# Alzheimer's Blood-Based Biomarkers: Ready for Prime Time?

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# Outline

- Why do we need biomarkers?
- Current availability of blood-based biomarkers
- Ready for Prime Time?
  - Factors that need to be considered for interpretation
  - Implementation of blood-based biomarkers at the population level


# Why Blood-Based Biomarkers?

# Need for biomarkers to diagnosis AD

- AD historically defined as a “clinical-pathologic” entity
  - ‘Definite’ at autopsy; ‘possible’/’probable’ clinically (McKhann G, et al. Neurology 1984)
  - A clinical syndrome does not specify etiology
- Biological definition (amyloid, tau, neurodegeneration) could provide greater understanding of underlying mechanisms
  - Especially important for clinical trials
- *New imaging and fluid technology make the in vivo diagnosis more feasible*
  - *AT(N) research framework* (Jack CR, et al. Alz Dem 2018)
    - *CSF and PET biomarkers*

# Blood-based biomarkers

- Technological advances leading to blood-based biomarkers for Alzheimer's disease (AD) are an incredible accomplishment
  - Less invasive, less costly, fewer contraindications
  - More accessible compared to PET and CSF (e.g., rural areas; primary care vs specialist)

- Multiple studies show the potential clinical utility of plasma measures of amyloid-beta 40 and 42 and phosphorylated tau as biomarkers of AD pathology
  - Aid in diagnosis of AD for symptomatic individuals

# BBM tests in clinical use or under development

| Manufacturer/test name | Test components (analytes) | Assay platform | Phase 1: preclinical exploratory studies<br>Phase 4: prospective studies, longitudinal studies, and real-world performance<br>Phase 5: implementation and impact on clinical outcomes | | Current status | | |
|---|---|---|---|---|---|---|---|
| | | | Phase 2 | Phase 3 | | | |
| | | | Assay development and analytical validation | Retrospective studies | RUO | CLIA | IVD status |
| $C_2N$/Precivity | Aβ42/40+ APOE (+age) | IP-LC-MS/MS | Kirmess et al.[148] | clinical performance evaluated in a cross-validation type of study,[39] as well as in an independent cohort[149] | | x | granted Breakthrough Device designation by FDA[150] |
| Quest/AD-Detect | Aβ42/40 | IP-LC-MS/MS | unpublished | unpublished | | x | |
| Araclon/ABtest-IA | Aβ42/40 | immunoassay | Pérez-Grijalba et al.[151] | clinical performance evaluated in a few discovery-type studies[151,152] | | CE mark | |
| Araclon/ABtest-MS | Aβ42/40 | LC-MS | unpublished | clinical performance evaluated in a few discovery-type studies[57,153] | x | | |
| Quanterix | Aβ42/40 | Simoa | Song et al.[154] | clinical performance evaluated in a few discovery-type studies[53,71,100,101,118,155] | x | | |
| Sysmex | Aβ42/40 | HISCL | Yamashita et al.[156] | clinical performance evaluated in a validation-type study where discovery and validation populations are from the same cohort[157] | x | | |
| Shimadzu | Aβ-based composite | MS | unpublished | clinical performance evaluated in a few studies, including a validation-type study[50,57,155] | x | | |
| Roche/Amyloid Plasma Panel | pTau181+ APOE4 | Elecsys | unpublished | clinical performance evaluated in a discovery-type study[115] | x | | granted Breakthrough Device designation by FDA[158] |
| Eli Lilly | pTau181 | MSD, Simoa | Bayoumy et al.[89] | clinical performance evaluated in discovery-type studies[77,86,89,90,100,105,110] | | x[a] | |
| Adx | pTau181 | Simoa | Bayoumy et al.[89] | clinical performance evaluated in discovery-type studies[89,110] | x | | |
| Quanterix | pTau181 | Simoa | Karikari et al.[76]; Bayoumy et al.[89] | clinical performance evaluated in discovery-type studies[89,90] | | x | granted Breakthrough Device designation by FDA[159] |
| Fujirebio | pTau181 | Lumipulse G | unpublished | clinical performance evaluated in a discovery-type study[110] | x | | |
| Eli Lilly | pTau217 | MSD, Simoa | Bayoumy et al.[89] | clinical performance evaluated in a few studies, including cross-validation studies[71,89,90,100,105,110,114,160] | x | x[a] | |
| Janssen | pTau217 | Simoa | Triana-Baltzer et al.[161] | clinical performance evaluated in discovery-type studies[110,160,161,162] | x | | |
| Adx | pTau217 | Simoa | Bayoumy et al.[89] | clinical performance evaluated in a discovery-type study[89] | x | | |
| Adx | pTau231 | Simoa | Bayoumy et al.[89] | clinical performance evaluated in a discovery-type study[89] | x | | |

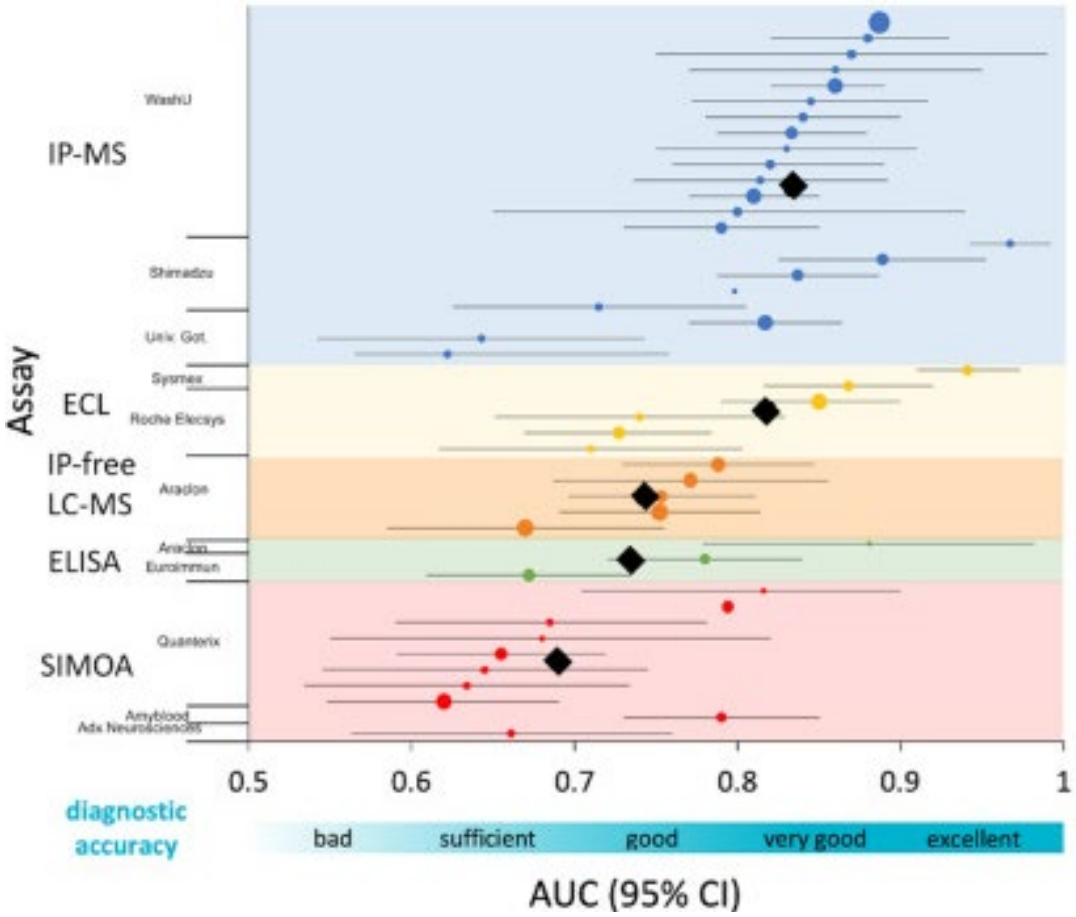
# Some currently available blood tests for AD

