

Reliable liquid biopsy for Alzheimer's disease pathology – are we really there?

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Liquid Biopsy for Alzheimer's Disease



Blood Biomarkers for Alzheimer's

 p-Tau (p-Tau217, p-Tau181) <small>Phosphorylated Tau</small>	 Aβ42 / Aβ40 Ratio <small>Amyloid-β Levels</small>	 NfL Neurofilament Light Chain	 GFAP Glial Activation
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How It Works





Clinical Uses


- Screening & Risk Assessment
- Trial Enrollment
- Treatment Monitoring

Benefits

- Minimally Invasive
- Lower Cost
- Early Detection

Detecting Alzheimer's Disease Risk Through a Simple Blood Test

 No PET Scan
  No Spinal Tap



Disclosures

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- WTH has patent or patent pending on
 - CSF diagnosis of FTLD-TDP (assigned to Emory);
 - CSF prognosis of SMA (assigned to Emory);
 - CSF prognosis of MCI due to Alzheimer's disease (assigned to Rutgers & Emory);
 - COVID-19 serology (assigned to Emory and licensed to Sigma-Millipore)

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rwjf robert wood johnson
foundation

All our patients, families, and healthy
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not be possible.



RUTGERS HEALTH

Clinical diagnostic accuracy for Alzheimer's disease (AD) remains poor

	Community sample of 134 patients with dementia, 1987-1996		National Alzheimer's Disease Coordinating Center, 2005-2010	
	Clinical AD (probable or possible)	Not clinically AD	Clinical AD (probable or possible)	Not clinically AD
AD pathology	80	14	511	107
No AD pathology	20	20	137	164

★ Sensitivity=85%
 Specificity=50%
 Accuracy=74%

Sensitivity=83%
 Specificity=54%
 Accuracy=73%

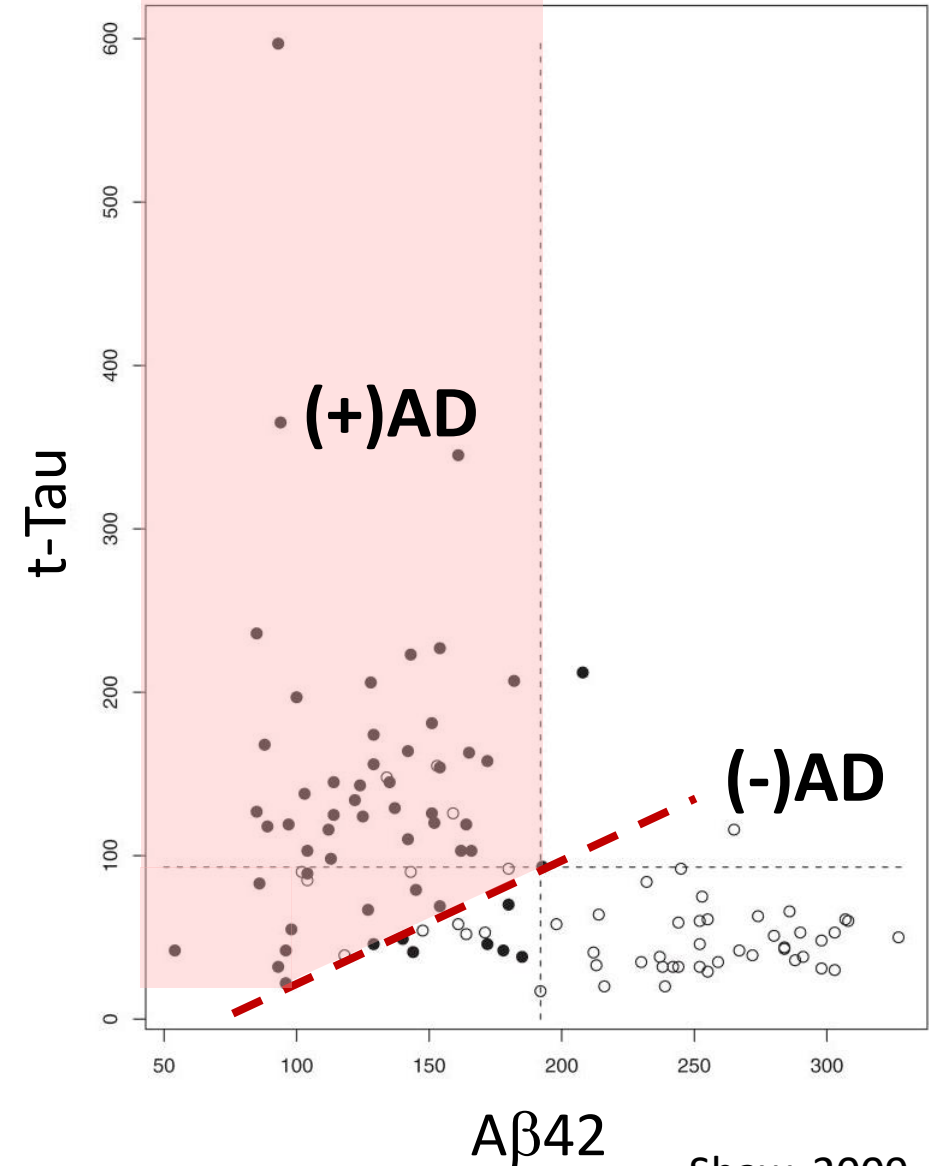
“7 million with AD”

