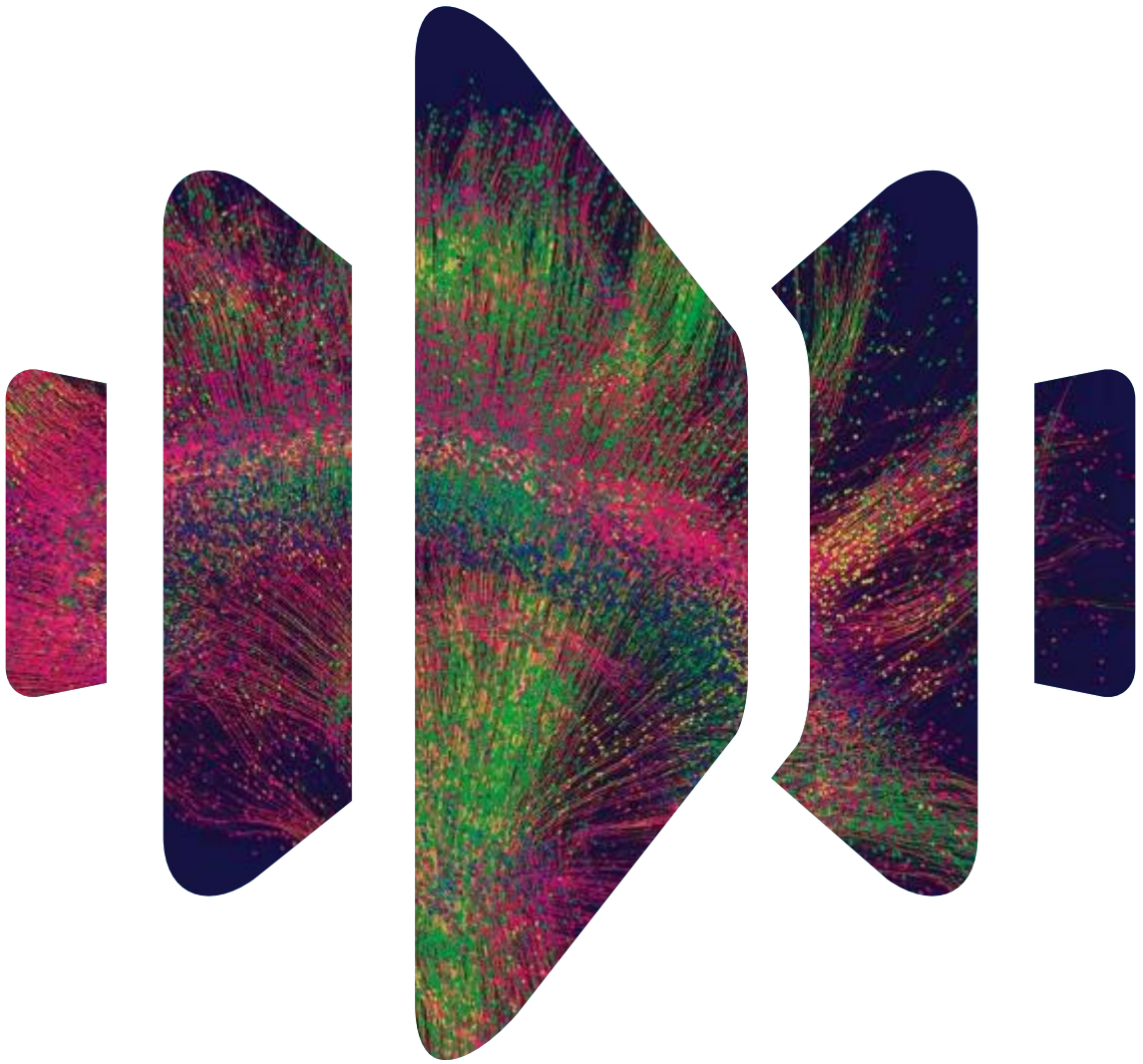


A multi-stage approach to screen Amyloid status using plasma p-Tau217 prior to confirmatory Imaging applied to the Bio-Hermes Trial.

