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Biomarkers

in Alzheimer´s Disease

Final Report

HTA-Information Service Rapid Review No.: 004

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1 Background and research question

1.1 Description of disease

Alzheimer´s Disease (AD) is a type of dementia that is characterised by loss of memory and cognitive decline. It affects thinking and behaviour, and the greatest known risk factor is increasing age [1]. The AD continuum can be structured into three phases: preclinical AD, mild cognitive impairment (MCI) due to AD (or prodromal AD), and dementia due to AD. In AD patients there is a progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles of hyperphosphorylated tau protein in the brain, which might lead to damage and eventual death of neurons over decades [2].

Alzheimer´s Disease (AD): preclinical AD, mild cognitive impairment (MCI) due to AD and dementia due to AD

Majority of AD cases occur sporadically as a complex disease with genetic and environmental factors. Only < 2,5 % have a monogenic genetic disposition and leads most commonly to familial early onset AD [3]. Early-onset AD is associated with single-gene mutations that influence beta-amyloid formation (e.g., amyloid precursor protein and presenilin). The risk of developing late-onset AD is increased with having apolipoprotein E (ApoE) ε4 allele (there are three allelic variants in humans, ε3 is the most common variant): one copy of the ε4 allele is associated with a two to threefold increase, while two copies of the gene may increase risk of AD by as much as 15 times.

accumulation of beta-amyloid protein plaques and neurofibrillary tangles of hyperphosphorylated tau protein in the brain

In order to diagnose a patient with AD or another type of dementia, several parameters need to be evaluated and tests need to be performed such as medical history, neurological exams, cognitive and functional assessments, brain imaging e.g. magnetic resonance imaging (MRI), computer tomography (CT), positron emission tomography (PET) and cerebrospinal fluid (CSF) or blood tests [4]. With such tests and exams, a probable diagnosis of AD can be made with a confidence of > 90%. Post-mortem verification of the AD pathology (plaques and tangles) is still the goldstandard. Early diagnosis of AD is still a challenge, since early symptoms are hard to discriminate from normal ageing and sometimes similar to other neurological disorders [3].

diagnosis of AD: medical history, neurological exams, cognitive and functional assessments, brain imaging, cerebrospinal fluid (CSF) or blood tests

1.2 Current (and future) treatment options

Current treatment of AD focuses on supportive care and treatment of dementia symptoms with medications that do not influence the course of the disease itself. Therefore medication that is able to modify the course of the disease i.e. that could slow down or stop its progression is needed (called disease-modifying treatments)[2].

focus of current treatment: treatment of dementia symptoms medication that is able to modify the course of the disease is needed

Relevant drugs that have recently been developed or are still in the pipeline [5] (further drugs might be on the horizon):

Lecanemab: approved by the FDA in January 2023

- **Lecanemab** (pharmaceutical company *Eisai*), approved by the U.S. Food and Drug Administration (FDA) in January 2023 under the accelerated approval pathway, which was converted to traditional approval in July 2023 [6], marketing authorisation application filed at the European Medicines Agency (EMA) – decision expected in first half of 2024.

Donanemab: application for traditional FDA approval planned in Q2 2023

- **Donanemab** (pharmaceutical company *Eli Lilly*), the FDA has rejected the application for accelerated approval of the drug, and additional data was requested. The company plans to seek traditional FDA approval based on the results of its ongoing TRAILBLAZER-ALZ 2 Phase III study [7], whose first results were published in July 2023 [8]. No information regarding a potential application at the EMA could be found.
- **Aducanumab** (pharmaceutical company *Biogen Inc.*; collaboration agreement with *Eisai* [9]) was granted accelerated approval by the FDA in June 2021. Data from post-marketing studies will determine if continued approval can be warranted. Data from a phase IIIb/IV confirmatory study (ENVISION trial) should be available by the end of 2026 [10]. *Biogen Netherlands B.V.* withdrew its application for a marketing authorisation at the EMA on 20 April 2022 based on interactions with the Committee for Medicinal Products for Human Use (CHMP) indicating that the data provided thus far would not be sufficient to support a positive opinion on the marketing authorization of Aducanumab [11].
- **Remternetug** (pharmaceutical company *Eli Lilly*), a phase III trial of Remternetug (called TRAILRUNNER-ALZ 1) is ongoing and is due to end in 2025.

1.3 Potential role of biomarkers

different classes of biomarkers:

diagnostic biomarker

monitoring biomarker

pharmacodynamic/ response biomarker

predictive biomarker

prognostic biomarker

safety biomarker

susceptibility/ risk biomarker

Biomarkers can be classified according to the "Biomarkers, Endpoints and other Tools (BEST)" resource from the FDA [12]:

- **Diagnostic biomarker**: detects or confirms the presence of a disease or condition of interest or identifies an individual with a subtype of the disease.
- **Monitoring biomarker**: is measured serially to assess the status of a disease or medical condition for evidence of exposure to a medical product or environmental agent, or to detect an effect of a medical product or biological agent.
- **Pharmacodynamic/ response biomarker**: when the level of a biomarker changes in response to exposure to a medical product or an environmental agent.
- **Predictive biomarker**: is defined by the finding that the presence or change in the biomarker predicts an individual (or group of individuals) more likely to experience a favourable or unfavorable effect from the exposure to a medical product or environmental agent.
- **Prognostic biomarker**: is used to identify the likelihood of a clinical event, disease recurrence, or disease progression in patients with a disease or medical condition of interest.

- **Safety biomarker**: is measured before or after an exposure to a medical intervention or environmental agent to indicate the likelihood, presence, or extent of a toxicity as an adverse event.
- **Susceptibility/ risk biomarker**: indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.

classification of biomarkers for AD

However, the attribution to the **classification** of biomarkers for AD might not always be very clear, i.e. some might fall under several categories depending on the aim of its use [13].

4 main types in AD: CSF biomarkers, blood biomarkers, PET imaging and MRI

Four main types of biomarkers are used in the context of AD: CSF biomarkers, blood biomarkers, PET imaging and MRI [14].

role of biomarkers in AD

The potential role of biomarkers in the context of AD were elaborated in the guidelines by the National Institute on Aging and Alzheimer's Association (NIA-AA) on the diagnostic criteria for AD dementia first in 2011 [15, 16]. Biomarker evidence was integrated into the diagnostic formulations for probable and possible AD dementia for use in research settings. The core clinical criteria remained to be met for the diagnosis of AD dementia, but biomarker evidence (based on imaging and cerebrospinal fluid measures) is expected to enhance the pathophysiological specificity of the diagnosis [16].

"A, T, N Framework" categorizes biomarkers into 3 groups: Aß deposition, pathologic tau, and neurodegeneration

The guideline was revised in 2018, resulting in the "**A, T, N Framework"**, a research framework intended to guide observational and interventional research (not routine clinical care). The diagnosis now focuses on pathology rather than phenotype, and in vivo evaluations with biomarkers, rather than postmortem examinations. The framework categorizes biomarkers into three groups based on their pathological process. For AD it includes **A** (reflecting cerebral amyloid pathology e.g. amyloid PET, CSF amyloid beta (Aß) protein), **T** (reflecting tau pathology e.g. tau PET, CSF phosphorylated tau (p-tau)) and **N** (reflecting neurodegeneration e.g. MRI, CSF levels of total tau (t-tau), fluordeoxyglucose (FDG) PET). A and T are specific for AD, N is shared with several neurodegenerative diseases [17-19]. The framework allows for comprehensive biomarker characterization and provides future flexibility by adding other biomarkers as they are discovered and validated. This detailed biomarker classification, alongside genetic and clinical data, paves the way for more tailored treatments as they emerge.

