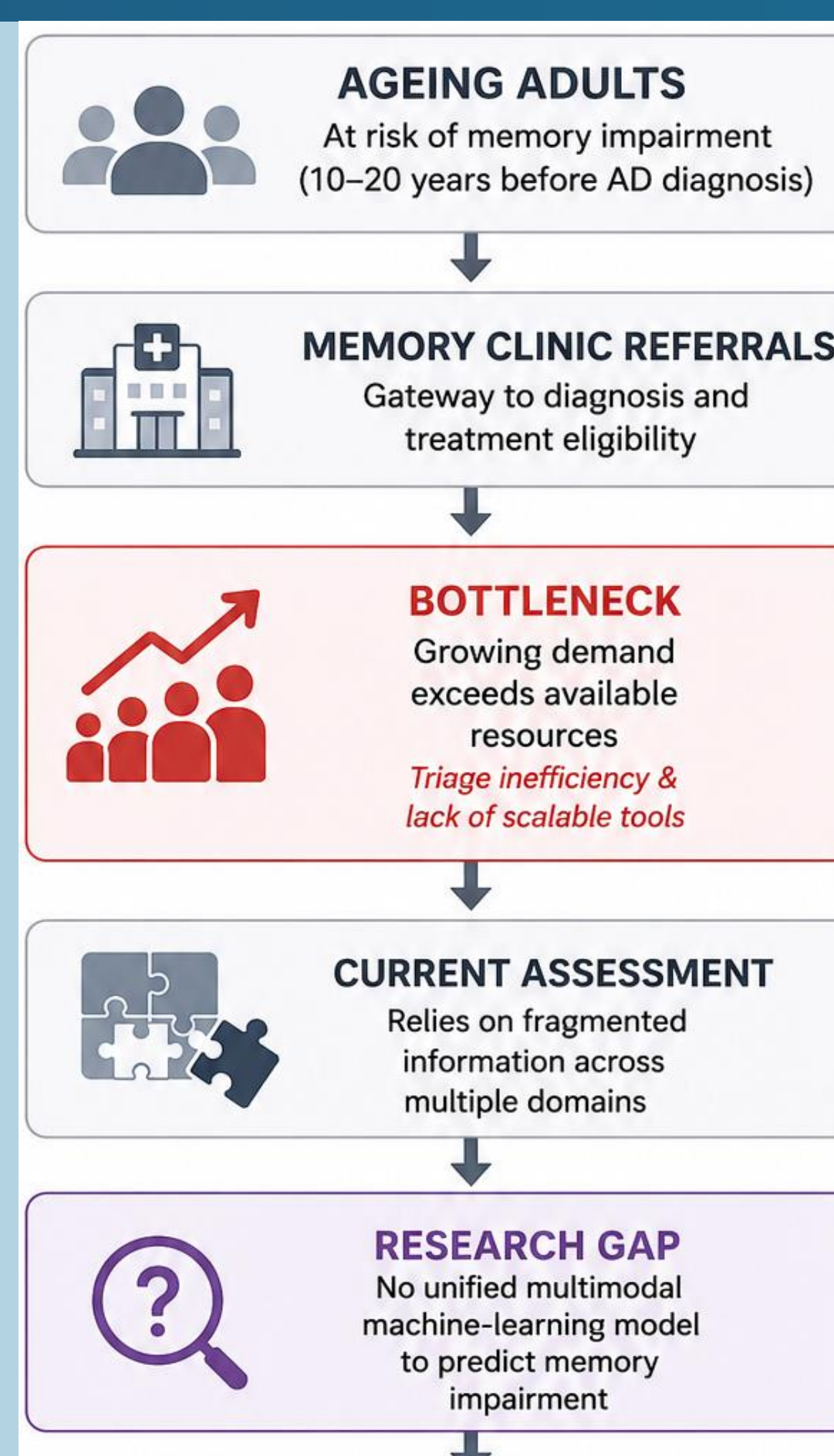


Introduction

- ❖ Memory impairment is often among the earliest domains affected in Alzheimer's disease (AD), reflecting brain changes shaped by a combination of genetic and lifestyle factors over time.^{1,2}
- ❖ Memory clinics are the gateway to timely diagnosis and treatment eligibility yet demand increasingly outpaces resources. Key drivers of this bottleneck are triage inefficiency and a lack of scalable tools.³
- ❖ Unified multimodal machine-learning models integrating precision neuroimaging with fluid markers of AD pathology and neurodegeneration, cognitive and psychiatric measures, genetics, mood, sleep, medical history, comorbidity burden, sociodemographic and lifestyle factors to predict memory impairment remain underexplored.



