

Systemic Immunoglobulin Isotype Signatures Distinguish Neuroprotective from Neurotoxic Immune Phenotypes in Alzheimer's Disease

Pranav Pancham¹ • Monique David¹ • Christopher Fowler² • Colin Masters³ • Ralph Martins³ • Mourad Tayebi¹

¹School of Medicine, Western Sydney University, NSW, Australia | ²The Florey Institute of Neuroscience & Mental Health, VIC, Australia | ³UWA Medical School, Perth, Australia

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BACKGROUND & RATIONALE

- AD exhibits marked clinical heterogeneity despite similar amyloid-beta (A β) pathology.
- Some amyloid-positive individuals maintain normal cognition (cognitive resilience), while others progress to dementia (vulnerable phenotype).
- Systemic immunoglobulin isotype profiles reflecting T helper cell-driven class switching may modulate neurodegeneration independent of A β burden.
- Current gold-standard diagnostics (PET, CSF) are invasive and costly (AUD \$3,000–\$5,000/scan).
- Blood-based immunoglobulin biomarkers offer a minimally invasive, scalable alternative for early AD risk stratification.

FIGURE 1 — DIAGNOSTIC LANDSCAPE

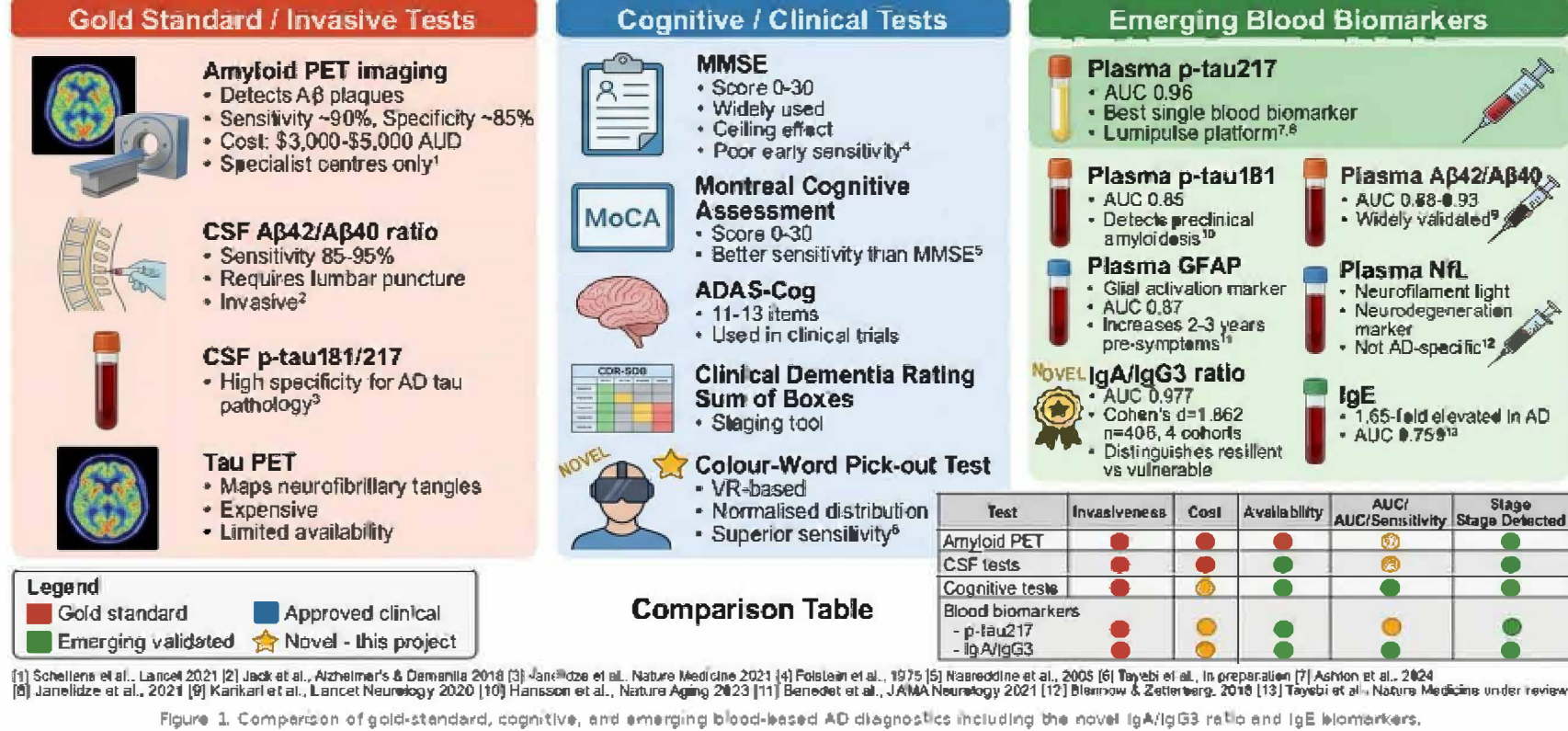


Figure 1. Comparison of gold-standard, cognitive, and emerging blood-based AD diagnostics including the novel IgA/IgG3 ratio and IgE biomarkers.

KNOWLEDGE GAP

- No validated blood-based isotype panel reliably distinguishes neuroprotective from neurotoxic systemic immune phenotypes.
- The functional role of IgE in A β immune modulation and its interaction with IgA/IgG3 remains unexplored.
- Multimodal integration of immunoglobulin biomarkers, gut microbiome signatures, and digital cognitive phenotyping for early AD risk classification is lacking.

METHODS

Multi-Cohort Cross-Sectional Study
n = 406 participants | 4 international cohorts
AIBL • KARVIAH • BioFINDER-1 • NICM-WSU
7 immunoglobulin isotypes quantified in serum (IgG1–4, IgA, IgE, IgM)
ROC analysis • Mann-Whitney U • Cohen's d • Cytokine sub-study (n=83)

Participants classified: A β -CU (n=135), A β +CU resilient (n=115), A β -CI (n=106), A β +CI vulnerable (n=67).
APOE- ϵ 4 stratification to assess genotype $\times$ isotype interactions.
MC65 neuronal cytotoxicity assay for functional neuroprotection validation.

STUDY COHORTS & PARTICIPANTS				
Group	n	A β Status	Cognition	
A β -CU	135	Negative	Unimpaired	
A β +CU (Res.)	115	Positive	Resilient	
A β -CI	106	Negative	Impaired	
A β +CI (Vul.)	67	Positive	Vulnerable	
TOTAL	406	—	4 cohorts	

