How Close are we to Stopping Alzheimer's Disease: a Research Update

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Center for Neurosciences
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Alzheimer's disease is the 6th leading cause of death and the only disease in the top 10 without a way to cure, prevent or even slow its progression.

This presentation will highlight:

- The progress and challenges of finding new treatments
- Results of clinical trials in Alzheimer's disease and what we have learned
- What's new on the research horizon

5 Million Americans

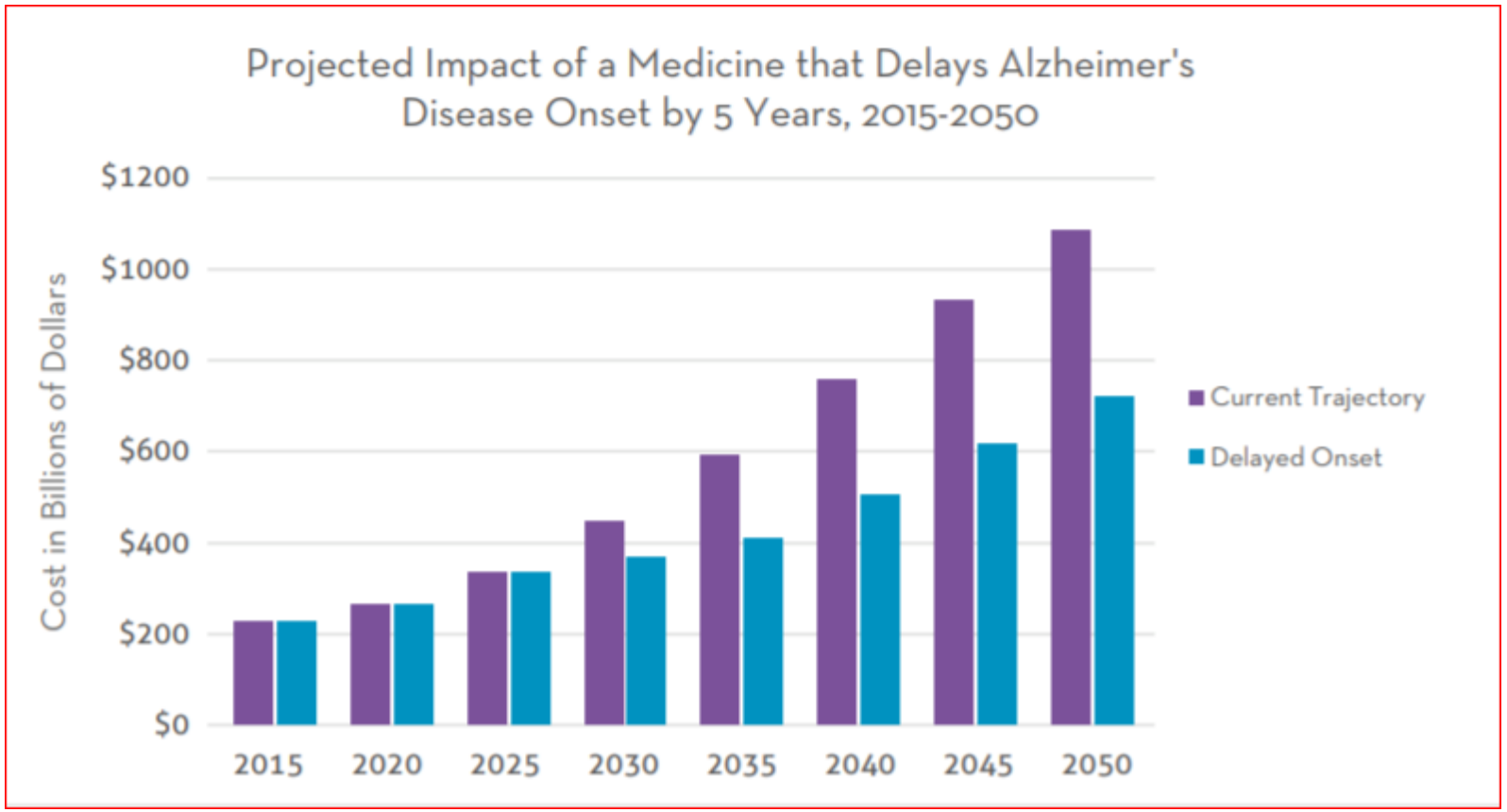
are living with Alzheimers

15 Million Americans

by 2050, the number of patients could triple without effective treatment

Today more than 5 million American with Alzheimer's disease. The disease ravages the minds of patients, burdens families and currently costs the health care system $226 billion a year.

These sobering statistics are projected to get much worse as the 76 million baby boomers age.



If a new medicine can be developed that delays the onset of Alzheimer's by just 5 years:

- It will decrease the frequency of Alzheimer's disease by 50%.
- It will save Americans $367 billion in long-term care and other health care costs by 2050.

