A path to preventing cognitive impairment due to Alzheimer's disease: initiatives beginning in the USA

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Antibody therapies can remove amyloid plaques from the brain and slow cognitive decline in people with Alzheimer's disease who are mildly impaired. These drugs are now being evaluated in participants who are cognitively unimpaired but positive for a biomarker of Alzheimer's disease for their safety, tolerability, disease-modifying and cognitive preserving effects, and ability to avert the onset of cognitive impairment. If these studies are successful, and the drugs get regulatory approval, they could accelerate the evaluation and approval of related Alzheimer's disease-modifying treatments in people who are unimpaired with or without a biomarker of the disease. Preclinical Alzheimer's disease therapies that modify the underlying disease in people who are unimpaired with a biomarker of Alzheimer's disease and primary prevention therapies that avert the onset of amyloid plaques in those with a negative test have the potential to substantially prevent ensuing biological and clinical manifestations of Alzheimer's disease. In this Policy View, we assess the challenges and opportunities that trials of these drug treatments will bring, and consider the blood tests, cognitive assessments, and post-marketing strategies needed to enable the approval, affordability, health-care insurance coverage, and equitable use. Our recommendations are intended for consideration in the USA, and relevant refinement in other countries.

Introduction

Alzheimer's disease is the most common cause of cognitive decline, affecting around 20% of people older than 65 years,[1] and imposes a substantial and growing burden on patients, families, and health-care systems. Unpaid informal care of family members or friends who progress to dementia amounts to more than US$250 billion annually in the USA, a figure expected to rise as the population ages.[1] Safe and effective interventions that prevent cognitive impairment due to Alzheimer's disease are therefore urgently needed.

Alzheimer's disease is defined biologically by the deposition of amyloid plaques and tau tangles in the brain.[2] The course of these pathological changes over about 25 years corresponds roughly to stages of cognitively unimpaired (preclinical), mild cognitive impairment, and disabling cognitive impairment (dementia). Trials have shown that plaque-clearing antibody therapies can slow

Panel 1: Aims and focus of this Policy View

- Explain the realistic prospect of regulatory approval for amyloid plaque-clearing antibody therapies as the first disease-modifying treatment in people who are cognitively unimpaired but have biomarker evidence of Alzheimer's disease
- Describe a potential path to accelerate the development and regulatory approval of next-generation drugs that are at least reasonably likely to avert cognitive impairment, starting with those that can clear amyloid plaques in people who are cognitively unimpaired but have a positive biomarker test, followed by those that prevent plaque deposition in individuals who have a negative test.
- Outline the evidence needed to show clinical value, cost-effectiveness, and affordability of prevention strategies, and to enable equitable access
- Recommend steps to implement the appropriate use of scalable screening tools
- Recommend steps to facilitate the development of primary prevention therapies.
- Recommend steps for the appropriate use and accessibility of secondary and primary prevention therapies

Our Policy View focuses on amyloid plaque-removing antibody therapies over other prevention therapies because they offer the earliest opportunity for Alzheimer's disease prevention. As such, they could set the stage for the accelerated evaluation, approval, and accessibility of other kinds of preventative therapies. Although many of the concepts that we discuss might apply to other pharmacological (eg, vaccines, small molecules, and gene therapies) and non-pharmacological (eg, including lifestyle and dietary interventions) therapies, those approaches are being covered in other forums. Our Policy View places an emphasis on recommendations that could be implemented in the USA, but which could be considered and revised as needed to address different perspectives and circumstances in other countries.

cognitive decline by approximately 30% in people with mild cognitive impairment or mild dementia due to Alzheimer's disease,[3,4] reinforcing the role of amyloid in the early development and potential prevention of the disease.[5] Although national regulatory agencies have differed in their assessment of these therapies for the early clinical stages of Alzheimer's disease, their real-world benefit might be similar to that of drugs used for the treatment of breast or lung cancer, multiple sclerosis, and rheumatoid arthritis,[6] and that experience has begun to provide further information about the potential benefits and risks of these drugs.[7] Amyloid plaque removal might yield greater benefits and fewer side-effects in cognitively unimpaired people, when amyloid plaques in brain tissue and cerebral blood vessels and downstream tau tangle and neurodegenerative changes are less extensive.[8,9] This hypothesis is being tested in pivotal trials (NCT04468659 and NCT05026866), with the first results expected by 2027.

