Biomarkers related to Alzheimer's Disease, Neuropathology, and Dementia for HCAP Studies

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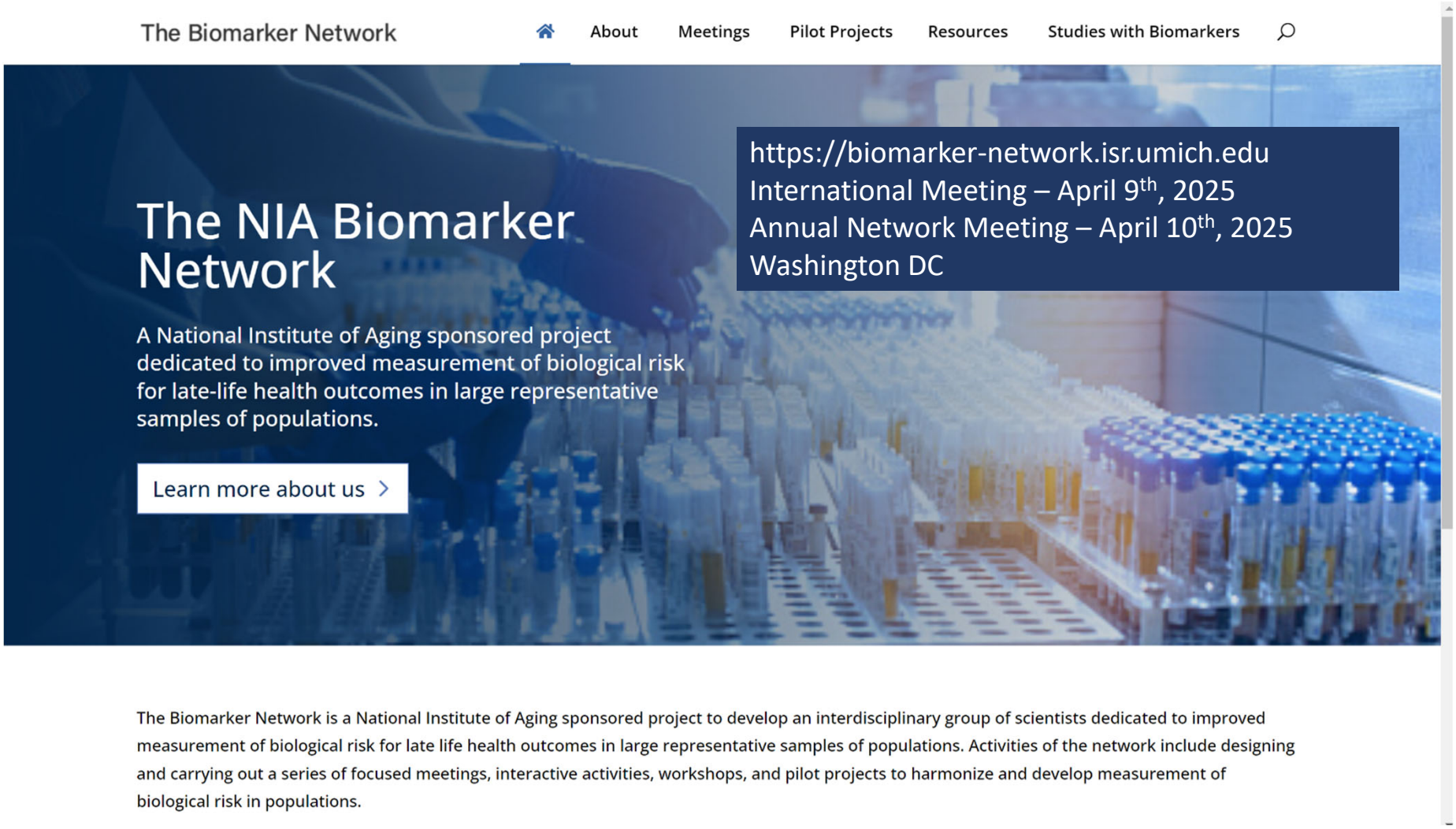
HCAP / ATN Meeting: September 30 – October 1, 2024


