



Imaging and molecular risk factors in developing amyloid related imaging abnormalities (ARIA) in Alzheimer's Disease patients treated with monoclonal antibodies

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Saima Rathore^{1,2,3}, Chad Hales^{2,3}, Liping Zhao⁴, Daniel Bartholomew^{2,3}, Allan I. Levey^{2,3}, James J. Lah^{2,3}

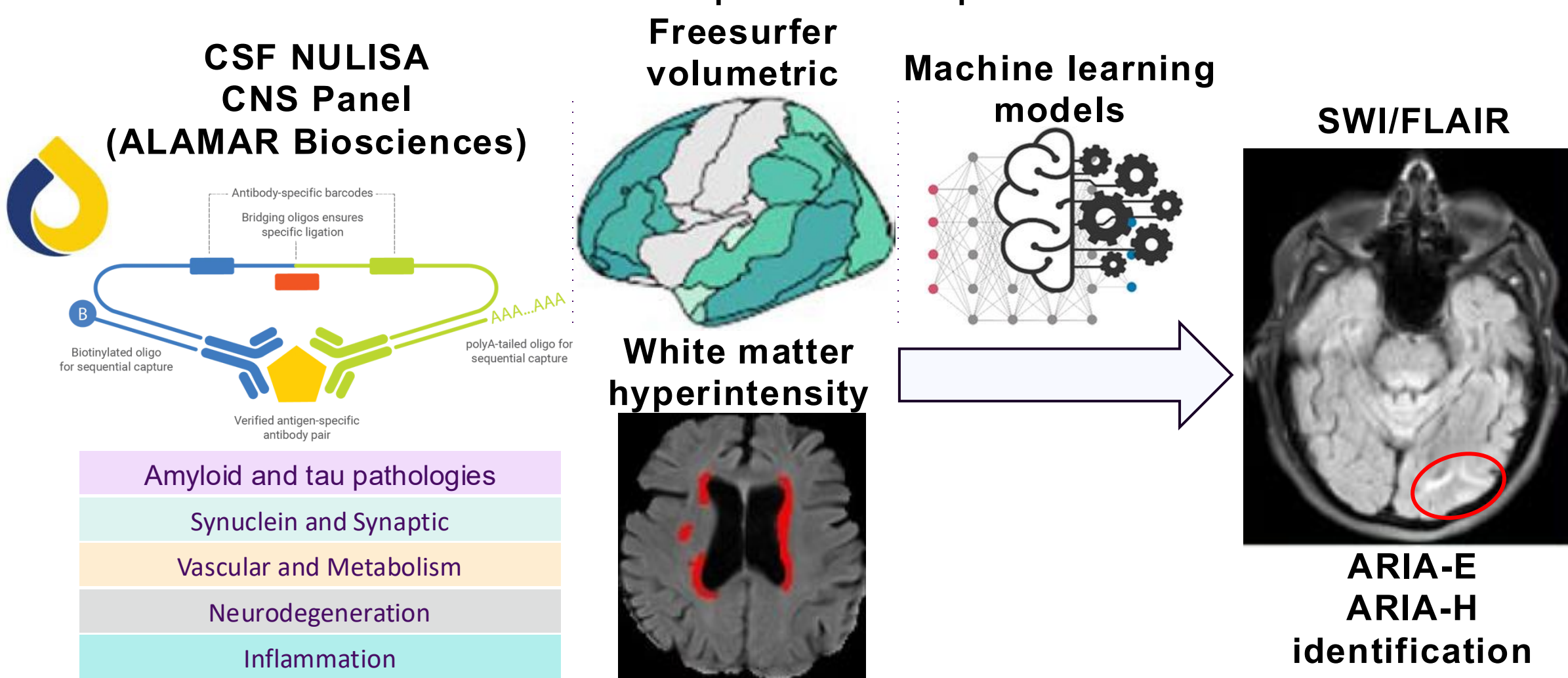
¹Department of Biomedical Informatics, ²Department of Neurology, ³Center for Neurodegenerative Disease, School of Medicine; ⁴Rollins School of Public Health; Emory University, GA, USA

Introduction

- Anti-amyloid monoclonal antibodies (mAbs) now offer disease-modifying potential in early Alzheimer's disease (AD) but carry important safety risks¹.
- A principal safety concern is amyloid-related imaging abnormalities (ARIA), detected on MRI, which present as edema/effusion (ARIA-E) or hemorrhage (ARIA-H).²
- Although mostly asymptomatic, ARIA can progress to serious neurological complications². Identifying biological risk factors for ARIA is essential for safer treatment selection.
- **Goal:** To define baseline molecular and imaging signatures that predict ARIA susceptibility.

