Blood levels of neurofilament light as trial biomarkers in degenerative ataxias

The examples of spinocerebellar ataxia type 1 (SCA1) and multiple system atrophy of cerebellar type (MSA-C)

Dr. Carlo Wilke

Hertie Institute for Clinical Brain Research (HIH) und Center for Neurology, Tübingen
German Center for Neurodegenerative Diseases (DZNE), Tübingen

Hertie-Institut für klinische Hirnforschung

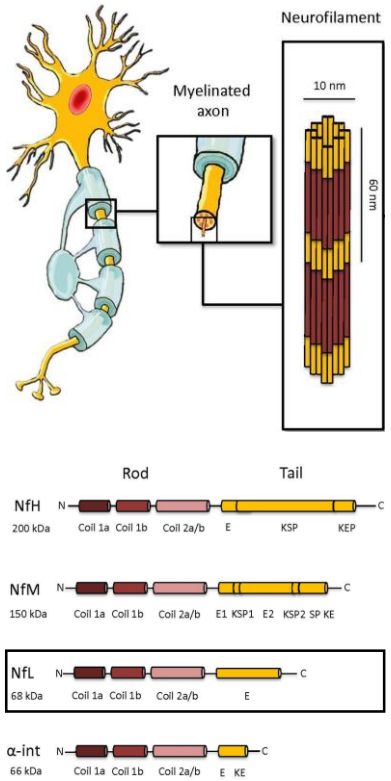
Universitätsklinikum Tübingen

DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft

Neurofilament light (NfL)

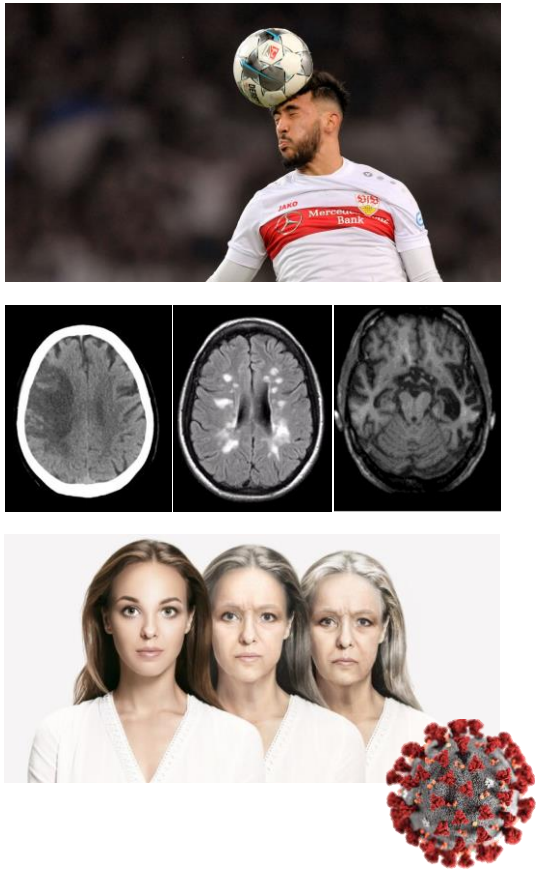
A generic biomarker of damage to large-calibre myelinated axons

