

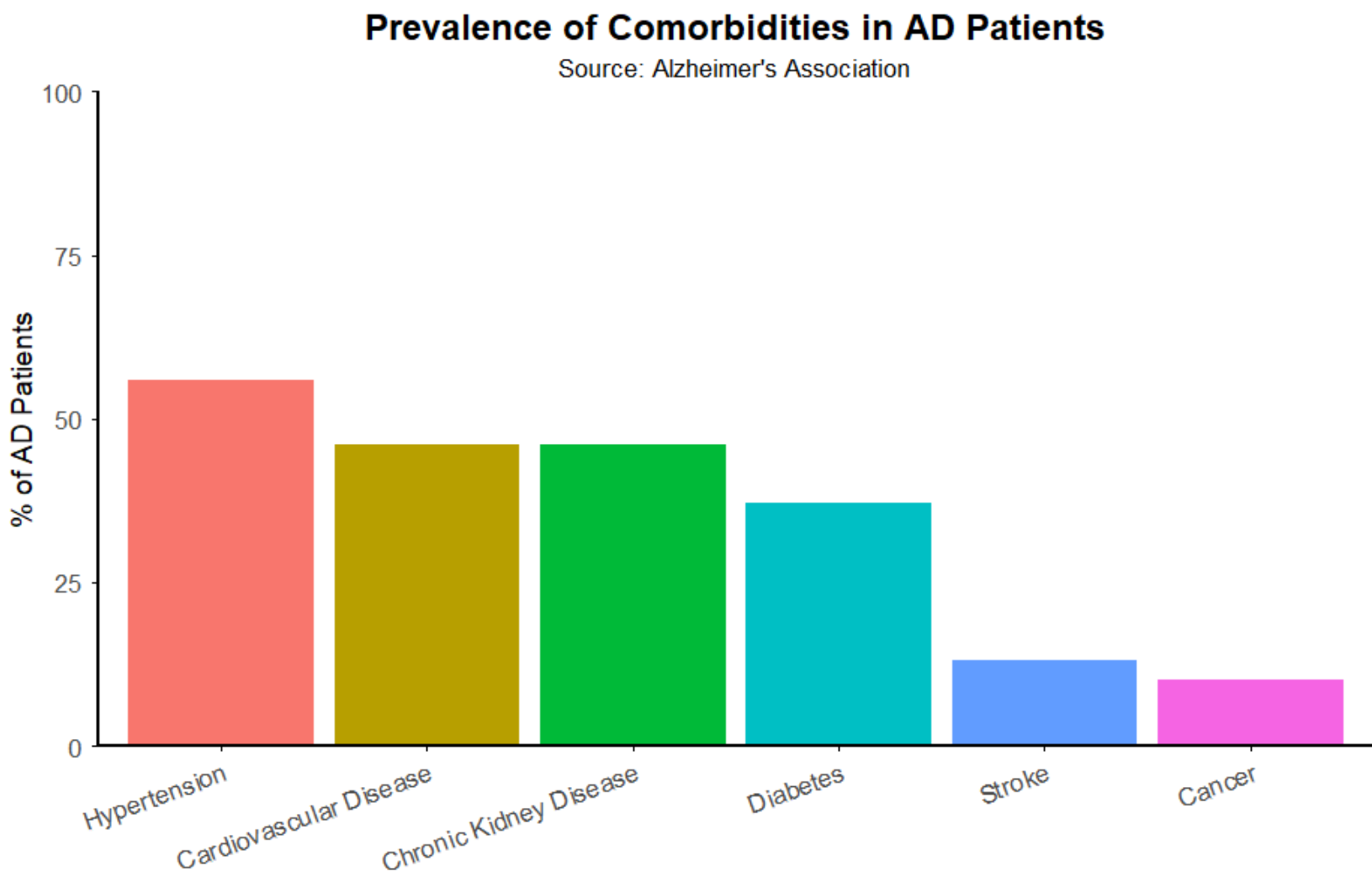
Blood-biomarker signatures implicate several pathways in common Alzheimer's disease comorbidities



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INTRODUCTION

- Validated biomarkers have been integrated into clinical practice
 - Diagnosis, prognosis, and treatment
- Biomarker signature panels outperform individual biomarkers at capturing disease pathophysiology
- In Alzheimer's disease (AD), the NULISaseq CNS 120 panel enables the quantification of 131 biomarkers that excellently identify core AD pathology.
- AD is a multifaceted condition influenced by non-AD pathologies, and with a patient population characterized by the prevalence of comorbidities.
- Biomarker signatures would allow for a more comprehensive evaluation and facilitate the application of precision medicine in everyday AD care.

