How to obtain brain MRI in monitoring of MS?

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Hannover Medical School

Magnims
Magnetic Resonance Imaging in Multiple Sclerosis

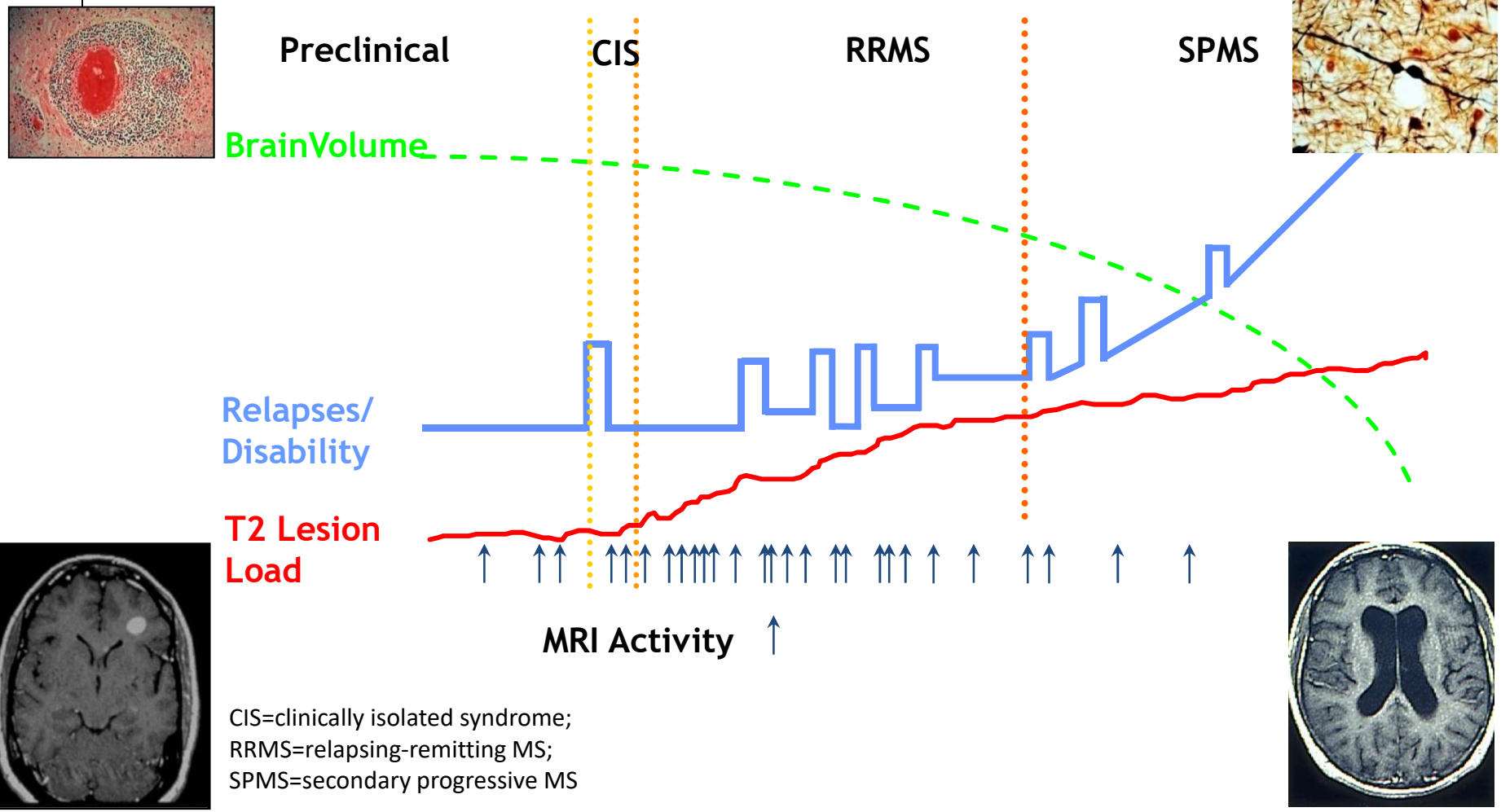
Disclosures

- Speaker honoraria:
  Janssen, Bayer Healthcare, Novartis, Biogen, Biologix, Springer Healthcare, Sanofi-Genzyme, Celgene, Roche, Genilac, Merck-Serono, Almirall
- Consultancy honoraria:
  Janssen, Roche, Novartis, Biogen, Merck-Serono
- Editorial board:
  European Radiology, Neuroradiology, Journal of Neuroimaging, Frontiers in Neurology

Content

- **Introduction**
- **Brain MRI for MS treatment efficacy monitoring**
  - Standardized MR acquisition protocol
  - Imaging outcome measures
- **Brain MRI for MS prognosis**
  - Baseline MR findings to predict MS disease course
- **Brain MRI for MS safety monitoring**
  - Standardized MR acquisition protocol
  - Risk-adapted MRI based pharmacovigilance
- **Conclusions**

