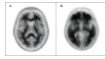


Clinical use of Alzheimer Disease Biomarkers in Diagnosing Dementia



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Objectives

- Understand the difference between dementia and Alzheimer disease
- Understand why and when biomarkers of Alzheimer disease can be helpful in diagnosing the cause of dementia
- Describe the three major types of Alzheimer disease biomarkers that are currently used in the clinic, including their benefits and limitations
- Describe some of the major challenges that need to be addressed by future biomarker studies

What is the difference between dementia and Alzheimer disease?

- Dementia is a decline in memory and thinking that impairs function
- Alzheimer disease is defined by the presence of amyloid plaques and tau tangles in the brain
- Alzheimer disease is the most common cause of dementia
- Many people (~25% of individuals older than age 70) start to accumulate amyloid plaques and tau tangles in the brain
- When individuals have high levels of amyloid plaques and tau tangles in the brain, they are at high risk of developing dementia
- Dementia caused by Alzheimer disease (Alzheimer disease dementia) usually starts with short-term memory impairment and progresses to include all cognitive domains



Dementia



Alzheimer disease

What are Alzheimer disease biomarkers?

- Imaging, fluid, cognitive, or other tests that are strongly correlated with Alzheimer disease brain pathology and/or symptoms caused by Alzheimer disease brain pathology
- Major Alzheimer disease biomarkers in clinical practice:
 - Levels of key proteins in the cerebrospinal fluid (CSF) or blood
 - Amyloid positron emission tomography (PET)
- Biomarkers can help clinicians to decide whether Alzheimer disease brain pathology is present and likely to be causing dementia



Alzheimer disease



Dementia

Current standard of care in dementia diagnosis

- Alzheimer disease dementia is diagnosed based on 1) ruling out other potential causes 2) establishing a history of a typical Alzheimer disease clinical syndrome
- Requires a comprehensive approach to evaluate for clinical features typical of AD and other causes of dementia, especially reversible causes of dementia
 - **Clinical history**- Was there an insidious onset, slow progression, and early impairment of memory?
 - **Medical history**- Does the patient have medical conditions that can cause cognitive impairment?
 - **Medication history**- Is the patient taking medications that impair cognition?
 - **Family history**- Did family members have dementia symptoms at approximately the patient's age?
 - **Psychometric testing**- Are there impairments on tasks of memory, orientation, attention/concentration, language, executive function, visuospatial function, etc.?
 - **Neurological exam**- Are there signs of language dysfunction, visuospatial dysfunction, stroke or parkinsonism?
 - **Blood work**- Are there metabolic issues that could cause cognitive impairment (blood chemistries, blood cell counts, thyroid function tests and vitamin B12 levels)
 - **Brain imaging**- Is there evidence of strokes or an atypical degree of brain atrophy?
- **AD biomarkers are rarely utilized (<5% of cases), usually because of high cost, lack of availability, or the conclusion that testing would not alter the diagnosis or management**

Without biomarkers...

- Even after a comprehensive evaluation, the diagnosed cause(s) of cognitive impairment is often unclear or incorrect
 - Uncertainty: When dementia specialists say they don't know the diagnosis, they are often right—they often don't know¹
 - Misdiagnosis: In numerous studies, including clinical trials, ~25% of individuals diagnosed with Alzheimer disease dementia by clinical criteria did not have brain amyloidosis²



¹Rabinovici JAMA 2019
²Karran NEJM 2014

Does an accurate diagnosis matter?

- No
 - Knowing the correct diagnosis may not alter long-term outcomes
 - "I don't want to know"
 - "There is nothing we can do about it anyway..."
- Yes
 - Patients and their families often want an accurate diagnosis so they can make good decisions about their future (e.g. retiring, moving, traveling)
 - Biomarker testing sometimes affects clinical decision making, such as whether to order medications (e.g. donepezil)¹
 - Patients and their families may want to consider treatment with amyloid-lowering drugs
 - Patients may want to participate in clinical trials
 - Without biomarkers, the diagnosis often remains uncertain and clinicians "wait and see" for month to years to decide whether cognitive impairment is likely due to Alzheimer disease

¹Rabinovici JAMA 2019

When should we use biomarkers?

- When biomarker testing is likely to affect diagnosis or management
 - Appropriate use criteria (AUC) for amyloid PET¹ and CSF biomarker² testing in clinical dementia diagnosis have been established that mostly recommend clinical use for atypical, early onset, and uncertain dementia
 - Biomarker confirmation of AD is essential in patients being considered for amyloid-lowering drugs³

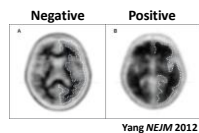
¹Johnson A&D 2013 ²Shaw A&D 2018 ³Cummings J PrevAD 2021

Case presentation

- 59 yo mechanic with a history of hypertension and depression who over one year started forgetting what his partner told him, had difficulty with some chores (loading the dishwasher), and was fired from his job for unclear reasons.
- He underwent testing at another institution and was reported to have "suboptimal effort." Their potential diagnoses included factitious disorder and malingering. He applied for disability and was denied.
- His neurological examination was largely normal and he seemed relatively unconcerned about his cognition. However, he scored a 23 on the MMSE and 10 on the Short Blessed, with impaired performance on tasks of attention, episodic memory, and orientation. He was unable to copy intersecting pentagons or draw a clock. Laboratories and outside brain imaging were normal.
- CSF biomarkers showed very low Aβ42 (231 pg/ml) and very high total tau (840 pg/ml) and ptau (100 pg/ml).
- The patient was diagnosed with Alzheimer disease dementia with visuospatial dysfunction (likely posterior cortical dysfunction).
- With a clear diagnosis, he received disability and his partner and friends were more understanding of his issues.
- Over the past several years, his dementia has progressed and he now needs help with dressing and other basic activities.

