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CONy & Teva Neuroscience MS Matters live webinar series

MS Matters: Biomarkers: The key to unlocking MS?

Thank you for joining. The webinar will begin shortly

This webinar is organised and funded by Teva Pharmaceuticals Europe B.V.
Date of Preparation: June 2019 | **HQ/MS/19/0008a**

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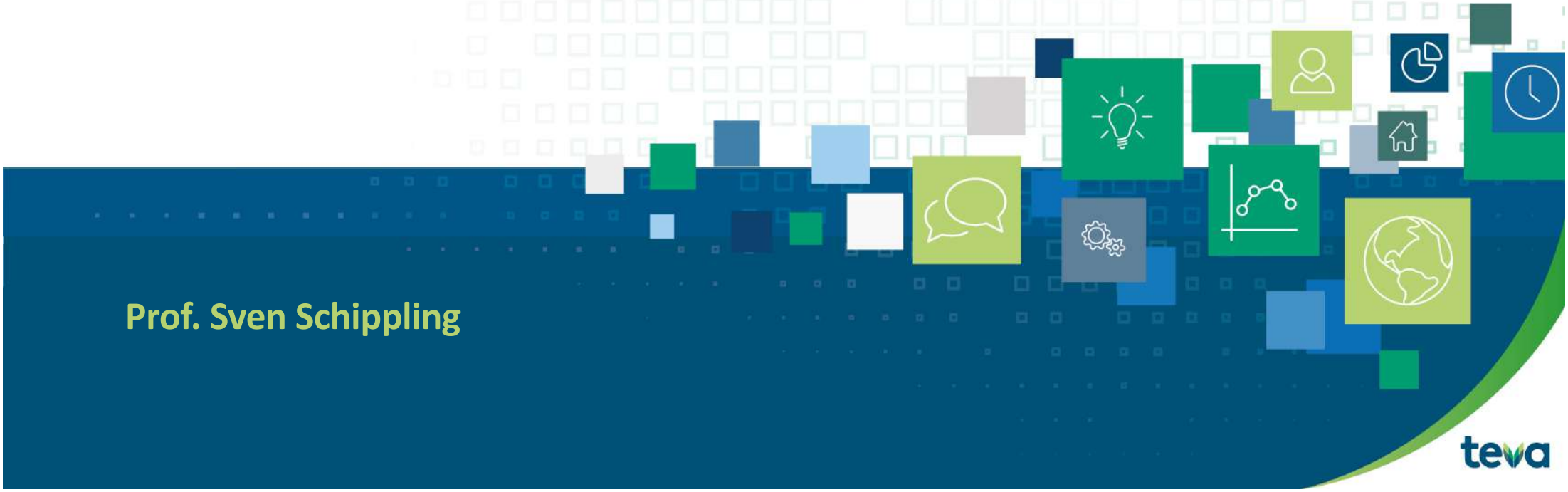
Welcome and Introduction

Prof. Sven Schippling



Faculty

Prof. Sven Schippling, Moderator

Deputy Head of the Department of Neuroimmunology and Clinical Multiple Sclerosis Research (nims) at the University Hospital Zürich, Switzerland

PD Dr med Dr phil Jens Kuhle, Co-presenter

Head of the Multiple Sclerosis Centre at the University Hospital Basel, Switzerland

Agenda

Time (CEST)	Title	Speaker
18:30	**Welcome and introduction**	Sven Schippling
18:35	**Existing biomarkers: Their importance in identifying disease progression and guiding treatment decisions**	Jens Kuhle
18:45	**Audience Q&A**	All
18:50	**Unmet need for novel biomarkers in MS: Could they provide answers to four key questions**	Sven Schippling
19:00	**Audience Q&A**	All
19:05	**What could potential new biomarkers in MS mean for patients?**	Both
19:20	**Audience Q&A**	All
19:25	**Closing remarks**	Sven Schippling

Conflicts of interest

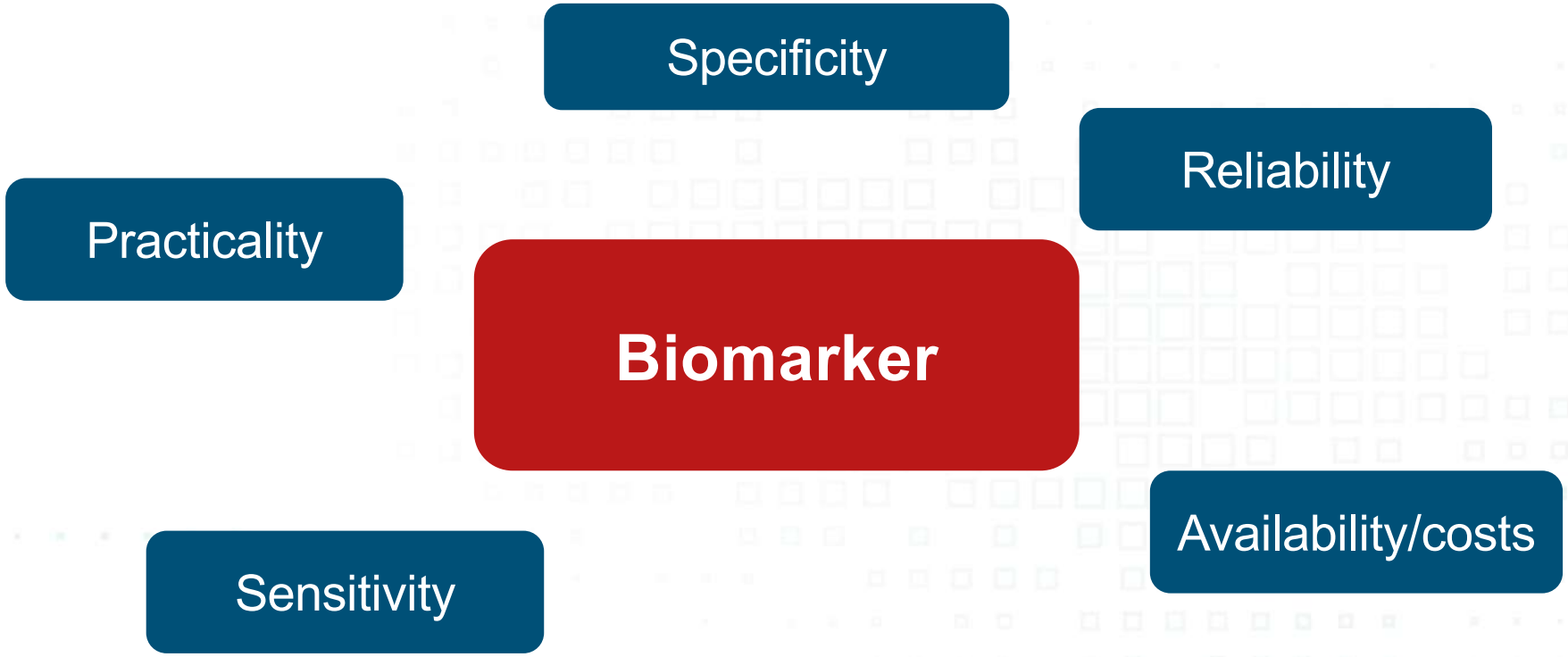
- Sven Schippling is supported by the Swiss National Science Foundation (SNF), the Swiss Multiple Sclerosis Society, the Betty and David Koetser Foundation for Brain Research and the Myelin Repair Foundation (USA)
- He is the Co-Director of the Clinical Research Priority Program for Multiple Sclerosis ($CRPP^{MS}$) supported by the University of Zurich, Switzerland
- He is a member of the International Clinical Consortium of the Guthy Jacksson NMO Charitable Foundation, California, USA
- He sits on the Steering committees of the OCTIMS, PASSOS, BENEFIT, REFINE, EMPIRE, ENSEMBLE and CLARIFY-MS trials, the MS in the 21st Century and the ParadigMS initiatives
- He is a founding member of the Neuromyelitis Optica Study Group (NEMOS), Germany, and the Drug Development Network (DDNZ), Zurich, Switzerland
- He received travel support as well as speaker´s fees from Actelion, Almirall, Bayer Healthcare, Biogen, Sanofi/Genzyme, Merck, Novartis, Roche, Santen, Teva

What are biomarkers for?

