The Alzheimer’s Association
Moving the Science Forward

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The Global Leader in Alzheimer’s Research
Types of Dementia

- Dementia is the loss of memory due to changes in the brain
- Alzheimer’s is the most common form
- Definite diagnosis used to require autopsy
- Many mixed cases
- Many memory disorders are reversible and not truly dementia
What is Alzheimer’s?

- Alzheimer’s is a universally fatal brain disease
- Alzheimer’s has a gradual onset
- Alzheimer’s is progressive, meaning it gets worse over time
- The vast majority of people with the disease develop “late onset” Alzheimer’s
- A very small number of people have inherited forms
What treatments are available?

• Currently, there are no therapies that can cure Alzheimer’s.

• Some drugs are available to temporarily improve symptoms—only slow worsening of symptoms for 6-12 mos. —only work in about half of people who take them.

• There are currently no drugs that stop or even slow the process of nerve cell death in Alzheimer’s.

• Some lifestyle factors may be associated with decreased risk for developing Alzheimer’s in the first place—eating healthy foods and exercising—remaining socially and mentally active.
History of Alzheimer’s Disease

tangles

plaques

alzheimer's association
THE BRAINS BEHIND SAVING YOURS.
What is a Biomarker?

- Biological marker to measure change
- Reliable predictor and indicator of disease and disease progression
- Examples include:
  - Glucose for insulin resistance and diabetes
  - T cell count for HIV/AIDS
  - Cholesterol for heart disease
Acceleration of Diagnostic for Alzheimer’s disease

- **2001**: First Alzheimer’s Association grant to Dr. William Klunk, PiB
- **2006**: Alzheimer’s Association funding of PiB Add On in ADNI ($2.1M)
- **2010**: FDA Testimony on standard for approval of Amyloid Imaging
- **2012**: FDA approval of first amyloid imaging agent
- **2013**: Testimony to CMS on Appropriate Use of Amyloid Imaging
- **2013**: FDA approval two additional amyloid imaging agents
Degrees of Prevention

Primary

Secondary

Tertiary

Normal

Preclinical [Accumulation pathology]

MCI

Dementia
Anti-Amyloid in Asymptomatic Alzheimer’s (A4) Study

- Age 65 to 85
- Clinically normal
- Positive Amyloid PET
- Testing solanezumab (Lilly)
- Secondary prevention
A4 Sites in North America and Australia
Drug Discovery and Development: A Long, Risky Road

- **Drug Discovery:**
  - 5,000 - 10,000 compounds
  - 3 - 6 years

- **Preclinical:**
  - 250

- **Clinical Trials:**
  - 5 phases:
    - Phase 1: 20-100 volunteers
    - Phase 2: 100-500 volunteers
    - Phase 3: 1,000-5,000 volunteers
  - 6 - 7 years

- **FDA Review:**
  - 0.5 - 2 years

- **Large-Scale Manufacturing:**
  - Post-marketing surveillance

**Pathway to Approval**
What Is a Clinical Study?

A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge.

There are two main types of clinical studies: observational studies and clinical trials.
Observational Studies

In an **observational study**, researchers assess health outcomes in groups of participants. Participants are **not** assigned to specific interventions by the researcher.

For example, researchers may observe a group of adults to learn more about the effects of different lifestyles on brain health.
Clinical Trials

In a clinical trial (also called an interventional study), participants receive specific interventions according to the research plan.

These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, for example, diet.
Clinical Trials

Researchers try to determine the safety and efficacy of the intervention by measuring outcomes in the participants.

For example, researchers may give a drug or treatment to participants who have high blood pressure to see whether their blood pressure decreases.
Who Conducts Clinical Studies?

Every clinical study is led by a principal investigator (PI), who is often a medical doctor.

Clinical studies also have a research team (or study team) that may include doctors, nurses, social workers, research pharmacists, study coordinators, and others.
Who Conducts Clinical Studies?

Clinical studies can be **sponsored**, or funded, by pharmaceutical companies, academic medical centers, voluntary groups, Federal agencies (such as the NIH, DoD, and VA), or other groups.

Physicians, health care providers, and other individuals can also sponsor clinical research.
Clinical studies can take place in many locations, including hospitals, universities, doctors' offices, and community clinics. The location depends on who is conducting the study.