Clinical AD (probable or possible)	Not clinically AD
5.9 m	1.1 m
1.6 m	1.7 m

Default accuracy is ~70% if you assume everyone walking through the door has AD.

CSF A β 42, t-Tau, p-Tau₁₈₁, A β 42/A β 40

CSF Biomarkers
Autopsy-confirmed data



Shaw, 2009.

Hu, McMillan, et al. *Neurology*, 2010
 Hu, Zhang, et al. *Neurology*, 2010
 Hu, Chen-Plotkin et al. *Acta Neuropath*, 2010
 Hu, Watts, et al. *Neurology*, 2013
 Hu, Watts, et al. *ACTN*, 2016
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 Howell, Watts, et al. *Alz Res Ther*, 2017
 Wharton, Kollhoff, et al. *Ann Neurol*, 2019
 Hu, Ozturk, et al. *Nat Commun*, 2021
 Kollhoff, Howell, et al. *Front Aging Neurosci*, 2018
 Hu, Kaluzova, et al. *Cell Rep Med*, 2024
 Nayyar, Li, et al. *Alzheimer Dement*, 2025
 Hu, Butts, et al. *J Neuroinflamm*, 2025
 Hu, Li, et al. *Alzheimer Dement*, 2026
 (hopefully) many more...

12 yr



2 yr



2 mo



CSF



Specialized support

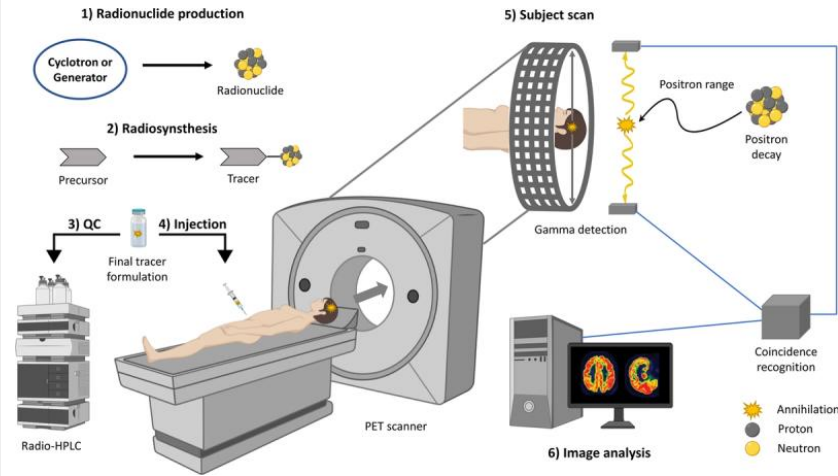
\$250-\$500

Test cost (without markup)

