To preserve brain health with aging:

- Exercise and physical activity (aerobic)
- Maintain ideal body weight - throughout life
- Mediterranean diet (fruits, vegetables, nuts, beans, fish, olive oil,...)
- More education (quantity and quality)
- Limit alcohol consumption (1-2 drinks/day)
- Mental activities, social connections and activities
- Avoid traumatic brain injury (seat belts, helmets, fall prevention,...)

World population is graying rapidly

Growth of the Elderly Population
1500 to 2050

Source: U.S. Bureau of the Census
Most common causes of neurodegeneration

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Prevalence (US/Western populations, per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>1240</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>320</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>52</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>14</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>14</td>
</tr>
<tr>
<td>Myotonic Dystrophy type 1</td>
<td>5.6</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>4.7</td>
</tr>
<tr>
<td>Spinocerebellar ataxias</td>
<td>3</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>2.8</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Mason et al., Neurology 2014
Prevalence of AD increases with age
Prevalence of AD is higher in minority populations

Risk factors for Alzheimer's disease

- Aging
- Family history/genetics
  - ApoE polymorphism
  - Minority (African-American, Hispanic)
  - Downs syndrome
- Diabetes, midlife obesity, metabolic syndrome
- Traumatic brain injury with loss of consciousness
- Smoking
- Stroke
- Low education, occupational level

Prevalence of dementia increases with age

PREVALENCE OF ALZHEIMER'S DISEASE
(BY DECADES IN U.S.A. FROM 1900-2050)

Federal Gov't Expenditures

People in US with Alzheimer's

Dr. Alzheimer's Disease
Dementia has many causes

- Alzheimer’s disease (AD) (now the #1 cause in US)
- Lewy body dementia (LBD), Parkinson’s disease with dementia (PDD)
- Vascular dementia (multiple strokes)
- Frontotemporal dementia (FTD), Pick’s disease
- Alcoholic dementia
- HIV associated neurocognitive disorder (HAND)
- Chronic traumatic encephalopathy (CTE), dementia pugilistica
- Hypothyroidism
- Vitamin B12 deficiency
- Depression/anxiety (pseudodementia)
- Normal Pressure Hydrocephalus (NPH)
- Creutzfeldt-Jakob disease (CJD), mad cow disease (prion diseases)
- Neurosyphilis (was #1 cause in US before antibiotics)
- Drugs (esp. anticholinergics - impairing memory)
- Factitious

Biomarkers

- Low Aβ42, high tau in cerebrospinal fluid
- Positive amyloid-PET
- Focal hypometabolism on FDG-PET
- Atrophy, white matter changes on MRI

Treatments

- Donepezil
- Rivastigmine
- Galantamine
- Memantine

Braak and Braak stages of AD, Kretzschmar 2009

APP catabolism

APP turnover

Aβ accumulation

Aβ oligomers, fibrils

Amyloid plaques

Neurotoxicity

Neurofibrillary tangles

Mild cognitive impairment

Microglial and astrogliosis

Inflammation

Focal encephalopathy

Neuronal morbidity

Synaptic and neurotransmitter loss

Neuronal mortality

Atrophy, white matter rarefaction

Dementia

Brain atrophy

Death

APP catabolism

Alzheimers.org

Aβ

NH₂

COOH

α-secretase

β-secretase (BACE-1)

β-secretase (presenilin)

AD

CSF Biomarkers

Shaw et al, Annals Neurology 2009

ADNI

CSF biomarkers

Turner, Alzheimer’s Disease, 2012
Amyloid and Tau PET Imaging

Amyloid-β (PiB)

Tau (T807)

Clinically Normal
Clinically Normal
Alzheimer's Dementia

FDG-PET: AD

MCI

Mean cortical SUVRs

75 year old M (left panel) with hypometabolism on FDG-PET (top), atrophy on MRI (middle), and abnormal amyloid PET (bottom) compared to a cognitively normal age-matched individual (right panel)

Jack et al., Neurology 2016

Age and ApoE4 genotype increase amyloid PET

Fleisher et al., Neurobiol Aging 2012

Biomarkers provide early warning of impending MCI and AD

Jack et al., Lancet Neurology 2013

Mean cortical SUVRs of healthy controls, ApoE4+ and ApoE4- individuals.
NIA-AA Research Framework
A/T/N classification of AD