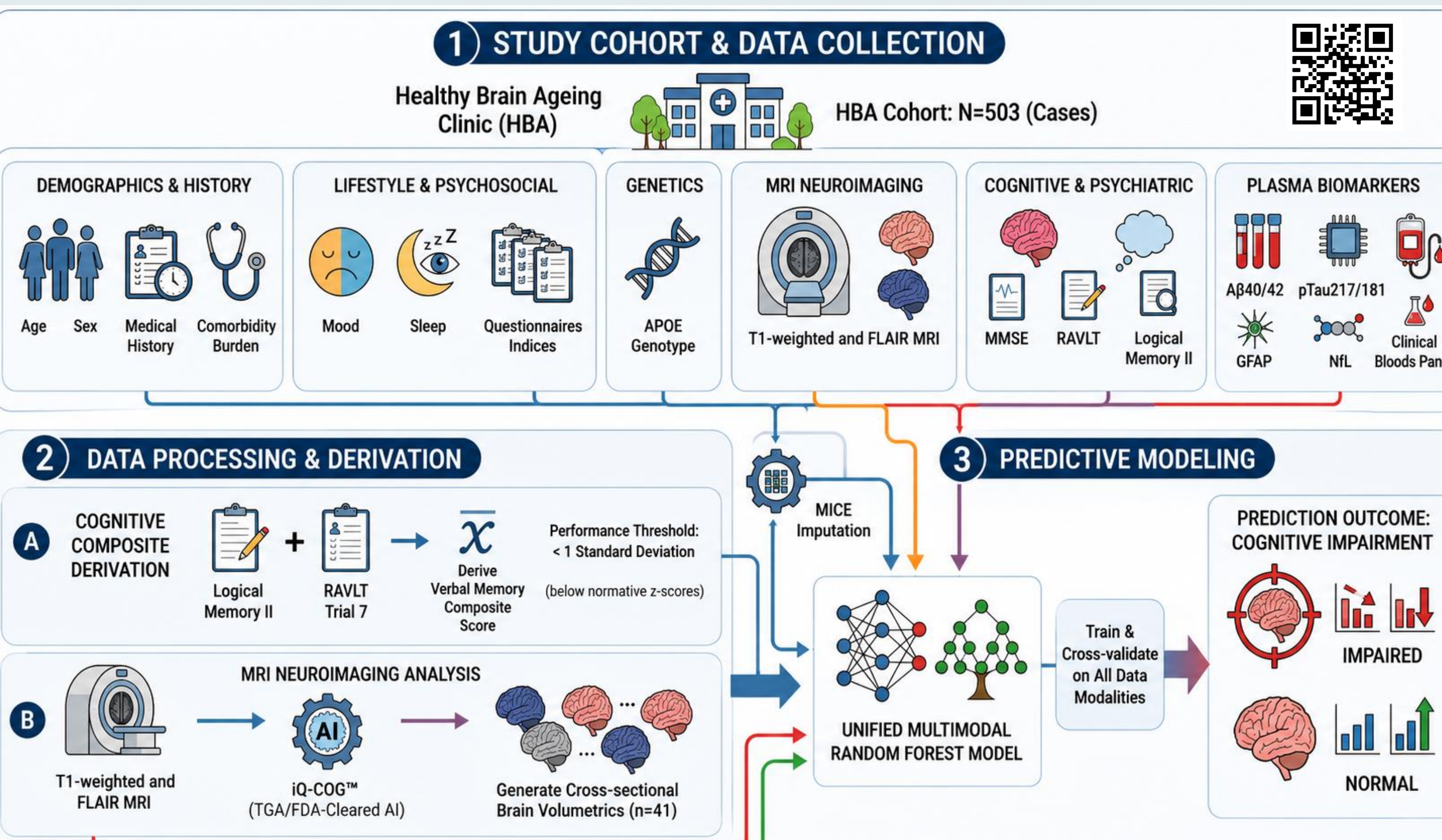
Aims and Hypotheses

In this study, we adopt a novel AI-enabled precision neuroimaging tool (iQ-COG™) and train machine-learning models to:

- Determine how accurately each parameter and modality can classify memory impairment,
- Assess whether integrating modalities synergistically enhances differentiation, and
- Identify the combination of predictors that yield the highest accuracy while staging by accessibility.

Methods

Scan QR code for more info!



Aβ, amyloid beta; APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; MICE, Multiple Imputation by Chained Equations; MMSE, Mini Mental State Exam; NFL, neurofilament light; pTau, phosphorylated tau; RAVLT, Rey Auditory Verbal Learning Test

Results

- ❖ There were 503 participants at baseline with matching multimodal data, and 105 predictors for machine-learning models.
- ❖ Univariately, MMSE alone could differentiate verbal memory impairment with AUROC 84.3% ± 0.8% (Table 1).
- ❖ Performance for each data modality were:
 - **Clinical** mean AUROC = 88.4% ± 2.0%
 - **Blood** mean AUROC = 89.3% ± 1.9%
 - **Neuroimaging** mean AUROC = 82.9% ± 0.35%
- ❖ The top 23 metrics (Table 1, Figure 1), yielded the highest AUROC of 92.8% (81.0% sensitivity, 90.4% specificity).
- ❖ Core 10 metrics with pTau217 yielded AUC 90.4%. Without pTau217, AUC and sensitivity dropped by 3.2% and 12%, although specificity was maintained at 89.3%.

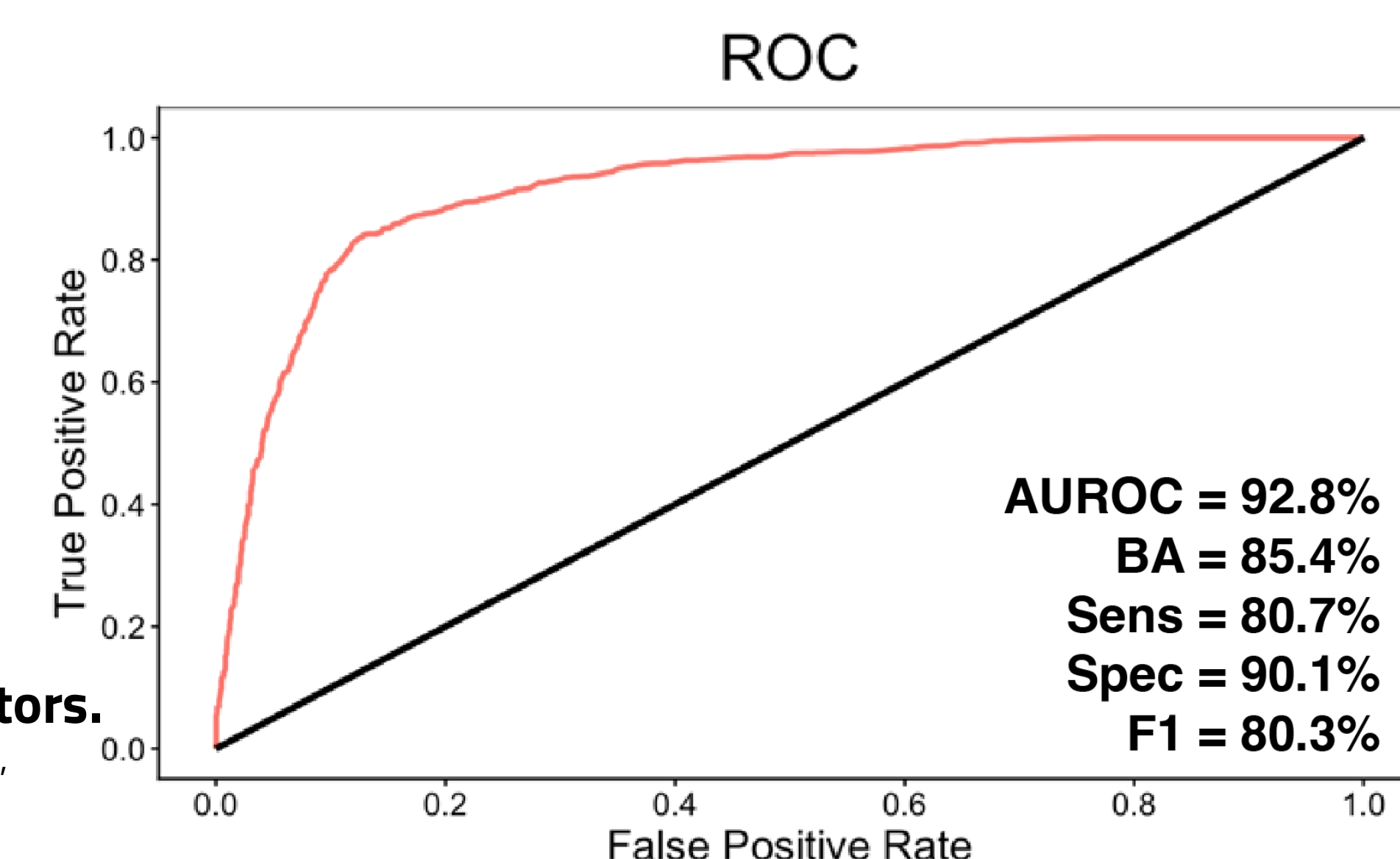
Table 1. Univariate mean AUROC performance across 30 iterations of data, with % model selection per feature