Richard Joules[1], Robin Wolz[1], Lynne Hughes[2], Richard Mohs[2], John Dwyer[2], Douglas Beauregard[2]

1: IXICO, London, UK
2: Global Alzheimer's Platform Foundation, Washington, DC, USA.

Disclosures

Robin Wolz and **Richard Joules** are employees, and **Lynne Hughes** is an advisor of **IXICO**

Lynne Hughes, **Richard Mohs**, **John Dwyer**, **Douglas Beauregard** are employees of the **Global Alzheimer's Platform Foundation (GAP)**

Bio-Hermes study

Bio-Hermes

17
Sites

1001
Enrolled

MMSE
RAVLT

pTau217
pTau181
Aβ42/40

18F-AV-45
PET

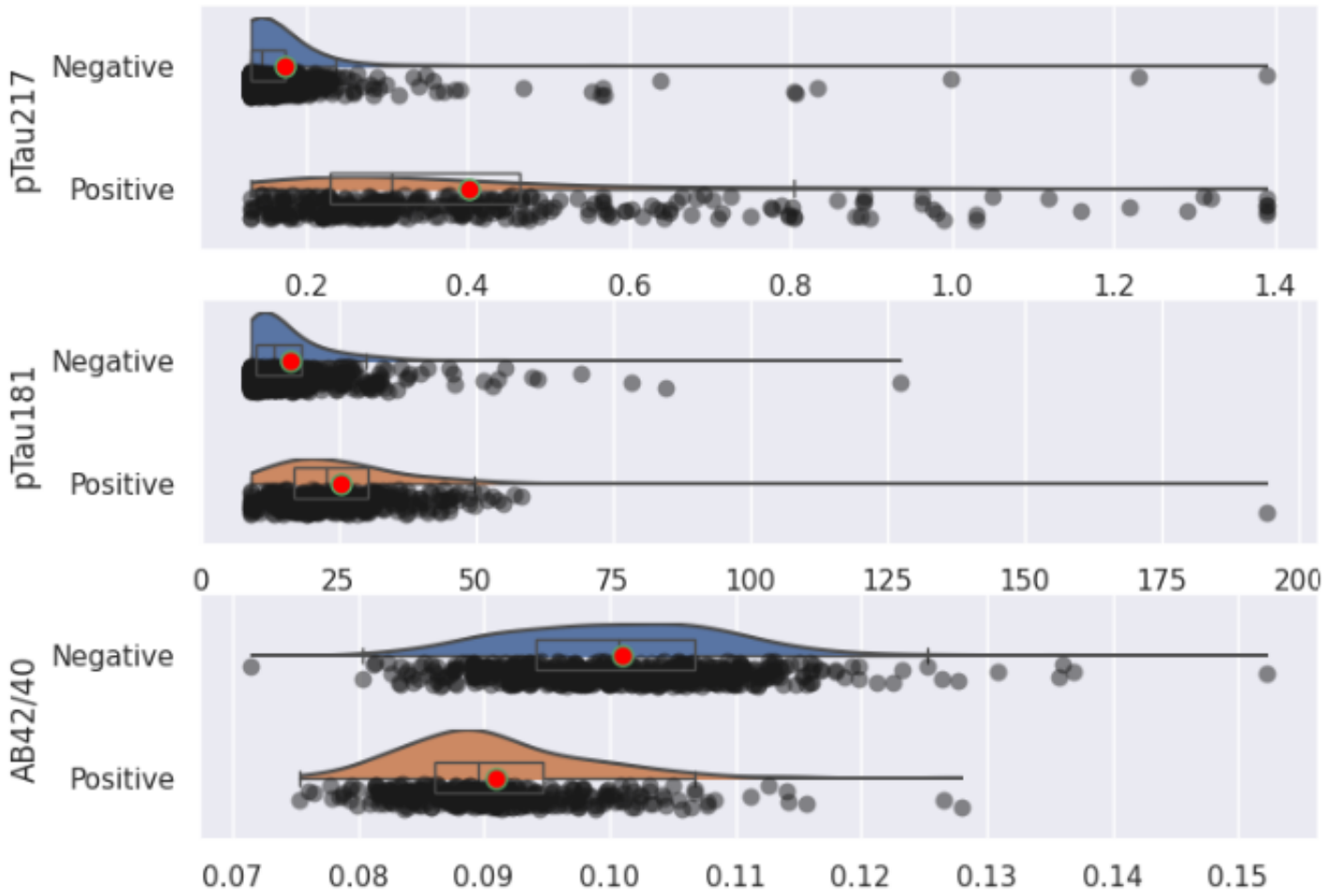
Visual Read

Bio-Hermes study

842 dataset of participants with complete plasma biomarkers, PET reads, and clinical scores were included in this analysis

