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PERSPECTIVE

How can secondary dementia prevention trials of Alzheimer's disease be clinically meaningful?

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Abstract

After clinical trial failures in symptomatic Alzheimer's disease (AD), our field has moved to earlier intervention in cognitively normal individuals with biomarker evidence of AD. This offers potential for dementia prevention, but mainly low and variable rates of progression to AD dementia reduce the usefulness of trials' data in decision making by potential prescribers. With results from several Phase 3 secondary prevention studies anticipated within the next few years and the Food and Drug Administration's recent endorsement of amyloid beta as a surrogate outcome biomarker for AD clinical trials, it is time to question the clinical significance of changes in biomarkers, adequacy of current trial durations, and criteria for treatment success if cognitively unimpaired patients and their doctors are to meaningfully evaluate the potential value of new agents. We argue for a change of direction toward trial designs that can unambiguously inform clinical decision making about dementia risk and progression.

1 | INTRODUCTION

Alzheimer's disease (AD) has long preclinical and prodromal phases lasting up to three decades prior to dementia onset.[1,2] In recent years, while disease-modifying therapies (DMTs) have failed to demonstrate substantial evidence of clinical efficacy in symptomatic AD, research in biomarker development has facilitated the definition of a preclinical AD phase, offering the potential for secondary dementia prevention.[3,4] As a consequence of treatment failures, the field has shifted toward conducting DMT trials in cognitively normal, AD biomarker-positive individuals, in the hope that this affords a better chance of preventing or delaying disease progression and subsequent dementia onset. Despite current restricted US coverage of anti-amyloid beta (Aβ) monoclonal antibodies for prodromal AD and mild AD dementia,[5] the US Food and Drug Administration's (FDA) recent endorsement of Aβ as a surrogate endpoint for AD clinical trials[6] means that future availability, at least selectively, of Aβ-lowering DMTs for AD biomarker-positive individuals is now likely. With seven ongoing Phase 3 prevention trials in preclinical AD due to report within the next few years, should we expect clinicians and health services to feel prepared to treat cognitively unimpaired individuals with AD, based on their data? In this article, we question whether current AD secondary prevention trial outcomes can be meaningfully interpreted in the context of our current understanding of the natural history of AD and its practical treatment and suggest alternative approaches for the field to consider (summarized in Table 1).

2 | BACKGROUND

Preclinical AD is proposed to be the early stage of a continuum, in which individuals have in vivo biomarker evidence of AD neuropathology (i.e., abnormal Aβ and pathological tau), but are essentially cognitively normal.[7,8] These cognitively unimpaired individuals, who correspond to Stages 1 and 2 in the FDA 2018 draft guidance,[9] include those who carry a rare autosomal dominant monogenic mutation causative of AD and will all convert to dementia (comprising <1% of AD dementia cases[10]), and older individuals who do not have fully

penetrant genetic mutations and have a substantially lower risk of developing dementia.These individuals, particularly the latter group, would not be recognized as having AD within clinical services for people with dementia or the public imagination. The argument that only earlier intervention is likely to successfully modify disease course is used to explain the failure of DMTs given "too late" in symptomatic AD and drives the pursuit of secondary prevention strategies.

Underlying the potential success of this approach is the degree to which the process under target in a defined preclinical population is both causally necessary and sufficient for the later emergence of the clinical syndrome. Yet, after three decades of research on the pathophysiology of the natural history of AD, we still lack conclusive evidence that these conditions apply to any process, and there is residual uncertainty about the specificity of AD biomarker positivity and their predictive accuracy for the subsequent development of AD dementia.[11] An earlier definition of preclinical AD, which required only Aβ positivity[4], was updated in 2018 to also require cerebrospinal fluid (CSF) phosphorylated tau (p-tau) or positron emission tomography (PET) tau positivity[8]. Of seven ongoing Phase 3 AD secondary prevention trials lasting an average of 3 years (Table 2), three have recruited Aβ-positive participants and one will select Aβ and tau-positive (A+T+) individuals based on p-tau levels. Apart from monogenic AD, most cognitively unimpaired people with only amyloidosis will not progress to dementia in their lifetime. For example, a 65-year-old female from this group has 10-year and lifetime risks of developing AD dementia of 2.5% and 29.3%, respectively.[12] Additional detection of p-tau levels representing early pathological tau changes is associated with a higher rate of clinical progression[13,14] but may not substantially increase dementia risk over 5-8 years in Aβ-positive cognitively unimpaired individuals[15,16]. Further challenges for preclinical AD trials are that differences in cognitive reserve[17] and age-related comorbidities[18] also influence the detection of cognitive impairment and subsequent expression of dementia in the presence of abnormal biomarkers, and trial outcomes informing on risk of progression to prodromal AD (mild cognitive impairment [MCI]) are limited by the observation that only a minority of these individuals progress to AD dementia within 5 years.[15,19] For preclinical AD individuals who do develop AD dementia, can we expect any treatment-related differences in trial outcomes, measured after an average of 3 years,[20] to be sufficiently informative, when such clinical progression can take up to three decades to manifest?