- Mass-spec based
  - C2N: Precivity 1 and 2
  - Quest: AD-Detect; p-tau217
    - DTC test no longer available

- Immunoassays – cpt codes for reimbursement
  - Labcorp: Sysmex amyloid-beta 42/40, Roche p-tau181, Roche NfL, Fujirebio p-tau217
  - Jensen ptau217 on simoa HD-X (Quanterix)
  - Alzpath ptau217 on simoa HD-X

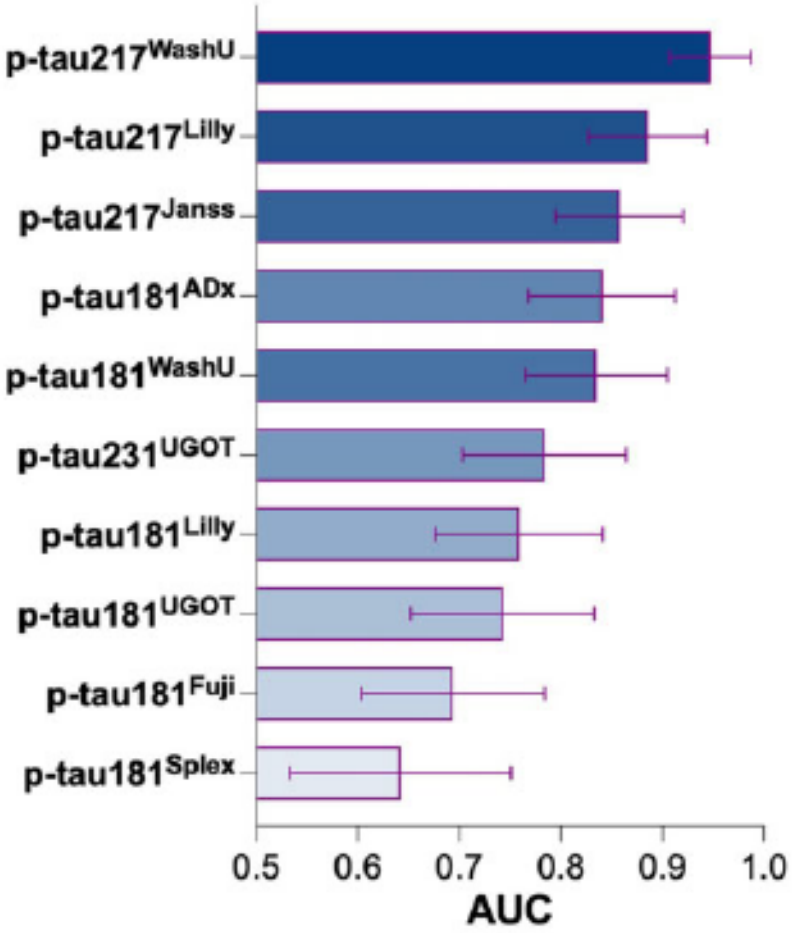
# Performance of BBM tests

## Plasma Aβ42/40 tests




Brand et al. *Alz Res Ther* 2023

## Plasma p-tau tests




Janelidze et al. *Brain* 2022

# Ready for Prime-time?

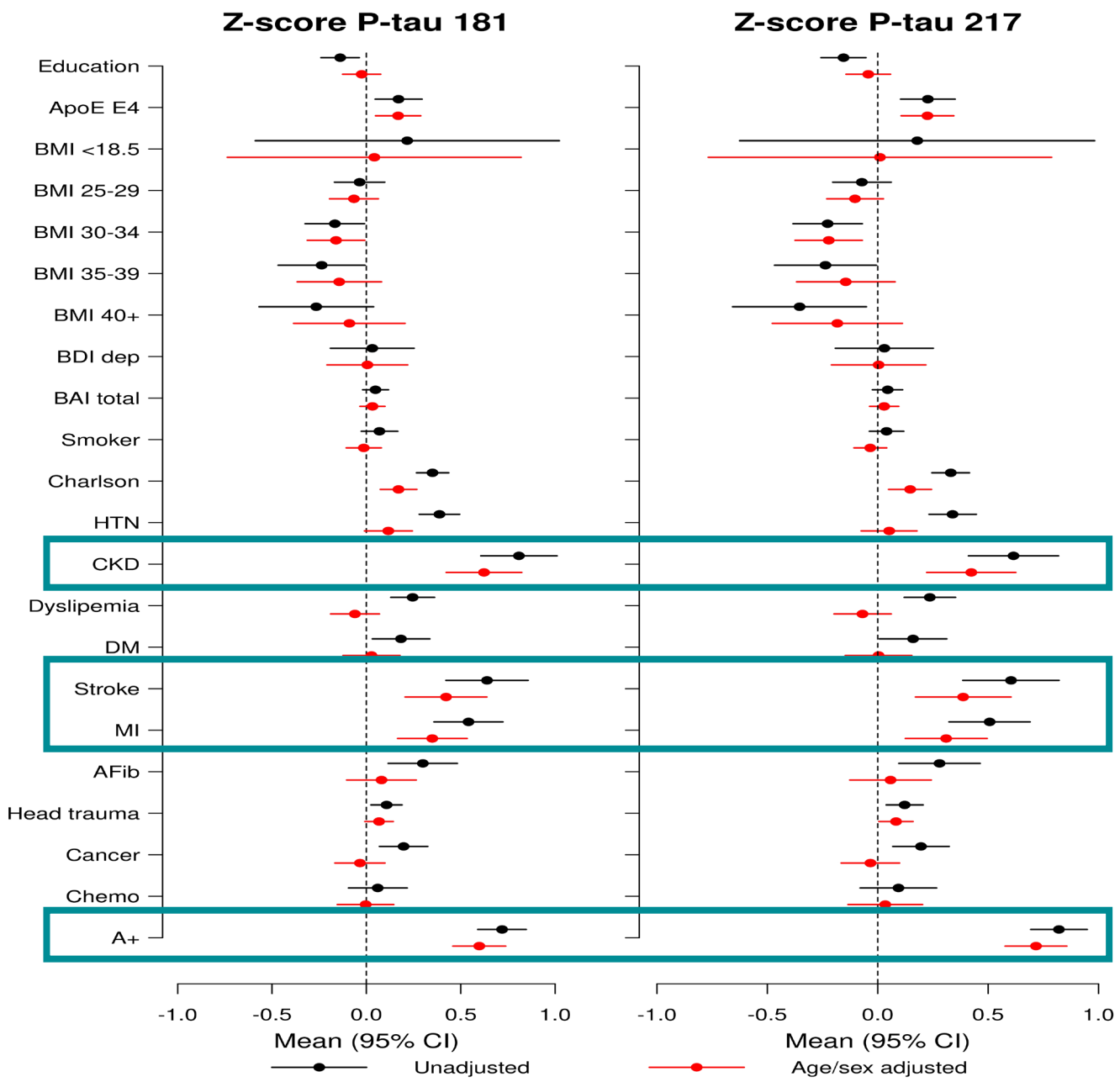
# Typical dementia patient (US)

- Average age of dementia onset is 83.7 years (Plassman et al., 2011)

