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Biomarkers:

The Key to Predicting and Preventing MS Relapses

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EUROPEAN MULTIPLE SCLEROSIS PLATFORM

Czech multiple sclerosis society MS UNIE ROSKA

Conflicts of Interest

- I. Vardakas has received consulting and/or speaker honoraria and/or travel support from Alexion, Novartis, Sanofi and UCB.
- No conflicts of interest related to the content of this presentation.

What are biomarkers?

Biomarkers:

↪ disease characteristics that can be **objectively measured**

Diagnostic	Monitoring	Predicting	Prognostic
Treatment Response	Safety	Susceptibility / Risk	

References: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Last Updated: 11, 2.02, Jan 2025

Why do we need biomarkers in MS care?

For Diagnosis:

- MS remains an **exclusion diagnosis**
  - ↪ combination of different biomarkers for MS diagnosis
  - ↪ distinction from relevant differential diagnoses

References: Jakimovski et al. Lancet 2024; Reich et al. N Engl J Med 2018; Montalban et al., ECTRIMS 2024

Why do we need biomarkers in MS care?

For Diagnosis:

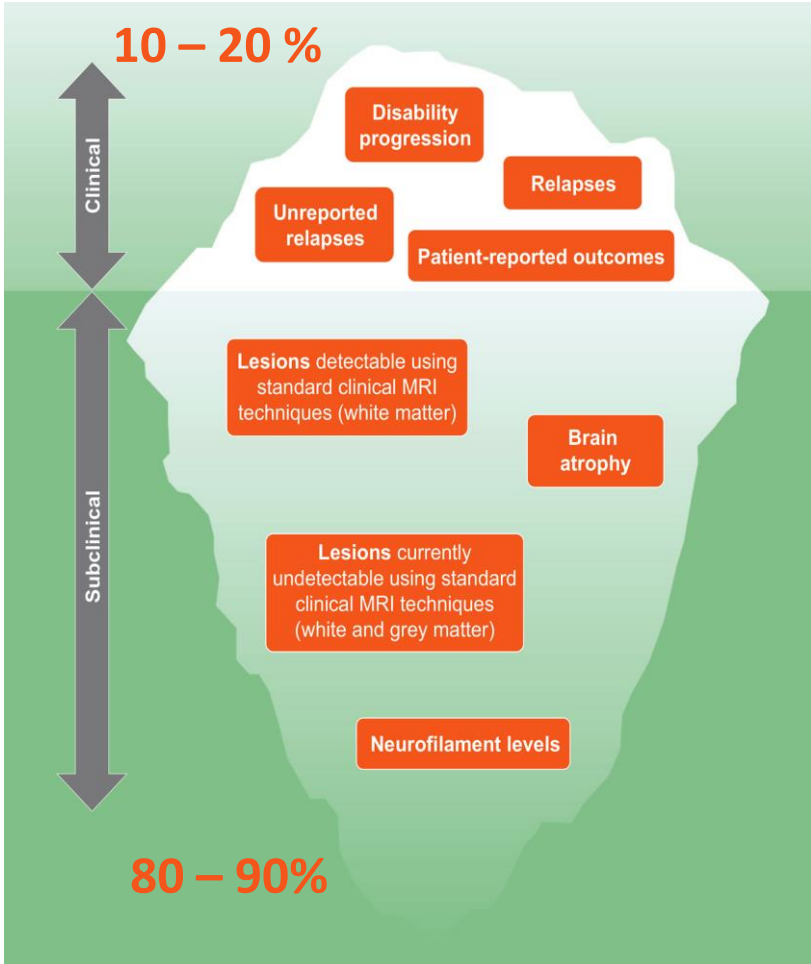
- MS remains an **exclusion diagnosis**
  - ⮑ combination of different biomarkers for MS diagnosis
  - ⮑ Introduction of new biomarkers:
    - ⮑ CSF:
      - ⮑ kappa-free light chains (κ-FLC)
    - ⮑ Specific MRI biomarkers:
      - ⮑ Central Vein Sign
      - ⮑ Paramagnetic Rim Lesions
    - ⮑ Optical Coherence Tomography

References: Jakimovski et al. Lancet 2024; Reich et al. N Engl J Med 2018; Montalban et al., ECTRIMS 2024

Why do we need biomarkers in MS care?

For Disease Monitoring:

- Disease course highly variable
- A minority of disease processes are clinically evident
- Multimodal approach
  - ⮡ **Imaging**
  - ⮡ **Fluid biomarkers**
  - ⮡ **Digital sensors**



References: Jakimovski et al. Lancet 2024; Reich et al. N Engl J Med 2018; Montalban et al., ECTRIMS 2024; Giovannoni et al., MSRD 2016 (Fig.)

Why do we need biomarkers in MS care?

Targets:

- Early diagnosis
- Sufficient suppression of inflammation
- Early detection of treatment failure

→ **Improved Long-Term Outcome**

- Personalization of MS treatment
- Assist Shared Decision Making

References: Jakimovski et al. Lancet 2024; Reich et al. N Engl J Med 2018; Montalban et al., ECTRIMS 2024; Giovannoni et al., MSRD 2016 (Fig.)

Imaging – MRI

Magnetic Resonance Imaging (MRI)

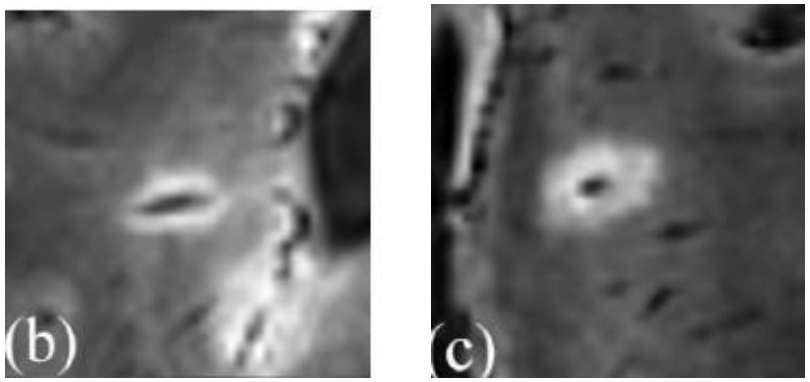
- Most valuable **diagnostic** and **monitoring** biomarker
- Increased importance with 2024 revisions of the McDonald criteria
  - ⮑ Without MRI no MS diagnosis possible
  - ⮑ Introduction of specific MRI biomarkers