The Biomarker Network
About
Meetings
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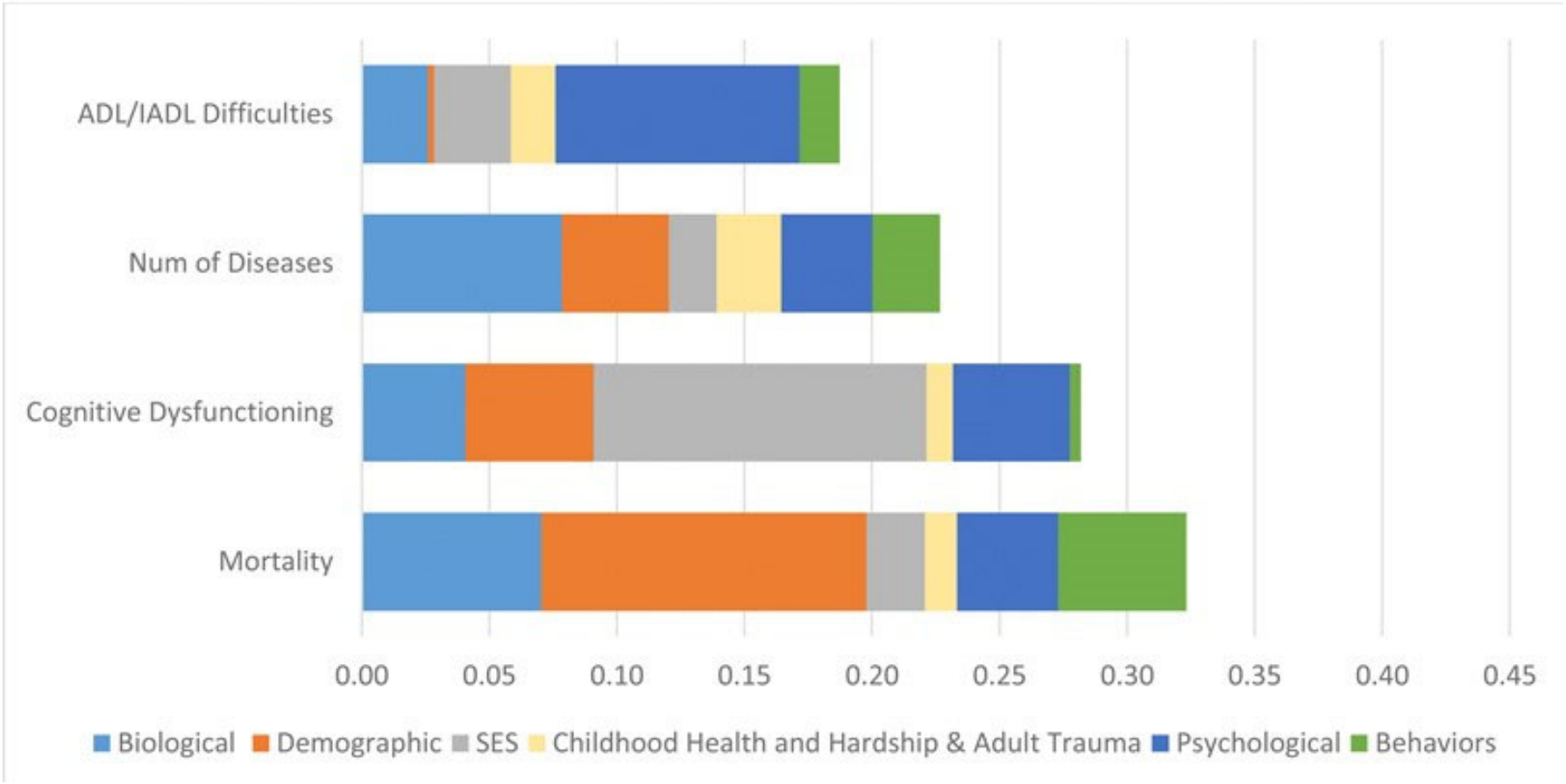
Studies with Biomarkers
The NIA Biomarker Network
A National Institute of Aging sponsored project dedicated to improved measurement of biological risk for late-life health outcomes in large representative samples of populations.
Learn more about us
https://biomarker-network.isr.umich.edu
International Meeting – April 9th, 2025
Annual Network Meeting – April 10th, 2025
Washington DC
The Biomarker Network is a National Institute of Aging sponsored project to develop an interdisciplinary group of scientists dedicated to improved measurement of biological risk for late life health outcomes in large representative samples of populations. Activities of the network include designing and carrying out a series of focused meetings, interactive activities, workshops, and pilot projects to harmonize and develop measurement of biological risk in populations.



R^2 attributed to Biological, Demographic, and Social Factors (N=1159) Crimmins et al., 2020

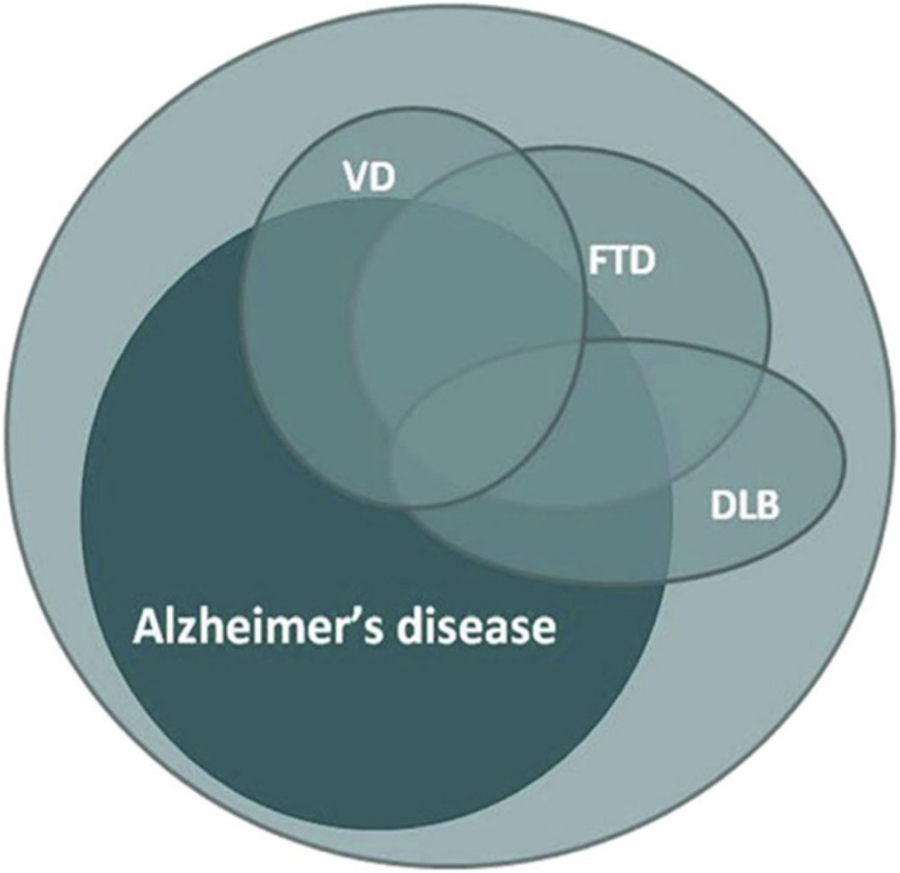
TYPES OF BIOMARKERS

Biomarker Type	Definition	Study Design Required
Investigative	Does not have a clear-cut pathological relevance, used in an explorative setting	------
Diagnostic	Classify individuals as either having or not having the disease (same point in time)	Cross-sectional study
Burden of disease	Assess severity or extent of disease (same point in time)	Cross-sectional study
Prognostic	Predict future onset of disease	Longitudinal / cohort study
Efficacy of intervention	Provide information about the efficacy of treatment or those at high risk for disease development	Longitudinal / cohort study

Alzheimers Dement. 2014 Jan; 10(1): 115–131.

ALZHEIMER'S DISEASE and ADRD BIOMARKERS

- Very difficult to diagnose based on clinical presentation alone
- "Messy" phenotype
  - AD
  - Vascular dementia
  - Fontotemporal dementia
  - Dementia with Lewy bodies
  - Mixed
  - Unspecified dementia
- This makes biomarker discovery and application difficult



Alzheimers Dement. 2014 Jan; 10(1): 115–131.

Characterize the general health of your population, capture risk factors

Cardiovascular disease and diabetes are well established risk factors for dementia

Estimate that approximately 40% of dementia cases worldwide could be prevented by targeting modifiable, primarily cardiovascular risk factors (Livingston, et al. Report of the Lancet Commission. *Lancet* 2020)

HbA1C or Fasting Glucose*
BMI (Height and Weight)
Systolic / Diastolic Blood Pressure
Total Cholesterol, LDL*, HDL, Triglycerides*
B-type natriuretic peptide, N-terminal pro (NT-proBNP)
Homocysteine
Liver functioning - (alanine aminotransferase (ALT) and aspartate aminotransferase (AST))
Albumin
Vitamin D
Cystatin C

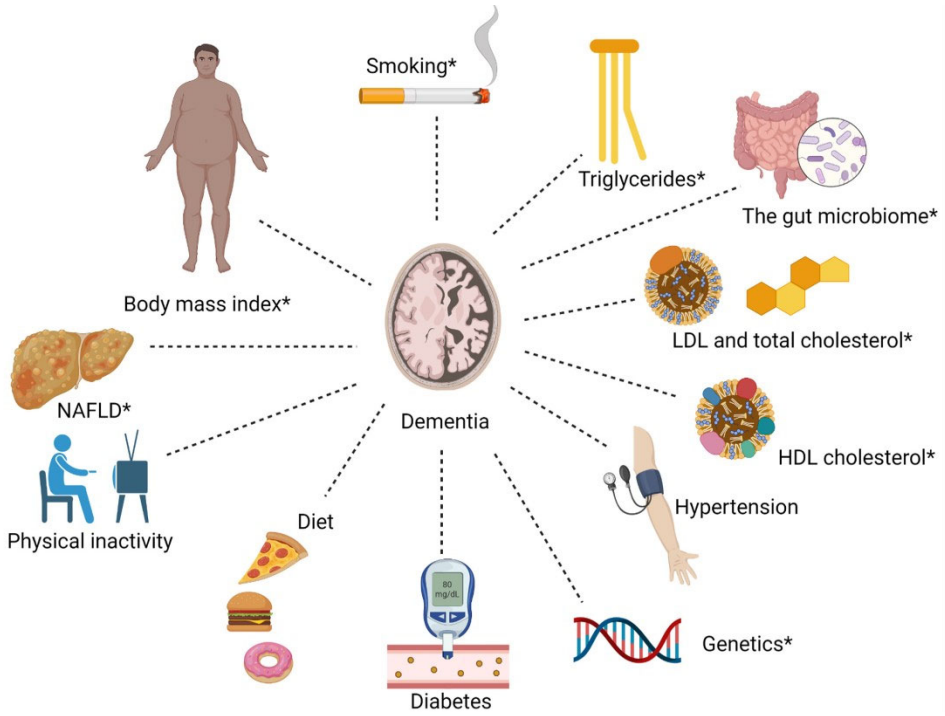


Figure adapted from Nordestgaard et al. *Int. J. Mol. Sci.* **2022**, *23*(17)

Smoking, Physical activity, Alcohol use

*Fasting required

GENETICS

APOE ε4 is a significant risk for AD

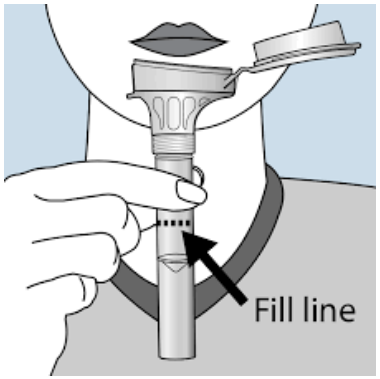
The frequency of APOE alleles varies across populations and continents

Determined by 2 nucleotide polymorphisms

Allele	ε2	ε3	ε4
Haplotype	rs429358 (T) rs7412 (T)	rs429358 (T) rs7412 (C)	rs429358 (C) rs7412 (C)

APOE ε4 allele (TaqMan PCR) - <$10 to assay

Collection from blood or saliva (e.g. Oragene OGR-500)



Blood-based Biomarkers of AD and Neuropathology

Scientific advances have made the use of blood samples, rather than cerebrospinal fluid, a source of neuropathological markers reflecting brain changes related to AD and dementia.

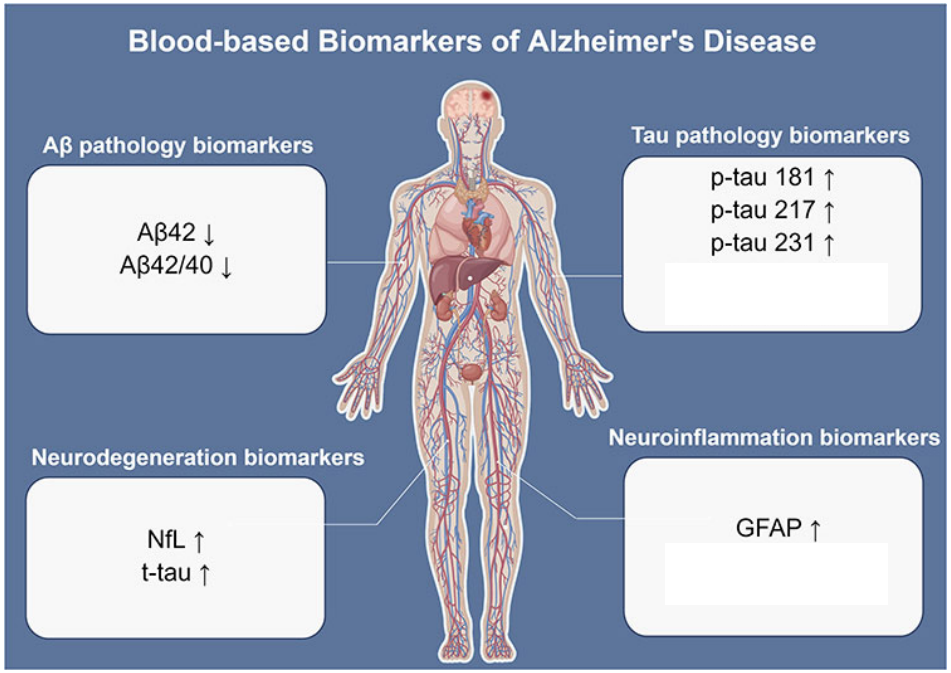
Biomarkers related to the AD and dementia

- Amyloid plaques – Beta Amyloid AB 42, AB 40 (A)
- Tangles – pTau (T)

Non specific biomarkers related to AD pathology

- Neuronal Damage – Neurofilament light chain - NfL (N)
- Neuroinflammation – Glial Fibrillary acidic protein- GFAP

These markers may help distinguish between different types of dementias (e.g. Aβ required for AD)



Blood-based Biomarkers of AD and Neuropathology

For best results, blood should be processed quickly (within 1-2 hrs)

Ideally all tests use plasma

Neuropathological biomarkers can be measured in population studies with delayed processing (24-48 hrs) with some caveats

Panikkar D, Vivek S, Crimmins E, Faul J, Langa KM, Thyagarajan B. Pre-Analytical Variables Influencing Stability of Blood-Based Biomarkers of Neuropathology. J Alzheimers Dis. 2023;95(2):735-748. PMID: 37574735.

Require specialized equipment and sensitive assays

Examples include:

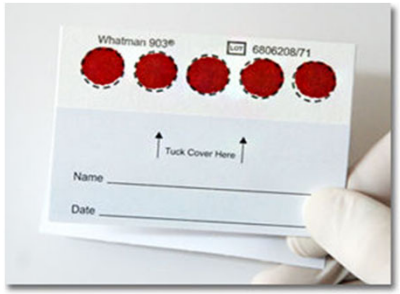
Immunoassay – e.g. Quanterix Simoa kits

Mesoscale Discovery

Immunoprecipitation-Mass Spec

High Sensitivity ELISAs

For now, only GFAP and NfL can be ascertained using dried blood spots



COGNITION AND INCIDENT DEMENTIA

Multinomial logistic regressions of Dementia/Death status in 2018, n=3923

	Onset in 2018 (OR)	Death in 2 years (OR)
zNfL	1.27**	1.38***
zGFAP	1.17	0.96
zAB42/40*100	1.01	0.91
zpTau181	1.01	0.80**

In HRS and LASI-DAD, NfL and GFAP associated with cognitive test performance

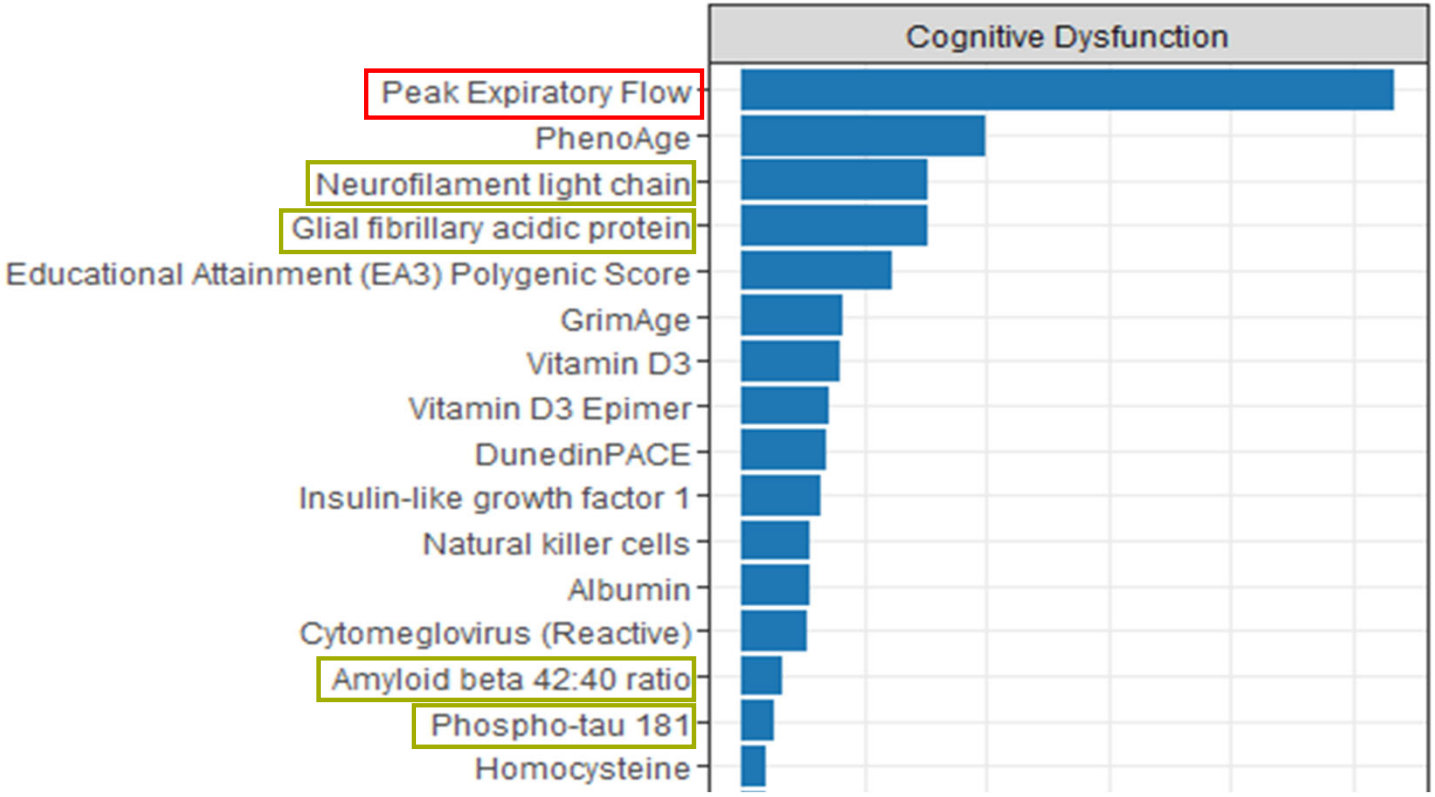
Multinomial logistic regressions of Dementia/Death status in 2020, n=3911

	Onset in 2020 (OR)	Death in 4 years (OR)
zNfL	1.56***	1.58***
zGFAP	1.06	0.97
zAB42/40*100	1.10	0.74**
zpTau181	0.90	1.14**

In HRS, NfL significant predictor of dementia onset and death 4 yrs out in persons with and without APOE ε4 alleles

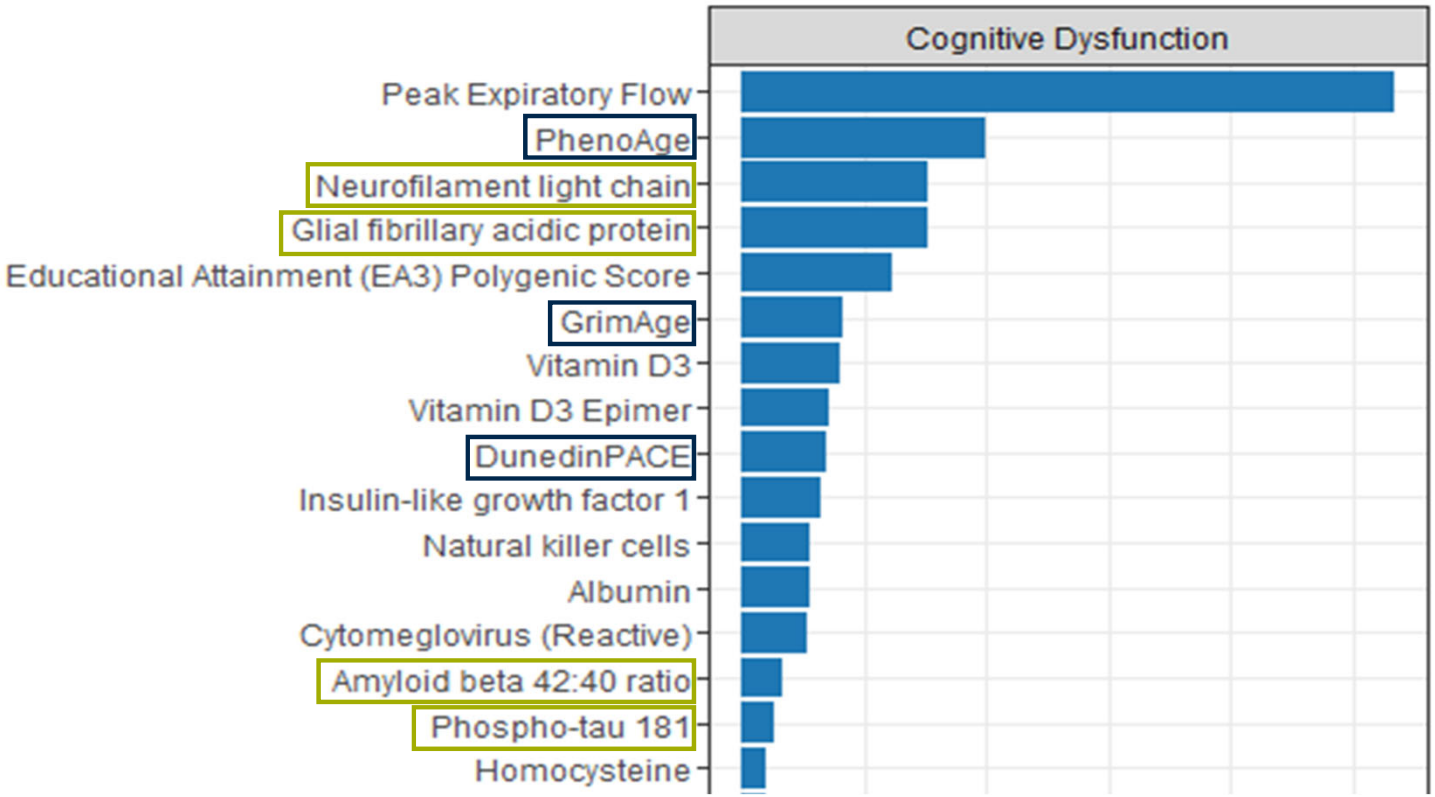
Age and gender controlled, ***p<.001, **p<.01, *p<.05

However: these markers are among the most important biomarkers out of 80 in predicting cognitive dysfunction in the HRS: List of 16 most important based on machine learning approach to selecting factors.



E. Klopack, M. Farina, B. Thyagarajan, J. Faul, E. Crimmins. How much can biomarkers explain sociodemographic inequalities in cognitive dysfunction and cognitive impairment? Results from a machine learning model in the Health and Retirement Study. Under Review.

Epigenetic Clocks are also important



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OTHER HEALTH MEASURES

- Depression (survey)
- Family History
- Hearing test
  - HearX etc. – Biomarker Network planning a webinar on this topic
- Olfactory capability
  - Sniffin' Sticks
- Vision testing
- Retinal Scans
- Metal exposure (Arsenic, Cadmium, Lead, Mercury) – whole blood needed

RECOMENDATIONS

- Blood collection EDTA Plasma and Serum, put what you can in storage at -80C
- Physical measures / survey measures are important risk factors too
- Genomics can be collected with EDTA (buffy coat) or saliva

Capture risk factors well:

Metabolic	HbA1C or Fasting Glucose
	BMI (Height and Weight)
Cardiovascular	Systolic / Diastolic Blood Pressure
	Cholesterol
	NT-proBNP
	Homocysteine
Respiratory	Peak Expiratory Flow
Renal	Cystatin-C

Inflammation / Nutrition	Albumin
	Vitamin D
Hepatic	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
Health Behaviors / Psych (Survey)	Smoking
	Alcohol Use
	Physical Activity

Then consider more specific markers / risk factors if collection protocols allow:

Neuropathology	Neurofilament light chain
	GFAP
	Amyloid beta 42:40 ratio
	P-tau 181 / P-tau 217

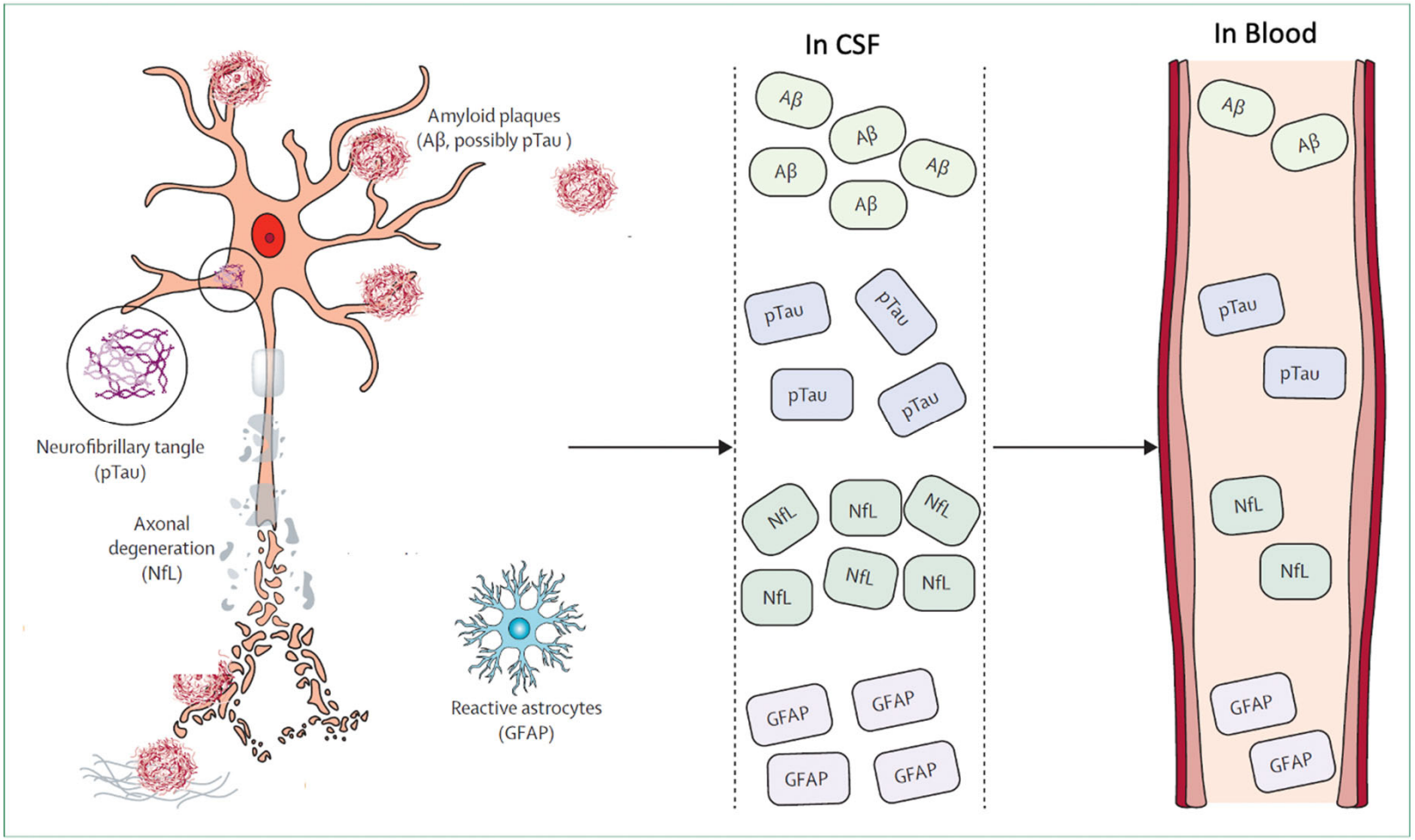
Genomic (Blood or Saliva)	APOE ε4 alleles
	DNA methylation

Environmental	Metals

Thank You!

The HRS is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan. Research reported in this study was also supported by NIA U01 AG058499-06 and The Alzheimer's Association HRS-18-586069C.

These biomarkers can be found in blood, but in lower levels than in CSF



Adapted Figure 1 from *Teunissen* et al., ***Lancet Neurol* 2022; 21: 66–77**

	Cognitive Stage		
AT(N) profiles	**Cognitively Unimpaired**	**MCI**	**Dementia**
A-T-(N)-	Normal AD biomarkers. cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
A+T-(N)-	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
A+T+(N)-	Preclinical Alzheimer's disease	Alzheimer's disease with MCI	Alzheimer's disease with dementia
A+T+(N)+			
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
A-T+(N)-	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
A-T-(N)+			
A-T+(N)+			

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.

Neurological	Innate Immune / Inflammatory	Adaptive Immune	Circulatory
NfL	TGFb	T cells	Mean corpuscular volume
GFAP	IL10	CD4+ T cells	White blood cell count
Ab42:Ab40	IL1RA	CD4+ Memory Cells	Red blood cell count
pTau181	IL6	CD4+ TemRA Cells	Platelet distribution width
BDNF	TNFr1	CD4+ Effector Memory Cells	Platelet count
Clusterin	CRP	CD4+ Naive Cells	Mean platelet volume
Nutrition	Albumin	CD8+ T cells	Mean corpuscular hemoglobin concentration
Vitamin D2	SuPAR	CD8+ Memory Cells	Mean corpuscular hemoglobin
Vitamin D3	GDF15	CD8+ TemRA Cells	Hemoglobin
D3 Epimer	Natural Killer Cells	CD8+ Effector Memory Cells	Hematocrit
Calcium	NK cells: CD56 high	CD8+ Naive Cells	Red cell distribution width
Ferritin	NK cells: CD56 low	B Cells	**Liver**
Potassium	Monocytes	IgD+ Memory B Cells	Protein
Sodium	Classical Monocytes	IgD- Memory B Cells	Bilirubin
Chloride	Non-classical Monocytes	Naïve B Cells	Alanine Aminotransferase
Endocrine	Basophils	Lymphocytes	Aspartate Aminotransferase
DHEAS	Eosinophils	CMV Reactive Status	Alkaline Phosphate
Respiratory	Neutrophils	**General Multi-system Aging**	**Lipid**
Peak Expiratory Flow	**Cardiovascular**	PhenoAge	HDL
CO_2	Homocysteine	GrimAge	LDL
Metabolic/Glycemic	NT-proBNP	DunedinPACE	Triglycerides
Fasting Glucose	Systolic BP	HorvathAge	Total Cholesterol
HbA1C	Diastolic BP	Telomere Length	**Renal**
BMI	Pulse rate	mtDNA Copy Number	BUN
		IGF1	Creatinine
			Cystatin C