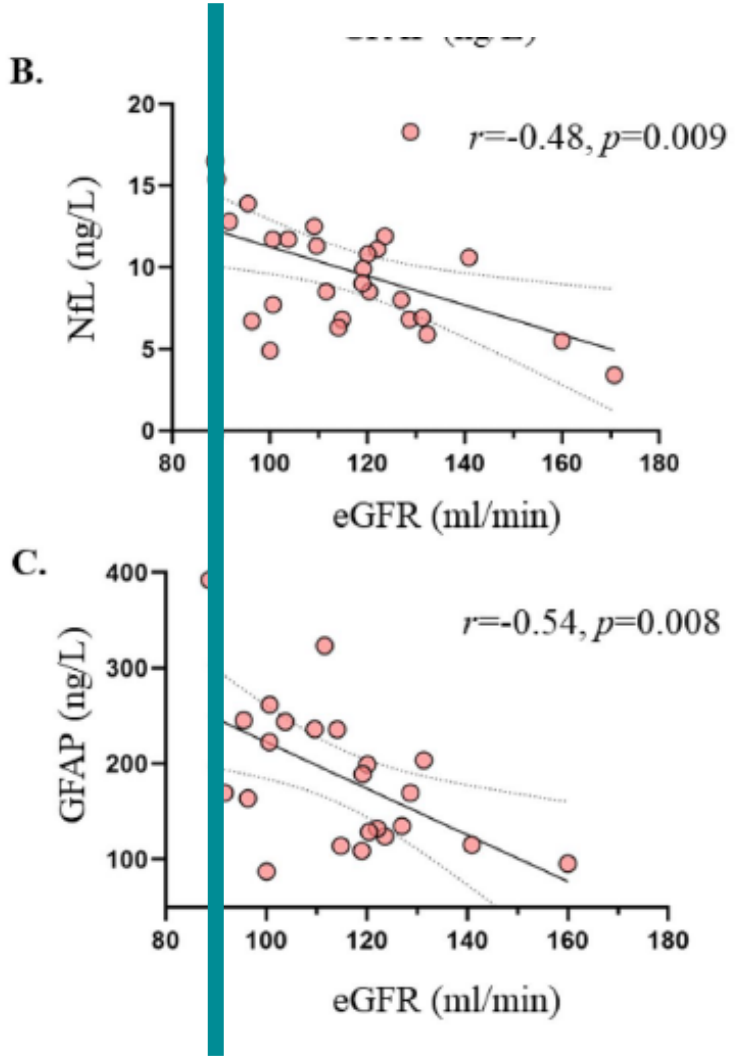
- ~60% of older adults with AD have three or more chronic conditions (Sanderson et al. 2002; Poblador-Plou et al. 2014)
  - Prevalence of chronic conditions even higher among African American and other underrepresented minorities as well as individuals of lower SES
  - Chronic conditions and frailty 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)
  - Polypharmacy often co-occurs with multiple chronic conditions, further affecting cognitive function

- Difficulty 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 [Mattke et al 2022]
    - Older adults with multiple chronic conditions less likely to be referred
    - PCPs often sole care provider

