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Invited State-Of-The-Art Review

Biomarkers in dementia disorders – a narrative review

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ABSTRACT

With the introduction of specific or unspecific biomarkers, the diagnosis of dementia disorders has changed from a purely clinical to a biological construct. This review presents biomarkers for the most common neurodegenerative disorders. Specific biomarkers for misfolded proteins have been developed for Alzheimer's disease and dementia with Lewy bodies. Unspecific biomarkers for neurodegeneration, synaptic dysfunction and neuroinflammation may also be helpful in diagnosing or staging dementia disorders.

KEY POINTS

- Specific biomarkers for neurodegenerative diseases can be measured in cerebrospinal fluid, plasma or by positron emission tomography
- New criteria and staging of Alzheimer's disease and dementia with Lewy bodies comprise the use of biomarkers
- Biomarkers of neurodegeneration aid in the diagnosis and staging of disease severity

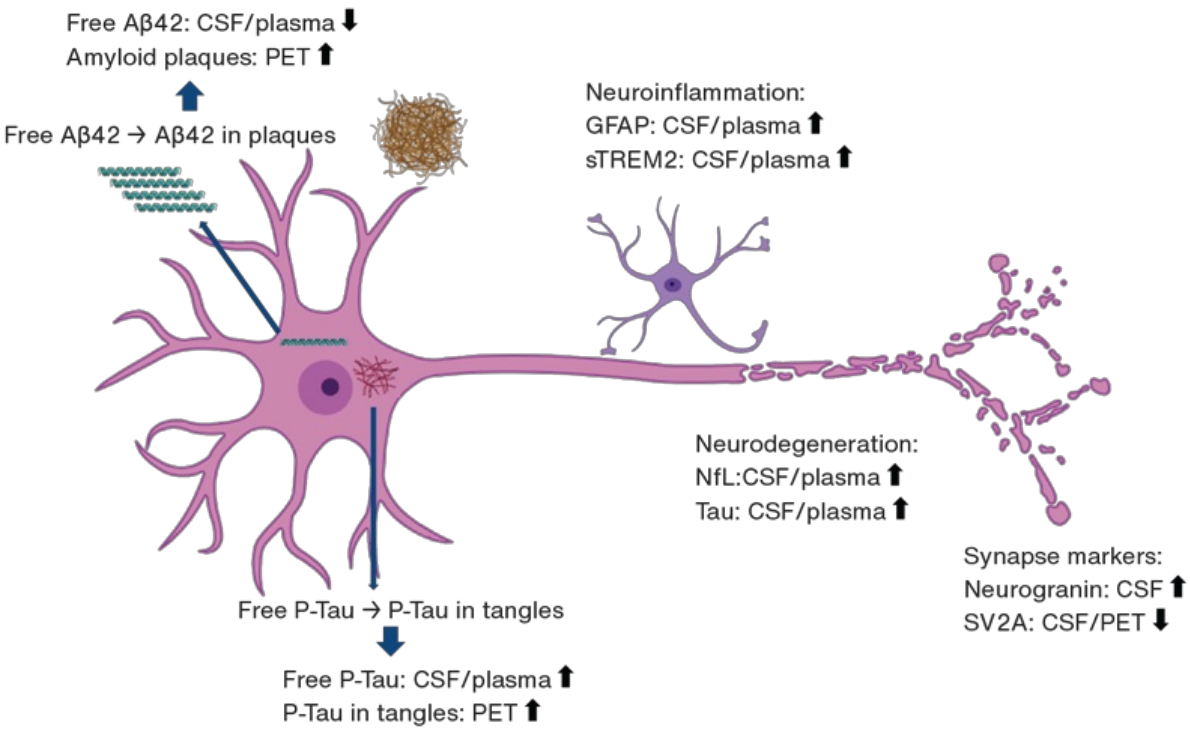
Dementia is a syndrome characterised by cognitive dysfunction and impairment of activities of daily living. Age is the most important risk factor, and with an ageing population, the prevalence of dementia is increasing. In Denmark, approximately 96,000 people are living with dementia, a number that will increase to 134,000 by 2035 [1]. The incidence remains stable at around 8-9,000 new cases annually [2]. The most common causes of dementia are Alzheimer's disease (AD) (55%), dementia due to cerebrovascular disease (25%), Lewy body dementia (4%) and frontotemporal dementia (2%). Dementia disorders vary with respect to genetic risk factors, symptoms, progression and medical treatment. Correct diagnosis enables the person with dementia and their close relatives to cope with the disease while receiving tailored assistance from the community. Specific medical treatment for some of these disorders stabilises the symptoms, and disease-modifying drugs for AD, which are currently being marketed, will likely be available in Denmark in the future. Biomarkers for dementia disorders allow for earlier and more accurate diagnoses. Even among clinical dementia specialists, the accuracy of a clinical diagnosis is only around 70-80%, and the use of biomarkers increases this accuracy [3].

