# Insights into the use of biomarkers in clinical trials in Alzheimer's disease

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## Summary

**Biomarkers have been instrumental in population selection and disease monitoring in clinical trials of recently FDA-approved drugs targeting amyloid-β to slow the progression of Alzheimer's disease (AD). As new therapeutic strategies and biomarker techniques emerge, the importance of biomarkers in drug development is growing exponentially. In this emerging landscape, biomarkers are expected to serve a wide range of contexts of use in clinical trials focusing on AD and related dementias. The joint FDA-NIH BEST (Biomarkers, EndpointS, and other Tools) framework provides standardised terminology to facilitate communication among stakeholders in this increasingly complex field. This review explores various applications of biomarkers relevant to AD clinical trials, using the BEST resource as a reference. For simplicity, we predominantly provide contextual characterizations of biomarkers use from the perspective of drugs targeting amyloid-β and tau proteins. However, general definitions and concepts can be extrapolated to other targets.**



Keywords: Alzheimer's disease; Clinical trials; Biomarkers; Disease-modifying therapies; BEST glossary

## Introduction

Alzheimer's disease (AD) is often conceptualised as a sequential cascade of pathophysiological events, beginning with the impact of amyloid-β (Aβ) on tau phosphorylation and aggregation, which when associated with neuronal and glial dysfunctions, eventually leads to dementia.[1,2] The absence of biomarkers to identify the presence of these pathophysiological processes has limited the ability to interpret the negative results of early clinical trials targeting Aβ.[3] The lack of biomarkers for population selection has raised the possibility that their negative results could be because other brain pathologies, unaffected by the drugs being studied, were causing symptoms in many participants.[3] Furthermore, the lack of biomarkers to track therapeutic response has raised questions about whether drugs reach their targets and produce the expected biological effects.[3] The lessons learned from these clinical trials have highlighted that it is imperative to use biomarkers for more informative drug development in the field of AD. Biomarkers can be defined as quantifiable characteristics of the body, serving as objective indicators of biological processes or pathological conditions.[4,5] A joint initiative led by the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) named BEST (Biomarkers, EndpointS, and other Tools) classifies biomarkers into diagnostic, predictive, prognostic, susceptibility, response, monitoring, and safety categories.[4] The FDA defines the context of use (COU) of biomarkers for drug development as the combination of their BEST category and their specific use in the clinical

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**Key messages**

- Clinicobiological selection of participants for AD clinical trials involves determining the presence of cognitive impairment, excluding individuals with clinical syndromes indicative of other brain conditions, and utilizing diagnostic biomarkers to confirm underlying pathology.
- Biological disease staging using biomarkers can provide a framework for predicting participants' disease progression (prognostic biomarker) and therapeutic benefit (predictive biomarker).
- Response biomarkers can offer inferential evidence that the drug engaged its target, produced the expected biological effect, and induced a downstream modification in the AD pathway.
- Although it is difficult to fully invalidate a drug mechanism in the presence of biomarker evidence of disease modification, clinical trials can support that the drug is unable to produce a meaningful clinical benefit in the respective clinicobiological contexts tested.
- Validated surrogate biomarkers offer a means to reduce resource utilization and accelerate drug development, particularly when detecting changes in clinical outcomes is challenging. Putative surrogate biomarkers that have not yet been validated should be used only after full consideration of their limitations and potential for misleading results.

trial.[6] In AD trials, biomarkers can serve as inferential indicators of pathophysiology for several possible COUs.[7] This review will discuss some COUs that biomarkers can play in refining population selection and tracking drug response (Table 1). While we recognise the importance of clinical trials targeting a variety of pathophysiological processes to mitigate AD,[8] such as those associated with the neuroimmune system and metabolism, this review will primarily discuss COUs with a focus on drugs targeting Aβ and tau proteins. We chose not to delve into other targets as they encompass a multitude of different proteins, each necessitating unique COU considerations. The primary purpose of this review is to discuss the adaptation of the BEST concepts to the AD field, rather than to provide an exhaustive description of all possible targets and COUs.

| BEST category | Specific use in clinical trials |
|---|---|
| 1. Diagnostic | Select individuals with brain pathology |
| 2. Predictive | Select individuals most likely to respond to treatment |
| 3. Prognostic | Select individuals most likely to progress |
| 4. Susceptibility | Select individuals most likely to develop pathology |
| 5. Response | **a. Target engagement** (drug engaged its target) |
| | **b. Biologic response** (drug effect on the target) |
| | **c. Disease modification** (drug effect on the AD pathway) |
| | **d. Surrogate Endpoint** (likelihood of clinical benefit) |
| 6. Monitoring | Serially monitor treatment response or toxicity |
| 7. Safety | Indicate the likelihood, presence, or extent of a side effect |