# Factors associated with plasma P-tau181 and P-tau217

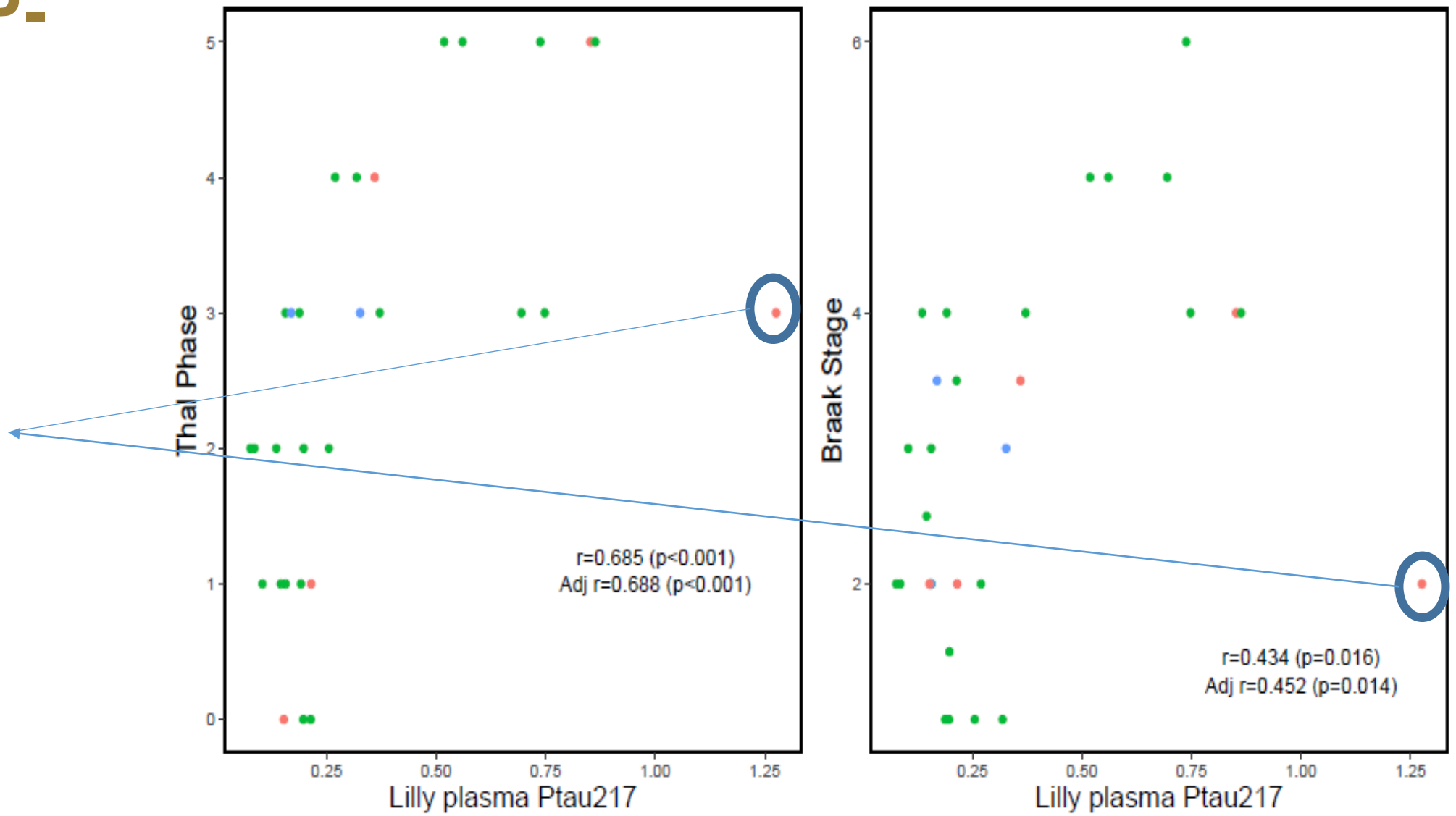


# NfL and GFAP related to eGFR



# Plasma P-tau vs autopsy

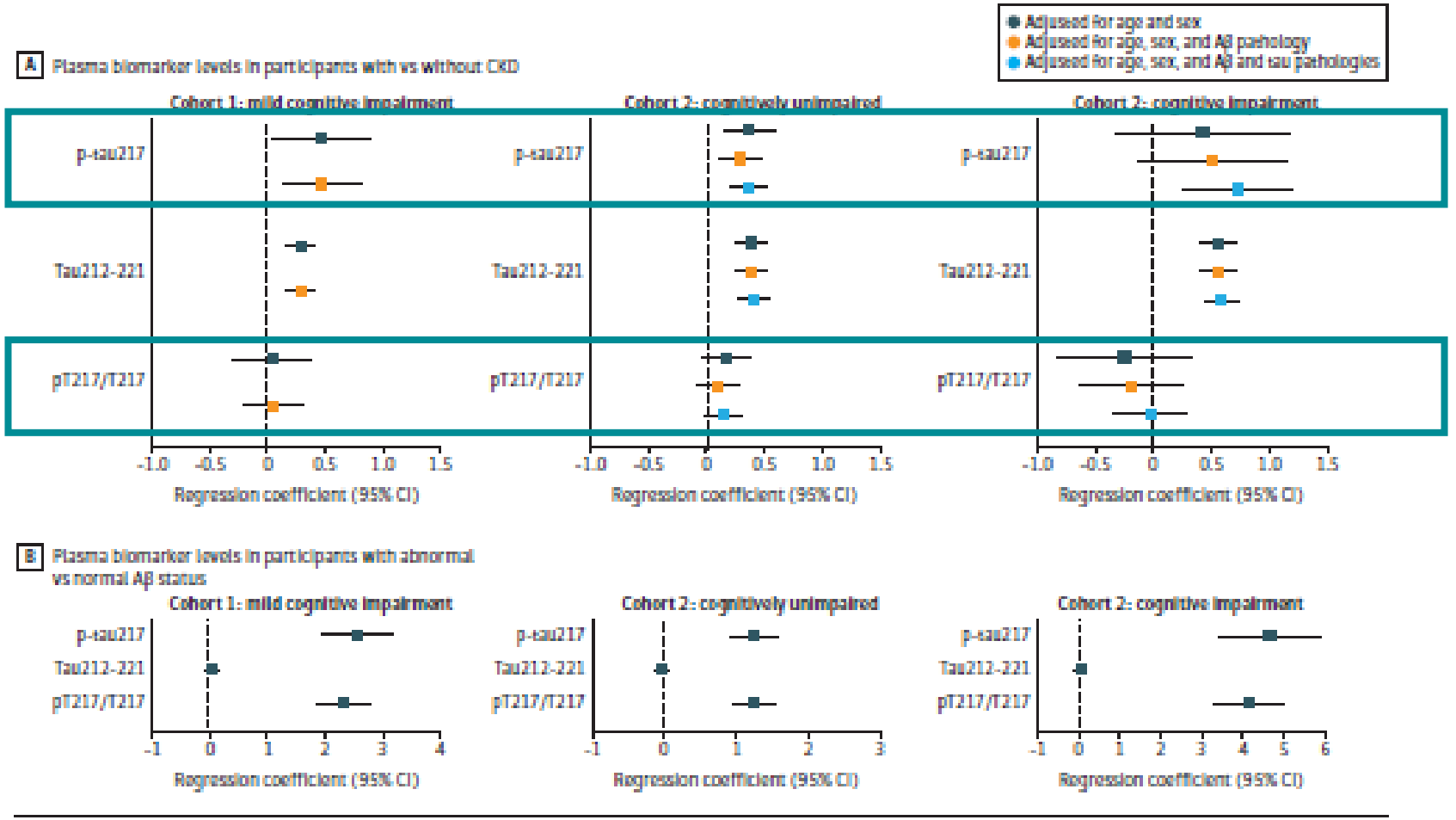
Serum creatinine=3.7

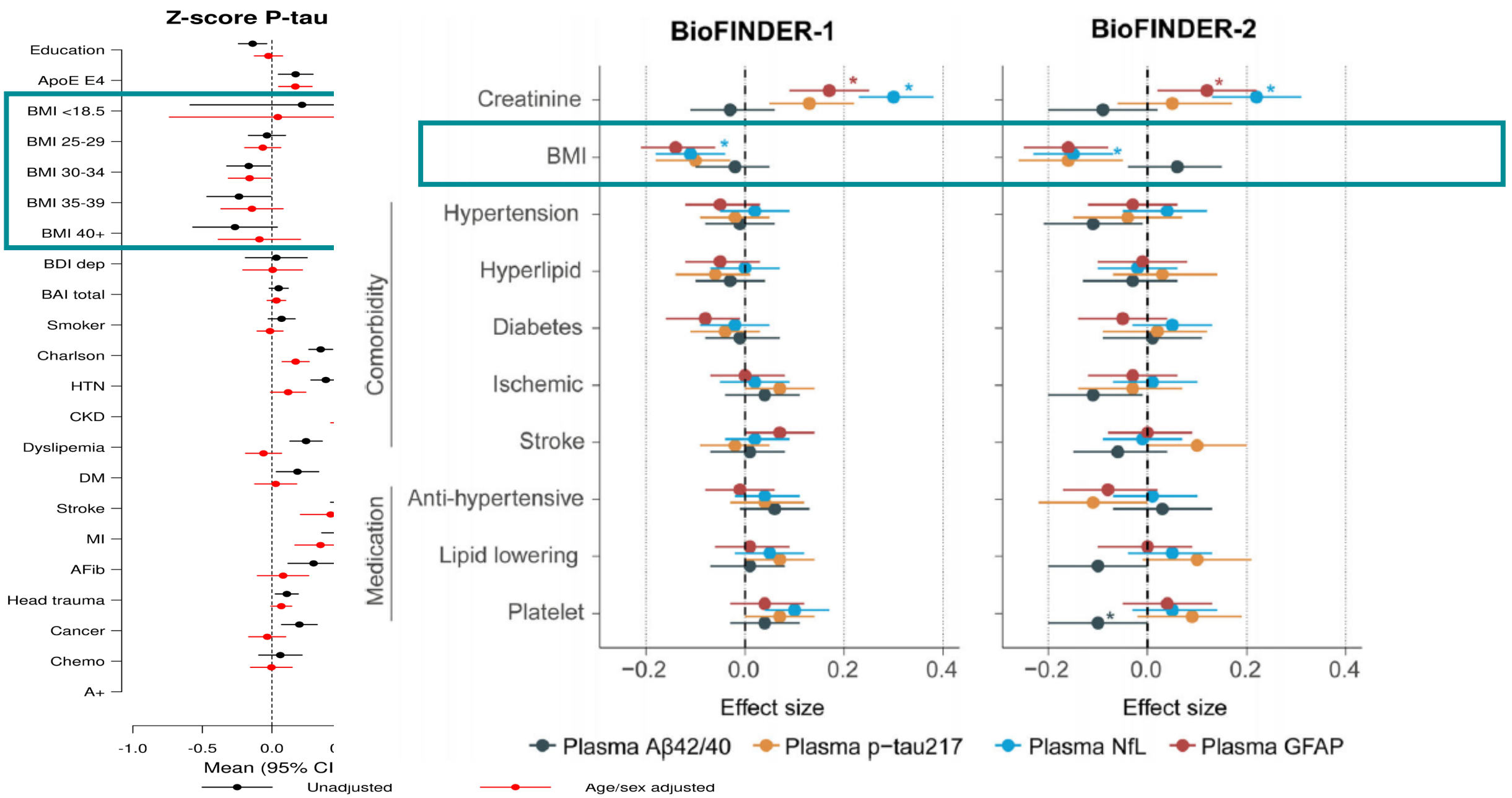



