

# ALZHEIMER'S DISEASE FOR THE INTERNIST

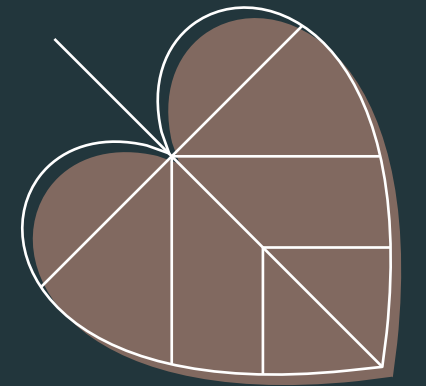
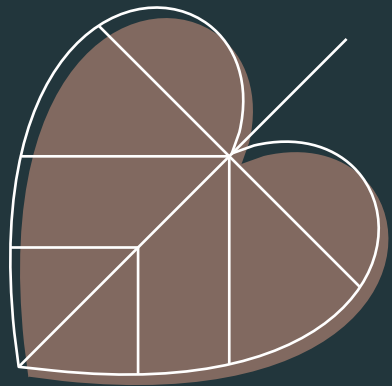
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Diagnostic and therapeutic updates for the internist.

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NO CONFLICT OF INTEREST

# AGENDA

- Facts and figures
- Primary care physician role in a changing field
- New diagnostics and therapeutics
- Updates on social resources

# ALZHEIMER'S DISEASE FACTS AND FIGURES 2024



Nearly **7 million Americans** are living with Alzheimer's. By 2050, this number is projected to rise to nearly 13 million.



Alzheimer's disease was the **fifth-leading cause of death** among people age 65 and older in 2021.



Health and long-term care costs for people living with dementia are projected to reach **\$360 billion** in 2024 and nearly \$1 trillion in 2050.

# PRIMARY CARE OPPORTUNITIES

- First point of contact
- Longitudinal trusting relationship with patients and families
  - A person that knows the patient well mentions a concern
  - Annual visit questionnaire – patient answers yes to concern about memory
  - No-shows and confusion about appointments and medication
  - Nonadherence in older patients may be a sign of cognitive difficulty
- Medicare covers separate visit to assess cognitive function/develop care plan
- Barriers:
  - Time and training needed to correctly administer/interpret cognitive assessments.
  - Low confidence disclosing diagnosis and post-diagnostic care for many
  - Lack of geriatricians, lack of specialists.
  - Lack of care navigators.



# COGNITION IN PRIMARY CARE

A program to facilitate detection of cognitive impairment and improve care for people with dementia.



# DEFINITIONS: FUNCTION IS KEY

## Subjective cognitive impairment: an at-risk state

- Patient reports cognitive changes, they are FULLY independent
- No clear change on formal neuropsychological testing

## Mild cognitive impairment (MCI)

- Patient reports cognitive changes which are objectively demonstrated.
- Patient is fully independent

## Dementia

- Subjective and objective cognitive decline
- Not caused by active substance abuse or other active medical conditions
- Activities of daily living are affected:

**Mild**                      Only IADLS affected (Instrumental Activities of Daily Living)

**Moderate** IADLS affected, starting to need reminders and prompting for ADLS (Activities of Daily Living)

**Severe**                      Requires full assistance with IADLS and ADLS

# UNDERDIAGNOSIS

- Often mistaken for “normal aging” by patients/families and providers.
  - About 8% of older Americans with MCI receive a diagnosis.
  - About 50% of patients Alzheimer’s disease receive a diagnosis in moderate-advanced stages
  - Many patients with Alzheimer’s never receive a diagnosis
  - Diagnosis is more often delayed in Black and Hispanic seniors
- Potential consequences of late or missed diagnosis (still limited information):
  - Missed opportunities for prevention (brain health, substance use, mood, hearing loss)
  - Delayed access to treatments and clinical trials for interested groups
  - Delayed or impossible planning
  - Higher cost of care, potential financial and physical harm (e.g. driving)
  - Negative impact on caregivers' and patients' mental health