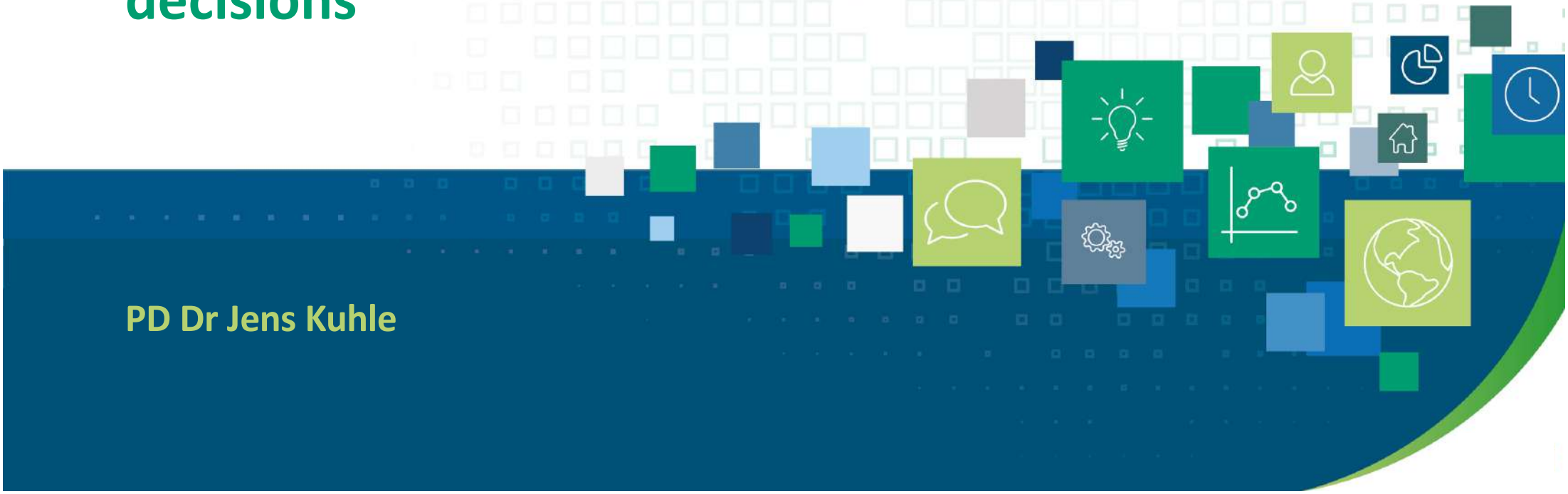
- Biomarkers can be used for:
  - Diagnosis
  - Progression monitoring
  - Treatment monitoring
  - Improving clinical trial design

Harris VK, et al. Degen Neurol and Neuromus Disease. 2017;7:19–29

What makes a good biomarker?



Existing biomarkers: Their importance in identifying disease progression and guiding treatment decisions



PD Dr Jens Kuhle

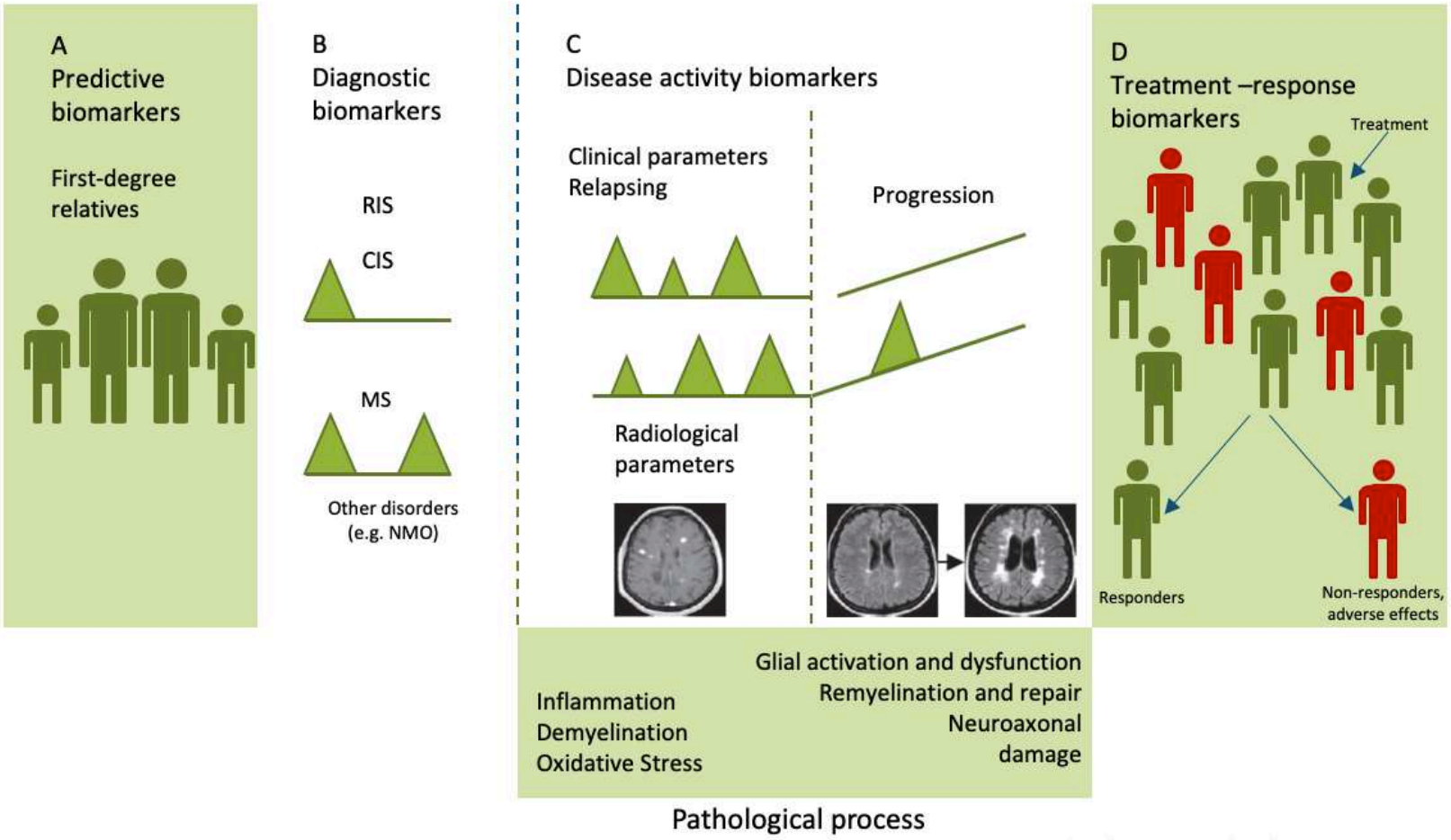
Disclosures of interest

- Jens Kuhle
  - Research support and speaker honoraria from:
    - Jens Kuhle served on scientific advisory boards for Novartis Pharmaceuticals, Merck, Biogen, Sanofi Genzyme, Roche and Bayer; has received funding for travel and/or speaker honoraria from Biogen, Sanofi Genzyme, Novartis, Merck Serono, Roche, Teva and the Swiss MS Society; and research support from Bayer, Biogen, Merck, Sanofi Genzyma, Novartis, Roche, ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation (320030_160221).

Definition of biomarkers

"A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." (NIH)

Different kinds of biomarkers

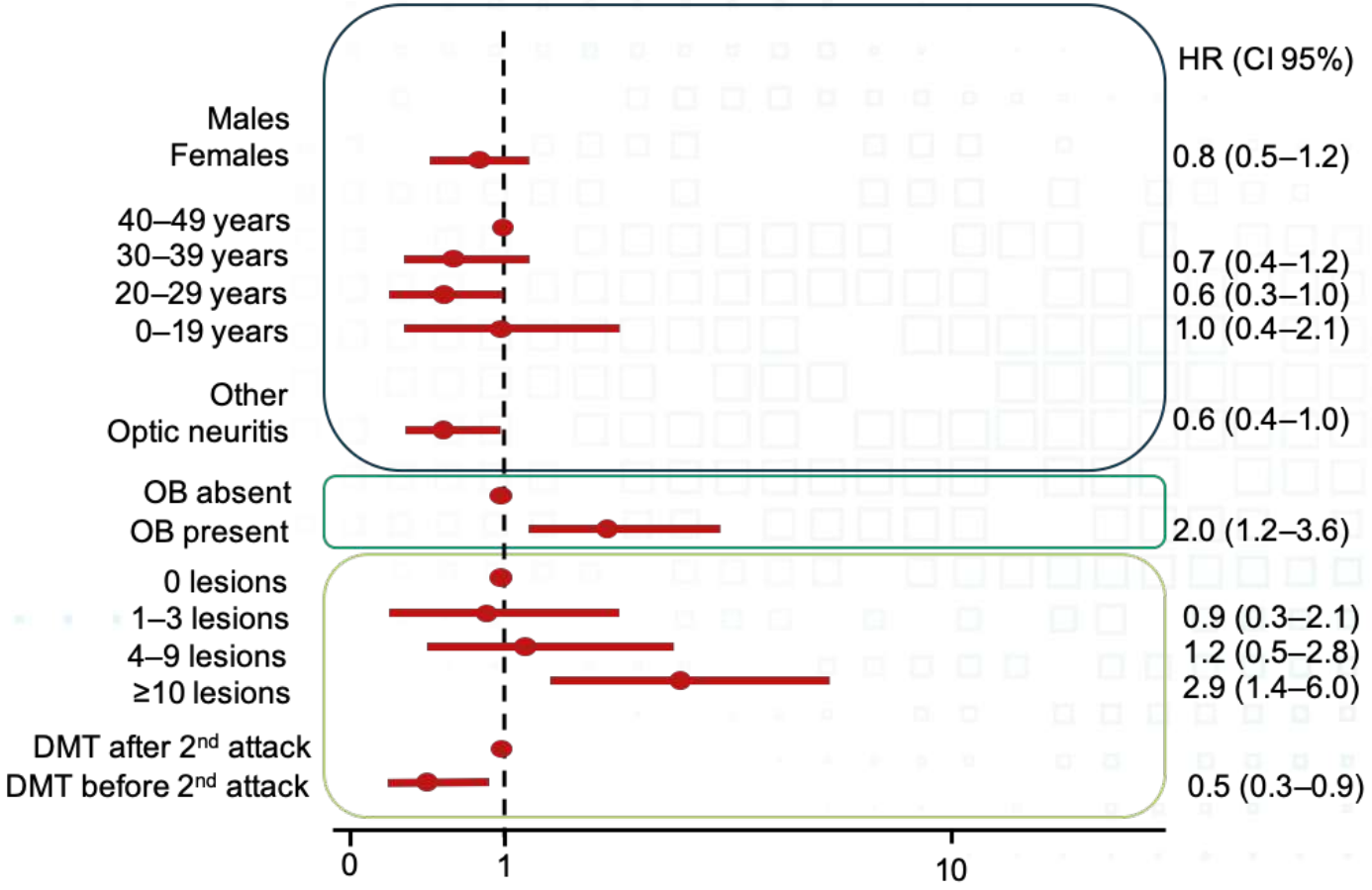


Comabella, et al. Lancet Neurol. 2014;13:113–26

Are there clinically useful and validated immunological biomarkers in MS? – YES!