Murray M & Mielke MM, unpublished

# Mitigating effects of CKD for interpretation

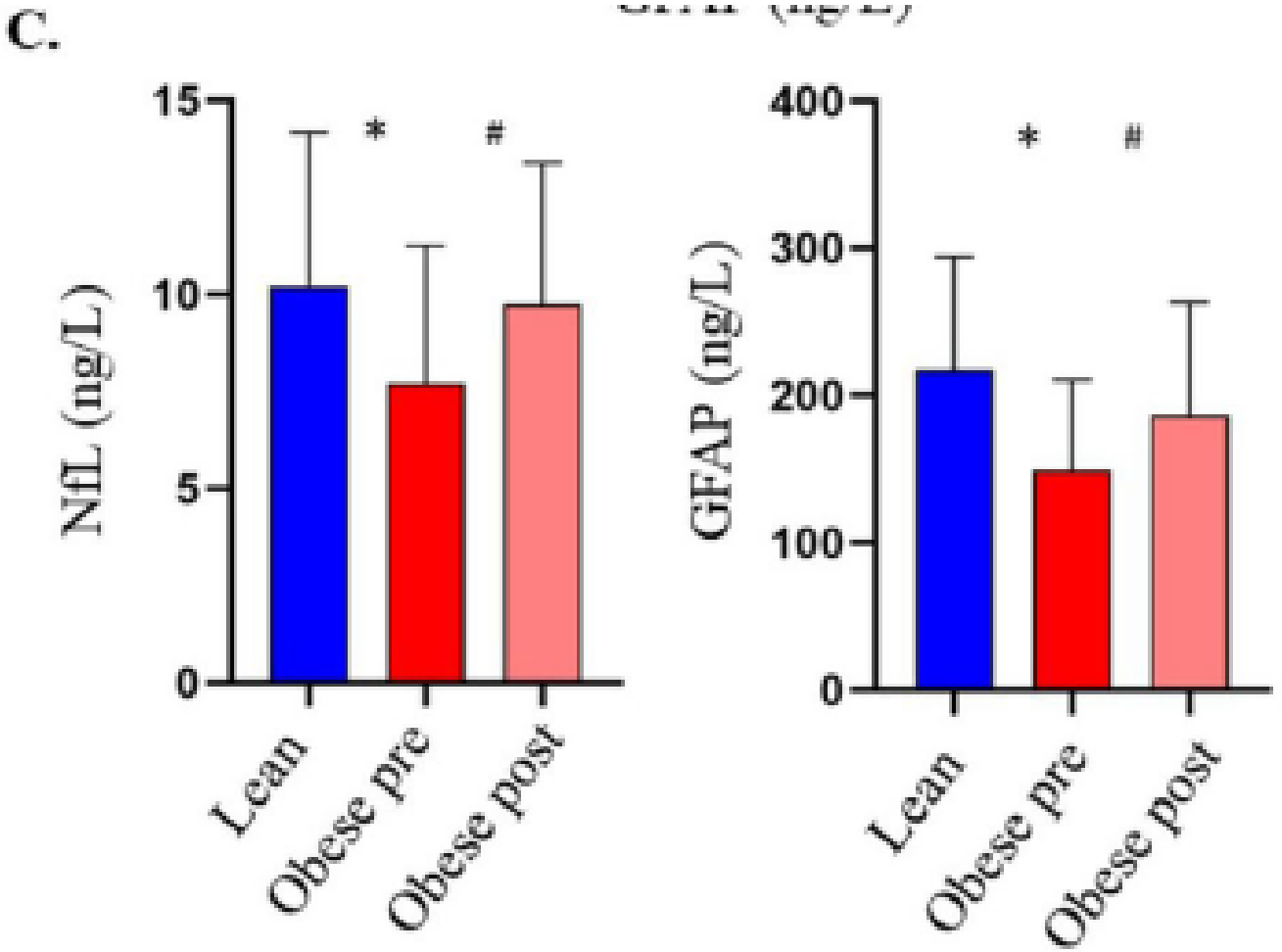
Figure 1. Associations of Plasma of Phosphorylated Tau (p-tau) 217, Tau212-221, and pT217/T217 With Chronic Kidney Disease (CKD) and Amyloid-β (Aβ) Status