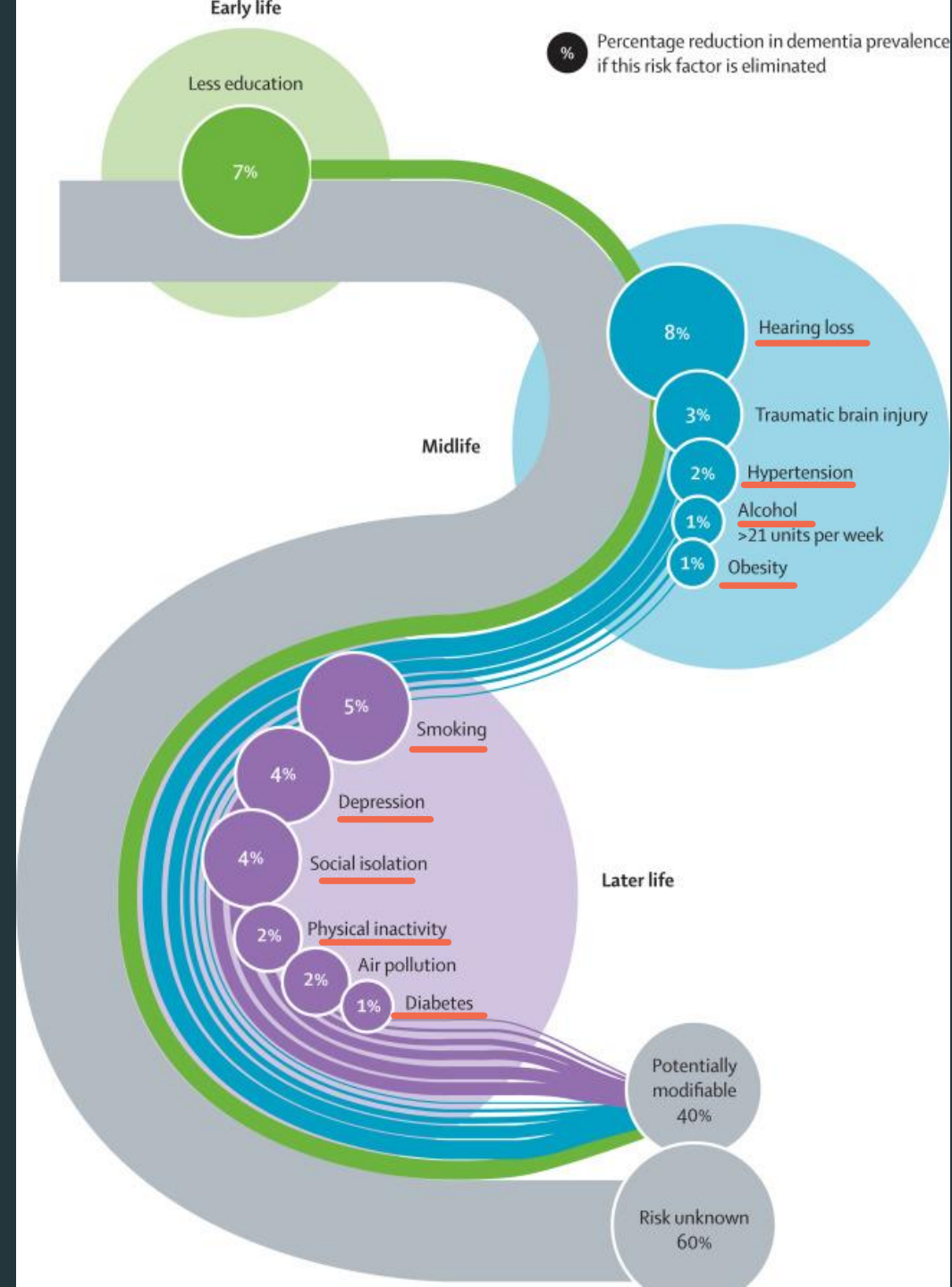


# PREVENTION

Up to 40% of all cases of dementia may be preventable

Factors often brought up at annual visit

- Hearing loss and smoking have the biggest impact
- Cardiovascular risk factor management
- Physical inactivity, social isolation, depression
- Address mood
- Address sleep
- Address polypharmacy (include OTC)