Current Treatments

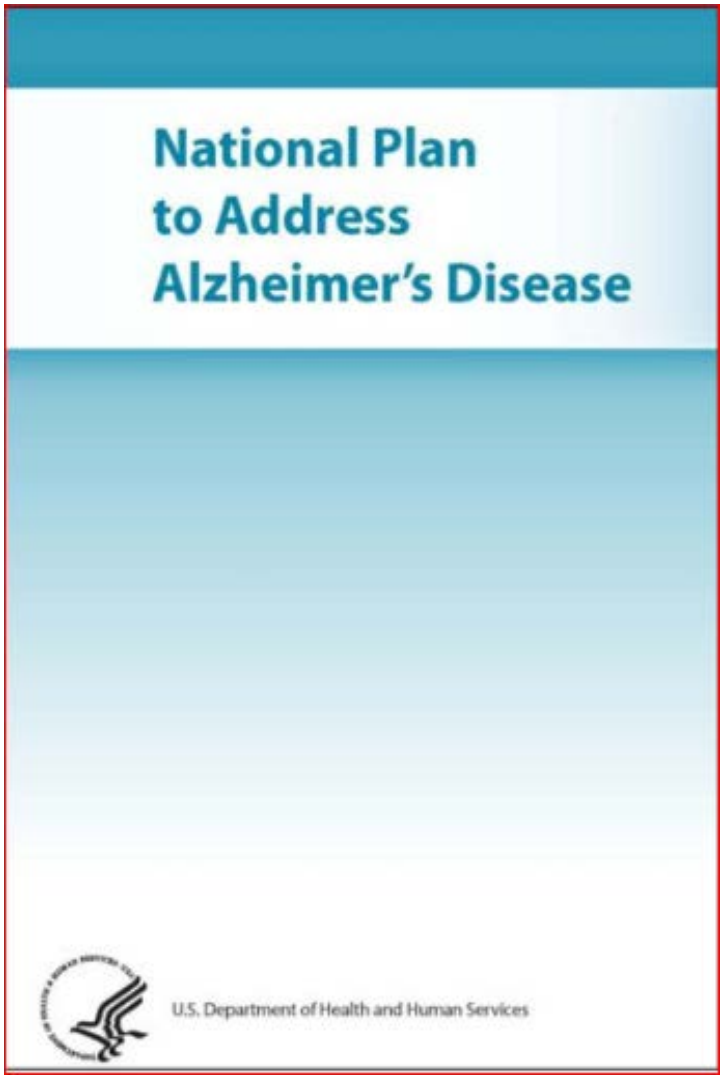
In 2018, there are 5 FDA-approved drugs to treat Alzheimer's. These provide some symptomatic relief, such as help with memory loss, confusion and problems thinking. However:

- They do NOT cure the disease or stop its progress, as they do not address the underlying causes of the disease.
- Their beneficial effects often decrease over time.

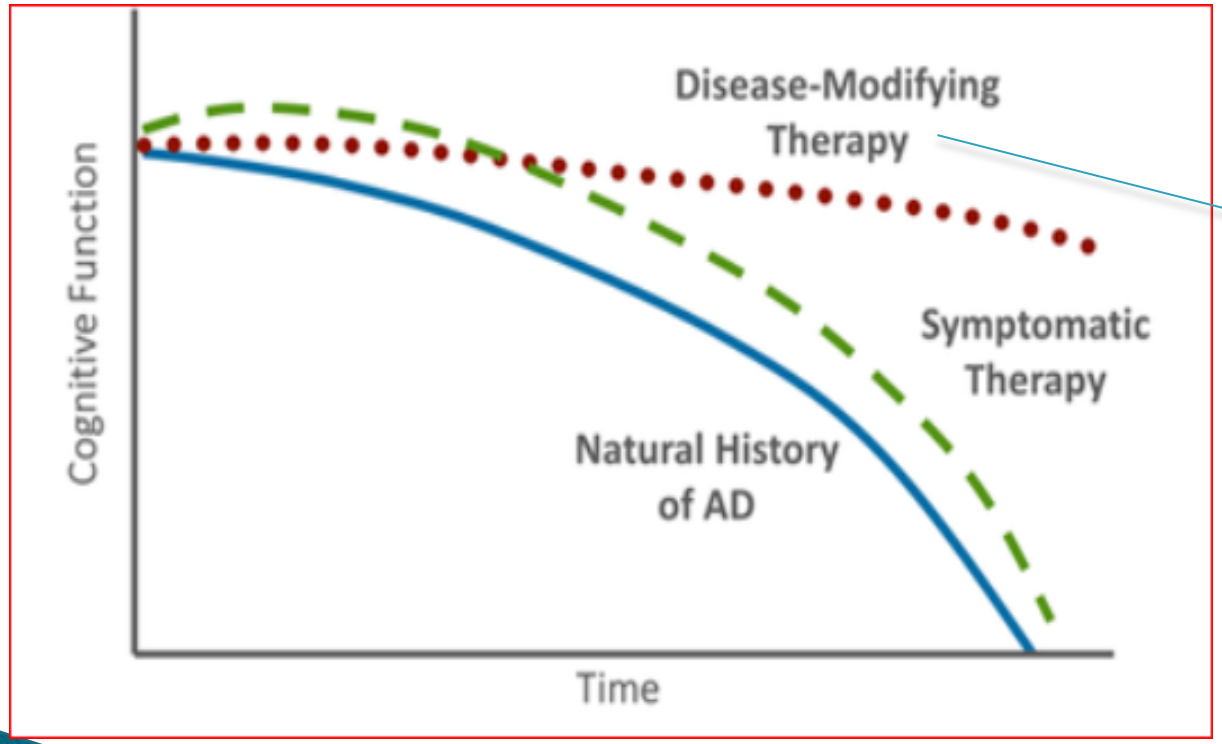
The Path to 2025

In 2011, the National Alzheimer's Plan Act became law – It created an integrated Nat'l Plan to overcome Alzheimer's disease.