Methods

- This study included 228 patients treated according to protocol-specific infusion schedules, and underwent clinical assessment and blood draws every six months, and follow-up safety MRI, yielding >2.2Y of treatment data (1239-timepoints).
- Proteomics generated using the NULISAseq™ CNS Panel (n=130).
- Imaging included T1-w, T2-w, FLAIR, and SWI sequences, with T1-w processed using FreeSurfer to derive regional cortical/subcortical volumes, and other modalities registered to T1-w space.
- ARIA-E and ARIA-H assessed on follow-up MRI by radiologists.
- Performed differential abundance analyses to identify protein-levels and imaging measurements associated with occurrence of ARIA.
- Machine-learning using random forest³ and LASSO⁴ across 100 runs was used to derive a predictive panel for onset.

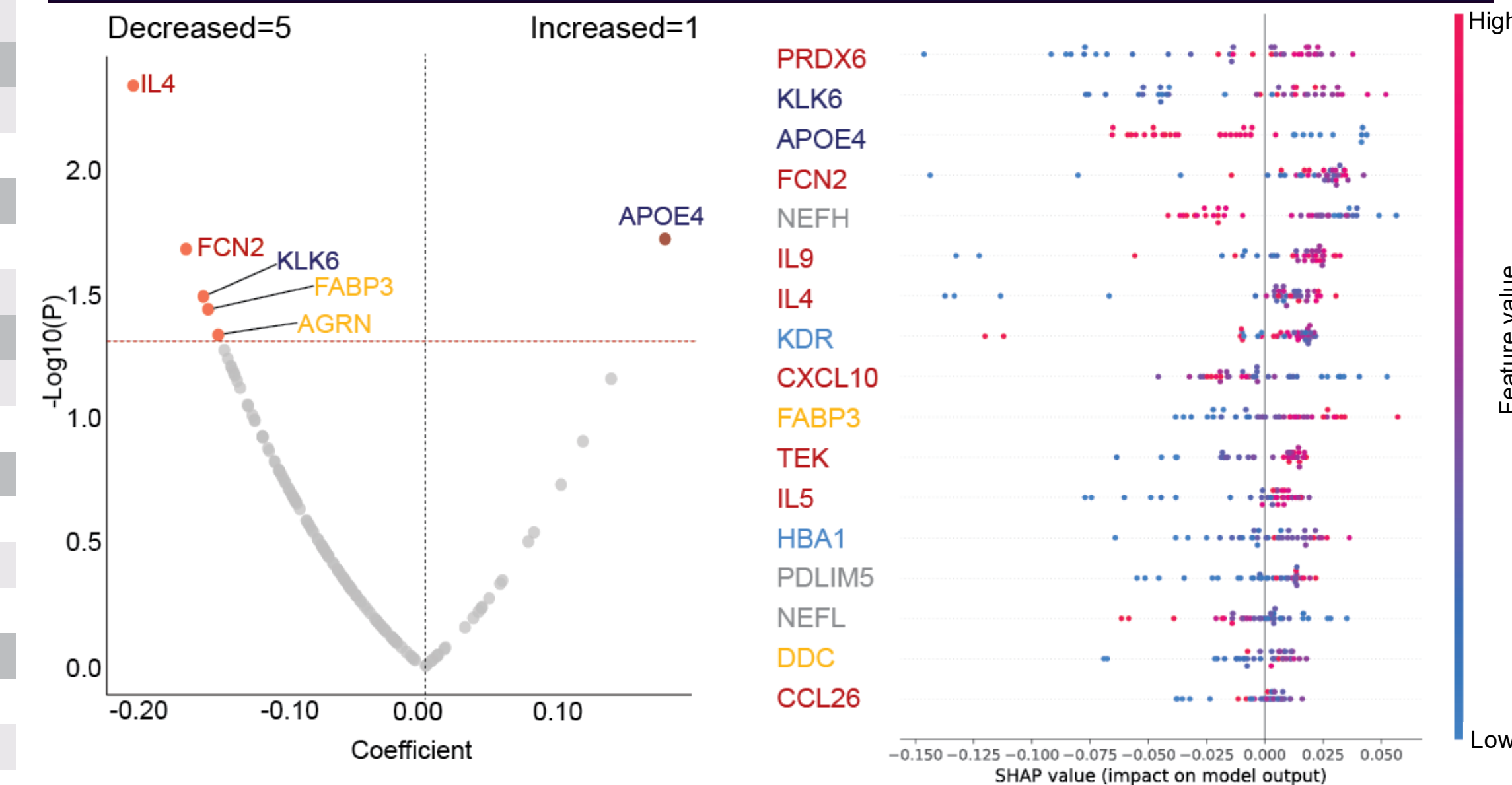


Results

Table: Summary demographics and clinical characteristics of participants who developed amyloid related imaging abnormalities (ARIA).