Physician



PET



\$4,000



blood tests



\$150-\$250

NONE

A Brief History of Blood Tests for AD

non-A β /non-Tau proteins

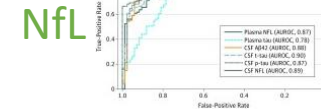
A β 42/A β 40 A β 42 quintiles

A β 1-42 Quartile
 <24.7 pg/ml
 24.7-45.9 pg/ml
 45.9-85.0 pg/ml
 >85.0 pg/ml

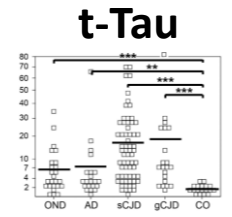
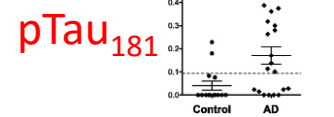
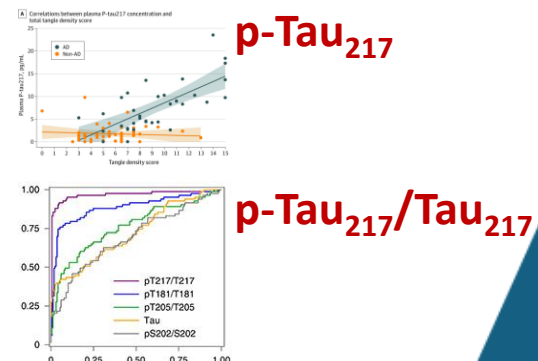
A β 42 & A β 40 elevated with age, not AD

18 protein panel

11 proteins + clinical + demographic



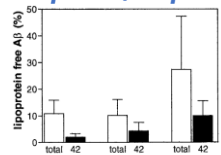
FDA NEWS RELEASE
 FDA Clears First Blood Test Used in Diagnosing Alzheimer's Disease



Elevated in mutant APP carriers

Lipoprotein-free A β 42/A β 40

A β 40 A β 42



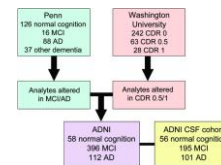
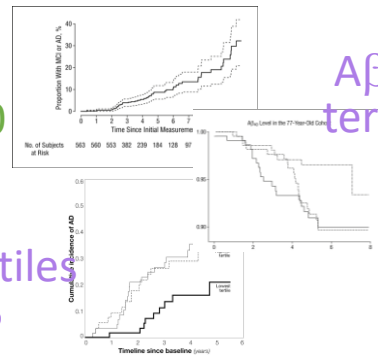
Elevated in DS, maybe AD

No difference

A β 42/A β 40 quintiles

A β 42 tertiles In DS

Panel protein levels susceptible to local clinical & lab practices



1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025



Tamaoka, 1996; Iwatsubo, 1998; Matsubara, 1999; Mayeux, 1999; Fukumoto, 2003; Graff-Radford, 2007; Schupf, 2007; Ray, 2007; Sundelof, 2008; O'Bryant, 2011; Hu, 2012; Mattson, 2017; Kovacs, 2017; Tatebe, 2017; Barthelemy, 2020; Palmqvist, 2020; FDA, 2025

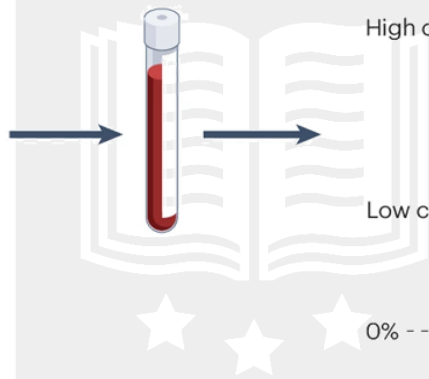
Caveats

People with cognitive symptoms

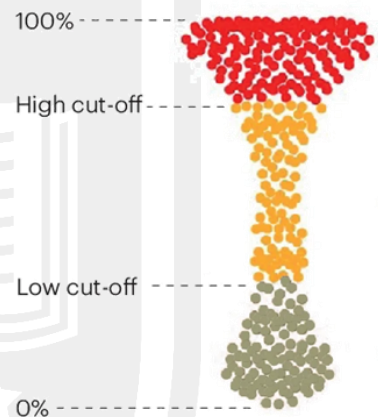


1766

Blood-based biomarker testing



Probability of amyloid PET positivity



Positive

Confirm amyloid pathology in some people

Intermediate

Should be <15–20% of people. Consider amyloid PET, CSF test or repeat of BBM in 1 yr depending on urgency