This review article presents well-established biomarkers with a primary focus on AD. Biomarkers for other dementia disorders and the status of new blood-based biomarkers will be discussed briefly. To contextualise biomarkers in diagnostics, it is essential to change the perception of dementia disorders. This paper accomplishes this using AD as an example.

The concept of Alzheimer's disease

Neither the International Classification of Diseases, 11th version (ICD-11) criteria [4], nor the Diagnostic and Statistical Manual of Mental Disorders, 5th version (DSM-5) criteria [5] specifically include biomarkers in the diagnostic criteria for AD. These clinical criteria make sense when diagnosing the syndrome of dementia but not when a specific brain disease must be diagnosed as the underlying cause of the dementia syndrome. Consequently, during the past 15 years, the perception of AD has changed from a clinical entity towards a biological definition. The most widely accepted model of the pathophysiological development of AD states that the extracellular aggregation of the protein β-amyloid1-42 (Aβ42) into plaques triggers a series of downstream events, including the aggregation of hyperphosphorylated Tau (P-tau) into intracellular tangles [6]. Hyperphosphorylation of Tau leads to microtubule instability and eventually promotes neurodegeneration, which spreads from the temporal lobe through interconnected networks of neurons to other cortical areas accompanied by neuroinflammation, oxidative stress and mitochondrial dysfunction [7]. Aβ42 is related to synaptic activity. Moreover, in a healthy brain, free Aβ42 is cleared from the brain to the cerebrospinal fluid (CSF) and blood, leading to high concentrations in these biofluids. In patients with AD, Aβ42 levels in the CSF and blood are reduced because free Aβ42 is shunted into plaques (**Figure 1**). Aβ42 aggregation increases with age and is found in 3% of cognitively normal persons aged 50- 59 years, increasing to more than 40% of cognitively elderly people above 85 years [8]. The prevalence is roughly the same as the prevalence of dementia due to AD 15-20 years later, suggesting a decade-long preclinical stage. This observation is also supported by long-term follow-up studies of at-risk subjects who are genetically susceptible to AD [9]. It also implies that many amyloid-positive elderly subjects will never live to experience Alzheimer-related cognitive symptoms.

FIGURE 1 Neuropathological events in Alzheimer's disease. For details, please see text.



Aβ42 = β-amyloid1-42; CSF = cerebrospinal fluid; GFAP = glial fibrillary acidic protein; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; NfL = neurofilament light chain; P-Tau: phosphorylated tau; SV2A = synaptic vesicle glycoprotein 2A.

