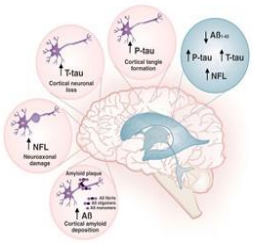
Fluid Biomarkers of Alzheimer disease



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Knight ADRC
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Disclosures: Suzanne Schindler, MD, PhD

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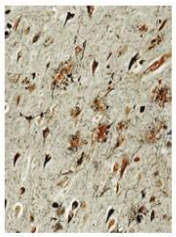
- Other: Dr. Schindler previously served as a sub-PI for the A4, DIAN-TU, and ENGAGE trials. Dr. Schindler participated in the IDEAS trial.

Dementia, Alzheimer disease, and biomarkers

- Dementia is a decline in memory and thinking that impairs functional abilities
- There are many causes of dementia
- Alzheimer disease (AD) is defined by the presence of amyloid plaques and tau tangles in the brain, not by the cognitive symptoms or the severity of dementia
- Alzheimer disease is the most common cause of dementia
- Tests that reflect Alzheimer disease brain pathology are referred to as Alzheimer disease biomarkers

Dementia

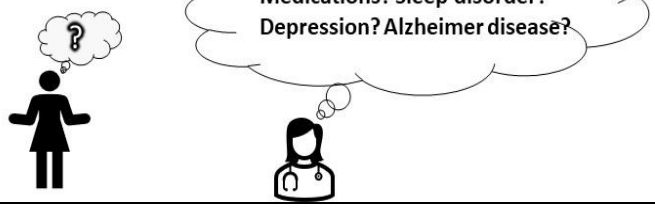


Alzheimer disease

Why do we need biomarkers?

Even after a comprehensive clinical evaluation, the diagnosed cause(s) of cognitive impairment is often uncertain or incorrect

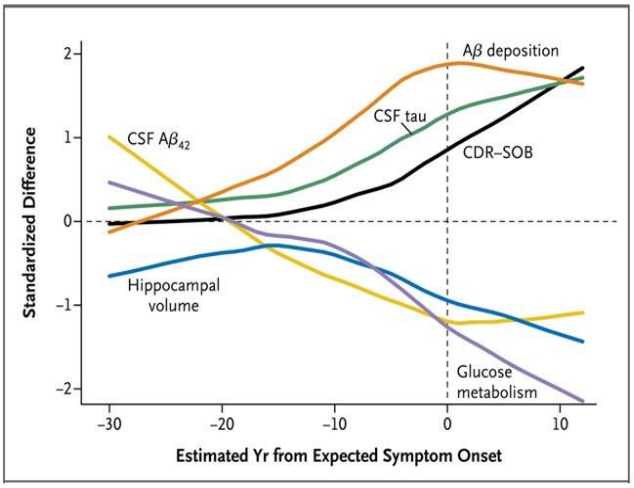
- Uncertainty: When dementia specialists say they don't know the diagnosis, they are often right—they often don't know—in one study, the diagnosis was changed 36% of the time after an amyloid PET scan[1]
- Misdiagnosis: In numerous studies, including clinical trials, ~25% of individuals diagnosed with Alzheimer disease dementia by clinical criteria did not have brain amyloidosis[2]



[1]Rabinovici *JAMA* 2019
[2]Karran *NEJM* 2014

Uses of Alzheimer disease biomarkers

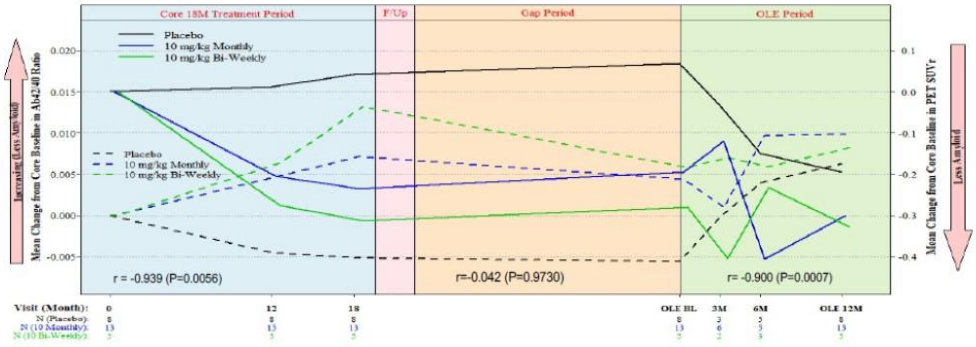
- **Research:** To understand the biology of Alzheimer disease