Amyloid PET

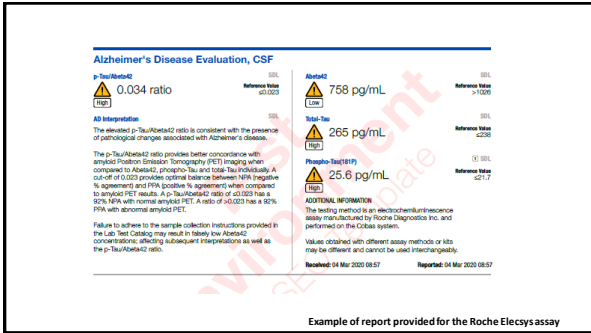
- Pros:
 - Accurate and well-established
 - Patients tolerate well
 - Acceptable for patients on anti-coagulation
 - Multiple FDA approved tracers
- Cons:
 - Expensive (~\$6,000 out-of-pocket)
 - Limited availability (only major medical centers)
 - Small amount of radiation, IV placement, requires lying flat for ~45 min
 - Dichotomous read (positive/negative), not as sophisticated as the quantitative measure that is used for research
 - The scan is only for amyloid—no other biomarkers are evaluated



CSF biomarkers

- Pros:
 - Accurate and well-established (especially new automated platforms)
 - Insurance typically reimburses most of cost (AD test is ~\$750-1,000)
 - Multiple conditions can be evaluated (e.g. labs can be run for autoimmune encephalopathy, CJD)
 - Multiple analytes can be measured and quantitative results are provided
- Cons:
 - Many patients perceive a LP as invasive
 - Post-LP issues (e.g. headache, back pain)
 - Major burden for providers/inadequate reimbursement
 - Not FDA approved (despite being widely used)





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Blood tests

- Pros**
 - Most individuals (including members of groups typically reluctant to undergo amyloid PET or CSF collection) are comfortable having blood drawn
 - Minimal burden to patient and provider
 - Lower costs may be possible (e.g. <\$1,000)
 - Scalable—little investment required to increase volume of tests
 - Multiple analytes can be measured and quantitative results are provided
- Cons**
 - Currently, only a single blood test is available for clinical use
 - Cost is currently \$1,250 (although a sliding scale is available)
 - No blood tests are yet reimbursed by insurance or FDA approved
 - Clinical use of blood tests is not yet well established
 - The accuracy of blood tests is not as well established

A possible new paradigm for dementia evaluation

- Patients with cognitive impairment in whom Alzheimer disease is a potential cause undergo an Alzheimer disease blood test as part of their initial work-up
- Clinicians use this information to guide their evaluation and management
 - The blood test is not assumed to provide the diagnosis, but is one key piece of information that is considered
 - Non-AD causes of cognitive impairment continue to be considered, even in patients with a positive blood test
 - Amyloid PET or CSF biomarkers are performed if clinicians and patients think it would be helpful to diagnosis and management
- Instead of Alzheimer disease being treated as a “rule-out” diagnosis that is given at the end of an extended work-up after evaluating all other possibilities, it is considered early on
- This paradigm could lead to earlier and more accurate diagnosis of Alzheimer disease and facilitate early treatment with AD-modifying drugs (if/when available)

Biomarkers: the next phase of research

The real goal of clinical biomarker testing is not to determine whether an individual is biomarker “positive” or “negative,” but answering this question:

Is Alzheimer disease causing cognitive impairment in this individual patient?

Improving interpretation of biomarker results

PROBLEM: Current AD biomarker tests are for brain amyloidosis, NOT for symptomatic Alzheimer disease, and brain amyloidosis isn't linearly correlated very well with symptomatic Alzheimer disease.

SOLUTIONS: 1) Create models that predict the risk of symptomatic AD, not just brain amyloidosis. 2) Incorporate biomarkers that mediate the relationship between brain amyloidosis and symptomatic AD.

Koscik, Betthausen...Johnson DADM 2020

Merluzzi...Bendlin Neurology 2018

Summary

- Accurate biomarkers are available that reveal whether high amounts of Alzheimer disease pathology are present in the brain
- Biomarkers have been infrequently used in clinical practice because of various drawbacks; blood tests may enable broader use
- We need to better understand the relationship between biomarker levels and cognitive impairment, and how this relationship is modified by factors like age, sex, APOE genotype, race, and comorbidities
- We need to ensure that our research advances are available to everyone who could benefit

The Knight ADRC Fluid Biomarker Core

With deep gratitude to our research participants

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 - Plasma A β 42/A β 40 and NFL predicts cognitive decline: Andy Aschenbrenner, Yan Li
 - Racial differences in plasma biomarkers: Tommy Karikari, Nicholas Ashton, Kaj Blennow, Henrik Zetterberg
 - Disparities in memory clinic population: Aditi Gupta, Abigail Lewis, Inez Oh, Albert Lai