*Table 1:* **Contexts of use of biomarkers for AD clinical trials.**

## Clinicobiological diagnosis

### Clinical assessment

Clinical steps in selecting AD participants for clinical trials include identification of (1) cognitive disorder and characterization of (2) clinical syndrome. **(1) Cognitive Disorder** (i.e., mild cognitive impairment (MCI) or dementia). A disorder can be defined as a set of problems that impair the body's functioning, without necessarily indicating a specific disease or condition.[9] The presence of both subjective and objective cognitive deficits has often been used to characterise individuals with perceived and confirmed cognitive impairment.[10] After a thorough medical interview, if neither the patient, family, nor physician subjectively notes cognitive decline compared to a prior state, an objective abnormality on cognitive testing alone does not strongly support a classification of cognitive impairment. This is because the abnormality may be indicative of premorbid conditions or a variety of challenges the patient may have faced on the day of testing. The fact that identification of cognitive impairment requires both subjective and objective evidence inevitably leads to two additional groups of individuals who meet only one of the two criteria (Table 2). Individuals with cognitive complaints but no objective deficit can be categorised as having subjective cognitive decline,[11] while individuals with an objective deficit that is not subjectively perceived may be categorized as having a subtle objective cognitive deficit.[12] Individuals with either subjective cognitive decline or subtle objective cognitive deficit have demonstrated an increased risk of progression to MCI.[11–13] If the subtle objective deficit is detected based on a single assessment relative to population test norms, it could be referred to as subtle objective cognitive impairment, while evidence of an abnormal longitudinal decline relative to the patient's own baseline testing could be referred to as subtle objective cognitive decline. The combination of subtle objective impairment and decline, which indicate participants' deficits relative to population norms and their own baseline, respectively, likely increases the chance that subtle objective cognitive deficit represents a transitional phase to MCI. Individuals with confirmed cognitive impairment who maintain functional independence in activities of daily living (ADL) are typically classified as MCI, while those who struggle with ADL are classified as having dementia.[10] Dementia can be further stratified into mild (difficulties with instrumental ADLs), moderate (difficulties with basic ADLs), and severe (fully dependent).[14] The FDA's recently updated draft guidance on this topic outlines a six-stage clinical classification for individuals with biomarker evidence of Alzheimer's pathology (Stage 1: no evidence of clinical impact; Stage 2: subtle objective or subjective deficits; Stage 3: mild but detectable functional impairment; Stages 4, 5, and 6: mild, moderate, and severe dementia).[15] Recent AD trials have often included patients with MCI or mild

dementia,[16–18] whereas earlier trials tended to include individuals with mild to moderate dementia.[19,20] Some recent clinical trials have also focused on cognitively unimpaired (CU) populations, in which the presence of a cognitive disorder is clinically excluded.[21] **(2) A Clinical Syndrome Reasonably Supporting AD as the Cause of Cognitive Disorder.** A syndrome can be defined as a group of signs and symptoms that collectively suggest a disease or condition, even when the direct pathological cause has not yet been confirmed.[9,22] When specific signs and symptoms of a cognitive disorder (i.e., MCI or dementia) suggest AD, it may be called Alzheimer's clinical syndrome,[23] which also includes atypical presentations.[24] During the initial syndromic evaluation of participants for clinical trials utilizing diagnostic biomarkers, it is not necessary for AD to be the most probable differential diagnosis; rather, it may be sufficient for AD to be reasonably postulated as the main cause of symptoms if the participant tests positive for the supportive diagnostic biomarkers. Therefore, when diagnostic biomarkers are available, more important than identifying Alzheimer's clinical syndrome is excluding individuals with pathognomonic features of other brain conditions. This process involves the analysis of participants' clinical characteristics by a clinician with the support of lab tests (e.g., vitamin B12, thyroid-stimulating hormone) and brain magnetic resonance imaging (MRI) to exclude other causes of cognitive deficits. There are several circumstances in which even a positive result for diagnostic biomarkers would not reasonably support AD as the main driver of clinical symptoms. These include, but are not limited to, atypical parkinsonian syndromes or a clear stepwise decline with a brain MRI showing major vascular pathology.[25,26] **Neuropsychiatric symptoms** could support clinical trial selection by providing a richer phenotypic characterization of Alzheimer's clinical syndrome or by indicating a distinct cognitive disorder characterised by mild behavioural impairment.[27]

| Impairment | Cognitively unimpaired | | | Cognitively impaired | | | |
|---|---|---|---|---|---|---|---|
| | Cognitively normal | Subjective cognitive decline | Subtle objective cognitive deficit | MCI | Dementia | | |
| | | | | | Mild | Moderate | Severe |
| Subjective | No | Yes | No | Yes | Yes | Yes | Yes |
| Objective | No | No | Yes | Yes | Yes | Yes | Yes |
| IADL | No | No | No | No | Yes | Yes | Yes |
| BADL | No | No | No | No | No | Yes | Yes |
| Fully Dependent | No | No | No | No | No | No | Yes |

BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living; MCI: mild cognitive impairment.

*Table 2:* **Cognitive disorders relevant for AD clinical trials.**

## Diagnostic biomarkers

Diagnostic biomarkers can be used to select individuals with the disease or medical condition, or a subtype thereof.[4,5] In AD, diagnostic biomarkers are commonly used in the context of identifying the hallmark pathological features of the disease, Aβ and tau pathologies.[28] Aβ (A+) and tau (T+) brain pathologies have been measured using CSF Aβ42 and phosphorylated tau (p-tau), respectively, as well as PET techniques in clinical trials and practice for many years.[29] Blood biomarkers of Aβ and tau have been proposed for screening patients who will later undergo CSF/PET confirmation,[30] while some recent studies suggest that they may have already achieved the accuracy necessary to replace CSF/PET as diagnostic tools.[31] It is important to emphasise that the T+ status discussed in this review is determined by biomarkers that identify AD-related tau pathology and would not consider tau biomarkers specific to other tauopathies. The performance of a biomarker in detecting brain pathology depends on the technique employed (i.e., PET differs from fluid-based methods) and the assumptions made to establish its abnormality cut-off.[29] Consequently, the resulting biomarker status may vary based on the analytical idiosyncrasies used and may not always truly reflect the underlying pathological environment of the brain tissue. For example, A+/T– individuals may have minimal levels of tau pathology in the brain that may not yet be detected by *in vivo* biomarkers.[32,33] Despite this limitation, an A+/T– profile can be useful for selecting a relatively homogeneous group of participants with absent or at least low levels of brain tau pathology. Biomarker studies support the existence of a significant proportion of older adults who are CU A+/T– and that their rates of clinical progression over five years are more akin to A–/T–than A+/T+.[34] This suggests that abnormality in Aβ biomarkers alone is not an optimal indicator of clinical progression within typical clinical trial periods. Therefore, to enrich clinical trial populations, it could be more informative to categorise individuals into A+/T– (i.e., Aβ pathology) who progress slowly, separately from A+/T+ (i.e., Alzheimer's pathology) who tend to progress at a faster rate.[34] Furthermore, when we consider the long clinical stability of CU A+/T– and the fact that Aβ is unlikely to protect these individuals against the development of other brain pathologies, it is reasonable to assume that some CU A+/T– will progress to cognitive impairment due to factors other than Aβ pathology. Thus, clinical trials including CI A+ without evidence of tau biomarkers could potentially select CI A+/T– in whom it is unclear whether Aβ is associated with cognitive symptoms. Use of anti-Aβ therapy in these individuals may lead to Aβ reduction that is less likely to result in imminent clinical benefit. Therefore, in line with the idea that AD is a cascade of events in which Aβ effects on tau lead to dementia,[1] the likelihood of an accurate AD diagnosis increases with the presence of both A+