- Oligoclonal bands (OCBs) in CSF and intrathecal IgG production are used for diagnosis (sensitive but not specific)
- Neutralising antibodies against certain injectable DMTs are used to identify non-responders
- Antibodies against The John Cunningham (JC) virus are used for risk stratification of PML during certain injectable treatments
- Antibodies against Varicella Zoster virus (VZV) are used to identify patients with increased risk for generalised VZV infection during certain oral DMT treatments
- Aquaporin 4 antibodies are used for stratification of patients (neuromyelitis optica spectrum vs MS)

OCBs as prognostic factor for progression from CIS to EDSS of 3



Tintore, et al. Brain 2015;138:1863–74

Exploratory biomarkers in MS – There are many!

- cytokines
- adhesion molecules
- chemokines and receptors
- MMPs and inhibitors
- proteomics
- cystatin C
- microRNAs
- C31/C4b
- sCD146
- sCD14
- sHLA I and sHLA II
- sHLA-G
- sNOGO-A
- anti-NOGO-A
- anti-MBP
- anti-MOG
- anti-HHV6
- anti-proteasome
- anti-CD46 and anti-CD59
- lipocalin 2
- VEGF
- AMCase and Chit
- fetuin-A
- APRIL
- CSF cells
- s/GPL
- HMGB1
- TOB1
- S100b and ferritin
- isoprostanes
- oxysterols
- pentosidine
- tau
- 14-3-3
- NAA and NSE
- anti-Tub and b-Tub
- anti-NEFL
- neurotrophic factors
- Tregs
- KCNK5
- FGF2 and PDGF-AA
- gMS classifier 1
- myeloid MVs
- sAPP, Ab peptides
- apoptosis-related molecules (e. g. TRAIL)
- co-signaling molecules
- GWAS genes
- candidate genes
- CIITA
- APLA
- IL17F
- ABCB1, ABCG2
- IL21

Problems for validation of biomarkers

- Standardised and validated acquisition and storage of biosamples
- Standardised and validated assay
- Large sample size
- Validation in independent cohort
- Well characterised patients

Unmet need for novel biomarkers in MS

Prof. Sven Schippling

What questions should be answered by novel biomarkers in MS?

Prediction of individual outcomes

Risk of side effects/safety concerns

Individualization of therapy

"Active disease" in the absence of relapses

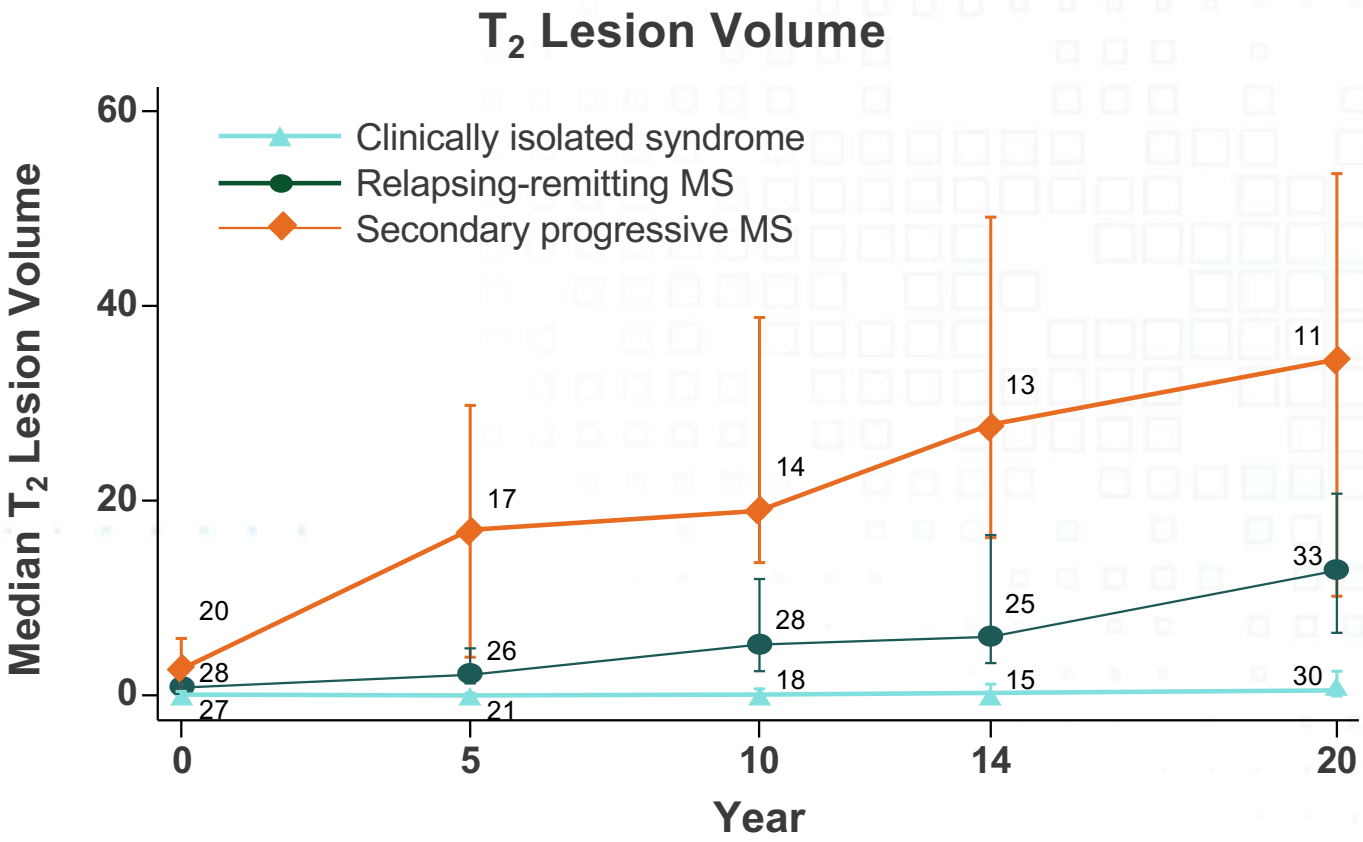
Response/non response on the individual level

Prognostic impact of baseline factors on future disability

Factors Associated With Favorable Prognosis	Factors Associated With Poor Prognosis
Young age at onset[1]	Older age at onset[1]
Female[2]	Male[2]
Initial presentation with an acute optic neuritis[2]	Cognitive impairment at initial presentation[6]
Full recovery from initial presentation[1]	Multifocal presentation[2]
Sensory symptoms at onset[3]	Sphincter, bowel and/or bladder involvement at onset[3]
No infratentorial lesions[4]	High lesion burden on brain MRI[4]
Minimal lesion burden on brain MRI[5]	Evidence of brain volume loss at disease onset[7]

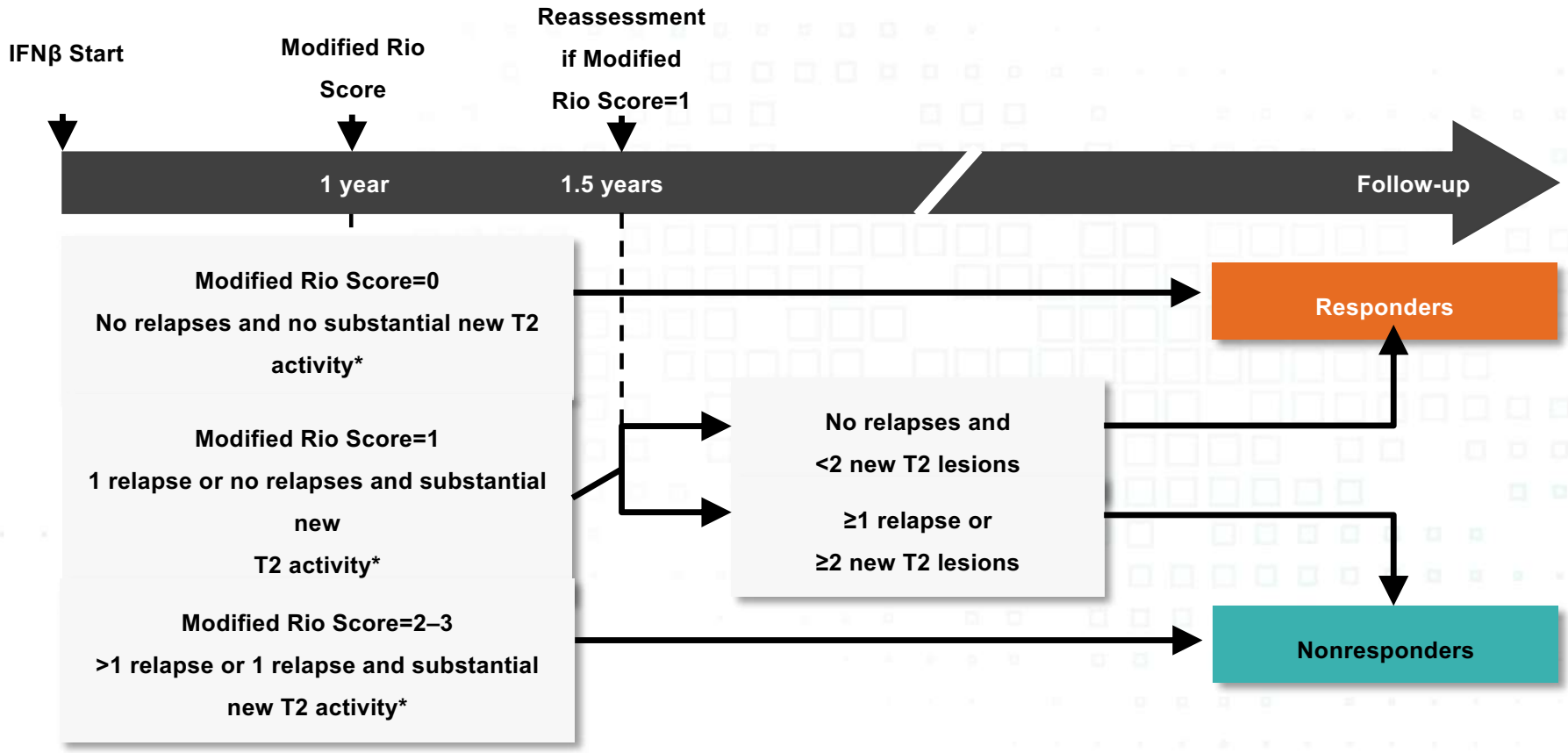
1. Confavreux C et al. *Brain* 2003;126:770-82; 2. Runmarker B, Anderson O. *Brain* 1993;116(Pt 1):117-34; 3. Langer-Gould a et al. Arch Neurol. 2006;63:1686-1691; 4. Zhang et al. Neurol India 2013;61(3):231–8; 5. Brex PA et al. *N Engl J Med* 2002;346:158-64; 6. Deloire M et al. *Mult Scler* 2010;16:581-7; 7. Fisher E et al. Neurology 2002; 59:1415-1420