# UPDATES IN THE FIELD





# NEW DIAGNOSTIC CRITERIA FOR AD

- Towards a biological definition of diagnosis.
- Not for widespread clinical use yet
- Likely will be adopted in several years
- Spurred by approval anti-amyloid treatments
- The preclinical period is also now part of the disease.

**TABLE 6** Clinical staging for individuals on the Alzheimer's disease continuum.

## Stage 0 Asymptomatic, deterministic gene<sup>a</sup>

No evidence of clinical change. Biomarkers in normal range.

## Stage 1 Asymptomatic, biomarker evidence only

Performance within expected range on objective cognitive tests.  
No evidence of recent cognitive decline or new symptoms.

## Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function

Normal performance within expected range on objective cognitive tests.  
Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years, and has been persistent for at least 6 months.  
May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range.  
May be documented through subjective report of cognitive decline.  
May be documented with recent-onset change in mood, anxiety, motivation not explained by life events.  
Remains fully independent with no or minimal functional impact on activities of daily living (ADLs)

## Stage 3 Cognitive impairment with early functional impact

Performance in the impaired/abnormal range on objective cognitive tests.  
Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments.  
Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete—either self-reported or corroborated by an observer).

## Stage 4 Dementia with mild functional impairment

Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.

## Stage 5 Dementia with moderate functional impairment

Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.

## Stage 6 Dementia with severe functional impairment

Progressive cognitive and functional impairment, and complete dependence for basic ADLs.



# ALZHEIMER'S BIOMARKERS

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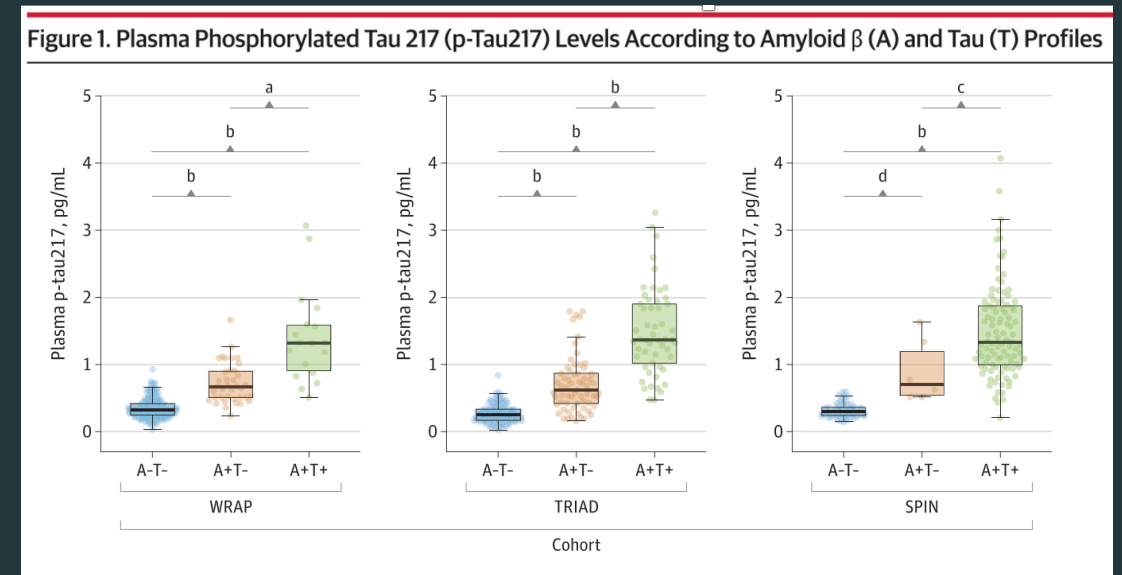
# UPDATES ON BLOOD BIOMARKERS