1.4 Questions to be answered in this report

questions in this report:

What is the current status of biomarkers in neurology with a focus on Alzheimer´s Disease (AD)?

available and validated biomarker in AD

- Question **(Q)1**: Which biomarkers (tests) are (commercially) available?
- **Q2**: What is the sensitivity and specificity of these biomarker tests? Specifically, what is the diagnostic accuracy of blood biomarker tests?

standardisation initiatives

- **Q3**: For which drugs would the respective biomarkers be relevant? (e.g., AD - β-amyloid - Lecanemab)
- **Q4**: Are there any standardisation initiatives for biomarkers (in Europe)?

2 Methods

Methods:

handsearch for all questions

To answer **Q1-4**, a hand search for relevant (review) publications was performed in dedicated databases such as PubMed and through internet search including manufacturer´s websites. In Table 1 "Overview of biomarkers in Alzheimer´s Disease" the publication by Canada´s Drug and Health Technology Agency (CADTH) [14] was taken as a basis and complemented by further search results (**Q1, Q2, Q4**).

primarily for systematic reviews

Regarding **Q2**: The information about sensitivity and specificity of respective biomarker tests was extracted/referenced from (review) publications and sources without checking the included diagnostic accuracy studies, since this was not in the scope of this rapid review – results are summarized in Table 1. Additionally, results from systematic reviews on diagnostic accuracy of blood biomarkers including a reference standard (standard diagnostic procedures) that differentiated patients with AD from patients with other dementia subtypes or from cognitively healthy controls were presented in Table 2. For these systematic reviews, a risk of bias assessment using the AMSTAR-2 (Assessment of Multiple Systematic Reviews) tool was conducted [20].

clinical guidelines

A supplementary hand search for **clinical guidelines** was performed. Inclusion criteria were 1) the guideline addresses Alzheimer's Disease, Dementia, and related diagnostics, 2) published 2016 or onwards.

3 Results

3.1 (Commercially) Available biomarker for Alzheimer ´s Disease

similar biomarkers were reported by different institutions:

Several institutions investigated biomarkers as a proof of Alzheimer pathology or AD:

IQWiG: CSF (tau and amyloid) and/or amyloid PET

The „Institute for Quality and Efficiency in Healthcare“ (**IQWiG**, „Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen”) used in their evidence report for the S3 guideline 2021 the following biomarkers as a proof of Alzheimer pathology or AD in their assessment about “Non-drug interventions for mild cognitive impairment and biomarker evidence”:

- **CSF** (to determine pathological tau-protein and amyloid deposits) and/or
- **Amyloid PET** (to determine amyloid deposits) [21].

Fraunhofer Institute: MRI, CSF (Aß, t-tau, p-tau) and amyloid PET

The “AData(Viewer) – Exploring the Alzheimer's Disease Data Landscape” from the **Fraunhofer Institute in Germany** showed (amongst other biomarkers) the following diagnostic biomarkers:

- **Hippocampus volume in MRI,**
- **CSF amyloid beta (Aß), CSF total tau (t-tau) and CSF phosphorylated tau (p-tau)** and
- **Amyloid PET** [22].

2011: Aß(1-42), t-tau and p-tau181 in CSF

Back in 2011, a publication stated that enzyme-linked immunosorbent assay (ELISA) measurement of **Aß(1-42), t-tau and p-tau181 in CSF** is the most advanced and accepted procedure for diagnosing probable AD with high specificity and sensitivity [3]. It might be the case that only a combination of several biomarkers will aid diagnosis of AD in the future [3].

2021/22 since 1st Alzheimer drugs are approved, demand for blood tests increases

With the advent of Alzheimer drugs since 2021/22, blood tests that are easy to use and not expensive are urgently required. These tests are not yet available in clinical praxis, only in research settings. **Blood biomarkers** detecting amyloid and tau pathologies specific to AD are: **Aß** and **p-tau**. The non-specific blood markers of neuronal (neurofilament light, ß-synuclein, ubiquitin-C-terminal-hydrolase-L1) and glial degeneration (glial fibrillary acidic protein) are relevant for various neurodegenerative diseases [23].

Several assays could be identified, however only a few of them hold a CE-mark, yet. Plasma p-tau, together with brief cognitive tests and ApoE genotyping, might greatly improve the diagnostic prediction of AD and facilitate recruitment for AD trials [24].

many commercially available (CE marked) biomarker were identified: MRI (n=1), CSF biomarkers(n=15), PET imaging (n=7), SPECT imaging (n=1), genetic testing (n= 4), blood biomarkers (n=17), and "other" category

however, the list might not be exhaustive

However, many different CE marked biomarker tests are commercially available. Several different biomarker categories were identified in the literature:

- MRI (n=1),
- CSF biomarkers (n=15),
- PET imaging (n=7),
- SPECT imaging (n=1),
- genetic testing (n= 4),
- blood-based biomarkers (n=17) and
- "other" category.

We aimed to identify the main categories and types of biomarkers in Table 1; however, the list might not be exhaustive. For related further information on each biomarker and individual products, see Table 1.

3.2 Sensitivity and specificity of biomarker for Alzheimer´s disease

information on sensitivity and specificity (if available) of different biomarkers are to be considered with caution

Where information was available, values for **sensitivity and specificity** were indicated, or at least the link to the source(s) were stated (see Table 1 "Overview of biomarkers in Alzheimer´s Disease"). Also, further diagnostic **performance parameters** (apart from **sensitivity and specificity, e.g. positive predicted value, negative predicted value** etc.) could be reported [25]. For some biomarkers, the provided values differed to some minor extent according to the source. Respective diagnostic accuracy studies were neither reviewed nor critically appraised. Results should be considered with caution.

publication 2023 [25]: in CSF greater accuracy for Aβ42/40 or p-tau181/ Aβ42 versus individual biomarker concentrations. In plasma biomarkers, Aβ42/40 and p-tau181 demonstrated high agreement with PET findings

A publication from 2023 concluded the following about the performance of diagnostic biomarkers of amyloid and tau pathology in AD:

> "*All available **PET amyloid and tau biomarkers** demonstrate high accuracy in identifying amyloid and tau Alzheimer's disease pathology, respectively, at autopsy. Among **cerebrospinal fluid biomarkers**, all showed accurate prediction of Alzheimer's disease pathology, either based on autopsy or PET findings; greater accuracy was evident for concentration **ratios** (**Aβ42/40 or p-tau181/ Aβ42**) versus individual biomarker concentrations. Among **plasma biomarkers, Aβ42/40** and **p-tau181** demonstrated high agreement with PET findings. Overall, we conclude that **commercially available PET, cerebrospinal fluid, and plasma assays accurately identify Alzheimer's disease amyloid and tau pathology**. The recent development of fully automated tests for fluid-based biomarkers improves test reliability*" [25].

CSF Biomarkers

For ***CSF (Aβ(1-42), t-tau, p-tau) a combined sensitivity of >95% and a specificity of >85%*** was shown in 2011 [3].

publication 2011 [3]: combined sensitivity >95% and specificity >85% of CSF Aß, t-tau, p-tau

The recently updated AWMF guideline [26] points out the importance of the **ratios *CSF Aβ42/40, CSF Aβ42/p-tau181 and CSF Aβ42/t-tau*** in clinical practice. Various studies have shown that all three ratios display similar diagnostic values, which tend to be higher than the diagnostic values for the individual markers. More detailed data to sensitivity and specificity can be found in Table 1.

AWMF guideline [26]: ratios CSF Aβ42/40, CSF Aβ42/p-tau181 and CSF Aβ42/t-tau

Blood biomarkers

For the diagnostic performance of **blood biomarkers,** three systematic reviews that aimed to **assess diagnostic accuracy of blood biomarkers for AD** were identified via hand search. A risk of bias assessment using the AMSTAR-2 tool was performed: the quality was rated as moderate (Qu 2021 [27]), as low (Chen 2021 [28], and as critically low (Hardy-Sosa 2022 [29]) – see Table 4 in the Appendix. The respective data extraction can be found in Table 2.

AMSTAR-2 assessment: moderate, low, critically low.
3 systematic reviews on diagnostic accuracy of blood biomarker

The **three included systematic reviews** highlight two main conclusions (based on the following study designs: case-control studies and longitudinal studies with ≥ 2-year follow-up [29]; cross-sectional and cohort studies [28], cross-sectional cohort studies and from longitudinal studies with clinical follow-up [27]:

3 systematic reviews:

1. All three publications [27-29] agree on the significant role of tau proteins (p-tau217, p-tau231, and p-tau181) as biomarkers for AD diagnosis, which are reported to have higher sensitivity and specificity than other blood biomarkers. Qu and Chen note the decreased sensitivity and specificity of Aβ and t-tau proteins in this regard, and Hardy-Sosa includes Aβ42/Aβ40 ratios in a promising panel of biomarkers. Qu also mentions the lack of specificity of blood neurofilament light (NfL) to discriminate AD from other neurodegenerative diseases.

significant role of tau proteins (p-tau217, p-tau231, and p-tau181) as biomarkers for AD diagnosis

2. Hardy-Sosa emphasizes the greater effectiveness of a panel of biomarkers, instead of relying on a single one. The authors propose a combination of Aβ42/Aβ40 ratio, p-tau217, and p-tau181 as a potential non-invasive and cost-effective method for diagnosing AD. They also suggest further markers like NfL and Enzyme b-secretase 1 (BACE1) for tracking disease progression and neurodegeneration. Chen also hints at this concept by pointing out the current limitation of detecting amnestic mild cognitive impairment (aMCI) with blood-based biomarkers, indicating the need for more comprehensive biomarker panels.

Aβ42/Aβ40 ratios

Qu reports a sensitivity and specificity of >80 % for **Aβ42*T-tau**, a sensitivity and specificity of >90 % for **p-tau217**, an area under the curve (AUC) of 0.630 - 0.997 for **p-tau231**; a sensitivity of 67–71 % and specificity of 66–86 % for **p-tau181**, a sensitivity of 67–84 % and specificity of 78–87 % for **NfL**, a sensitivity of 63–97 % and specificity of 50–91 % for **t-tau** and a sensitivity of 74–96 % and specificity of 50–95% for **Aβ42/Aβ40**, which show good diagnostic accuracy in identifying AD and aMCI patients from controls [27].

good diagnostic accuracy of blood biomarkers in identifying AD and aMCI patients from controls

Chen indicates for the **plasma Aβ42** a sensitivity of 88 % and a specificity of 81 %, for the **plasma tau** a sensitivity of 90 % and a specificity of 87 % in differentiating patients with AD from the controls. For differentiating aMCI

from the controls, a sensitivity of 86 % and a specificity of 90 % for the plasma **Aβ42** and a sensitivity of 79 % and a specificity of 94 % for the **plasma tau** are shown [28]. See also Table 2.

Overall, while these publications underscore the importance of tau proteins as reliable biomarkers, they also highlight the need for continuous advancements in detection technology, the utility of combined biomarkers for improved diagnosis and disease tracking, and the requirement for further validation of these markers in larger, diverse population cohorts.

need for continuous advancements in detection technology, further validation in larger, diverse population cohorts

Additionally, two systematic reviews could not identify **blood biomarker studies** within their inclusion criteria, although they would have been part of the research question:

- A **Cochrane systematic review** (Kokkinou et al 2021) aimed to determine the diagnostic accuracy of plasma and CSF ABeta42 for distinguishing Alzheimer's disease dementia (ADD) from other forms of dementia in people who meet the general diagnostic criteria for a dementia syndrome in a specialist care setting [30]. They only considered cross-sectional studies in which **people with ADD were differentiated from patients with other dementia subtypes and not from cognitively healthy controls**. Participants with mild cognitive impairment were not included. No studies of plasma ABeta42 met the inclusion criteria.

2 systematic reviews could not identify blood biomarker studies within their inclusion criteria

- The aim of another **systematic review** (Fink 2020) was to summarize evidence on biomarker accuracy in brain imaging (CT, MRI or functional PET or SPECT) in contemporary use, CSF tests (ß-amyloid 42, t-tau, p-tau, Aß42/Aß40 ratio, tau/Aß42 ratio, or neurofilament light protein), **blood tests (Aß42, Aß42/Aß40 ratio, or amyloid precursor protein)**, or combinations of these for **distinguishing neuropathologically defined AD from non-AD** (for example, no AD pathology, or pathology of Lewy body disease or frontotemporal lobar degeneration) among older adults with dementia. No eligible studies addressed the accuracy of blood tests [31].

Information on regulatory status of specific products

Where information on the **regulatory status** of the biomarkers could be identified, respective notes were made in Table 1 “Overview of biomarkers in Alzheimer´s Disease”. However, this information could not be gathered for all individual diagnostic tests.

3.3 Companion biomarker for drug selection

biomarkers used in Lecanemab and Donanemab trials

Furthermore, Table 1 indicates which biomarkers were used in the phase III RCT - CLARITY AD Study (**Lecanemab**) and in the phase III RCT - TRAILBLAZER-ALZ 2 Study (**Donanemab**). Please note that no specific product names/manufacturers were mentioned in the publications regarding the studies.

Table 1: Overview of biomarkers in Alzheimer´s Disease

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
Core cerebrospinal fluid (CSF) biomarker	CSF Amyloid-beta (Aß)1-42		Elecsys ® β-Amyloid (1-42) CSF II (Roche) Lumipulse® G β-Amyloid 1-42 (Fujirebio) INNOTEST® β-AMYLOID (1-42) (Fujirebio) Beta-amyloid (1-42) (Euroimmun/Perkin Elmer) Amyloid-beta (1-42) CSF ELISA (TECAN/IBL International) ADmark® Phospho-Tau/Total-Tau/A Beta42 (Athena Diagnostics)	(FDA) 510(k) approval (Dec 2022) [32] CE marked [33] FDA approval (May 2022) [34] CE marked [35] CE marked [36] CE marked [37] CE marked [38] No CE mark [39] Runs as a Laboratory Developed Test (LDT) in the US [25]	For detecting AD pathology, sensitivities ranged from 84%-96.4%, specificities from 72%-76.9% and accuracy from 72%-87% for CSF Aß1-42. For the clinical diagnosis of AD, a meta-analysis cited by the AWMF guideline indicated a sensitivity of 80% and a specificity of 82%. For differentiating AD dementia from vascular dementia: 79% sensitivity and 69% specificity was shown. See further information in the AWMF guideline on dementia [26]. According to Humpel 2011 [3] the 3 CSF biomarkers (Aß1-42, t-tau and p-tau181) together yield a combined sensitivity of >95% and a specificity of >85%. "Under a multiparametric view of Aβ1-42, t-tau and p-tau, a sensitivity of 89 % and a specificity of 90 % for differentiating patients with AD from disease controls is reported." [40] Further information can also be found in the publication by Iaccarino 2023 [25].	Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	References: Wells 2022 [14], Roche [41], Iaccarino 2023 [25]	Well-established in clinical practice

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
CSF biomarker	CSF Aβ1-40		Lumipulse® G β-Amyloid 1-40 (Fujirebio) INNOTEST® β-AMYLOID (1-40) (Fujirebio) Beta-amyloid (1-42) Euroimmun/Perkin Elmer Amyloid-beta (1-40) CSF ELISA (TECAN/IBL International)	FDA approval (May 2022) [34] CE-marked [42] CE marked [36] CE marked [37] CE marked [38]		Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	References: Lin 2023 [2]	Well-established in clinical practice
CSF biomarker	CSF Aβ1-42/Aβ1-40 ratio		ABtest-IA (Araclon Biotech) Lumipulse G β-amyloid Ratio (1-42/1-40) (Fujirebo)	CE marked [43, 44] FDA approval through the De Novo premarket review pathway (May 2022) [45]	To detect AD pathology, the AWMF guideline indicates a sensitivity of 87% and a specificity of 88% (AUC: 0.90) for the ratio of Aβ42/Aβ40. This is a higher diagnostic accuracy than Aβ42 alone, with a sensitivity of 76% and a specificity of 77% (AUC: 0.81).		Iaccarino 2023 [25]	Well-established in clinical practice

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
					To differentiate AD dementia from non-AD dementia, the findings for Aβ42 ranged between 67%-100% in sensitivity and 40%-89% in specificity, with AUCs of 0.58-0.95. For the Aβ42/Aβ40 ratio, sensitivities ranged from 51%-95% and specificities between 57%-100%, with AUCs of 0.71-0.95. Further information can be found in the AWMF guideline on dementia [26]			
CSF biomarker	CSF total-tau (t-tau)		Elecsys® Total-Tau CSF (tTau) (Roche) Lumipulse® G total Tau (Fujirebio) INNOTEST® hTAU Ag (Fujirebio) Total tau Euroimmun/Perkin Elmer hTau total ELISA (TECAN/IBL International) S-PLEX Human Tau (total) Kit (Meso Scale Diagnostics LLC)	FDA 510(k) approval [46] CE marked [33] CE marked [35] CE marked [36] CE marked [37] CE marked [38] No CE mark (for research use only) [47, 48] No CE mark [39]	According to Humpel 2011 [3] the 3 CSF with ELISA biomarkers together yield a combined sensitivity of >95% and a specificity of >85% "Under a multiparametric view of Aβ1-42, total tau and phos-pho-tau, a sensitivity of 89 % and a specificity of 90 % for differentiating patients with AD from disease controls is reported." [40]	Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	References: Wells 2022 [14], Roche [41]	Well-established in clinical practice

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
			ADmark® Phospho-Tau/Total-Tau/A Beta42 (Athena Diagnostics)	Runs as a Laboratory Developed Test (LDT) in the US [25]	To detect AD pathology, the AWMF guideline indicates a sensitivity of 69.6%, a specificity of 92.3%, and 80.6% accuracy for CSF t-tau. To differentiate AD dementia from non-AD dementia, a sensitivity of 69.6%, a specificity of 92.3%, and an accuracy of 80.6% was reported. For the clinical diagnosis of AD, for the combined use of Aβ42 and t-tau, a sensitivity of 89% and a specificity of 87% was reported. See further information in AWMF guideline on dementia [26]			
CSF biomarker	CSF phospho-tau181 (p-tau181)		Elecsys® Phospho-Tau (181P) CSF (Roche) Lumipulse® G pTau 181 (Fujirebio) INNOTEST® PHOSPHO-TAU (181P) (Fujirebio) pTau(181) (Euroimmun/Perkin Elmer) phosphoTAU ELISA (TECAN/IBL International)	(FDA) 510(k) approval (Dec 2022) [32, 49] CE marked [33] CE marked [35] CE marked [36] CE marked [37] CE marked [38]	The AWMF guideline indicates a sensitivity of 67.9%, a specificity of 73.1%, and 70.4% accuracy to detect AD pathology for CSF p-tau. For the clinical diagnosis of AD, sensitivities range from 78%-80%, specificities from 88%-83%. For differentiating AD dementia from vascular dementia a sensitivity of 88% and a specificity of 78% was shown. Differentiating AD dementia from non-AD dementia, an AUC of 0.81 was reported. See further information in AWMF guideline on dementia [26].	Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	References: Wells 2022 [14], Roche [41], Iaccarino 2023 [25]	Well-established in clinical practice

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
			S-PLEX Human Tau (pT181) Kit (Meso Scale Diagnostics LLC) ADmark® Phospho-Tau/Total-Tau/A Beta42 (Athena Diagnostics)	No CE mark (for research use only) [47, 48] No CE mark [39] Runs as a Laboratory Developed Test (LDT) in the US [25]	According to Humpel 2011 [3] the 3 CSF biomarkers together yield a combined sensitivity of >95% and a specificity of >85% "Under a multiparametric view of Aβ1-42, total tau and phos-pho-tau, a sensitivity of 89 % and a specificity of 90 % for differentiating patients with AD from disease controls is reported." [40] Further information can also be found in the publication by Iaccarino 2023 [25]			
CSF biomarker	CSF p-tau181/Aß42 ratio (or Aß42/p-tau181 ratio)		Elecsys β-Amyloid (1-42) CSF II and Elecsys Phospho-Tau (181P) Lumipulse® G pTau181 (Fujirebio)	CE marked [33] FDA 510(k) approval [49] CE marked [35]	The CSF P-tau 181P /Aβ1-42 ratio is a useful indicator of presence of pathologic neuritic plaques in the brain with an overall accuracy of 90.2% [50]. Based on information provided in the AWMF guideline, the Aβ42/p-Tau 181 ratio, a sensitivity of 91.1%, a specificity of 71.2%, and an accuracy of 81.5% were shown. See further information in AWMF guideline on dementia [26].		References: Iaccarino 2023 [25]	Well-established in clinical practice

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
CSF biomarker	CSF t-tau/Aß42 ratio (or Aß42/t-tau)		Elecsys β-Amyloid (1-42) CSF II and Elecsys® Total-Tau CSF (tTau) (Roche)	FDA 510(k) approval [46] CE marked [33]	Based on information provided in the AWMF guideline, the Aβ42/t-tau ratio showed a sensitivity of 85.7%, a specificity of 84.6%, and an accuracy of 85.2%. See further information in AWMF guideline on dementia [4].			Well-established in clinical practice
CSF biomarker	CSF p-tau217		S-PLEX Human Tau (pT217) Kit (Meso Scale Diagnostics LLC)	No CE mark (for research use only) [47, 48].			References: Janelidze 2020 [51]	Not available in clinical practice, anticipated to see greater adoption in the future
CSF biomarker	MTBR-tau243						References: Horie 2023 [52, 53]	Not available in clinical practice, experimental (used in clinical studies only)
CSF biomarker	Non-phospho-tau	measures the TAU fraction non-physphorylated at T175/T181 in human CSF as an aid in the diagnosis of Alzheimer's disease	pTAUrel ELISA (TECAN/IBL International)	CE marked [38]				Not available in clinical practice, experimental (used in clinical studies only)
CSF biomarker	CSF Neurogranin					Used in phase III RCT - CLARITY AD study (Lecanemab) [2]		Not available in clinical practice, experimental (used in clinical studies only)

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
CSF biomarker	CSF Neurofilament Light Chain (NfL)	Monitoring parameter	Lumipulse® G NfL CSF (Fujirebio) NF-light® (Neurofilament-light) ELISA (TECAN/IBL International)	No CE mark [35] CE-mark [54]		Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	Regarding TECAN/IBL International) product: does not specifically mention AD, only briefly in the instruction for use document	Not available in clinical practice, anticipated to see greater adoption in the future
CSF biomarker	Triggering receptor expressed on myeloid cells 2 (TREM2)	Soluble TREM2 (sTREM2) is the ectodomain released in a soluble form. CSF sTREM2 is known to increase 5 years before the expected symptom onset in AD.	INNOTEST® sTREM2 (Fujirebio)	No CE mark [36]				Not available in clinical practice, experimental (used in clinical studies only)
CSF biomarker	Aß1-38		Amyloid-beta (1-38) High Sensitive ELISA (TECAN/IBL International)	No CE mark [38]				Not available in clinical practice, experimental (used in clinical studies only)
CSF biomarker	Aß1-43	Many types of Aβ molecules are targeted in AD research. One hypothesis, the so-called tripeptide hypothesis claims that Aβ40 is produced by cleaving from Aβ49 through Aβ46 and Aβ43. For that reason the interest in Aβ43 molecules has been growing.	Amyloid-beta (1-43)(FL) ELISA (TECAN/IBL International)	No CE mark [38]				Not available inclinical practice, experimental (used in clinical studies only)