Increase in T2 lesion load and disease evolution



Fisniku, Brex et al., Brain 2008

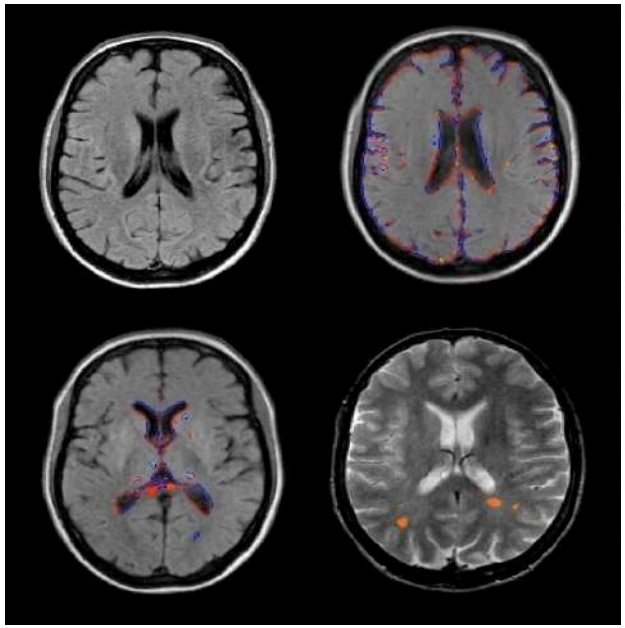
Assessing treatment response – The Modified Rio Score



*Substantial new T2 activity is defined as >4–5 new T2 lesions in 1 year of treatment, or >1–2 new T2 lesions if the reference MRI scan to assess new T2 lesion formation is obtained at least 6 months after initiating therapy

Sormani MP, De Stefano N. *Nat Rev Neurol*. 2013;9:504-512; Sormani MP et al. *Mult Scler.* 2013;19:605-612; Freedman MS et al. *Can J Neurol. Sci.* 2013;40:307-323.

Predictive value of brain atrophy – Group level evidence

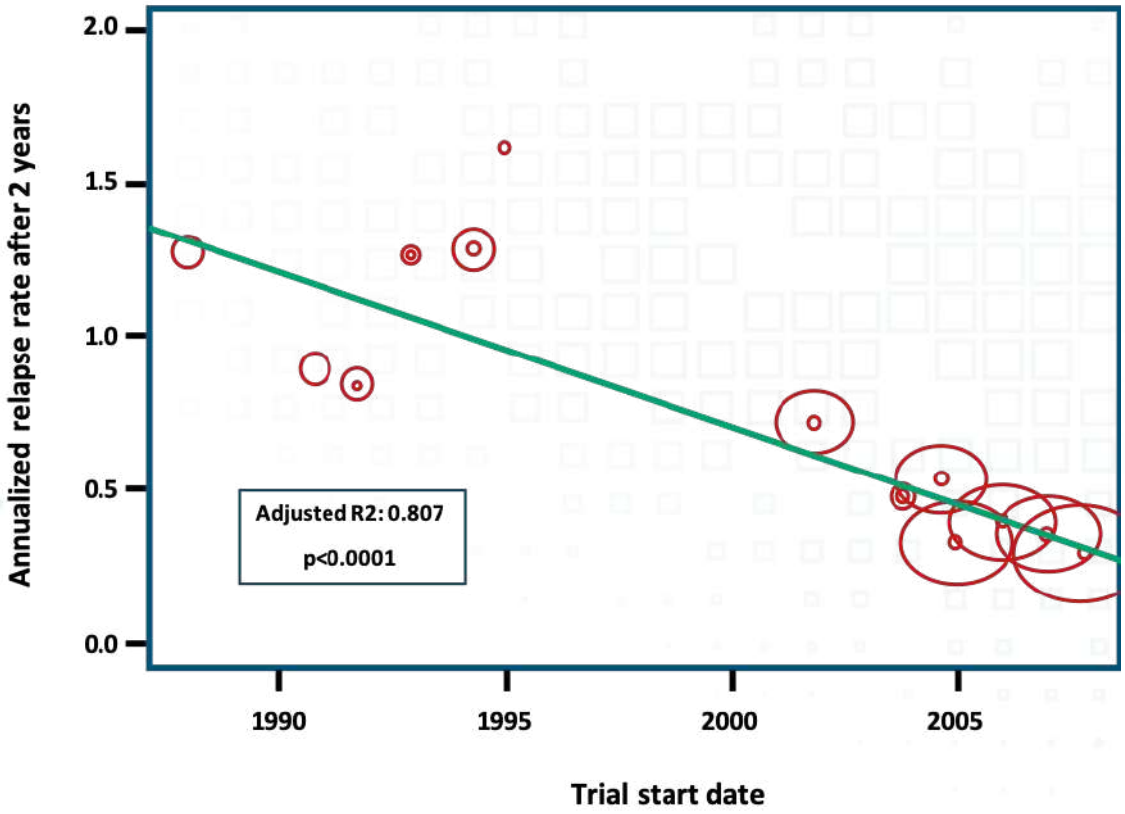


- **8 MAGNIMS centres, 261 patients with short interval (1–2 year) MRI**
  - using pseudo-T_1 images
- **Model included:**
  - centre, DMT usage, baseline EDSS

Central atrophy and lesion volume change predicted 10-year EDSS (R^2 = 0.72*)

*Relapse onset group only. Central atrophy defined as ventricular volume change
DMT, disease-modifying therapy; MAGNIMS, Magnetic Resonance Imaging in MS; R^2, coefficient of determination
Popescu V *et al. J Neurol Neurosurg Psychiatry* 2013.

Clinical event rates in placebo cohorts of phase III trials



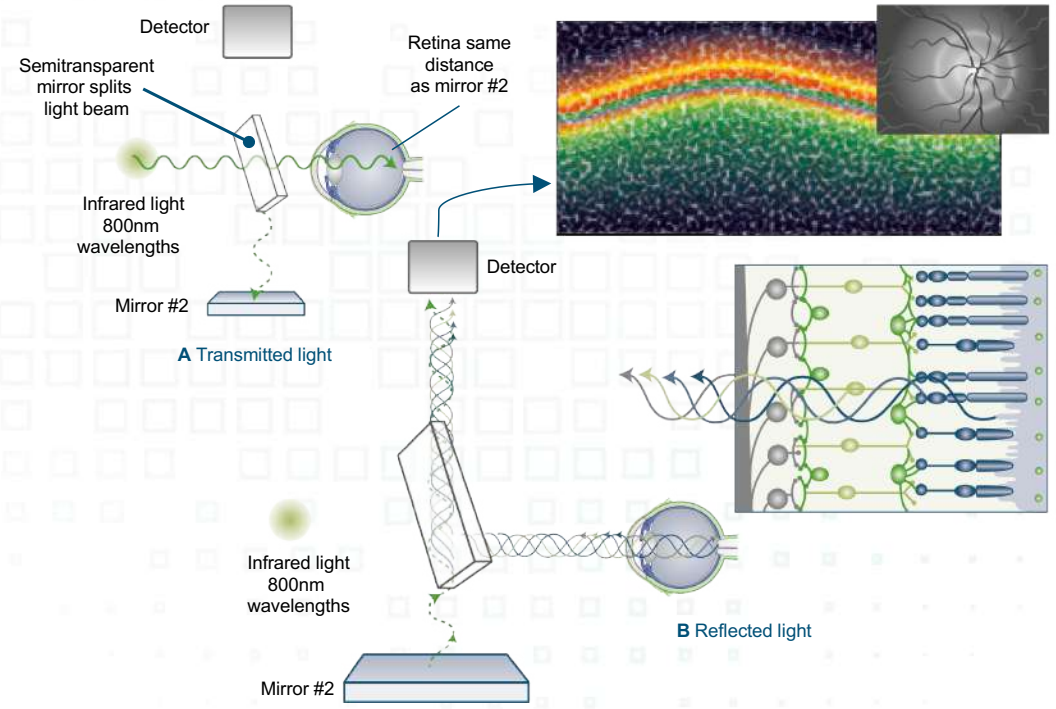
Stellmann, *et al*. *PLoS One*, 2012

What could potential new biomarkers in MS mean for patients?