Phosphorylation of Tau can occur at various sites of the protein. Some phosphorylations arise early in the disease when the first amyloid plaques are formed but are not yet detectable by PET using amyloid radioligands [10]. Increasing levels of P-tau217 and P-tau231 in the CSF and blood have thus been found to be good markers of early amyloid aggregation (Figure 1). Subsequently, when P-tau aggregates into tangles, P-tau217 in the CSF and blood predominantly reflects tangle formation. Tangles and subsequent neurodegeneration with loss of neurotransmitters, synapses and neuronal networks correlate with clinical symptoms. Biomarkers for neurodegeneration include structural magnetic resonance imaging (MRI), showing atrophy in vulnerable areas such as the mesial temporal lobe and hippocampus [11].

Furthermore, PET, using ^{18}F-fluoro-deoxy-glucose as a tracer for glucose metabolism, shows hypometabolism in temporal and parietal cortical areas. Neurodegeneration may also be estimated in the CSF and blood by increased levels of neurofilament light chain (NfL), representing axonal degeneration, and increased levels of non-phosphorylated Tau, representing general neuronal degeneration. As mentioned, protein accumulation does not occur in a vacuum, and glial fibrillary acidic protein (GFAP) expressed by astrocytes and soluble triggering receptor expressed on myeloid Cells 2 (sTREM2) seem to be promising biomarkers of neuroinflammation [12]. Markers of synaptic dysfunction include neurogranin, which binds to postsynaptic membranes, and synaptic vesicle glycoprotein 2A (SV2A), which is found in all synapses [13] (Figure 1). Because biomarkers of neurodegeneration, neuroinflammation and synaptic dysfunction are all unspecific, changes in these markers may occur in many brain diseases. Conversely, non-specificity also implies that they can be beneficial for detecting pathology in diseases without specific biomarkers.

Alzheimer's disease as a biological diagnosis

In 2011, research clinical criteria for AD were updated to include biomarkers for Alzheimer's pathology in patients with a clinical phenotype of AD [14]. According to this approach, biomarkers are applied when the aetiology is uncertain. This is often the case in younger patients, patients with milder cognitive impairment and patients with atypical phenotypes. In 2018, AD was defined by pathological events using the Amyloid/Tau/Neurodegeneration (A/T/N) nomenclature according to the amyloid cascade model (**Figure 2**) [15]. The clinical phenotype and biomarkers still form part of the staging of disease severity. However, in the latest proposed revision of these criteria, it was suggested that AD should be defined by biomarkers only, starting with the first appearance of amyloid plaques in the brain [16]. This implies that a person with normal cognition who is biomarker-positive for amyloid plaques has AD.

FIGURE 2 The figure shows a staging system of Alzheimer's disease and related biomarkers reflecting plaques, tangles and neurodegeneration biomarkers for aetiology, disease staging, inflammation and co-pathology.

A (Aβ42 in amyloid plaques)
Biofluids[a]: Aβ42/40 ratio, P-Tau181/Aβ42 ratio, Tau/Aβ42 ratio
PET-scanning: Amyloid

T (P-Tau in tangles)
Biofluids[a]: P-Tau181, P-Tau217
PET-scanning: Tau

N (Neurodegeneration)
Biofluids[a]: NfL, Tau, Neurogranin, SV2A
PET: FDG, SV2A
MRI: Structural

I (Inflammation)
Biofluids[a]: GFAP

V (Vascular brain injury co-pathology)
MRI/CT: Structural (infarction, white matter lesions)

S (Alpha-synuclein co-pathology)
Biofluids[a]: Alpha-synuclein

Aβ42 = β-amyloid1-42; CSF = cerebrospinal fluid; GFAP = glial fibrillary acidic protein; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; NfL = neurofilament light chain; P-Tau = phosphorylated tau; SV2A = synaptic vesicle glycoprotein 2A.
a) CSF or plasma.

