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The role of cerebrospinal fluid and other biomarker modalities in the Alzheimer's disease diagnostic revolution

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Abstract

A major transformation in dementia diagnosis and care appears imminent and will depend on three major types of biomarkers: molecular imaging, blood-based biomarkers, and cerebrospinal fluid biomarkers. Each modality has unique strengths and limitations that suggest its optimal uses in research, clinical trials, and clinical diagnosis.

After two decades during which numerous experimental treatments for Alzheimer disease (AD) failed to demonstrate clinical benefit, recent trials have shown that altering both the pathobiology and the clinical course of AD may be possible[1,2]. AD biomarkers—tests that reflect the specific brain pathology of AD, including amyloid plaques and neurofibrillary tangles—have been essential to recent advances. Specialized molecular imaging techniques, cerebrospinal fluid (CSF) biomarkers, and more recently blood-based biomarkers (BBBM), have allowed investigators to identify cognitively unimpaired individuals who are at high risk for developing mild cognitive impairment (MCI) or dementia due to AD; confirm AD brain pathology in individuals suspected of having MCI or dementia due to AD; and verify that drugs have expected biological effects such as reducing amyloid plaque burden. Despite the high utility of AD biomarkers in research and clinical trials, their use in clinical practice has been limited because disease-modifying treatments (DMTs)

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Dr Schindler has received honoraria for educational presentations and serving as a member of the Biospecimen Review Committee with the National Centralized Repository for Alzheimer Disease and the Alzheimer Disease Center Clinical Task Force. Dr Schindler has a non-compensated relationship as a board member with the Greater Missouri Alzheimer's Association. Dr Schindler has analyzed blood-based biomarker data provided by C2N Diagnostics to Washington University and has served on a Scientific Advisory Board for Eisai.

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were not available and therefore confirmation of AD pathology was often not expected to significantly affect patient outcomes. However, the United States (US) Food and Drug Administration recently approved two putative DMTs, aducanumab and lecanemab, under the accelerated approval pathway based on the reduction of amyloid-plaque burden being "reasonably likely to predict clinical benefit." It is now possible, and increasingly probable, that DMTs will be incorporated into care for select patients with MCI or mild dementia due to AD. Confirmation of AD pathology will be required prior to initiation of DMTs, which may increase the need for AD biomarker testing by orders of magnitude. During this new era in which a major transformation in dementia diagnosis and care seem imminent, the optimal uses of different AD biomarker modalities must be considered. While molecular imaging, CSF biomarkers, and BBBM usually agree regarding which individuals have significant AD brain pathology, the varying characteristics of these modalities affect which type of test may be most appropriate for different patient profiles and various research and clinical uses. We will outline the strengths and limitations of molecular imaging, BBBM, and CSF biomarkers (Table 1), and describe the research and clinical contexts in which each modality may be particularly helpful. We will then focus on CSF testing, which is currently the most widely used AD biomarker modality in dementia specialty clinics around the world.

Roles of molecular imaging, BBBM, and CSF biomarkers

Molecular imaging provides uniquely detailed information on AD pathology that has high utility in research and clinical trials. Imaging with PET radioligands enables visualization of the spatial distribution of amyloid and tau pathology throughout the brain, information that is not provided by fluid biomarkers. Further, molecular imaging measures represent the lifetime accumulation of AD pathology, whereas fluid biomarkers reflect biomarker levels in CSF or blood at the time of fluid collection and are less direct measures of overall AD pathology. The localization, burden and neurophysiological impact of AD pathology drives cognitive-behavioral symptoms and therefore molecular imaging measures are widely used in AD research and clinical trials. However, clinical use of amyloid PET and tau PET are greatly limited due to low rates of insurance reimbursement or low access outside very limited settings and circumstances, such as Veterans Health Administration specialty clinics, evidence development registry studies covered by the Centers for Medicare and Medicaid Services [CMS] including the New Imaging Dementia-Evidence for Amyloid Scanning [New IDEAS] study, and select AD observational studies and clinical trials. The lack of reimbursement for amyloid PET and tau PET scans is likely related to their high cost: amyloid PET scans typically cost approximately $5,000-7,000 compared to less than $1,000 for CSF biomarkers. While reimbursement policies are likely to evolve when a DMT gains standard FDA approval, insurers may still place restrictions on the number of scans or indications for coverage (e.g., CMS has previously allowed one amyloid PET scan per beneficiary per lifetime, and then only under coverage with evidence development). Even if amyloid PET or tau PET are reimbursed by insurance, the need for highly specialized equipment and personnel will limit locations where scans can be performed. For some individuals, concerns about radiation, including cumulative risks (even if very small), can affect their willingness to undergo PET scans. Overall, while molecular imaging provides an unparalleled level of detail regarding spatial distribution and burden of amyloid and

tau pathology that is useful for research and clinical trial purposes, this modality may not be practical for routine clinical care in the US, and is even less practical in lower/middle-income countries.