Success is not guaranteed, but stakeholders must prepare the research enterprise, and get health-care systems ready, for the potential approval of the first effective Alzheimer's disease prevention therapies and others likely to follow. Early preparation will be essential to inform decisions on regulatory approval, clinical implementation, cost-effectiveness, affordability, and equitable access.[5,10] Although many of the principles and challenges that we describe are globally relevant, our

Panel 2: Terminology

- Alzheimer's disease: a progressive sequence of biological changes in the brain, including deposition of amyloid plaques, tau tangles, and eventual neuronal death.[2] Diagnosis is based on PET, CSF, or blood biomarkers (eg, plasma p-tau217) , that are indicators of at least moderately frequent neuritic amyloid β (Aβ) plaques.[2] Alzheimer's disease has several clinical stages, including cognitively unimpaired (preclinical stages I and II), mild cognitive impairment (stage III), and mild, moderate, or severe dementia (stages IV–VI).[2] Efforts are underway to find biomarkers that further inform a person's tau tangle, neurodegenerative, and neuroinflammatory stages and the presence, absence, and severity of comorbid neuropathologies (eg, Lewy bodies, TDP-43, cerebral amyloid angiopathy, and over vascular brain injuries), such that they further inform a person's prognosis and beneficial or adverse treatment responses.[2,11]
- Preclinical or unimpaired Alzheimer's disease: the stage of Alzheimer's disease that is applied to individuals who are cognitively unimpaired but have at least moderately frequent neuritic plaques.[2,12] Individuals with elevated amyloid deposition on PET scans or plasma p-tau217 might have a faster progression to mild cognitive impairment or dementia. In one study, those in the highest biomarker tertiles had a 50% risk of progression within 5 years.[13] In another, 15–20% of individuals with preclinical Alzheimer's disease had amyloid PET or CSF (eg, MTBR-tau243) biomarker evidence of tau tangle pathology and increased risk of cognitive decline.[14] Some experts debate whether to use the term preclinical Alzheimer's disease versus at risk of Alzheimer's disease when referring to people who are cognitively unimpaired with biomarker evidence of the disease.[15] These different viewpoints might be resolved as effective non-pharmacological and pharmacological prevention therapies emerge, and data from population studies provide information about the risk of mild cognitive impairment or dementia in these individuals, giving the diagnosis prognostic relevance. Multidomain lifestyle interventions can improve cognitive performance in people with or without the *APOE ε4* gene (the major genetic risk factor for Alzheimer's disease),[16] including those with or without biomarker evidence of Alzheimer's disease.
- Primary Alzheimer's disease prevention therapies: treatments used in people who are cognitively unimpaired without biomarker evidence of preclinical Alzheimer's disease, aiming to prevent the onset of moderately frequent amyloid plaques and subsequent biological, cognitive, and other clinical manifestations. Antibody and vaccine therapies could remove early plaques as they form, whereas other treatments could prevent the production or aggregation of Aβ42 peptides or act through alternative mechanisms.[17]
- Secondary Alzheimer's disease prevention therapies: treatments used in cognitively unimpaired individuals with biomarker evidence of amyloid plaques in the brain, aiming to delay or prevent further biological, cognitive, and clinical progression, including onset of mild cognitive impairment or dementia. The term follows the WHO definition of secondary prevention: treating asymptomatic individuals with biological evidence of disease to prevent its clinical manifestation.[17] Secondary prevention therapies could avert clinical manifestations of Alzheimer's disease by either treating or compensating for the underlying disease.
- Preclinical or unimpaired Alzheimer's disease therapies: secondary prevention therapies that work by treating (ie, removing, modifying, or slowing progression of) the underlying pathological changes as reflected by their biomarker effects. Unless otherwise stated, the secondary prevention trials noted in this Policy View refer to the evaluation of disease-modifying drug therapies in people who are cognitively unimpaired but are positive for an Alzheimer's disease biomarker test.

Relationships between amyloid plaque deposition, the cognitively unimpaired (preclinical), mild cognitive impairment, and dementia stages of Alzheimer's disease, and the use of primary and secondary prevention therapies (including those secondary prevention therapies that treat the underlying pathophysiological disease) are illustrated in the figure.

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See **Online** for appendix

Policy View focuses on the US context, where recent US Food and Drug Administration (FDA) guidance, Centers for Medicare & Medicaid Services and other health-care insurance policies, and health-care systems create unique opportunities and challenges for Alzheimer's disease prevention.