Furthermore, biomarkers for aetiology (amyloid and P-tau in the CSF, amyloid-PET imaging, Figure 2) are now distinguished from biomarkers for disease staging (mainly Tau-PET, but also new Tau biomarkers) [16]. Additionally, biomarkers for non-specific processes related to AD (neuroinflammation, neurodegeneration) and co-pathology (vascular pathology, alpha-synuclein pathology) are now incorporated into the criteria to classify the extent of pathological processes [16]. This shift from a clinical-biological definition to a purely biomarker-driven definition is based on the wish to classify patients by their pathology rather than clinical syndrome. With the advent of new drugs targeting specific Alzheimer's pathologies, this classification also becomes crucial when selecting eligible patients. However, some criticism has been raised of this approach, mainly in relation to the classification of cognitively healthy elderly people as having a disease that may not manifest through clinical

symptoms in their lifetime. It is indisputable, however, that specific biomarkers are becoming increasingly employed in diagnosing AD.

Specific biomarkers for Alzheimer's disease

In CSF and blood, free Aβ42 is lower in patients with AD than in controls, whereas free P-tau is higher (Figure 1). The ratios in the CSF of Aβ42/Aβ40 (another form of amyloid) and P-tau181/Aβ42 or Tau/Aβ42 have shown a higher accuracy in diagnosing amyloid plaques (measured by PET) in the brain using the area under the curve (AUC), increasing from 0.81-0.86 for individual biomarkers to 0.94 for ratios [17]. For differential diagnosis, AD biomarkers in the CSF were able to separate AD from non-AD dementia disorders with a diagnostic accuracy of 80-90% [18,19]. Recently, a study found that plasma P-tau217 seems to predict both plaques and tangles-positivity (measured by PET) with the same accuracy as Aβ42/Aβ40 and P-tau181/Aβ42 ratios in the CSF [20]. Most of these results are obtained in research cohorts employing state-of-the-art analytic methods, and the accuracy of new plasma assays needs to be confirmed in mixed memory clinic populations and ultimately validated in a general practitioner setting. PET imaging is often used as the gold standard for plaque and tangle formation, and amyloid-PET is often used when CSF marker results are ambiguous. Tau-PET is only starting to get implemented and may be helpful for diagnosing other diseases with tau accumulation where patterns differ from those of AD [21]. Both CSF and blood biomarkers are good predictors of progression in persons with mild cognitive impairment of unknown aetiology. In such persons, a positive biomarker points to an early prodromal stage of AD and a high likelihood of progressing to the dementia stage [22, 23]. However, in established AD dementia, neither amyloid-PET, CSF, nor blood biomarkers are good disease severity markers, whereas Tau-PET more accurately reflects increasing disease pathology [24].

Specific biomarkers for dementia with Lewy bodies

Until recently, specific biomarkers of neurodegenerative diseases within the Parkinson's spectrum were limited to PET imaging using tracers of dopaminergic deficits. Both Parkinson's disease, dementia with Lewy bodies and multiple system atrophy are characterised by the aggregation of misfolded α-synuclein in neurons or glial cells. Seed amplification assays (SAA) can now demonstrate misfolded α-synuclein in CSF and skin with a high accuracy [25]. This has encouraged a transition from a strictly clinical diagnostic method to a biological understanding of "neuronal α-synucleinopathies" similar to what has been observed in AD [26].

Specific biomarkers for frontotemporal dementia

The two major types of protein aggregation in frontotemporal lobar degeneration (FTLD), which includes the clinical phenotypes of frontotemporal dementia, are misfolded Tau and TAR DNA-binding protein of 43 kDa (TDP-43) accumulation. It is challenging to predict the underlying pathology based on clinical phenotypes, and although neuroimaging may increase the likelihood of an FTLD aetiology, topographical atrophy or hypometabolism patterns cannot reliably distinguish between pathological subtypes. Furthermore, no specific biomarkers in CSF or blood for Tau or TDP-43 aggregation in FTLD are in clinical use.

Unspecific biomarkers for neurodegeneration and neuroinflammation

The topographical abnormalities identified by MRI and fluorodeoxyglucose (FDG)-PET are instrumental in diagnosing and staging the severity of various neurodegenerative diseases and may also aid in identifying neurodegeneration or neuronal dysfunction in individuals with atypical, unclear or very mild symptoms [27].

