

Preparing for the appropriate and accessible use of Alzheimer's prevention therapies

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Disclosures

Alzheimer's Prevention Initiative (API) and other uncompensated prevention research and advisory roles

Working with Lilly on Trailblazer-ALZ 3, Trailrunner-ALZ 3 and a potential primary prevention trial. NIH-supported API ADAD Colombia Trial Program (drugs supplied by Lilly and Roche). Scientific advisor, Lilly and Roche.

ALZpath co-founder, advisor and shareholder

P-tau217 capture antibody, licensed for plasma p-tau217 assays on several diagnostics and research immunoassay platforms.

Inventor, 2005 patent (assigned to Banner Health, will not be deployed)

Using biomarker endpoints in cognitively unimpaired people at genetic and/or biomarker risk to accelerate the evaluation of AD prevention therapies.

Compensated scientific advisor roles

Alzheon, Beren Therapeutics, Cognition Therapeutics, Denali Therapeutics, Enigma Diagnostics, New Amsterdam Therapeutics, Retromer Therapeutics, Vaxxinity.

Terminology

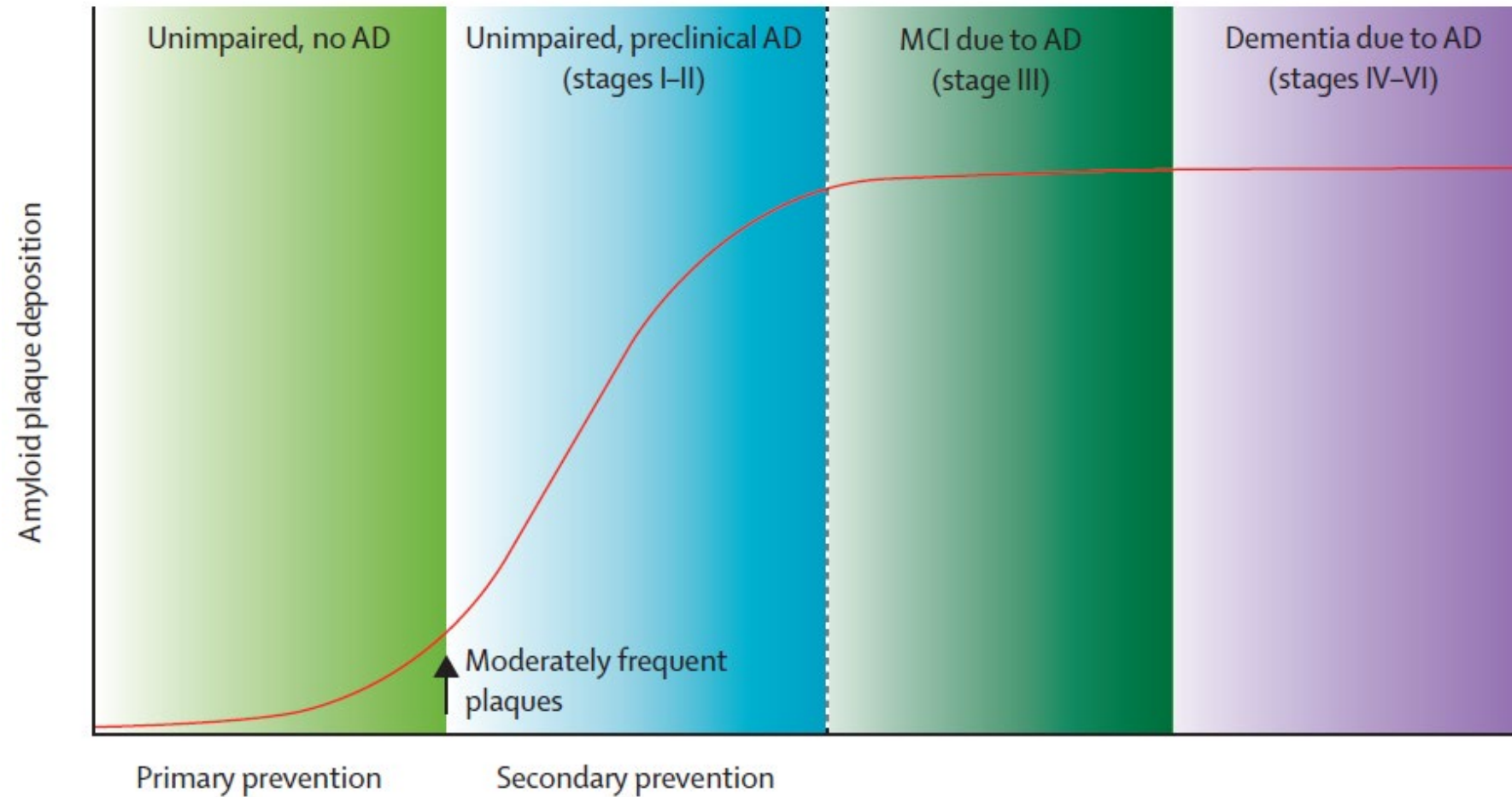
- **Secondary Alzheimer's prevention therapies**