	Total	White non-Hispanic	Black non-Hispanic	Hispanic	Other
Number	842	620	97	93	32
Age mean (std)	72.3 (6.7)	72.9 (6.6)	70.2 (6.1)	70.4 (6.9)	72.5 (6.4)
Female %	56.9%	53.7%	73.2%	61.3%	56.2%
MMSE mean (std)	26.5 (2.9)	26.9 (2.8)	25.3 (2.8)	25.4 (3.1)	26.4 (3.2)
APOE e4 carries %	37.2%	37.3%	39.2%	30.1%	50.0%
AB+ vis read %	37.5%	39.2%	25.8%	35.5%	46.9%

BBM distribution: amyloid status



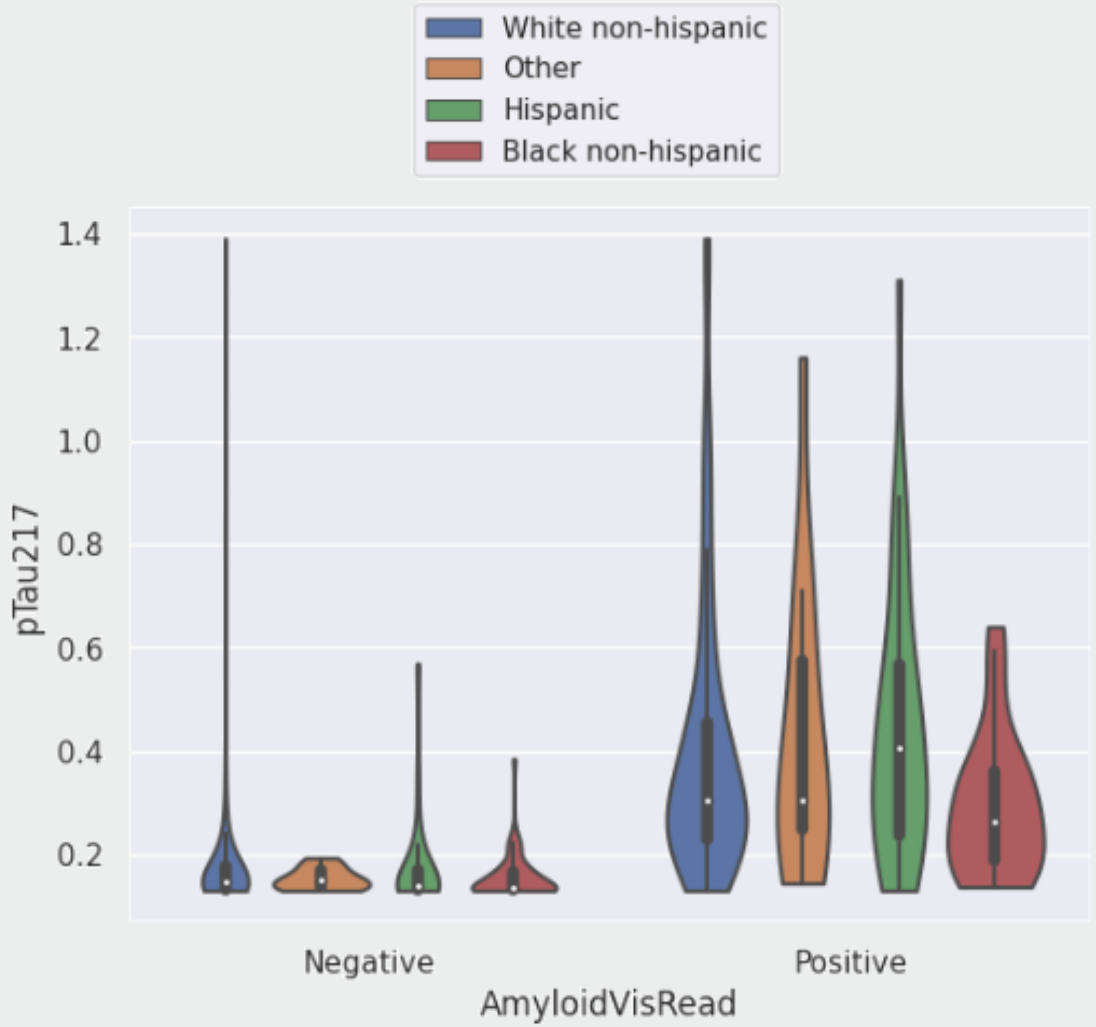
Plasma biomarker	Amyloid Positive	Amyloid Positive	p-value
pTau217 (pg/ml)	0.403 (0.264)	0.174 (0.110)	<0.001
pTau181 (U/ml)	25.269 (14.234)	16.157 (10.528)	<0.001
AB42/40	0.091 (0.008)	0.101 (0.009)	<0.001