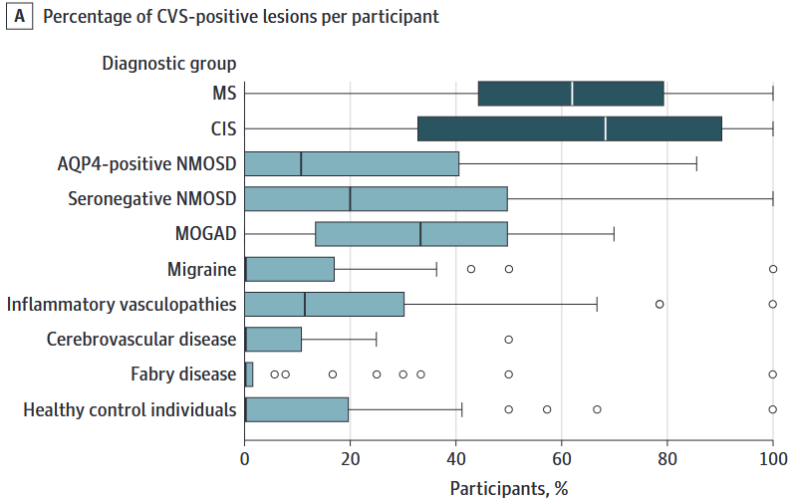
References: Wattjes et al., Lancet Neur 2021; Montalban et al., ECTRIMS 2024

Specific MRI Biomarkers

Central Vein Sign (CVS):

- thin line or small dot
- runs through the lesion
- positioned centrally in the lesion





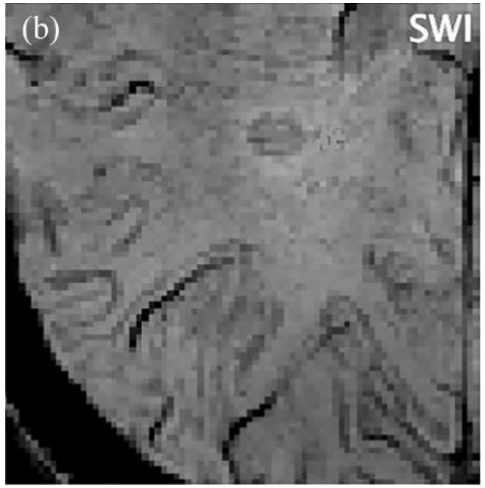
	Sensitivity	Specificity
Select-1*	89%	34%
Select-2*	86%	51%
Select-3*	81%	68%
Select-4*	73%	76%
Select-5*	68%	85%
Select-6*	65%	98%

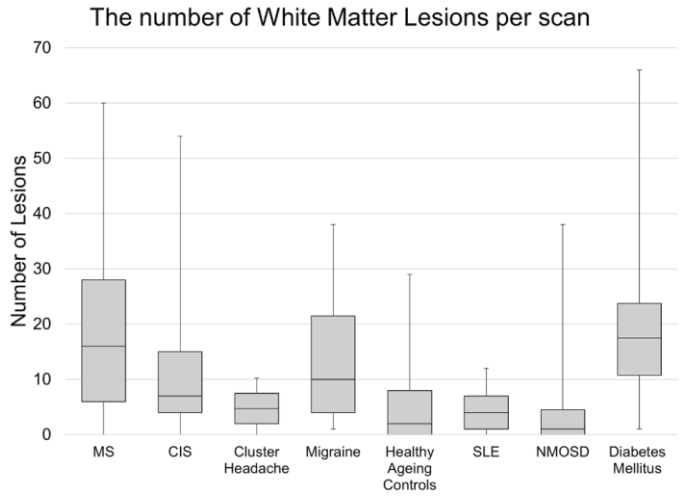
References: Wattjes et al., Lancet Neur 2021; Montalban et al., ECTRIMS 2024; , Cagol et al., JAMA Neur 2024, Daboul et al., MSJ 2024 (Fig.), Sati et al., Nature Rev Neur 2016

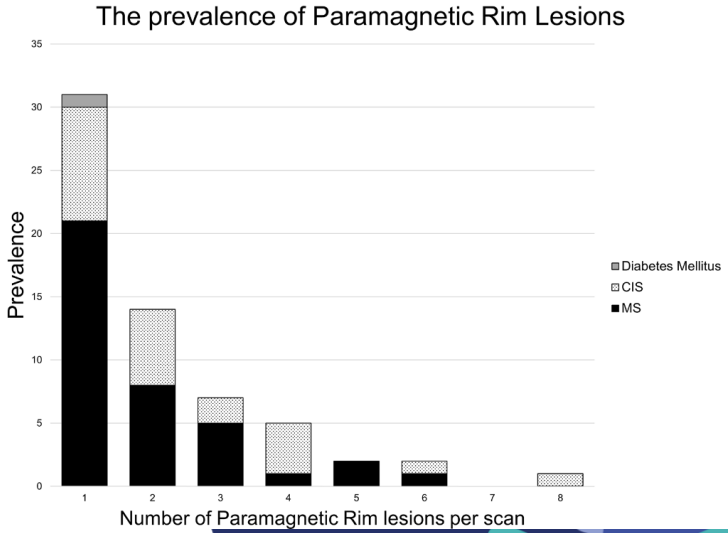
Specific MRI Biomarkers

Paramagnetic Rim Lesions (PRL):

- Highly specific for MS
- Prognostic value:
  - ↪ 1/3 of MRI lesions in SPMS and PPMS