- Treatments that are started in cognitively unimpaired people who are biomarker-positive for at least moderately frequent neuritic A β plaques and aim to avert further biological, cognitive and clinical manifestations of AD

- **Primary Alzheimer's prevention therapies**

- Treatments that are started in cognitively unimpaired people who are biomarker-negative for at least moderately frequent neuritic A β plaques and aim to avert the biological, cognitive and clinical manifestations of AD

Alzheimer's stages and their relationship to primary and secondary prevention



A realistic chance to find and support access to...

The first of two effective secondary Alzheimer's prevention therapies in 2027.

Next-generation secondary therapies soon after that.

The first effective primary Alzheimer's prevention therapy in about five years.

Other prevention therapies to follow.

Some reasons why

- Amyloid plaque-clearing antibody treatments that work in mildly impaired patients
- Ongoing prevention trials with clinically meaningful endpoints
- Possible surrogate biomarker opportunities if the first trials are successful
- Cognitive health-promoting lifestyle interventions
- Emerging blood tests and other potentially scalable tools
- Other treatments to follow



amyloid peptides



amyloid plaques



tau tangles

Now is the time to prepare for prevention, even if the timeline to prevention isn't guaranteed

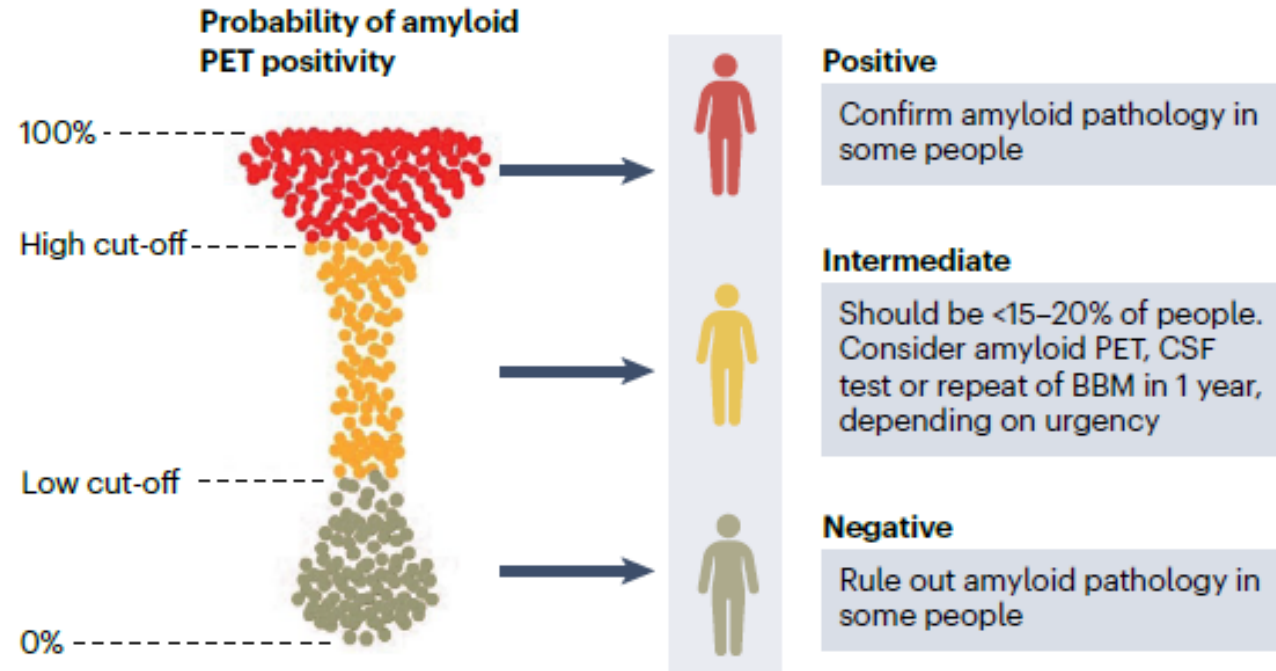
Prepare for treatments that substantially prevent the clinical onset of AD and the scalable strategies needed to inform their appropriate, widely accessible and cost-effective use

Proceed with determination, urgency, and care, identify and address critical issues in parallel, and appreciate the stakes of not doing so along the way

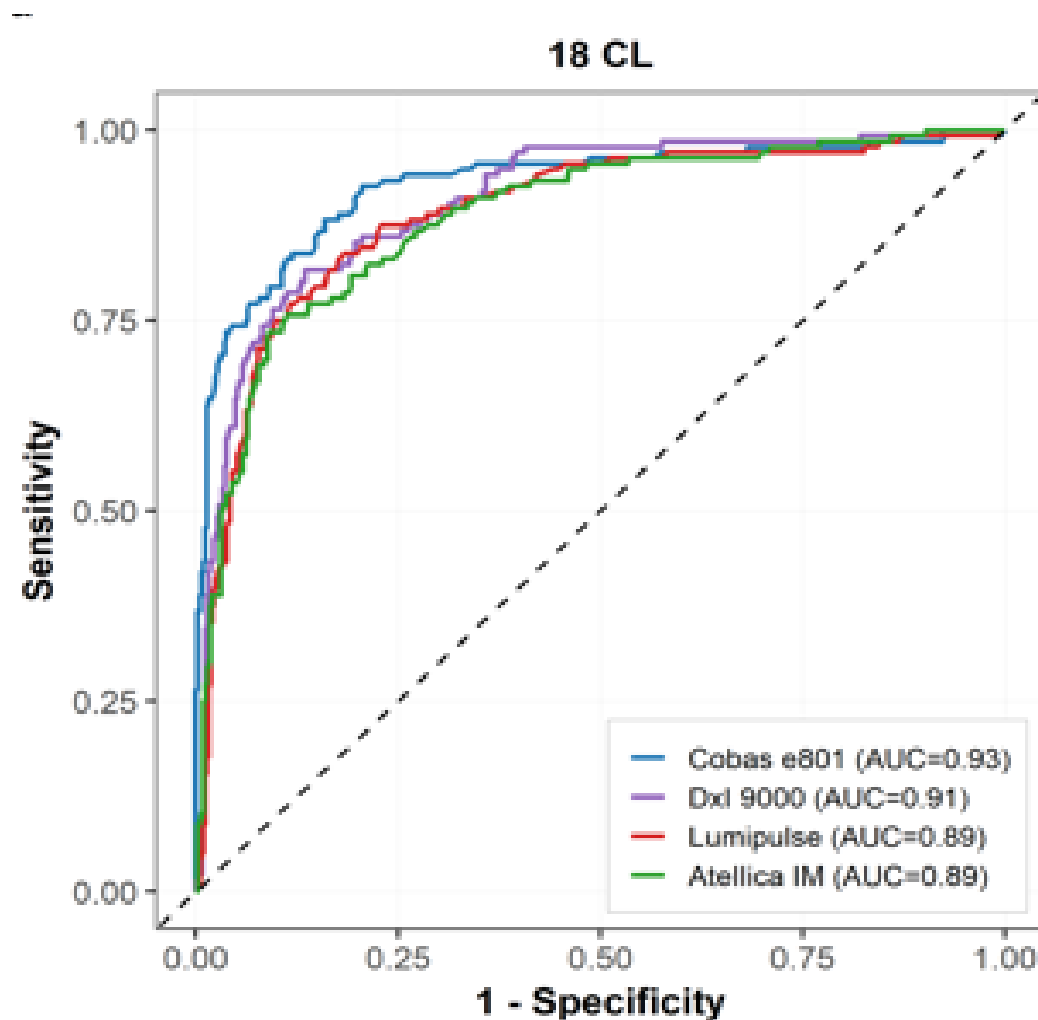
Alzheimer's blood tests

e.g., Palmqvist et al, *JAMA* 2020 (p-Tau217); Horie et al, *Nature Med* 2025 (eMTBR-Tau243)

Plasma p-Tau217

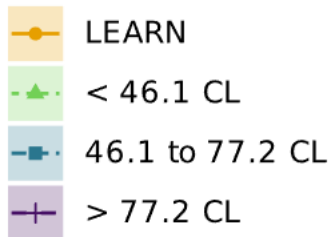
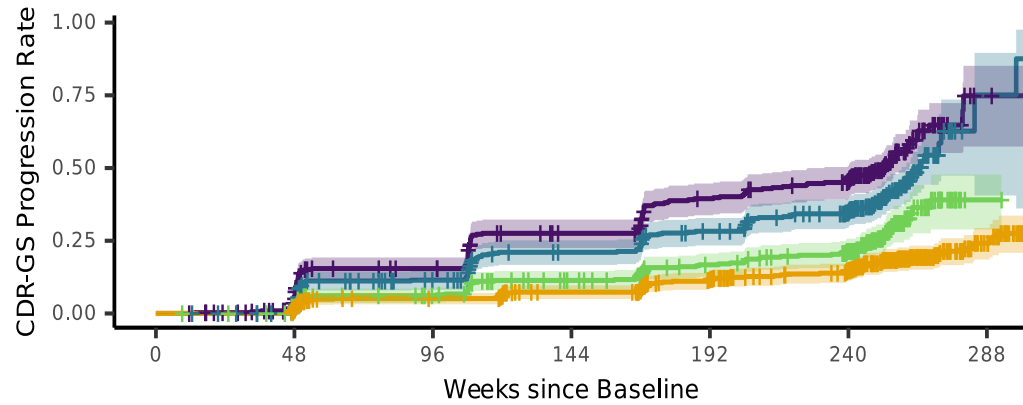


Plasma p-Tau217: Diagnostic accuracy compared to an amyloid PET standard-of-truth in 590 cognitively unimpaired research participants



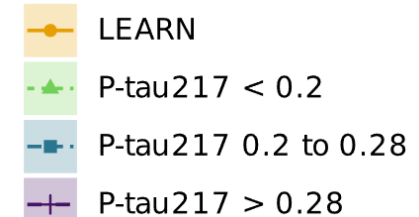
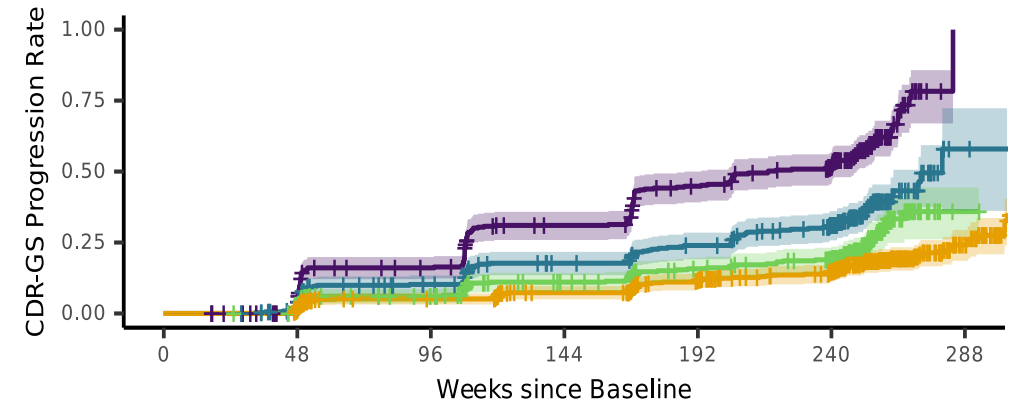
Risk of progression to MCI or dementia in persons with biomarker evidence of preclinical AD

Baseline Amyloid PET



>50% of people with the highest AD biomarker levels progressed to MCI or dementia within 5 years
(a smaller percentage in other studies)

Baseline Plasma pTau217



Sperling et al, *JPAD* 2024; see also Jack et al, *Lancet Neurol* 2025, Moscoso et al, *JAMA* 2025, Buckley et al, *JAMA* 2026, and Denking et al, *CTAD Abstract* 2026 (in press)

Find and support approval of effective secondary and primary prevention therapies

1. Complete the ongoing Trailblazer ALZ-3 and AHEAD secondary prevention trials of the amyloid plaque-clearing antibody therapies donanemab and lecanemab in cognitively unimpaired persons with biomarker evidence of at least moderately frequent amyloid plaques using clinically meaningful endpoints.
2. Demonstrate that the treatments' amyloid plaque-clearing biomarker effects are at least reasonably likely to be associated with a clinical benefit.
3. Use these data and the totality of evidence to qualify a treatment's amyloid plaque-clearing biomarker effect as a surrogate endpoint and hasten the evaluation and approval of next-generation plaque-clearing antibody therapies (e.g., remternetug, trontinemab) in ongoing secondary prevention trials.
4. Also use these data and the totality of evidence to qualify a treatment's amyloid plaque-averting biomarker effects as a surrogate endpoint to hasten the evaluation and approval of infrequently administered amyloid plaque-clearing treatments in cognitively unimpaired older adults without biomarker evidence of at least moderately frequent amyloid plaques in the first primary prevention trials; and extend this approach to other potentially amyloid plaque-averting drug therapies.
5. Introduce large-scale post-marketing studies, including brief annual digital or AI cognitive assessments, to further inform the short- and long-term benefits and risks of secondary and primary prevention therapies in real-world patients.

Further inform the role of Alzheimer's blood tests in cognitively unimpaired people

1. Further inform the value and appropriate use of plasma p-Tau217 as a preventative screening blood test to:
 - a. Confirm the presence, absence and severity of at least moderately frequent neuritic plaques; and clarify the use of orthogonal PET, CSF, or blood biomarkers, a person's clinical stage, age, APOE or other genetic test results, and follow-up blood tests in those with intermediate test results.
 - b. Calculate a person's estimated cumulative annual risk over at 1 to 10 or more years based on a person's p-Tau217 and APOE test results, age, sex and educational level; further inform decisions about the use of effective preventative drug therapies when they become available; and support adherence to health-promoting lifestyle interventions in those with a positive blood test.
 - c. Support their appropriate use, accessibility and coverage by the time the first effective secondary prevention therapies become available.
2. Clarify the extent to which it can be used to monitor the complete clearance of amyloid plaques and inform the use of less frequent maintenance treatment doses.
3. Establish the scalable digital and agentic AI tools needed to inform and counsel patients about their AD biomarker and APOE test results; and support access to these tools by the time they see their results in their patient portal.
4. Further develop blood tests, like eMTBR-tau243, to further inform a person's pathophysiological diagnosis, disease stage, comorbid neuropathological diseases, prognosis, differential response to treatment.
5. Educate, inform and offer protections for unimpaired people with Alzheimer's biomarker changes.

Set the stage for highly accessible preventative screening and treatment programs

1. Educate, inform and incorporate feedback from patients, primary, secondary and tertiary healthcare providers about the value of preventative screening and treatment programs; help them understand what it means to be cognitively unimpaired with Alzheimer's biomarker projections; and prepare to provide relevant employment, insurance, and stigmatization protections.
2. Establish the standardized diagnostic criteria that will be embraced by patients and providers from different clinical settings and countries; incorporate relevant prognostic and treatment considerations in the discussion; and engage primary care providers in these efforts.
3. Set the stage for primary, secondary and tertiary care providers to ask those patients who are over age 55 or younger but at risk for early-onset AD about memory and thinking problems and have preventative screening blood tests after the first secondary prevention therapies become available.
4. Establish the scalable health care delivery program needed to screen, diagnosis, and offer established medical and non-medical treatment options for cognitively unimpaired older adults. Establish the specialized workforce teams needed to do the heavy lifting for primary care providers; offer scalable blood tests, digital and agentic AI cognitive assessment, risk disclosure and memory navigator tools; and refer a minority of these individuals to sub-specialists when needed.

Consider the program's cost-effectiveness, cost-containment strategies and number needed to treat to avert one adverse outcome

Final Thoughts

Acknowledgements

My BAI, BSHRI, and API colleagues

Our other academic, industry, NIH, FDA and EMA colleagues

Our NIH, industry, state and philanthropic supporters

Our valued research participants