neuronal intermediate filament, enriched in large-calibre axons

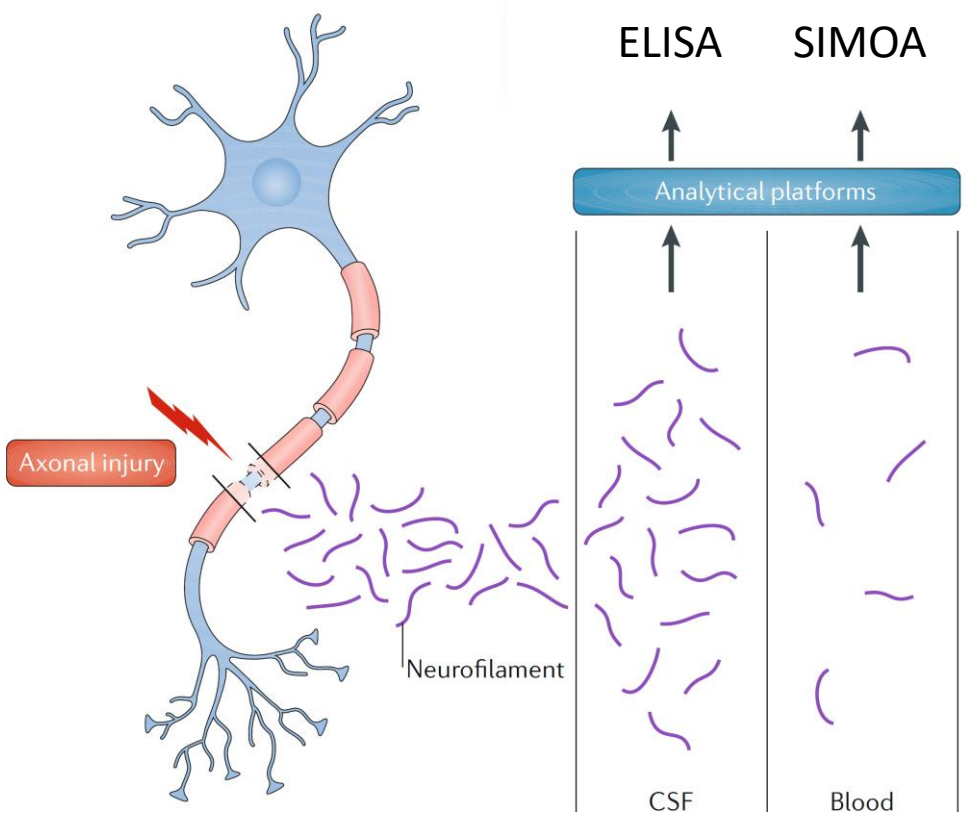


Gaetani et al. 2019, JNNP

release following axonal damage, irrespective of lesion mechanism

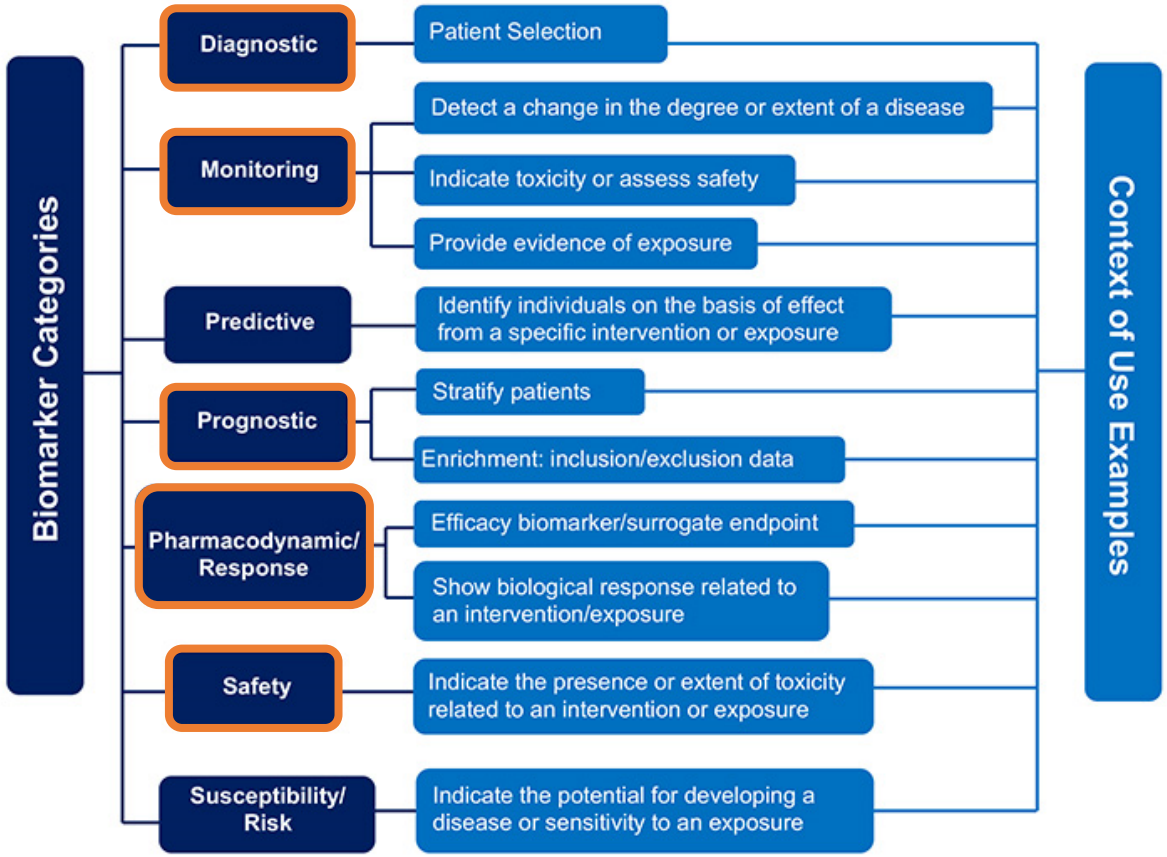


reliable quantification and preanalytical robustness



Khalil et al. 2018, Nat. Rev. Neurol.

The need for trial biomarkers in degenerative ataxias
Specifying the context of use (COU)



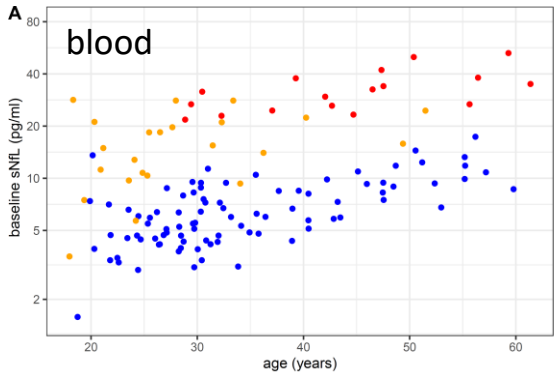
For what biomarker purpose may blood levels of Neurofilament Light (NfL) be used in ataxia trials?