Negative

Rule out amyloid pathology in some people

90% sensitivity 90% specificity



2

1

90% sensitivity 85% specificity



3

Doctor's opinion Test result	<u>Might be</u> Alzheimer's disease	<u>Might NOT be</u> Alzheimer's disease
Positive	Supports doctor's opinion	Not useful
Intermediate	Not useful	Not useful
Negative	Not useful	Supports doctor's opinion



How do we evaluate a test?

1. How reliable is this test?

- Adjacent aliquots, within the same day – *good*
- Adjacent aliquots, across weeks – *good*

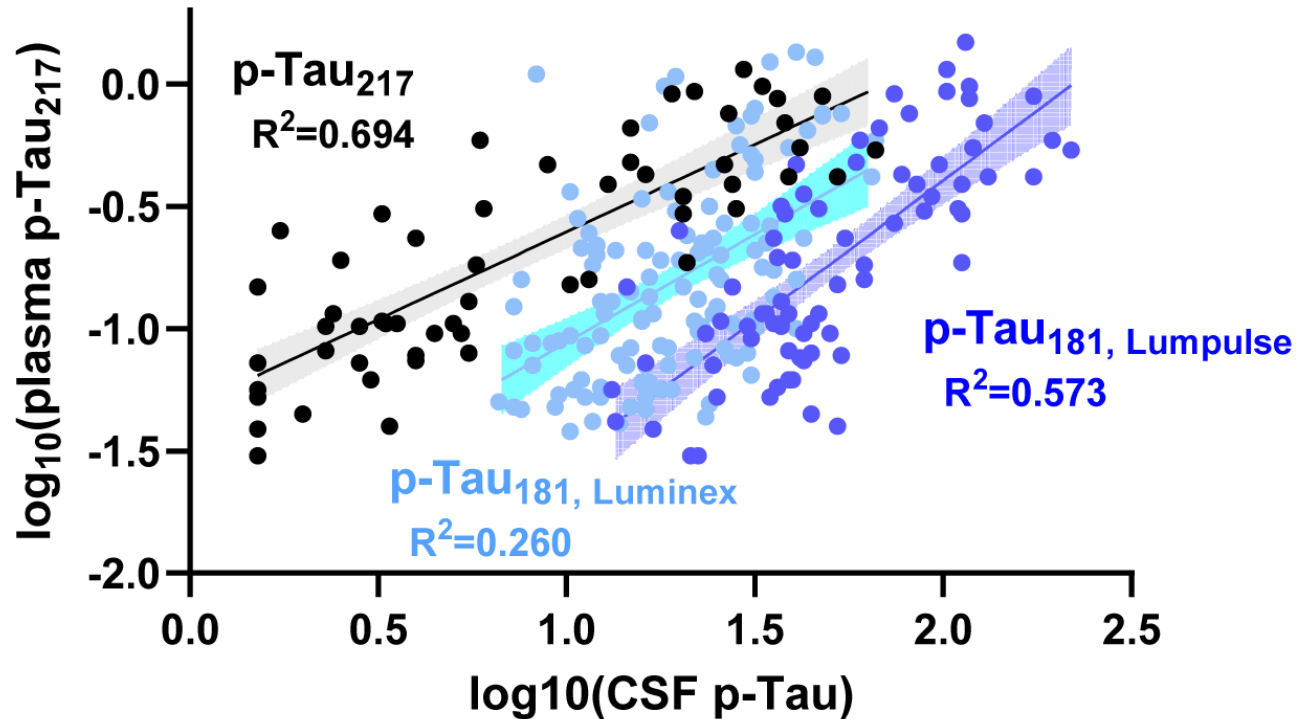
2. What is the biological basis for this putative BIOmarker?