Sometimes, the same study is conducted in many different locations. These are called **multisite** studies.
Participant Experience: What to Expect

• Usually starts with a ‘screening’ call or visit, during which a member of the study team will ask questions about current health and medical history
• Medical tests may also be performed
• Determining eligibility to take part in the trial
• Inclusion/Exclusion criteria
Participant Experience: What to Expect

- Some study visits can be quite long – several hours or more
- Participants may be asked to do other study related activities between visits, such as keeping a journal
- Visits will usually include physical tests and exams, along with psychological and cognitive tests
Participant Experience: What to Expect

- **Blood tests** are very common
- Becoming more common to also do **genetic testing** for risk genes such as APOE-e4
Participant Experience: What to Expect

**Cognitive ratings and tests**, such as the Alzheimer’s Disease Assessment Scale – Cognitive Behavior (ADAS-Cog)
Participant Experience: What to Expect

Biomarker tests are becoming more common in some large clinical trials

- **Lumbar puncture** (spinal tap) for cerebrospinal fluid (CSF)
- **Amyloid PET** scan for brain amyloid levels
Research Protections

Participants in clinical studies are protected in many ways

- Institutional Review Boards (IRBs)
- Office for Human Research Protections (OHRP)
- Data Safety Monitoring Boards (DSMBs)
- Food and Drug Administration (FDA)
- Informed Consent
alzheimer's association

trialmatch

115,000+
user profiles

961
sites

258
studies

alz.org/trialmatch
Alzheimer’s Disease Neuroimaging Initiative (ADNI)

- To validate biomarkers for clinical AD trials
- To standardize biomarkers for clinical AD trials
- To optimize biomarkers for clinical AD trials
- AD trials include Phase 2 (POC) and Phase 3
- To provide all the data to those designing trials
- To help create a world wide network for AD trials
- Ultimately to facilitate development of a surrogate biomarker outcome measure: tau?
ACCOMPLISHMENTS OF ADNI
(1 year left)

• Amyloid phenotyping with PET and CSF
• Standardized methods for MRI, PET, and cognitive measurements
• Provided data for designing trials
• World wide network of clinical sites
• Pilot tau study started
• Pilot on-line cognitive testing
WW-ADNI is a collaborative effort of scientists from around the world and is the umbrella organization for neuroimaging initiatives being carried out through:

- North American ADNI
- European ADNI
- Japan ADNI
- Australian ADNI (AIBL)
- Taiwan ADNI
- Korea ADNI
- China ADNI
- Argentina ADNI

World Wide ADNI (WW-ADNI) unites leading international investigators in a common effort to:

- Help predict and monitor the onset and progression of Alzheimer's disease
- Establish globally recognized standards to identify and diagnose Alzheimer's disease
- Document cognitive changes linked to physical changes
- Share data across the international research community

The Alzheimer's Association is proud to be a major sponsor of WW-ADNI as part of our global research strategy to defeat Alzheimer's disease.
GAAIN: The Global Data Network for Alzheimer’s

Collaboration to provide researchers around the globe with access to a vast repository of Alzheimer’s research data, and the tools to analyze it.
Amyloid PET: Early Detection of Alzheimer’s disease

- **Normal**
  - No pathological lesions
  - No symptoms

- **Pre-Clinical Stage**
  - First pathological lesions
  - No symptoms

- **Mild Cognitive Impairment**
  - Mild pathology
  - Memory Impairment

- **Alzheimer’s disease**
  - Intense pathology
  - Dementia

Disease progression / Pathological continuum
IDEAS (Imaging Dementia Evidence for Amyloid Scanning) STUDY

- 2013 CMS denied coverage except......

- Coverage with Evidence Development (CED) Demonstrate that technology improves health outcomes for people with Alzheimer’s

IDEAS Study Protocol:

- 4-year, $100 million new dollars, 2016

- Announced on April 16 by the Alzheimer’s Association and the American College of Radiology (ACR).

- $80M CMS, $19M Manufacturers, $1M Alzheimer’s Association

Image adapted from Clark et al. (2011) JAMA 305(1).
Goal: To determine clinical usefulness, value in diagnosing Alzheimer’s (and other dementias) of a brain PET scan that detects amyloid plaques – a core feature of AD.

18,488 Medicare beneficiaries, 65 or older, w/ uncertain diagnosis will be enrolled at approximately 300 sites throughout the United States.

Data from this study will help determine if Medicare will reimburse the cost of amyloid PET scans for diagnostically uncertain cases. Medicare does not currently cover amyloid PET scans.
Current Alzheimer’s Therapies: Symptomatic

Cholinesterase Inhibitors
- Tacrine (Cognex)
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

Glutamate Moderators
- Memantine (Namenda)

Combination Therapies
- Donepezil & memantine (Namzaric)
### Diagnostic and Therapeutic Agents in Phase I and II Clinical Trials in Alzheimer’s Disease

#### Diagnostic Agents

- [11C]PIB
- [18F]DPA-714
- [18F]NAV4694
- [18F]-T807 (AV-1451)