2.1 | Is Aβ the right target?

The prevailing hypothesis that early Aβ accumulation triggers downstream neurodegenerative processes resulting in AD clinical symptoms[21] was launched by the discovery of dominantly inherited mutations that increase Aβ aggregation (in amyloid precursor protein [APP],[22] presenilin [*PSEN*] 1 and 2[23] genes), responsible for familial AD. The consequent and dominant "amyloid hypothesis" has driven drug development for the past three decades, culminating in the FDA's controversial accelerated approval of aducanumab, based on

RESEARCH IN CONTEXT

1. **Systematic review**: Relevant Phase 3 clinical trials in Alzheimer's disease were identified by searches of ClinicalTrials.gov up to March 2023 using additional search terms 'preclinical', 'prevent', 'asymptomatic', and 'risk'. Studies were either active (and not yet recruiting, recruiting, enrolling by invitation, or not recruiting) or inactive (suspended, terminated, completed, withdrawn or unknown status). The TOMMORROW trial did not appear in the search results and was additionally included.
2. **Interpretation**: The questionable clinical significance of biomarker changes and adequacy of current trial durations limit the ability of patients and their doctors to meaningfully evaluate the potential value of new agents for the secondary prevention of dementia. We summarize challenges for preclinical AD clinical trial design, their impact on trial outcome interpretation, and alternative approaches for the Field to consider.
3. **Future directions**: Preclinical AD trial designs that can unambiguously inform clinical decision-making about dementia risk and progression are needed. Meanwhile, a proportionate balance in drug development, with greater research focus on non-Aβ targets, symptomatic treatments, and social interventions is justified.

designation of Aβ as a surrogate clinical trial outcome for AD clinical trials, in June 2021.[6]

Evidence supports that elevated Aβ deposition and memory deficits co-occur at a group level.[1,24,25] However, with the possible exception of monogenic AD, Aβ may not be sufficient on its own to produce the clinical manifestations of AD.[26] If this is the case, Aβ reduction alone will not prevent dementia onset, and this is consistent with the failure of any anti-Aβ clinical trial to show substantial evidence of clinical benefit. While it has been suggested that studies of combination therapies targeting both Aβ and non-Aβ targets or risk factors simultaneously may be a better approach,[27] these present greater logistical challenges and would be difficult to interpret, especially given the current lack of any individual validated treatment target.[28]

A current minority voice in the field questions whether Aβ is even necessary for development and progression of symptomatic AD, citing evidence for its protective effects as a potential by-product of upstream pathological processes,[29] but these alternative lines of enquiry lag behind research on amyloid and tau aggregation. Drug development remains predominantly focused on Aβ-lowering capabilities, which comprise 15.4% and 19% of DMTs at the clinical[20] and pre-clinical[30] development stages, respectively. Correspondingly, Aβ reduction (measured using PET, or in CSF or plasma) is increasingly used as an outcome measure and Aβ positivity is an entry criterion for a

TABLE 1 Summary of challenges for preclinical AD trial design and interpretation of outcomes, and alternative approaches

Challenge/problem in preclinical AD trial design	Impact on trial outcome interpretation	Alternative approaches
Especially that Aβ is now an FDA surrogate endpoint for AD clinical trials, drug development is predominantly focused on Aβ-lowering capabilities, and Aβ reduction is increasingly used as an outcome measure.	The degree to which Aβ (or any individual treatment target) is both causally necessary and sufficient for the later emergence of AD dementia is unclear.	Until a convincing link between reduction of Aβ and dementia risk is established, a proportionate balance in drug development is needed, with greater research focus on non-Aβ targets, symptomatic treatments, and social interventions. Biomarkers may be best clinically used aiding clinicians' diagnostic confidence and accuracy in symptomatic patients.
Aβ-lowering agents have been associated with amyloid-related imaging abnormalities (ARIA), which for high-dose 10 mg/kg aducanumab, affected 43% of recipients in Phase 3 trials, 1 in 4 of which were symptomatic, and linked to cognitive worsening and even death.	A higher frequency of ARIA in treatment groups is likely to contribute to functional unblinding and therefore bias caregiver/patient reporting of subjective outcomes, especially on functional abilities, leading to inflated treatment effects.	Consider randomizing an appropriately powered placebo subgroup to undergo additional dummy surveillance MRI scans, and/or include more objective functional endpoints.
Change on a sensitive neuropsychological test or AD biomarker are generally prespecified primary outcomes for preclinical AD trials, as a statistically significant difference on either can provide adequate support for FDA regulatory approval.	The degree to which changes in either outcome over the trial period translate to dementia risk reduction up to three decades later, that is, the MCID, for this group is unknown.	Trials need to report reduction of dementia risk (compared to baseline risk) to allow patients, clinicians, and health-care providers to judge the potential benefit of any intervention. The extension of current longitudinal AD cohorts over the next 1–2 decades may provide a deeper understanding of the natural history of AD, particularly late-onset disease, how progression of the earliest pathological, biomarker and cognitive changes relate to subsequent dementia onset, and provide empirical evidence for the MCID for preclinical AD.
The duration of trials (up to 4 years) is short relative to the long duration (up to three decades) between preclinical AD and dementia onset.	For the minority of trials that do measure clinical progression to AD dementia, the short durations limit the ability to detect any treatment-related differences in dementia risk reduction.	Longer Phase 3 clinical trials or long-term follow-up of participants, and/or greater and more accurate enrichment of clinical trial populations (using combined biological, neuroimaging, genetic, cognitive, behavioral, digital, and sociodemographic data) or recruitment of only monogenic AD, may sufficiently increase statistical power to detect clinically meaningful treatment-related effects over the duration of the trial.
Ongoing Phase 3 trials have selected participants based on age combined with one of biomarker positivity, family history, or genetics. Apart from monogenic AD, this will be a heterogenous population who have mainly low and widely varying dementia risk, most of whom will not progress to dementia in their lifetime and in those who do, a proportion may develop a non-AD dementia.	The current selection criteria of ongoing trials contribute to limit the statistical power to show any treatment-related differences in clinical progression and AD dementia risk reduction. The benefit and meaningfulness of dementia risk reduction will depend on the participant's baseline dementia risk.	As above. It will also be important for future trials to report whether and how a participant's dementia risk has been reduced compared to their risk if they received no treatment. For example, a treatment-related reduction in dementia risk from 50% to 25% is more likely to be seen as a clear benefit compared to a reduction from 15% to 10%.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; DMT, disease-modifying therapy; FDA, Food and Drug Administration; MCID, minimum clinically important difference.

