Understanding Alzheimer’s Disease
Research: What does it mean to me?

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Senior Research Scientist

Alzheimer’s Disease
What does current evidence mean to me?

- Vitamin D Tied to Alzheimer’s Risk
- Stanley University found a cure for Alzheimer’s disease
- DNA Methylation Involved in Alzheimer’s Disease
- Skin may help spot Alzheimer’s and Parkinson’s disease

To help answer the question:
- What we know
- What we think we know
- What we need to know
- Why we don’t know
Alzheimer’s Disease
What does current evidence mean to me?

Neuropathologic changes over time

Misfolding & aggregation of Aβ & Tau, followed by plaques & tangles
Oxidative, nitrosative, & inflammatory damage
Cell death

Biological onset
Clinical onset

Epidemiology of Alzheimer’s Disease
Projected US Prevalence: 2010 - 2050

Figure 5. Projected Number of People Age 65 and Older (Total and by Age Group) in the U.S. Population With Alzheimer’s Disease, 2010 to 2050

Alz Facts and Figures 2014

Alzheimer’s Disease
What does current evidence mean to me?

Inside the Brain: Unraveling the mystery of Alzheimer’s Disease

Alzheimer’s Disease
What we know

- Factors that increase risk
  - Age
    - 11% at 65 yrs – 50% at 85 yrs
  - Genetics
    - Early onset (familial AD) – rare genetic mutations
      - 1 parent with mutation = 50% chance of children will get AD
    - Family History (genetics and/or shared environment)
      - APOE
        - e4 allele
          - 25% of population; among individuals with AD = 40%
          - earlier onset compared to those without e4

Alzheimer’s Disease
What we need to know better

- Role of cardiovascular risk factors

  - High blood pressure
  - Stroke
  - Diabetes
  - Plaques and tangles more likely to cause AD in presence of damage to brain vasculature

Alzheimer’s Disease
What we need to know better

Heart and brain connection

- First panel shows a heart with the words “Let’s go somewhere.”
- Second panel shows a brain with the words “I’m the hero.”
- Third panel shows a brain with the words “There’s so much we need to do today. Can you sleep?”
- Fourth panel shows a brain with the words “Yeah, I’m so tired.”

**3/5/2015**
Biomarkers
Who, what, when, how, why

Some of what we know…

...old and new

Biomarkers and AD
Neuroimaging Biomarkers

MRI Volumetric studies of medial temporal region atrophy

PET Studies demonstrate PIB uptake patterns in the neocortex indicating amyloid plaque burden

MRI and PIB-PET comparing individual with AD and neurocognitively normal control

Biomarkers and AD
Multiplex Discovery/Validation – Protein Markers

Protein Biomarkers
- Neuropeptides
- Thioflavin T
- Amyloid plaques
- Tau
- Fibrillar proteins
- Nf-H
- Peptide and phosphatase
- Inflammatory markers
- Cell adhesion markers
- GFAP

Craig Shaples et al., PLoS ONE 2011

©Bryant et al., Arch Neurol 2010
Roadmap for Alzheimer’s Research: Translating knowledge to action

Changing Trajectories

**Preclinical**
- Modifying risk
- Delay onset
- Prevention

**Clinical**
- Preserve function
- Improve quality
- Aging in place

Alzheimer’s Disease
What we think we know

At time T, individuals with same biomarker profile but different clinical outcomes

Preclinical AD
Risk profile for biological onset

<table>
<thead>
<tr>
<th>Proposed staging framework for likelihood of progression to AD</th>
<th>Aβ</th>
<th>Neuronal injury markers</th>
<th>Cognitive change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1: Hypothetical amyloid signature (high Aβ, low cerebrospinal fluid tau)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 2: Neuritic plaques (increased Aβ and tau)</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 3: Neuritic plaques + Mild Cognitive Impairment (MCI)</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>


Jack et al. Lancet Neurol 2013
Translating evidence to prevention
Potential benefit from exercise

Obisesan et al. Int J Alz Dis 2012
Querfurth & LaFerla NEJM 2010

Alzheimer's is a heterogeneous, multifactorial disorder
If not amyloid and tau, then what?
If not just amyloid and tau, then what else?
Pathways to drug discovery
A long, expensive, and risky road

• In 2013, 73 treatments and diagnostics in development for AD
• Over $1.2 billion from laboratory to US patent

www.phrma.org

Pathways to drug discovery
A long, expensive, and risky road

• Timeline of approved treatments for AD

<table>
<thead>
<tr>
<th></th>
<th>Cognex (tinzaprelin)</th>
<th>Aricept (donepezil)</th>
<th>Exelon (rivastigmine)</th>
<th>Razadyne (galantamine)</th>
<th>Namenda (memantine)</th>
</tr>
</thead>
</table>

2002 - 2012
• 413 trials representing 244 unique compounds (Clintrials.gov)
• Failure rate – 99.6%
  • for Cancer, failure rate is 81%
• Fewer drugs entering Phase 1

Urgent need to increase drugs in pipeline

Cummings et al Alz Res & Therapy 2014

Economics of Alzheimer’s Disease:
Research Spending vs Cost of Care (US)

NIH funding on research vs total cost of care, 2013

<table>
<thead>
<tr>
<th></th>
<th>Research</th>
<th>Cost*</th>
<th>Ratio Research : Cost of Care</th>
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<tbody>
<tr>
<td>Alzheimer’s</td>
<td>0.5</td>
<td>214.1</td>
<td>1:428</td>
</tr>
<tr>
<td>Cancer</td>
<td>5.8</td>
<td>125</td>
<td>1:22</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>2.1</td>
<td>109</td>
<td>1:52</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>3.1</td>
<td>16.3</td>
<td>1:5</td>
</tr>
</tbody>
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2025 Goal – prevention and treatment for AD

“...without quadrupling research funding to $2 billion a year, that goal is virtually remote.”
Robert Egge, VP Public Policy, Alz Association

* Sources: Alzheimer’s (AAN Report 2014), Cancer (BMI report, 2013), Heart disease (CDC), HIV (CDC)
Prevention of Alzheimer’s Disease
Compressing morbidity – Prevention by delay

<table>
<thead>
<tr>
<th>2014 Prevalence</th>
<th>Impact of 5% Reduction (number of individuals less)</th>
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<tbody>
<tr>
<td></td>
<td>Annual</td>
</tr>
<tr>
<td>US</td>
<td>5 million</td>
</tr>
<tr>
<td></td>
<td>1.25 million</td>
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<tr>
<td>MN</td>
<td>100,000</td>
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<tr>
<td></td>
<td>25,000</td>
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Prevention of Alzheimer’s Disease
Compressing morbidity – Healthy Lifestyles

Mental activity
Social activity
Physical activity
Dietary habits

We don’t stop playing because we grow old; we grow old because we stop playing.
George Bernard Shaw