#### Therapeutic Agents

- AADvac1
- ABT-957
- Aducanumab (BIIB037)
- Allopregnenalone
- ANAVEX2-73
- Atomoxetine
- AZD0530
- BAN2401
- Bexarotene
- BI 409306
- Blood plasma
- Bryostatin 1
- CPC-201
- Crenezumab (MABT5102A)
- DAIO-B
- DBS-f (Deep brain stimulation of the fornix)
- E2609
- Encenicline
- Exendin-4
- GC021109
- IVIg
- JNJ-54861911
- KHK6640
- Ladostigil
- Levetiracetam
- Liraoglutide
- Lu AF20513
- LY3002813
- LY3202626
- MEDI1814
- Mesenchymal stem cells
- Metformin
- MK-7622
- NIC5-15
- Nicotinamide
- PQ912
- PXT00864
- Rasagiline
- RO4602522
- RPh201
- R-Pramipexole
- Sargramostim
- S-Equol
- Simvastatin
- T-817MA
- Tetrahydrobiopterin
- TPI-287
- TMS (transcranial magnetic stimulation)

(Compiled April 17, 2015)
# Therapeutic Agents in Phase III Clinical Trials for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Company/Developer</th>
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<tbody>
<tr>
<td>AZD3293</td>
<td>Astrazeneca/Lilly</td>
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<tr>
<td></td>
<td>BACE inhibitor</td>
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<tr>
<td>Encenicline/MT-4666</td>
<td>Forum Pharmaceuticals</td>
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<tr>
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<td>Mitsubishi/Tanabe Pharmaceutical Corp.</td>
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<tr>
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<td>Nicotinic receptor agonist</td>
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<td>Gantenerumab</td>
<td>Hoffman-La Roche</td>
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<td></td>
<td>Monoclonal antibody against beta-amyloid</td>
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<td></td>
<td>Part of DIAN-TU</td>
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<tr>
<td>Insulin</td>
<td>Alzheimer’s Disease Cooperative Study</td>
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<tr>
<td>IVIg and Albumin</td>
<td>Grifols</td>
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<td>Intravenous immunoglobulin</td>
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<td>LU AE58054</td>
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<td>5HT6 receptor antagonist</td>
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<tr>
<td>Masitinib</td>
<td>AB Science</td>
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<td>Inhibitor of c-KIT cell signaling</td>
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<td>MK-8931</td>
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<td>BACE inhibitor</td>
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<td>Nilvadipine</td>
<td>St. James Hospital</td>
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<td>Calcium Channel Blocker</td>
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<td>Pioglitazone</td>
<td>Takeda</td>
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<td>PPAR-gamma activator</td>
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<tr>
<td>Sodium Oligo-mannurate (GV-971)</td>
<td>Shanghai Greenvalley Pharmaceuticals</td>
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<tr>
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<td>Inhibits beta-amyloid aggregation</td>
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<td>Solanezumab</td>
<td>Eli Lilly</td>
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<td>Humanized antibody against beta-amyloid</td>
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<td>TRx0237</td>
<td>TauRX</td>
</tr>
<tr>
<td></td>
<td>Tau aggregation inhibitor</td>
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Possible Prevention of Alzheimer’s?

**Primary Prevention**
- Delay onset of AD pathology
  - Decrease Aβ₄₂ production
  - Prevent tangle formation

**Secondary prevention**
- Delay onset of cognitive impairment in individuals with evidence of pathology
  - Decrease accumulated Aβ burden
  - Decrease neurodegeneration with anti-tau or neuroprotective agents

**Tertiary prevention and treatment**
- Delay onset or progression of dementia
  - Neuroprotection-prevent neuronal loss
  - Enhance function of remaining neurons
  - Neurotransmitter repletion

Clinical disease stage:
- No pathology
- Preclinical
- MCI
- Dementia
Phase 1b Results for Aducanumab

- BIIB037 or Aducanumab shows solid safety and tolerability profile (Phase 1b) in PRIME trial
- Monoclonal antibody targeting beta-amyloid clumps
- Had a dose dependent slowing of cognition loss in individuals with mild disease/confirmed beta-amyloid in brain
- Measures of cognition show statistical benefit at 54 weeks and reduced levels of beta-amyloid
- Need larger, longer trial (Phase 3)
Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association

- Most important and impactful Alzheimer’s journal
- Our journal website is visited 54,000 times per month, and articles from the journal are downloaded more than 32,000 times per month
- New open access journal launched in March – Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring
• **Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association**
  - Flagship journal of the Alzheimer’s Association
  - Covers full spectrum of Alzheimer’s & dementia research
  - Celebrating 10th anniversary in July, 2015

• **Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring**
  - Open access journal of the Alzheimer’s Association
  - Focus on diagnostic and biomarker research
  - Launched in March, 2015

• **Alzheimer’s & Dementia: Translational Research & Clinical Intervention**
  - Open access journal of the Alzheimer’s Association
  - Focus on therapeutic research and clinical trials
  - Launching later this year
Convening & Connecting Scientists Around the Globe

Alzheimer’s Association
International Conference® 2015

July 18–23
Washington, D.C., United States

alz.org/AAIC
The Alzheimer's Epidemic Continues to Grow...