- **Committed to a path to prevent or effectively treat AD by 2025.**
- Optimize care quality and efficiency.
- Expand support for patients and families.
- Enhance public awareness.
- Track progress and drive improvement.

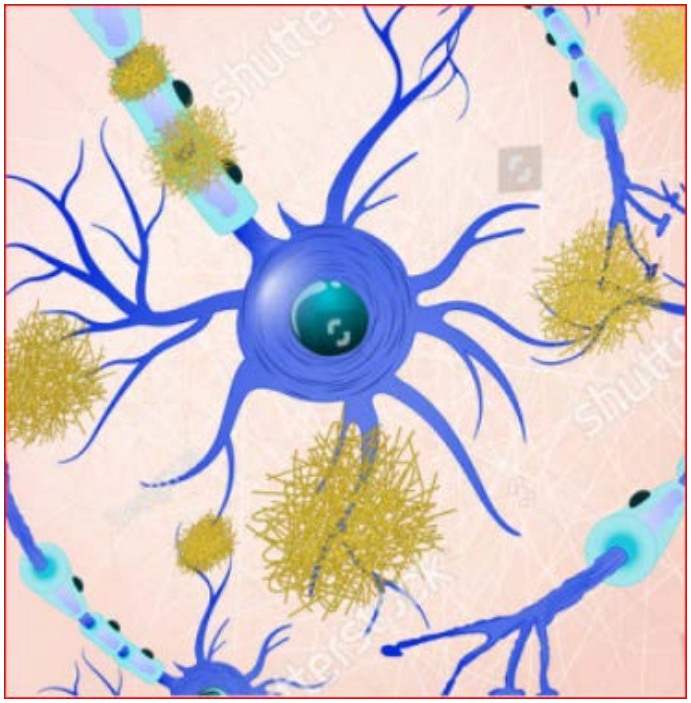


The Focus of Current Clinical Trials: Disease Modifying Therapies



Numerous disease modifying therapies have failed in clinical trials. However, many are currently in development.

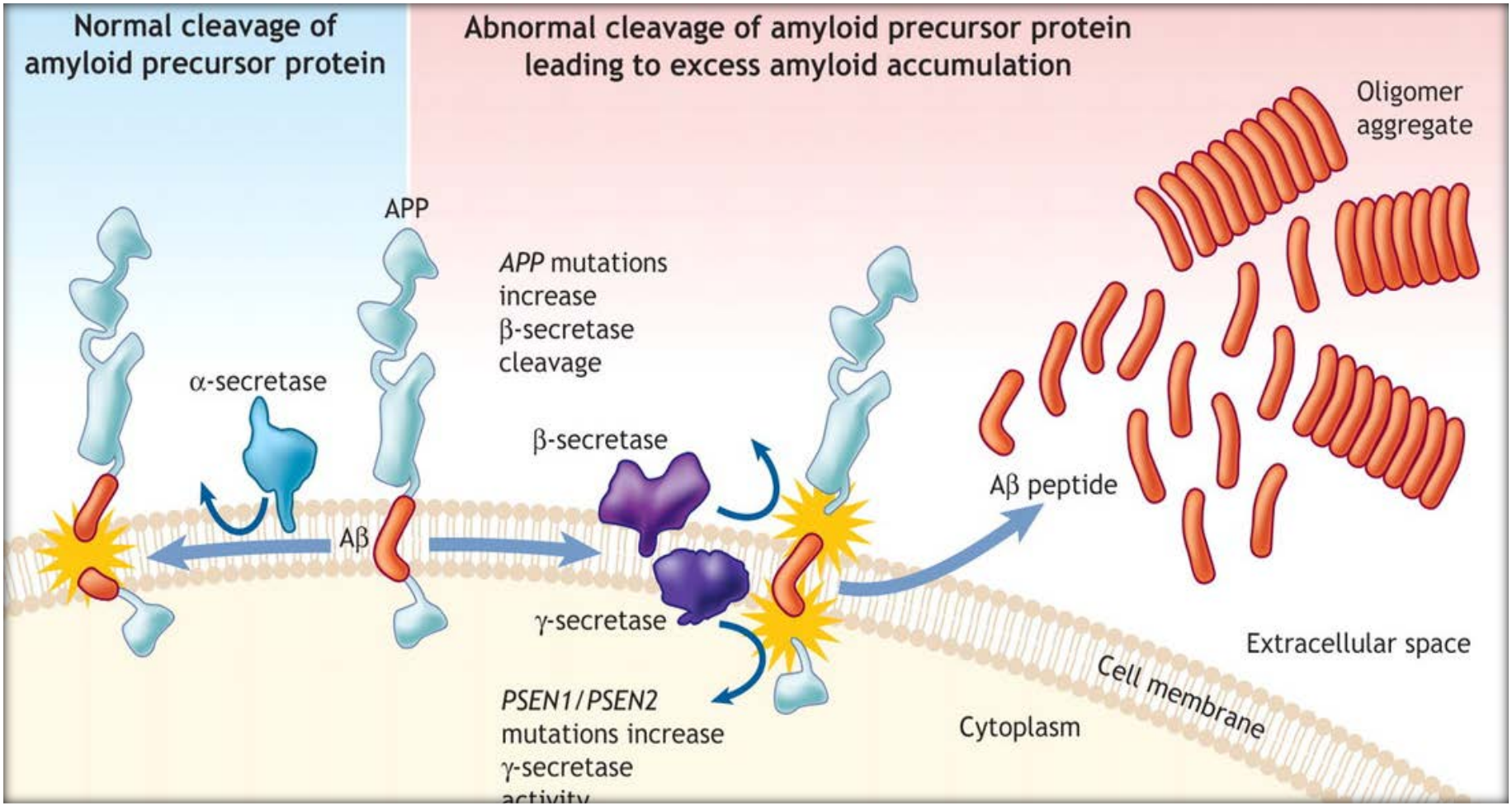
Amyloid Hypothesis



The theory that Alzheimer's disease is caused by an accumulation of amyloid deposits that stick together to form "plaques".