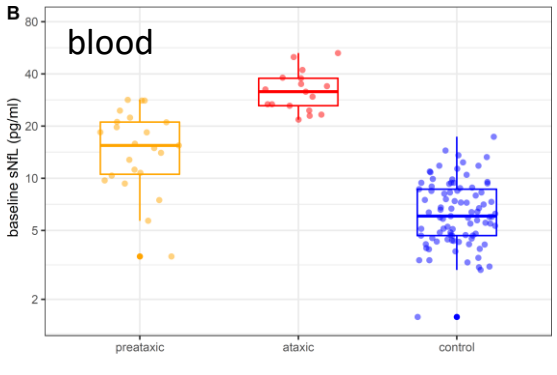
diagnostic biomarker	differentiation of sporadic diseases with similar syndrome, but different progression (e.g., MSA-C vs. SAOA)
monitoring biomarker	early detection and quantification of neuronal damage
prognostic biomarker	prediction of: clinical onset, phenotypic conversion, and future disease progression
treatment-response biomarker	capture of treatment response
toxicity biomarker	capture of undesired treatment effects

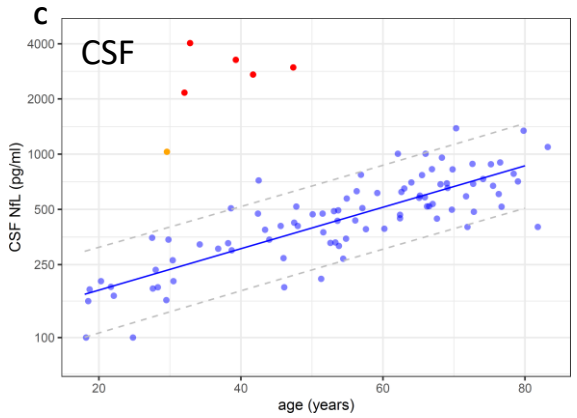
modified from: https://www.fda.gov/drugs/biomarker-qualification-program/context-use

NfL levels as *monitoring* biomarker in SCA1

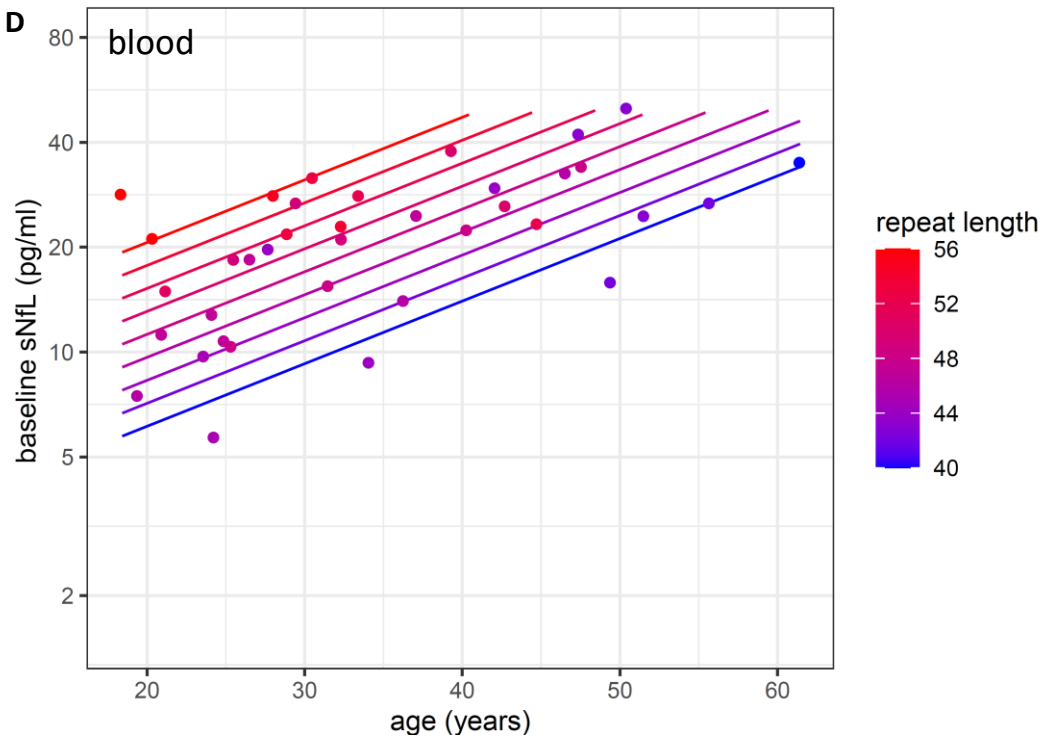
Early detection and quantification of neuronal damage