Prof. Sven Schippling and PD Dr Jens Kuhle

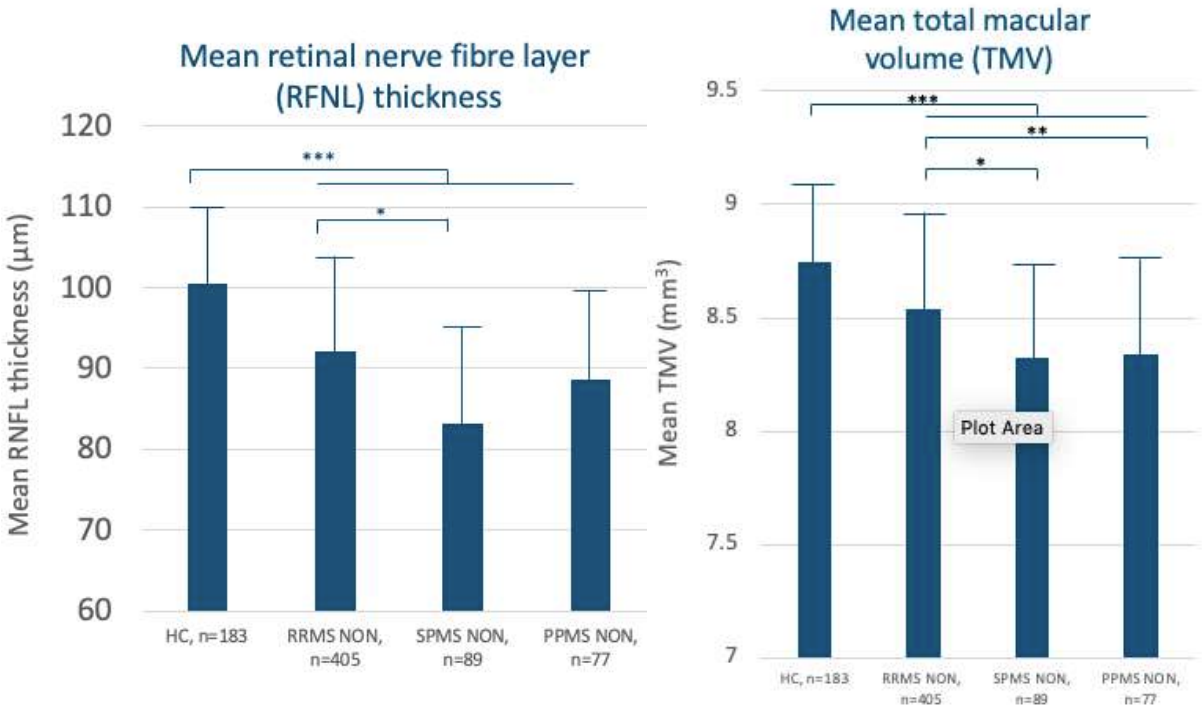
Optical coherence tomography

- Optical coherence tomography (OCT) allows:
  - Rapid, non-invasive quantification of retinal nerve fibre layer thickness and macular volume by low coherent near infrared light
  - *In vivo* pathology of retina



Adapted from Frohman EM, et al. Nat Clin Pract Neurol. 2008;4:664–75.

OCT findings in MS patients without a history of optic neuritis



- Significant difference between the groups: * p<0.05; **p<0.01; ***p<0.001

HC=healthy control

RRMS=relapsing-remitting MS

SPMS=secondary progressive MS

PPMS=primary progressive MS

NON=No optic neuritis

Adapted from Oberwahrenbrock T, et al. 2012.

Oberwahrenbrock T, et al. Mult Scler Int. Epub 2012.

Ganglion cell loss in relation to visual disability in MS

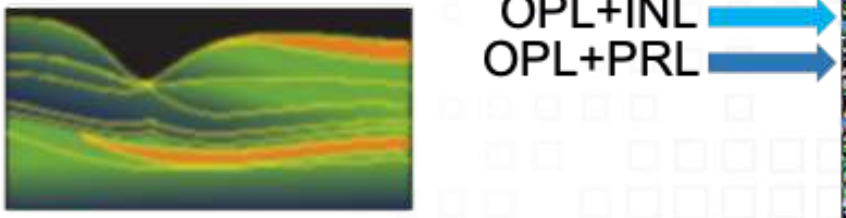
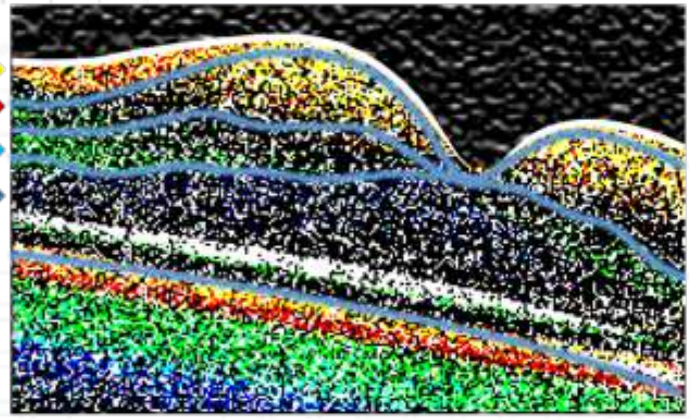
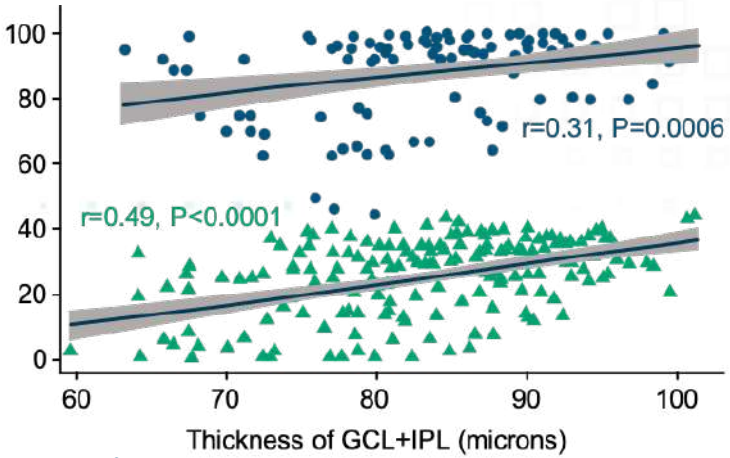


Photo courtesy of James Fujimoto, PhD





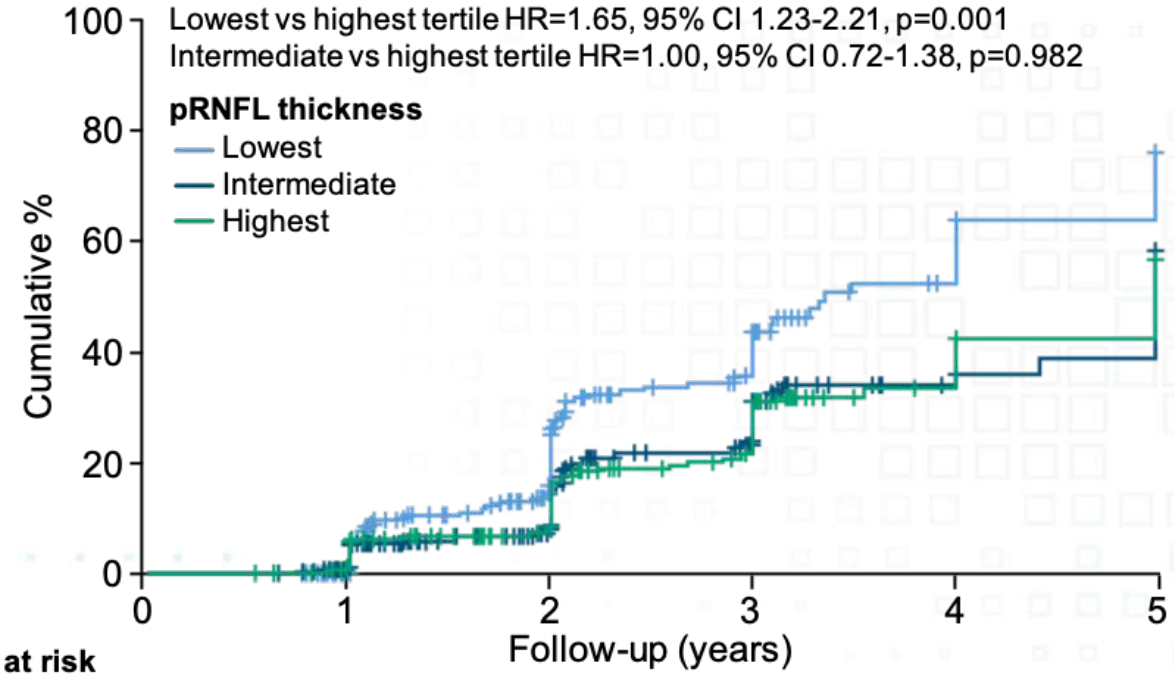
Adapted from Walter SD, et al. 2012.