These amyloid deposits are toxic to nerve cells and set off a cascade of events that lead to nerve cell death and brain tissue loss.

It is still unknown whether these amyloid deposits, are the <u>cause</u> or the <u>effect</u> of Alzheimer's disease.



Amyloid as a Target for New Therapies

- decrease amyloid production
- clear amyloid deposits

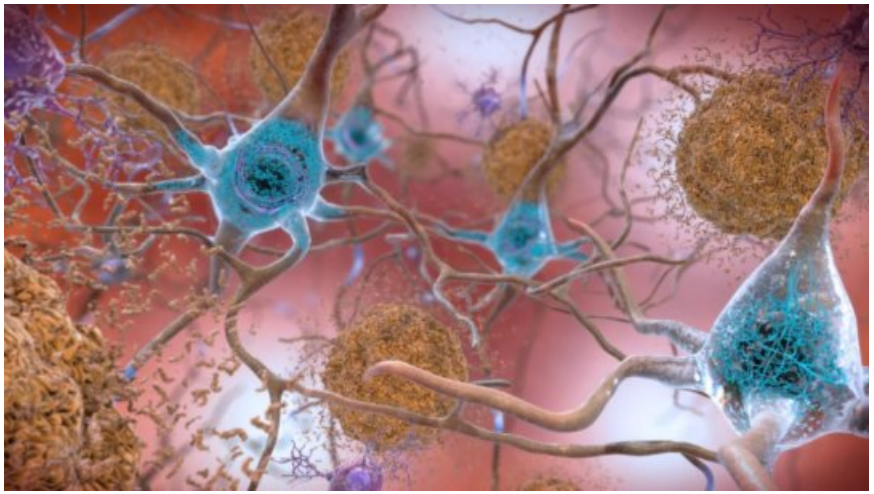
What are the Results of 10+ years of studies of Anti-Amyloid Therapies?

The Good News – many drugs in development have been able to reduce amyloid levels in the brain.

The Bad News – so far in clinical studies these drugs do not seem to slow down cognitive decline.

Other Targets for New Drugs

- **Tau** therapies attack the protein that causes tangles before it can damage nerve cells



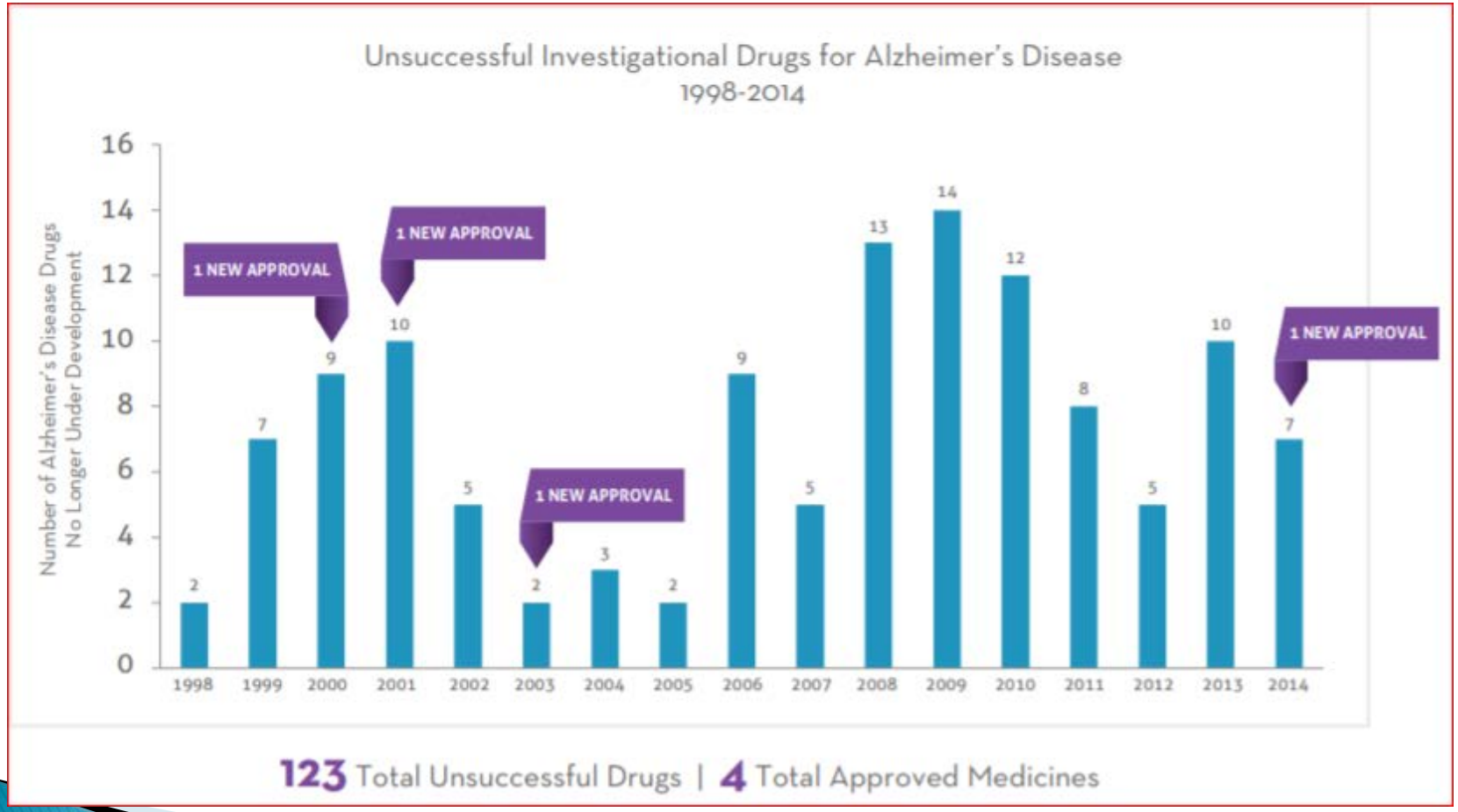
- Others treatments tame inflammation, replace neurochemical deficits, provide neuro-protection, increase insulin in the brain or promote nerve cell regeneration