number of Phase 2 and 3 DMT clinical trials.[20] The focus on Aβ is likely to further intensify now that the FDA has endorsed Aβ as a surrogate endpoint for AD clinical trials.

At the time of writing, seven ongoing secondary prevention Phase 3 trials are expected to report their findings within the next few years (Table 2), with many more Phase 2 studies under way. Most (five of seven) of the Phase 3 trials are investigating anti-Aβ monoclonal antibodies (lecanemab, solanezumab, and gantenerumab),[31–35] one of which is specifically enrolling preclinical dominantly inherited AD participants.[32] Two Phase 3 trials are targeting cardiovascular risk factors: one via an omega-3 fish-oil–based drug, icosapent ethyl (a Phase 2/3 study),[36] and the second through the effect of exercise with or without a drug combination of losartan, amlodipine, and atorvastatin.[37]

TABLE 2 Phase 3 preclinical AD trials from clinicaltrials.gov database

Drug/study	Preclinical AD sample	Study start date and status	(Estimated) completion date	(Estimated) sample size	Randomization and masking methods	Primary endpoint		Secondary endpoints		Planned duration (years)
						Biomarker/ cognitive	Global clinical/ functional	Biomarker/ cognitive	Global clinical/ functional	
Active										
Gantenerumab/ SKYLINE[35]	60–80 years; "evidence of cerebral amyloid accumulation"; RBANS DMI ≥ 80	Jun 2022; Recruiting	Oct 2028	1200	Two-arm parallel-group, double masking	PACC5	–	Brain amyloid and tau load; CSF and blood amyloid, tau and NfL; MRI volume measures	Time to clinical progression to MCI or dementia due to AD; A-IADL-Q-SV; CFIa; CDR-SB	211 weeks (4 years)
Lecanemab/ AHEAD 3-45[33]	55–80 years; elevated brain amyloid pathology by amyloid PET: defined as approximately > 40 Centiloids on screening scan; MMSE ≥ 27; WMS-R LM II ≥ 6.	Jul 2020; Recruiting	Oct 2027	1400	Four-arm parallel-group, quadruple masking	PACC5	-	Amyloid and tau PET SUVR	CFI	216 weeks (4.1 years)
	Early preclinical AD: 55–80 years; intermediate levels of brain amyloid pathology by amyloid PET: defined as approximately 20–40 Centiloids on screening scan; MMSE ≥ 27; WMS-R LM II ≥ 6.					Amyloid PET SUVR	–	Tau PET SUVR	–	216 (4.1 years)
Donanemab/ TRAILBLAZER-ALZ 3[34]	55–80 years, a phosphorylated tau (p-tau) consistent with the presence of amyloid and early-tau pathology; TICS-M score "reflective of intact cognitive functioning"	Aug 2021; Recruiting	Nov 2027	3300	Two-arm parallel-group, double masking	–	CDR-GS	ISLT; CPAL; iDSSTm; Category Fluency; FNAME; BPS-O; CBB; MoCA	CDR-SB; CFI	182 weeks (3.5 years)

(Continues)

TABLE 2 (Continued)