- NEI-VFQ-25 Composite (best QOL = 100 points)
- Low-Contrast 2.5% (number of letters identified correctly)
- 95% Confidence Interval from SE of Predication for Fitted Line

GCL=ganglion cell layer; INL=inner nuclear layer; IPL=inner plexiform layer; NEI-VFQ=National Eye Institute Visual Functioning Questionnaire; OPL=outer plexiform layer; PRL=photoreceptor layer; QOL=quality of life

Walter SD, et al. Ophthalmology 2012;119:1250–7.

Retinal thickness is associated with worsening of MS



Number at risk

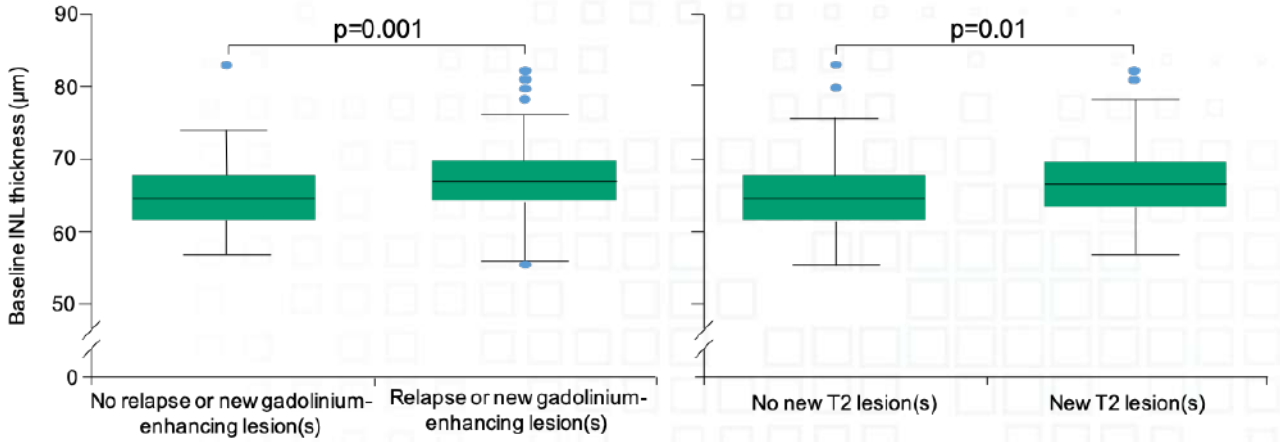
Lowest pRNFL	297	278	175	89	29	15
Intermediate pRNFL	290	268	179	96	35	22
Highes pRNFL	292	272	206	123	45	24

- Patients with a pRNFL of ≤87 µm (Spectralis) (lowest) or ≤88 µm (Cirrus) had double the risk of disability worsening at any time after the first and up to the 3rd year of follow up compared with thicker pRNFL thickness cohorts
- Risk increased almost four times after the 3rd year and up to the 5th year of follow up

pRNFL=peripapillary

Adapted from Martinez-Lapiscina EH, et al. Lancet Neurol. 2016;15:574–84.

Retinal inner nuclear layer (INL) thickening and future disease activity

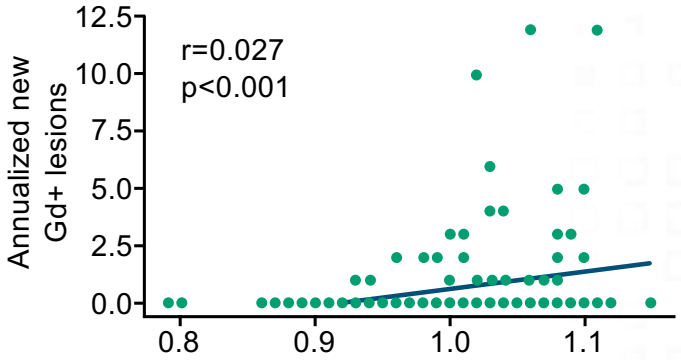


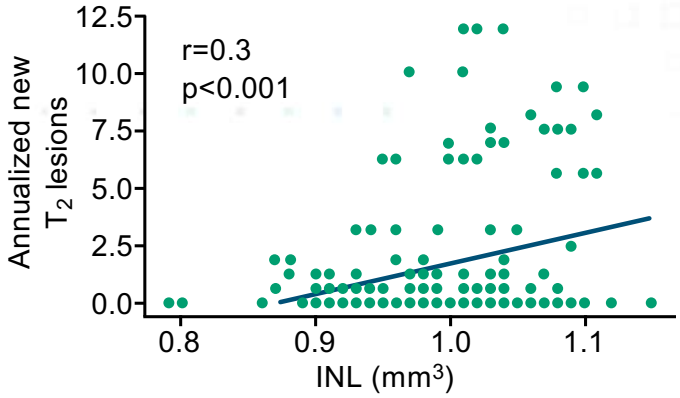
	Univariate model*				Multivariate model*†			
	Odds ratio per 5 µm increase in INL thickness in RRMS (95% CI)	p-value	Odds ratio per 5 µm increase in INL thickness in MS (95% CI)	p-value	Odds ratio per 5 µm increase in INL thickness in RRMS (95% CI)	p-value	Odds ratio per 5 µm increase in INL thickness in MS (95% CI)	p-value
Non-ocular relapse	1.76 (1.61–2.67)	0.008	..	..	1.77 (1.14–2.74)	0.010	..	..
EDSS progression‡§	1.48 (1.02–2.15)	0.039	1.41 (1.03–1.95)	0.034	1.49 (1.01–2.21)	0.047	1.40 (1.001–1.94)	0.049
New gadolinium-enhancing lesion¶	1.90 (1.24–2.90)	0.003	1.70 (1.16–2.50)	0.007	1.98 (1.29–3.03)	0.002	1.71 (1.16–2.52)	0.007
New T2 lesion¶	1.59 (1.08–2.34)	0.020	1.51 (1.08–2.09)	0.015	1.56 (1.03–2.37)	0.035	1.46 (1.05–2.02)	0.025
Relapse or new gadolinium-enhancing lesion¶	1.92 (1.27–2.90)	0.002	..	..	1.95 (1.27–2.99)	0.002	..	..

INL=inner nuclear layer. RRMS=relapsing remitting multiple sclerosis. EDSS=expanded disability status scale. *Adjusted for within-subject inter eye correlation. †Additionally adjusted for age, sex, disease duration, and history of optic neuritis. ‡EDSS progression defined as a ≥1 point increase if baselines EDSS <6.0 and a ≥0.5 point increase if baseline EDSS ≥6.0. §Available for 118 patients with RRMS, 25 SPMS and 14 PPMS. ¶Available for 120 patients with RRMS, 24 with SPMS, and 14 with PPMS

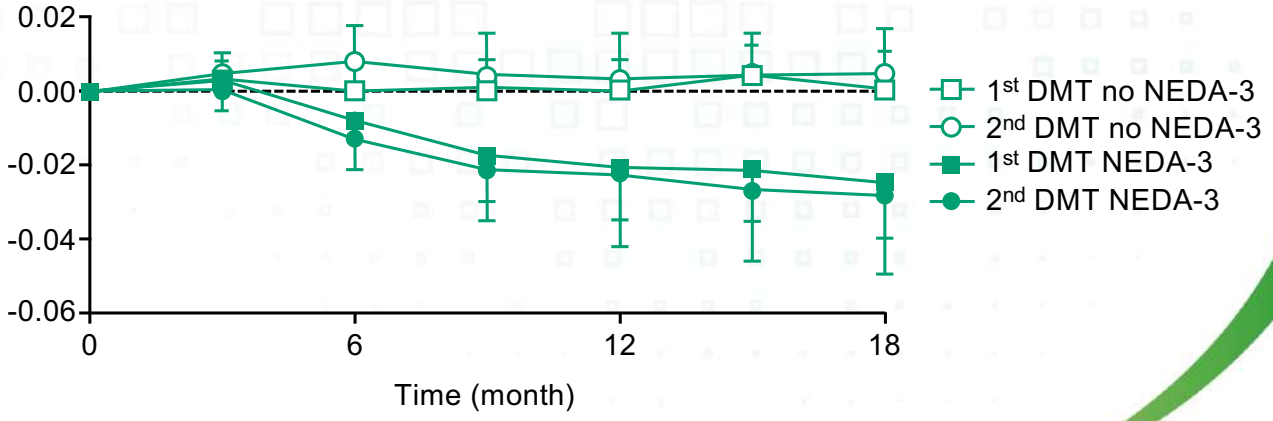
Saidha et al. Lancet Neurol 2012

Macular INL thickening and treatment response





	Increase in T_2 lesions		Increase in Gd+ lesions		Relapse		NEDA-3	
	Odds ratio for a 1% rise of layer reduction (95% CI)	p-value	Odds ratio for a 1% rise of layer reduction (95% CI)	p-value	Odds ratio for a 1% rise of layer reduction (95% CI)	p-value	Odds ratio for a 1% rise of layer reduction (95% CI)	p-value
TMV	1.74 (1.01; 2.99)	0.044	3.29 (1.30; 8.30)	0.011	1.37 (0.66; 2.84)	0.40	0.73 (0.44; 1.20)	0.22
INL	0.58 (0.43; 0.79)	0.0004	0.81 (0.56; 1.15)	0.23	0.65 (0.45; 0.95)	0.027	1.79 (1.33; 2.42)	0.0001

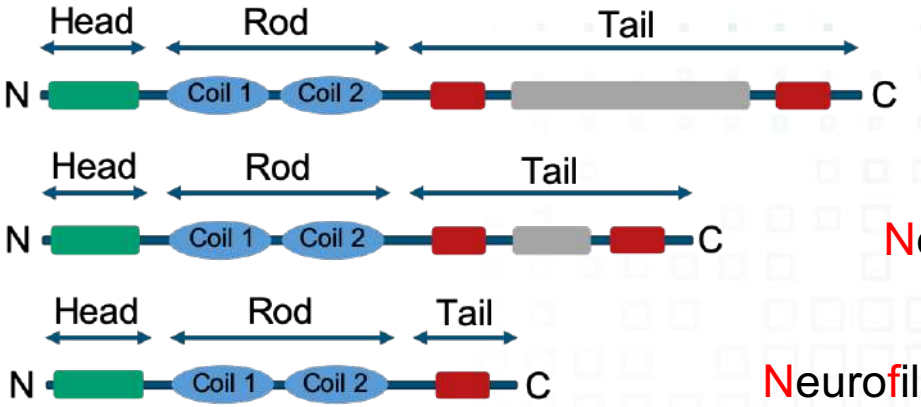


Knier et al. Brain, 2016

Promising inflammatory biomarkers in MS

Biomarker	Biomarker type	Findings in MS
IgG oligoclonal bands	Diagnostic	Implemented in clinical practice for diagnostic support of MS and high predictive value for identification of CIS converters. IgG OCBs in CSF are present in over 95% of MS patients
IgM oligoclonal bands	Diagnostic and disease activity	IgM antibodies are involved in the intrathecal B-cell response in patients with MS. The presence of IgM OCB increases the risk of conversion from CIS to CDMS and is associated with aggressive disease courses
Kappa free light chains	Diagnostic	Excess kappa light chains are secreted as free light chains and can be detected in CSF and serum. Elevated CSF levels of kFLC in MS patients support their role in disease diagnosis
Chemokine ligand 13	Disease activity	Involved in B-cell migration to the CNS during inflammation. Levels are raised in MS patients with an active course of the disease
Matrix metalloproteinase-9	Disease activity	MMP-9 is involved in leukocyte trafficking to the CNS, myelin breakdown, release of pro-inflammatory cytokines and axonal damage. MMP-9 concentrations are increased in MS patients during relapses and are linked to clinical and radiological disease activity
Osteopontin	Disease activity	Protein with pleiotropic roles and involved in the development and progression of several autoimmune diseases. OPN levels are elevated in RRMS patients during relapses. There are controversial data regarding its role as a prognostic biomarker of disease severity
Soluble CD27	Disease activity	T cells activated by the T-cell receptor / CD3 complex release a soluble form of CD27 (sCD27). High sCD27 levels were associated with shorter time to MS
Chitinase 3-like 1	Diagnostic and prognostic	Elevated levels in CIS patients correlate with shorter time to conversion to CDMS and disability progression, supporting a role in the identification of CIS converters

Neurofilaments



Neurofilament Heavy (NfH): 190–210 kDa

Neurofilament Medium (NfM): 150 kDa

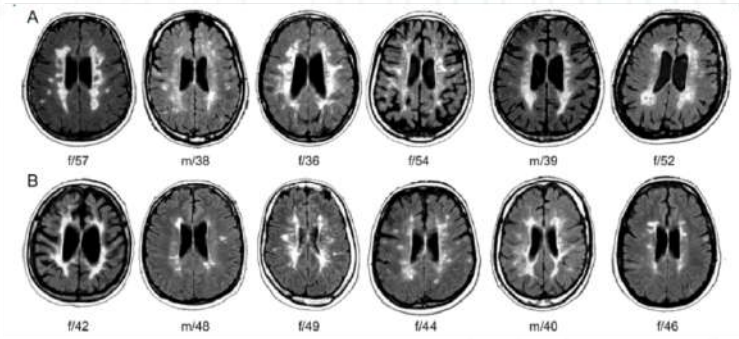
Neurofilament Light (NfL): 68 kDa[1]

- Highly specific neuronal proteins, very stable in vitro[2]
- Important structural and functional proteins (85% of the cytoskeleton proteins), determine axon diameter[3–5]
- NfL in CSF reflects axonal damage (MS[6], AD[7], ALS[8], PD[9] and trauma[10])
- NfL in blood was below assay detection limits for a long time as levels are 50–100 fold lower than CSF levels

1. Teunissen CE, et al. MSJ. 2012;18:552–56; 2. Gaiottino J, et al. Plos One 2013;8:e75091; 3. Fuchs E, et al. Science 1998;279:514–9; 4. Morris JR, et al. J Cell Biol. 1982;92:192–8; 5. Yuan A, et al. Mol Psychiatry 2015;20:986–94; 6. Kuhle J, et al. MSJ. 2016;1–10; 7. Zetterberg H, et al. JAMA Neurol. 2016;73:60–7; 8. Weydt P, et al. Ann Neurol. 2016;79:152–58 9. Bacioglu M, et al. Neuron 2016;91:56–6; 10. Bergman J, et al. Neurol Neuroimmunol Neuroinflamm. 2016;3:e271.

Significant challenges in treating MS, despite successes in suppressing relapse activity

- Halting progression
- 'measuring MS': prediction, monitoring



'Benign MS'

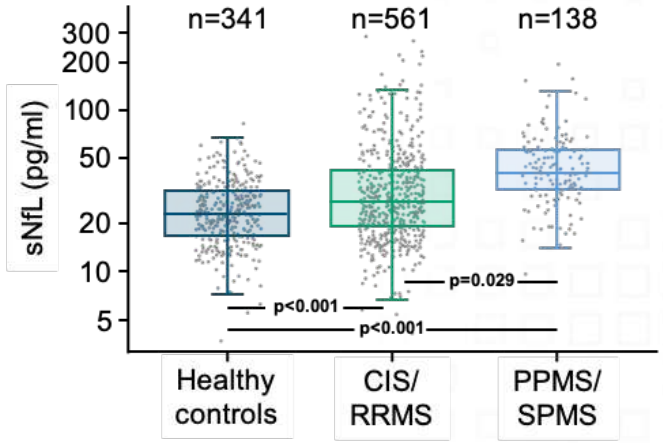
SPMS

Strasser-Fuchs, et al. Mult Scler. 2008;14:205–11

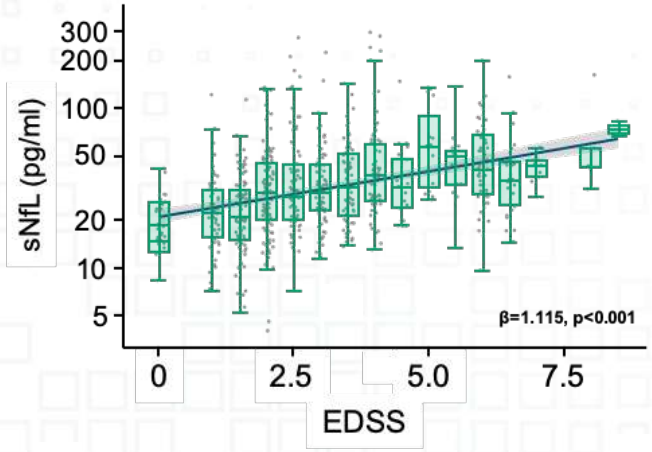
What is the current evidence for NfL to monitor MS?

1. Blood NfL as a measure of current disease activity
2. Blood NfL as a measure of treatment response
3. Blood NfL as a prognostic marker for disease course

Multivariable model predicting serum NfL



- Patients had higher sNfL than HC



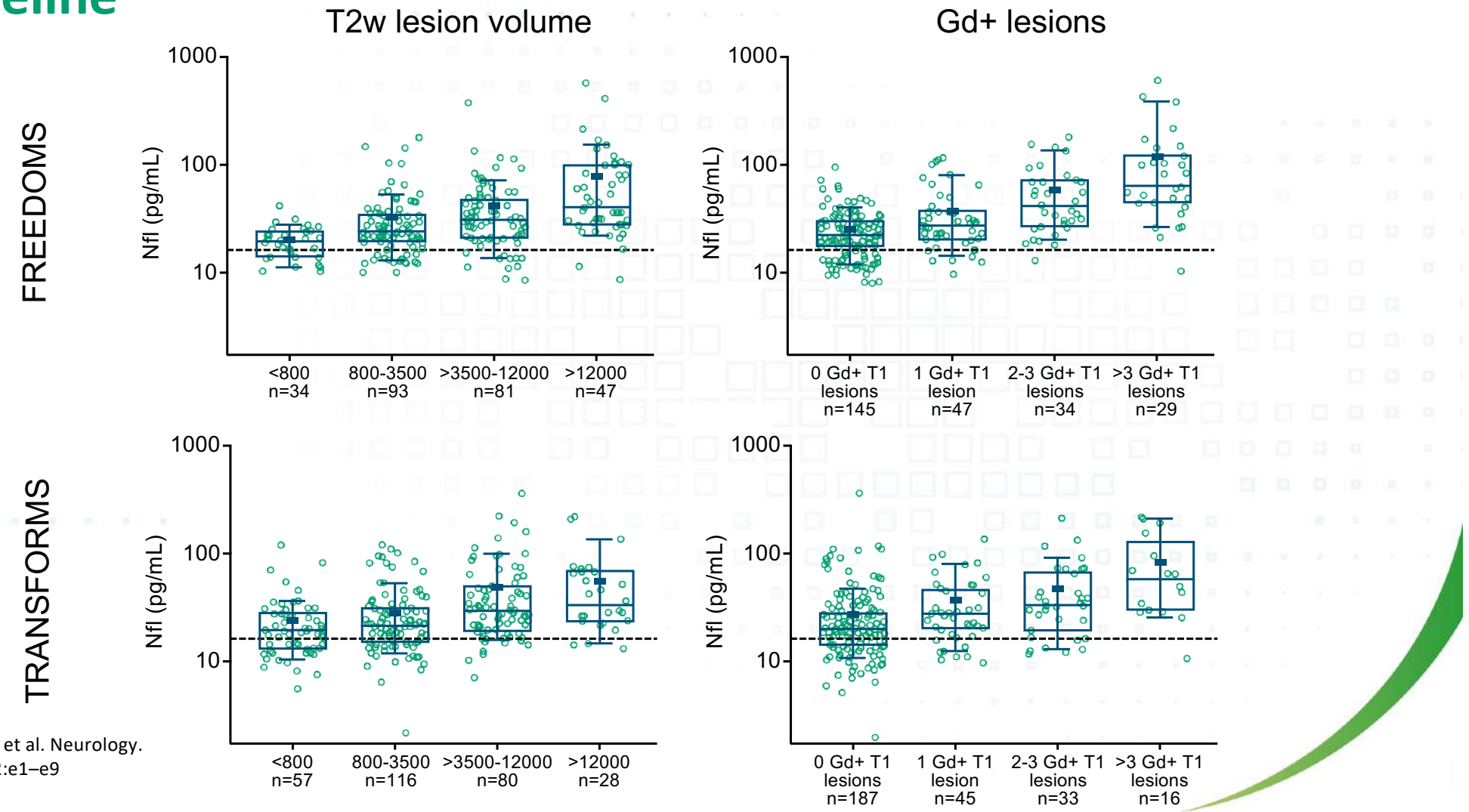
- sNfL was positively associated with EDSS

Predictor	Samples (n)	NfL_{se} (pg/ml)	Multivariable		
			β	95% CI	p
Age	719		1.012	1.005–1.019	**<0.001**
Gender	F: 474 vs. M: 245	29.1 30.9	0.991	0.858–1.145	0.905
EDSS	719		1.105	1.063–1.149	**<0.001**
Disease course	CIS/RRMS: 581 vs. PPMS/SPMS: 138	27.2 41.4	0.924	0.742–1.151	0.483
Relapse (<60 d)	No: 643 vs. Yes: 76	28.9 39.3	1.430	1.156–1.768	**<0.001**
Recent EDSS worsening	No: 615 Yes: 51	29.0 38.5	1.119	0.962–1.303	0.146
DMT	Untreated: 162 DMT treated: 557	38.0 27.0	0.818	0.716–0.934	**0.003**

Disanto G, et al. Ann Neurol, 2017;81:857–70.

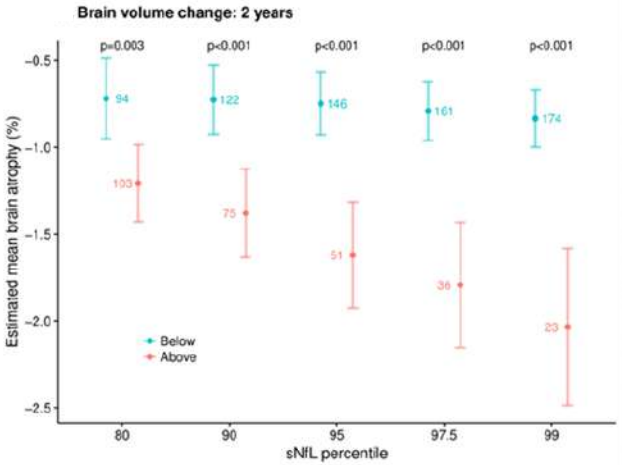
SMSC Swiss MS Cohort

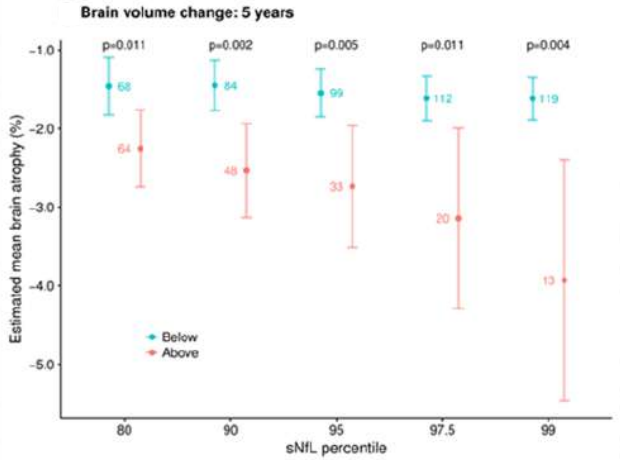
Plasma NfL correlates with T2 lesion volume/Gd+ at baseline



Kuhle J, et al. Neurology. 2019;92:e1–e9

Baseline serum NfL as predictor of % brain volume change over 2 and 5 years



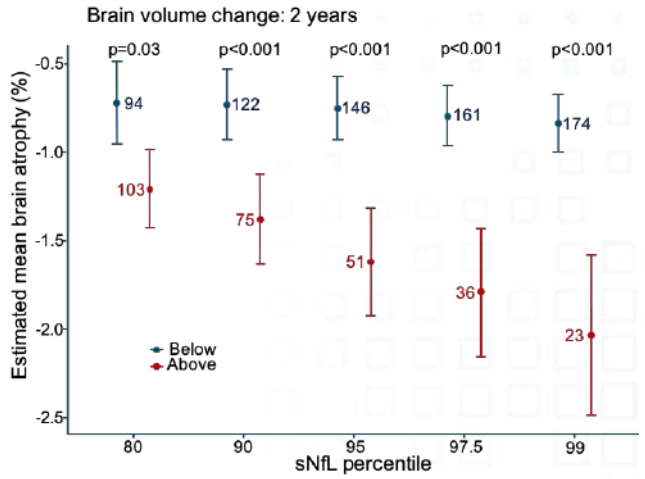


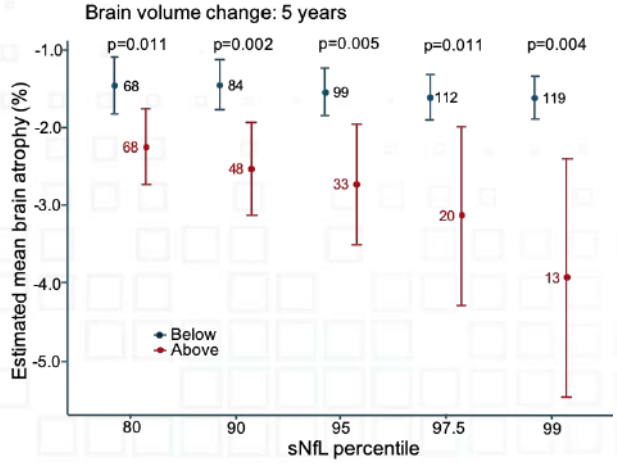
Baseline variables (197 observations)	Multivariable		
	β_{add}	95%CI	*p*
sNfL (per 10 pg/ml)	-0.134	-0.194–-0.073	<0.001
EDSS	-0.151	-0.271–-0.031	0.014

Baseline variables (132 observations)		Multivariable		
		β_{add}	95%CI	*p*
sNfL (per 10 pg/ml)		-0.287	-0.432--0.142	<0.001
Age (years)		0.008	-0.025-0.040	0.642
Sex	F (170)	-	-	-
	M (83)	-0.229	-0.845-0.387	0.463
EDSS		-0.294	-0.545--0.042	0.023
Disease course	RMS (196)	-	-	-
	PMS (57)	0.118	-0.734-0.971	0.784
T2 lesion vol. (per cm^3)		-0.028	-0.081-0.025	0.294
CEL		-0.055	-0.328-0.219	0.693
nBV (per 100 cm^3)		0.167	-0.235-0.570	0.412

Barro C, et al. Brain 2018;141:2382–91

Baseline serum NfL as predictor of % brain volume change over 2 and 5 years





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Baseline variables (132 observations)		Multivariable		
		β_{add}	95%CI	*p*
sNfL (per 10 pg/ml)		-0.287	-0.432 to -0.142	<0.001
Age (years)		0.008	-0.025 to 0.040	0.642
Sex	F (87)	-	-	-
	M (45)	-0.229	-0.845 to 0.387	0.463
EDSS		-0.294	-0.545 to -0.042	0.023
Disease course	RMS (97)	-	-	-
	PMS (35)	0.118	-0.734 to 0.971	0.784
T2 lesion vol. (per cm^3)		-0.028	-0.081 to 0.025	0.294
CEL		-0.055	-0.328 to 0.219	0.693
nBV (per 100 cm^3)		0.167	-0.235 to 0.570	0.412

Barro C, et al. Brain 2018;141:2382–91

Closing remarks

Prof. Sven Schippling

Closing remarks

- Requirements of a good biomarker include: specificity, sensitivity and practicality
- Existing biomarkers have a variety of limitations with regard to driving optimal treatment of patients with MS
- Novel biomarkers, such as optical coherence tomography and neurofilament light chain represent potential technologies for monitoring:
  - Disease activity
  - Treatment response
  - Disease course

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Thank you!