and T+. This is consistent with earlier notions of preclinical AD,[13] cognitive impairment due to AD,[35] as well as the neuropathological diagnosis of AD.[36] As previous studies have shown that changes in both soluble and insoluble tau species can occur in response to Aβ pathology and may represent different facets of the same process,[1] we postulate that in the presence of A+, evidence of tau abnormality measured using either fluid or PET indicates Alzheimer's pathology. Among individuals who are A+/T+, potential discrepancies in tau positivity resulting from the use of fluid or PET could be attributed to different stages of the disease. While individuals at an earlier stage may show abnormal tau phosphorylation in the absence of detectable tau PET abnormality,[37] later stages are characterised by the regional progression of tau PET accumulation.[33,38,39] Differentiating T+ status, whether defined by fluid or PET, may be relevant for potential anti-tau trials targeting A−/T+ populations, as this differentiation could highlight individuals following distinct pathophysiological pathways. Although cognitive changes in individuals who are A−/T+, as determined by abnormal CSF p-tau, appear to mirror that of A−/T−,[40] those identified as A−/T+ through tau tangle PET consistently demonstrate more rapid neurodegeneration and cognitive impairment.[33,41]Together, these results suggest that it can be useful for clinical trials to measure AD-related tau biomarkers using both fluid and PET to better stage A+/T+ and classify A−/T+ participants. Table 3 shows pathological profiles of individuals classified using Aβ and tau biomarkers. Clinical trials that did not use diagnostic biomarkers for population selection enrolled a high proportion of participants who were found not to have AD pathology.[42–45] Most recent clinical trials used only Aβ biomarkers to enrich their populations,[16–18] whereas Donanemab trials were enriched with participants who had an A+/T+ biomarker profile.[46,47]

## Clinicobiological assessment

As mentioned above, selecting participants for AD clinical trials involves (1) identifying the cognitive disorder or its absence (e.g., CU), (2) assessing whether signs and symptoms are compatible with AD, and (3) using diagnostic biomarkers to support the presence of AD pathology. Together, these three steps provide clinicobiological profiles that enable the selection of participants most appropriate for different clinical trial designs. Here, we will use the term "with" either in the absence of a cognitive disorder or when the likelihood that the pathology indicated by the biomarker is causing the clinical symptoms is moderate to low. In contrast, we will use the term "due to" when there is a high likelihood that the pathology indicated by the biomarker is causing the symptoms. It is worth emphasizing that the "due to" label should be determined not only by biomarkers but also by assessing whether the medical history and physical examination are consistent with the disease. Table 4 summarises the groups defined following the notions described above, which can provide insights into the eligibility of participants for clinical trials. For example, CU with Aβ pathology (A+/T−) or Alzheimer's pathology (A+/T+) could be the target of anti-Aβ or anti-tau trials to prevent or reduce tau pathology, respectively. Individuals with cognitive impairment and Aβ pathology alone may not be the ideal group for anti-Aβ or anti-tau trials due to the high probability that pathologies other than Aβ and tau are the main cause of their current symptoms. Individuals with cognitive impairment who are A−/T+ due to an abnormal tau tangle PET scan, suggesting tangle-predominant pathology, exhibit accelerated cognitive decline and could therefore potentially be selected for trials aimed at mitigating tangle formation.[33,41] Cognitive impairment due to AD (A+/T+) is the natural clinicobiological profile for trials testing anti-Aβ and anti-tau therapies, as it is the most likely to identify participants on the AD pathway. However, individuals with cognitive impairment and an A+/T+ biomarker profile, in whom the clinical syndrome is pathognomonic of other forms of dementia (considered here as "due to" [another disease] "with" concomitant Alzheimer's pathology), should probably not be enrolled into anti-Aβ or anti-tau trials under normal circumstances. For example, individuals with an A+/T+ biomarker profile who experience fluctuating cognition, recurrent visual hallucinations, and parkinsonism will likely have their symptoms largely influenced by alpha-synuclein. In fact, most patients with Lewy body dementia are positive for Aβ and/or tau markers.[48] Further studies are needed to clarify the benefit that drugs designed to mitigate Alzheimer's pathology may have in individuals A+/T+ in whom other diseases are the primary driver of symptoms. When robust biomarkers to identify the multiple brain pathologies associated with cognitive deficits are available, we will no longer need to exclude A+/T+ individuals with clinical features of other diseases, as negative biomarkers for these conditions will do so reliably.

| Biomarker profile | Pathology |
|---|---|
| A−/T− | Normal biomarkers |
| A+/T− | Aβ pathology |
| A−/T+ | Abnormal tau phosphorylation and/or tau tangle pathology |
| A+/T+ | Alzheimer's pathology |

A: Aβ status; AD: Alzheimer's disease; T: tau status. Aβ pathology indicates an abnormal Aβ biomarker with normal fluid p-tau and tau tangle PET. Abnormal tau phosphorylation consists of abnormal fluid p-tau with normal tau tangle PET. Tau tangle pathology consists of an abnormal tau tangle PET biomarker regardless of fluid p-tau levels. Alzheimer's pathology consists of abnormal Aβ plus fluid p-tau and/or tau tangle PET.