- Can we measure p-Tau₂₁₇ in CSF? - *yes*
- Does CSF p-Tau₂₁₇ increase before CSF p-Tau₁₈₁? – *no, that's garbage science*

3. Does the racial disparity in CSF p-Tau translate to plasma p-Tau?

- Does plasma p-Tau₂₁₇ track CSF p-Tau₂₁₇ and p-Tau₁₈₁?
- What other factors influence plasma p-Tau₂₁₇ levels?

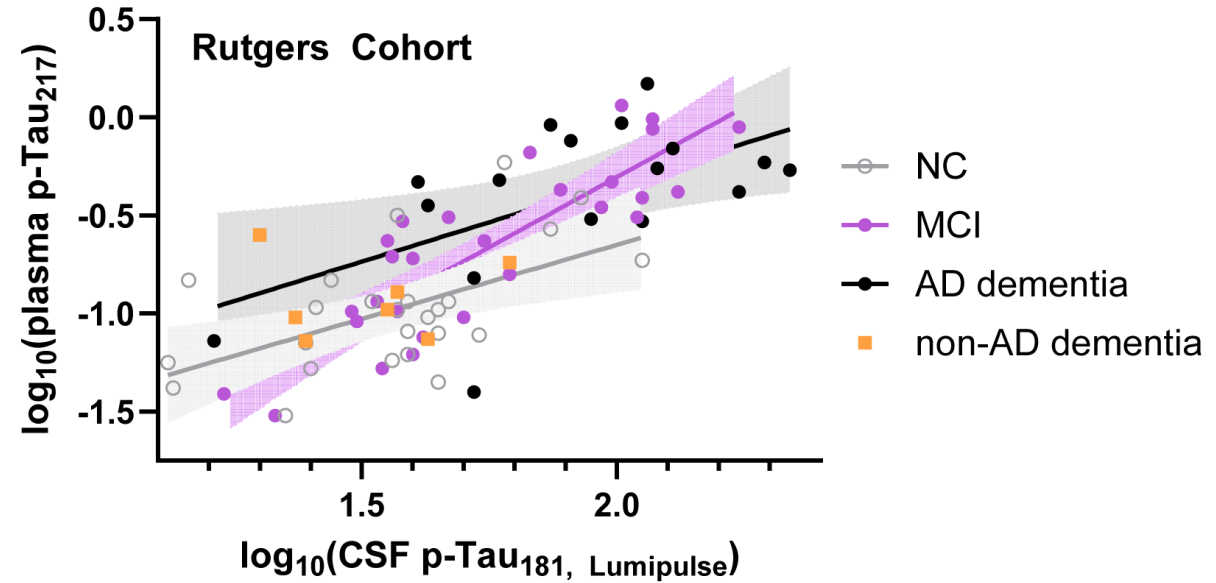
Same p-Tau target, plasma vs CSF & Different p-Tau targets, plasma vs CSF