Feature	Selection across models (%)	Mean AUROC (%)
MMSE	100	84.3
Hippocampal Volume (mL)	100	78.7
Parietal Volume (mL)	100	78.6
Hippocampal Centile	100	77.8
Temporal Volume (mL)	100	77.0
Plasma pTau217 (pg/mL)	97	77.8
Cortical Grey Matter Volume (mL)	97	77.0
Left Parietal Centile	97	75.8
Plasma pTau217/Aβ42 ratio	97	75.5
Left Temporal Centile	97	74.5
Plasma GFAP (pg/mL)	97	71.8
Years of Education	97	65.6
Plasma pTau181 (pg/mL)	93	73.8
Grey Matter Volume (mL)	93	73.4
Plasma eGFR	93	71.5
Carer FAQ score	93	70.1
Number of ApoE4 alleles	93	67.0
Whole Brain Centile	93	62.7
Plasma NfL (pg/mL)	90	70.7
Creatinine	90	69.3
Temporal Asymmetry	90	51.0
Right HOI	87	67.5
Plasma Cholesterol (mmol/L)	87	64.3
Plasma Aβ42/40 ratio	83	64.9
PSQI score	83	60.9

Bolded parameters were selected for final model and staged according to accessibility.
Aβ, amyloid beta; APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; HOI, hippocampal occupancy index; MMSE, Mini Mental State Exam; NfL, neurofilament light; PSQI, Pittsburgh Sleep Quality Index; pTau, phosphorylated tau

Figure 1. Unified multimodal machine-learning models demonstrate superior differentiation, peaking at AUROC 92.8% using the top 23 predictors.

AUROC, area under the receiver operating curve; BA, balanced accuracy; Sens, sensitivity; Spec, specificity



Conclusion

- ❖ Integration of precision neuroimaging with advanced patient and biomarker profiling yielded superior differentiation of memory impairment compared to unimodal models
- ❖ The top 23 metrics yielded the highest accuracy AUC 92.8%, with excellent specificity and great sensitivity. Reducing this down to the top 10 (MMSE, hippocampal, parietal and temporal metrics with pTau217 and years of education) maintained AUC at 90.4%.
- ❖ This work provides evidence for scalable, translational frameworks for clinical triage, and could help overcome bottlenecks in memory clinics and aid current early detection strategies

Acknowledgements:

We thank all participants and clinical staff of the Healthy Brain Ageing Clinic. This research was supported by the NHMRC and the Brain and Mind Centre.