Bateman *NEJM* 2012

Uses of Alzheimer disease biomarkers

- **Clinical trials:**
  - To screen potential participants for Alzheimer disease
  - To monitor the effects of treatments



Swanson et al. AAIC 2021 presentation

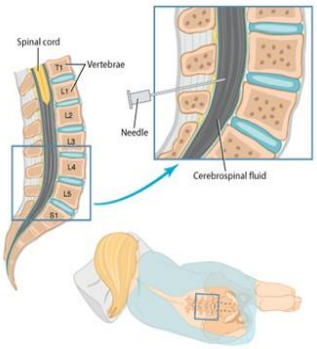
Uses of Alzheimer disease biomarkers

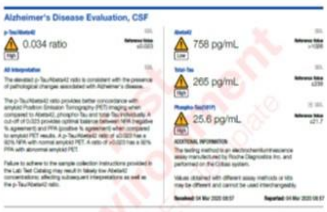
- **Clinic:**
  - To improve the accuracy of Alzheimer disease diagnosis (currently used in <5% of cases)
  - Appropriate use criteria (AUC) for amyloid PET[1] and cerebrospinal fluid (CSF) biomarker[2] testing in clinical dementia diagnosis have been established that mostly recommend clinical use for atypical, early onset, and uncertain dementia
  - Biomarker confirmation of AD is essential in patients being considered for amyloid-lowering drugs[3]

[1]Johnson *A&D* 2013 [2]Shaw *A&D* 2018 [3]Cummings *JPrevAD* 2021

Cerebrospinal fluid (CSF) biomarkers

- **Pros:**
  - Insurance typically reimburses most of cost (a test is ~$750)
  - High performance automated assays, extremely high agreement with amyloid PET
  - Not FDA approved (despite being widely used)
  - Multiple conditions can be evaluated
  - Continuous values provided for multiple analytes
- **Cons:**
  - Patients perceive a spinal tap as invasive
  - Spinal tap complications (e.g. headache, back pain)
  - Major burden for providers/inadequate reimbursement for time



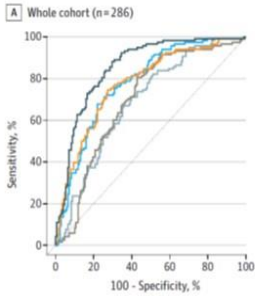


Blood biomarkers

- **Pros:**
  - Very well accepted by patients with no major contraindications
  - Potentially much more accessible than amyloid PET or CSF biomarkers, including to diverse groups
  - Much more scalable than imaging or spinal taps
- **Cons:**
  - Only a single test is currently available: PrecivityAD (plasma Aβ42/Aβ40 + apoE proteotype + age)
  - Currently expensive (~$1,250 out-of-pocket) and not reimbursed by insurance, but sliding scale fees are available
  - Accuracy (agreement with amyloid PET) is high, but not as high as CSF biomarkers
  - Not FDA approved yet, not widely used yet

Plasma biomarker assays under development

- Aβ42/Aβ40: Araclon, Roche, Euroimmun, Adx Neurosciences, Quanterix, Amsterdam University Medical Center, University of Gothenburg[1]
- p-tau181, p-tau231, p-tau217: Fujirebio, Quanterix, Eli Lilly, Janssen[2,3]
- GFAP, NfL: Quanterix[4,5]
- There may be substantial differences between assays and analytes
- Some assays are extremely promising

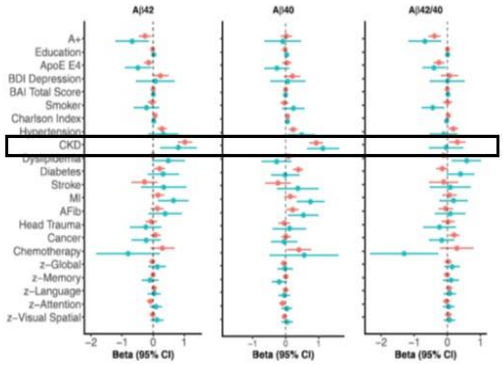


[1]Janelidze *JAMA* Neurol 2021

[2]Mielke *JAMA* Neurol 2021
[3]Triana-Baltzer A&D 2021
[4]Benedet *Brain* 2020
[5]Benedet *JAMA* Neurol 2021

