NEUROPATHOLOGICAL BIOMARKERS – HRS PILOT RESULTS

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HRS | HEALTH AND RETIREMENT STUDY

HCAP PILOT- GOALS

- *What was missing was replication of blood-based markers in representative population-based samples of older adults, including individuals from racial / ethnic minorities.*
- HRS conducted a pilot to test promising biomarkers of neurodegeneration.

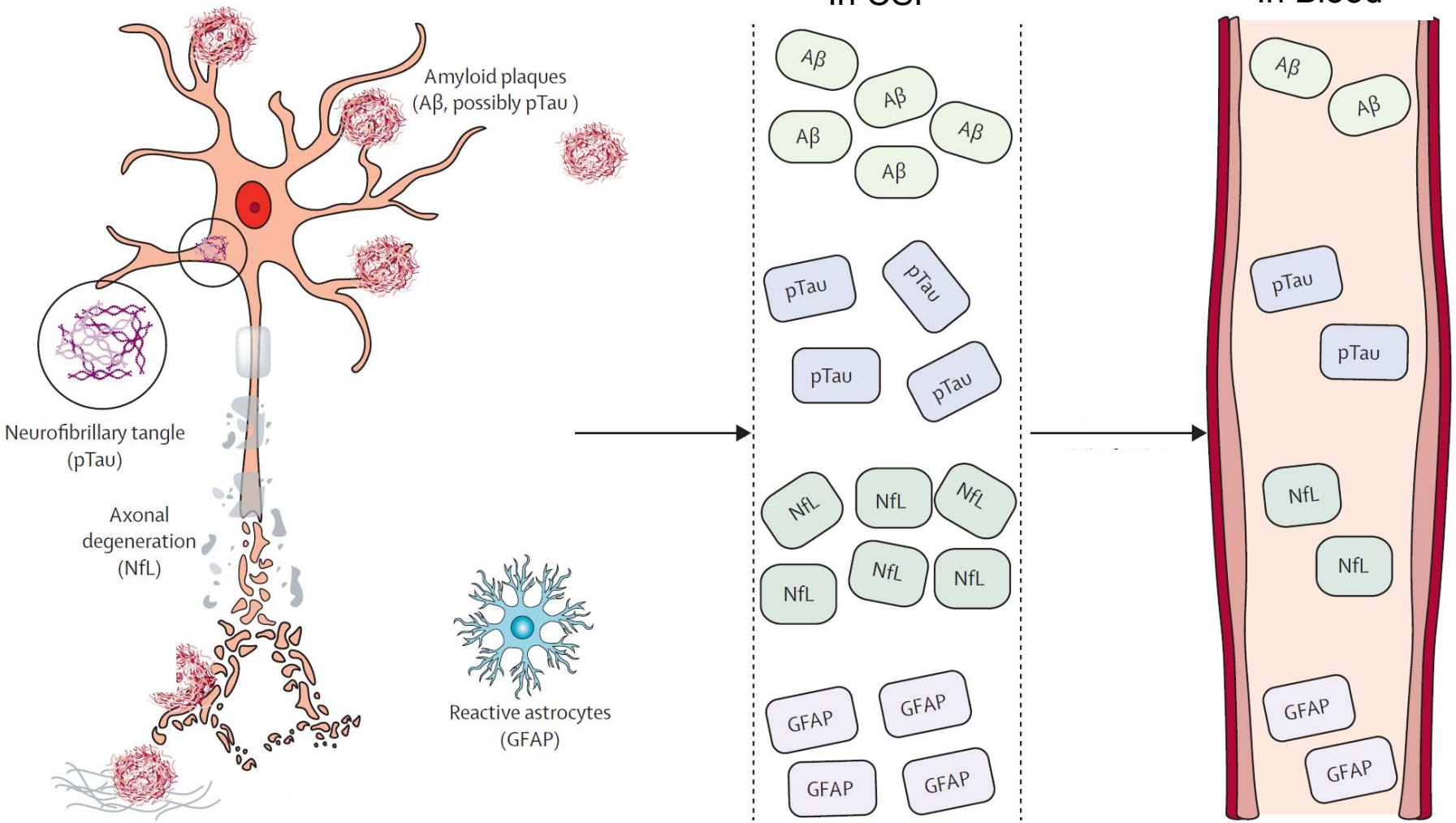
  Priorities:

  (1) highly reliable and replicable in blood (plasma/serum);

  (2) have validated correlations with AD/ADRD neuropathology from cerebrospinal fluid (CSF) or autopsy measures;

  (3) are found in higher concentrations in people with cognitive impairment and AD/ADRD;
- Final list based on consultation with dementia experts at the NIA Intramural Research Program