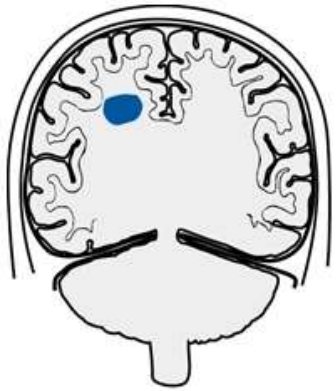
Introduction: MS disease course



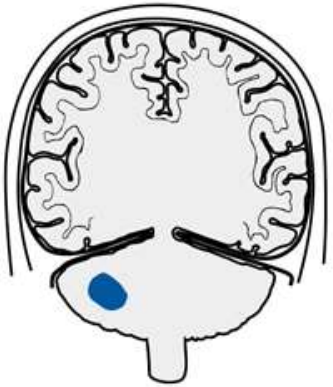
CIS=clinically isolated syndrome;
RRMS=relapsing-remitting MS;
SPMS=secondary progressive MS

Noseworthy JH et al. *N Engl J Med.* 2000;343:938-952;
Weinshenker BG et al. *Brain.* 1989;112:133-146;
Trapp BD et al. *Curr Opin Neurol.* 1999;12:295-302.

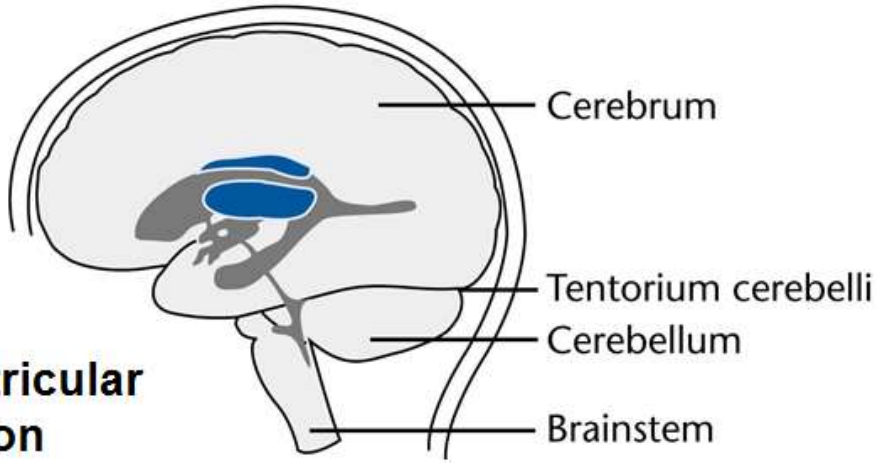
MS pathology: lesion distribution