Advances in the development of BBBM have occurred very rapidly over recent years. BBBMs have major practical advantages that make them ideal screening tests for research and clinical trials, and also, as they mature, for clinical diagnostic purposes [3]. Currently, a wide variety of BBBM analytes are under investigation in research studies and clinical trials, including Aβ42/Aβ40, p-tau181, p-tau231, p-tau217, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP)[4]. While BBBM do not provide data on the spatial distribution of AD pathology, and may reflect the burden of more advanced AD pathology to a lesser extent than molecular imaging, the best assays for plasma Aβ42/Aβ40 and p-tau217 demonstrate very high agreement with amyloid PET in identifying individuals with AD brain pathology[5,6]. Although a limited number of BBBM are currently available for clinical use, the cost of each test is approximately $500-$1,250, significantly less than molecular imaging. More importantly, blood collection is widely accessible and acceptable to most individuals, including individuals from minoritized groups, which may enable much broader AD biomarker testing[7]. Because highly specialized staff is not required for blood collection, BBBM may be the only AD biomarker modality that could quickly scale up to enable testing of hundreds-of-thousands or even millions of individuals per year, which may be required if DMTs become widely available. However, there is broad consensus that the accuracy and robustness of BBBM must be rigorously validated in diverse and representative real-world cohorts and varied clinical settings before their widespread clinical use can be recommended[8]. While real-world validation studies are pending, BBBM are being used in research, clinical trials, and clinical diagnosis in situations where their practical advantages outweigh concerns, or when a confirmatory test with a second modality (molecular imaging or CSF biomarkers) can be performed.

CSF testing can be extremely informative in the clinical evaluation of dementia, especially in patients with atypical, young-onset or rapidly progressive presentations. Unlike molecular imaging scans, which provide information on single pathology-type (e.g., amyloid or tau), CSF testing can be used to evaluate a myriad of potential etiologies including infectious, inflammatory, neoplastic, or neurodegenerative conditions[9]. Also, unlike molecular imaging and BBBM, CSF biomarkers are typically reimbursed by US insurers, including Medicare. Unfortunately, while lumbar puncture (LP) is safe and well-tolerated, some individuals perceive LP as risky and/or invasive; this perception is especially prevalent among individuals identifying with minoritized groups that may distrust medical and research institutions and medical procedures for well-founded ethical, inclusion, equity-related, and historical reasons. Negative perceptions of LP by potential participants is a major reason that CSF testing is not performed or is optional in many research studies and clinical trials. Another inherent limitation of LP is the requirement for specialized personnel, making CSF collection much less available than blood collection. Further, some patients have contraindications to LP such as anti-coagulant use. Despite the drawbacks, the comprehensiveness, maturity and robustness of CSF-based tests have made them the most frequently used AD biomarker modality in dementia specialty clinics in the US and globally,

and therefore we will examine the role of CSF biomarkers in this rapidly evolving area in more detail.