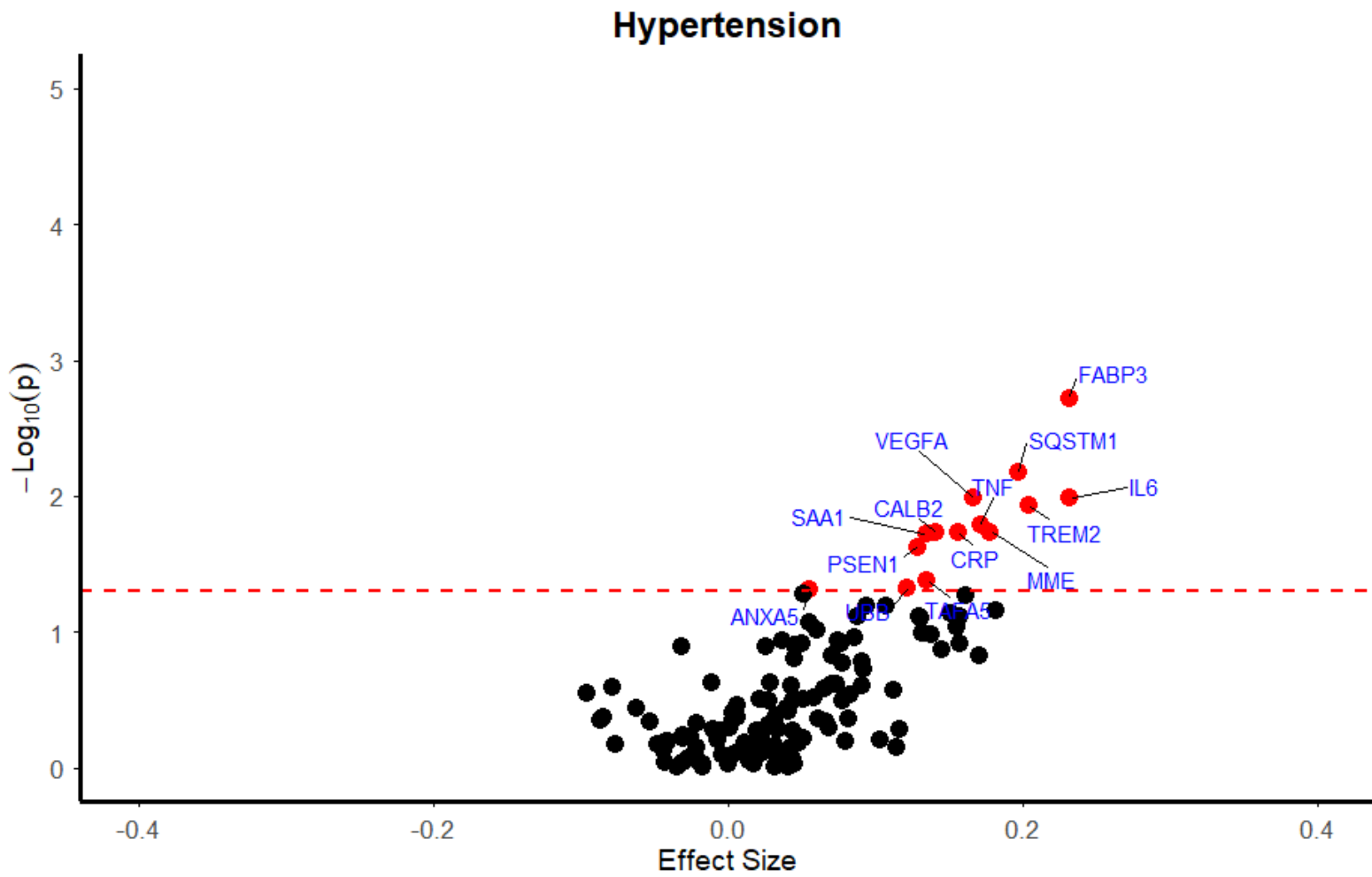


METHODS

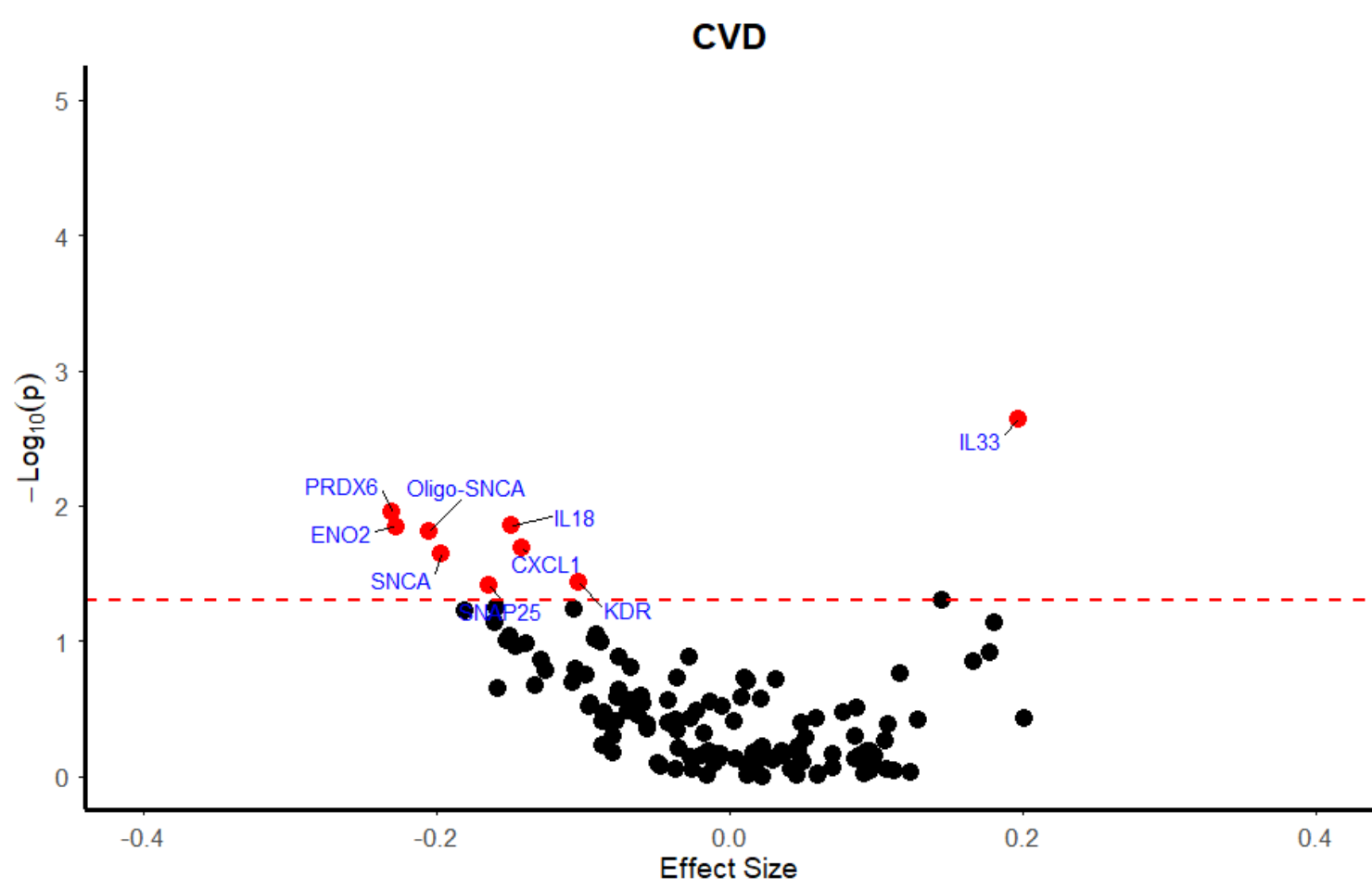
- Univariate age and sex-adjusted logistic regression was used to determine biomarkers with significant changes

Summary of Participant Characteristics (N = 1397)	
Age	70 ± 10 years
Sex	Female (52.3%)
Race	Non-Hispanic White (92%)
Comorbidities	Hypertension (18.4%)
	Cardiovascular Disease* (7.1%)
	Type 2 Diabetes (7.4%)
Cognitive Status	AD-Dementia (33.9%)
	Cognitively Normal (28%)
	MCI (22.2%)
	Non-AD Dementia (14.8%)
Abbreviations: AD – Alzheimer's disease; MCI – Mild Cognitive Impairment	
*Cardiovascular disease – patient has one or more of the following: Atrial fibrillation, angina, history of angioplasty and/or bypass surgery, congestive heart failure, history of myocardial infarction, pacemaker, and/or valves.	

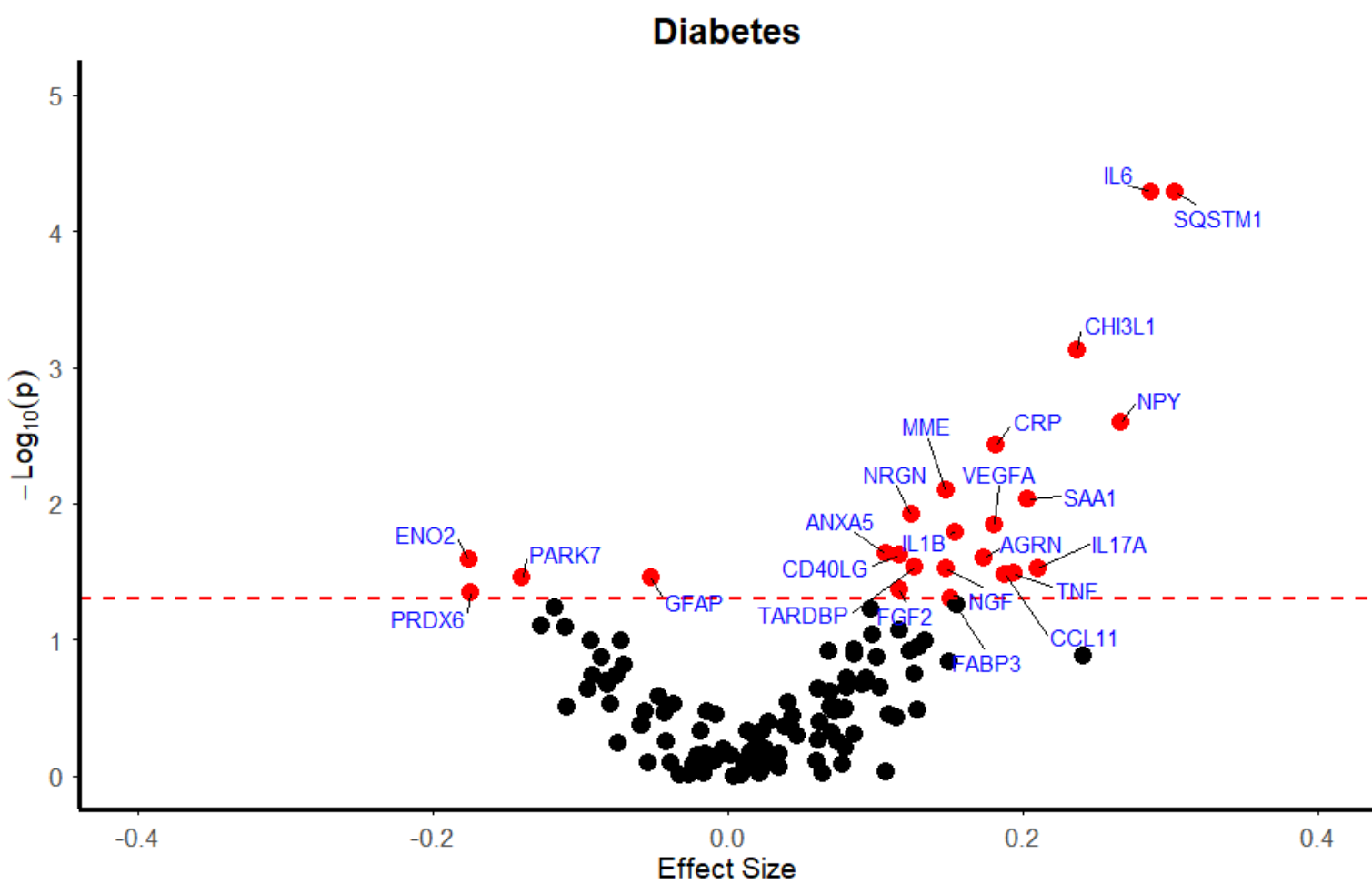
RESULTS



Hypertension				
Functional Classification	Biomarker	Protein	Effect Size	P-value
Systemic inflammation	CRP	C-Reactive protein	0.1562	0.0183
	IL-6	Interleukin 6	0.2316	0.0104
	SAA1	Serum amyloid A1	0.1350	0.0191
Neuroinflammation and signaling	TNF	Tumor necrosis factor α	0.1711	0.0164
	TREM2	Triggering receptor expressed on myeloid cells 2	0.2040	0.0118
	SQSTM1	Sequestosome 1	0.1965	0.0066
Pathological protein aggregation	PSEN1	Presenilin 1	0.1286	0.0236
	UBB	Ubiquitin B	0.1220	0.0474
	MME	Neprilysin	0.1779	0.0183
Neuronal and synaptic function	CALB2	Calbindin 2	0.1413	0.0185
	TAF A5	TAF A chemokine-like family member 5 (FAM19A5)	0.1351	0.0415
Vascular stress and remodeling	VEGF-A	Vascular endothelial growth factor A	0.1663	0.0102
	ANXA5	Annexin A5	0.0553	0.0486
Neuronal and glial injury	FABP3	Fatty acid binding protein 3	0.2318	0.0019



Cardiovascular Disease				
Functional Classification	Biomarker	Protein	Effect Size	P-value
Systemic inflammation	IL-18	Interleukin 18	-0.1493	0.014
	CXCL1	C-X-C motif chemokine ligand 1	-0.1417	0.0204
Neuroinflammation and signaling	IL-33	Interleukin 33	0.1971	0.0023
Oxidative stress and cellular response	PRDX6	Peroxiredoxin	-0.2303	0.011
Pathological protein aggregation	Oligo-SNCA	Oligomeric α-synuclein	-0.2046	0.0153
	SNCA	α-synuclein	-0.1966	0.0227
Neuronal and synaptic function	SNAP25	Synaptosomal associated protein 25	-0.1638	0.0382
Vascular stress and remodeling	KDR	Kinase insert domain-receptor (VEGFR2)	-0.1032	0.0364
Neuronal and glial injury	ENO2	Neuron-specific enolase	-0.2277	0.0142



- Prolonged systemic and neuronal inflammation not linked to oxidative stress or glial injury
- Indications of permanent injury, remodeling, and pathological protein aggregation in the vasculature and the brain

Diabetes				
Functional Classification	Biomarker	Protein	Effect Size	P-value
Systemic inflammation	CRP	C-Reactive protein	0.1817	0.0037
	SAA1	Serum amyloid A1	0.2034	0.0093
	IL-6	Interleukin 6	0.287	0.0001
	IL-1B	Interleukin 1B	0.1543	0.0161
	TNF	Tumor necrosis factor α	0.1938	0.0324
Neuro-inflammation and signaling	IL-17A	Interleukin 17A	0.21	0.0296
	CCL11	Eotaxin 1	0.1877	0.0332
	CD40LG	CD40 ligand (CD154)	0.1162	0.0241
	CH3L1	Chitinase-3-like protein	0.2367	0.0007
	PARK7	Parkinsonism-associated deglycase (DJ-1)	-0.1393	0.0352
Oxidative stress and cellular response	PRDX6	Peroxiredoxin-6	-0.174	0.0451
	TDP-43	Tar-DNA binding protein 43	0.1269	0.0293
Pathological protein aggregation	SQSTM1	Sequestosome 1	0.3034	0.0001
	MME	Neprilysin	0.1476	0.0081
	NRGN	Neurogranin	0.1243	0.0119
	NPY	Neuropeptide 1	0.2666	0.0025
Neuronal function and regeneration	NGF	Nerve growth factor	0.1479	0.0303
	FGF2	Fibroblast growth factor 2	0.116	0.0426
	AGRN	Agtrin	0.1738	0.0249
	VEGF-A	Vascular endothelial growth factor-A	0.181	0.0144
Vascular stress and remodeling	ANXA5	Annexin A5	0.1068	0.0233
	GFAP	Glial fibrillary acidic protein	-0.0523	0.0346
Neuronal and glial injury	ENO2	Neuron-specific enolase	-0.1755	0.0257
	FABP3	Fatty acid-binding protein 3	0.1513	0.0496

CONCLUSIONS

- Common Alzheimer's comorbidities are associated with major pathologies that can exacerbate AD-dementia and increase burden on patients, caregivers, and the system.
- Biomarker signature panels offer more details than individual measurements about specific patterns of pathological manifestations and progression of disease.
- Longitudinal data is needed in order to confirm disease progression mechanisms, especially for cardiovascular disease.
- Signature panels are especially advantageous in precision medicine because they permit for a more holistic patient evaluation and therefore a more personalized treatment plan.

ACKNOWLEDGEMENTS

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