Joules et al, CTAD 2024

BBM distribution: ethnic and racial groups

Plasmas Biomarker mean (sd)	White non-Hispanic		Black non-Hispanic	
	AB-	AB+	AB-	AB+
n	377	243	72	25
pTau217 pg/ml	0.178 (0.123)	0.407 (0.271)	0.156 (0.040)	0.293 (0.135)
pTau181 U/ml	17.016 (11.714)	25.940 (15.273)	14.382 (6.440)	21.271 (7.583)
AB42/40	0.100 (0.009)	0.090 (0.007)	0.105 (0.010)	0.095 (0.008)

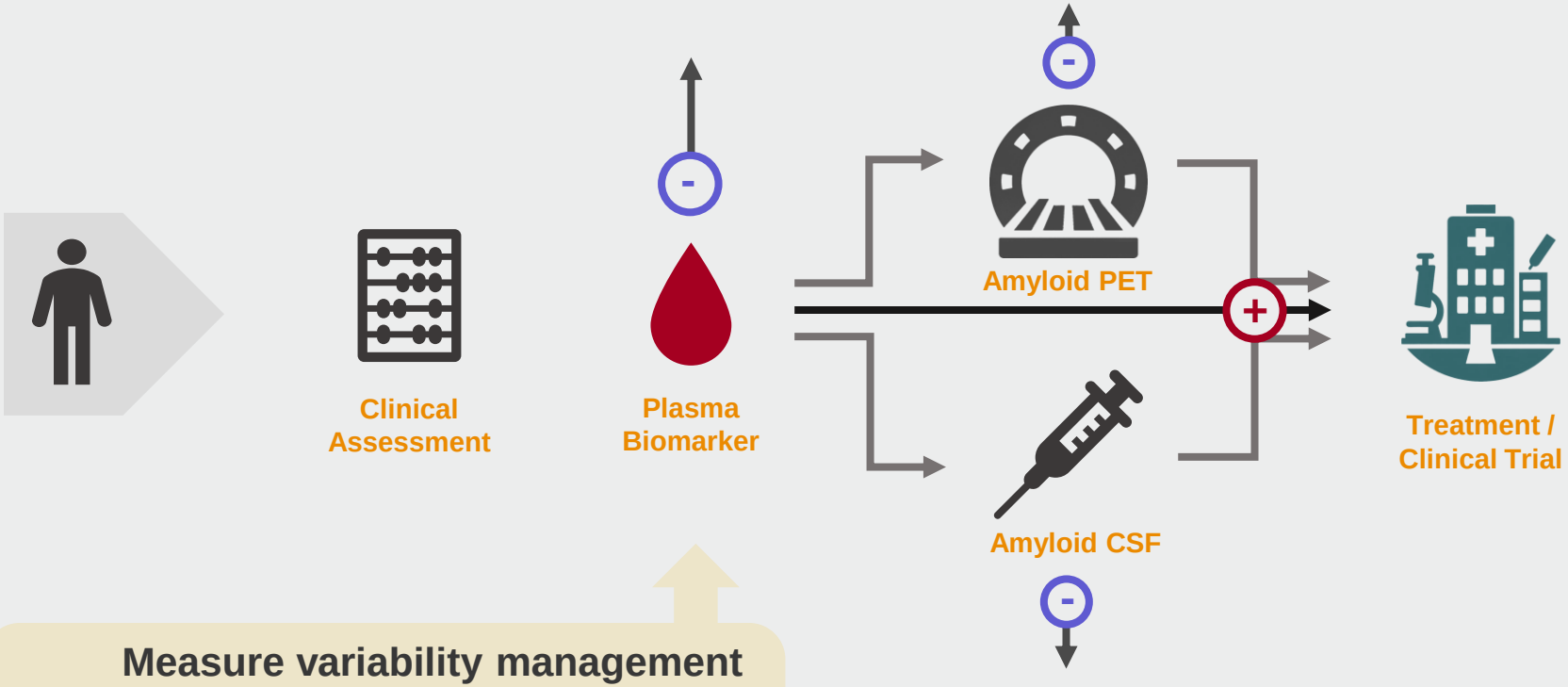
Differences between AB- and AB+ groups across both populations are significant with Mann-Whitney U test and $p<0.05$