Clinical use of CSF testing

CSF testing is often the preferred diagnostic modality for patients evaluated in dementia specialty clinics, especially for patients with atypical presentations and/or a wide differential diagnosis. Routine CSF data, including opening pressure, cell counts, total protein and glucose, are helpful in evaluating for infectious or inflammatory conditions. There are also many additional CSF tests available for neuroinflammatory, neoplastic and infectious conditions including immunoglobulin profile, oligoclonal bands, autoantibody panels, cytology and/or flow cytometry, and PCR tests for specific pathogens. Real-time quaking-induced conversion (RTQuic) assays for the pathogenic form of prion protein are highly sensitive and specific tests for Creutzfeldt-Jacob disease [9]. Assays for misfolded α-synuclein may identify individuals with Parkinson disease, Dementia with Lewy Bodies, Multiple System Atrophy, and other disorders[10]. Neurofilament light is elevated in multiple neurological disorders for which there are no specific biomarkers and can serve as an indicator that a neurological disorder is present[11]. There are now two FDA approved CSF tests for AD, which both include the concentrations of a panel of CSF biomarkers (e.g., amyloid-β peptide 42 [Aβ42] and 40 [Aβ40], total tau, and tau phosphorylated at position 181 [p-tau181]). CSF biomarker ratios including Aβ42 (e.g., Aβ42/Aβ40 or p-tau181/Aβ42) are more accurate in predicting amyloid PET status, clinical symptoms, and post-mortem AD neuropathologic changes compared to single analytes[9,12]. While the plethora of available CSF tests is very useful for evaluating patients with atypical clinical presentations (e.g., rapidly progressive dementia), the CSF biomarker ratio is often the only informative test in patients with a typical AD presentation. Therefore, a comprehensive CSF evaluation is often unnecessary and a sufficiently accurate and well-validated BBBM could be used to evaluate for the presence of AD brain pathology in many cases. Recent guidelines recommend a confirmatory test (e.g., amyloid PET or CSF biomarkers) if possible after BBBM testing[8], but if the diagnostic disagreement between CSF and BBBM decreases to near zero[5], BBBM testing without confirmatory testing would be reasonable in typical AD presentations and comprehensive CSF testing may be reserved for patients with atypical presentations or complex profiles.

The future of CSF biomarkers

Even with the advent of BBBM, CSF testing will continue to be a key modality in AD research, clinical trials, and clinical diagnosis, and is likely to aid the development of additional BBBM for AD and other neurodegenerative disorders. The proximity of CSF to the brain milieu, as well as the relatively simple composition of CSF compared to blood, enables robust detection of disease-associated changes that may be more difficult to detect in blood. Recently described specific CSF tau species represent improved biomarkers of AD that better reflect amyloid (p-tau217 and p-tau231) and tau pathology (p-tau205 and the microtubule binding region of tau including position 243 [MTBR243]) as well as clinical symptoms (p-tau217, p-tau205, and MTBR243)[13,14]. A mass spectrometry technique for measuring CSF tau species in AD was recently applied to non-AD dementias

and yielded the first biomarker of primary tauopathies[15]. Misfolded proteins such as PrP and α-synuclein have thus far only been robustly detectable in CSF[10]. While some of these measures are likely to be rapidly developed into BBBM clinical tests (e.g., p-tau217, p-tau231), the cutting edge of biomarker research and development may require CSF. Continued inclusion of CSF collection in research and clinical trials, when possible, will help to fuel development of better CSF tests, and lead to advances in BBBM tests.

Conclusion

A major transformation in dementia care appears imminent and will depend on the use of AD biomarkers. Molecular imaging, with its associated high costs and limited accessibility, may be best suited to research and clinical trials, which benefit from highly detailed information on the spatial distribution and burden of pathology. In the coming years, BBBM will enable AD screening (and/or prognostic, predictive, or DMT effect/pharmacodynamic monitoring) at a scale that cannot be rivaled by other modalities, but currently a confirmatory test is recommended when possible until these assays are fully validated. CSF biomarkers provide highly accurate, robust and validated benchmarks useful in research, clinical trials, and clinical diagnosis, but have accessibility limitations compared to BBBM. If DMTs become widely clinically available, BBBM could screen a large number of individuals potentially appropriate for treatment, while molecular imaging and/or CSF testing could be used for confirmatory testing. As BBBM are further validated and become more widely used, CSF testing will remain useful in the evaluation of patients with atypical presentations or complex profiles and to advance the development of improved biomarkers for AD and related disorders.

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Table 1.

Relative strengths and weaknesses of AD biomarker modalities.

Two green checkmarks denote a strength, an orange checkmark denotes neither a strength or weakness, and a red x denotes a weakness.

	Molecular imaging	CSF biomarkers	BBBM
Scientific aspects			
Diagnostic performance	✓✓	✓✓	✓
Strength of validation	✓✓	✓✓	✓
Reflects spatial distribution of pathology	✓✓	✗	✗
Reflects amount of pathology	✓✓	✓	✓
Enables evaluation of multiple pathologies	✗	✓✓	✓
Practical aspects			
Cost of test	✗	✓	✓
Cost to individual (reimbursed)	✗	✓✓	✗
Availability	✗	✓	✓
Acceptability	✓	✓	✓✓