Setting Acceptable Performance Standards for Alzheimer's Disease Blood Tests

Plain Language Summary of "Acceptable performance of blood biomarker tests of amyloid pathology — recommendations from the Global CEO Initiative on Alzheimer's Disease" Schindler, et. al. (2024) Nature Reviews Neurology

Key Takeaways

Blood tests for the amyloid pathology characteristic of Alzheimer's disease are **more acceptable and accessible** to patients than traditional biomarker tests but their performance can vary.

An expert workgroup was convened to recommend **minimum acceptable performance standards** for blood tests used in clinical settings.

For blood tests used to identify individuals **more likely to have amyloid pathology** but that require a second test for confirmation, a sensitivity of 90% or higher and a specificity of 85% or higher is recommended.

For blood tests used to **confirm the presence of amyloid pathology**, the workgroup recommends a sensitivity and specificity of 90% or higher.

The use of blood tests that meet these performance standards could enable more people to receive an **accurate and timely Alzheimer's disease diagnosis** and potentially benefit from new treatments.

Who created these recommendations?

- This work was sponsored by The Global CEO Initiative on Alzheimer's Disease (CEOi), a non-profit organization working to advance patient care.
- CEOi brought together expert academics and clinicians, representatives from diagnostics companies and pharmaceutical companies, and patient advocacy groups to generate these recommendations.

Alzheimer's disease is defined by brain changes, including accumulation of the protein beta-amyloid into amyloid plaques and the protein tau into tangles, and damage to brain cells.

- **Biomarkers of amyloid pathology** are typically used in clinical practice as an indicator of Alzheimer's disease pathology.
- Alzheimer's disease can be diagnosed in the context of **a comprehensive clinical evaluation** that rules out other potential causes of cognitive impairment and a **positive biomarker test** for amyloid pathology.

Blood biomarker tests offer an acceptable and accessible method for detecting amyloid pathology.

- Although amyloid PET and CSF tests for amyloid pathology have been available for many years, these methods have drawbacks including perceived invasiveness, limited accessibility outside of specialty care settings, high costs, and inadequate reimbursement.
- **Blood tests offer distinct advantages** over amyloid PET and CSF tests: they are more acceptable to patients, more accessible in primary care and rural settings, and less expensive.
- Accessibility of tests is critically important given that **85%** of diagnoses are made by clinicians who are not dementia specialists.[1]

Two major clinical uses for blood tests are expected:

- **Triaging patients who are likely to have amyloid pathology** for further evaluation including a more accurate confirmatory test.
- **Confirming the presence of Alzheimer's pathology** without the need for any additional biomarker testing.

Interpretation of blood test results depends on the clinical use:

	Positive Result	Intermediate Values	Negative Result
Triage	Increased likelihood of amyloid pathology but a more accurate confirmatory test is required for confirmation	Blood tests may have an intermediate zone to improve accuracy of classifying individuals with or without amyloid pathology. A blood test should not be used if more than 15–20% of individuals in a typical clinical population fall into this intermediate zone. If a blood test result is intermediate, the appropriate next step varies by patient and care setting.	Unlikely to have amyloid pathology
Confirm Amyloid Pathology	Amyloid pathology is present and no further testing is needed		Amyloid pathology is absent

Key metrics to consider when interpreting the performance blood tests:		
Performance Metric	**Definition**	**How Metric was Used**
Reference Standard	Benchmark used to measure and compare the performance of a diagnostic test	Amyloid PET was the reference standard to determine acceptable sensitivity and sensitivity for blood tests
Sensitivity	Proportion of true positives that are correctly identified by a diagnostic test	Sensitivity of a blood biomarker test is the percentage of amyloid PET-positive individuals with a positive blood test
Specificity	Proportion of true negatives that are correctly identified by a diagnostic test	Specificity of a blood test is the percentage of amyloid PET-negative individuals with a negative blood test
Positive Predictive Value (PPV)*	Likelihood that a positive result reflects the presence of the condition being tested for	PPV of a blood biomarker test is the likelihood that an individual with a positive blood test is amyloid PET-positive
Negative Predictive Value (NPV)*	Likelihood that a negative result reflects the absence of the condition being tested for	NPV of a blood biomarker test is the likelihood that an individual with a negative blood test is amyloid PET-negative

