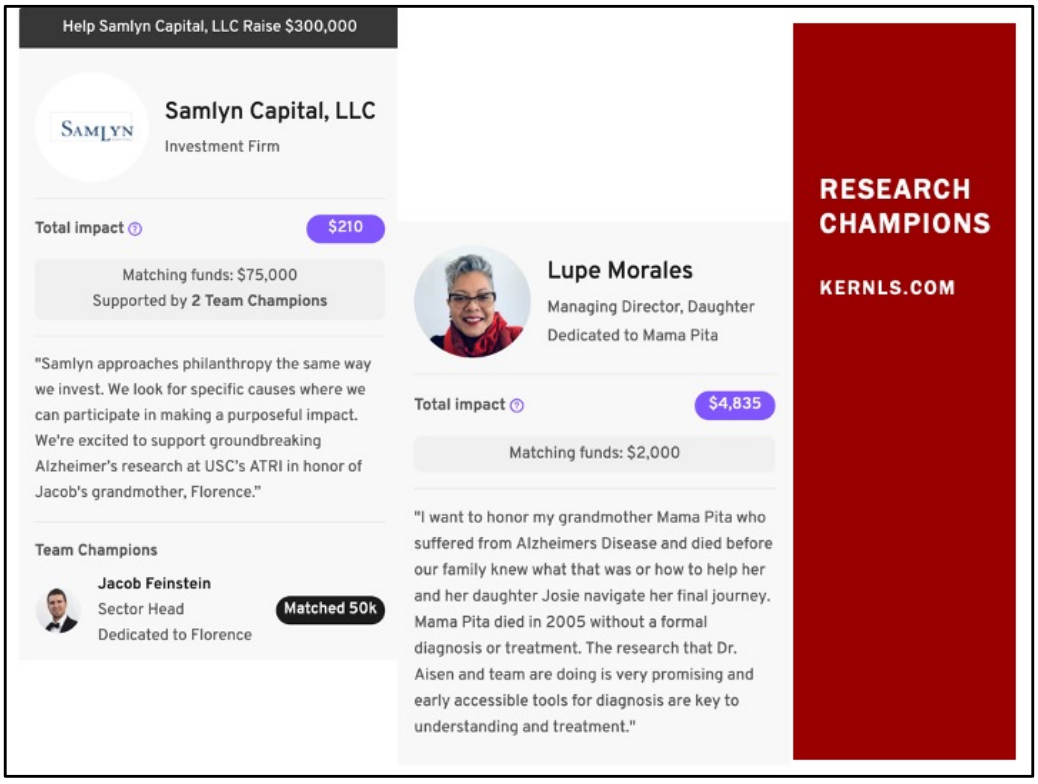
https://keck.usc.edu/atri-talk-to-me-better-trials-better-treatments-for-alzheimer-may-4-2021/

Subscribe to our events or view past ones all posted on our current website news page:

Latest Science event recordings:
https://keck.usc.edu/atri-latest-science-the-path-forward-february-2021/

https://keck.usc.edu/atri-latest-science-the-path-forward-january-15-2021/

https://keck.usc.edu/atri-launches-latest-science-and-path-forward-program/



https://kernls.com/projects/alzheimers-disease-detection

Champions take a more active role in supporting a research project. They help drive awareness and donations by promoting the project with their network and/or matching donations.