Drug/study	Preclinical AD sample	Study start date and status	(Estimated) completion date	(Estimated) sample size	Randomization and masking methods	Primary endpoint		Secondary endpoints		Planned duration (years)
						Biomarker/ cognitive	Global clinical/ functional	Biomarker/ cognitive	Global clinical/ functional	
Solanezumab/A4[31]	65–85 years, PET evidence of brain amyloid pathology at screening; MMSE ≥ 25; WMS-R LM II = 6–18	Feb 2014; Active, not recruiting	Jun 2023	1150	Two-arm parallel-group, quadruple masking	PACC	–	Mean composite SUVR, CSF tau and amyloid.	CFI; ADCS-ADLPI	240 weeks (4.6 years) (open-label 336, 6.4 years)
Gantenerumab or solanezumab/DIAN-TU[32]	18–80 years, have AD-causing mutation, or DIAD mutation in their family; cognitively normal within 15 years of the predicted age of cognitive symptom onset	Dec 2012; Recruiting	Jul 2022	490	Five-arm parallel-group; quadruple masking (one arm is open-label)	DIAN-MCE	–	Not reported	Not reported	Up to 208 weeks (4.0 years)
Icosapent ethyl (Phase 2/3)/BRAVE-EPA[36]	50–75 years; "cognitively healthy"	Jun 2017; Active, not recruiting	Jan 2023	150	Two-arm parallel-group; quadruple masking	Regional cerebral blood flow using arterial spin-labeling MRI	–	CSF beta-amyloid, total tau, and phosphory-lated tau; PACC	–	18 months (1.5 years)
Aerobic exercise training and/or vascular risk reduction (combined losartan, amlodipine and atorvastatin)/rrAD[37]	60–85 years, high-risk individuals with ≥1 first degree relative with AD or other dementia, or subjective cognitive decline; MMSE ≥ 26	Feb 2017; Active, not recruiting	Jan 2022	513	Four-arm factorial assignment; single masking (outcomes assessor)	Global cognition composite score (formed of ADCS-PACC and NIH-TB Cognition Battery	–	Domain-specific neurocogni-tive function assessed by using the tests included in the ADCS-PACC and NIH-TB Cognition; multiple MRI brain measures.	–	2 years

(Continues)

TABLE 2 (Continued)

Drug/study	Preclinical AD sample	Study start date and status	(Estimated) completion date	(Estimated) sample size	Randomization and masking methods	Primary endpoint		Secondary endpoints		Planned duration (years)
						Biomarker/ cognitive	Global clinical/ functional	Biomarker/ cognitive	Global clinical/ functional	
Inactive										
Atabecestat/EARLY (Phase 2/3)[38]	60–85 years, evidence of amyloid accumulation via CSF or PET measures, participants aged 60–64 additionally need family history of AD, *APOE* ε4 genotype, or previously known amyloid accumulation on CSF/PET	Oct 2015; Terminated (drug arm group had raised liver enzymes)	Dec 2018	557	Three-arm parallel-group; double masking	PACC at 24 months (2 years)	–	RBANS, NABDLTS at 24 months	CFI, ADCS-ADLPI, CDR-SB, at 24 months	Up to 54 months (4.5 years)
Ganterenumab or solenezumab/DIAN-TU (Phase 2/3)[40]	18–80 years old, have AD-causing mutation, or DIAD mutation in their family; cognitively normal within 15 years of the predicted age of cognitive symptom onset	Dec 2012; Completed and published	Mar 2020	194	Four-arm parallel-group; quadruple masking	DIAN-MCE at weeks 52, 104, 156, 208	–	Solanezumab: multiple cognitive domain scores; plasma/CSF/brain amyloid and tau measures	Gantenerumab: CDR-SB and FAB. Solanezumab: CDR, CDR-SB, FAS	Up to 208 weeks (4.0 years)
CNP520/GS2 (Phase 2/3)[39]	60–75 years old, carrier of at least one *APOE* ε4 gene, and if heterozygotes then requires elevated amyloid via PET or CSF; "cognitively unimpaired as evaluated by screening memory tests"	Aug 2017; Terminated (due to safety issues)	Mar 2020	1145	Three- arm parallel-group; quadruple masking	APCC score	Time to diagnosis of MCI or dementia due to AD	RBANS; CSF/PET tau and amyloid measures	CDR-SB; ECog-Subject and Ecog-Informant	5–8 years
CAD106 or CNP520/GS1 (Phase 2/3)[41]	60–75 years old, homozygous *APOE* ε4; MMSE ≥ 24	Nov 2015; Terminated (due to safety issues)	Apr 2020	480	Four-arm parallel-group; quadruple masking	APCC	Time to diagnosis of MCI or dementia due to AD	RBANS; CSF/PET tau and amyloid measures	CDR-SB; ECog-Subject and Ecog-Informant	5–8 years
Estrogens (estrogen and/or progesterone)/ PREPARE[43]	Women ≥65 years old, family history of memory problems	Not reported; Completed, unpublished	Sep 2007	Not reported	Parallel-group; double masking	Not reported	Not reported	Not reported	Not reported	3 years