preataxic carrier
ataxic carrier
healthy control



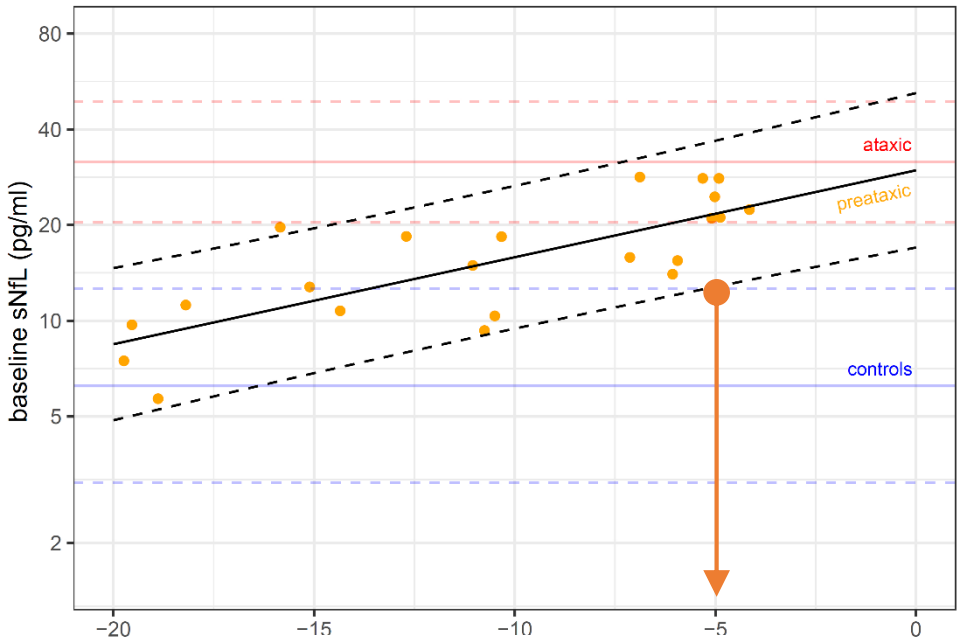
Note the logarithmic scale of the y-axis.

Wilke et al. 2022, Neurology

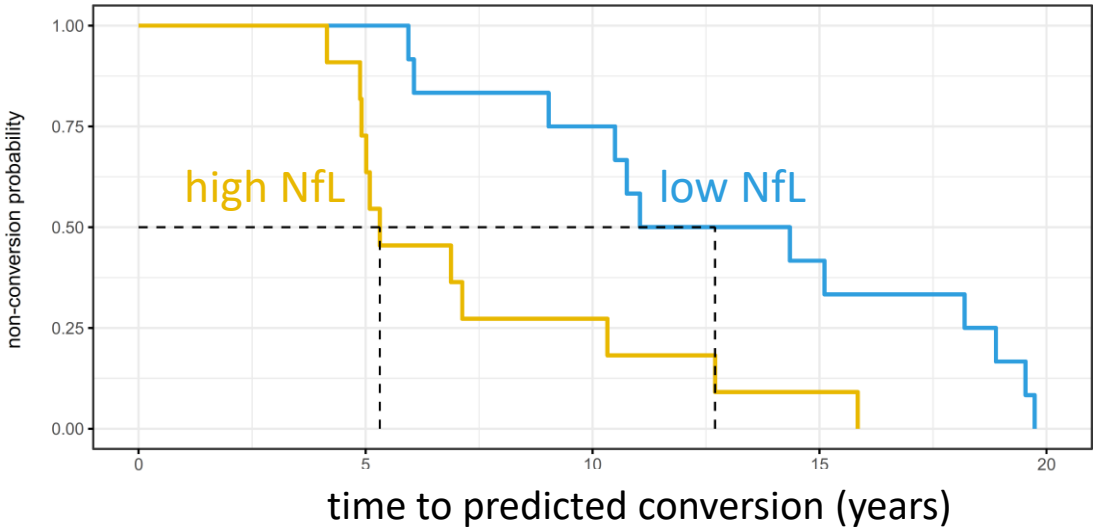
NfL levels as *prognostic* biomarker in SCA1