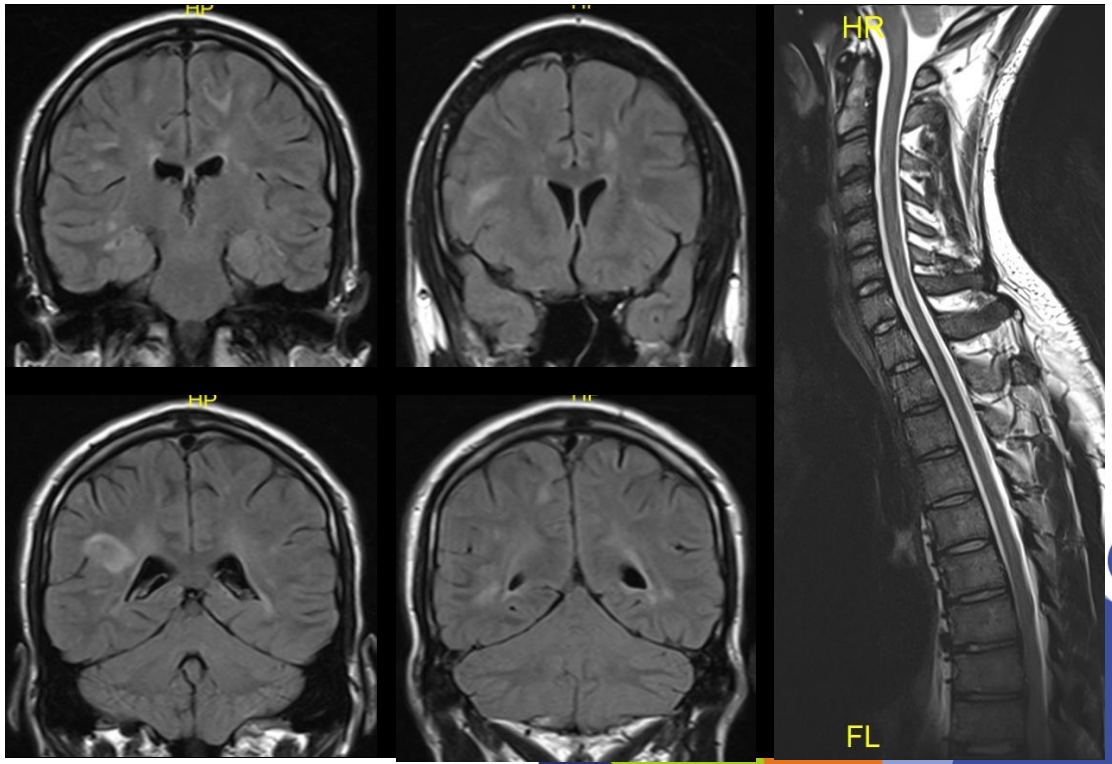




References: Montalban et al., ECTRIMS 2024, Calvi et al., MSJ 2020, Calvi et al., Neurology 2022; Meaton et al., MSJ 2022 (Figs.)

Case Report 1 – Identifying Risk Factors

- male, 20y
- First attack:
  - Optic Neuritis, right eye
  - Good recovery after two steroid courses (VA 0.9)
- EDSS 1.5

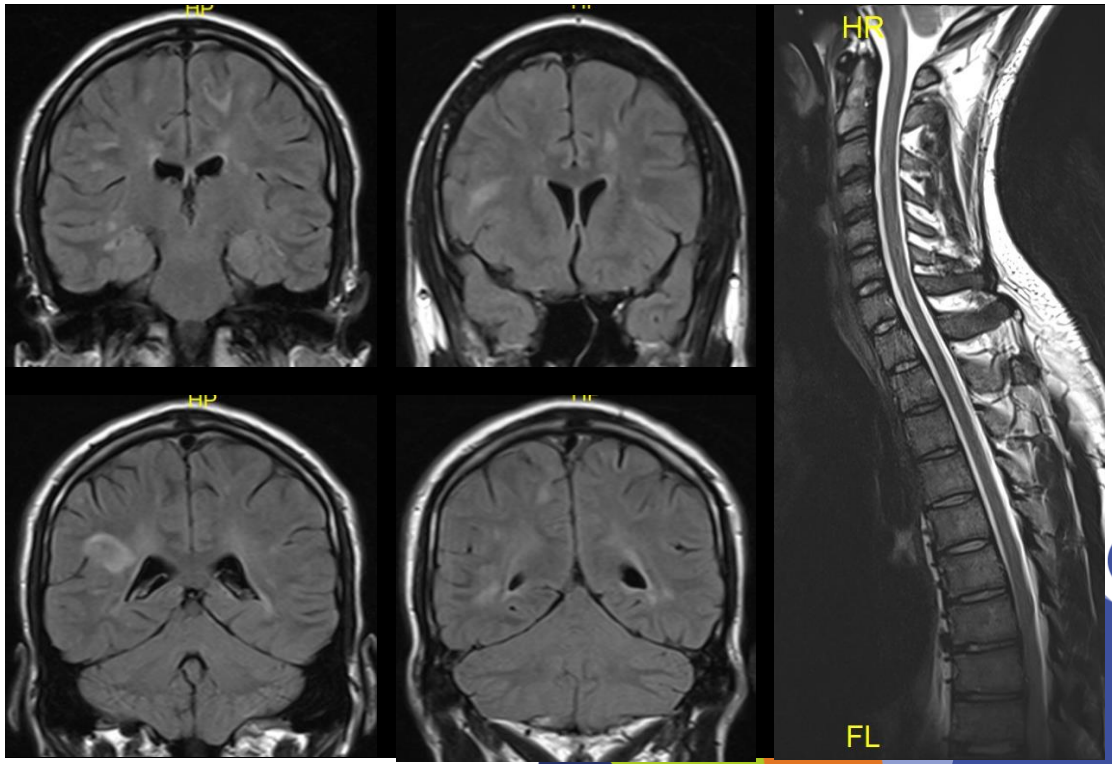


References: own case

Case Report 1 – Identifying Risk Factors

but:

- **MRI:**
- > 40 MS lesions at diagnosis
- Localisation:
  - Periventricular
  - Juxtacortical / Cortical
  - Infratentorial
  - Spinal

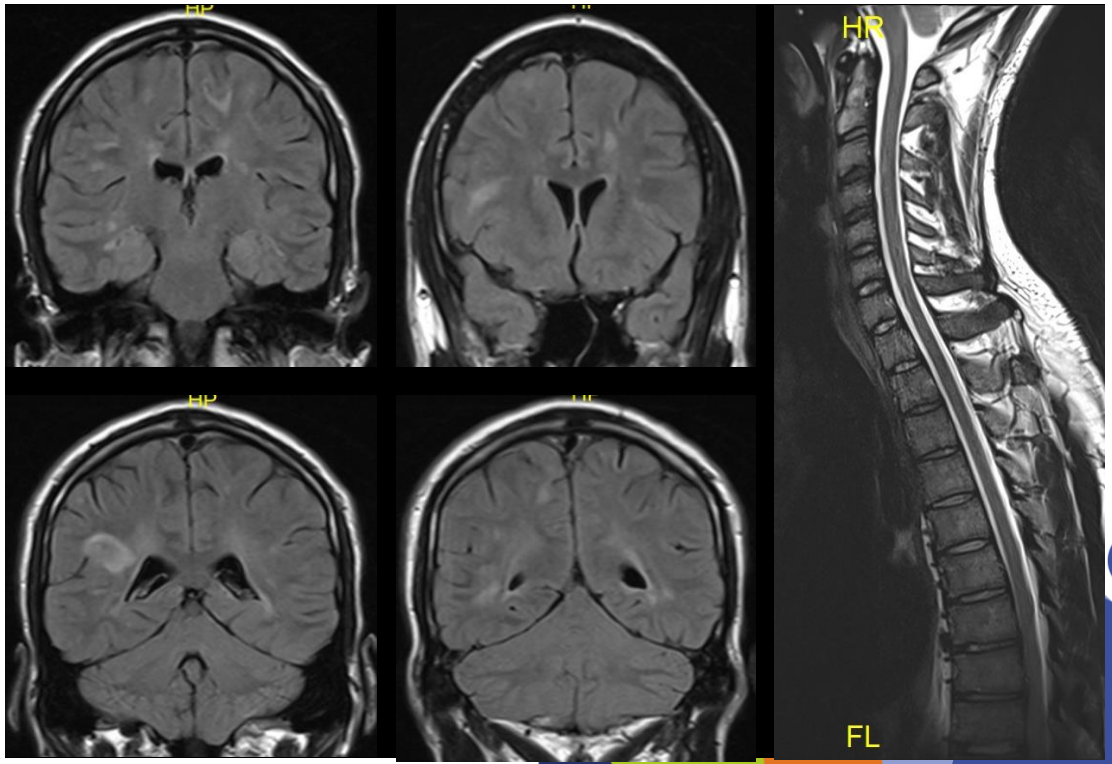


References: own case

Case Report 1 – Identifying Risk Factors

but:

- Beck's Depression Inventory:
  - **moderate depression**
- Fatigue Scale for Motor and Cognitive Functions:
  - **moderate fatigue**
- SDMT: **below average**
- 9-Hole-Peg-Test (right-handed):
  - **right 22,8 sec (>) left 20,1 sec**



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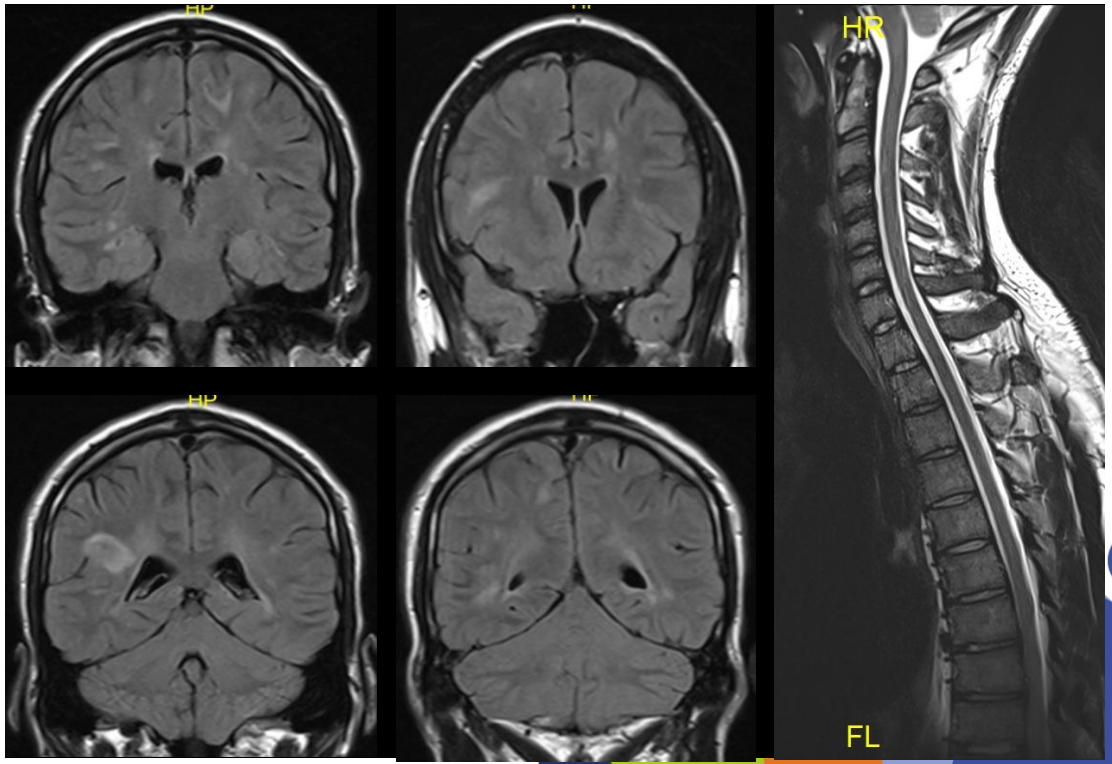
Indication for direct treatment with high-efficacy DMT



References: own case

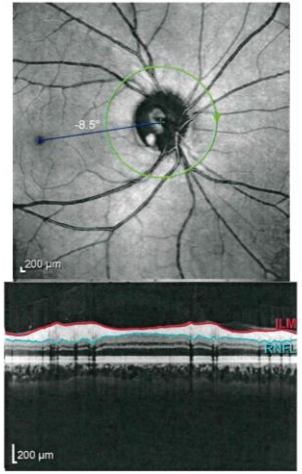
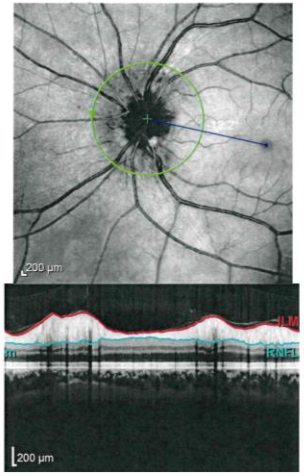
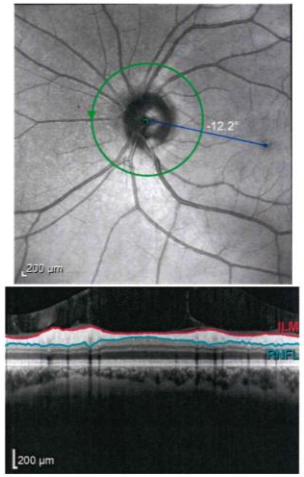
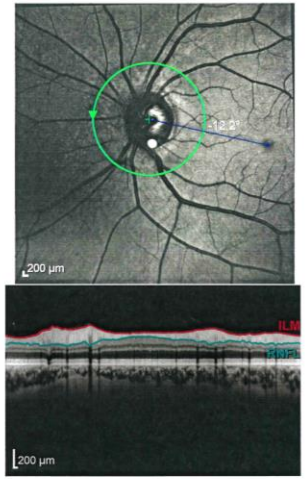
Imaging –
Optical Coherence Tomography

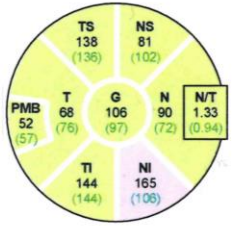
Optical Coherence Tomography

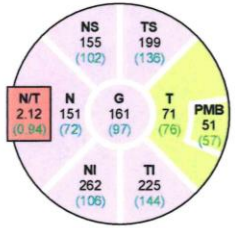
- Examination of the eye background
- Useful for Diagnosing Optic Neuritis
- Usually different patterns between MS and NMOSD/MOGAD

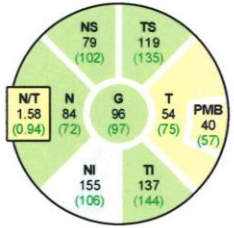
References: Petzold et al., Lancet Neur 2022, Montalban et al., ECTRIMS 2024