5.3 million Americans of ALL Ages will have Alzheimer's in 2015.

6 TH LEADING CAUSE OF DEATH IN THE U.S.

Of the top 10 killers, Alzheimer's is the only one that cannot be prevented, cured or even slowed.

Total cost of care for those with Alzheimer's, with more than two-thirds paid by Medicare and Medicaid.

Source: Centers for Disease Control and Prevention (cdc.gov/nchs/fastats/leading-causes-of-death.htm)
Landscape of Alzheimer’s: Hope In Research

- 6th leading cause of death across all ages
- 5th leading cause of death for those aged 65 and older
- Only cause of death among the top 10 in America without a way to prevent, cure or even slow its progression.

Change in the number of deaths from 2000 to 2010

Based on preliminary 2010
New Alzheimer’s Economic “Trajectory” Report

- Alzheimer’s costs increase from $226 billion in 2015 to $1.1 trillion in 2050

- Big burden on Medicare:
  - 2015: Nearly 1 in 5 Medicare dollars spent on people with Alzheimer’s
  - 2050: Nearly 1 in 3

- If we meet National Plan’s 2025 goal and have treatment that delays onset:
  - America would save $220 billion over just the first five years
  - A $2 billion per year research investment by the federal government would be recouped within three years
National Plan to Address Alzheimer’s disease

• Research goal: Prevent and Effectively Treat Alzheimer’s by 2025

• Key strategies:
  – Increase clinical studies enrollment
  – Expand the scale and scope of research
  – Accelerate drug development
Challenge
Needed to move past status quo and on to growth
For that, no substitute for Congressional engagement
Then… AAA requires the NIH to submit this Alzheimer’s budget directly to Congress and the President.

With comment only from the Secretary of HHS and the Alzheimer’s Advisory Council.
Leaders for G8 countries commit to work together to Prevent and Effectively Treat Alzheimer’s Disease by 2025.

USA
France
Germany
Italy
Canada
Japan
UK
<Russia>
World Dementia Council

• Purpose: To draw together international expertise to stimulate innovation & to co-ordinate international efforts

• Areas of focus:
  – Big Data
  – Regulatory Issues
  – Finance
  – Public Health
Global Prevalence of Dementia

• Kenneth Langa, Is the Risk of Alzheimer's Disease Declining in the World?
• Gabriele Doblhammer, Short-term Trends in Germany
• Claudia L. Satizabal, Temporal trends in Dementia Incidence in the Framingham Study.
• Yuri Takeuchi, Prevalence estimates of dementia in Colombia
• Marc Wortmann, ADI, New global prevalence data on dementia
FHS: Decline in Incidence of Dementia

- Increase in the age of onset of dementia in Framingham also seen
- Similar reports from Sweden, The Netherlands, Germany and the UK

Source: Claudia L. Satizabal, Boston University, Framingham Heart Study, AAIC 2014
But … Some Countries Report Increasing Incidence of Dementia

- **China**
  - ADI estimates dementia prevalence increased from 5% to 7%
- **Sub-Saharan Africa**
  - ADI estimates dementia prevalence increased from ~3% to 4.76%
- **Colombia**
  - Estimate approximately 260,000 people with Alzheimer’s by 2020
  - Current estimates may be off by 50%
Increasing Global Prevalence of Dementia (2010-2050)

Source: The Global Impact of Dementia 2013-2050, Alzheimer’s Disease International
How do we make sense of this?

What does it mean?
Bad News?

- Increased global diabetes and obesity (other known risk factors of Alzheimer’s)
- Some countries do not have access to increased education and/or management cardiovascular factors

Good News?

• Increased access & management cardiovascular risk factors, such as Hypertension:
  – Worldwide: Systolic BP down 1mm Hg /decade since 1980
  – Treatment in US: 58% in 1990; 75% in 2008
  – Control in US: 27% in 1990; 50% in 2008

• Education boom in high income countries:
  – Significantly more formal schooling earlier in life in older adults today
  – 53% of age 65+ in US finished HS in 1990; 80% in 2010
  – 11% of age 65+ finished college in 1990; 23% in 2010

THE END OF ALZHEIMER’S STARTS WITH YOU

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alz.org