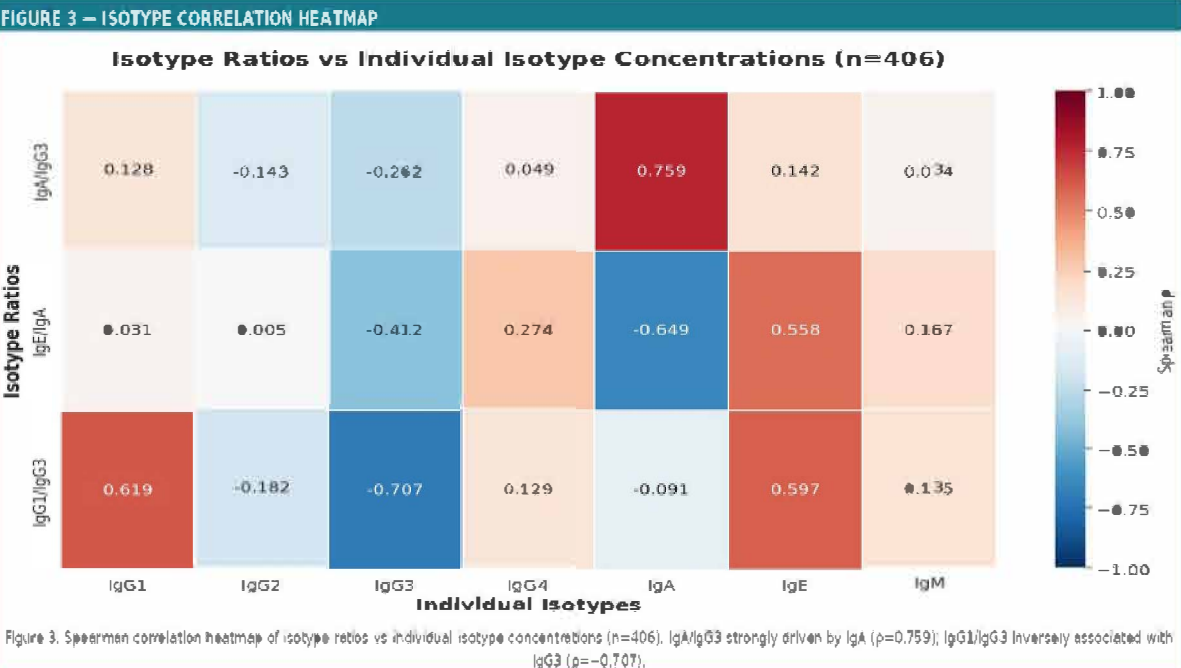
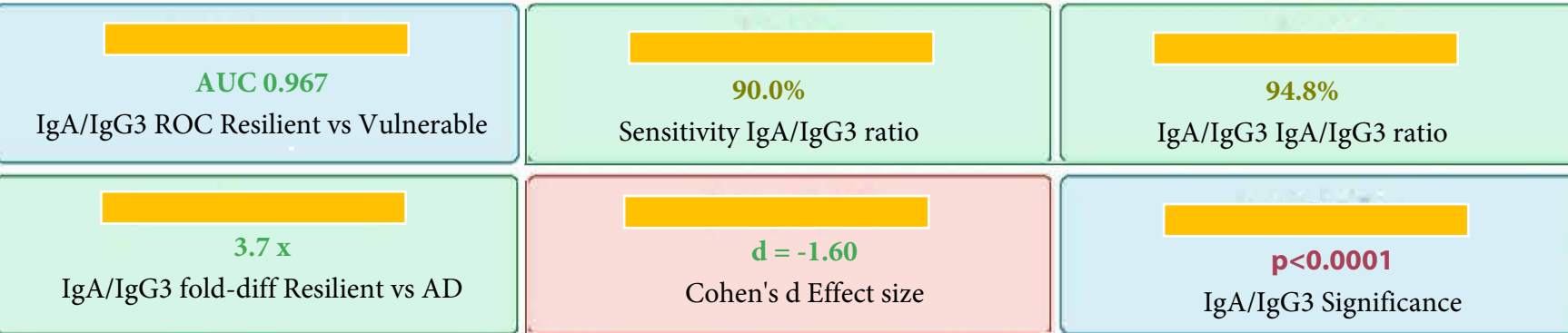


Figure 3. Spearman correlation heatmap of isotype ratios vs individual isotype concentrations (n=406). IgA/IgG3 strongly driven by IgA (p=0.759). IgG1/IgG3 inversely associated with IgG3 (p=0.707).

KEY RESULTS



FINDING 1 — IGA/IGG3 RATIO

- IgA/IgG3: A β -CU (resilient) = 0.365 $\pm$ 0.294 vs A β +CI (vulnerable) = 1.338 $\pm$ 1.015.
- 3.7-fold difference (p<0.0001, Cohen's d = -1.599) — exceptional discriminatory power.
- IgA/IgG3 inversely correlated with pro-inflammatory IL-17A (p=-0.553, p=0.05) and IFN- γ (p=-0.616, p=0.03).
- Low IgA/IgG3 validated as neuroprotective in MC65 neuronal cytotoxicity assay.

