The use of biomarkers for the accurate and timely diagnosis of Alzheimer's disease in clinical practice

Diagnostic paradigm shift

A diagnostic paradigm shift is required whereby clinical symptoms and biomarkers assessment of AD pathology are combined within the diagnostic process to achieve a timely and accurate diagnosis of AD.[1-3]

Detection

- Symptoms
- Patient and family history

Diagnosis

- Standard blood test and neurological examination
- Cognitive and functional assessments
- Structural imaging
- Biomarkers
  CONFIRMATORY TESTS

Treatment

Impact of biomarker utilisation

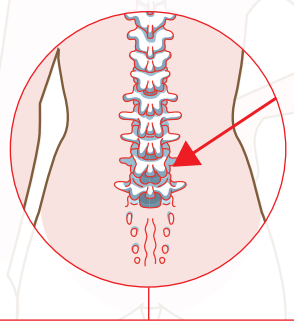
Using biomarkers can add precision to diagnosis and enhance physicians' diagnostic confidence[4,5]

Improves patient management whereby physicians develop a comprehensive treatment plan and administer the correct care according to the diagnosis[1,4,5]

Improves patient management by allowing access to trials and empowering patients to address modifiable risk factors and be involved in decision-making[6-8]

Biomarkers in AD

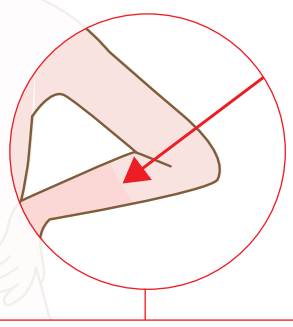
CSF[1,9,10,12-19]



Pathology	What is Measured	AD*
Amyloid **T**au	$A\beta_{42}$, $A\beta_{42}/A\beta_{40}$ concentration	↓
	P-tau181/$A\beta_{42}$ concentration	↑
	P-tau181, P-tau217 and P-tau231 concentration	↑

Assays	Advantages	Disadvantages
CSF assays	- Simultaneous information on the Aβ and tau biomarkers - More accessible and scalable, and less expensive than PET by 10-15-fold - No radiation exposure - Inter/intra-lab reliability	- No localisation and does not detect regional Aβ or tau deposition - Cannot be used to stage AD - Invasive, can be uncomfortable for patients - Collection can be difficult – requires standardised techniques and procedural skill

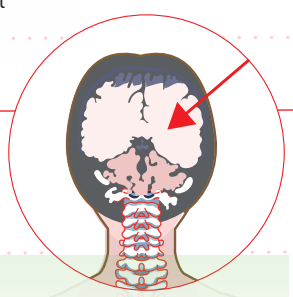
Blood[1,2,9,11,17,24,25]



Pathology	What is Measured	AD*
Amyloid **T**au	$A\beta_{42}$, $A\beta_{42}/A\beta_{40}$ concentration	↓
	P-tau181, P-tau217 and P-tau231 concentration	↑

Assays	Advantages	Disadvantages
Blood-based assays	- Multiple biomarkers can be assessed and measurements can be repeated - Easy to collect, though require standardised collection techniques - Less invasive than CSF - More accessible and scalable, and less expensive than PET and CSF	- No localisation and cannot be used to stage AD - Additional validation would be required for accuracy - Pre-analytical factors can affect results - Not yet widely available although broader access anticipated

PET[1,9,17,20-23]



Pathology	What is Measured	AD*
Amyloid **T**au	Tracer binding to Aβ plaques	↑
	Tracer binding to NFTs	↑

Assays	Advantages	Disadvantages
Amyloid and/or tau PET	- Less invasive than other procedures to assess biomarkers - Provide *in vivo* localisation of amyloid or tau, matching pathology spreading patterns - Allow quantification of pathology load - Can be used for staging AD	- Has limited access outside specialised memory clinics - Is more expensive than other methodologies - Has the potential for image interpretation errors - Exposure to radiation - Currently able to assess one biomarker at a time

*Arrow indicates direction of change in measure in individuals with AD vs healthy individuals.

Conclusion

- **The use of biomarkers combined with clinical symptoms is key to ensure the timely and accurate diagnosis of AD in patients exhibiting initial symptoms of the disorder [4,5]**

- Using CSF/PET biomarkers may add precision to diagnosis and enhance physicians' diagnostic confidence[5]
- Access to biomarker data may impact treatment decisions in most patients with MCI or dementia[4]
- Biomarkers are changing the field and should be used based on availability to physicians[16]

References

1. Hampel H, et al. *Nat Aging*. 2022;2:692-703. 2. Hansson O, et al. *Alzheimers Dement*. 2022;18:2669-2686. 3. Porsteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;8:371-386. 4. Rabinovici GD, et al. *JAMA*. 2019;321:1286-1294. 5. Hazan J, et al. *J Neurol Neurosurg Psychiatry*. 2023;94:113-120. 6. Dubois B, et al. *J Alzheimers Dis*. 2016;49:617-631. 7. National Health Service. Guidance on dementia coding. https://dementiapartnerships.com/wp-content/uploads/sites/2/nhs-london-read-code-guidance.pdf, accessed April 2023. 8. Liss JL, et al. *J Intern Med*. 2021;290:310-334. 9. Iaccarino L, et al. *J Prev Alzheimers Dis*. 2023. 2023;10:426-442. 10. Leuzy A, et al. *Neurology*. 2021;97:e1681-e1694. 11. Bayoumy S, et al. *Alzheimers Res Ther*. 2021;13:198. 12. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14:535-562. 13.Hansson O, et al. *Alzheimers Res Ther*. 2019;11:34. 14. Lee JC, et al. *Exp Mol Med*. 2019;51:1-10. 15. Vanderstichele H, et al. *Alzheimers Dement*. 2012;8:65-73. 16. Dubois B, et al. *Lancet Neurol*. 2021;20:484-496.17. Zetterberg H, Blennow K. *Mol Neurodegener*. 2021;16:10. 18. Hansson O, et al. *Alzheimers Dement (Amst)*. 2020;12:e12137. 19. Zetterberg H, et al. *Alzheimers Dement (Amst)*. 2019;11:784-786. 20. Johnson KA, et al. *Cold Spring Harb Perspect Med*. 2012;2:a006213. 21. Suppiah S, et al. *Diagnostics (Basel)*. 2019;9:65. 22. Jack CR Jr, et al. *Acta Neuropathol*. 2013;126:doi:10.1007/s00401-013-1185-7. 23. van Oostveen WM, de Lange ECM. *Int J Mol Sci*. 2021;22:2110. 24. Teunissen CE, et al. *Lancet Neurol*. 2022;21:66-77. 25. Shen X-N, et al. *Alzheimers Dement (Amst)*. 2020;12:e12104.

Aβ=amyloid beta; AD=Alzheimer's disease; CSF=cerebrospinal fluid; MCI=mild cognitive impairment; NFT=neurofibrillary tangle; PET=positron emission tomography; P-tau=phosphorylated tau.