For diseases where specific biomarkers are not currently available, typical FDG-PET topographical patterns may enhance the likelihood of a specific dementia disorder, as demonstrated in their utility in distinguishing between AD and DLB [28]. Furthermore, in patients with mixed pathologies, FDG-PET may assist in differential diagnosis [29].

Plasma NfL may be used as a screening tool in the diagnostic evaluation of patients with cognitive dysfunction, because it enables the differentiation of neurodegenerative from non-neurodegenerative disorders with a reasonable sensitivity and specificity of 80% [30]. Among dementia disorders, NfL levels are highest in FTLD; however, the overlap of NfL levels across various clinical conditions may limit its utility as a routine diagnostic marker [31]. NfL levels are also elevated in vascular dementia with axonal damage due to subcortical ischemic lesions [32] or stroke [33] and in traumatic brain injury [34]. A combination of NfL and GFAP in plasma has recently shown a reasonable ability to distinguish FTLD-Tau from FTLD-TDP43, with AUCs around 0.80 to 0.88 [35]. Even though GFAP is a non-specific marker of neuroinflammation, its elevation in AD is relatively large compared to other non-AD dementia disorders [36], suggesting that neuroinflammation is a significant contributor to the pathophysiology of AD. Interestingly, plasma levels of GFAP are more closely associated with amyloid plaques in the brain than GFAP in the CSF [37], and plasma GFAP may be a promising marker for monitoring neuroinflammation in AD. sTREM2 seems to reflect an early inflammatory response to amyloid aggregation and may aid in understanding AD pathological propagation [38]. Synaptic biomarkers such as neurogranin and SV2A are still in the early phase of validation but show some promise in tracking synaptic dysfunction in several dementia disorders [39, 40].

Conclusion

Biomarkers of specific pathologies, namely markers of protein accumulation measured in biofluids or through PET scanning, have been increasingly utilised in the diagnosis and prognostication of AD. The shift from a clinical to a clinical-biological concept of AD impacts diagnostic accuracy and facilitates the identification of patients eligible for disease-modifying treatments. New α-synuclein assays have paved the way for a similar shift in the diagnostic framework for α-synucleinopathies, including Lewy body dementia and Parkinson's disease. While biomarkers for atrophy, hypometabolism, neuroinflammation and synaptic dysfunction are non-specific, they serve as valuable tools for identifying concomitant pathology and diagnosing disorders for which no specific biomarkers are presently available.