Phases of Clinical Trials

Prior to beginning a clinical study, an Investigation New Drug application is submitted to the FDA. Then various phases of the study commence.

	Phase 1	Phase 2	Phase 3 "Pivotal"
# of participants	20-100	100's	300-3000
Length of Study	Several months	Several months to 2 yrs	1 to 4 years
Purpose	Safety and dosage	Efficacy and side-effects	Efficacy and adverse reactions
Advance to next phase	70%	33%	25-30%

Clinical Trial Failures – Between 1998–2014 a total of 123 drug trials for AD were halted and only 4 drugs were approved.



2018: a year of ups and downs in Alzheimer's Disease Research

HEALTH NEWS JANUARY 7, 2018 / 12:59 PM / 7 MONTHS AGO

Pfizer ends research for new Alzheimer's, Parkinson's drugs

HEALTH NEWS FEBRUARY 13, 2018 / 3:14 PM / 6 MONTHS AGO

Merck scraps another late-stage Alzheimer's drug study

Reuters Staff

HEALTH NEWS JUNE 12, 2018 / 6:00 AM / 2 MONTHS AGO

Lilly-AstraZeneca latest to abandon Alzheimer's drug trials

ALZHEIMER'S NEWS TODAY

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Roche Set to Start Two Phase 3 Trials of Gantenerumab in People with Early to Mild Alzheimer's

MARCH 12, 2018 BY JOSE MARQUES LOPES IN NEWS.

Eisai-Biogen to Advance Alzheimer's Drug, Provide Fresh Hope

By Reuters

July 24, 2018

New Alzheimer's Drug Slows Memory loss in Early Trial Results
July 25, 2018

Biogen and Eisai Phase 2 Trial of Ban2401:

- The drug was able to both reduce the plaques in the brains of patients and slow cognitive decline by 30 percent in patients with early Alzheimer's disease.
- However more information from larger, longer studies will be needed to prove benefit.

Research Setbacks

" Every study provides an opportunity to learn more about the science and how to improve the next study. Each shot on goal, whether a hit or a miss, positive or negative, brings us closer toward an effective treatment."

Maria Carrillo, PhD
Chief Scientific Officer
Alzheimer's Association

Clinical Trial Failures– what have we learned?

- **EARLY TREATMENT IS CRITICAL** – Treating Alzheimer's once dementia has started is probably too late for disease modifying therapy to work.
- **EFFECTIVE *BIOMARKERS MUST BE USED** – In order to improve the accuracy of *early diagnosis,* use of objective tests, like PET scans, are being used in clinical trials.
- **BETTER MEASURES TO TEST EFFECTIVENESS ARE NEEDED** – The assessments used to evaluate if the drug works may be insensitive to disease progression, especially in the earliest stages AD.

Stopping Alzheimer's Disease by 2025: How Close are We?

- It takes an average of 13 years for a drug to go from the lab to FDA approval.
- For a drug to be approved by 2025, it must be in Phase 2 or 3 of a drug trial right now.
- There are currently 80 drugs in this phase of development, however given the high rate of failure of AD drugs, this goal is in jeopardy.