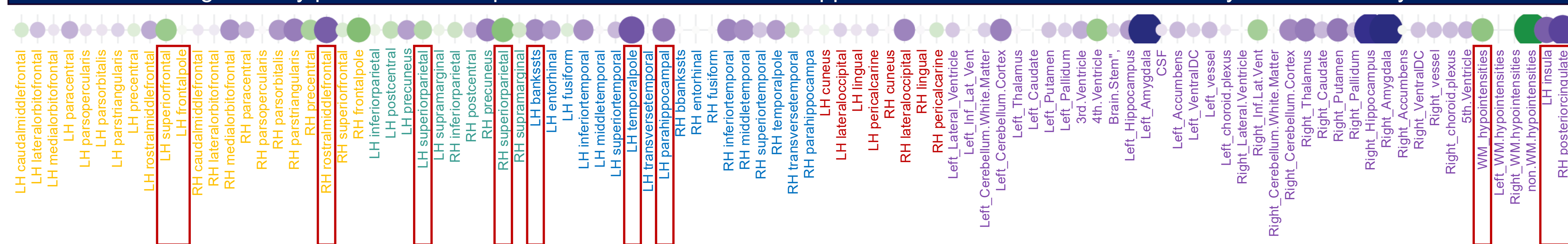
	No ARIA	ARIA-E	ARIA-H	ARIA-E and ARIA-H
No participants	165 (71.4%)	5 (2.16%)	40 (17.3%)	21 (9.09%)
Age				
Mean (SD)	72.51 (7.41)	72.8 (4.55)	74.74 (6.20)	73.88 (5.50)
Median [Min, Max]	74 [52, 86]	72 [69, 80]	75 [54, 83]	74 [65, 86]
Sex				
Female, n (%)	64 (49.61%)	3 (60%)	18 (52.94%)	11 (68.75%)
Male, n (%)	64 (49.61%)	2 (40%)	14 (41.18%)	5 (31.25%)
Race				
Others, n (%)	14 (10.85%)	0 (0.00%)	3 (8.72%)	3 (18.75%)
White, n (%)	115 (89.15%)	5 (100.00%)	31 (91.18%)	13 (81.25%)
APOE Genotype				
Non-carriers, n (%)	66 (41.24%)	0 (0.00%)	8 (21.05%)	6 (30.00%)
Heterozygous, n (%)	83 (51.88%)	5 (100.00%)	25 (65.79%)	10 (50.00%)
Homozygous, n (%)	11 (6.88%)	0 (0.00%)	5 (13.16%)	4 (20.00%)
MoCA (Before Treatment)				
Total: Mean (SD)	21.19 (4.50)	---	20.09 (4.25)	19.94 (3.64)
Attention: Mean (SD)	11.08 (6.20)	---	11.5 (6.76)	10.66 (6.31)
Language: Mean (SD)	4.65 (1.09)	---	4.32 (1.25)	4.50 (1.31)
Memory: Mean (SD)	5.77 (3.68)	---	6.69 (3.55)	6 (3.84)

Machine-learning classification identified a 17-protein predictive panel spanning axon guidance, synaptic organization, neuronal differentiation, coagulation, ECM-remodeling, and immune activation.

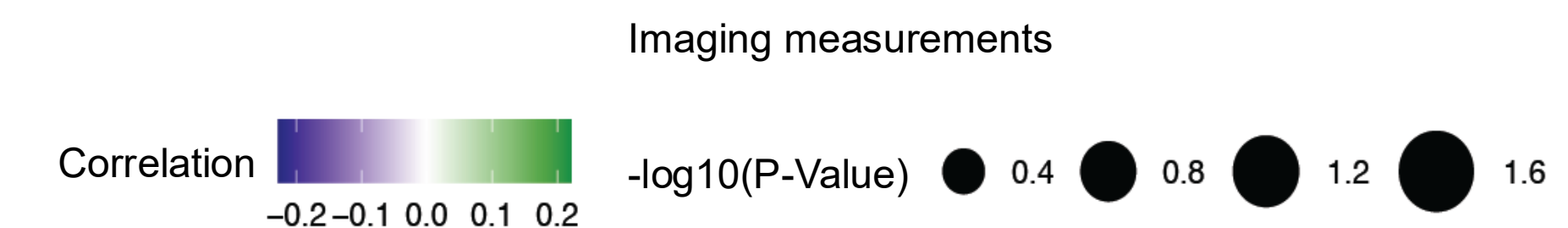


Median AUC = 0.76 (95% CI: 0.64-0.89)

A multiparametric, multiregional MRI-derived volumetric panel spanning frontal, cingulate, insular, temporal, parietal, and white matter regions significantly predicted subsequent ARIA occurrence and mapped onto established networks of amyloid vulnerability.

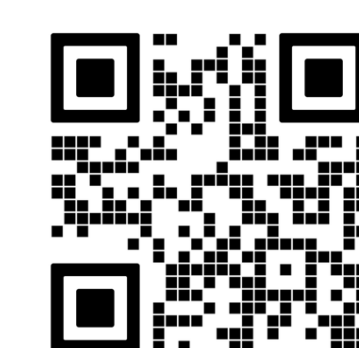


Median AUC=0.80 (95% CI: 0.71-0.90)



Before mAb start, proteomics and MRI reveal vulnerability to ARIA. Two complementary risk models (17-proteins, AUC=0.76; MRI, AUC=0.80) point to a multi-pathway basis for ARIA and a strategy for safer patient selection.

Acknowledgements/Contacts



Email: saima.rathore@email.emory.edu

References:

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