PET, positron emission tomography.
* The PPV and NPV are strongly influenced by the prevalence of amyloid pathology in the population being tested. In clinical practice, the prevalence of amyloid pathology varies according to patient and provider characteristics. Clinicians should refine the estimated likelihood of amyloid pathology for an individual patient on the basis of their complete diagnostic work-up.
The PPV and NPV of a blood test can be estimated using a free online calculator accessed here: **https://amyloid.shinyapps.io/NPV_PPV/.**

Expert recommendations for blood tests for triaging or confirmation of amyloid pathology in primary care and secondary care.

The clinical setting (primary or secondary care) and the type of use (triaging or confirming diagnosis) influences the recommended performance standard of blood tests for Alzheimer's disease. Information on how to interpret blood tests that include an intermediate zone can be found in the published recommendations.[2] Blood tests should only be used for patients with evidence of cognitive impairment.

	Blood biomarker test for use in primary care		Blood biomarker test for use in secondary care	
	Triage test	**Confirmation test**	**Triage test**	**Confirmation test**
Target patient population	Alzheimer's disease is **suspected after assessment for other conditions**		Alzheimer's disease is **suspected after a comprehensive assessment** for other conditions	
	Age >55 years*	Age >65 years*	No age cut-off	
Accuracy required	**Sensitivity ≥90%** **Specificity ≥85%** †	**Sensitivity ≥90%** **Specificity ≥90%**	**Sensitivity ≥90%** **Specificity ≥85%**	**Sensitivity ≥90%** **Specificity ≥90%**
Intended use	• **Positive test:** Identifies individuals who are likely to have amyloid pathology but require a second test for confirmation • **Negative test:** Identifies individuals who are unlikely to have amyloid pathology	• **Positive test:** Confirms amyloid pathology when considered with all clinical findings • **Negative test:** Identifies individuals who are unlikely to have amyloid pathology	• **Positive test:** Identifies individuals who likely have amyloid pathology but require a second test for confirmation • **Negative test:** Identifies individuals who are unlikely to have amyloid pathology	• **Positive test:** Confirms amyloid pathology when considered with all clinical findings • **Negative test:** Identifies individuals who are unlikely to have amyloid pathology

*The prevalence of amyloid pathology in younger adults typically seen in primary care settings is very low; therefore, appropriate age cutoffs have been recommended. However, younger patients with a high suspicion of amyloid pathology could be tested.

†A specificity of 75% may be acceptable in secondary care settings with high capacity for follow-up amyloid PET or CSF biomarker testing.

Additional key information

Blood tests are likely the **only biomarker method scalable enough** to test all people who might benefit from an accurate Alzheimer's diagnosis.

Several blood biomarkers tests of amyloid pathology that are currently available may meet the recommended performance standards.

Incorporating high-performance blood biomarker tests in clinical care could **enable many more people with cognitive impairment to receive an accurate and timely diagnosis and potentially access new treatments** for early Alzheimer's disease.

For more information, visit www.alzbiomarkerhub.org

Adapted from: Schindler, S.E. et al. Acceptable performance of blood biomarker tests of amyloid pathology — recommendations from the Global CEO Initiative on Alzheimer's Disease. Nat Rev Neurol, 20, 426–439 (2024).

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References

1. Drabo, E. F. et al. Longitudinal analysis of dementia diagnosis and specialty care among racially diverse Medicare beneficiaries. Alzheimers Dement. 15, 1402–1411 (2019).
2. Schindler, S.E. et al. Acceptable performance of blood biomarker tests of amyloid pathology — recommendations from the Global CEO Initiative on Alzheimer's Disease. Nat Rev Neurol, 20, 426–439 (2024).

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