*2017 Drug Development Pipeline

- There are currently 105 drugs in the development pipeline and of these, 70% are disease modifiers & 30% are symptomatic treatments
- The trials include a wide range of population including: normal volunteers, cognitively normal at-risk individuals, prodromal AD (MCI) and AD dementia
- Phase 3 trials require a require a substantial number of participants (2000 is average) and typically last 18 months
- 60% of the studies are sponsored by the pharmaceutical industry

*Cummings, Lee, Mortsdorf, Ritter, Khong: Alzheimer's and Dementia: Translational Research & Clinical Interventions, 3 (2017)

Finding Clinical Trials

- www.Clinicaltrials.gov

- https://Trialmatch.alz.org

Center for Neurosciences:
Committed to Ending Alzheimer's

The Center for Neurosciences has conducted a total of seven phase III Alzheimer's disease studies

GRADUATE Study

A clinical study that will assess how safe and effective an investigational drug is at slowing the progression of early (also known as 'prodromal') or mild Alzheimer's disease. To qualify, participants must:

- Be 50-90 year old
- Have mild Alzheimer's disease or memory problems that may the early symptoms of the condition
- Have someone they see frequently and who is willing to act as their "study partner"

Center for NEUROSCIENCES

If you would like more information, please contact:

Ashley Nix, Study Coordinator

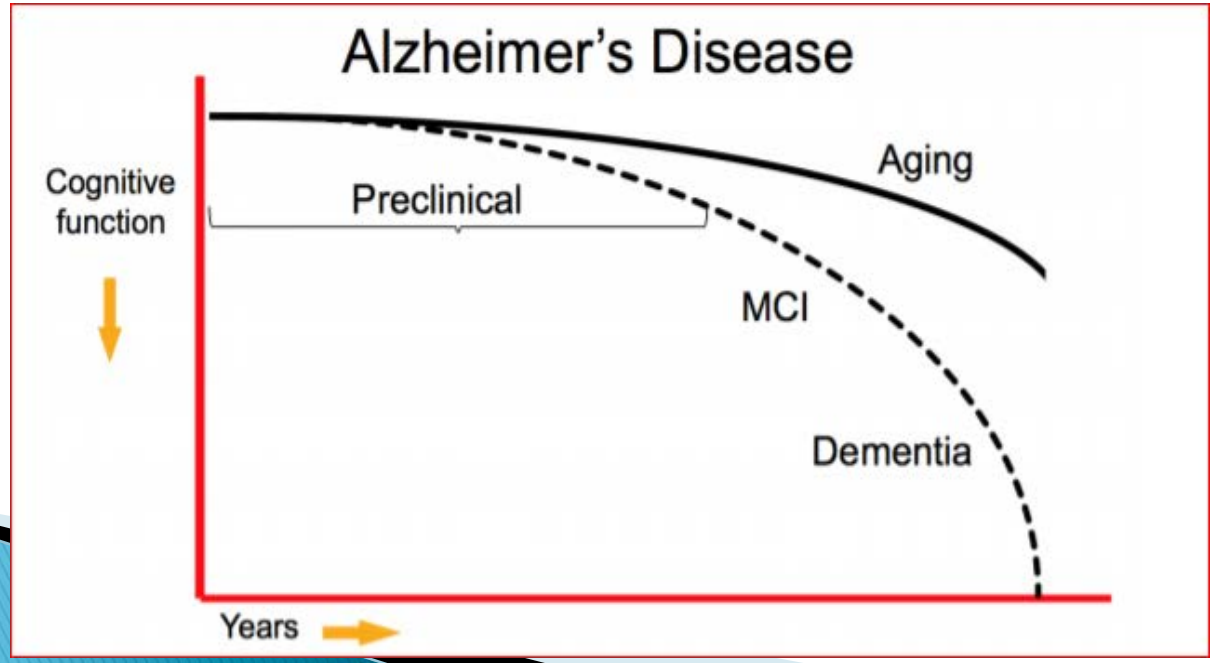
520-795-7750

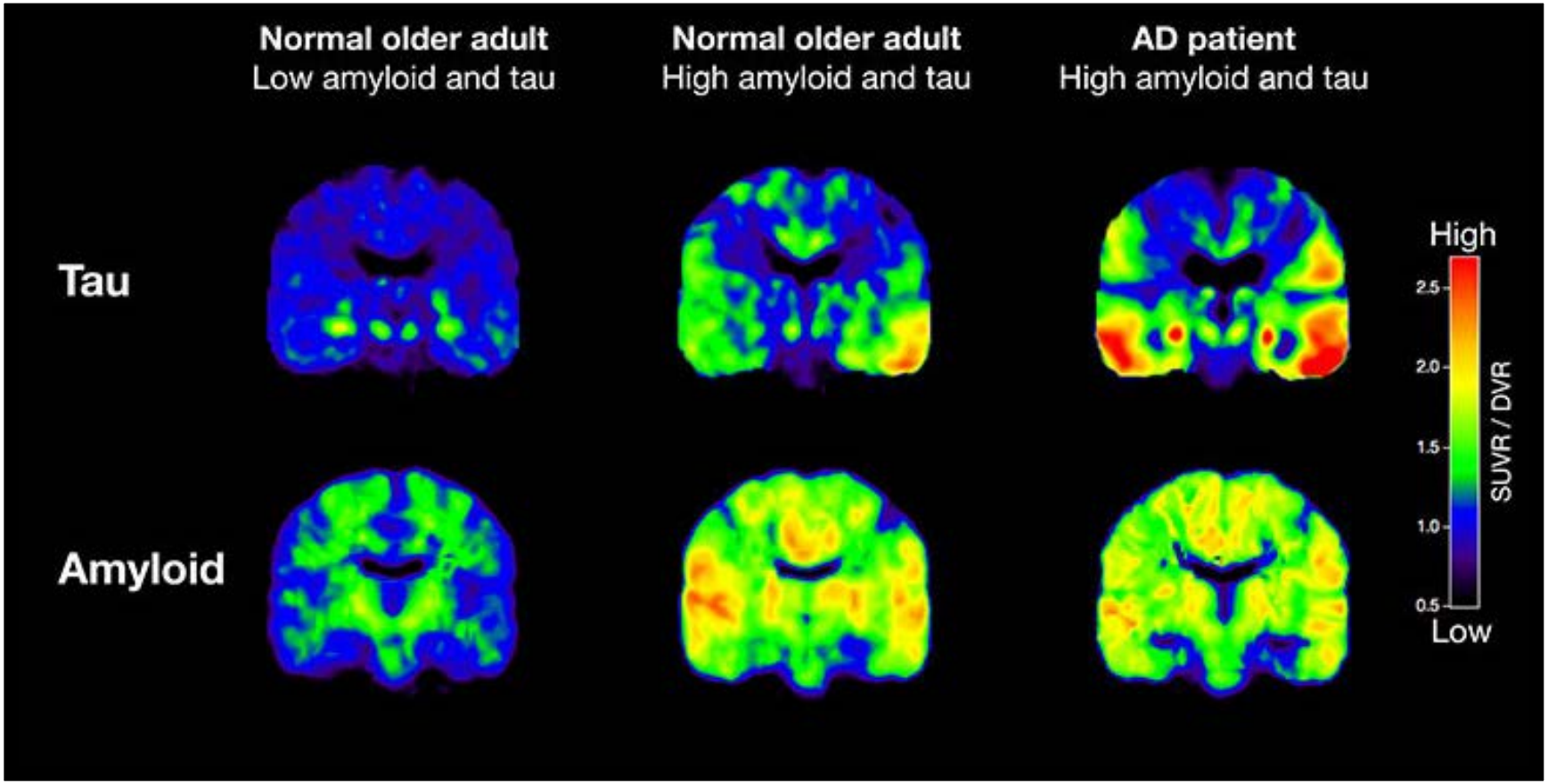
What Else is New on the Alzheimer's Research Horizon?