We summarise the aims of this Policy View in panel 1.

Historical foundations and US policy drivers for preventing cognitive impairment due to Alzheimer's disease

Our Policy View focuses on drugs for primary and secondary prevention (definitions for the prevention terminology that we use are presented in panel 2; figure). There is growing evidence that lifestyle changes, diet, and other interventions can delay the onset of mild cognitive impairment and dementia. Physical activity, cognitive engagement, heart-healthy diets, and managing hypertension, high cholesterol levels, and diabetes can improve cognition and reduce the risk of mild cognitive impairment and dementia.[16,19–23] However, biomarker studies are needed to determine the biological effects of these benefits (ie, whether they are related to Alzheimer's disease pathways or other mechanisms) and how those benefits compare between people with and without preclinical Alzheimer's disease.

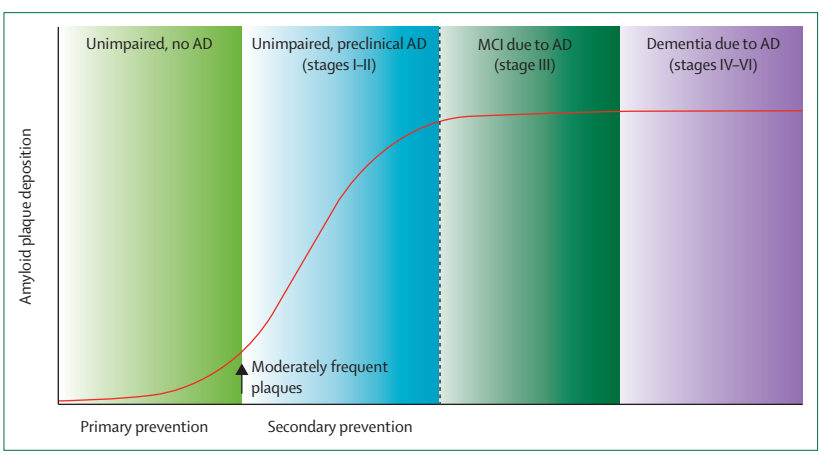


Figure: **Prevention of cognitive impairment and the stages of Alzheimer's disease**
AD=Alzheimer's disease. Schematic representation of neuritic amyloid-β plaque deposition in the brain during the cognitively unimpaired, mildly impaired, and severely impaired (dementia) stages of Alzheimer's disease, including the stages of amyloid plaque deposition at which primary and secondary prevention therapies could be initiated to sustain cognitive function or avert its onset. The red line illustrates the trajectory of amyloid plaque deposition, which can be measured by PET, CSF, or blood tests. The downstream tau tangle, neurodegenerative, and other pathophysiological changes are not shown. In people who are cognitively unimpaired, preclinical Alzheimer's disease is defined by the presence of at least moderately frequent neuritic plaques. The two preclinical stages are distinguished by the presence or absence of subtle cognitive changes that do not meet criteria for mild cognitive impairment but can be detected using sensitive neuropsychological or longitudinal assessments. Primary prevention therapies are started before the deposition of moderately frequent plaques to avert progression to Alzheimer's disease. Secondary prevention therapies (eg, preclinical Alzheimer's disease treatments) are started after the deposition of moderately frequent plaques to sustain cognitive function and avert progression to the mild cognitive impairment and dementia stages of Alzheimer's disease by treating or compensating for the underlying disease. Preclinical Alzheimer's disease treatments are secondary prevention therapies that target the underlying disease (eg, these drugs can remove amyloid plaques or avert downstream pathophysiological changes).
Figure adapted from Jack Jr, 2024,[2] and Jack Jr, 2010,[18] with permission from Elsevier.

The first eight randomised, placebo-controlled trials designed to specifically interfere with Alzheimer's disease mechanisms did not meet their primary endpoints, but they informed the design of other studies, launching a new era in Alzheimer's disease prevention research. We list these trials and summarise the major features of these pioneering studies in table 1, and provide additional historical information in the appendix (p 6).

Eleven ongoing or planned Alzheimer's disease prevention trials are summarised in table 2; other studies are in earlier planning stages. These trials have created a realistic opportunity to identify effective secondary and primary prevention therapies in the next few years.[10]

Regulatory and related considerations

Although the success of ongoing and planned prevention trials is not certain, there is a realistic chance for regulatory approval of the first effective secondary prevention therapy reasonably soon, followed by next-generation secondary prevention therapies soon after, then the first effective primary prevention therapy soon after that, and finally additional therapies with potentially better safety, efficacy, or accessibility.[10] The hypothetical scenario that we envision for the quickest way towards regulatory approval of secondary and primary prevention therapies, surrogate markers, and other considerations are provided in the appendix (p 7).

Secondary prevention

The FDA has offered recommendations for the development of secondary prevention therapies.[24] Approval of these drugs can be based on their clinical effects, such as a meaningful slowing of cognitive decline or delayed onset of cognitive impairment, measured through suitable endpoints (ie, the Clinical Dementia Rating [CDR] scale,[25] or time-to-event analyses, measuring the progression from cognitively unimpaired to mild cognitive impairment or dementia). Recognising the long time, usually 4–5 years, needed to evaluate prevention therapies using such clinical endpoints, the FDA would also consider a "persuasive effect on cognition as measured by sensitive neuropsychological tests."[24] We suggest that sufficiently delaying the onset of mild cognitive impairment or dementia (eg, measured by use of a CDR Global Score or adjudicated mild cognitive impairment or dementia diagnosis), reducing the number of participants who become impaired, or slowing decline in a composite cognitive test score that is sensitive to cognitive worsening in the preclinical stages of Alzheimer's disease, would be clinically meaningful. "If the first biomarker effects of preclinical amyloid plaque-clearing biomarker treatments for Alzheimer's disease are associated with a clinically meaningful benefit, it might be possible to qualify the amyloid plaque biomarker as a surrogate endpoint. A surrogate biomarker could also accelerate the evaluation and approval of these drugs based on their ability to substantially prevent the onset of moderately frequent

	Phase	Participants	Drug	Primary outcome	Results	Lessons learned
API ADAD (NCT01998841)	2	N=252 CU *PSEN1 E280A* mutation carriers, 30–60 years	Crenezumab	Dual endpoints: change in API ADAD CC or FCSRT	No difference between drug and placebo; no plaque reduction; possible amyloid oligomer engagement	Prevention trials, and data and sample sharing commitments are feasible from scientific, operational, regulatory, and industry perspectives
DIAN-TU (NCT04623242)	2/3	N=194 CDR 0–1, autosomal dominant mutation carriers, 18–80 years	Gantenerumab; solanezumab	Change in DIAN-MCE	No difference between drug and placebo; partial plaque reduction	Gap between amyloid reduction and clinical benefit in asymptomatic trials could require longer trials for prevention studies
API Generation Study 1 (NCT02565511)	2/3	N=480 CU, *APOE4* HM, 60–75 years	CAD106; umibecestat	Dual endpoints: time to MCI or dementia, or change in APCC	Terminated early, mild cognitive worsening on umibecestat (reversible); less plaque accumulation on CAD106	How and when to disclose information about a person's genetic and biomarker risk
API Generation Study 2 (NCT03131453)	2/3	N=1145 CU, *APOE4* HM and Aβ+ HT, 60–75 years	Umibecest	Dual endpoints: time to MCI dementia or change in APCC	Terminated early, cognitive worsening on umibecestat (reversible)	Recruitment value of prevention trial registries
TOMMORROW (NCT01931566)	3	N=3494 CU, *TOMM40* and *APOE*, 65–83 years	Pioglitazone	Time to MCI or dementia	Interim futility, terminated early	Feasibility of screening a very large number of participants
A4 (NCT02008357)	3	N=1169 CU, Aβ+, 65–85 years	Solanezumab	Change in PACC	No difference between drug and placebo; no plaque reduction	Higher levels of baseline amyloid or p-tau217 are associated with more rapid decline
EARLY (NCT02569398)	2/3	N=557 CU, Aβ+, 60–85 years	Atabecestat	Change in PACC	Terminated early, cognitive worsening	Important to monitor cognitive function frequently to detect any adverse effects
SKYLINE (NCT05256134)	3	N=25 CU, Aβ+, 60–80 years	Gantenerumab	Change in PACC	Gantenerumab programme terminated early	NA

Aβ+=amyloid positive. APCC=Alzheimer's Prevention Initiative Composite Cognitive test score. CC=cognitive composite. CU=cognitively unimpaired. CDR=clinical dementia rating. DIAN-MCE=Dominantly Inherited Alzheimer Network-multivariate cognitive endpoint. HM=homozygotes. HT=heterozygotes. MCI=mild cognitive impairment. NA=not applicable. PACC=Preclinical Alzheimer Cognitive Composite score.

Table 1: **Completed prevention trials that targeted Alzheimer's disease pathology**

plaques in primary prevention trials of at-risk people who are unimpaired but have a negative test

Primary prevention

Regulatory agencies have not yet offered formal recommendations about the selection criteria of participants and the endpoints in the design of trials that the regulators would consider for evaluating the approval of primary Alzheimer's disease prevention therapies. Issues that deserve further consideration include (1) ages at which to intervene based on a person's genetic risk (ie, the presence of one or two *APOE* ε4 alleles, mutations that cause autosomal dominant Alzheimer's disease or Down syndrome), (2) whether an amyloid PET scan or blood biomarker of amyloid plaque deposition could be used to accelerate the evaluation and approval of primary prevention therapies, (3) the number of participants needed to treat to avert one adverse outcome, since many people who would be eligible to receive a primary prevention therapy will not benefit in their lifetime, (4) the number of participants needed to confirm safety, and (5) the development of post-marketing strategies to further clarify the clinical benefit of a primary prevention drug in real-world populations. Regulatory approval would depend on evidence of safety, number needed to treat, and the totality of evidence obtained by use of a supporting biomarker as a surrogate endpoint.

Accelerated versus traditional approval

The ongoing secondary Alzheimer's disease prevention trials of lecanemab and donanemab (NCT04468659 and NCT05026866, respectively) use composite cognitive test scores, continuous clinical ratings, or time to clinical event, rather than amyloid plaque reduction measured by amyloid PET scans, as their primary clinical endpoints. We support this approach for two major reasons. First, evidence on clinical outcomes will help regulators, Centers for Medicare & Medicaid Services, and other health-care insurers, clinicians, and patients evaluate the value and use of these treatments. Second, if plaque clearance—as measured by amyloid PET—is clearly associated with clinical benefit, amyloid PET scans could become a surrogate endpoint in secondary prevention trials for the evaluation of second-generation treatments that remove or avert the re-accumulation of amyloid plaques and, in primary prevention trials, for treatments that avert the onset of amyloid deposition.

Lessons learnt from other therapeutic areas about the evaluation and deployment of prevention therapies are discussed in the appendix (p 8).

The advantages of blood tests

High concentrations of phospho-tau217 (p-tau217) in plasma are an indicator of amyloid plaques in the brain.[26] This biomarker has begun to facilitate the screening of participants and the evaluation of treatments in Alzheimer's disease prevention trials,[27] and could be an accessible and cost-effective test to inform people who are cognitively unimpaired about their prognosis when prevention therapies become available.

The first of several promising plasma p-tau217 or p-tau217/Aβ42 assays under development was cleared for

	Phase	Participants	Drug	Primary outcome	Potential readout
Trailblazer-ALZ 3 (NCT05026866)	3	N=2196 CU, p-tau217+,60–80 years	Donanemab	Time to CDR-GS progression	1–2 years*
AHEAD–A45 (NCT04468659)	3	N approximately 1000 CU, Aβ+ (>40 CL), 55–80 years	Lecanemab	Change in PACC5	2028–31
AHEAD–A3 (NCT04468659)	3	N approximately 400 CU, Aβ+ (20–40 CL), 55–80 years	Lecanemab	Decrease in Aβ PET	2028–31
Trailrunner-ALZ 3 (NCT06653153)	3	N approximately 1400 CU and MCI, p-tau217+, 55–80 years	Remternetug	Time to CDR-GS progression	2030
DIAN-TU Tau NexGen (NCT05269394)	2/3	N=197 autosomal dominant mutation carriers, EYO –10 to +10	E2814 (tau antibody), lecanemab	Change in DIAN-MCE	2028
DIAN-TU Primary Prevention (NCT06647498)	2/3	N approximately 280 autosomal dominant mutation carriers, EYO –25 to –11	Remternetug	Change in Aβ PET	2034
GABRIELLA (NCT06402838)	2	N=256 CU and MCI, Aβ+, 60–85 years	RO7269162 (nivegacetor; GSM)	Safety, change in Aβ PET	2026
Retain (NCT06544616)	2	N=498 CU, Aβ+, tau PET+, 55–75 years	JNJ-64042056 (active tau immunotherapy)	Change in PACC5	2031
API ADAD Program (NCT06996730)	2/3	N approximately 240 CU and mildly impaired *PSEN1 E280A* mutation carriers, 30–60 years	Donanemab, RO7269162 (nivegacetor), combination	Decrease in Aβ PET in those >11 CL, avert increase in those <11 CL	Initiation: 2026
PrevenTRON	3	CU, Aβ+	Trontinemab	TBD	TBD
Primary Prevention Trial	TBD	CU, Aβ–, age and *APOE4* carriers TBD	TBD	Progression to Aβ+	Initiation: TBD

Aβ+=amyloid positive. CDR-GS=Clinical Dementia Rating–Global Score. CU=cognitively unimpaired. DIAN-MCE=Dominantly Inherited Alzheimer Network-multivariate cognitive endpoint. EYO=estimated years to symptom onset. GSM=gamma secretase modulator. MCI=mild cognitive impairment. NA=not applicable. TBD=to be determined. PACC5=Preclinical Alzheimer Cognitive Composite score 5. *Although the completion date was projected for 2027, the study will readout when the target number of progression events are accrued.

Table 2: **Ongoing and planned prevention trials targeting Alzheimer's disease pathology**

use by the FDA only for clinical use in people for suspected mild cognitive impairment or Alzheimer's disease.[28] These tests show high diagnostic accuracy for amyloid brain deposition in people who are cognitively unimpaired.[29–32] Although the tests can have over 90% sensitivity and specificity, their positive predictive value (the chance that a positive test actually reflects amyloid deposition in the brain) is limited by the low prevalence of amyloid plaques in cognitively unimpaired individuals, particularly at young age.

Efforts are underway to refine these blood tests to be sufficient as a confirmatory diagnostic test that could reduce the need for a confirmatory amyloid PET scan or CSF assay in indeterminant cases (ie, those with an intermediate concentration that has insufficient positive or negative predictive value; appendix p 9). Our recommendation would be to use follow-up plasma p-tau217 tests in people who are cognitively unimpaired with an indeterminate blood test over time to clarify their biomarker status and eligibility for a preclinical Alzheimer's disease treatment.

For more on the **21st Century Cures Act** see https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

Blood tests are not yet recommended for the diagnosis of preclinical Alzheimer's disease in people who are cognitively unimpaired.[33] This recommendation could change when pharmacological and non-pharmacological prevention treatments are available and analyses of blood samples from large population-based studies clarify the extent to which a positive or negative blood test can inform individuals about their subsequent risk of mild cognitive impairment or dementia. In the meantime, researchers continue to work on developing plasma assays to further inform an individual's prognosis and response to treatment. Scalable cognitive assessments, including digital and artificial intelligence tools, are urgently needed to discriminate the presence and severity of cognitive impairment. These tools could be widely deployed in primary care settings when they become reliable and easy to use (appendix p 10).

Accessible individual risk disclosure

With the expected rise in demand for Alzheimer's disease biomarker and genetic testing, and a shortage of trained memory care providers, novel approaches are needed to communicate results without overburdening the health-care workforce. US regulations, such as the 21st Century Cures Act, which requires health-care providers to give patients immediate electronic access to test results through patient portals without previous provider review, add urgency to this challenge. Efforts are underway to adapt existing AI-powered, self-directed platforms that integrate with electronic medical records, to help individuals understand and contextualise their genetic and biomarker test results before and after clinician consultations, while expanding access to disclosure resources (NCT06459583).[34]

Alzheimer's disease biomarker results (eg, plasma p-tau217 concentrations and amyloid PET scans), *APOE* ε4 genotype, and autosomal dominant Alzheimer's disease mutation status can affect treatment eligibility, response, and risk of adverse events. Prevention treatments will require biomarker and genetic testing, and appropriate disclosure of findings to inform their use. These digital platforms should assist health-care providers in meeting rising demand, and offer tailored education based on the type of information disclosed. The disclosure content will need to include educational information before testing or returning the results (often referred to as pre-education) to address potential implications for family members, health-care partners, insurance, finances, emotional impact, stigma, and how test results relate to prognosis, treatment decisions, and other potential risks and benefits.[35,36]

Ethical and other considerations

Biomarker and genetic tests that can identify people at risk of cognitive impairment and that might be used to determine access to prevention therapies raise ethical, legal, and other social challenges. These challenges include risk of social stigma, employment and insurance discrimination, limited access to long-term health care and support services, and questions about consent and autonomy. Guidance is needed on the ethical, legal, and social provisions required to support the responsible adoption of new diagnostics and therapies.[37] Additional topics that can raise concerns include direct-to-consumer blood and genetic tests, and

***Panel 3*: Priority recommendations of our Policy View**

1 To further develop and deploy the screening tests needed to inform a person about their Alzheimer's disease biomarker and genetic test results, their prognosis and clinical stage, and appropriate options for prevention therapy:
   - Use blood samples from population-based longitudinal studies to estimate the risk of mild cognitive impairment and dementia due to Alzheimer's disease over time based on the person's age, plasma p-tau217, and *APOE* test results, alone or in conjunction with other relevant risk factors.
   - Use this information to further inform decisions about pharmacological and lifestyle treatment options in people who are unimpaired with or without biomarker evidence of Alzheimer's disease.
   - In people who are unimpaired with indeterminate Alzheimer's disease blood test results, find accessible ways to further inform the biological diagnosis, probabilistic risk of cognitive impairment, and preventative treatment options by monitoring blood tests over time.
   - Further develop and deploy digital, artificial intelligence (AI), and other scalable cognitive assessment tools to evaluate the presence, absence, or severity of cognitive impairment.

2 To accelerate the development of preclinical Alzheimer's disease treatments and primary prevention therapies:
   - Confirm that the amyloid plaque-clearing biomarker effects of donanemab and lecanemab are associated with a clinically meaningful benefit in ongoing secondary prevention trials.
   - If those trials and the totality of evidence linking biomarker evidence of plaque reduction to a clinical benefit in people who are unimpaired but have biomarker evidence of Alzheimer's disease, consider using those biomarkers as surrogate endpoints to accelerate the evaluation and potential approval of next-generation treatments that are shown to safely clear amyloid plaques in other secondary prevention trials, as well as those treatments that are shown to safely avert the onset of moderately frequent amyloid plaques in primary prevention trials.
   - Begin to design and conduct primary prevention trials that will define a path to traditional regulatory approval. Considerations should include the evidence needed to conclude that the surrogate biomarker endpoints are at least reasonably likely to predict a clinically meaningful outcome in primary prevention trials, the criteria for identifying people who are at risk but without biomarker evidence of Alzheimer's disease, and the sample sizes needed to support safety and efficacy determinations.

3 To further inform and support equitable access to secondary and primary prevention therapies:
   - Establish post-marketing strategies to further inform the benefits, risks, generalisability, and appropriate use of preclinical Alzheimer's disease treatments and primary prevention therapies in as many people as possible, including those in different real-world settings and under-represented groups. Capitalise on highly scalable cognitive assessments, blood tests, and results to support that effort.
   - Develop cheaper, safer, and more easily administered drugs, less frequent dosing strategies, more accessible biomarker, genetic, and cognitive screening tests, and treatment delivery strategies that can spare demands on primary care providers.
   - Continue to evaluate the cost-effectiveness, total cost, and accessibility of secondary and primary prevention therapies, with special attention to underserved populations and low-resource settings.
   - Develop a policy framework that involves all stakeholders from different regions, incorporates different perspectives, requirements, and policies, and optimises the appropriate use, accessibility, and global impact of effective prevention programmes.

the required infrastructure to ensure access to treatment and other services for patients and care givers. This guidance must account for the disparities in health-care access that are tied to socioeconomic and geographical factors.[38]

Cost-effectiveness, affordability, and accessibility

In addition to being safe and effective (ie, either avoiding or delaying the onset of cognitive symptoms), to ensure broad access, secondary and primary Alzheimer's disease prevention programmes must offer good value and remain affordable for all citizens, health-care insurers, and health-care providers.[39] These goals can be achieved by reducing screening and diagnostic costs through low-cost blood tests and automated cognitive assessments that can identify the individuals who are at high risk of cognitive impairment,[13] and by minimising treatment costs through optimised treatment schedules and affordable drug prices. As in other areas of prevention, Alzheimer's disease prevention programmes are unlikely to reduce the net cost of health care. Although the specific cost of preventing one case of cognitive impairment might be modest, the overall cost of averting one case of clinically manifest Alzheimer's disease is high because of the need to screen a large number of people to find one treatment candidate, and the number needed to treat to avert one event (appendix p 11).

However, value is assessed not on the ability of a prevention programme to reduce the direct cost of medical and formal social care, but rather on its cost-effectiveness—that is, the health benefits achieved per dollar spent, relative to other available options. This cost–benefit ratio is typically measured as the incremental net cost (treatment and administration costs minus avoided medical and social care costs) per quality-adjusted life-year (QALY) gained. In the USA, a QALY is typically valued between $100 000 and $150 000, although this measure is controversial as it could undervalue benefits in older people or in people with severe health conditions.[40,41]

Search strategy and selection criteria

On Feb 11–12, 2025, we convened experts from academia, industry, US and European regulatory agencies, advocacy organisations, and health-care institutions to explore the opportunities and challenges of Alzheimer's disease prevention in a symposium in Arlington, VA, USA (appendix pp 2–4 for agenda and presenters). Recommendations of our Policy View result from the discussions held at this symposium. References for this Policy View were identified through PubMed and Embase searches of English-language articles published from Jan 1, 2010, to Aug 31, 2025, using combinations of the MeSH and free-text terms "Alzheimer's," "preclinical Alzheimer's," "prevention," "biomarker," "surrogate biomarker, "blood-based biomarkers," amyloid," "regulatory policy," and "cost-effectiveness" (appendix p 5).

Preliminary results suggest that a preclinical Alzheimer's disease-modifying treatment programme, and even a primary prevention programme that targets *APOE* ε*4* carriers, would be cost-effective.[42,43] Affordability or budget impact of such programmes could be a concern, given that about 25% of the overall population are *APOE* ε*4* carriers, but costs can be mitigated by risk-based targeting, responsible drug pricing, and by the fact that, historically, novel screening programmes usually have a slow uptake.[44]

Equitable screening and prevention programmes

Given the large number of adults older than 55 years (and younger people with risk factors) who might need access to screening and preventive treatment, and the limited availability of specialists and time-constrained primary care providers, new strategies to set up these interventions are essential. These strategies can include scalable blood tests; user-friendly, potentially self-administered cognitive assessments; and tools to implement biomarker and genetic test disclosure when effective therapies become available. Dedicated programmes for screening, treatment, and monitoring will be needed to avoid overburdening health-care providers. Policy makers, systems engineers, and health-care professionals (especially those in primary care) should begin developing these strategies now, with the involvement of patients and family advocates.

Post-marketing surveillance studies

Even if not required by regulators for traditional approval, post-marketing real-world evidence strategies are crucial to inform Centers for Medicare & Medicaid Services and other health-care insurers, policy makers, health-care providers, and citizens about the benefits of secondary and primary Alzheimer's disease prevention therapies, including in individuals from disadvantaged backgrounds and with comorbidities and concomitant medical treatments, and over long follow-ups. It will be important to leverage electronic health records and data from automated cognitive assessments and plasma biomarkers to compare outcomes across different treatment durations and therapeutic agents.

Conclusions and future directions

We offer a number of recommendations to guide the regulatory approval, clinical and economic value assessment, and accessibility of sufficiently safe and effective secondary and primary Alzheimer's disease prevention therapies, as well as the screening tools needed to support their use, starting now (panel 3).

There is now an opportunity to advance the approval of effective Alzheimer's disease prevention therapies. A shared sense of urgency, commitment, and collaboration among a wide range of stakeholders is required to implement access to treatments that are sufficiently safe and effective, and substantially avert the burden of Alzheimer's disease in the next few years.

Contributors
EMR chaired the Alzheimer's Prevention Initiative symposium and coordinated the effort to prepare this manuscript. JLC moderated the symposium. RCA, JBL, and JLC contributed to the design and structure of the Policy View and writing of major sections. PSA, NA, AA, HHF, JDG, JH, CRJ, SCJ, JK, MS-C, GDR, CR, RAS, HZ, and SM contributed to prevention trials, biomarkers, regulatory, and health-system perspectives. MW, KAW-B, GR, and GV contributed to the policy, advocacy, and dissemination framework. All authors contributed to revising the manuscript critically and approved the final version for submission. EMR had final responsibility for the decision to submit the paper.

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