Predicting conversion of preataxic carriers to the ataxic stage

NfL levels increase with proximity to ataxia onset



Stratifying the risk of conversion in preataxic carriers

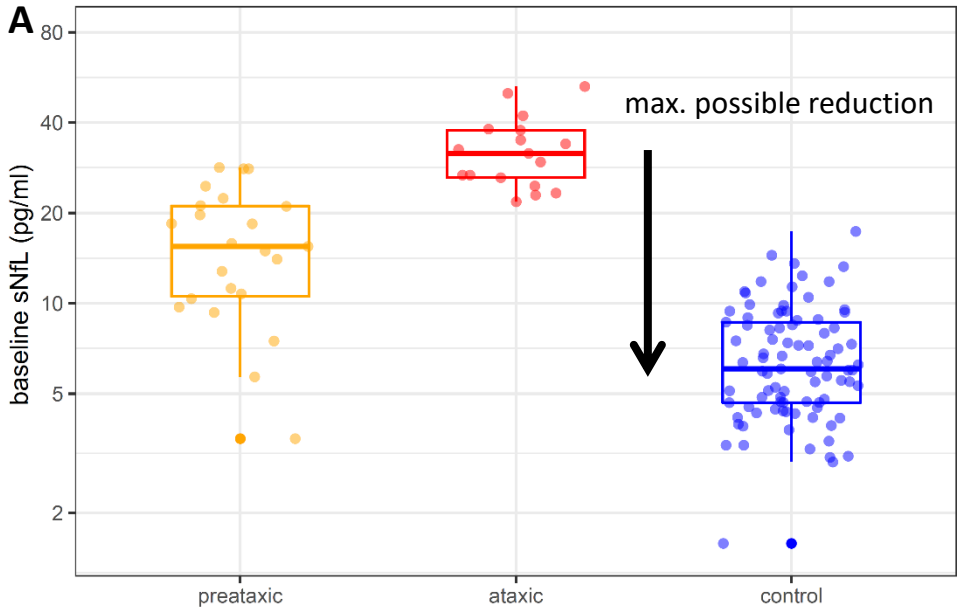


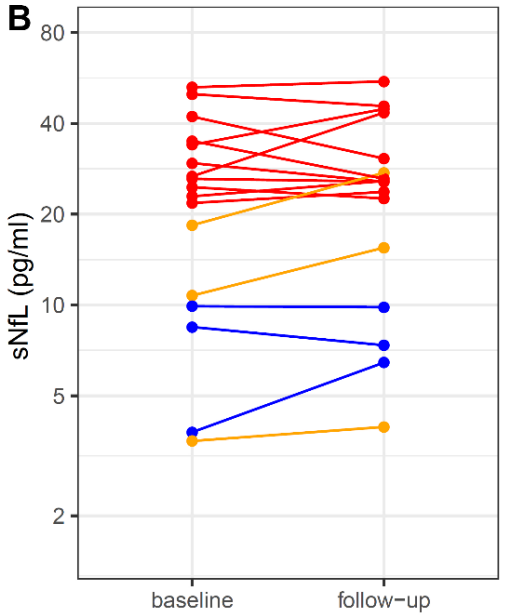
Time to ataxia onset was estimated based on repeat count.
Findings based on the ***predicted*** onset were confirmed
in carriers with ***observed*** ataxia onset during follow-up.

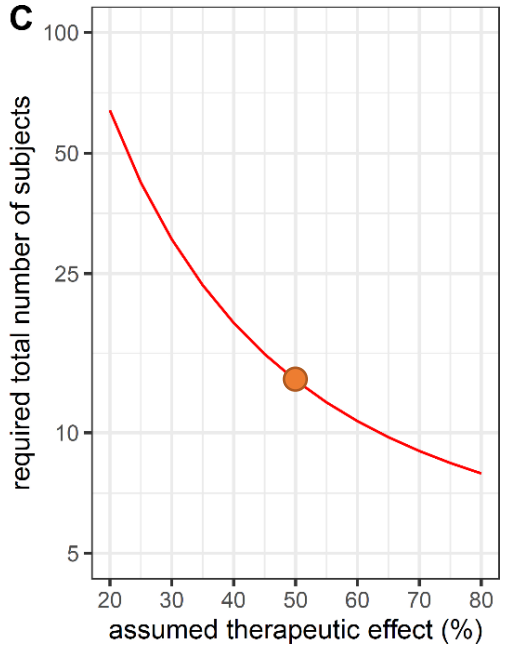
Wilke et al. 2022, Neurology

NfL levels as *treatment-response* biomarker in SCA1

Capturing the reduction of neuronal decay in treatment trials







Intention: **reduction of elevated NfL levels towards the NfL levels of healthy controls**
(100% = complete normalisation)

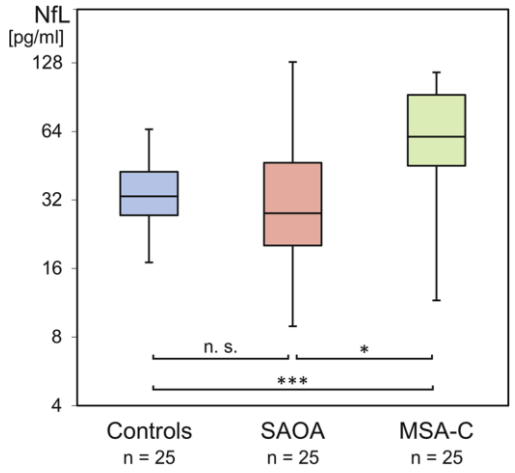
High intra-individual stability of elevated NfL levels in ataxic carriers
- interval: 2.7 years (2.0-3.4)
- high signal-to-noise ratio

NfL as outcome variable might allow reduction of required sample sizes.
(e.g., n=14 for 50% reduction)