*Table 3:* **Aβ and tau biomarker profiles.**

## Predictive biomarkers

Predictive biomarkers can be used to select individuals most likely to benefit from a therapeutic intervention.[4] Predictive biomarkers may be characteristics of the participant, such as genetics, or of the disease or condition, such as tissue protein level.[4] The identification of predictive biomarkers typically requires a comparison of the drug's effects on the outcome between individuals with and without the biomarker abnormality in randomised clinical trials.[4] The predictive biomarker could initially be inferred from the drug mechanism and/or investigated post hoc in completed trials, and subsequently used as an a priori hypothesis.[4] It would be advantageous if the predictive biomarker used for trial enrichment were not overly complex or costly, as its use might be necessary to identify the intended population in clinical practice following regulatory approval. Given the current uncertainty about whether remission of one pathology in the AD cascade will resolve subsequent pathologies that are more closely related to cognitive deficits, it might be beneficial to enrol trial participants who exhibit minimal levels of pathologies that occur downstream from the pathology being targeted by the drug to increase the chance of clinical benefit. In this context, biological disease staging using biomarkers can offer a framework for predicting therapeutic benefit. In practical terms, if the drug cannot resolve downstream pathologies, the trial should enrol participants at a biomarker stage that is equal to or earlier than the stage indicated by the targeted pathology, to increase the chance of clinically meaningful results. Within this framework, the probability of a therapy yielding enduring clinical benefits could best be understood by the biomarker abnormalities that will remain after treatment (Fig. 1). Most AD clinical trials have not used predictive biomarkers to increase the likelihood of clinical benefit.[16–18] On the other hand, the TRAILBLAZER-ALZ 2 trial segregated individuals into low and high tau PET groups under the assumption that participants with low tau PET would benefit the most from the anti-Aβ therapy.[46]

## Prognostic biomarkers

Prognostic biomarkers can be used to select among participants with the disease or medical condition those most likely to progress.[4] Under the premise that AD occurs in a sequence of pathological events, the abnormality of a biomarker will have greater imminent prognostic value for an immediately subsequent process in the cascade. A wide range of biomarkers have been associated with an increased risk of pathological and clinical progression in AD. In the early stages of the AD cascade, studies indicate that CU populations with abnormal Aβ and plasma glial fibrillary acidic protein (GFAP) biomarkers are at an increased risk of accelerated tau phosphorylation and aggregation.[49] Thus, clinical trials could enrol CU individuals with abnormalities in both Aβ and GFAP biomarkers to increase the likelihood that they will experience AD-related progression. CSF or plasma p-tau biomarker abnormalities appear to precede and are therefore good prognostic markers for tau-PET accumulation.[50] Braak stages derived from tau PET were associated with an increased chance of deposition of tau tangle PET in brain regions comprising subsequent but not earlier Braak stages.[51] Tau-PET and neurodegeneration (e.g., fluid neurofilament light chain (NfL), structural MRI) biomarkers are expected to become abnormal later in the disease,[52] making them suitable prognostic biomarkers for imminent cognitive impairment. Interestingly, the use of cut-offs in diagnostic biomarkers other than those used for determining the presence of brain pathology has allowed these biomarkers to also be used in the context of prognosis. For example, AHEAD A3 (Centiloid 20–40) and 45 (Centiloid >40) trials were enriched with Centiloid Aβ PET levels that increase the likelihood that their participants will show progression on the trials' proposed endpoints, Aβ PET and cognition, respectively.[53] Similarly, optimised cut-off values for CSF Aβ and p-tau were related to brain hypometabolism in an AD-like pattern among CU A+/T+.[54] APOEε4 status has also been associated with a higher chance of tau PET accumulation in CU individuals with Aβ pathology or Alzheimer's pathology.[55] Clinical trials targeting Aβ,[56] neuroinflammation,[57] lipid metabolism,[58] and the GABAergic system[59] have used the APOEε4 genotype to enrich their populations with participants

| Cognitive disorder | Clinical syndrome | A/T biomarker profile | Condition/disease |
|---|---|---|---|
| CU | No | A+/T− | with Aβ pathology |
| | | A−/T+ | with abnormal tau phosphorylation |
| | | | with tau tangle pathology |
| | | A+/T+ | with Alzheimer's pathology |
| MCI or dementia | AD in the differential | A+/T− | with Aβ pathology |
| | | A−/T+ | with abnormal tau phosphorylation |
| | | | due to tau tangle-predominant pathology |
| | | A+/T+ | due to Alzheimer's disease |
| | | A−/T+ (post-treatment) | due to Alzheimer's disease with Aβ in remission[a] |
| | Main characteristics pathognomonic of other disease | A+/T+ | due to [other disease] with Alzheimer's pathology |

A: Aβ status; AD: Alzheimer's disease; CU: cognitively unimpaired; MCI: mild cognitive impairment; T: tau status. The term "Alzheimer's pathology" is used to indicate the presence of A+/T+ biomarker abnormalities, whereas the term "Alzheimer's disease" is used when A+/T+ abnormalities are the most likely cause of cognitive symptoms. [a]We use the term "remission" to indicate the reduction of Aβ after therapy because this may be a transient state as Aβ pathology may return. The term remission can also be accompanied by "partial" or "complete", which can be used to indicate the degree of response to therapy.

