Fluid Biomarkers of Alzheimer disease

May 2, 2022

Suzanne E. Schindler, MD, PhD
Associate Professor of Neurology

Disclosures: Suzanne Schindler, MD, PhD

- Research support/grants: Career development, salary and research support is primarily from K23AG053426 and R01AG070941
- Dr. Schindler is analyzing biomarker data provided to Washington University by C2N Diagnostics; no financial incentives or research funding were provided to Dr. Schindler in return.
- C2N Diagnostics was cofounded by Dr. Randall Bateman and Dr. David Holtzman, of Washington University. Washington University has a financial interest in C2N Diagnostics.
- Stock/Equity: None
- Consulting/Employment: None
- Speakers Bureau/Honoraria: Dr. Schindler receives honoraria as a member of the biorepository review committee for the non-profit National Centralized Repository for Alzheimer’s Disease (NCRAD); she has received honoraria for participating in expert panels and reviewing grants, all for non-profit organizations
- 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

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 scan¹
• 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
Uses of Alzheimer disease biomarkers

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

![Graph showing biomarkers over time](image)

*Bateman NEJM 2012*

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Uses of Alzheimer disease biomarkers

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

![Graph showing clinical trial results](image)

*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\textsuperscript{1} and cerebrospinal fluid (CSF) biomarker\textsuperscript{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\textsuperscript{3}

\textsuperscript{1}Johnson A&D 2013 \textsuperscript{2}Shaw A&D 2018 \textsuperscript{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
  - Janelidze *JAMA Neurol* 2021
- p-tau181, p-tau231, p-tau217: Fujirebio, Quanterix, Eli Lilly, Janssen
  - Mielke *JAMA Neurol* 2021
  - Triana-Baltzer A&D 2021
- GFAP, NfL: Quanterix
  - Benedet *Brain* 2020
  - Benedet *JAMA Neurol* 2021

- There may be substantial differences between assays and analytes
- Some assays are extremely promising
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

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<table>
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\(^1\)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](image)
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

Acknowledgements

- Deep gratitude to our research participants
- Mentors: John Morris, Randall Bateman, Anne Fagan
- Close collaborators: Randy Bateman, Yan Li, Mahendra Gupta, Nico Barthelemy, Andy Aschenbrenner, Chengjie Xiong, Tammie Benzinger, Brian Gordon, Sarah Hartz, Jessica Mozerksy