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Preferred methodological reporting for blood-based biomarker research for the Alzheimer's Disease and Related Dementias research community

Are you conducting blood-based biomarker research for Alzheimer's disease or other neurodegenerative diseases?

The Alzheimer's Association's Evidence-Synthesis and Knowledge Translation (Guideline Development) Program, in collaboration with a guideline panel of clinical and subject-matter experts, recently published an evidence-based clinical practice guideline (CPG) on the use of blood-based biomarkers (BBMs) for Alzheimer's disease in specialty care settings.[1]

This guideline was accompanied by a **systematic review** that summarizes the body of evidence relevant to the clinical topic.[2] In that review, methodologists identified several ways study authors could improve their study conduct and reporting to **better support translational research** and future guideline development.

Incomplete or unclear reporting in primary studies can directly affect the conclusions of systematic reviews. When essential information is missing, otherwise eligible studies may be excluded. Even when studies are included, inadequate reporting of methods, outcomes, or sources of bias often leads to weakening the overall findings of the systematic review and hence downgrading the certainty of evidence.

By following the preferred methodological reporting suggestions below, you can:

INCREASE

Increase the likelihood that your study will be included in systematic reviews

IMPROVE

Improve the overall certainty of the included evidence

SUPPORT

Ultimately support guideline panels in formulating stronger, clearer and more actionable recommendations for clinical practice

When preparing evidence reviews, each major study design has an established preferred reporting guideline and a corresponding risk-of-bias (RoB) assessment tool.

Specifically, diagnostic test accuracy studies should follow Standards for Reporting of Diagnostic Accuracy **(STARD)** and be evaluated with the Quality Assessment of Diagnostic Accuracy Studies 2 **(QUADAS-2)** tool. Together, these paired reporting checklists and RoB tools promote transparency, reproducibility and structured methodological assessment across diverse study designs.

In addition to the above preferred reporting items, we further emphasize that the primary study authors:

1 REPORT KEY NUMBERS FOR BIOMARKER PERFORMANCE

Consider including these details in supplementary files if they cannot be accommodated in the main manuscript. Table 1 below provides an example of these key numbers.

a. The number of true positives (Tp), true negatives (Tn), false positives (Fp) and false negatives (Fn) according to cognitive status.

b. Thresholds/cutoffs that have been used (if applicable) and method used to determine the threshold. The threshold should preferably be regulatory approved cutoffs or those reported by the in-house laboratory (if applicable).

c. The corresponding sensitivity (Sn), specificity (Sp) and diagnostic accuracy for the chosen reference test.

TEST	Threshold (Youden)	Accuracy	Sn	Sp	Tp	Tn	Fp	Fn
Plasma p-tau181	>0.21 pg/mL	84%	86%	88%	245	420	57	40
Plasma Aβ42/40	>0.053	83%	78%	95%	213	455	24	60

Table 1: *Detection of amyloid PET positivity in participants with MCI (n = 800).* **Disclaimer:** *hypothetical data for illustration purposes only.*

2 CLEARLY DESCRIBE THE METHODS

Transparency improves the usability of evidence for secondary research and decision-making.

a. **Recruitment:**
Describe how participants were recruited, including the clinical setting (e.g., memory clinic), the enrollment process and any inclusion/exclusion criteria.
For example: "Participants were recruited from a memory clinic based on clinical referrals from primary care for cognitive assessment. During January 2021 to January 2023, patients who met the inclusion criteria were invited to participate."

b. **Blinding:**
Report whether biomarker analyses were conducted in a blinded manner.
For example: "All BBM samples were analyzed by staff blinded to the results of CSF or amyloid PET."

c. **Missing data:**
Report missing data and how the missing or replaced data were handled, if applicable.

d. **Timing:**
Report the time between reference and index tests. Aim for the shortest possible interval.
For example: "The time between blood collection and PET scan was 36 days on average (range: 2-59 days)."

3 PRIORITIZE USING THE SAME REFERENCE STANDARD TO CLASSIFY PARTICIPANTS

Mixed reference standards introduce classification bias, limiting the certainty of the evidence. When this is not feasible, which is common in clinical settings, perform a sensitivity analysis restricted to participants with the same reference test.

For example, if Alzheimer's pathology is defined by CSF (n = 650) or amyloid PET (n = 50), repeat the analyses with only CSF-confirmed participants (n = 650) and report these results in the supplement.

Additionally, it is important to report the prevalence of AD pathology for each sub-population according to the reference standard.

Glossary

Accuracy:
The proportion of all test results (positive and negative) that are correct. Can be calculated as (number of true positives + number of true negatives) / total number of individuals.

False negative (Fn):
A test result that incorrectly indicates the absence of a condition when it is actually present.

False positive (Fp):
A test result that incorrectly indicates the presence of a condition when it is actually absent.

Index test:
The diagnostic test being evaluated for its performance, e.g., p-tau217.

Reference test:
The method used to determine the true disease status, e.g., amyloid PET.

Sensitivity (Sn):
The ability of a test to correctly identify those with the condition, the true positives. Can be calculated as the number of true positives / (number of true positives + number of false negatives).

Specificity (Sp):
The ability of a test to correctly identify those without the condition, the true negatives. Can be calculated as the number of true negatives / (number of true negatives + number of false positives).

Threshold/cutoff:
The specific value of a biomarker or test result that separates "positive" results from "negative" results.

True negative (Tn):
A test result that correctly indicates the absence of a condition when it is truly absent.

True positive (Tp):
A test result that correctly indicates the presence of a condition when it is truly present.

Disease Prevalence:
The number of individuals with the disease (a positive reference test) / the total number of individuals tested.

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For additional information and professional resources, visit **alz.org/ALZPro.**

1. Palmqvist S, Whitson HE, Allen LA, et al. Alzheimer's Association Clinical Practice Guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings. Alzheimer's Dement. 2025; 21:e70535. doi: 10.1002/alz.70535.

2. Pahlke et al. Blood-based biomarkers for detecting Alzheimer's disease pathology in cognitively impaired individuals within specialized care settings: A systematic review and meta-analysis. Alzheimer's Dement. 2025 Nov;21(11):e70828. doi: 10.1002/alz.70828.

About the Alzheimer's Association

The Alzheimer's Association is a worldwide voluntary health organization dedicated to Alzheimer's care, support and research. Our mission is to lead the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection and maximizing quality care and support. Our vision is a world without Alzheimer's and all other dementia®. Visit **alz.org** or call 800.272.3900.

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