## ○ pTAU 217

- Found to be a robust testing option with scalability potential
- Helps early detection and longitudinal follow up:
  - correlates with extracellular amyloid accumulation
  - Correlates with atrophy and cognitive decline.
- Spurious elevations in patients with CKD.
- 20% intermediate results need to be followed with CSF or PET

## ○ Abeta42/40

- less robust,
- not scalable,
- false positives in patients who take neprilysin inhibitors





A blurred laboratory setting with a syringe and a vial in the foreground. The syringe is on the left, and the vial is on the right. The text 'ANTIAMYLOID ANTIBODIES' is overlaid in the center. A horizontal line is positioned below the text.

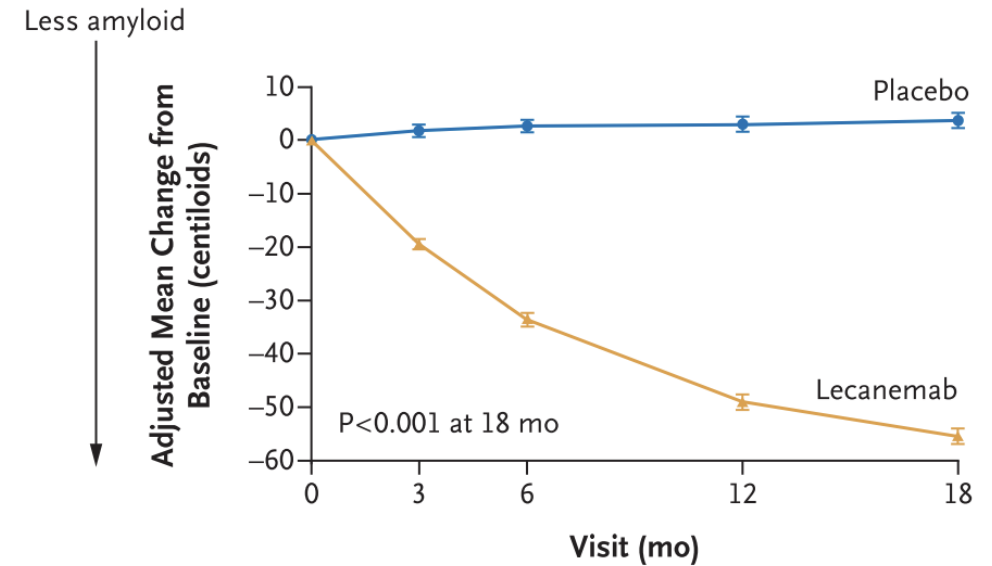
# ANTIAMYLOID ANTIBODIES

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# LECANEMAB

- Targets soluble amyloid beta protofibrils.
- 10mg/kg IV every two weeks for 1.5 years. Possible maintenance after
- Participants 50-90 years with MCI-AD or mild AD
- Amyloid positivity by PET or CSF A beta 42
- Primary endpoint: change from baseline to 18 months in CDR-SB Score: Adjusted mean difference -0.45 (-0.67 -0.23),  $p < 0.001$
- Brain bleeding (ARIA- H) in 14% (vs. 7.7 % placebo), plus 5% CSS
- Brain swelling (ARIA -E) in 12.6% (vs. 1.7% placebo)
- Worse side effects in ApoE  $\epsilon$ 4 carriers