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
Blood based biomarker	Aß1-42		Lumipulse® G β-Amyloid 1-42 Plasma (Fujirebio)	No CE mark [35]				Not available in clinical practice, anticipated to see greater adoption in the future
Blood based biomarker	Aß42	To detect toxic forms of the Aß peptide.	Soba-AD platform (AltPep Inc.)	FDA: Breakthrough Device Designation			References: Wells 2022 [14]	Not available in clinical practice, experimental (used in clinical studies only)
Blood based biomarker	Aβ1-40		Lumipulse® G β-Amyloid 1-40 Plasma (Fujirebio) Simoa Aß40 Advantage Kit (Quanterix)	No CE mark [35]			References: Wells 2022 [14]	Not available in clinical practice, anticipated to see greater adoption in the future
Blood based biomarker	Aß42/Aß40 ratio	The idea essentially is to gauge whether Aß is leaving the blood and, presumably, starting to form plaques in the brain. It is designed to monitor Aβ42/Aß40 changes over time [55]	Quest AD-Detect ABtest-IA (Araclon Biotech) ABtest-MS (Araclon Biotech) Amyloid-β automated immunoassay system HISCL™-5000/ HISCL™-800 (Sysmex) Amyblood (ADx Neurosciences)	FDA Clinical Laboratory Improvement Amendments (CLIA)-certified No CE-mark [25] CE marked [43, 44] CE marked [43, 44] No FDA approval [25]	Further information can be found in the publication by Iaccarino 2023 [25]	Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	References:Larson (2023) [56], Iaccarino 2023 [25], Wells 2022 [14]	Not available in clinical practice, anticipated to see greater adoption in the future

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
Blood based biomarker	Plasma p-tau181	Predictive biomarker	Lumipulse® G pTau 181 Plasma (Fujirebio) AlzoSure Predict (Diadem) Simoa pTau-181 assay (Quanterix) [57]	No CE mark [35] FDA: Breakthrough Device Designation CE-marked [58] FDA Breakthrough Device Designation (Nov 2021) [59] Runs as a Laboratory Developed Test [25] No CE-mark [25]	Further information can be found in the publication by Iaccarino 2023 [25]	Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	References: References: Wells 2022 [14]; Iaccarino 2023 [25]; Janelidze 2020 [60], Thijssen 2020 [61]	Not available in clinical practice, anticipated to see greater adoption in the future
Blood based biomarker	Plasma p-tau217		Simoa P-tau (Quanterix) 217				Reference: Milà-Alomà [62], Palmqvist 2020 [63]	Not available in clinical practice, anticipated to see greater adoption in the future
Blood based biomarker	Plasma p-tau231		Simoa P-tau (Quanterix) 231				Reference: Milà-Alomà [62]	Not available in clinical practice, experimental (used in clinical studies only)
Blood based biomarker	Brain-derived tau (BD-tau)	The new BD-tau blood test selectively detects specifically BD-tau, instead of other tau-type proteins produced by cells outside of the brain	Not marketed yet? identified by neuroscientists at the University of Pennsylvania School of Medicine and the University of Gothenburg, Sweden	Larger scale clinical validation is still needed			Reference: Donner (2023) [57]	Not available in clinical practice, experimental (used in clinical studies only)

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
Blood based biomarker	Neurofilament Light Chain (NfL)		Lumipulse® G NfL Blood NF-light™ Serum ELISA (TECAN/IBL International)	No CE mark [35] No CE mark [64]		Used in phase III RCT - CLARITY AD study (Lecanemab) [2]	References: Alcolea 2023 [23]	Not available in clinical practice, anticipated to see greater adoption in the future
Blood based biomarker	APOE, and Aß42/Aß40 ratio	Looks for apolipoprotein E (APOE) genotype and amyloid-beta-42/40 ratios	PrecivityAD (C2N Diagnostics)	FDA: Breakthrough Device Designation (2019), FDA Clinical Laboratory Improvement Amendments (CLIA)-certified (Nov 2020) [56] CE-mark (Dec 2020) [65]	Sensitivity: 93% (under certain cut-off conditions), specificity: 77% (under certain cut-off conditions) [14] Further information can also be found in the publication by Iaccarino 2023 [25]		References: Wells 2022 [14], Agency for Care Effectiveness (ACE) 2022 [66], Iaccarino 2023 [25]	Not available in clinical practice, anticipated to see greater adoption in the future
Blood based biomarker	ß-synuclein						References: Alcolea 2023 [23]	Not available in clinical practice, experimental (used in clinical studies only)
Blood based biomarker	Ubiquitin-C-terminal-hydrolase-L1						References: Alcolea 2023 [23]	Not available in clinical practice, experimental (used in clinical studies only)
Blood based biomarker	S100ß and neuron-specific enolase (NSE)						References: Delaby 2023 [17]	Not available in clinical practice, experimental (used in clinical studies only)

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
Blood based biomarker	Glial fibrillary acidic protein (GFAP)						References: Alcolea 2023 [23], Delaby 2023 [17], Filippi 2023 [10]; Pereira 2021 [67]	Not available in clinical practice, experimental (used in clinical studies only)
Blood based biomarker	Triggering receptor expressed on myeloid cells 2 (TREM2)						References: Delaby 2023 [17]	Not available in clinical practice, experimental (used in clinical studies only)
Blood based biomarker	YKL-40						References: Delaby 2023 [17]	Not available in clinical practice, experimental (used in clinical studies only)
Blood based biomarker	Cytokines-chemokines						References: Delaby 2023 [17]	Not available in clinical practice, experimental (used in clinical studies only)
Genetic testing	APOE	Various tests for the measurement of ApoE4 only, or of all isoforms of the apolipoprotein E (ApoE2, ApoE3, ApoE4) in human plasma.	Lumipulse® G ApoE4 (Fujirebio) Lumipulse® G Pan-ApoE (Fujirebio) ADmark® ApoE Genotype Analysis and Interpretation (Symptomatic)/Athena Diagnostics	No CE mark, for research use only [35] No CE mark, for research use only [35] No CE mark [39] Runs as a Laboratory Developed Test (LDT) in the US.	See information in AWMF guideline on dementia [26]		References: Larson (2023) [56]	Well-established in clinical practice, but not available everywhere.
Genetic testing	PSEN1	Relevant for the diagnosis of monogenic familial AD.					References: Larson (2023) [56]	Well-established in clinical practice, but not available everywhere.

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
		Ethical considerations (potential psychosocial impact) [56]. Limited use for diagnosis of late-onset AD; no strongly associated mutations.						
Genetic testing	PSEN2	Relevant for diagnosis of monogenic familial AD. Ethical considerations (potential psychosocial impact) [56]. Limited use for diagnosis of late-onset AD; no strongly associated mutations.					References: Larson (2023) [56]	Well-established in clinical practice, but not available everywhere.
Genetic testing	Amyloid precursor protein (APP)	Relevant for diagnosis of monogenic familial AD. Ethical considerations (potential psychosocial impact) [56].					References: Larson (2023) [56]	Well-established in clinical practice, but not available everywhere.

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
		Limited use for diagnosis of late-onset AD; no strongly associated mutations.						
PET imaging	Amyloid PET	Florbetaben F18 injection	Neuraceq (Piramal Imaging SA and Isologic Innovative Radiopharmaceuticals/Life Molecular Imaging)	FDA: yes (2014) EMA: yes (2014) [25]	In a study (Sabri 2015) cited by the AWMF guideline, Florbetaben F18 had a sensitivity of 98% (95% CI: 94%-100%) and a specificity of 89% (95% CI: 77%-100%) for the detection of moderate to severe amyloid plaque pathology. Further information can be found in the publication by Iaccarino 2023 [25]		References: Wells 2022 [14], Young 2020 [69], Iaccarino 2023 [25]	Well-established in clinical practice, but not available everywhere
PET imaging	Amyloid PET	Florbetapir F18 injection	Amyvid (Avid Radiopharmaceuticals/ Eli Lilly and Company)	FDA: yes (2012) EMA: yes [25]	In a study (Clark 2012) cited by the AWMF guideline, Florbetapir F18 showed a sensitivity of 92% (95% CI: 78%-98%) and a specificity of 100% (95% CI: 80%-100%) for the detection of moderate to severe amyloid plaque pathology. Further information can be found in the publication by Iaccarino 2023 [25]	Used in phase III RCT - CLARITY AD study (Lecanemab) [2] Used in phase III RCT - TRAILBLAZER-ALZ 2 Study (Donanemab) as secondary endpoint [70]	References: Wells 2022 [14], Young 2020 [69], Iaccarino 2023 [25]	Well-established in clinical practice, but not available everywhere

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
PET imaging	Amyloid PET	Flutemetamol F18 injection	Vizamyl (GE Healthcare)	FDA: yes (2013) EMA: yes [25]	In a study (Ikonomovic 2016) cited in the AWMF guideline Flutemetamol F18 showed a sensitivity of 91% and a specificity of 90% for detecting moderate to severe amyloid plaque pathology. Further information can be found in the publication by Iaccarino 2023 [25]		References: Wells 2022 [14], Young 2020 [69], Iaccarino 2023 [25]	Well-established in clinical practice, but not available everywhere
PET imaging	Amyloid PET	Pittsburgh compound B C11	None	No CE mark [26].	In a study (La Joie 2018) cited in the AWMF guideline, a sensitivity of 89% and a specificity of 86% and an AUC of 0.91 for moderate to severe amyloid plaque pathology was shown. The guideline also highlights the experimental use of this marker and hints that it is not suitable for wider clinical use.		References: Agency for Care Effectiveness (ACE) 2022 [66], Young 2020 [69]	Well-established in clinical practice, but not available everywhere.
PET imaging	Amyloid PET	NAV4694 F18					References: Young 2020 [69]	Not available in clinical practice, experimental (used in clinical studies only).
PET imaging	Tau PET (neurofibrillary tangles) Several tau tracers for PET available (see Table 1 in Young 2020 [69])	Flortaucipir F18 (AV1451)	Tauvid (Avid Radiopharmaceuticals/ Eli Lilly and Company)	FDA approval (2020) [71] EMA: no [25]	Further information can be found in the publication by Iaccarino 2023 [25]	Used in phase III RCT - TRAILBLAZER-ALZ 2 Study (Donanemab) as secondary endpoint [70]	References: Wells 2022 [14], Young 2020 [69], Iaccarino 2023 [25]	Not available in clinical practice, anticipated to see greater adoption in the future (in Austria not yet available, in Germany available at some universities).

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
PET imaging	FDG-PET	FDG F18	None	FDA: yes	Two FDG-PET studies demonstrated 89% sensitivity and 74% specificity in differentiating AD dementia from non-AD dementia. A meta-analysis on FDG-PET involving 20 studies revealed 90% sensitivity and 89% specificity in distinguishing clinically diagnosed AD dementia from non-dementia controls. See information in AWMF guideline on dementia [26].		References: Wells 2022 [14], Young 2020 [69]	Well-established in clinical practice, but not available everywhere.
SPECT	[99mTc] HMPAO-SPECT				Three HMPAO-SPECT studies revealed 64% sensitivity and 83% specificity in differentiating AD dementia from non-AD dementia. Eleven HMPAO-SPECT studies indicated 80% sensitivity and 85% specificity.See information in AWMF guideline on dementia [26]		References: AWMF guideline on dementia [26]	Well-established in clinical practice, but not available everywhere.
Volumetric MRI (whole brain, ventricular volume, hippocampus volume)					The AWMF guideline presents two meta-analysis, one showing the differentiation between AD dementia and healthy individuals with a sensitivity of 83% and specificity of 89% (AUC: 0.93), the other one showing the differentiation between AD from non-AD dementia with a sensitivity of 84% and specificity of 76% (AUC: 0.85).	Used in phase III RCT - CLARITY AD study (Lecanemab) [2] Used in phase III RCT - TRAILBLAZER-ALZ 2 Study (Donanemab) as secondary endpoint [70]	References: Wells 2022 [14]	Well-established in clinical practice, but not available everywhere.

Category of biomarker	Type of biomarker	Further information on biomarker (if applicable)	Trademark name	Regulatory approval status	Sensitivity/specificity of the biomarker (no separate information on the single tests listed under trademark column)	Relevant for medication (if applicable)	Comments	Austria-relevant information based on expert input
Other	Lipid/salivary/ olfactory, biomarkers, retinal and ocular changes novel biomarkers						References: Wells 2022 [14]	Not available in clinical practice, experimental (used in clinical studies only).

Table 2 presents the systematic reviews that included blood biomarker diagnostic accuracy studies.

Table 2: *Systematic reviews and meta-analyses evaluating diagnostic accuracy of blood biomarkers*

Author/year	**Qu 2021 [27]**	Chen 2021 [28]	Hardy-Sosa 2022 [29]
AMSTAR-2 risk of bias assessment	**moderate**	**low**	**Critically low**
Indication	Amnestic mild cognitive impairment (aMCI); Alzheimer's disease (AD)	Amnestic mild cognitive impairment (aMCI); Alzheimer's disease (AD)	Alzheimer's disease (AD) characterization, diagnosis, and prognosis
Country	China	Taiwan	Cuba
Sponsor/conflict of interest	None of the authors have financial disclosures and conflicts of interest. This study was supported by grants from the National Natural Science Foundation of China (91849126), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX03) and ZJlab, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University.	The authors report no declarations of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. We are thankful for the National Nature and Science Foundation of China (NSFC, grant 61871105) and CNS Program of UESTC (No. Y0301902610100201).
Objective	To discover the blood biomarkers for distinguishing AD cases from the normal controls, AD cases from the aMCI patients, or aMCI cases from controls.	To examine the diagnostic accuracy of blood-based biomarkers for detecting AD and aMCI.	To provide an update on the research and development of AD blood-based biomarkers panels and their diagnostic applications for the prediction of AD, accessible to middle- and low-income countries.
Included studies	The blood biomarkers were conducted in the systematic review of 32 eligible studies	A total of 17 studies (n = 2,083) were included.	76 articles met the inclusion criteria for systematic review Most of the studies investigated AD cases vs. healthy controls or conversion from MCI to AD.

Diagnostic accuracy (sensitivity/specificity)	Aβ42*T-tau (AUC = 0.841 - 0.995; sensitivity and specificity >80 %), P-tau 217 (AUC = 0.970 - 0.980, sensitivity and specificity >90 %), P-tau 231 (AUC = 0.63 0 - 0.997); P-tau 181 (AUC = 0.610 - 0.840; sensitivity 67–71 %; specificity 66–86 %), NfL (AUC = 0.590 - 0.920; sensitivity 67–84 %; specificity 78–87 %), T-tau (AUC = 0.490 - 0.993; sensitivity 63–97 %; specificity 50–91 %) and Aβ42/Aβ40 (AUC = 0.490 - 0.977; sensitivity 74–96 %; specificity 50–95 %) show good diagnostic accuracy in identifying AD and aMCI patients from controls.	In differentiating patients with AD from the controls, the diagnostic odds ratio (DOR) was 32.2 for the plasma Aβ42 (sensitivity = 88 %, specificity = 81 %), 29.1 for the plasma Aβ oligomer (sensitivity = 80 %, specificity = 88 %), and 52.1 for the plasma tau (sensitivity = 90 %, specificity = 87 %). For differentiating aMCI from the controls, the DOR was 60.4 for the plasma Aβ42 (sensitivity = 86 %, specificity = 90 %) and 49.1 for the plasma tau (sensitivity = 79 %, specificity = 94 %). The use of ultra-high sensitive technology explained the heterogeneity in the diagnostic performance of blood-based biomarkers (P = 0.01).	Majority of the studies reported plasma and serum as the main source for biomarker determination in blood. Protein-based biomarker panels were reported to aid in AD diagnosis and prognosis with better accuracy than individual biomarkers. Conventional (amyloid-beta and tau) and neuroinflammatory biomarkers, such as amyloid beta-42, amyloid beta-40, total tau, phosphorylated tau-181, and other tau isoforms, were the most represented. We found the combination of amyloid beta-42/amyloid beta-40 ratio and ApoE+4 status to be most represented with high accuracy for predicting amyloid beta-positron emission tomography status.”
Conclusion of study authors	Therein, P-tau 217 and P-tau 231 are proven a significantly higher accuracy than established plasma biomarkers, and blood neurofilament light (NfL) is thought lack of specificity to discriminate AD from other neurodegenerative diseases. Moreover, with the improvement of the assays, the sensitivity and specificity of Aβ and T-tau are decreased, and an individual biomarker is not sufficiently specific and sensitive for AD diagnosis.	A more reliable, cost-effective, and less-invasive test is an essential requirement in the field of AD. The development of ultra-high sensitive biomarker detection and analysis systems can enable blood-based biomarkers to be used for accurate AD diagnosis at the preclinical phase of AD. The findings of our study suggest that plasma tau biomarkers have higher DOR, sensitivity, and specificity for detecting AD than plasma Aβ biomarkers. However, evidence is still limited for detecting aMCI by blood-based biomarkers. In conclusion, plasma tau levels might be used as an easily accessible, minimally invasive biomarker for the early diagnosis of AD.	As shown in our review, a wide variety of blood-based biomarker panels have been recently examined for early AD diagnosis and prediction of MCI conversion to AD. Protein biomarker panels outperformed single candidate markers in detection of the disease. Aβ42/Aβ40 ratio in plasma in combination with age, ApoE+4 status, and gender, seems to be a promising panel for the prediction of amyloidosis due to AD; thus, it may be of use as a less invasive and cost-effective screening tool. The combination of plasma Aβ42/Aβ40, p-tau217, and p-tau181 seems to be a potential non-invasive and costeffective biomarker for diagnosing AD, while other individual markers like plasma p-tau181, NF-L, and Enzyme b-secretase 1 (BACE1) may be used as markers of disease progression and neurodegeneration. Further validation studies on the proposed biomarkers in larger cohorts from various populations and longitudinal studies are needed.
Other relevant information		A letter of critique was published by Hsu et al in 2023 [72] with the following statement: “We believe that there were substantial methodological flaws in their meta-analysis. These methodological flaws included no comprehensive literature search details, neglect of the negative result research, no prespecified cut-off values, erroneous data input in their meta-analysis, and the issue of prevalence determined by the included studies. These factors potentially contributed to overestimation of the discriminative accuracy of blood-based biomarkers. Subsequently, the conclusion that blood-based biomarkers are effective tools for detecting Alzheimer’s disease is debatable without correction of these	

		methodological flaws and providing robust and trustworthy estimates.”	

Abbreviations: Aβ: amyloid beta, AD: Alzheimer’s disease, aMCI: Amnestic mild cognitive impairment, apolipoprotein E (ApoE), AUC: area under the curve, DOR: diagnostic odds ratio, NfL: neurofilament light, p-tau: phosphorylated tau, t-tau: total tau

Only a limited number of **clinical guidelines** with respect to AD and dementia were identified - see Table 3 “Recent clinical guidelines in the field of Alzheimer´s Disease, Dementia, and related diagnostics”. Mostly mentioned biomarkers were CSF Aβ1-42, Aβ1-40, total-Tau, p181Tau and FDG-PET imaging.

clinical guidelines

Table 3: Recent clinical guidelines in the field of Alzheimer´s Disease, Dementia, and related diagnostics

Author/ Year	Guidelines Commission of the German Society for Neurology (DGN) and the German Society for CSF Diagnostics and Clinical Neurochemistry (DGLN) (2019) [40]	National Institute for Health and Care Excellence (NICE) (2018) [73]	German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology (DGPPN), German Society for Neurology (DGN), in cooperation with the German Alzheimer Society e.V. (2023) [26]	European Medicines Agency (EMA)/ Committee for Medicinal Products for Human Use (CHMP) (2018) [74]
Title	Lumbar puncture and spinal cord diagnostics (original title: S1-Leitlinie Lumbalpunktion und Liquordiagnostik) Valid until July 2024 (published at AWMF online)	Dementia: assessment, management and support for people living with dementia and their carers	Dementias (original title: S3-Leitlinie Demenzen) (published at AWMF online) Preliminary guideline published on 01.09.2023- final publication expected in October 2023	Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease
Language	German	English	German	English
Statement regarding biomarker (s)	For AD especially **Aβ1-42, Aβ1-40, t-tau, p-tau181** are relevant. Selective decrease in Aβ1-42 or Aβ1-42/1-40 serves as evidence of amyloid pathology, which is typical of AD. Increased total-tau is an indicator of neuronal cell loss and therefore less specific for AD. Phospho-tau as a marker for hyperphosphorylated tau is also increased in AD. **In development**: p-tau variants, α-synuclein, neurofilaments, and blood-based markers	If the diagnosis is uncertain and AD is suspected, consider either: • **FDG-PET** (fluorodeoxyglucose-positron emission tomography-CT), or **perfusion SPECT** (single-photon emission CT) if FDG-PET is unavailable or • examining **cerebrospinal fluid** for: — **either t-tau or t-tau and p-tau181** and — **either Aß1–42 or Aß1–42 and Aß1–40**. If a diagnosis cannot be made after one of these tests, consider using the other one. • Be aware that the older a person is, the more likely they are to get a false positive with cerebrospinal fluid examination. • Do not rule out AD based solely on the results of CT or MRI scans. • Do not use Apolipoprotein E genotyping or electroencephalography to diagnose AD.	The three essential CSF biomarkers used in AD diagnosis are **Aβ42, p-tau**, and **t-tau**. The most commonly used variant of p-tau in clinical diagnostics is **p-tau181**. Decreased level of Aß42 is associated with a higher risk of dementia. The use of ratio of **Aβ42/40**, **Aß42/p-tau** or **Aß42/t-tau** is superior to the sole quantification of single biomarkers in determining Alzheimer pathology. Structural **MRI** is recommended, especially for the assessment of regional atrophy, including the medial temporal lobe, and the extent of vascular lesions in the etiological differential diagnosis of primary dementia diseases.	**CSF markers as well as MRI and PET imaging markers** are qualified for the enrichment of study populations Context of use of these biomarkers remains to be qualified in preclinical AD. For the purpose of trial enrichment **CSF and PET amyloid biomarkers** are strongly correlated, however it is not clear how much this depends on the type of assay and the cut-off, or different underlying biological processes that these methods are capable of probing their use as interchangeable enrichment measures should be justified by data to ensure that a homogeneous population is selected.Assays operating characteristics should be specified when known. Although the performance of CSF Aβ42 assays has substantially improved it is also advised to measure not only **Aβ42** but also **t-tau or p-tau levels.** Aβ42 and tau ratio was found to have a higher positive predictive value than Aβ42 alone. **APOE ε4 status** may be used as one of the means of enrichmentin a clinical trial population. However, generalizability will have to be justified if only patients with this specific genotype are included without any data in non-carriers.

		• Be aware that young-onset AD has a genetic cause in some people.	**FDG-PET** examination is recommended if, after ruling out reversible causes and following clinical and neuropsychological evaluations and, if necessary, CSF biomarkers, the cause of dementia or mild cognitive impairment remains unclear. **Perfusion-SPECT** (HMPAO-SPECT) might be an alternative when FDG-PET is not available. The routione use of **Apolipoprotein-E genotype** (ApoE) for diagnosis, differential diagnosis, or prognostic considerations in dementia is not recommended. **Please be aware that further detailed recommendations can be found in the guideline.**	Downstream topographical markers of brain regional structural and metabolic changes (e.g. hippocampal atrophy assessed by **MRI,** cortical hypometabolism by **FDG PET**) while having insufficient pathological specificity may be particularly valuable for detection and quantification of disease progression. **So far, one specific biomarker cannot be endorsed over other alternatives for the purpose of identifying those patients who may progress more rapidly**. Hence increasing clinical trial efficiency and **qualification opinion procedures** are encouraged. Many activities are underway on new biomarkers that may emerge in the future, e.g. **tau PET imaging, biomarkers for neuroinflammation, blood or metabolic signatures**.
Level of recommendation	-	-	See respective recommendations	-

Abbreviations: Aβ: amyloid beta, AD: Alzheimer's Disease, ApoE: apolipoprotein E, AWMF: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V., CSF: cerebrospinal fluid, CT: computer tomography, FDG: fluorodeoxyglucose, MRI: magnetic resonance imaging, p-tau: phosphorylated tau, PET: positron emission tomography, SPECT: single-photon emission, t-tau: total tau,

3.4 Standardisation initiatives in Europe

standardisation and validation of biomarkers/ diagnostic tests is necessary

several initiatives are ongoing:

There are **several initiatives** focusing on standardisation and validation of biomarkers/diagnostic tests:

Image Biomarker Standardization Initiative

The **Image Biomarker Standardization Initiative** aims to standardise quantitative radiomics for high-throughput image-based phenotyping. The field of radiomics deals with extraction of large numbers of features from medical images that quantify its phenotypic characteristics in an automated, high-throughput manner. Such features may aid detection of AD. This initiative focused on establishing a nomenclature and definitions for radiomics features; on establishing a general radiomics image processing scheme for calculation of features from imaging; and on providing data sets and associated reference values for verification and calibration of software implementations for image processing and feature computation; and on providing a set of reporting guidelines for studies involving radiomic analyses. As a result, the initiative produced and validated reference values for radiomics features, which enable verification of radiomics software and therefore might enhance reproducibility of radiomics studies [75].

Innovative Medicines Initiative (IMI) project called European Platform for Neurodegenerative Diseases (EPND)

There is an ongoing **Innovative Medicines Initiative (IMI) project called European Platform for Neurodegenerative Diseases (EPND)** that aims to establish a collaborative platform between existing European research infrastructures to accelerate biomarker discovery for neurodegenerative diseases [76]. The EPND catalogue offers an extensive list of international cohorts with neurodegenerative diseases/biomarker studies [77].

Global Biomarker Standardization Consortium (GBSC)

The **Global Biomarker Standardization Consortium (GBSC)**, which was created by the Alzheimer's Association®, involves key researchers, clinicians, industry, regulatory and government leaders in the fields of AD and dementias. Its aim is to reach consensus on standardisation and validation of biomarker tests for use in clinical practice. In 2009, a **Quality Control (QC) programme** was initiated to establish a tool for monitoring the performance of CSF biomarker measurements between research laboratories. Its long-term goal is to improve the quality of the whole chain of procedures associated with CSF and blood biomarker measurements that would stabilise results over time and harmonise biomarker values between international laboratories. Furthermore, the **Standardization of Alzheimer's Blood Biomarkers (SABB) programme** (initiated in 2018) works on the evaluation of pre-analytical factors and on the definition of consensus procedures for collection and processing of blood samples so that measurement of AD biomarkers could be standardised in clinical use [78].

recommendations for validation of biomarker as IVD/ companion diagnostics from

MedTech Europe

MedTech Europe proposed that predictive biomarker assays used in early clinical trials may be validated using a fit-for-purpose approach that can help inform the level of assay validation needed for the use of an assay in an interventional study. Often no commercial assays are available for the specific intended use and assays are co-developed with the drug. The intended purpose of these assays varies and might change during the drug development process. Late stage trials often support the regulatory marketing authorisation of the drug and the CE-marking of the assay as a companion diagnostic [79].

EMA

The EMA performed a review of medicinal products approved by the EMA that showed that the levels of detail provided for biomarker and diagnostic tests varied in the European Public Assessment Report (EPAR) and the Summary of Product Characteristics (SmPCs). With the new Regulation (EU) 2017/746 on in vitro diagnostic medical devices, manufacturers will need to consult regulatory authorities during the review of companion diagnostics

FDA (incl. proposed study designs)

conformity assessment. The opportunity to include more consistent and transparent information in the documents was highlighted [80].

Outside of Europe: the **FDA** requires a context of use process for use of a biomarker as a drug development tool in clinical trials: 1) letter of intent, 2) qualification plan, 3) full qualification package, 4) qualification recommendation. Cummings and Kinney suggested a five-phase in vitro diagnostic and diagnostic imaging data generation process to structure the biomarker development process: phase 1) non-clinical exploratory studies, phase 2) clinical assay development and validation, phase 3) retrospective and longitudinal studies, phase 4) prospective studies and real world evidence, phase 5) implementation and studies of impact on clinical outcomes and cost-effectiveness as well as the assessment of reimbursement [13].

4 Discussion and Conclusion

Many kinds of biomarker are (commercially) available or will be available soon. Due to the advent of Alzheimer drugs the need for non-invasive and inexpensive tests is increasing. However, it is noteworthy that only a limited number of blood biomarkers have obtained the CE mark, and these, as of now, have not yet been incorporated into clinical guidelines or clinical practice.

many different biomarkers are available, but limited number of blood biomarkers

The German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology (DGPPN) and the German Society for Neurology (DGN) recently updated **the clinical guideline "Dementias" (original title: S3-Leitlinie Demenzen)** and published a preliminary report on 01.09.2023 via the „Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V." (AWMF)/"Association of the Scientific Medical Societies in Germany" online [26]. Even this new guideline has not included blood biomarkers in their recommendations, but it emphasizes the significance of CSF, particularly highlighting the importance of the **ratios CSF Aβ42/40, CSF Aβ42/p-tau181 and CSF Aβ42/t-tau** in clinical practice. Various studies have shown that all three ratios display similar diagnostic values, which tend to be higher than the diagnostic values for the individual markers.

Recently updated German S3-guideline on Dementias

Even though **blood biomarkers** have a potential to detect AD in an early and minimally invasive manner, and to be used for differential diagnosis of dementia and for monitoring the disease, they are not validated for broad application in clinical practice (yet). There are difficulties in comparing these blood biomarkers amongst each other due to different evaluations of their performances in various contexts as well as due to the use of different analytical procedures. Furthermore, they have often been used in combination with each other. The next step from **using biomarkers in research** is their **validation in therapeutic clinical trials**: they can be used for both stratification of patients and as indirect markers of efficacy or target engagement. Another further step would be to **use biomarkers in clinical practice.** Currently blood-based biomarkers are used in addition to CSF and neuroimaging biomarkers for AD diagnostic, and for screening and follow-up of patients at risk [17].

blood biomarkers: potential to detect AD in an early and minimally invasive manner, but not validated yet

and not yet implemented in clinical guidelines/ practice

In summary, the quality of the available evidence about diagnostic accuracy of blood biomarkers is moderate to critically low. Further evidence is needed to be able to compare the diagnostic accuracy of the different biomarker types.

available evidence about diagnostic accuracy is limited

Key to the implementation of a biomarker is **harmonisation of the procedure and availability of certified reference materials and methods** [81]. Standardisation and validation of biomarkers is important, some efforts are ongoing.

key is harmonisation of the procedure and availability of certified reference materials and methods

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6 Appendix

Table 4: Risk of Bias Assessment of Systematic Reviews with AMSTAR-2 [20]

Author, year (indication)	Chen 2021 [28]	Qu 2021 [27]	Hardy-Sosa 2022 [29]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes	Yes	No
5. Did the review authors perform study selection in duplicate?	No	No	No
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	n.a.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Yes	n.a.
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	Yes	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	n.a.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes
Overall confidence	**Low**	**Moderate**	**Critically low**

Abbreviations: AMSTAR: A Measurement Tool to Assess Systematic Reviews, n.a.: not applicable, RCT: randomised controlled trial

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