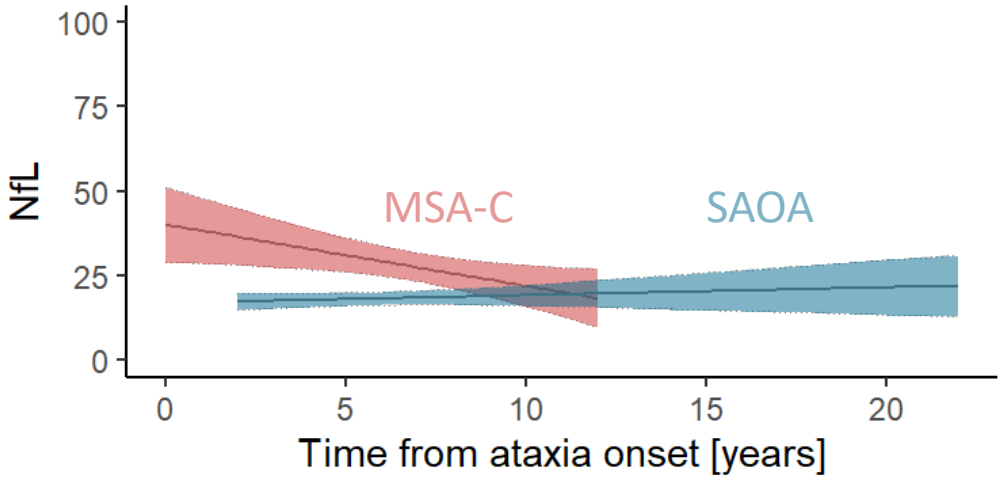
Wilke et al. 2022, Neurology

NfL levels as *diagnostic* biomarker in MSA-C

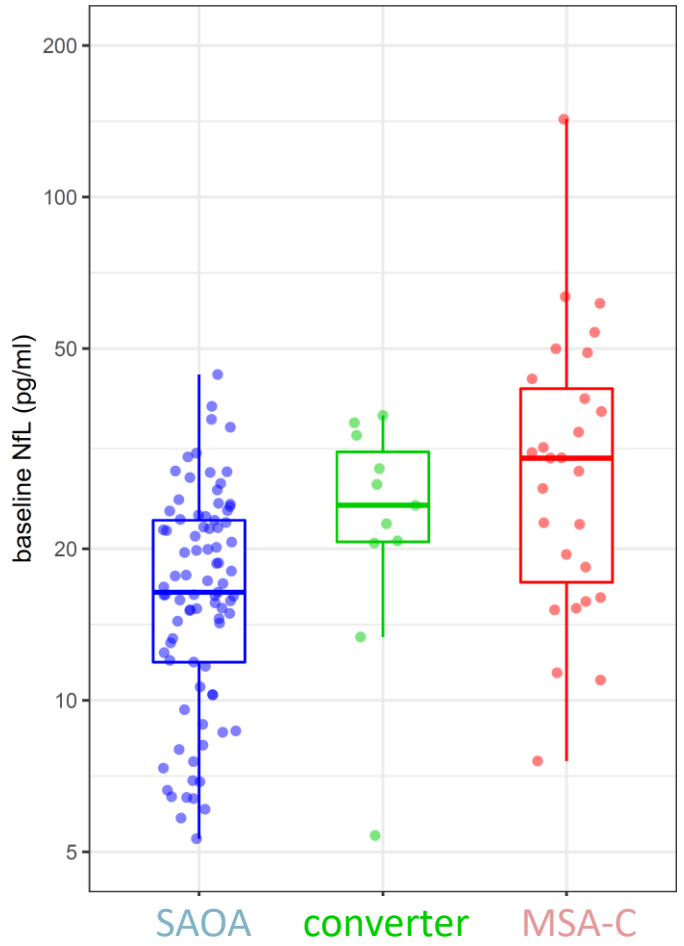
Differentiating MSA-C from Sporadic Adult-Onset Ataxia (SAOA)