Joules et al, CTAD 2024

Potential screening process utilising BBMs

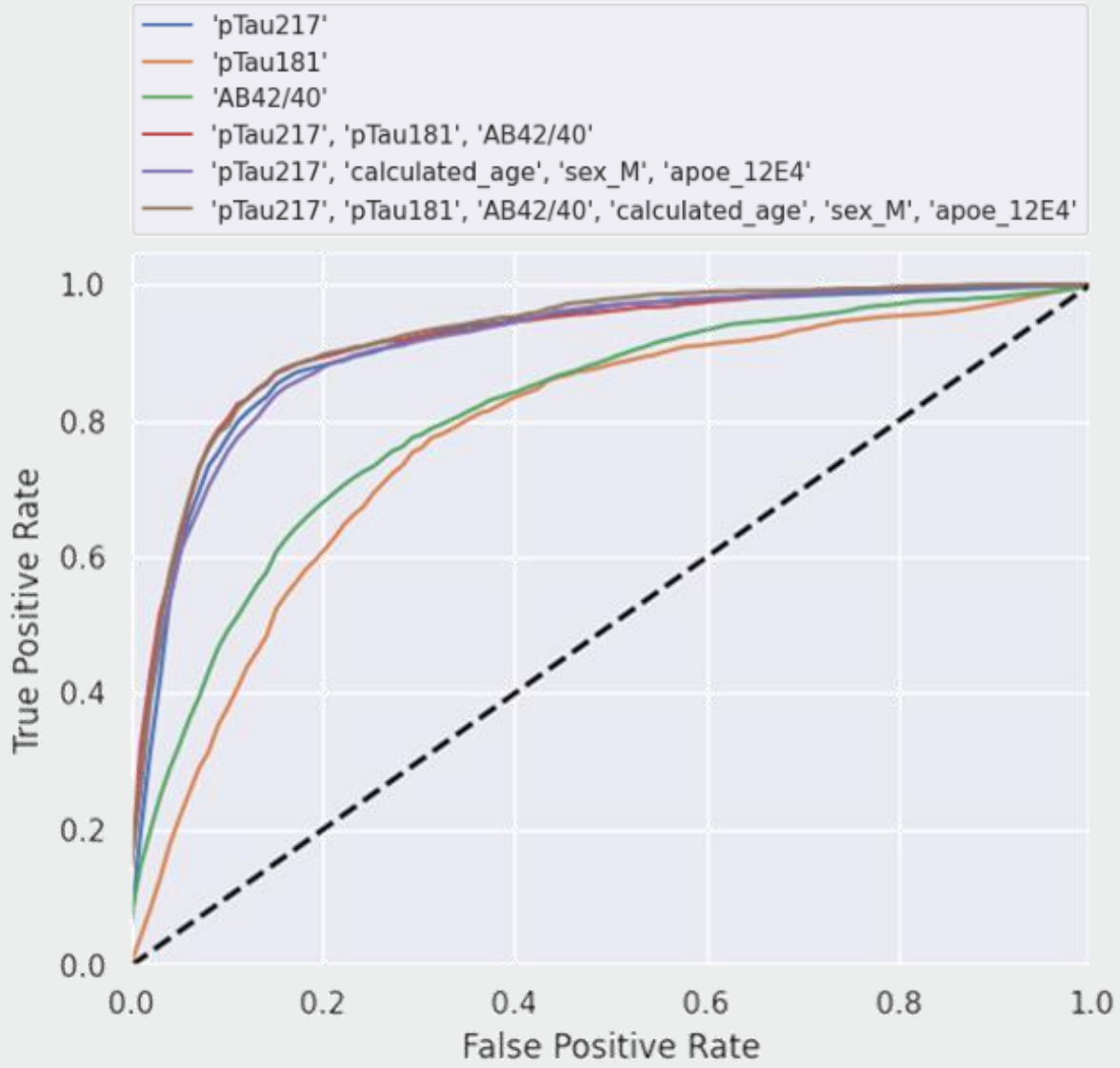
Plasma Biomarkers provide an attractive possibility of a **staged screening** approach, **reduce inefficiency** and patient burden