FIGURE 2 — ISOTYPE RATIO DISTRIBUTIONS

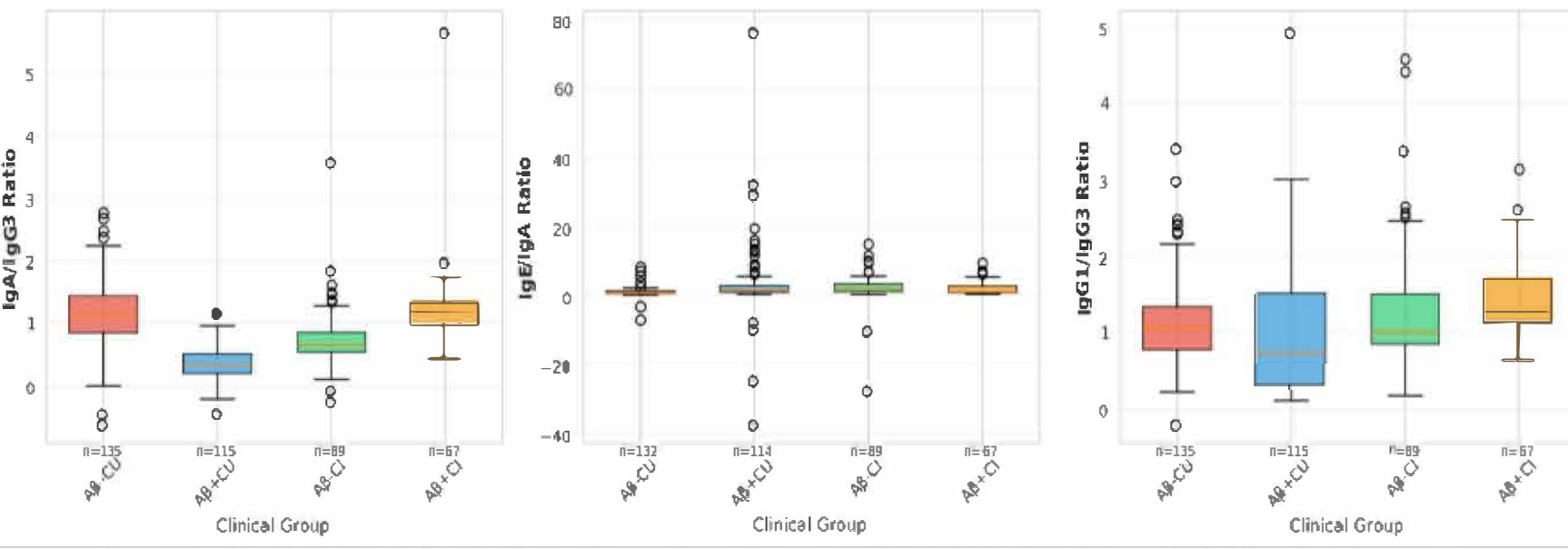


Figure 2. Box plots of IgA/IgG3, IgE/IgA and IgG1/IgG3 ratios across four clinical groups (A β -CU, A β +CU, A β -CI, A β +CI). Lowest IgA/IgG3 in resilient (A β +CU) group.