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REFERENCES

1. Alzheimer Europe. Dementia in Europe Yearbook 2019: Estimating the prevalence of dementia in Europe. 2019. https://www.alzheimer-europe.org/sites/default/files/alzheimer_europe_dementia_in_europe_yearbook_2019.pdf (12 Feb 2025)
2. Taudorf L, Nørgaard A, Islamoska S, et al. Declining incidence of dementia: A national registry-based study over 20 years. *Alzheimers Dement*. 2019;15(11):1383-91. https://doi.org/10.1016/j.jalz.2019.07.006
3. Bloudek LM, Spackman DE, Blankenburg M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. *J Alzheimers Dis*. 2011;26(4):627-45. https://doi.org/10.3233/JAD-2011-110458
4. World Health Organization (WHO). International Classification of Diseases (ICD-11). Eleventh Revision. 2019. https://www.who.int/standards/classifications/classification-of-diseases (12 Feb 2025)
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. 2013. https://doi.org/10.1176/appi.books.9780890425596
6. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016;8(6):595-608. https://doi.org/10.15252/emmm.201606210
7. Musiek ES, Holtzman DM. Three dimensions of the amyloid hypothesis: time, space and "wingmen". Nat Neurosci 2015;18:800-6. https://doi.org/10.1038/nn.4018
8. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924-38. https://doi.org/10.1001/jama.2015.4668
9. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease [published correction appears in N Engl J Med. 2012 Aug 23;367(8):780]. N Engl J Med. 2012;367(9):795-804. https://doi.org/10.1056/NEJMoa1202753
10. Milà-Alomà M, Ashton NJ, Shekari M, et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease [published correction appears in Nat Med. 2022 Sep;28(9):1965. doi: 10.1038/s41591-022-02037-1.]. Nat Med. 2022;28(9):1797-1801. https://doi.org/10.1038/s41591-022-01925-w
11. Burton EJ, Barber R, Mukaetova-Ladinska EB, et al. Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. Brain. 2009;132(Pt 1):195-203. https://doi.org/10.1093/brain/awn298
12. Simrén J, Elmgren A, Blennow K, Zetterberg H. Fluid biomarkers in Alzheimer's disease. Adv Clin Chem. 2023;112:249-81. https://doi.org/10.1016/bs.acc.2022.09.006
13. Colom-Cadena M, Spires-Jones T, Zetterberg H, et al. The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. Alzheimers Res Ther. 2020;12(1):21. https://doi.org/10.1186/s13195-020-00588-4
14. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-9. https://doi.org/10.1016/j.jalz.2011.03.005
15. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535-62. https://doi.org/10.1016/j.jalz.2018.02.018
16. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimer's & Dementia 2024;20:5143-69. https://doi.org/10.1002/alz.13859
17. Doecke JD, Ward L, Burnham SC, et al. Elecsys CSF biomarker immunoassays demonstrate concordance with amyloid-PET imaging. Alzheimers Res Ther.2020;12(1):36. https://doi.org/10.1186/s13195-020-00595-5
18. Mattsson-Carlgren N, Grinberg LT, Boxer A, et al. Cerebrospinal Fluid Biomarkers in Autopsy-Confirmed Alzheimer Disease and Frontotemporal Lobar Degeneration. Neurology 2022;98. https://doi.org/10.1212/WNL.0000000000200040
19. Engelborghs S, De Vreese K, Van de Casteele T, et al. Diagnostic performance of a CSF-biomarker panel in autopsy-confirmed dementia. Neurobiol Aging 2008;29:1143-59. https://doi.org/10.1016/j.neurobiolaging.2007.02.016
20. Barthélemy NR, Salvadó G, Schindler SE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. Nat Med 2024;30:1085-95. https://doi.org/10.1038/s41591-024-02869-z
21. Groot C, Villeneuve S, Smith R, et al. Tau PET Imaging in Neurodegenerative Disorders. J Nucl Med. 2022;63(Suppl 1):20S-26S. https://doi.org/10.2967/jnumed.121.263196
22. Salvadó G, Larsson V, Cody KA, et al. Optimal combinations of CSF biomarkers for predicting cognitive decline and clinical

conversion in cognitively unimpaired participants and mild cognitive impairment patients: A multi-cohort study. *Alzheimers Dement*. 2023;19(7):2943-55. https://doi.org/10.1002/alz.12907