Wilke et al. 2018, J. Neurology



Önder & Faber, et al., under review
data source: SPORTAX-Registry

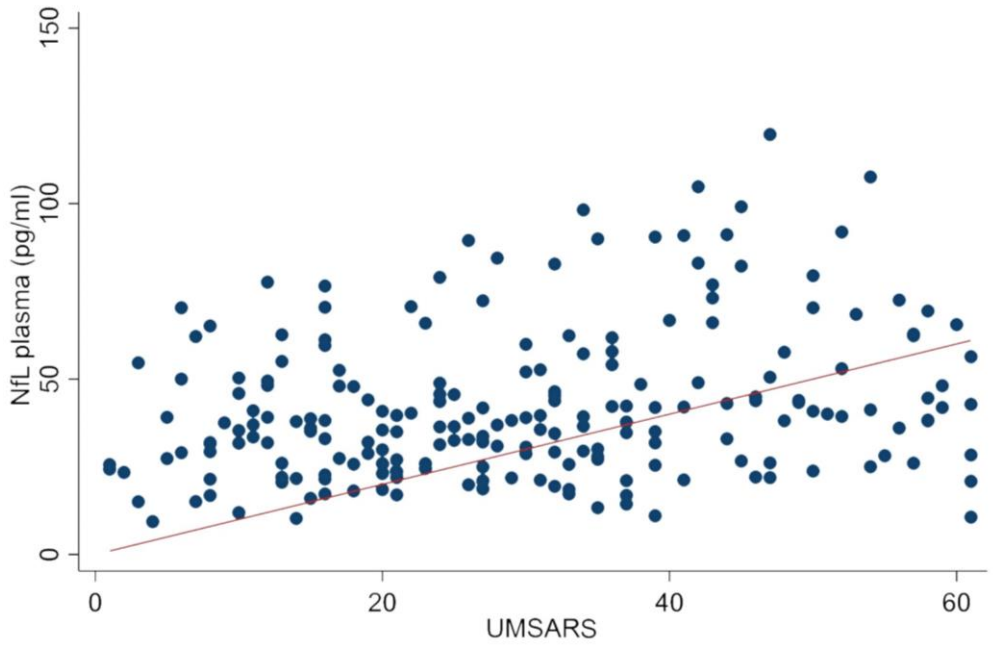


data provided by: SPORTAX-Registry

NfL levels as *prognostic* biomarker in MSA-C

Stratifying disease severity and predicting patient survival

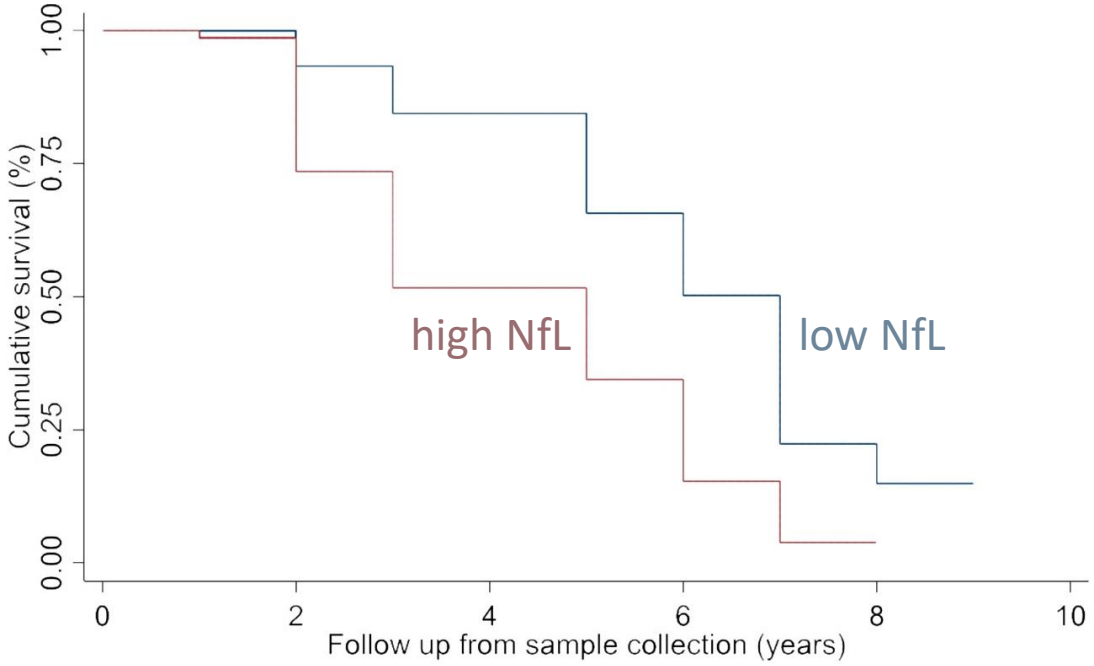
NfL levels increase with UMSARS score



UMSARS: Unified Multiple System Atrophy Rating Scale

Chelban et al. 2022, Brain

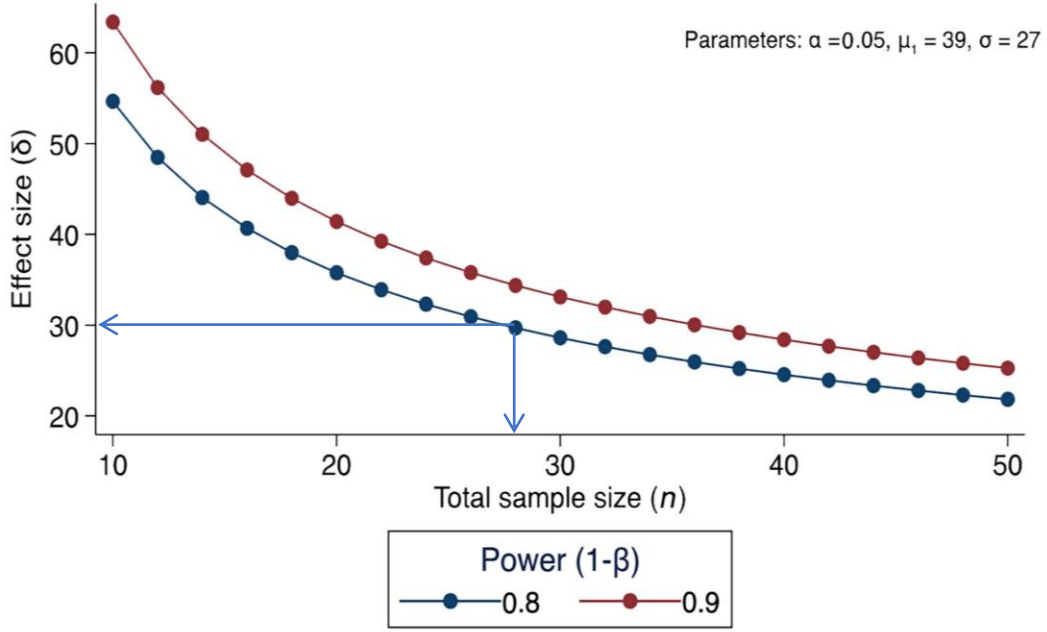
High NfL levels correlate with shorter survival