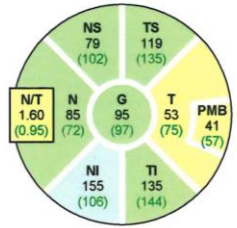
Optical Coherence Tomography

	Attack	6m	12m
Right Eye			
Left Eye			









References: own case

Fluid Biomarkers – kappa-Free Light Chain

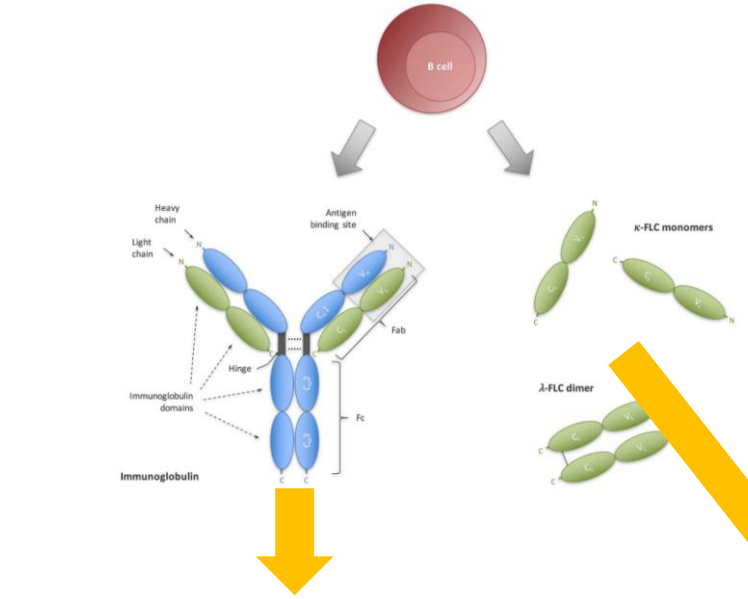
kappa – Free Light Chain (κ-FLC)

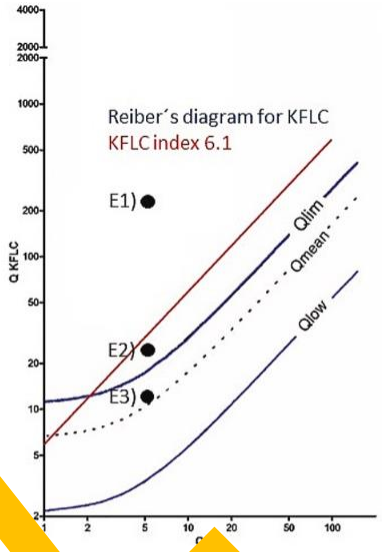
Oligoclonal bands (OCB) reliable but:

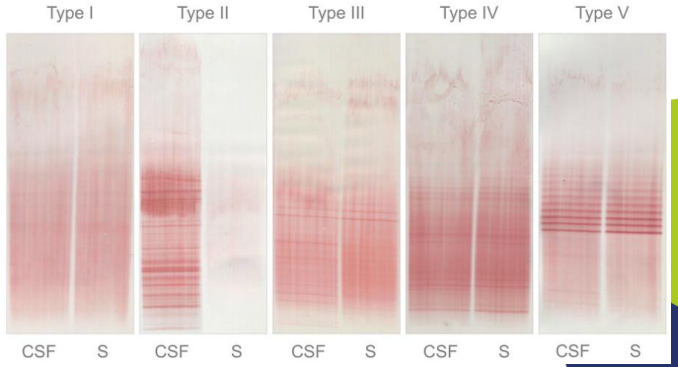
- technically demanding
- rater dependent
- limited availability

κ-FLC:

- studies on diagnostic value in MS
- Interchangeable with OCB (proposed McDonald Criteria 2024)
- examiner-independent
- cost-effective
- we need standardization!







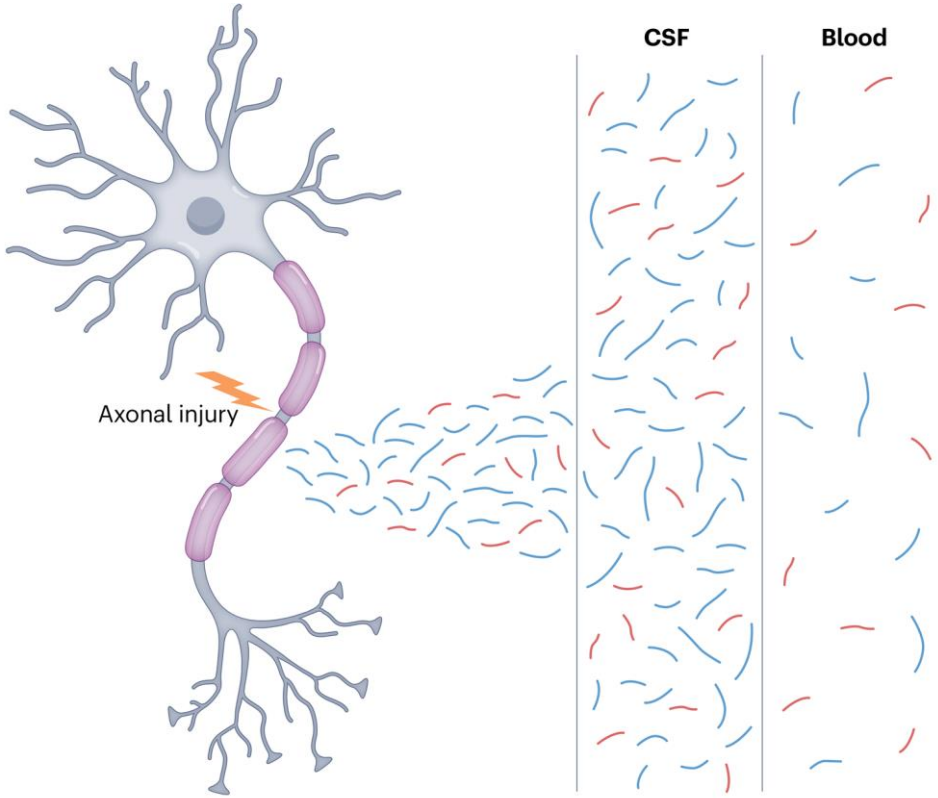
References: Senel M et al., PLoS One 2014; Presslauer S et al; MSJ 2016; Arrambide G et al., Brain 2018; Hegen et al, MSJ 2023; Konen et al. Autoimmun Rev 2025 (Fig.)