Mielke MM, et al. Nature Medicine 2022; Pichet Binette, et al. Alz Dem 2022

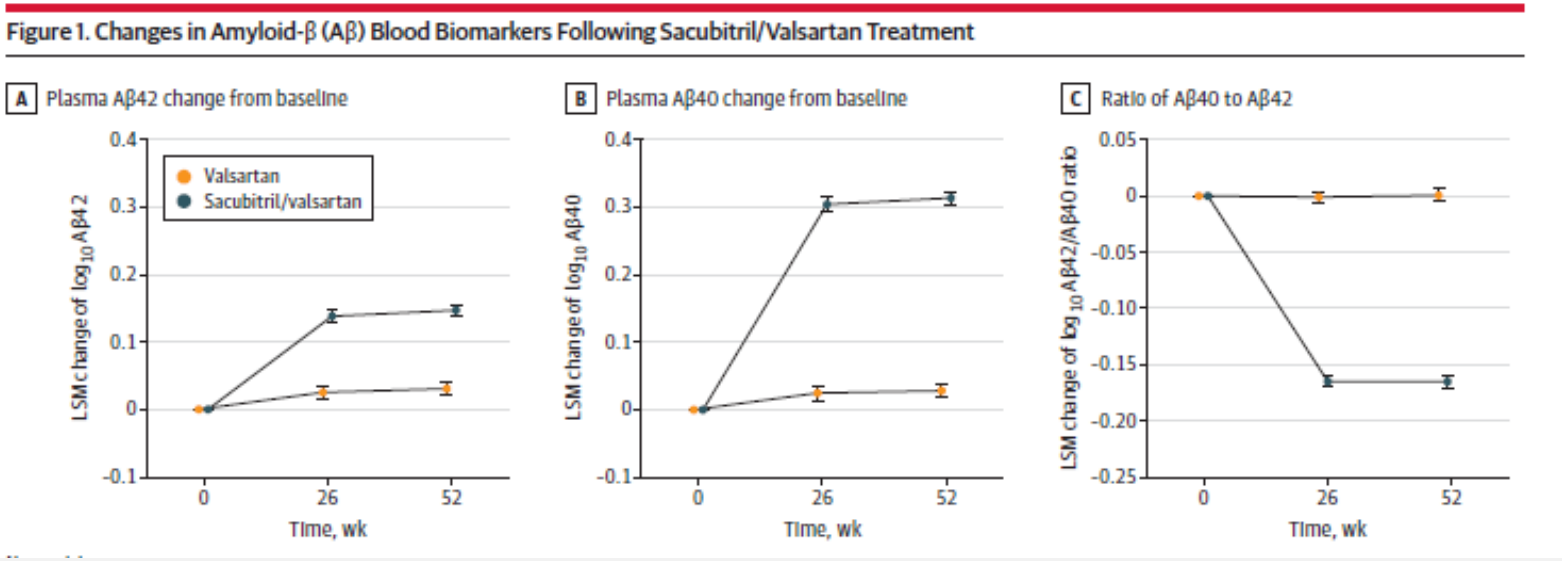
# NFL and GFAP related to BMI




Rebelos E et al. Scientific Reports 2022

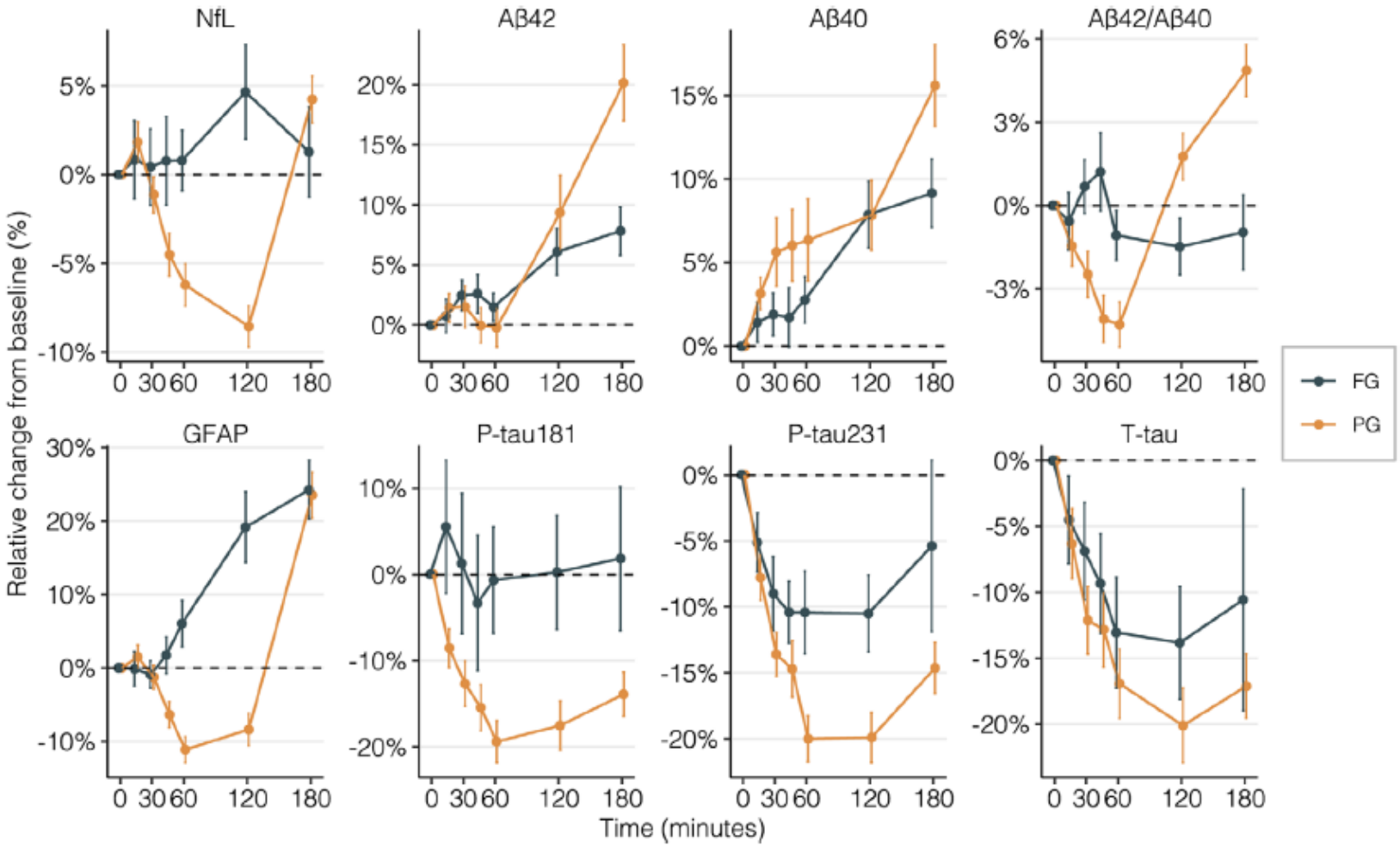
# Blood amyloid and cardiac conditions

- Amyloid-beta (Aβ) accumulates in heart of AD patients and induces AD-related cardiac amyloidosis (Troncone L et al. 2016; Schaich CL et al. 2019)
- Higher levels of plasma Aβ40 and Aβ42 associated with incident heart failure (Zhu F et al, 2023)
- Sacubitril (Neprilysin inhibitor + valsartan) lowers plasma Aβ42/40 ratio (Brum WS et al. 2023), but not CSF Aβ42/40 ratio (Langenickel TH et al, 2016)



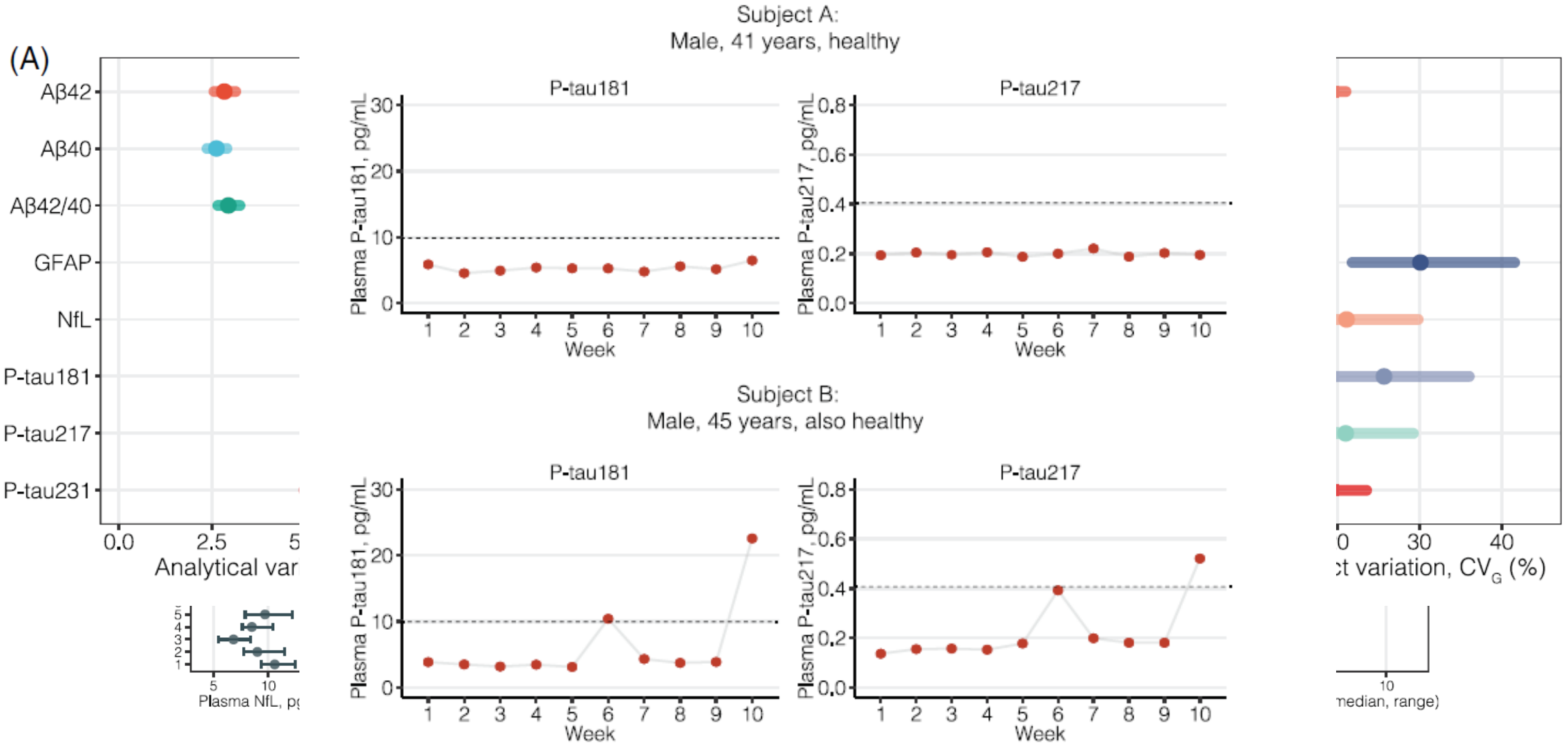

**No Change in P-tau217

# Impact of fasting status?




Huber H et al. Alz Dem 2023

# Biological Variation



# Summary

- CKD increases AD blood-based biomarkers
  - Physiological vs. risk factor
  - Lack of correct interpretation could lead to false positive diagnosis
- Increasing BMI associated with lower levels of biomarkers
  - Unclear how to consider this factor – ratios could help but may need to ascertain recent weight gain or loss; use of GLP-1 agonists?
- Need to examine multiple conditions – effects of CKD and high BMI on the blood levels; additional medications
  - Develop an algorithm?
- Need further examination of blood amyloid-beta levels in context of cardiac function and medications

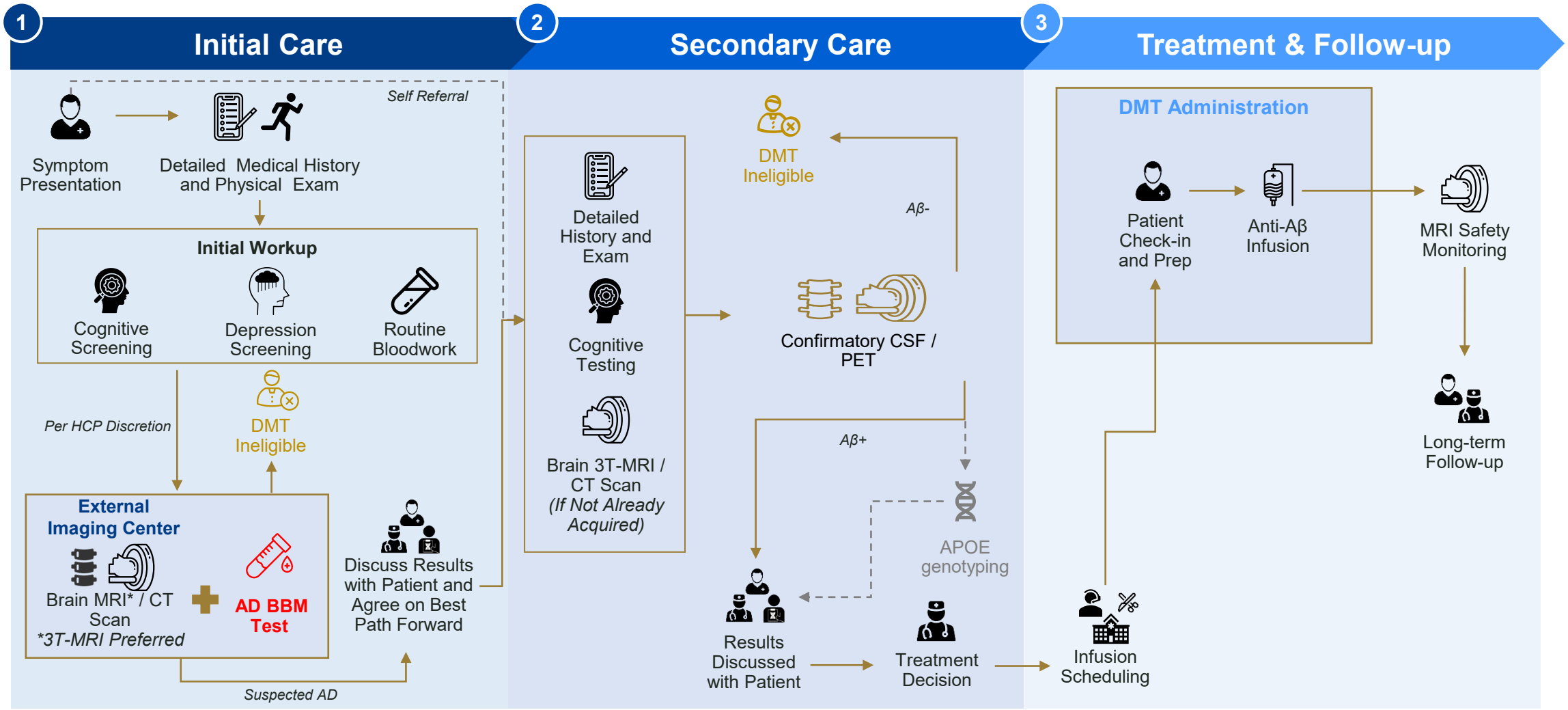
# Triage vs Confirmation

# Patient Journey: Triaging Tool

## BBM Testing for DMT Eligibility

**Legend**

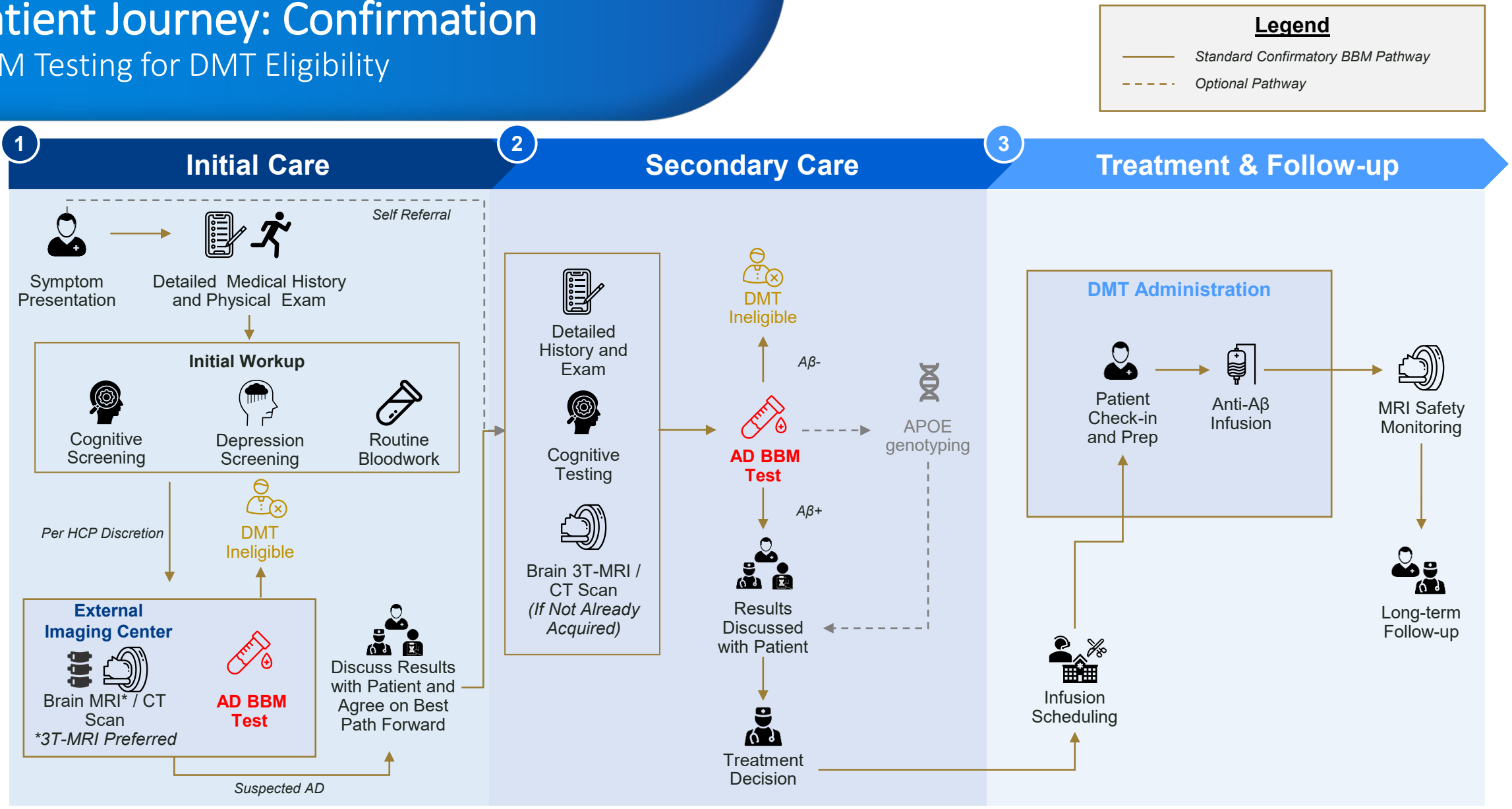
- *Standard Triaging BBM Pathway*
- *Optional Pathway*