Pathological Mechanisms Involved in AD and Associated Biofluid Biomarkers



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

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HCAP PILOT ASSAYS

- Aβ42/Aβ40 ratio
- Phosphorylated Tau Protein 181 (pTau181)
- Neurofilament Light Chain (NfL)
- Glial Fibrillary Acidic Protein (GFAP)
- Olink Proteomics Neurology Panel

HCAP PILOT ASSAYS – RESULTS TO DATE

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HCAP PILOT – HRS SAMPLE

- HRS respondents over 50 years, n=4,214
- Sample overlaps with the HRS 2016 measures of DNA methylation, RNAseq, etc.
- Sample inclusive of the entire HCAP 2016 sample with venous blood (n=2,392)
- Cognitive tests included immediate and delayed word recall, serial 7s, and backward counting (total score range 0-27)
- Langa/Weir diagnostic algorithm
- 726 Black, 638 Hispanic, 153 Dementia (in 2016)

Correlations among neuropathological biomarkers (N=4,214)

	AB42/40 Ratio	NfL	pTau-181	GFAP
AB42/40 Ratio		-0.0027	-0.0378*	0.0007
NfL			0.2962***	0.4644***
pTau-181				0.2989***
GFAP				

***p<.001; **p<.01; *p<.05

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Regressions of each neuropathological biomarker on the HRS cognitive functioning score (n=4,214)

	Total		White		Black		Hispanic	
Cognitive functioning score (0-27)								
	b	p	B	p	b	p	b	p
AB42/40[2]	0.04	0.094	**0.06**	**0.042**	-0.09	0.382	-0.09	0.333
NfL	**-0.02**	**<.0001**	**-0.02**	**<.0001**	**-0.01**	**0.012**	**-0.01**	**0.003**
pTau-181	**-0.08**	**0.011**	**-0.09**	**0.013**	-0.04	0.598	-0.09	0.203
GFAP	**-0.005**	**<.0001**	**-0.005**	**0.0003**	-0.00	0.860	**-0.01**	**0.032**

For regressions, we rescaled AB42/40 by multiplying 100
Adjusted for age, sex, batch

HRS

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Combined model								
AB42/40²	0.04	0.158	0.05	0.067	-0.10	0.320	0.12	0.221
NfL	**-0.02**	**<.0001**	**-0.02**	**<.0001**	**-0.01**	**0.010**	**-0.01**	**0.017**
pTau-181	-0.03	0.423	-0.04	0.250	-0.004	0.959	-0.05	0.461
GFAP	**-0.003**	**0.026**	-0.002	0.088	0.001	0.548	-0.01	0.132

For regressions, we rescaled AB42/40 by multiplying 100
Adjusted for age, sex, batch

HRS

Regressions of each neuropathological biomarker on predicted dementia (n=4,214)

	Total		White		Black		Hispanic	
Dementia								
	OR	**p**	**OR**	**p**	**OR**	**p**	**OR**	**p**
AB42/40[2]	1.00	0.989	0.90	0.253	0.90	0.446	1.06	0.515
NfL	**1.00**	**0.045**	1.01	0.058	1.00	0.610	1.00	0.619
pTau-181	1.02	0.425	**1.06**	**0.047**	1.00	0.994	0.84	0.230
GFAP	**1.00**	**0.001**	**1.01**	**0.0002**	1.00	0.937	1.00	0.691

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HRS

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Combined model								
AB42/40[2]	1.01	0.815	0.93	0.433	0.90	0.451	1.03	0.754
NfL	1.00	0.272	1.00	0.462	1.00	0.593	1.00	0.505
pTau-181	1.01	0.746	1.05	0.151	1.00	0.892	0.83	0.249
GFAP	**1.00**	**0.007**	**1.00**	**0.003**	1.00	0.843	1.00	0.383

For regressions, we rescaled AB42/40 by multiplying 100
Adjusted for age, sex, batch

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HCAP PILOT – LONGITUDINAL PREDICTION

- An additional 202 respondents convert to dementia between 2016 and 2020
- Mortality competing risk

	By 2018	By 2020
No onset (from normal/CIND to normal/CIND)	94.08%	87.22%
New dementia (from normal/CIND to demented)	2.01%	3.17%
Death	3.91%	9.62%

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HCAP PILOT – LONGITUDINAL PREDICTION

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**

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**

Age and gender controlled, ***p<.001, **p<.01, *0<.05

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HCAP PILOT – SUMMARY

Summary:

- Markers are moderately correlated
- Results are not consistent across race/ethnic groups
- NfL promising across groups and prospectively
- The biomarker story is likely to be complex
    - Dementia is a “messy” phenotype
    - Individual markers may help distinguish between different types of dementias (e.g. Aβ required for AD)

THANK YOU!

HRS