Measure variability management

Hansson; Alzhemers Dement; 2022
Schindler; Nature; 2024
Brum; Nature Aging; 2023

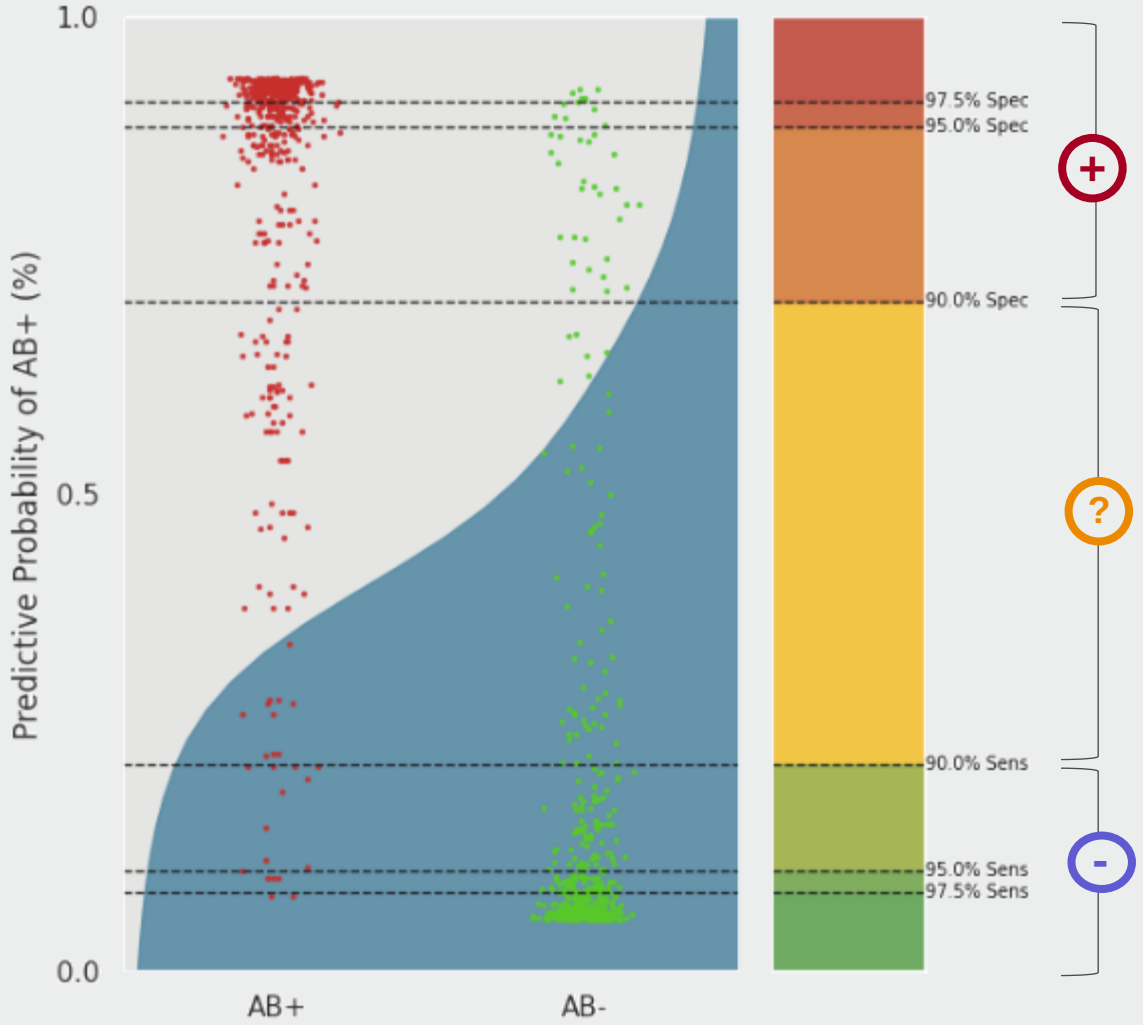
ROC analysis to predict amyloid status



Feature set	AUC	95% Confidence
pTau217	0.908	[0.878 – 0.945]
pTau181	0.777	[0.734 – 0.834]
AB42/40	0.810	[0.739 – 0.860]
pTau217, age, sex, apoE ε4	0.910	[0.875 – 0.941]
pTau217, pTau181, AB42/40	0.917	[0.888 – 0.948]
pTau217, pTau181, AB42/40, age, sex, apoE ε4	0.921	[0.893 – 0.950]