Interpreting biomarker levels

- Traditionally, cut-offs have been applied to dichotomize individuals as biomarker "positive" or "negative"
- Biomarker levels associated with brain amyloidosis and/or symptomatic AD may vary by individual level factors (e.g., age, sex, education, race, *APOE* genotype, metabolic factors, comorbidities[1-3])
- It is possible that some biomarkers measures (e.g., ratios) may be more consistent across conditions

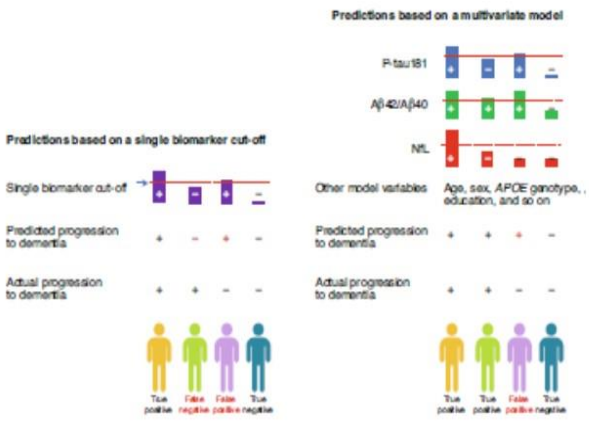


[1]Syrjanen A&D 2021

[2]Morris JAMA Neurol 2019 [3]Deters Neurology 2021

Individualized prediction

- Models can define biomarker levels associated with brain amyloidosis or symptomatic AD after adjustment for key variables
- A cut-off for each person can be defined based on individual characteristics



Schindler *Nature Aging* 2021

Consistency of biomarkers across racial/ethnic groups

- Most biomarkers have been studied in cohorts that are 95%+ non-Hispanic white
- Plasma Aβ42/Aβ40 predicted brain amyloidosis consistently across white and African American groups, but African Americans were less likely to have brain amyloidosis at a given p-tau181, p-tau231, or NfL value[1]
- Biomarkers must be evaluated in diverse populations to ensure accuracy and consistency across groups

Plasma Aβ42/Aβ40

Parameter	Estimate	SE	p =
Intercept	13.0	4.7	0.005
Plasma Aβ42/Aβ40 (pg/ml)	-220	46	<0.0001
Race (African American)	0.058	0.274	N.S.
Sex (female)	0.843	0.568	N.S.
Age (years)	0.109	0.04	0.007
APOE ε4 status (carrier)	0.865	0.269	0.001
Cognitive status (CDR>0)	1.11	0.41	0.007

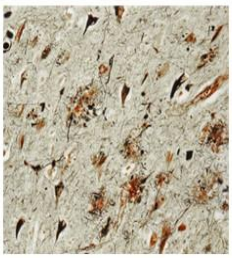
Plasma p-tau181

Parameter	Estimate	SE	p =
Intercept	-8.69	2.71	0.001
Ln (plasma p-tau181)	1.53	0.57	0.007
Race (African American)	-0.59	0.22	0.007
Sex (female)	-0.21	0.44	N.S.
Age (years)	0.072	0.035	0.04
APOE ε4 status (carrier)	0.87	0.23	0.0002
Cognitive status (CDR>0)	1.02	0.39	0.009

[1]Schindler *Neurology* 2022

Tests for symptomatic Alzheimer disease

- Many cognitively normal, older individuals have significant levels of Alzheimer disease brain pathology
- Biomarker tests need to not only tell us about Alzheimer disease brain pathology, but also whether individuals are likely to have symptoms from this pathology
- Biomarker tests in cognitively normal individuals would be most helpful if they predicted not just if, but when, individuals would develop symptoms



Dementia

Accelerating translation of blood tests into the clinic

- Lack of awareness about the high rate of dementia misdiagnosis when biomarkers are not used
- Some researchers see amyloid PET/CSF biomarkers as the standard of care, and think that blood tests won't be "ready" until they are as accurate as amyloid PET/CSF biomarkers; but, ~95% of patients don't get amyloid PET/CSF biomarkers
- Having more blood tests available, and more data on performance of the tests in clinical cohorts, will increase acceptance of blood tests
- A major barrier to blood tests is the lack of insurance coverage for the tests—the tests must be reimbursed before we can use them on a broad scale
- Approval of additional Alzheimer disease treatments would greatly increase the need for biomarker testing, and would require greater use of blood tests

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