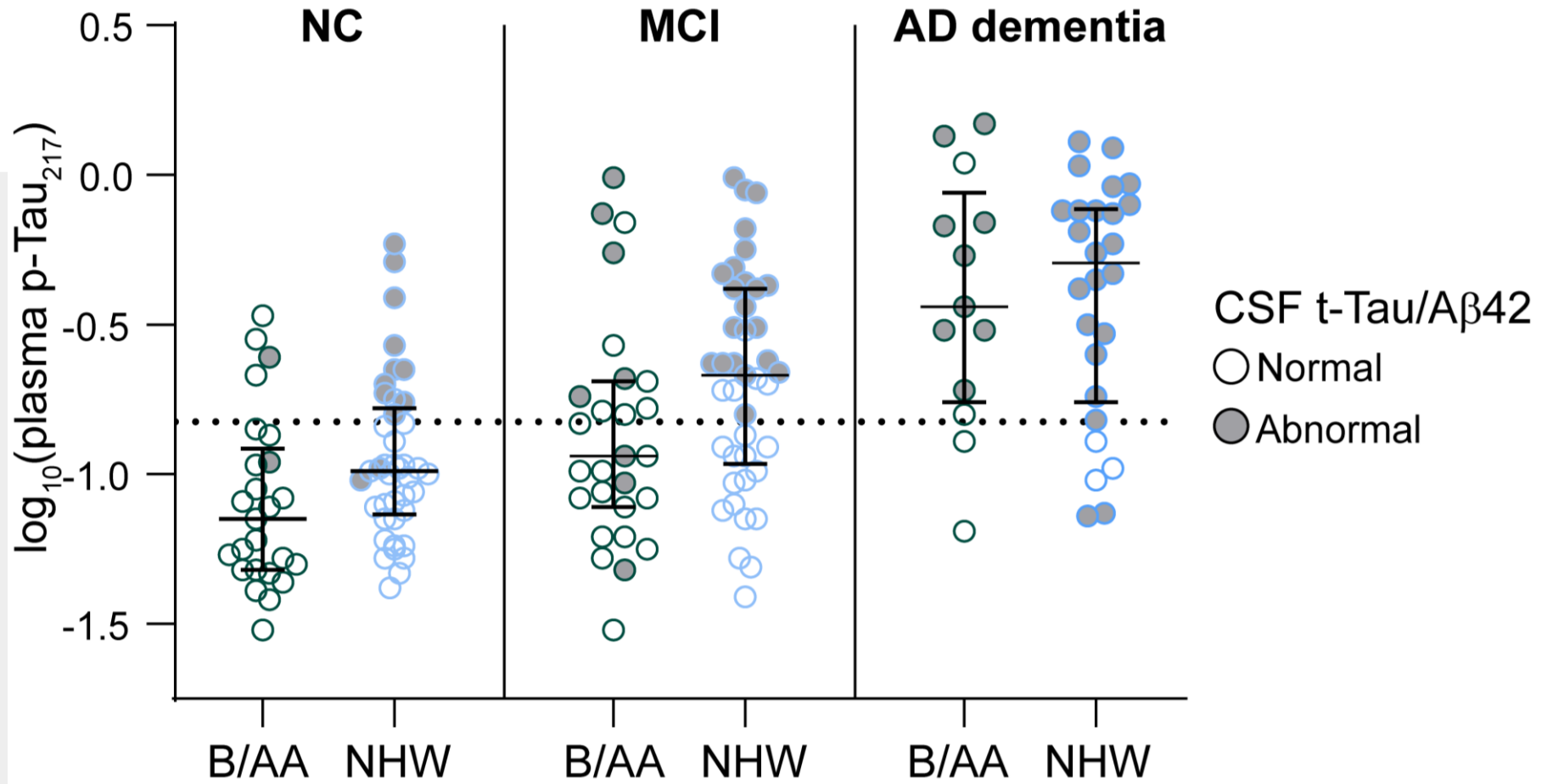