## B Amyloid Burden on PET

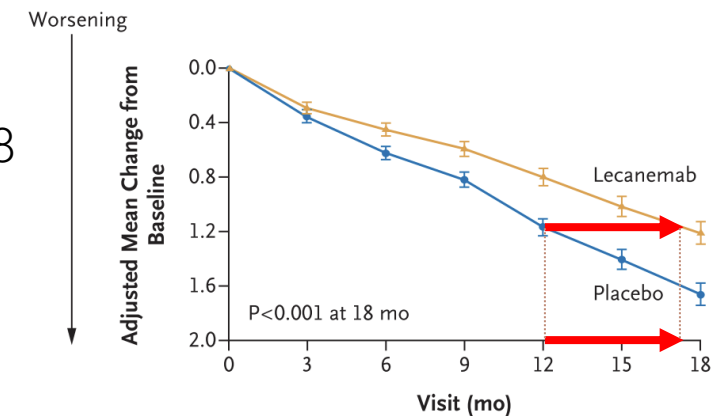


### No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

## A CDR-SB Score

Score range: 1-18  
Difference - 0.45

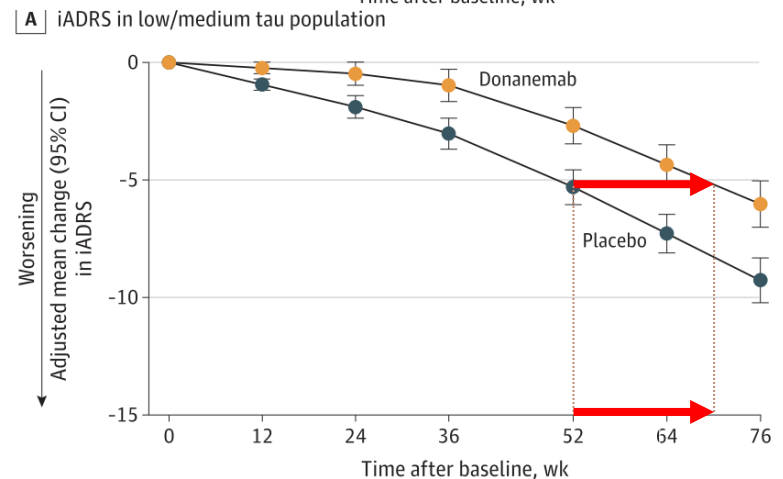
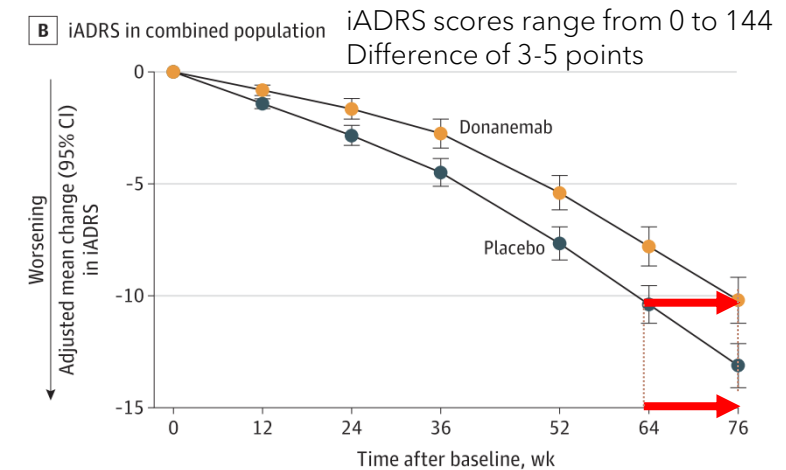
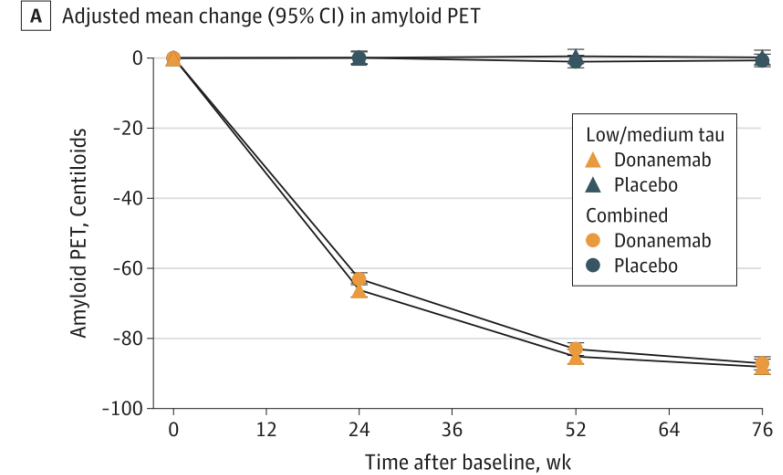