Fluid Biomarkers – Neurofilament light chain (NfL)

Neurofilament light chain (NfL)

- Short-term integration into clinical routine expected

- Major structural protein of the neural cell
- Release in CSF after axonal damage
- In Serum 2-3% of the CSF levels

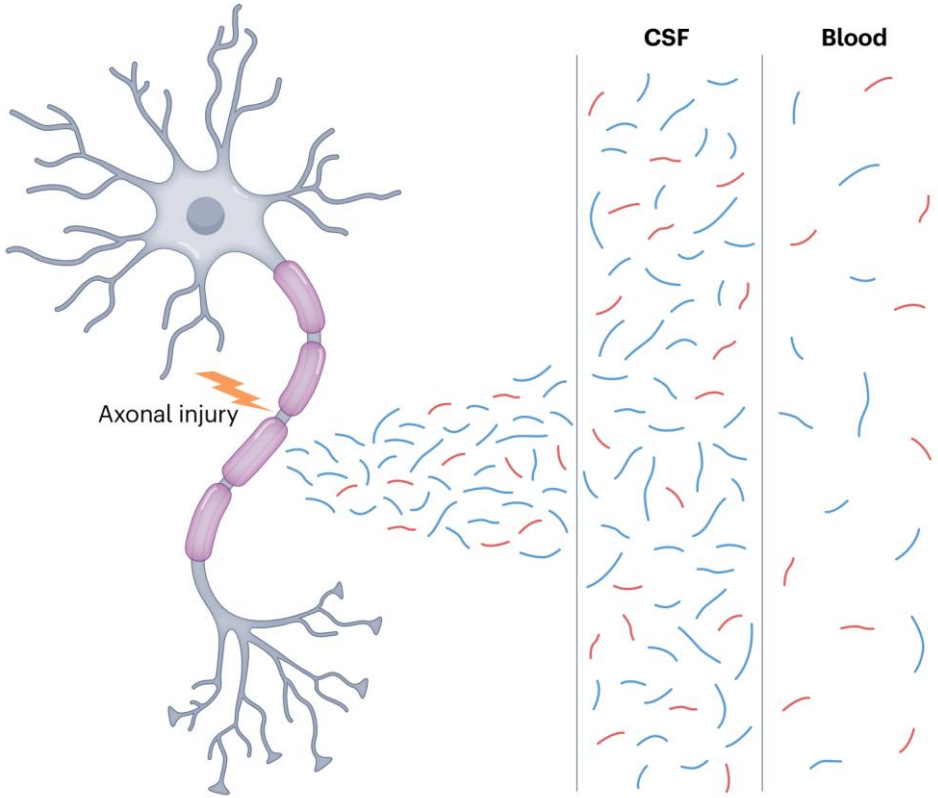


References: Kuhle et al., Clin Chem Lab Med 2016; Bittner et al., Brain 2021; Bjornevik et al., JAMA Neurol 2020; Khalil et al., Nature Reviews Neurology, 2024 (Fig.)

Neurofilament light chain (NfL)

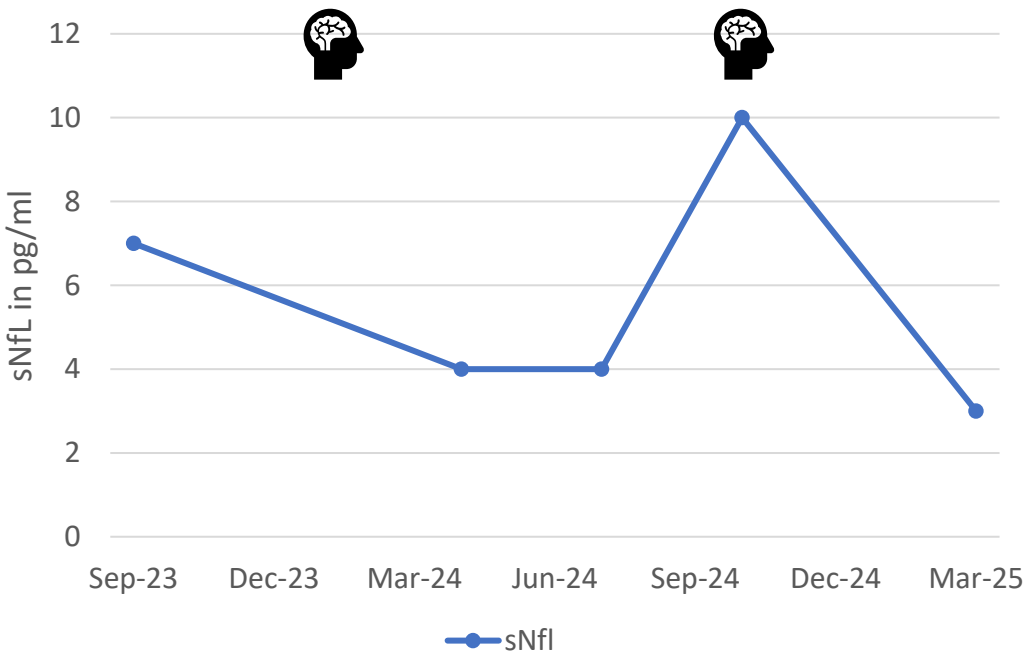
In MS:

- ↑ up to 6 years before first attack
- Correlates with:
  - ↪ Relapse risk
  - ↪ New T2 lesions oder active lesion in MRI
- ↑ at treatment failure
- ↑ at CNS complications of MS treatments (e.g. PML)

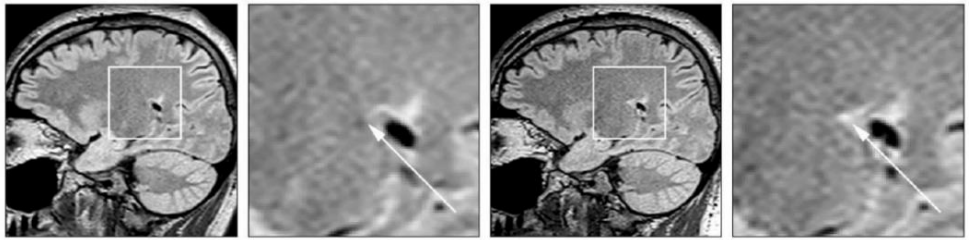


References: Kuhle et al., Clin Chem Lab Med 2016; Bittner et al., Brain 2021; Bjornevik et al., JAMA Neurol 2020; Khalil et al., Nature Reviews Neurology, 2024 (Fig.)

