Next Steps and Opportunities
NASEM Multimodal CNS Biomarker Workshop

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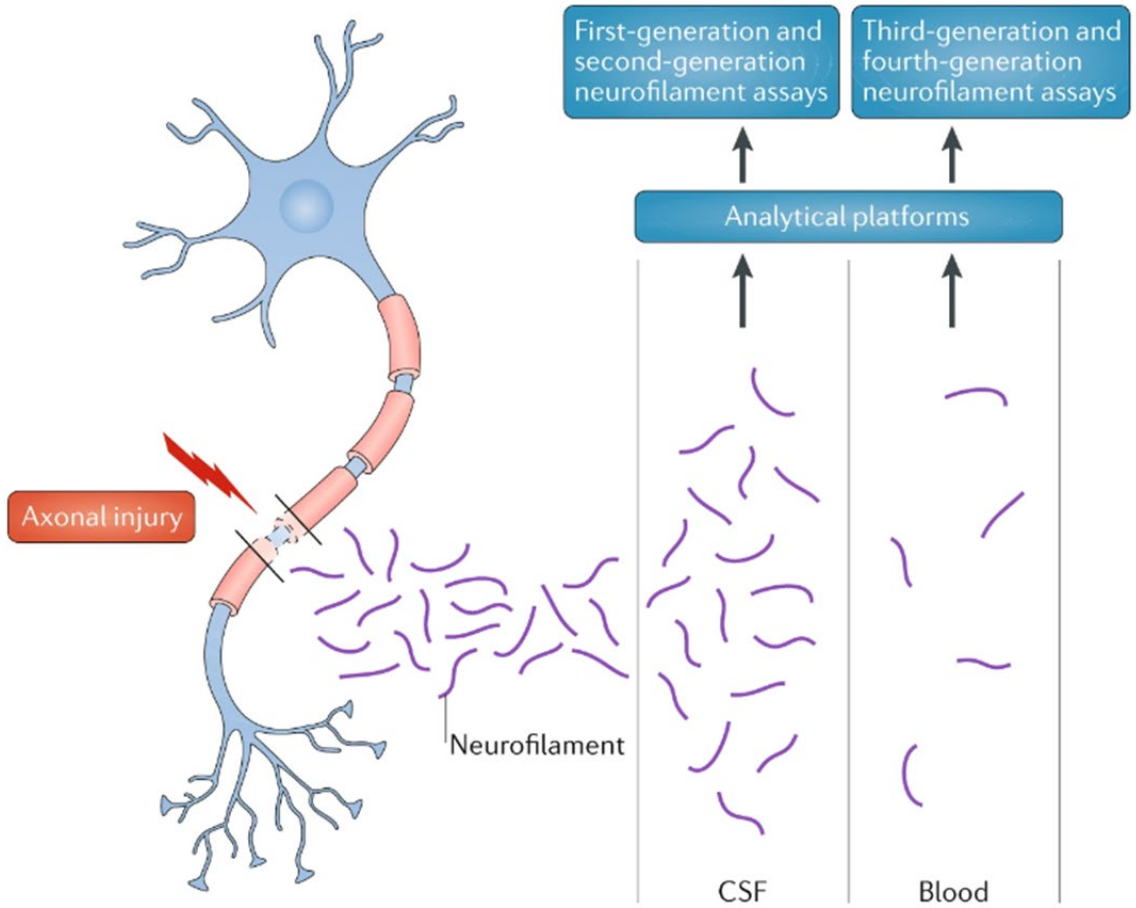
Disclosures

- Scientific Advisory Boards/Consulting:
  - Alexion
  - Viela Bio/Horizon Therapeutics
  - Roche/Genentech
  - Ad Scientiam
- Speaker honoraria:
  - Alexion
  - Biogen
- Research Funding:
  - Roche/Genentech
  - UCB
  - CorEvitas