### No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

# DONANEMAB

- Targets insoluble Amyloid beta in plaques
- Study done in adults aged 60-85
  - Combined population
  - Low/medium Tau population (measured by qualitative tau PET assessments)
- MMSE 20-28, positive PET and positive TAU
- 700 mg x3 and 1400 mg thereafter every month, for 1.5 years
- Amyloid PET levels checked at 6 mo and 1 year: switch to placebo if:
  - Amyloid < 11 centiloids at any point
  - Amyloid 11-24 centiloids on two consecutive PET scans.
- Primary end point iADRS scores (0-144, lower is worse). Difference of 3-5 pts
- Brain bleeding (ARIA- H) in 19.7% (vs. 7.4 % placebo)
- Brain swelling (ARIA -E) in 24% (vs. 1.9% placebo)
- Worse side effects in ApoE ε4 carriers





# IMPLEMENTATION

## Exclusion criteria

- Presence of hemorrhages (> 4 microhemorrhages, or one hemorrhage > 10mm)
- Presence of cortical superficial siderosis.
- Multiple lacunar strokes or severe cerebrovascular disease
- Patients on anticoagulation

Carriers of APO E e4 are at heightened risk of bleeding and swelling

## Radiology learning curve

## Costs

- Repeat MRIs
- Amyloid PET scans
- Genetic testing
- Traveling

Community learning curve - real world is different than clinical trials!

- EHR update to include potential contraindication to thrombolysis
- Real-life challenges of follow up
- No Tau PET available

Only a minority of patients will qualify (approximately 6-8%)

Modest benefits - it's ok to not choose this.

Despite heavy advertisement it is NOT life-changing.



# MEDICARE GUIDE PROGRAM GUIDING AN IMPROVED DEMENTIA EXPERIENCE

For Medicare part B participants not enrolled in PACE and not in long-term living facilities

- 24/7 access to support line
- Caregiver training, education and support services.
- Objective is to age in place as possible.
- Trying to address drivers of poor-quality dementia care:
  - Standardized approach to dementia care
  - Providing alternative payment methodology to participants
  - Addressing unpaid caregiver needs
  - Respite services
  - Screening for health-related social needs

# LOCAL AND NATIONAL RESOURCES

Area agency on Aging (AAA): <https://eldercare.acl.gov/>

- 1-800-677-1116
- Every county in the United States has an AAA.
- Names of local AAAs may vary.
- AAAs help adults, families, and professionals facing aging and disability issues get the information and support they need to make informed decisions.

Alzheimer's association: <https://www.alz.org/help-support>

- 24/7 National Helpline 800.272.3900.
- Staffed by social workers with translators available.
- Provides urgent advice.
- Makes referrals to local chapters and programs.
- Free service available to all.

Powerful tools for caregivers

<https://www.powerfultoolsforcaregivers.org/>

Caregivers who take these free classes demonstrate:

- Increased self-care behaviors.
- Reduced guilt, anger and depression.
- Increased confidence and coping skills.
- Increased use of community resources

Dementia Roadmap <https://www.dshs.wa.gov/altsa/dementia-action-collaborative>

A 28-page guide available in English or Spanish for families and caregivers that explains:

- What to do when a person experiences changes in memory and thinking.
- What to expect and steps to take if someone in your family has been diagnosed with Alzheimer's or other dementia.

*\*This guide is specific to Washington State; similar guides for a national audience are in development.*



## TAKE HOME POINTS

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- Role of prevention: 40% of dementia possibly preventable
- Opportunities for longitudinal follow up
- Near future implementation of new biomarkers for AD
- Limited benefit and potential risk of anti-amyloid RX
- Teaching caregivers to navigate care longitudinally.

... It starts in primary care