FINDING 2 — IGE DYSREGULATION

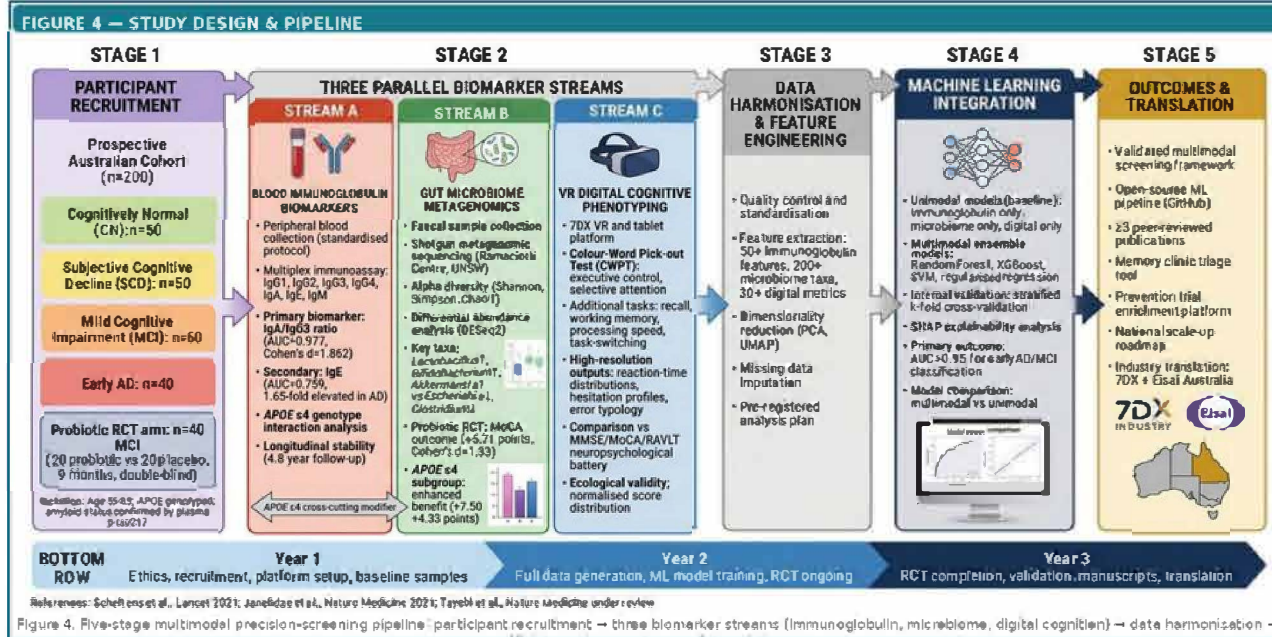
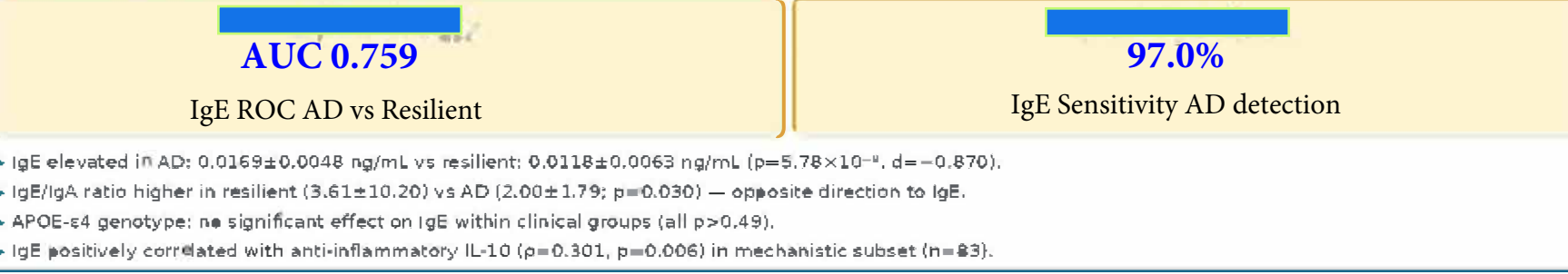
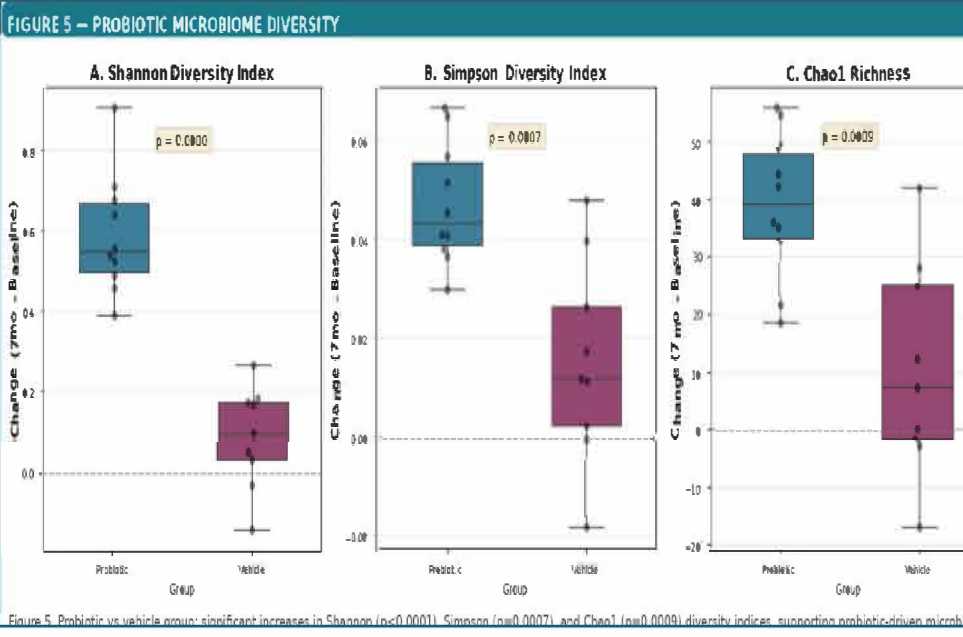


Figure 4. Five-stage multimodal precision-screening pipeline: participant recruitment — three biomarker streams (immunoglobulin, microbiome, digital cognitive) — data harmonisation —



Dr Mourad Tayebi DVM MSc PhD I Associate Professor in Biomedical Sciences & Head of Neuroimmunology Laboratory School of Medicine - Building 30.2.26 - Western Sydney University
Cnr David Pilgrim Drive & Goldsmith Avenue Campbelltown 2560 NSW Australia
P: +61 (02) 4620 3671 E: tayebi@westernsydney.edu.au