- Early detection
- Alzheimer's "prevention"
- Delaying onset of Alzheimer's

Pre-Clinical Alzheimer's Disease:
Redefining the earliest stages of Alzheimer's disease

- It is now known that 30% of all cognitively normal older adults have changes in the brain consistent with the diagnosis of Alzheimer's.
- These changes are occurring 15-20 years before the appearance of clinical symptoms.



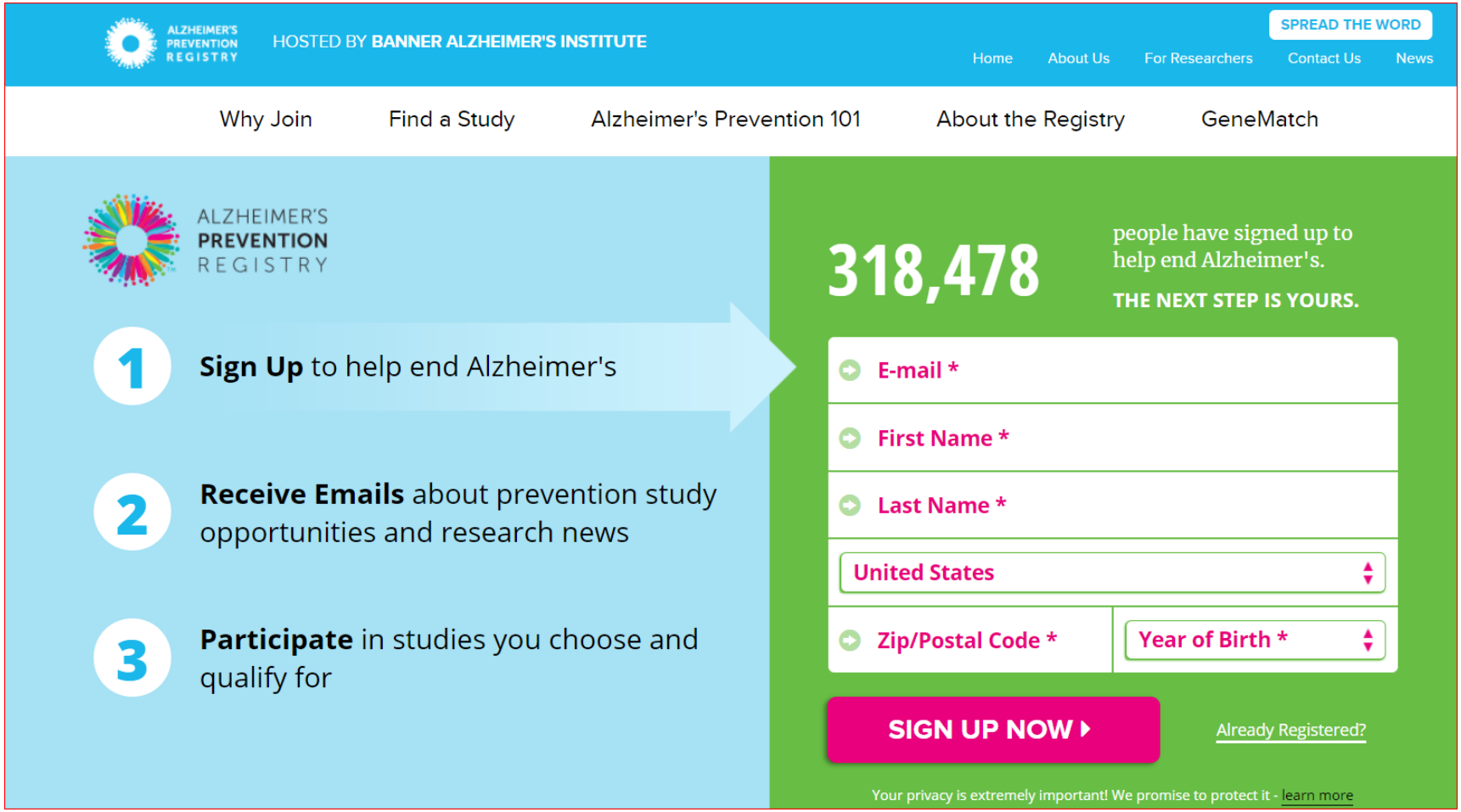


Early detection of pre-clinical Alzheimer's with PET Scans

Alzheimer's Prevention:
A future of Alzheimer's research

- "Prevention" Studies
  - Genetically at-risk populations
  - Cognitively normal
  - Positive Amyloid PET scan – **Secondary** Prevention
- Antioquia Columbia
  - 5000 individuals with genetic mutation (PSen1) which causes early-onset Alzheimer's (<50 yrs). If you have mutation,100% chance you will get AD.
  - Clinical Trial which tests a drug that targets amyloid before the first symptoms start:
    - Those with mutation are treated with antibody
    - Those without mutation are given placebo

Alzheimer's Prevention Registry –www.endalz.org



Lifestyle modifications that reduce risk of cognitive decline

- Physical exercise
- Avoid Alcohol
- Mediterranean diet
- Stress Reduction
- Cognitive activity
- Remain socially engaged
- Manage medical risks:
  - Control BP and Cholesterol
  - Weight reduction
  - Smoking cessation
- Get good sleep

Caffeine may delay AD

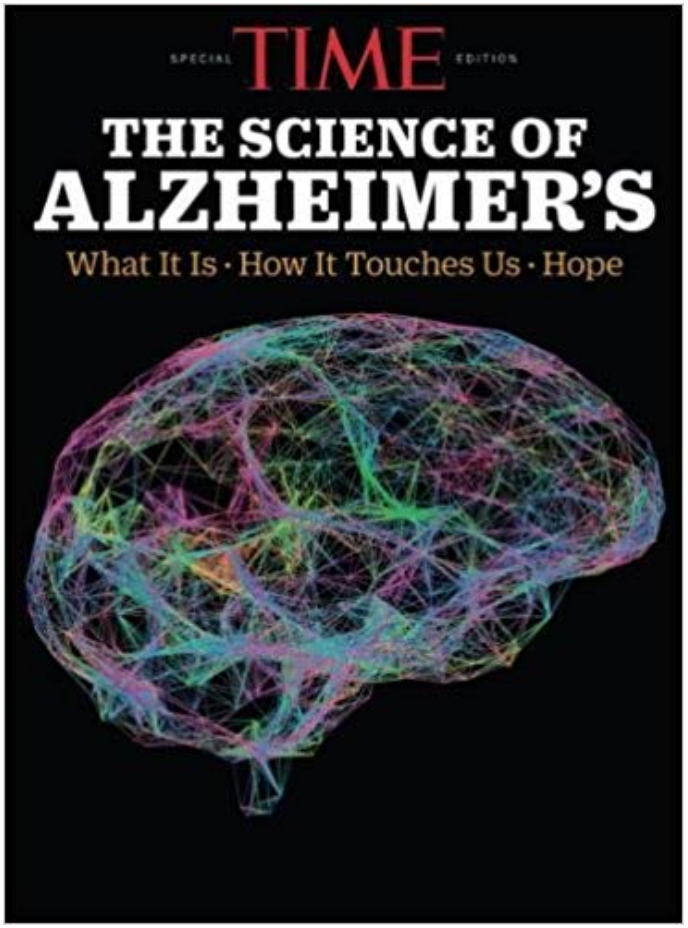
- Moderate caffeine consumption appears to have disease modifying effects in older adults who are already showing signs of memory impairment (MCI).
