Implementing AD Blood Biomarkers in the Community

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Background

- Research studies suggest AD blood-based biomarkers (BBMs) can be used for clinical diagnosis and prognosis, and accurately predict who has AD pathology
- With continuing approval of disease modifying therapies and the need to identify AD pathology for treatment access, BBMs have many benefits
  - More feasible at the population-level and countries with limited resources; less expensive
  - Less invasive – important for those with contraindications to lumbar puncture or imaging
- Hansson et al. 2022 – Alz Assoc appropriate use recommendations
  - Use of BBMs to prescreen for clinical trials and in memory clinics with follow-up confirmation via CSF/PET; not for diagnostic use in primary care
- Multiple AD BBMs are now available for clinical use
  - When and how should they be used?

Typical dementia patient

- Average age of dementia onset is 83 years (Plassman et al., 2011)
- ~60% of older adults with AD have three or more chronic conditions (Sanderson et al. 2002; Poblador-Plou et al. 2014)
  - Prevalence of chronic conditions even higher among African American and other underrepresented minorities as well as individuals of lower SES
  - Chronic conditions and frailty are also risk factors for AD
    - Affect the expression of AD pathology with regards to cognitive function, disease stage, and neuropathological burden (Wallace et al, 2019; Calvin et al, 2022; Ben Hassen et al, 2022)
- Difficult to diagnose dementia and dementia type in primary care, and to predict disease progression
  - Estimated 50-70% of symptomatic patients with ADRD are not recognized or incorrectly diagnosed in primary care (Hansson, 2022)
  - Limited capacity of ADRD specialists: Estimated average wait time for referral for an older adult presenting with cognitive impairment ~ 50 months (possibly reduced with blood biomarker) [Mattke et al 2022]
    - Older adults with multiple chronic conditions less likely to be referred
    - PCPs often sole care provider

Physician comfort with diagnosis

- Survey of primary care physicians (PCPs): as residents, received ~8 hours of training on AD and related dementias (Paczynski & Day, 2022)

- Compared to neurologists, PCPs are: (Bernstein et al, 2019)
  - Less confident in interpreting cognitive tests (20% highly confident)
  - Less confident in correctly identifying individuals with cognitive impairment (21% highly confident) and correctly diagnosing (13% highly confident)
  - Less confident in interpreting brain imaging findings (14% highly confident)
    - More likely to order a CT than a MRI

- Primary Care Physician Survey (Alzheimer's Association Facts and Figures 2022)
  - Most PCPs (86%) state early intervention can slow cognitive decline
  - 18% recommend testing for AD biomarkers
  - 20% report being familiar with clinical trials in MCI due to AD
    - ~8% recommend trial participation
  - 23% familiar with emerging disease-modifying treatments

Next steps?

- Given limited # of specialists; many patients with cognitive impairment will never be referred

- *What considerations are needed for integration of BBMs in primary care?*

  - Process barriers and facilitators
  - Ethical considerations
  - Patient preferences

Interpreting blood biomarker results

Barriers

- Insufficient guidance around proper interpretation – grey zone
  - Impact of comorbidities
- What are the implications of a result for the patient?
- Limited knowledge of cutpoints for use in the general population

Facilitators

- Ongoing real-world studies will help understand cutpoints and utility of BBMs
- BBMs may be helpful if well understood that positive result is not equivalent to a formal AD diagnosis
  - Just one aspect of clinical diagnosis

Assessing cognitive change

- Current focus on symptomatic patients – how to assess?

Barriers

- Insufficient guidance on cognitive screening
- Screening is relatively insensitive and non-specific;
  - Race/ethnic variations can lead to overdiagnosis; high education to underdiagnosis
- Resource intensive
  - Staffing shortages

Facilitators

- Digital tools
- Trained support staff – better integration with Medicare Wellness Visit

Unclear value, cost & reimbursement

Barriers

- Need to quantify value for various stakeholders (e.g., patients, providers, payers)
- Costs of tests and whether they will be covered
- Administrative burden for physician/practices (e.g., prior authorization)

Facilitators

- Will need to develop cost-effective evidence to support adoption
- DMTs require biomarker confirmation; blood tests preferred to those more expensive/invasive – depends on accuracy

Education of healthcare workforce/patients

- BBMs should be interpreted in the context of health history; not used alone for diagnosis
  - With positive results – should still consider other pathologies

- Before testing: discussion of personalized choices around the risks and benefits of undergoing AD BBMs take time
  - PCPs have limited time – incorporation of patient navigators?

- After testing: written, understandable, printed feedback should be given and orally discussed with patients and families
  - Especially important for cognitive impaired patients
  - Considerations for those without families/support systems
  - Patient portal

Patient Preference

- Multiple studies have assessed the impact of disclosure of amyloid PET or *APOE* on cognitively unimpaired individuals or MCI/dementia in clinical trials or other centers (Grill et al 2020; van der Schaar et al 2022)
  - Fewer studies among the general population, especially underrepresented minorities and those with low education or low SES
  - Most research has been in research settings by experienced providers

- Critical need for qualitative studies to understand what patients, families and caregivers across diverse settings understand about biomarkers, and what they want to know and when
  - Both in clinical practice and research (Study Participants Bill or Rights, Walter et al, JAD 2022)

- Cost considerations – even if drug available, want to know biomarker status if too costly or infeasible (e.g. limited access to treatment)?
  - Antidotes of wanting or not wanting to know results

Ethical Aspects

- Consideration of stigma and discrimination
  - Vary by race/ethnicity, SES, and other social determinates of health

- Impact of including biomarker result in medical record
  - Life or long-term care insurance
  - Driving and other restrictions
  - Privacy concerns

Which biomarker to use and how?

- Multiple tests for clinical use are available and more will be in the near future
  - Amyloid, P-tau, neurofilament light, APOE
  - Which should be first choice?
  - How many should be assayed?

- Use of Algorithms
  - Studies suggest consideration of multiple biomarkers may be best predictors of pathology
  - Use of APOE in algorithms limits generalizability and could exacerbate health disparities
    - APOE may need to be measured for risk of ARIA-E and used as a separate biomarker

Discussion

- We are at an unprecedented time with DMTs for Alzheimer's disease and the use of BBMs – many opportunities and challenges
  - Multiple BBMs now clinically available
  - Too few specialists to refer to – diagnosis will need to be incorporated into primary care
- Several aspects must be considered prior to widespread use of BBMs
- Urgent need for both patient and provider education and tools
  - Also for general public – what BBMs are and are not
- Potential need to revamp diagnostic pathway
  - Better understanding of barriers and need for education and resources, particularly from non-academic affiliated health care providers

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