Chelban et al. 2022, Brain

NfL levels as *treatment-response* biomarker in MSA-C

Capturing the reduction of neuronal decay in treatment trials

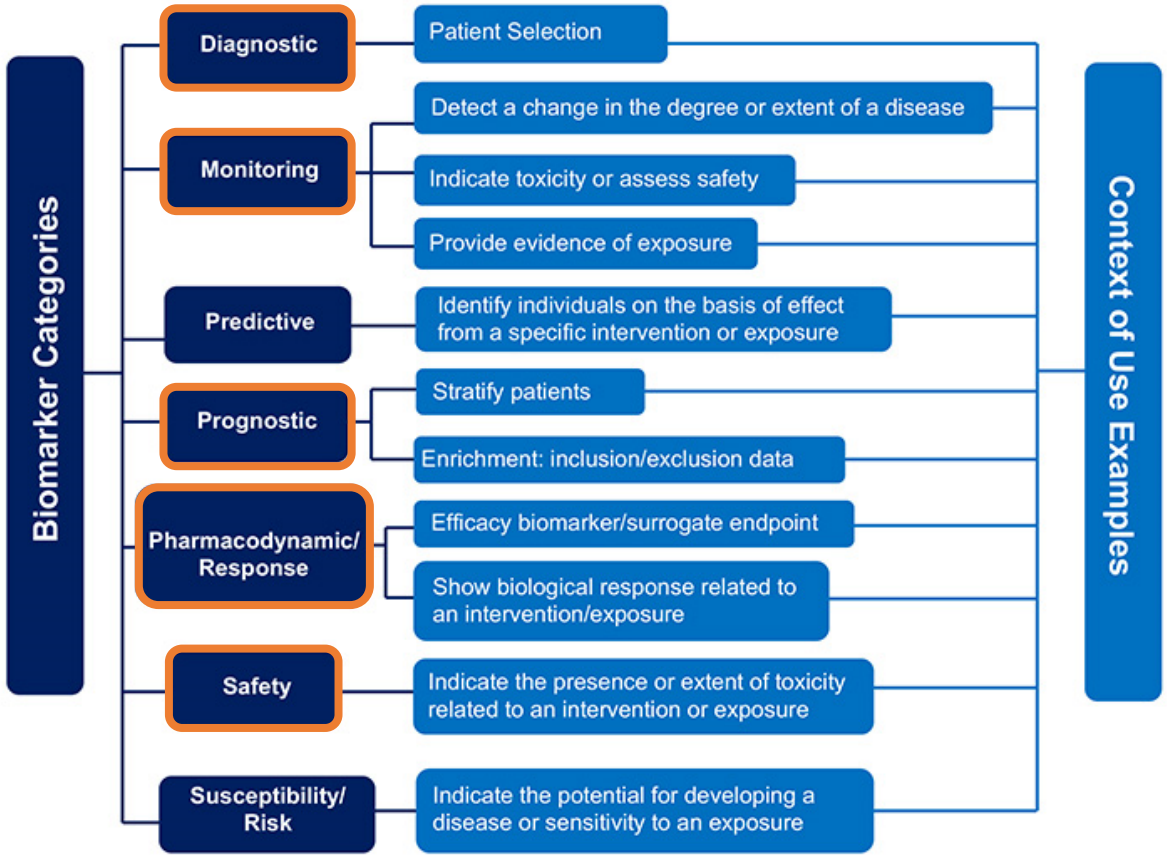


sample size estimates assuming intervention trial
with follow-up duration of 12 months:
28 subjects (in total) for detecting 30% NfL reduction

Chelban et al. 2022, Brain

Blood levels of NfL as trial biomarkers in degenerative ataxias

Take-home messages



For what biomarker purpose might blood levels of Neurofilament Light (NfL) be used in ataxia trials?

	SCA1	MSA-C
diagnostic biomarker		✓
monitoring biomarker	✓	✓
prognostic biomarker	✓	✓
treatment-response biomarker	✓	✓

independent validation of current evidence required

modified from: https://www.fda.gov/drugs/biomarker-qualification-program/context-use

Blood levels of NfL as trial biomarkers in degenerative ataxias
Acknowledgements

Hertie-Institute for Clinical Brain Research (HIH) and
German Center for Neurodegenerative Diseases (DZNE),
University of Tübingen, Germany
Matthis Synofzik, David Mengel, Ludger Schöls

Institute of Medical Genetics and Applied Genomics,
University of Tübingen, Germany
Jeannette Hübener-Schmid, Olaf Rieß

Department of Neurology, University Hospital Bonn, Germany
Jennifer Faber, Demet Önder, Thomas Klockgether

University College London, Institute of Neurology, United Kingdom
Viorica Chelban, Henry Houlden

European integrated project on spinocerebellar ataxias (EuroSCA)
Prospective study of individuals at risk for spinocerebellar ataxia (RiSCA)

Sporadic degenerative ataxia with adult onset – Natural History Study (SPORTAX)

Blood levels of neurofilament light as trial biomarkers in degenerative ataxias

The examples of spinocerebellar ataxia type 1 (SCA1) and multiple system atrophy of cerebellar type (MSA-C)

Dr. Carlo Wilke

Hertie Institute for Clinical Brain Research (HIH) und Center for Neurology, Tübingen
German Center for Neurodegenerative Diseases (DZNE), Tübingen

Hertie-Institut für klinische Hirnforschung

Universitätsklinikum Tübingen

DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft