The Good News About Prevention Trials

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Outline

• More about the Alzheimer’s Association
• Dementia vs. Alzheimer’s - definitions
• Current understanding of Alzheimer’s
• On-going prevention trials today
• Future of prevention studies
• Impact of possible prevention
Objectives During Today’s Conversation:

- Discuss the progress being made in clinical trials generally
- Identify the research as it relates to prevention trials
Alzheimer’s Association: Who We Are

OUR VISION: A world without Alzheimer’s disease®.

OUR MISSION: To eliminate Alzheimer's disease through the advancement of research; to provide and enhance care and support for all affected; and to reduce the risk of dementia through the promotion of brain health.
DEMENTIA

An “umbrella” term used to describe a range of symptoms associated with cognitive impairment.

ALZHEIMER’S 50%-75%
VASCULAR 20%-30%
LEWY BODIES 10%-25%
FRONTOTEMPORAL 10%-15%

MIXED DEMENTIA = >1 NEUROPATHOLOGY - PREVALENCE UNKNOWN
Alzheimer’s Epidemic Continues to Grow…

5.5 million Americans of ALL Ages will have Alzheimer’s dementia in 2017

6th 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.

Source: Centers for Disease Control and Prevention (cdc.gov/nchs/fastats/leading-causes-of-death.htm)
National Plan to Address Alzheimer’s disease

“Prevent and Effectively Treat Alzheimer’s by 2025”
Prevention of Alzheimer’s?

Primary Prevention
Delay onset of AD pathology
• Decrease Aβ_{42} 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
Plaques & Tangles: Hallmarks of Alzheimer’s Disease
Continuum of Alzheimer’s Disease

Normal Alzheimer’s disease

Adapted from Sperling et al. 2011
Brain Changes

Changes in Memory, Thinking, Function

- Alpha Synuclein
- TDP-43
- \( A\beta \)
- TAU
- Other (i.e. Inflammation, Metabolism, etc)
- Vascular Disease

Adapted from Dr. Ronald Petersen, Mayo Clinic
Brain Changes Biomarker Therapy

Adapted from Dr. Ronald Petersen, Mayo Clinic
PET Beta Amyloid Imaging

Normal Aging Alzheimer’s Disease

Figures courtesy of Drs Keith Johnson/Reisa Sperling
Funded Dr. William Klunk for first studies on beta-amyloid imaging

Added Amyloid PET Imaging to the Alzheimer’s Disease Neuroimaging Initiative

Alzheimer’s & Dementia publishes revised diagnostic NIA- Alzheimer’s Association guidelines

FDA approves beta-amyloid imaging agents for clinical use

Launched IDEAS Study, working to ensure individuals can access beta-amyloid imaging
Beta Amyloid & Tau PET Imaging

70 y/o MMSE = 27

Beta Amyloid

PiB

T807

Tau

SUVR

2.0

1.0

NFT stage III

Courtesy of Keith Johnson, MD
First study AAIC 2013

alzheimer's association
Impact of Beta Amyloid PET Imaging on the Research Landscape

- Increase our understanding of disease; biological changes begin decade or more before clinical symptoms
- Enable specific recruitment of volunteers for clinical trials
- Opened door to possibility of prevention to intervene earliest time point (i.e. DIAN-TU)

Figure adapted from Clark et al. (2011) JAMA 305(1).
Pathway to Approval for Drug Development

Adapted from PhRMA Annual report
Current Landscape of Clinical Trials for Alzheimer’s & Dementia

Phase I
- 80 Total Trials
  - 50 experimental medications
  - 3 medical devise
  - 9 diagnostic trials
  - 18 experimental medications for non-AD dementias

Phase II
- 122 Total Trials
  - 79 experimental medications
  - 7 medical devise
  - 6 diagnostic trials
  - 30 experimental medications for non-AD dementias

Phase III
- 47 Total Trials
  - 16 registration trials
  - 5 for agitation or sleep
  - 10 academic trials
  - 3 medical devise
  - 2 diagnostic trials
  - 11 trials for non-AD dementias

11 Clinical trials with Computerized Devises for Alzheimer’s and Cognitive Decline for detection and / or cognitive training.

As of 1/2017
In the News: Published Report of Aducanumab Phase 1B

• First seen at AAIC 2015
• Using beta-amyloid PET for enrollment
• Promising Phase 1 monoclonal antibody Aducanumab
  – Lowering levels of beta-amyloid, as measured by PET
  – Saw improvement in cognition, as measured by CDRsb & MMSE
• Currently recruited for Phase 3

Adapted from Sevigny et al. Nature 2016
Continuum of Alzheimer’s Disease

Continuum of Alzheimer’s Disease

Normal

Alzheimer’s disease

Adapted from Sperling et al. 2011
Collaboration for Alzheimer’s Prevention

Dominantly Inherited Alzheimer Network Trials Unit

ALZHEIMER’S PREVENTION INITIATIVE
TOMMORROW Trial

- Algorithm for enrollment:
  - APOE status
  - TOMM40
- Takeda-Zinfandel alliance
- 5,800 volunteers enrolled
  - End-point is conversion to Mild Cognitive Impairment
- Low dose pioglitazone (Actos)
Alzheimer’s Prevention Initiative

ADAD Trial
- Largest single kindred with familial Alzheimer’s
- In Colombia
- Crenezumab (Genentech)

ApoE4 Trial
- 1,300 adults, age 60-75 with two copies APOE4
- Two drugs:
  - CAD106 – active immunotherapy (Novartis)
  - CNP520 – beta secretase inhibitor (Novartis)
- $10M philanthropic partnership with the Alzheimer’s Association, GHR Foundation & anonymous partner
Alzheimer’s Prevention Initiative
The Generation Study

- Two Copies of APOE4
- 1,300 adults, age 60-75
- Partnering with Novartis – two drugs:
  - CAD106: active immunotherapy
  - Beta secretase inhibitor
- Received NIH $33.2 million
- Alzheimer’s Association, with partners, committed $10M
The Generation Study (CAPI015A2201J) Recruitment Funnel

- General Population within age range ~58-74 years
- Genotyping (e.g. GeneMatch) (~100k-120k estimated)
- Consenting for clinical study
- Eligibility Criteria
- Randomized (~600)

Estimated that 100k-120k GeneMatch completions are needed to randomize approximately 600 patients in the US.

Participants in age range are still active and may not have time to dedicate to a clinical trial.

Targeted population (APOE4 Homozygotes) are limited; Eligible participants can fail on cognitive assessments.
DIAN-TU

- DIAN-TU to investigate up multiple potential drugs in individuals with dominantly inherited Alzheimer's

- $4.2M from ALZ launched DIAN-TU in Dec 2011

- Received $6 million from NIH in fall 2013

- Received an additional $23 million from NIH in fall 2014
Anti-Amyloid in Asymptomatic Alzheimer’s Study (A4)

- Clinically normal, age 65-85
- Positive amyloid PET
- Testing solanezumab (Lilly)
- Diverse population
- Lead Investigators: Dr. Reisa Sperling and Dr. Paul Aisen
- LEARN leverages work of A4
Sites in US, Canada, and Australia

Adapted from Dr. Reisa Sperling
LEARN

• Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) is a natural history of 400 people with low/intermed levels amyloid
• Leveraging the A4 trial with focus on diverse populations
• Funded by the Alzheimer’s Association
• First tau imaging study launched

JT Chien et al. Journal of Alz Dis 2013
Challenges of Rapid and Efficient Recruitment and Screening for A4 Prevention Trial

Provided by Dr. Reisa Sperling
Current Landscape of Clinical Studies

- Today, 150 ongoing trials listed in clinicaltrials.gov in need of 70,000 volunteers (ADEAR)
- Alzheimer’s Association TrialMatch lists 265 ongoing trials actively recruiting
- Will only **grow** in the coming years
- Increasing numbers of trials are seeking asymptomatic volunteers (ADNI3, A4, EMERGE, ENGAGE, EARLY, etc.)
How can we move to primary prevention?

**Primary Prevention**
Delay onset of AD pathology
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**Secondary prevention**
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**Tertiary prevention and treatment**
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Ante-Amyloid Prevention of Alzheimer’s – A3 Moving Toward Primary Prevention!
A new national 18-month clinical trial of exercise to test whether exercise is ‘medicine’ to slow progression of a memory impairment and Alzheimer’s disease

Provided by Dr. Laura Baker
Intervention & Measures

• Intervention: Using a participating YMCA, exercise 45 minutes per session, 4 times per week; supervision twice per week for 12 months, and graduating to independent exercise for the last 6 months of the study (through Month 18)
  
  ➢ Aerobic exercise: 70-80% of maximum heart rate for 30 minutes of each 45 minute session
  ➢ Stretching, Balance, Range of Motion exercise: 30% of maximum heart rate for 45 minutes per session

• Measures of Interest: Cognition, daily function abilities, markers of Alzheimer pathology in the brain obtained through brain imaging, and fluid collection)

• More info: TrialMatch or http://www.adcs.org/Studies/Exert.aspx

Provided by Dr. Laura Baker
FINGER Study: Receipe of Lifestyle Interventions for Cognition

- Gold standard of testing any type of therapy/intervention – Randomized Control Trial (RCT)
- Large, rigorous study of 1,200 individuals
  - Half received intervention and half received standard of care
- First solid evidence that recipe of lifestyle interventions reduces cognitive decline
- Needs to be replicated in more diverse populations
- Results first presented at AAIC 2014

Kivipelto et al., Alzheimer & Dementia 2013
Partially funded by the Alzheimer's Association
10 Ways to LOVE Your Brain
If we **delay** onset of Alzheimer’s by 5 years...

**DELAYED ONSET**
If we develop a treatment by 2025 that delays the onset of Alzheimer’s by just five years, then:

- **Families would save** $87 billion in 2050.
- **In total, America would save** $367 billion in 2050.

**5.7 MILLION**
people expected to develop Alzheimer’s would not in 2050.
In Summary ... 

• Alzheimer’s disease impacts millions of families today, and more tomorrow without a way to stop or slow its progression
• Significant advances in our understanding of the disease, tools for early diagnosis and detection
• Growing landscape of clinical trials, including prevention of individuals at increased risk
• Field is developing next generation of clinical trials – possibility of primary prevention
• There is **HOPE** in research
Questions?