(Continues)

TABLE 2 (Continued)

Drug/study	Preclinical AD sample	Study start date and status	(Estimated) completion date	(Estimated) sample size	Randomization and masking methods	Primary endpoint		Secondary endpoints		Planned duration (years)
						Biomarker/ cognitive	Global clinical/ functional	Biomarker/ cognitive	Global clinical/ functional	
Anti-inflammatories (naproxen or celecoxib)/ADAPT[42]	≥70 years old, family history of memory problems/dementia/AD	Jan 2001; Suspended (due to safety concerns) and published	May 2007	2625	Parallel-group; double masking	–	Time to AD diagnosis	–	Incidence of all-cause dementia and aMCI	5–7 years (achieved 3 years)
Pioglitazone/ TOMMORROW[44]	65–83 years old; MMSE ≥ 25; cognitively normal with ≥1 memory test > 1.5 standard deviation of the demographically corrected normative mean.	Aug 2013; Terminated (lack of efficacy) and published	Sep 2018	3494	Parallel-group assignment of "high-risk" group (based on biomarker risk algorithm based on age and two genotypes) to drug or placebo, low-risk group assigned to placebo; quadruple masking	–	Time to diagnosis of MCI due to AD	Composite Score on a Cognitive Test Battery	ADCS ADL-PI	5 years

Abbreviations: AD, Alzheimer's disease; ADCS-ADLPI, Alzheimer's Disease Cooperative Study-Activities of Daily Living Prevention Instrument; ADCS-PACC, Alzheimer's Disease Cooperative Study-Preclinical Alzheimer Cognitive Composite; A-IADL-Q-SV, Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; APCC, Alzheimer's Prevention Initiative Composite Cognitive; *APOE*, apolipoprotein E; BPS-O, Behavioral Pattern Separation-Object test; CBB, Cogstate Brief Battery; CFI, Cognitive Function Index; CFIa, Cognitive Function Instrument Acute; CPAL, Continuous Paired Associate Learning; CSF, cerebrospinal fluid; DIAD, dominantly inherited Alzheimer's disease; DIAN-MCE, Dominantly Inherited Alzheimer Network-Multivariate Cognitive Endpoint; ECog, Everyday Cognition Scale; FAS, Functional Assessment Scale; FNAME, Face Name Association Test; iDSSTm, International Daily Symbol Substitution Test-Medicines; ISLT, International Shopping List Test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NABDLTs, Neuropsychological Assessment Battery Daily Living Tests; NIH-TB, National Institutes of Health Toolbox; PACC5, Preclinical Alzheimer Cognitive Composite 5 (ADCS-PACC plus category fluency); PET SUVR, positron emission tomography standardized uptake value ratio; RBANS (DMI), Repeatable Battery for the Assessment of Neuropsychological Status (Delayed Memory Index); TICS-M, Telephone Interview for Cognitive Status modified; WMS-R LM II, Wechsler Memory Scale-Revised Logical Memory subscale II.

Note: The ClinicalTrials.gov database was searched up to March 2022 for Phase 3 clinical trials in Alzheimer's disease that were either active (and not yet recruiting, recruiting, enrolling by invitation, or not recruiting) or inactive (suspended, terminated, completed, withdrawn or unknown status) using additional search terms "preclinical," "prevent," "asymptomatic," and "risk." The TOMMORROW trial did not appear in the search results and was additionally included.

3 | PERSPECTIVES

3.1 | How would outcomes of secondary dementia prevention trials be clinically informative?

Assuming that they have positive results, potential prescribers will use the data from dementia secondary prevention trials to inform their treatment decisions and discussions that they will have with patients. When we look at choice of primary outcome in the active trials (Table 2), five studies will report change from baseline on a cognitive scale over 2 to 4.5 years (one includes an open-label extension up to 6.4 years), and only one study will report time to clinical progression, using the Clinical Dementia Rating-Global Score [CDR-GS], over 3.5 years (one ongoing study will also report time to progression to MCI/dementia as a secondary outcome measure over 4 years). Seven earlier Phase 3 preclinical AD studies have completed or been terminated (Table 2); four of these investigated Aβ-lowering agents via beta-secretase (BACE) inhibition,[38,39] anti-Aβ monoclonal antibodies,[40] or immunotherapy,[41] and three investigated the effects of anti-inflammatory drugs,[42] estrogens,[43] and an anti-diabetic medication.[44] Of three trials that were published, all reported negative findings based on cognitive outcomes[45] or time to AD diagnosis[46,47] over 3 to 4 years. Clinical trials are expensive and there will always be pressure to keep time to outcome to the minimum, but if studies do not or cannot detect treatment effects on AD dementia progression within the trial period, what firm conclusions can be drawn about subsequent clinical progression based on the effect of small, short-term drug–placebo differences in neuropsychological and/or functional scales over periods that are almost an order of magnitude longer than trial treatment periods?