23. Saloner R, VandeVrede L, Asken BM, et al. Plasma phosphorylated tau-217 exhibits sex-specific prognostication of cognitive decline and brain atrophy in cognitively unimpaired adults. Alzheimers Dement. 2024;20(1):376-87. https://doi.org/10.1002/alz.13454
24. Therriault J, Pascoal TA, Lussier FZ, et al. Biomarker modeling of Alzheimer's disease using PET-based Braak staging. Nat Aging 2022;2:526-35. https://doi.org/10.1038/s43587-022-00204-0
25. Arnold MR, Coughlin DG, Brumbach BH, et al. α&;Synuclein seed amplification in CSF and brain from patients with different brain distributions of pathological α&;synuclein in the context of co&;pathology and non&;LBD diagnoses. Ann Neurol 2022;92:650-62. https://doi.org/10.1002/ana.26453
26. Simuni T, Chahine LM, Poston K, et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. Lancet Neurol 2024;23:178-90. https://doi.org/10.1016/S1474-4422(23)00405-2
27. Gramkow MH, Gjerum L, Koikkalainen J, et al. Prognostic value of complementary biomarkers of neurodegeneration in a mixed memory clinic cohort. PeerJ 2020;8:e9498. https://doi.org/10.7717/peerj.9498
28. Gjerum L, Frederiksen KS, Henriksen OM, et al. Evaluating 2-[18F]FDG-PET in differential diagnosis of dementia using a data-driven decision model. Neuroimage Clin 2020;27:102267. https://doi.org/10.1016/j.nicl.2020.102267
29. Minoshima S, Cross D, Thientunyakit T, et al. 18 F-FDG PET Imaging in Neurodegenerative Dementing Disorders: Insights into Subtype Classification, Emerging Disease Categories, and Mixed Dementia with Copathologies. J Nuclear Med 2022;63:2S-12S. https://doi.org/10.2967/jnumed.121.263194
30. Simonsen AH, Gleerup HS, Musaeus CS, et al. Neurofilament light chain levels in serum among a large mixed memory clinic cohort: Confounders and diagnostic usefulness. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2023;15. https://doi.org/10.1002/dad2.12512
31. Delaby C, Alcolea D, Carmona-Iragui M, et al. Differential levels of neurofilament light protein in cerebrospinal fluid in patients with a wide range of neurodegenerative disorders. Sci Rep 2020;10:9161. https://doi.org/10.1038/s41598-020-66090-x
32. Duering M, Konieczny MJ, Tiedt S, et al. Serum Neurofilament light chain levels are related to small vessel disease burden. J Stroke 2018;20:228-38. https://doi.org/10.5853/jos.2017.02565
33. Holmegaard L, Jensen C, Pedersen A, et al. Circulating levels of neurofilament light chain as a biomarker of infarct and white matter hyperintensity volumes after ischemic stroke. Sci Rep 2024;14:16180. https://doi.org/10.1038/s41598-024-67232-1
34. Andersson E, Öst M, Dalla K, et al. Acute-phase neurofilament light and glial fibrillary acidic proteins in cerebrospinal fluid predict long-term outcome after severe traumatic brain injury. Neurocrit Care 2024; https://doi.org/10.1007/s12028-024-01998-0
35. Cousins KAQ, Shaw LM, Chen-Plotkin A, et al. Distinguishing frontotemporal lobar degeneration Tau from TDP-43 using plasma biomarkers. JAMA Neurol 2022;79:1155-64. https://doi.org/10.1001/jamaneurol.2022.3265
36. Pereira JB, Janelidze S, Smith R, et al. Plasma GFAP is an early marker of amyloid-β but not tau pathology in Alzheimer's disease. Brain 2021;144:3505-16. https://doi.org/10.1093/brain/awab223
37. Benedet AL, Milà-Alomà M, Vrillon A, et al. Differences between plasma and cerebrospinal fluid glial fibrillary acidic protein levels across the Alzheimer disease continuum. JAMA Neurol 2021;78:1471. https://doi.org/10.1001/jamaneurol.2021.3671
38. Biel D, Suárez&;Calvet M, Hager P, et al. sTREM2 is associated with amyloid&;related p&;tau increases and glucose hypermetabolism in Alzheimer's disease. EMBO Mol Med 2023;15. https://doi.org/10.15252/emmm.202216987
39. Bavarsad MS, Grinberg LT. SV2A PET imaging in human neurodegenerative diseases. Front Aging Neurosci 2024;16. https://doi.org/10.3389/fnagi.2024.1380561
40. Willemse EAJ, Sieben A, Somers C, et al. Neurogranin as biomarker in CSF is non-specific to Alzheimer's disease dementia. Neurobiol Aging 2021;108:99-109. https://doi.org/10.1016/j.neurobiolaging.2021.08.002