- *One study showed that individuals with MCI who had higher blood caffeine levels did not progress to Alzheimer's disease 2-4 years later, compared too their counterparts with lower caffeine levels

*Arendash GW, Cao C; Caffeine and coffee as therapeutics against Alzheimer's disease. J Alzheimers Dis. 2010;20 Suppl 1:S117-26

Summary

- Future Alzheimer's research will change the therapeutic focus from patients with early AD to patients who are pre-symptomatic.
- Non-invasive and affordable biomarkers will be needed to identify these patients.
- Though early clinical trials that target amyloid have been negative, there are many more in process that may ultimately prove or disprove the amyloid hypothesis.
- Our best hope for preventing Alzheimer's is identifying it before symptoms even start and then delaying the onset of the disease as long as possible.

Conclusion



Science's battle against Alzheimer's disease plays out in labs, university & clinics around the world. Every day there are victories and defeat, advances and retreats, all suggesting that progress–however incremental–is being steadily made.

Center for Neurosciences is hosting a Memory Screening Day

- MMSE will be performed & *result will be provided
- Register here today for this free event

*While result is not a diagnosis, it can suggest if someone should see a their provider for a full evaluation.

11/16/2018
At the Brain Bus
East Parking Lot

Research Participants

Let us recognize and thank study volunteers. The are Medical Heroes because they make it possible for there to be new medical treatments that benefit all of us.