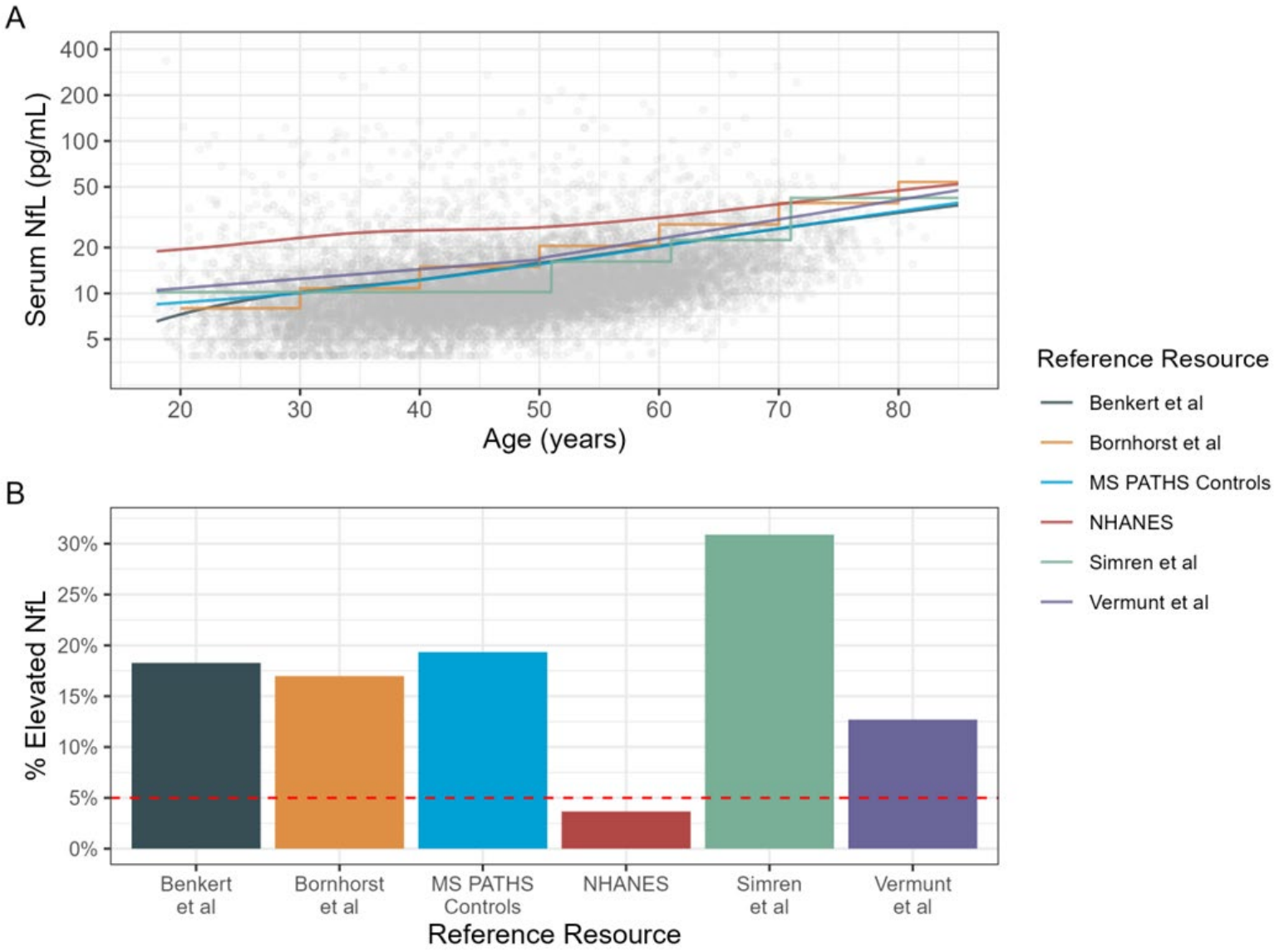
Neurofilament Light Chain

- Neurofilaments are intermediate filament heteropolymers composed of light, medium and heavy chains
- Neurofilaments are the dominant proteins of the neural cytoskeleton and are released into the extra-cellular space following neuro-axonal injury
- Neurofilament light chain (NfL) especially has been shown to be a promising biomarker of neuro-axonal injury and degeneration.
- Early studies focused on quantification of NfL in the cerebrospinal fluid (CSF), since levels in the blood are more challenging to quantify with conventional ELISA
- More recently, advanced immunoassays have enabled detection of NfL in the blood (serum or plasma) with high accuracy and reliability



Khalil M et al. Nat Rev Neurol. 2018:14:577-589.

Blood NfL interpretation varies markedly by reference



- Serum NfL measured in 12,855 blood sample from 6,687 people with MS in a multi-center study (Siemens Healthineers; Atellica® IM).
- Six published reference populations were used to classify NfL as elevated or normal utilizing age-specific 95th percentile cut-offs.
- As necessary, Siemens Atellica serum NfL measurements were converted to Quanterix Simoa serum NfL or plasma NfL measurements based on equations derived from a subset of participants with paired measurements available on both platforms.
- Depending on the selection of the reference resource, the proportion of NfL measurements classified as elevated varied markedly, from 3.7% to 30.9%.

References
1. Fitzgerald et al. *Ann Neurol* 2022. 2. Sotirchos et al. *Ann Clin Transl Neurol* 2022. 3. Benkert et al. *Lancet Neurol* 2022.
4. Vermunt et al. *Ann Clin Transl Neurol* 2022 5. Simrén et al. *Brain Commun* 2022. 6. Bornhorst et al. *Clin Chim Acta* 2022

labcorp

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Use a keyword, test name or number

Neurofilament Light Chain, Serum

TEST: 140455 CPT: 83520

Updated on 03/5/2023

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Age (y)	(pg/mL)
0 to 4 y	<1.97
5 to 9 y	<1.64
10 to 14 y	<1.43
15 to 19 y	<1.60
20 to 29 y	<1.65
30 to 39 y	<1.88
40 to 49 y	<2.14
50 to 59 y	<3.79
60 to 69 y	<4.62
70 to 79 y	<7.65
>79 y	<11.56

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TEST ID : **NFLC**

Order This Test

Neurofilament Light Chain, Plasma

REFERENCE VALUES

<20 years: Not established

20 to 29 years: < or =8.4 pg/mL

30 to 39 years: < or =11.4 pg/mL

40 to 49 years: < or =15.4 pg/mL

50 to 59 years: < or =20.8 pg/mL

60 to 69 years: < or =28.0 pg/mL

70 to 79 years: < or =37.9 pg/mL

> or =80 years: < or =51.2 pg/mL

Conclusions

- Issues related to representativeness of the underlying reference population and inter-laboratory/platform variability need to be considered when interpreting NfL (or other unimodal or multimodal biomarkers) relative to reference ranges.
- At present, clinicians should be especially cautious in interpreting NfL for clinical decision-making
- Efforts to standardize NfL measurement and reporting across laboratories & platforms will be important for the incorporation of NfL in routine clinical practice
- Important to validate thresholds for clinical decision-making depending on targeted disease and COU (need rigorous validation per FDA qualification guidance)
- As NfL is a non-specific biomarker, development of multi-modal biomarker approaches incorporating NfL in combination with disease-specific biomarkers (and other non-specific biomarkers) are expected to be important to better capture and monitor disease pathology.