- **A**: Aggregated β-amyloid or associated pathologic state
  - CSF Aβ42 or 42/40 ratio
  - Amyloid PET
- **T**: Aggregated tau (neurofibrillary tangles) or associated tau pathology
  - CSF p-tau
  - Tau PET
- **N**: Neurodegeneration or neuronal injury
  - Anatomic MRI
  - FDG-PET
  - CSF total tau

Jack et al., Neurology 2016

Research Studies

- **Biomarker discovery and validation** (normal, MCI, AD) – longitudinal studies of natural history
  - NIA: Alzheimer’s disease neuroimaging initiative (ADNI)
  - DOD-ADNI (veterans with PTSD, TBI or both)
  - NIA: BIOCARD
  - NIA: LEARN (amyloid PET negative participants)
  - CMS/Alzheimer’s Association: IDEAS

Research Studies

- **Therapeutic trials** (MCI, prodromal AD, AD)
  - Biogen: Aducanumab (anti-amyloid antibody)
  - Roche: Crenezumab (anti-amyloid antibody)
  - Lilly: BACE-I Inhibitor
  - NIA: Intranasal insulin
  - NIA: Nicotine patch
  - ADDF: Nilotinib (a tyrosine kinase inhibitor)
  - Anti-tau antibody

Research Studies

- **Prevention studies** (normal older individuals at risk)
  - NIA/Lilly: Solanezumab (A4) (anti-amyloid antibody)
  - Novartis: Alzheimer Prevention Initiative for ApoE4/4 individuals, BACE-I or active vaccine (GENERATION 1)
  - Novartis: Alzheimer Prevention Initiative for ApoE4/x individuals, BACE-I (GENERATION 2)
  - NIA/Janssen: BACE-I (EARLY)

Amyloid plaque reduction with aducanumab

Aducanumab effect (change from baseline) on CDR-SB and MMSE


National Registries - for education and to learn about research opportunities

Alzheimer’s Prevention Registry (55-75 years old), GeneMatch
• endalznow.org
Brain Health Registry
• brainhealthregistry.org
Healthy Brains
• healthybrains.org
Alzheimer Prevention Trials (50+ years old)
• aptwebstudy.org

Trends in clinical AD research

• Biomarkers for diagnosis, prognosis, drug efficacy...
  – PET imaging – amyloid, tau
  – Cerebrospinal fluid proteins – Abeta, tau, others?
  – Blood proteins?
  – Other -omics?
• Shift to the left – to MCI, preclinical/prodromal AD
  – MCI trials
  – Prevention trials of normal individuals at risk
• Precision medicine
  – Treatment/prevention tailored do individual genotype

Summary

• We are witnessing a growing epidemic of dementia - most of which is AD
• The amyloid hypothesis is alive and well, and does not exclude other important and essential pathologic processes
• The genetics of familial AD provides the strongest evidence for the amyloid hypothesis
• Despite recent high-profile failures, many active trials inhibit Ab/amyloid generation or promote Ab/amyloid clearance
• Other AD trials target other essential pathologic processes, with the probable result of a therapeutic cocktail (as now)

Summary

• Current (FDA-approved) therapies for AD provide consistent yet modest, temporary, and palliative benefits
• We are searching for disease-modifying treatments to halt dementia progression, or prevent dementia onset
• We are in need of validated biomarkers for: screening, diagnosis, prognosis, evidence of efficacy, reduction of clinical trial size, length, and cost
• Treatments are increasingly target individuals with MCI and healthy high-risk individuals – prevention!
• Future treatments will be tailored to ApoE genotype (pharmacogenomics, personalized medicine, precision medicine)

Patient Referral?

• Second opinion for diagnosis, clinical care
• Research information visit to discuss research opportunities
• May be only 1 visit (biomarker discovery) or monthly visits up to 3-5 years (treatment trials)
• No cost - research participants compensated
• 50-85, healthy or diagnosed with MCI or mild AD eligible
• Must have a study partner to accompany participant on some visits
• Chance of placebo 50% or less, but usually open-label extension (offered active drug after double-blind period)
• MRI required (no pacemakers)
• Spinal fluid collection optional (no anticoagulants)