Ultimately, in our opinion, to judge the potential benefit of any intervention for preclinical AD, the most important outcome for cognitively unimpaired patients, clinicians, and health-care providers is reduction of dementia risk. Favorable quantitative changes in biomarker level(s) and/or cognitive scores may satisfy FDA approval criteria for preclinical AD populations,[9] but these still have uncertain prognostic utility with regard to dementia prevention, and the relatively short durations (on average 3 years[20]) of secondary prevention trials limit their ability to shed light on this trajectory. Given that AD dementia, and not earlier AD stages, directly and unequivocally impacts individuals and society and constitutes a public health priority,[48] it is timely to ask whether secondary prevention studies, in the form of ongoing (and future) Phase 3 trials, can provide outcomes data that can meaningfully inform the treatment of AD dementia. If not, we should question whether it is worth conducting these at all, until and unless they can.

3.2 | Challenges of preclinical AD trial design and interpretation

In their 2018 guidance for industry,[9] the FDA considers that AD biomarker change may form the basis for accelerated approval for Stage 1 patients (who have no subjective or detectable neuropsychological abnormalities), and effects on sensitive neuropsychological tests may provide adequate support for approval for Stage 2 patients (who have subtle but detectable cognitive deficits but no functional impairment). The FDA also recommends that sponsors conduct studies of sufficient duration to evaluate patients as they transition to the next FDA-defined AD stage. However, since Aβ reduction was considered "reasonably likely to confer clinical benefit" and designated an FDA surrogate endpoint for AD clinical trials in June 2021,[6] it is plausible that Aβ reduction alone will now be sufficient to obtain future accelerated approval for preclinical AD interventions.

As well as the need to convincingly establish any link between Aβ reduction and cognitive benefit, which remains controversial,[45,49,50] it is important to understand how each of these outcomes in preclinical AD trials translates to dementia risk reduction. As discussed already, the duration of current Phase 3 clinical randomized controlled trials, the gold standard tool to measure efficacy and safety, is only up to ≈4 years (Table 2). In contrast, observational data support a temporal sequence of AD biomarker trajectories, starting with the detection of Aβ abnormalities as early as three decades before dementia onset.[1,2,51–53] This makes it difficult for trials to demonstrate any clinically meaningful efficacy in dementia prevention because they are too brief to show convincing change in the long and slow course of dementia. A recently completed clinical trial of solanezumab and gantenerumab in asymptomatic dominantly inherited AD individuals showed no cognitive benefit versus placebo over an average of 4 years. However, these individuals also showed no cognitive decline over the trial duration,[45] limiting the ability to detect any treatment effects. Without convincing evidence of change in clinical progression outcomes, any small differences on sensitive neuropsychological tests may reflect differences in placebo or practice effects, or side effects and monitoring regimens leading to functional unblinding between drug and placebo groups. It is notable that the reliability and validity of composite scales, such as the Preclinical Alzheimer Cognitive Composite (PACC), recommended as primary outcomes in early-stage AD trials as they combine several cognitive subscales with or without functional activity scales, have generally not been established prior to their use in clinical trials[54] and may unhelpfully amplify small but clinically insignificant differences on their component subtests.

The question of how to make clinical sense of the magnitude of early biomarker or cognitive changes in preclinical AD was raised in an earlier study.[55] This study found that on average, cognitively unimpaired Aβ+ individuals approached early MCI cognitive performance levels, defined as performance between 1.0 and 1.5 standard deviation below the normative mean on a standard test, by 6 years after baseline, and suggested that one point of additional decline on the PACC in the Aβ+ compared to Aβ− group could be interpreted as clinically meaningful decline. However, in our opinion, early MCI is not a sufficiently clear and clinically meaningful endpoint, as these individuals experience no loss of function and most are unlikely to develop AD dementia within 5 years.[16,56,57] Even if clinically meaningful decline *were* defined as progression to early MCI, current trials would need a treatment effect of 40% to 50% to delay the cognitive decline of Aβ+ participants from reaching this milestone by 3 years;[55] in other words, they

are almost certainly underpowered and/or insufficiently long enough to detect any clinically relevant effects. In the absence of a time-to-dementia endpoint in preclinical AD trials, we need to understand the smallest change in an outcome that constitutes a clinically meaningful treatment effect, that is, the minimum clinically important difference (MCID), which has yet to be empirically determined in relation to dementia risk for this population. As MCID is likely to be a key consideration for payors such as the US Centers for Medicaid and Medicare coverage in establishing the "necessity" of any AD treatment,[5] the absence of a MCID is unlikely to justify the conflation of small significant differences in biomarker or cognitive outcomes with meaningful benefits over risks for patients. Even if a treatment were completely safe, similar considerations apply in determining a reasonable cost for these treatments, as was clear in the decision by the Institute for Clinical and Economic Review (ICER) in their recent evaluation of comparative clinical effectiveness and value of aducanumab.[58]