- **In the current landscape**, BBMs will be used as a tool to reduce burden in secondary care by triaging patients prior to conducting confirmatory CSF / PET tests
- **In the future, BBMs** will be used to confirm brain amyloidosis to simplify the diagnostic journey for patients and alleviate bottlenecks in specialty care by eliminating the need for confirmatory CSF / PET testing

# Patient Journey: Confirmation

## BBM Testing for DMT Eligibility

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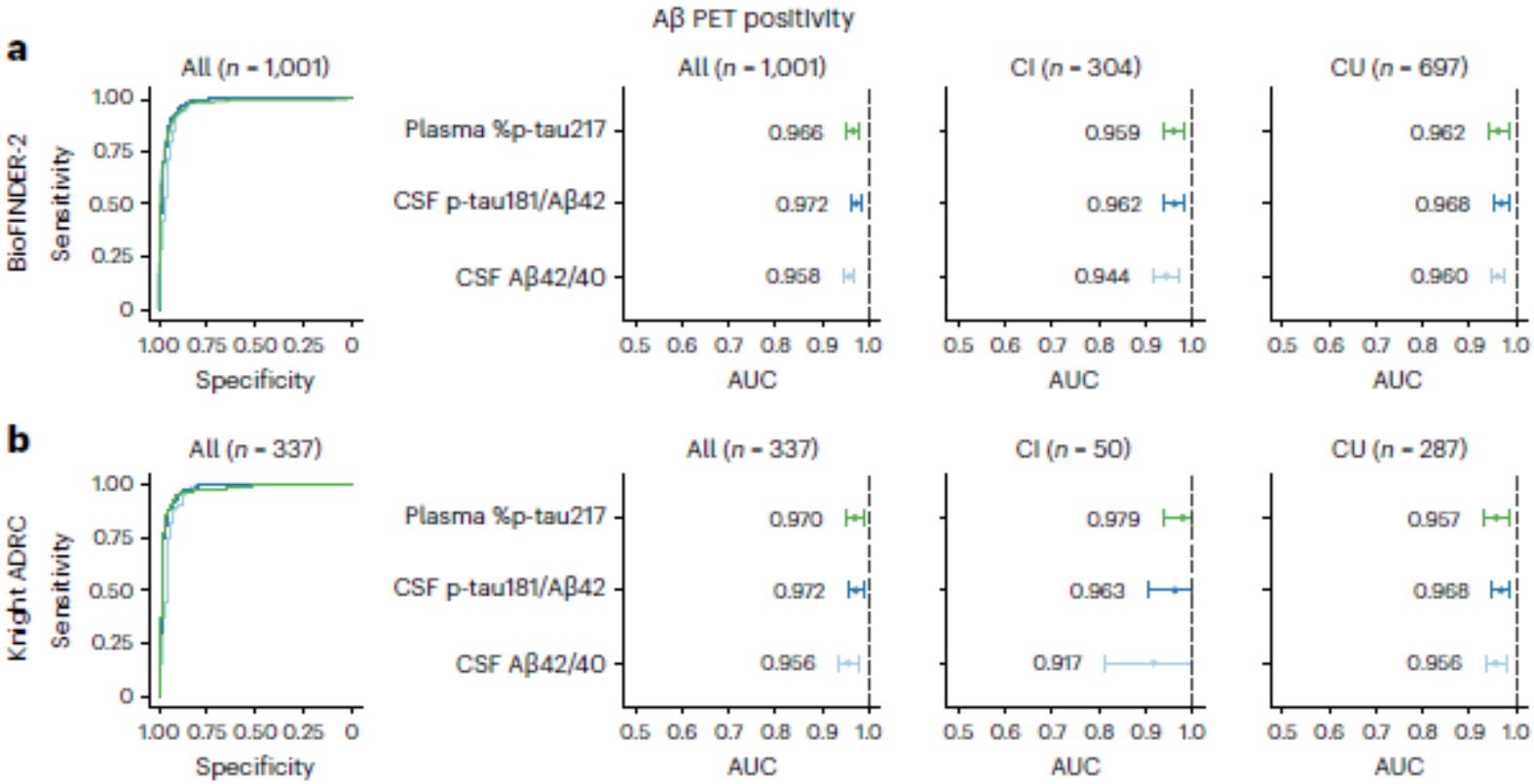
# Plasma as good as CSF?



# Interpretation and Limitations

- Results suggest plasma could be as good as CSF, but…..
  - All assays done in batch – not prospectively obtained and assayed individually
    - Not real-world
  - Mean age ~70 and healthier than general population
    - Ability to undergo both PET and CSF – highly unique group
  - Very little/no racial/ethnic diversity

- Not enough evidence to use as a confirmatory diagnostic


# When to use and how to implement?

# Diagnostic considerations?

- AD pathologies begin decades prior to symptoms and increase with age
  - Possibility of positive test being incidental
  - A blood test in isolation of a clinical assessment for cognitive changes should *not* be done
  - *Need objective evidence of cognitive impairment*, and not just subjective changes, prior to having a blood test

- Positive blood biomarker test may indicate AD pathology – but the true 'cause' of symptoms?
  - Multiple brain pathologies increase with age – 'pure AD' rare in older adults
  - Potential for sub-optimal treatment due to disregard for other pathologies?
  - Continued education to focus on the patient as a whole – treatment of vascular risk factors may be most helpful

# Ethical Aspects

- Given ease of obtaining blood biomarkers (vs. CSF or PET), what is the cost-benefit ratio of assessing AD pathology among individuals with multiple chronic conditions and limited life expectancy
  - What about those who may not tolerate IV infusion or who cannot afford it?
  - Those who have contraindications to CSF/PET or who don't want further testing?
  - Guidelines need to be developed (in line with patient input)
- Impact of including biomarker result in medical record
  - Results immediately available to patients in patient portal
    - Poses much concern with understanding of biomarker vs. disease and stigma
  - Driving, long-term care insurance, other legal ramifications?
    - Arias JJ et al JAMA Neurology 2023 – impact of GINA
  - Need to disclose potential effects of a diagnosis prior to blood test – time/reimbursement
- Patient preference
  - 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
  - Access – if can't afford further tests/follow-up or don't want – is it ethical to just do a blood draw?  How might this enhance health disparities?

# Summary

- We are at an unprecedented time with DMTs for AD and the use of blood-based biomarkers
  - Primary care will have a critical role

- Although blood AD biomarkers are promising, many questions remain.  Yet, they are available and already used in the real-world including primary care
  - While funding is needed to continue discovering new and better biomarkers, funding for how to use and implement in the general population – especially diverse populations -  is also critical
  - Poor implementation (e.g., too many false positives, increased stigma) will lose trust of patients/providers!
  - Need to educate – amyloid pathology vs symptomatology

- We need guidelines with patient and HCP input
  - How and when to implement
    - i.e., objective cognitive impairment and not in isolation, patient preference/choice
  - How to interpret
    - i.e., multiple chronic conditions
  - Need to include primary care providers, including both academic and non-academic affiliated in discussions of how to move forward – what are the barriers?

- Several ethical and other aspects must also be considered prior to widespread use of blood biomarkers at the population level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