Case Report 2



Anzahl (Mindestdurchmesser 3 mm bei 3D; 5 mm bei 2D)	Aktuelle Untersuchung vom	Vergleich mit der Voruntersuchung vom
	T2-Läsionen (±Interratervariabilität)	Neue oder vergrößerte T2-Läsionen (±Interratervariabilität)
Total	7 (±1)	1
Kortikal / juxtakortikal	1	1
Periventrikulär	5 (±1)	
Tiefe weiße Substanz	1	
Infratentoriell	0	0

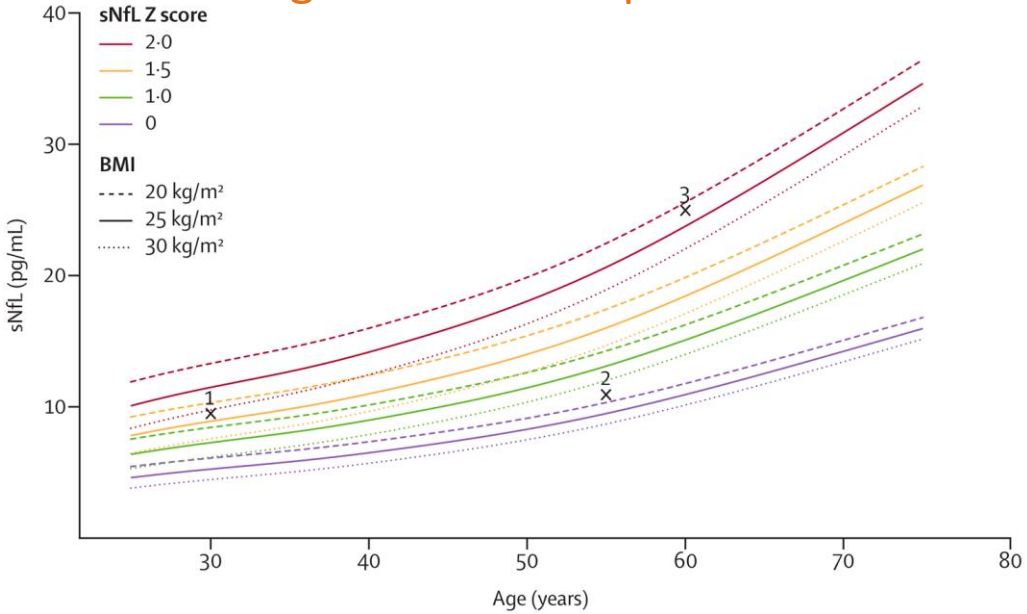


References: own case

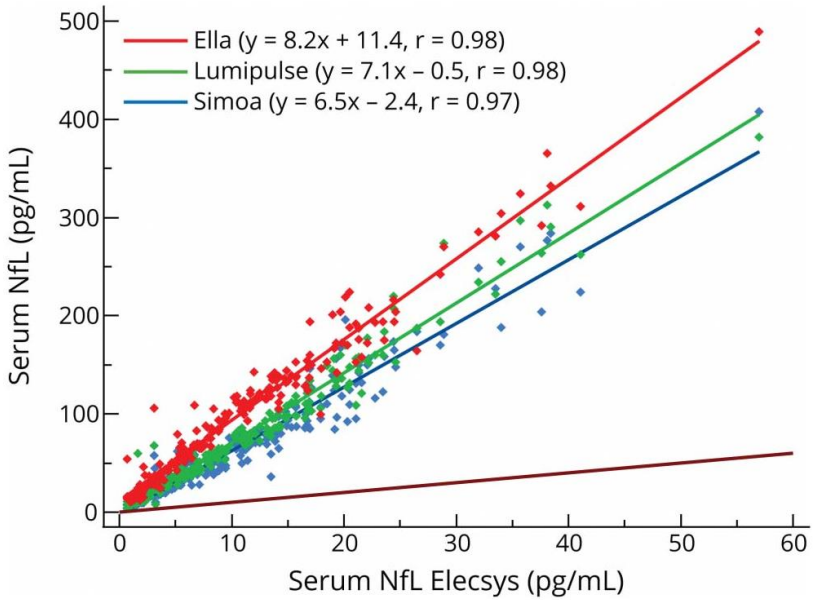
Neurofilament light chain (NfL)

Challenges:

Age- and BMI-dependent



Different assays (techniques)
→ different absolute values



Accessible at:
https://shiny.dkfbasel.ch/baseInflreference/

References: Benkert et al., Lancet Neurology, 2022 (Fig.), Mondesert et al., Neurology, 2025 (Fig.)

Fluid Biomarkers – The Future: Glial Fibrillary Acidic Assay (GFAP)

Glial Fibrillary Acidic Assay (GFAP)

- Signature protein of astrocytes (30-40% of brain cells)
- Release in CSF after astrocyte damage, but also astrocyte activation

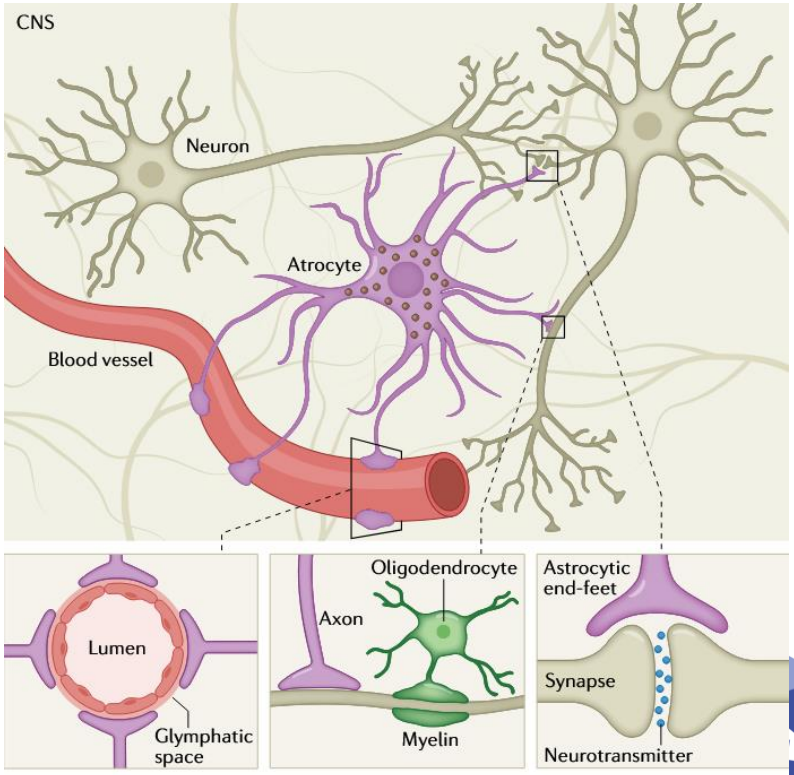


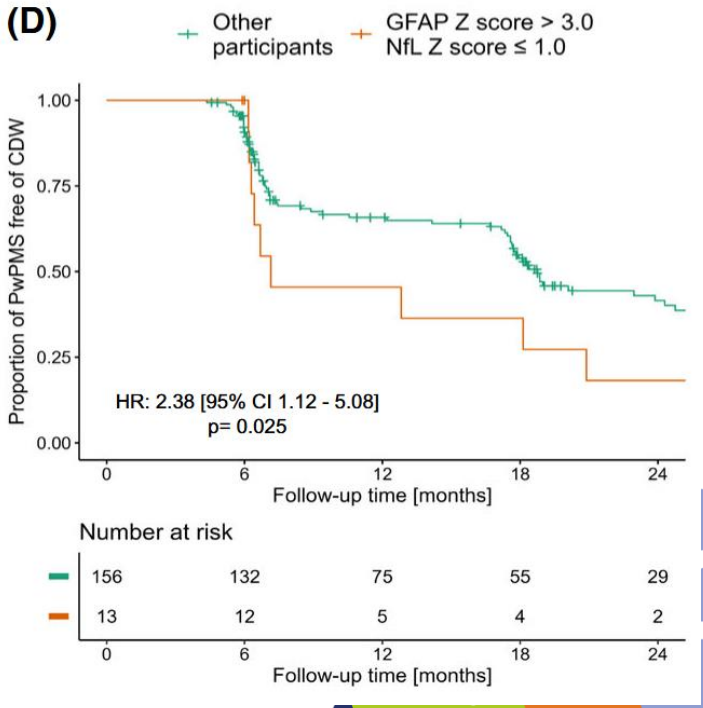
Fig. 1 | **Astrocytes have multiple physiological roles in the CNS.** Astrocytic end-feet containing glial fibrillary acidic protein (brown circles) are an essential component of the blood–brain barrier and the glymphatic system[157]. Astrocytes are critical in maintaining axonal metabolic homeostasis[158] and contribute to tripartite synapses[159].

References: Abdelhak et al., Nature Rev Neur 2022 (Fig.); Abdelhak et al., Annals Clin Transl Neur 2023; Barro et al., Neurology 2022, Monreal et al., Brain 2023; Madill et al., Annals Clin Transl Neur 2024

Glial Fibrillary Acidic Assay (GFAP)

In MS:

- ↑ in progressive MS and active relapsing MS
- Correlates with:
  - ⤷ severity of disability (EDSS)
  - ⤷ Lesion volume
  - ⤷ Brain atrophy
- Predicts:
  - ⤷ future progression
  - ⤷ need of future gait aid
  - ⤷ future conversion to SPMS



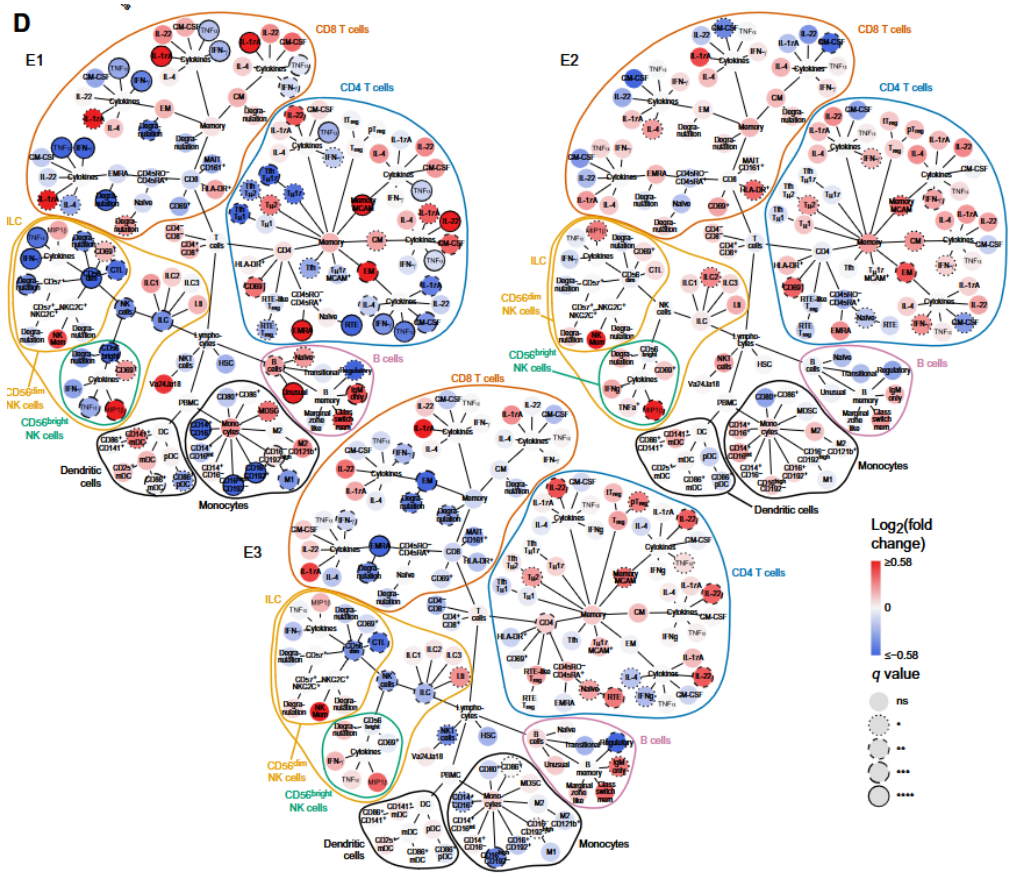
References: Abdelhak et al., Nature Rev Neur 2022 (Fig.); Abdelhak et al., Annals Clin Transl Neur 2023 (Fíg.); Barro et al., Neurology 2022, Monreal et al., Brain 2023; Madill et al., Annals Clin Transl Neur 2024

Fluid Biomarkers – The Future: Proteomics

MS Endophenotypes

- Combination of:
  - ⮡ Cell signatures (high-dimensional flow cytometry)
  - ⮡ Protein signatures (serum proteomics)

- Identification of **three** distint peripheral blood endophenotypes:
  - ⮡ Endophenotype 3 (after 4 years follow up):
    - ⮡ Higher disease progression
    - ⮡ Higher MRI activity



References: Gross et al., Science Transl. Med 2024

Take home Message

Take Home Message

- **Combined use** of imaging and fluid biomarkers can change MS care
  - ⮑ Individualized risk assessment
  - ⮑ Personalized treatment in all disease phases
  - ⮑ Create evidence for Shared Decision Making
- **MRI:** most important diagnostic and monitoring biomarker
- **Fluid biomarkers**
  - ⮑ κ-FLC can assist MS diagnosis
  - ⮑ NfL: Assessment of ongoing inflammation / Short-Term integration in clinical routine expected
  - ⮑ GFAP: ongoing studies on predictive value for disability progression