Characteristics of the potentially heterogeneous preclinical AD population deserve close consideration, as several factors will limit the statistical power of preclinical AD trials to show meaningful clinical differences. Most ongoing Phase 3 trials have selected participants based on age combined with Aβ or p-tau biomarker positivity, family history, or genetics (Table 2). Detectable abnormal Aβ is associated with a higher risk of subsequent development of cognitive symptoms or more rapid cognitive decline[13,14,59–63], but with the exception of monogenic AD, which is also less likely to involve substantial comorbid age-related influences,[64,65] the overall rate of progression to MCI and dementia is relatively low. Up to around one third of older cognitively normal individuals with elevated brain Aβ may progress to prodromal or symptomatic AD (CDR $\geq$0.5) within 4 to 5 years, compared to up to 15% of those with normal Aβ levels,[13,59,66] but the increased risk conferred by abnormal Aβ has not been consistently established.[67] The risk of progression appears to be higher in the presence of tau aggregates [57] or p-tau[13,14] and additional neurodegenerative markers[15,60,61], as well as genetic status in the form of apolipoprotein E (*APOE*) ε4 allele hetero- or homozygosity[59,63] or poorer baseline cognitive performance.[63] Within the older preclinical AD trial population, there is also likely to be a proportion of asymptomatic biomarker-positive individuals who show biomarker profile sequences in which tau or neurodegeneration markers are detected first,[68,69] raising the possibility that some participants have early stage non-AD neurodegenerative processes (e.g., involving Lewy bodies, TDP-43, or vascular disease) and may not subsequently be recognized as having AD dementia. Owing to these diagnostic uncertainties and the uncertain predictive accuracy of AD biomarker positivity for symptomatic AD, it has been recommended that any AD diagnosis applied clinically should be accompanied by AD-specific symptoms.[11]

3.3 | Balancing potential benefits with risks and costs of treatment

Owing in part to the long preclinical AD phase, a significant proportion of older preclinical AD individuals may never develop dementia during their lifetime. Thus, any potential benefit of intervening at this early stage will need to be clearly defined and usefully explained so that it can be carefully weighed against side effects and costs. As well as needing clinical trials to report *whether* any intervention has reduced the risk of developing dementia, it is important that outcome data can be presented to show *how* a participant's dementia risk has been reduced compared to their risk if they received no treatment, because of the relatively lower but variable risk of developing dementia in cognitively unimpaired AD biomarker positive individuals. Therefore, it would be important for future trials to be able to answer: what was the participant's risk of developing dementia before receiving treatment and by how much did the treatment reduce the risk that they will progress to dementia in 3, 5, or 10 years' time? A potential patient who is told that their risk of developing dementia over the next 3, 5, or 10 years is 50%, but after treatment would reduce to 25%, is more likely to regard this as a clear benefit compared to someone who is told that their risk of developing dementia over the same period is 15%, but that treatment would reduce it to 10%.

Screening for the secondary prevention of any condition requires a robust understanding of the potential harms from overdiagnosis, overtreatment, false positive and false negative diagnoses, and complications from treatment.[70] AD biomarker screening via plasma, CSF, and PET techniques is invasive and potentially costly, and a diagnosis of preclinical AD may have ethical, social, and legal ramifications.[7,71] For aducanumab, the first DMT to obtain FDA accelerated approval, patients are required to undergo (and clinicians need to oversee) monthly intravenous infusions and regular magnetic resonance imaging (MRI) scans to detect potential amyloid related imaging abnormalities (ARIA),[72] which affected 43% of high-dose 10 mg/kg aducanumab recipients in Phase 3 trials, one in four of which were symptomatic[73] and linked to cognitive worsening and even death. How many doses of aducanumab are needed for optimal treatment and when to stop treatment also remain unclear.

As approximately one third of cognitively normal older individuals have biomarker evidence of elevated Aβ, with a reported range of 10% to 45%[2,13,66,74,75], of whom a significant proportion will also have detectable tauopathy[13,15], a potentially huge population of asymptomatic AD individuals could be detected through biomarker screening and undergo further investigation and treatment. The cutoff method for PET or CSF abnormal amyloid measures will therefore have implications for preclinical AD prevalence.[75] Even if only higher risk individuals were to be screened based on their family history or known genetic profile (e.g., monogenic AD or *APOE* ε4 hetero/homozygosity), the availability of a drug for AD secondary prevention would mean significant restructuring and refinancing of regional and national health services, alongside an expansion of clinicians' responsibilities and caseloads.

3.4 | Are there alternative approaches?

We need a deeper understanding of the natural history of AD, particularly late-onset disease, and how progression of the earliest pathological and corresponding biomarker changes relate to subsequent cognitive and functional decline, to make clinical sense of findings

from Phase 3 secondary prevention trials. Questions remain around how specific risk factors, including individual and multiple biomarker trajectories, cognitive performance and reserve, genetics, and age-related comorbidities influence disease progression and dementia risk. As most population-based studies have necessarily estimated long-term trajectories and dementia risk using models at the group level, the extension of current longitudinal biomarker and cognitive cohorts across the AD continuum over the next one to two decades will become increasingly informative. We also need to understand lifetime dementia risk for preclinical AD (A+T+) individuals.

In theory, longer Phase 3 clinical trials or long-term follow-up of study participants may inform dementia risk, but these are likely to be less attractive options for sponsors because of expense. Although measuring the risk of prodromal AD (MCI) would require shorter follow-up times, this essentially merely replaces one uncertainty with another as a significant proportion of MCI individuals do not progress to AD dementia within 6 years of follow up[15,19,56]. Longer follow-up times may also inevitably increase the risk of participant attrition, functional unblinding due to treatment-associated side effects, and confounding influences from age-related comorbidities. To mitigate the effect of functional unblinding due to treatment-related side effects on the reporting of subjective outcomes (especially relating to functional abilities), sponsors may consider randomizing an appropriately powered placebo subgroup to undergo additional dummy surveillance MRI scans, and/or including more objective functional endpoints.

Combined with a focus on clinical progression outcomes, greater enrichment of clinical trial populations may increase statistical power to detect treatment effects over the duration of the trial. A combination of biological markers, including fluid (Aβ, p-tau, neurofilament light chain), neuroimaging (hippocampal atrophy, amyloid/tau PET), and genetic (*APOE* ε4 or monogenic mutations) measures, as well as cognitive,[76] behavioral,[77,78] digital,[79] and sociodemographic data[12] (age, vascular risk factors, education, race/ethnicity), may provide better prognostic trajectories for preclinical AD[80,81] compared to individual biomarkers alone. Recruitment of Aβ-positive cognitively unimpaired participants who are also tau-PET positive may provide a higher likelihood of clinical progression to MCI and dementia over 3-5 years compared to Aβ and p-tau positivity[15,82,83] , although these individuals are relatively rare (<10% of cognitively unimpaired adults), and a small proportion will still develop a non-AD dementia. Using the rate of change[1] or magnitude[24,66] of amyloid biomarkers, instead of a dichotomous positive/negative measure based on a single cut-off at a single point in time, may help to more accurately identify the stage of disease progression and risk of cognitive decline and dementia. This would also help to inform treatment decisions in potential patients who could better appreciate the personalized stratified risks and benefits of treatments. Research is also needed on whether any intervention could generalize to atypical clinical presentations with underlying AD pathology (such as progressive non-fluent aphasia, logopenic aphasia, or posterior cortical atrophy).[84,85]

A proportionate balance in drug development direction is also important, with greater research focus needed on the prognostic potential of non-Aβ targets,[86] such as differences in tau or neurofilament light chain accumulation, synaptic plasticity, blood–brain barrier function, and neurochemical deficits.[87] Given the challenges and uncertain advantages associated with current Phase 3 secondary prevention studies, there is also a need to redress the disproportionate research focus on DMTs, which comprise 83% of AD drugs in development,[20] compared to symptomatic (10% cognitive and 7% neuropsychiatric) treatments. During the time between preclinical AD and dementia onset, which may be as long as 30 years, millions of individuals will develop dementia in the United States alone.[88] Effective symptomatic and social interventions that can optimize these individuals' quality of life and functioning and reduce caregiver burden would have immediate, direct, and measurable impact. Until biomarkers can provide accurate and reliable prognostic utility in terms of dementia risk, their most useful clinical contribution may be aiding clinicians' diagnostic confidence and accuracy where there is clinical uncertainty in symptomatic patients.

4 | CONCLUSIONS

The recent FDA regulatory endorsement of an unvalidated surrogate biomarker (Aβ) for AD clinical trials[89] makes it timely to question the clinical meaningfulness of changes in biomarker and/or cognitive outcomes in ongoing preclinical AD Phase 3 trials. With the exception of monogenic AD, the preclinical AD population included in trials is heterogeneous with low and widely varying baseline dementia risk; most of these people will not progress to dementia in their lifetime and in those that do, a proportion will develop a non-AD dementia. Currently, any treatment-related differences in biomarker or cognitive outcomes still have uncertain prognostic utility in preclinical AD individuals, and trials are underpowered and insufficiently long enough to understand how any differences might translate to reduction in dementia risk. Without use of clinical outcomes that are valid markers of progression to dementia and trial durations that allow a substantial proportion of participants to transition to an unambiguous symptomatic state, success of secondary prevention will be difficult to evaluate. Current approaches run the risk of the approval of drugs for asymptomatic AD in which treatment-related outcomes have not been quantified in ways that patients, their doctors, and health-care providers can understand and use to make informed decisions about potential benefits over known risks and costs. We have already seen with aducanumab that such uncertainty paralyzes clinical decision making, with negligible uptake and provision of treatment despite huge therapeutic need and patient group optimism. A greater focus on symptomatic and social interventions that reflects their potential to provide more direct and measurable benefits for individuals with AD dementia is justified.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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