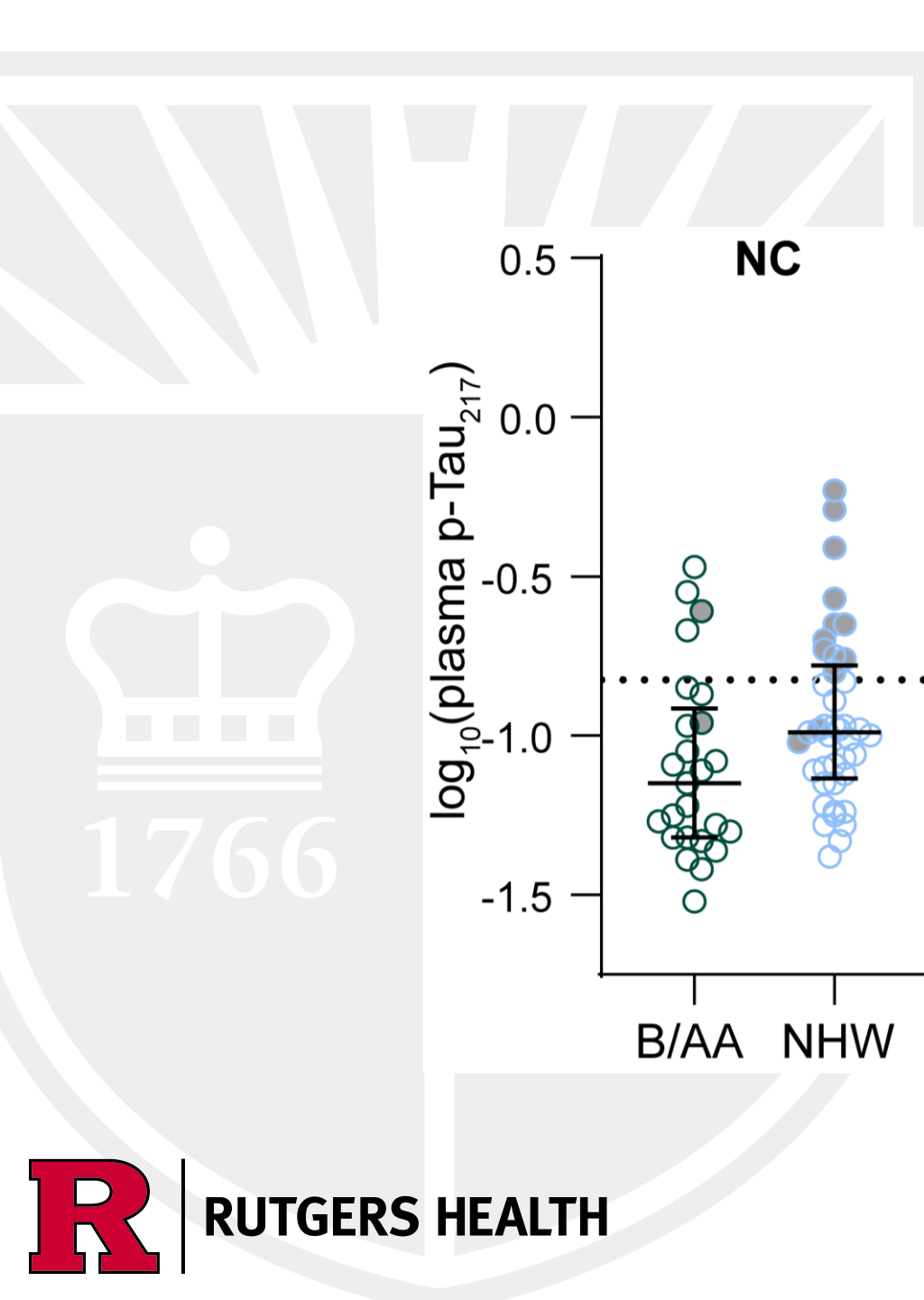