*Table 4:* **Clinicobiological categorization relevant for AD clinical trials.**

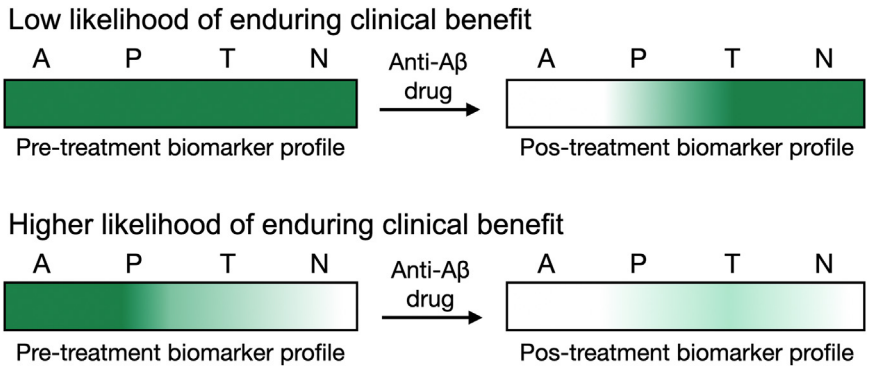


***Fig. 1:*** **Biomarkers profile predictive of anti-Aβ therapy benefit. A** (Aβ); **P** (tau Phosphorylation), **T** (tau Tangle) **N** (Neurodegeneration). Green = pathological burden.

more likely to experience AD-related progression. Recently, trialists and researchers have delved into complex models using multidimensional data and machine learning algorithms to identify individuals most prone to progress within clinical trial periods.[60]

## Susceptibility/risk biomarkers

Susceptibility biomarkers can be used to select among participants who do not have the disease or medical condition those who are more likely to develop it.[4] A biomarker is classified into the susceptibility rather than prognostic category based on the absence of the disease or condition.[4] Consequently, the classification of a biomarker into the susceptibility category may vary based on the criteria utilised to define who has the disease or condition. Depending on the COU established, susceptibility biomarkers can help to indicate who will develop clinical AD or biological AD. In clinical settings, AI-based biomarkers derived from electronic health record data could be used to identify individuals without cognitive impairment who are susceptible to developing clinical AD. This could help flag people within the health system who would benefit most from more intensive diagnostic monitoring or preventive strategies.[4] On the other hand, in clinical trials, susceptibility biomarkers could be used to indicate the likelihood of developing biological AD among populations negative for Aβ and/or tau markers to test drugs to prevent Alzheimer's pathology. If Alzheimer's pathology is characterised by A+ plus T+, Aβ biomarkers could be considered indicators of susceptibility to Alzheimer's pathology in individuals with an A+/T– biomarker profile. Recent studies have suggested that the presence of an abnormal plasma GFAP biomarker may indicate an even greater susceptibility of individuals A+/T– to develop Alzheimer's pathology (A+/T+).[49] Genetic variants associated with Alzheimer's pathology have been utilised for years as susceptibility biomarkers in clinical trials and practice. The presence of mutations in the amyloid precursor protein and presenilin 1 and 2 genes are the strongest susceptibility biomarkers for AD, with nearly 100% of mutation carriers manifesting autosomal-dominant AD.[61] APOEε4 genotype increases the risk for sporadic AD,[62] especially among homozygous carriers who have been reported to develop Alzheimer's pathology in most cases.[63]

## Response biomarkers

Biomarkers that change in response to a therapeutic intervention can be classified as response biomarkers.[5] In AD trials, changes in biomarkers can provide inferential evidence to determine whether: (**a**) the drug engages its target (target engagement), (**b**) the drug-target interaction induces the expected biological activity (biological response), (**c**) the biological response is linked to a modification in the AD pathway (disease modification), and (**d**) clinical benefit is likely (surrogate).

### Target engagement

Response biomarkers can be used to provide evidence that the drug engaged its target in living patients.[4] Verification of target engagement in clinical studies is important as they may face challenges not always seen *in vitro* and in animal models, such as dose limitation due to safety and differences in tissue penetrance and physiological and pathological environments.[64,65] Target engagement can be directly assessed using assays that identify drug–protein interactions in biofluids.[66] Although some advanced PET techniques can directly verify drug-target occupancy, various methodological challenges limit their application in AD drug development.[67] Most AD clinical trials rely on observations of the drug's biological activity on the target as indirect evidence of target engagement, because to elicit this effect the drug must first engage its target in the expected compartment/organ.[68,69] For example, the biological activity of an anti-Aβ therapy resulting in a

reduction of Aβ pathology in CSF or PET indicates an effective interaction between the anti-Aβ agent and Aβ in the brain.[46] For anti-tau therapies, changes in CSF total/phosphorylated tau[70,71] or markers of tau aggregation[70] have been used to support an interaction between drugs and target.[72] While evidence related to drug biological activity can reliably indicate successful target engagement,[66] its interpretation is limited when the drug does not elicit the predicted effect on the biomarker. For instance, if a hypothetical anti-tau therapy fails to modify a tau biomarker, it becomes challenging to identify whether this can be attributed to inadequate target engagement, the inability of the biomarker to represent the drug-target pathway, or a flaw in the drug mechanism itself.[73,74] Pfizer and AstraZeneca concluded that more than a third of their failed Phase II trials across multiple areas could not effectively invalidate the drug's mechanism due to a limited understanding of target exposure and engagement.[65,74,75] Notably, the fact that the progression of Aβ and tau proteins occurs across different pathophysiological species, from oligomers to aggregates,[76,77] imposes an additional layer of complexity in ascertaining target engagement in AD. The assessment of target engagement for drugs targeting these proteins may be more informative using biomarkers that represent or are as proximal as possible to the target protein species. For example, for drugs that aim to mitigate Aβ preplaque conformations, target engagement can be tested more reliably using biomarkers for oligomeric Aβ,[68] whereas for drugs targeting fibrillar Aβ using Aβ PET.[78] Tau-lowering drugs can target a variety of tau-related processes that, broadly speaking, can be related to proximal tau expression and modifications or distal tau aggregation.[8] The use of tau biomarkers for target engagement that are distant from, or not in equilibrium with, the targeted tau species can produce inconclusive results. For instance, a reduction in tau PET uptake when evaluating a therapy that targets tau expression can support target engagement and an equilibrium between the drug target and distal tau aggregation. Conversely, the absence of change in tau PET in the same trial could represent a lack of target engagement or simply that the drug target did not sufficiently contribute to the tau aggregation measured by the tau PET tracer. This distinction can be important in deciding whether the drug should be abandoned due to pharmacodynamic or pharmacokinetic concerns, or whether it can be used in combination therapies or repurposed for other conditions. The assessment of target engagement for the emerging tau immunotherapies could benefit from the use of fluid assays that measure the specific epitope targeted or those in the same domain.[79] For instance, the microtubule-binding region (MTBR) of tau represents a small fraction of total tau in CSF,[73] suggesting that MTBR-specific assays can potentially increase the sensitivity of target engagement for MTBR-directed therapies compared to N-terminal or total tau assays.[80] AD clinical trials that failed to slow clinical progression and did not produce evidence of target engagement had a limited ability to establish mechanism failure.[3] Most recent clinical trials testing anti-Aβ or anti-tau drugs used evidence of effects on CSF/PET Aβ and tau, respectively, to support drug-target interaction.[19,20,69] Clinical trial reports showing population-level mean biomarker reductions in the treatment group provide good insights into the potential for target engagement.[81] However, population-level observations may obscure interindividual heterogeneities in target engagement, such as those caused by differences in the integrity of the blood–brain barrier and other factors associated with drug tissue distribution and elimination.[64,82] The most informative studies have reported target engagement as the percentage of individuals showing evidence of drug-target interaction in the brain compartment.[68]

### Biological response

Response biomarkers can be used to confirm that the drug produced the expected biological effect on the target.[4,83] Changes in fluid or PET biomarkers, regardless of their magnitude, can substantiate the engagement of anti-Aβ and anti-tau therapies with their respective targets. Although this may be difficult to achieve, the ideal outcome when assessing biological response would be the complete remission of protein biomarkers to their normal levels. This is due to the current lack of data that excludes the possibility that residual levels of pathological proteins may continue to cause the symptoms. It could be argued that a reduction in protein levels measured directly in the brain using PET biomarkers provides a more robust indicator of biological response compared to reductions in brain proteins measured indirectly through CSF and blood biomarkers. This is because post-treatment changes in biofluids are more likely than changes in PET to reflect transient shifts in equilibrium between compartments (i.e., brain and fluids), which may not always represent the pathological environment of brain tissue. On the other hand, a remission of the PET biomarker to normal levels is more likely to indicate the physical absence of the proteinopathy in the brain tissue. Although assessing biological response at the population level using mean biomarker reduction in the treatment group is important for estimating the net effect of the drug on biomarkers,[68] understanding the proportion of participants who achieved complete remission of the pathology can help determine whether the effect of eliminating the target pathology was thoroughly tested in most participants in the trial.[47] Furthermore, individual-level assessments can facilitate the understanding of biological response in the context of characteristics of people (e.g., demographics) and disease (e.g., severity, duration). The anti-Aβ monoclonal antibodies that showed the highest

proportion of complete biological remission leading to Aβ PET negativity were Lecanemab (81%),[84] Gantenerumab (80%) in a 36-month extension,[85] Donanemab low (80%) and high (68%) tau PET groups,[46] and Aducanumab EMERGE (48%) and ENGAGE (31%).[16] Some anti-Aβ drugs have shown negligible remissions of Aβ PET to normal levels in their Phase II or III trials.[21,86–91] There is currently no consensus regarding cut-off values for determining Aβ PET positivity. Therefore, the use of different cut-offs to determine Aβ PET positivity in some of these trials limits the comparability of the proportions of participants who achieved complete remission of Aβ plaques after treatment.

### Disease modification

Response biomarkers can be used to determine whether the biological effect on the target induced a downstream effect in the AD pathway. If we consider that AD progresses in a cascade of events,[1] evidence of a biological response on the target, together with an associated effect on downstream biomarkers in the disease pathway, could increase the likelihood of a true modification of AD progression. A clear distinction between biological response and downstream AD modification has the potential to provide valuable information for interpreting clinical trial outcomes. For example, a drug that exclusively reduces Aβ plaques could decrease Aβ PET without having a downstream effect in the AD pathway, if Aβ pre-plaque conformations are responsible for triggering tau and neurodegeneration.[92] Similarly, it could be postulated that a reduction in tau PET uptake after an anti-tau therapy could have been artificially produced by reducing off-target tracer.[93] In both cases, changes in biomarkers of downstream pathologies may support that the drug's mechanism lies in the pathway leading to dementia. Clinical trials in which an adequate biological response did not translate into an effect on the disease pathway could be interpreted as an indication that the drug mechanism was adequately examined and found to be ineffective. In contrast, it can be challenging to invalidate a mechanism based on trials that show no clinical benefit but strong evidence of downstream modification in the AD pathway due to a lack of knowledge about the timing, magnitude, and duration of the effect needed to alter clinical outcomes. Although it is difficult to fully invalidate a drug target in the presence of robust disease modification, a trial may support that the drug is unable to produce a meaningful clinical benefit in the respective clinicobiological context tested. For example, evidence indicates the inability of adequate Aβ plaque removal to translate into a significant clinical benefit over 1.5 years in individuals with already high levels of tau tangle pathology.[46] The collective observation of a set of clinical trials demonstrating negligible clinical benefits across the clinicobiological spectrum of AD, despite complete remission of the targeted pathology, may support contextual invalidation of the mechanism even in the presence of disease modification. Still, negative outcomes from open-label extensions and registries may be required to substantiate the invalidation of the mechanism over longer periods of pathological remission. The anti-Aβ monoclonal antibodies Lecanemab and Donanemab reduced CSF and/or plasma p-tau and GFAP.[18,46,94] Aducanumab decreased p-tau levels measured in CSF and plasma.[16] Lecanemab, but not Donanemab, decreased plasma NfL.[18,94] Lecanemab and Aducanumab, but not Donanemab, reduced temporal lobe tau PET uptake.[16,46,95] Gantenerumab reduced CSF p-tau and did not alter tau PET uptake.[17] In a recent post hoc analysis, Gantenerumab did not modify the trajectory of CSF NfL but was associated with an increase in CSF sTREM2 and a decrease in plasma GFAP levels.[96] Bapineuzumab reduced CSF p-tau only among APOEε4 carriers.[90] Solanezumab and Crenezumab showed no evidence of a reduction in tau biomarkers in CSF and PET.[19,21,87,91] Solanezumab did not decrease but increased CSF NfL neurodegeneration and did not affect microglial (TREM2) or astrocytic (GFAP) biomarkers.[96] While some anti-tau therapies have shown downstream effects on NfL (e.g., AADvac1,[97] HMTM[98]), others have not (e.g., Semorinemab[99]).

### Surrogate endpoint

Response biomarkers can be used as substitutes for clinical endpoints.[4,5] Randomised clinical trials that test drug effects on clinical outcome assessments provide the highest level of evidence for a clinical benefit.[4,100] To reduce resource utilization and/or accelerate drug development, indirect measures such as biomarkers are often considered surrogates or substitutes for clinical outcomes.[4] The FDA reported that between 2010 and 2012, approximately 45% of new drugs were approved based on the results of surrogate endpoints.[101] FDA classifies surrogate endpoints into validated, candidate, and reasonably likely.[4] A validated surrogate endpoint is supported by clear mechanistic rationale and robust clinical data.[4] Clinical validation of a surrogate endpoint for a specific COU requires both (1) a strong correlation with the clinical outcome and (2) statistical inference supporting that the net effect of the intervention on the surrogate endpoint predicts its net effect on the clinical outcome.[102–107] Analysis of data from multiple randomised controlled trials is generally necessary to confidently meet the second requirement, ensuring that the surrogate endpoint is generalizable across drugs in the class.[5,108] Thus, while observational studies can provide supportive data, they typically cannot validate a surrogate endpoint.[4] Due to the complexities involved in meeting the second requirement, there are currently no validated surrogate biomarkers in the field of AD. Yet, putative surrogate endpoints that are not fully validated are often utilised to support clinical trials. A candidate surrogate endpoint is still being evaluated for its capacity

to predict the clinical benefit.[4] A reasonably likely surrogate endpoint has a strong mechanistic and/or epidemiological rationale but lacks robust clinical validation, such as that derived from the analysis of multiple randomised controlled trials.[109] They should be used only after full consideration of their limitations and the fact that they may produce misleading conclusions.[110] Reasonably likely surrogate endpoints can be used for FDA accelerated approvals, but due to the residual uncertainty regarding clinical benefit that is typical of this approval route, post-market confirmatory trials are generally required.[4,108] The FDA accelerated approval program was created in the 1990s in response to the HIV pandemic to bring drugs to market more quickly based on changes to unvalidated surrogates that were reasonably likely to predict clinical benefit.[111] Over the past decade, the majority of accelerated approvals have occurred in the field of oncology.[112] In the realm of neurodegenerative conditions, a drug designed to halt the progression of amyotrophic lateral sclerosis recently received accelerated approval based on reducing plasma NfL.[113,114] In AD, it has been proposed that a reduction in Aβ PET uptake is reasonably likely to predict clinical benefit when testing anti-Aβ therapies.[115] In practice, some recent clinical trials have demonstrated that reducing Aβ PET parallels clinical benefit,[18,46] whereas others have shown that no clinical benefit was observed with Aβ PET reduction.[17] Changes in biomarkers that indicate distant pathologies in the causal pathway of clinical symptoms, such as Aβ, are known to have the potential to produce conflicting conclusions about clinical benefit.[106,107] This may be attributed to the fact that symptomatic patients already present varying degrees of downstream pathologies that are more closely associated with their clinical symptoms. Given the strong correlation between tau tangles and neurodegeneration with clinical symptoms,[116,117] it can be postulated that biomarkers for these pathologies have the potential to be used as surrogates for clinical outcomes. The longitudinal hierarchical accumulation of tau tangles PET following Braak stages suggests that trials using tau PET as an endpoint could select participants at similar Braak stages to avoid misinterpretation of their results.[33,118] Suppose that two participants, one with baseline tau PET indicating Braak II and another indicating Braak VI, participate in the same trial testing drug effects on tau PET regions encompassing Braak I-III. In this circumstance, the participant at Braak VI would naturally exhibit a decelerated rate of tau accumulation in the region compared to the participant at Braak II. This difference, which is related to their different stages of tau propagation, could be misinterpreted as a therapeutic effect.[51] Several recent clinical trials have used changes in CSF and blood biomarkers, such as p-tau and NfL, as exploratory endpoints.[18,46,70,97] There are clear advantages to using fluid biomarkers as endpoints in clinical trials, such as the possibility of concomitantly evaluating drug effects on multiple biological processes. However, the utility of changes in fluid biomarkers as surrogates for clinical outcomes in AD trials is unclear. In fact, it remains unclear whether pathological changes measured in biofluids following drug exposure can even be surrogates for changes in brain tissue pathology. Evidence suggests that drug-induced reduction in fluid p-tau does not necessarily equate to a reduction in brain tau PET uptake.[46] Furthermore, a decrease in NfL, theoretically representing less brain degeneration in the treatment group, has been observed in parallel with a reduction in brain volume.[84,119] Other current limitations primarily involving the use of blood biomarkers as endpoints include a poor understanding of factors associated with biological and analytical variation of available assays which, if not taken into consideration, could greatly affect their longitudinal quantification in clinical trials.[120,121]

## Monitoring biomarkers

Monitoring biomarkers can be used to serially assess the status of a disease or medical condition or the effects of exposure to therapy.[4] This includes repeated measurements of biomarkers across a wide range of BEST categories, including those related to population selection, drug response, and safety.[4] Monitoring biomarkers are most commonly used in contexts of tracking ongoing response to treatment or the emergence of toxicity. Biomarkers can also be repeatedly measured to quantify rates of change and magnitudes of drug effects over time points.[4] Serial biomarkers collected after drug discontinuation can potentially inform expected periods of pathology/biomarker remission after treatment, which can help to clarify the need for additional drug exposure. Serial Aβ PET measurements have been used to monitor continued biological response to anti-Aβ therapies.[18,85] Serial tau PET can investigate continued biological response or disease modification in the context of anti-tau and anti-Aβ therapies, respectively.[18,46] Repeated brain MRI acquisitions to detect amyloid-related imaging abnormalities (ARIA) represent an intersection between monitoring and safety biomarkers, helping to control drug toxicity and the need for drug discontinuation.[122]

## Safety biomarkers

Safety biomarkers can be used to indicate the probability, presence, or extent of an adverse event.[1] The use of brain MRI to monitor the presence of brain bleeding and swelling, which can contraindicate or lead to the discontinuation of anti-Aβ therapies, is currently the best-known example of the use of safety biomarkers in AD clinical trials.[123] APOEε4 genotype may be considered a safety biomarker in the context where homozygous carriers are at greater risk of developing ARIA when treated with anti-Aβ therapies.[124] The need for additional drug- or class-specific safety biomarkers may arise with different

drug targets/mechanisms. For example, BACE inhibitors have been shown to decrease lymphocytes and increase alanine transaminase,[125,126] which should be monitored when testing these medications.

## Conclusion

Biomarkers hold significant potential for enhancing and expediting the development of drugs for AD and related dementias. The BEST glossary provides a means to standardise the terminology used for various biomarker applications, fostering discussions within and beyond the AD field. Baseline biomarker values can help identify participants with AD (diagnostic) or those likely to develop AD (susceptibility), who are most likely to progress during the clinical trial period (prognosis), or who could potentially benefit most from therapy (predictive) with less chance of side effects (safety). Changes in biomarkers following drug exposure can provide evidence of drug-target interaction (target engagement), biological effect on the target (biological response), and whether the biological effect is linked to a downstream effect in the AD pathway (disease modification) or possible clinical benefit (surrogate). Biomarkers can also be repeatedly measured (monitoring) to track changes in treatment response or toxicity. While the baseline levels of both biofluid and PET protein markers provide a robust foundation for population selection, additional data are needed to better understand the significance of changes in fluid levels in response to drug therapies. It is crucial to separately characterise, whenever possible, the different COU of biomarkers for accurate interpretation of positive and negative clinical trial results. For example, if a trial selected the appropriate population and confirmed target engagement with a sufficient biological response but without evidence of downstream disease modification or clinical benefit, this would support an interpretation that the mechanism was adequately tested and invalidated. Conversely, if the same clinical trial had shown robust modification in biomarkers downstream in the AD pathway, the notion that the trial adequately tested the mechanism could be questioned, given that the timing and duration of effects necessary to influence cognition remain uncertain. In this case, it may be necessary to collectively observe the results of numerous trials that span the clinicobiological spectrum of AD, including long-term extensions and registries, to comprehensively evaluate the drug mechanism. In clinical trials that do not use biomarkers, invalidating mechanisms will always be challenging due to uncertainties about whether the appropriate population was selected, and whether the drug reached the brain, sustained target engagement, and exerted the expected effect.

## Outstanding questions

The use of biomarkers in AD clinical trials has broadened, resulting in more complex interpretations of their outcomes. This has heightened the demand for standardised terminologies and interpretations to streamline communication. However, certain definitions and concepts, such as those pertaining to population selection and enrichment, target engagement, drugs' biological activity, disease modification, and surrogacy, are frequently used interchangeably, leaving room for variations in their interpretation across studies.

### Contributors

Conceptualisation: TAP; Literature search: TAP and BB; Figure and tables: TAP; Writing - original draft: TAP. Writing - review & editing: CSA, FL, LC, CKS, JF, PR-N, ERZ, PCLF and BB. All authors approved the final version of the manuscript for submission.

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TAP received support to attend meetings from the Alzheimer's Association. LC has received support to attend meetings from the Alzheimer's Association and IMPACT-AD. CKS has received support to attend meetings from the Alzheimer's Association and payment for lectures from the Busse Research Award for Biomedical Research. CSA has received support to attend meetings from the Alzheimer's Association. JF reported receiving personal fees for service on the advisory boards, adjudication committees, or speaker honoraria from AC Immune, Adamed, Alzheon, Biogen, Esteve, Laboratorios Carnot, Ionis, Lilly, LMI, Lundbeck, Perha, Roche, Zambon and, outside the submitted work. JF reports holding a patent for markers of synaptopathy in neurodegenerative disease (licence to Adx, EPI8382175.0). PR-N received payment for lectures and has served on scientific advisory boards and/or as a consultant for Novo Nordisk, and Eisai. ERZ is on the scientific advisory board of Nintx, Novo Nordisk and is on the scientific advisory board and is a co-founder of MASIMA. MASIMA is a Brazilian company that provides brain scan analytical tools to hospitals. ERZ has never received royalties of financial gains from MASIMA. ERZ has received support to attend meetings from Alzheimer's Association, CNPq, and CAPES. PCLF has received support to attend meetings from the Alzheimer's Association. BB has received support to attend meetings from the Alzheimer's Association.

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**Appendix A. Supplementary data**

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105322.

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