Detailed analysis in:
Mohs et al, Alzheimers Dement. 2024 Apr;20(4):2752-2765

Application of two-stage screening scenarios

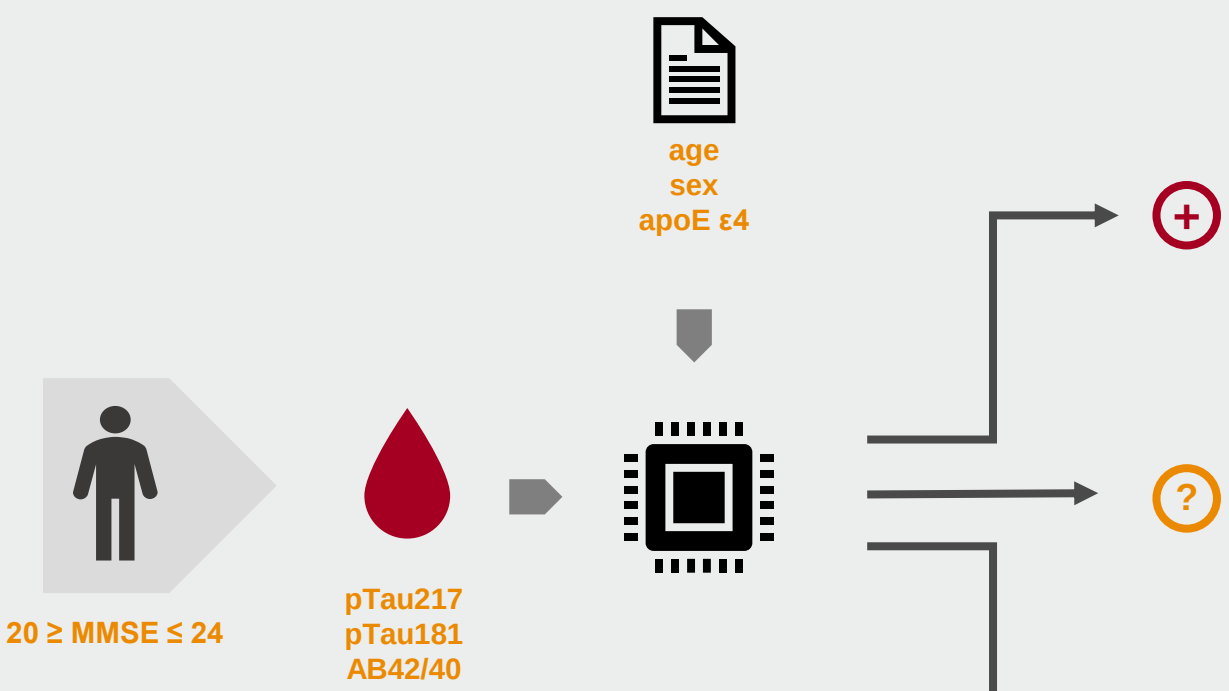


Varying thresholds based on patient and care setting
Brum; Nature Aging 3, 1079-1090 (2023)

Threshold	90	95	97.5	90	95	97.5
Model	Accuracy Median (sd)			Ambiguous % Median (sd)		
pTau217	**0.88 (0.04)**	0.92 (0.03)	0.93 (0.04)	**12 (4.3)**	33 (5.2)	49 (10.3)
pTau181	**0.78 (0.07)**	0.76 (0.13)	0.71 (0.18)	**49 (7.1)**	69 (10.2)	79 (12.3)
AB42/40	**0.80 (0.06)**	0.82 (0.07)	0.83 (0.10)	**38 (7.3)**	65 (6.6)	73 (6/7)
pTau217 age, sex, ε4	**0.90 (0.04)**	0.94 (0.03)	0.96 (0.03)	**15 (3.7)**	33 (6.4)	53 (8.5)
pTau217, pTau181, AB42/40 Age, sex, ε4	**0.91 (0.04)**	0.93 (0.03)	0.93 (0.04)	**8 (2.7)**	31 (5.2)	47 (6.5)

Joules et al, CTAD 2024

Application of two-stage screening scenarios



Threshold - population %

90:	55%
95:	46%
97.5:	30%

- **Trial enrolment**
- **Confirmatory screening**

90:	12%
95:	33%
97.5:	48%

- **Follow up screening with PET / CSF**

90:	32%
95:	24%
97.5:	21%

- **Not enrolled**

Joules et al, CTAD 2024

Application of two-stage screening scenarios

Example CSF/PET screening rates for a target recruitment of 1,000 participants, based on Bio-Hermes population characteristics and an initial clinical screening criteria of 20 ≥ MMSE ≤ 24 and a BBM Model

Threshold	90	95	97.5	90	95	97.5
BBM Model	AB- Rejection, Confirmation of AB+ N Second stage screening			AB+ Enrolment, AB- Rejection N Second stage screening		
pTau217	1174	**1243**	1346	257	**673**	1006
pTau181	1404	**1525**	1568	1000	**1361**	1462
AB42/40	1407	**1563**	1607	1008	**1434**	1529
pTau217 age, sex, ε4	1199	**1281**	1403	350	**783**	1138
pTau217, pTau181, AB42/40 Age, sex, ε4	1163	**1255**	1370	212	**709**	1063

PET/CSF only screening pass rate = 57%, n screened = 1,750

Joules et al, CTAD 2024

Summary and conclusion

A staged screening process utilising a multi-threshold approach with plasma biomarkers enables potential savings in screening measures

Combining multiple plasma biomarkers has minor reduction of uncertainty in prediction of AB status in the brain depending on thresholds used

Reduction in potential population bias when combining multiple biomarkers?