Plasma p-Tau₂₁₇ correlates better with both CSF p-Tau's measured on the same platform than CSF p-Tau measured on a different platform.

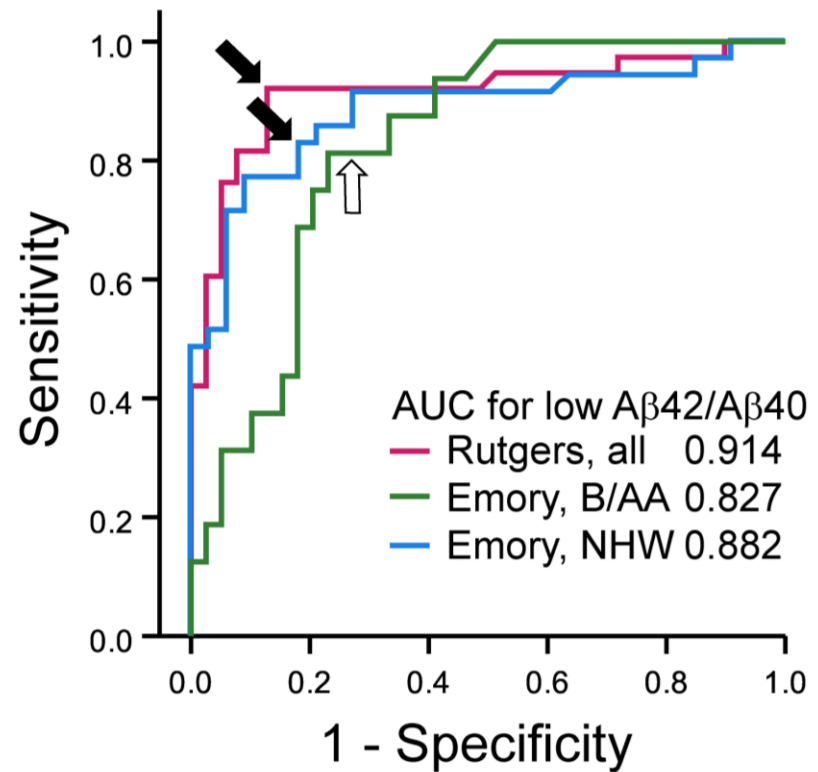
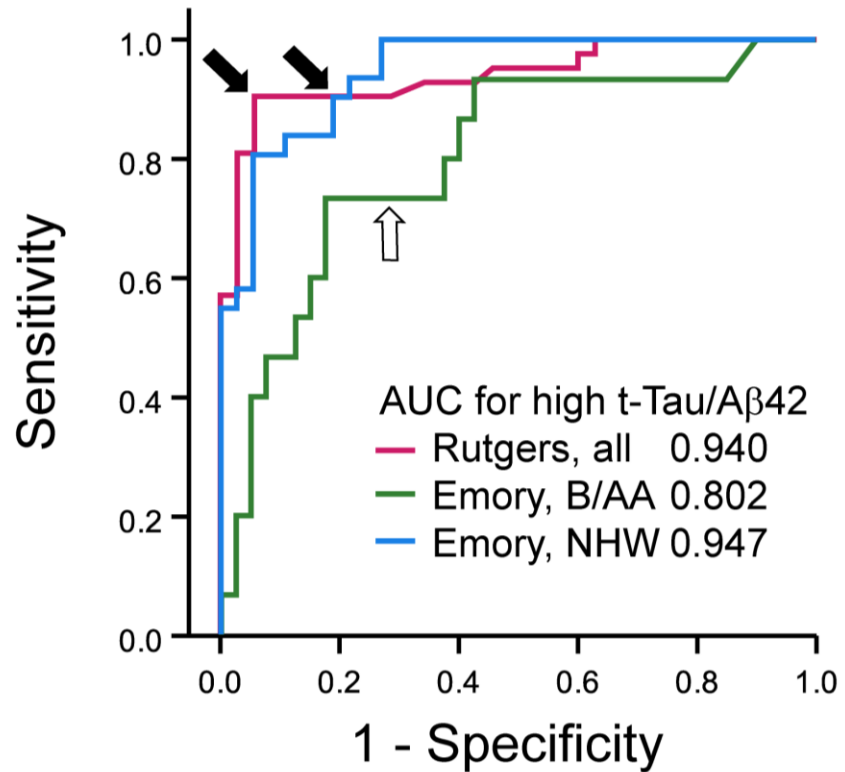
Plasma p-Tau₂₁₇ levels influenced by:

- CSF p-Tau₁₈₁, **AND**
- Renal dysfunction, **AND**
- Symptomatic AD (MCI or dementia)
- **AND** ***Black/African American race?***
 - CSF t-Tau and p-Tau₁₈₁ lower in B/AA older, middle-aged, and younger adults than NHW





Clinical Implication



Summary on plasma p-Tau

- Plasma p-Tau₂₁₇ is a promising biomarker especially when predicting CSF p-Tau₂₁₇ within a **uniform subgroup** (race, diagnosis, renal function)
- Reported performance in identifying AD neuropathologic changes likely **inflated** by biased study design
- **Racial disparities in CSF t-Tau & p-Tau are replicated and potentially amplified in plasma**