Juxtacortical lesion

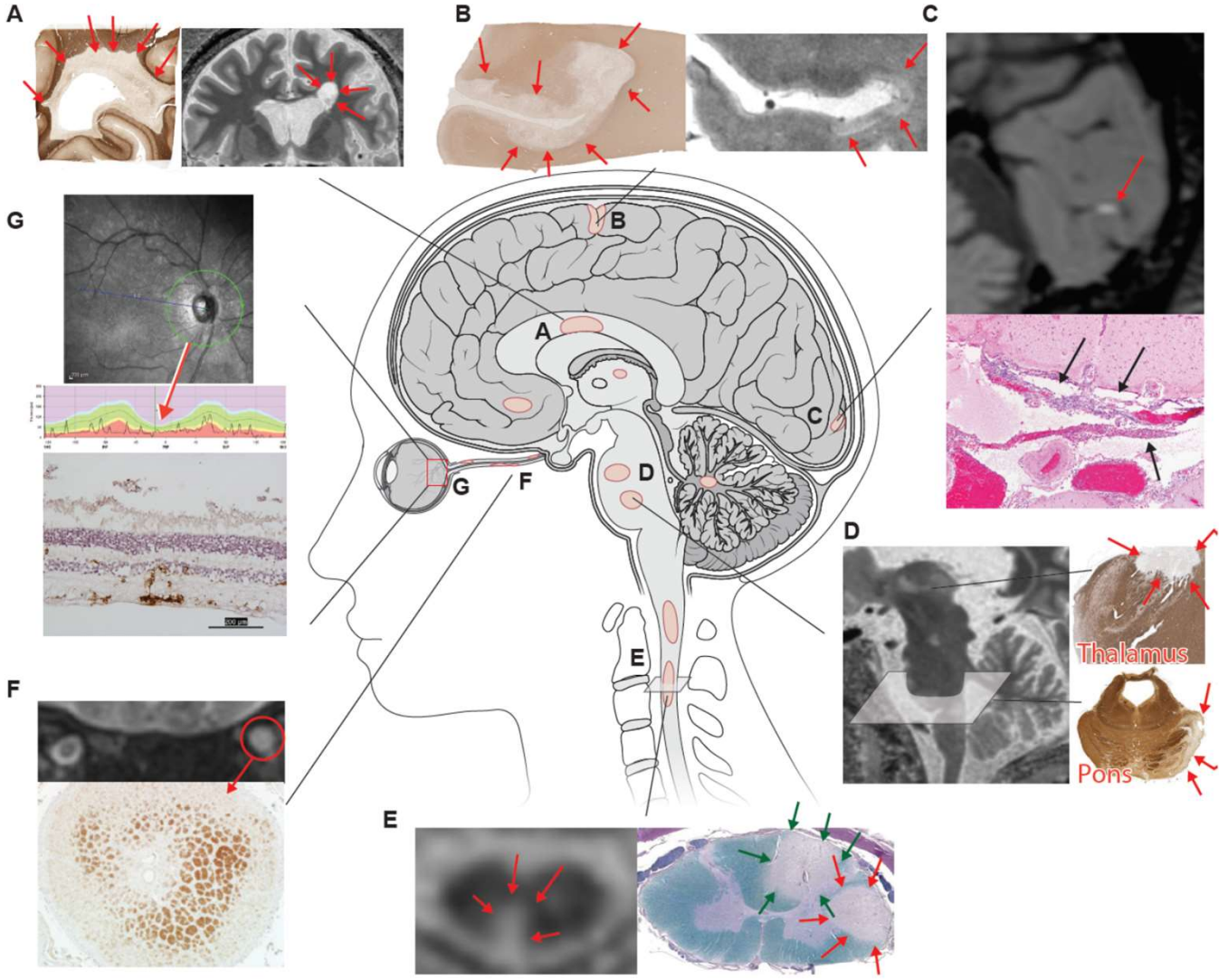


Infratentorial lesion



Periventricular lesion

Multiple Sclerosis: lesion distribution



Reich DS et al. *N Engl J Med* 2018;378:169-180

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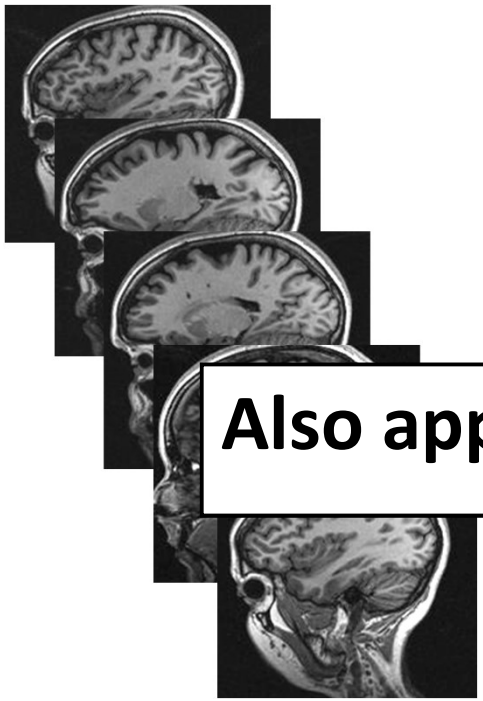
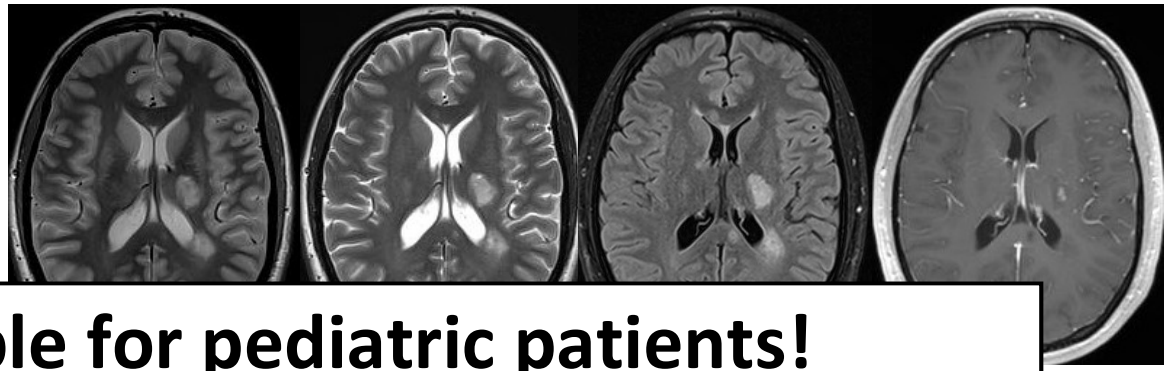
Standardized brain MRI protocol: diagnosis





Also applicable for pediatric patients!

delay ≥ 5 minutes

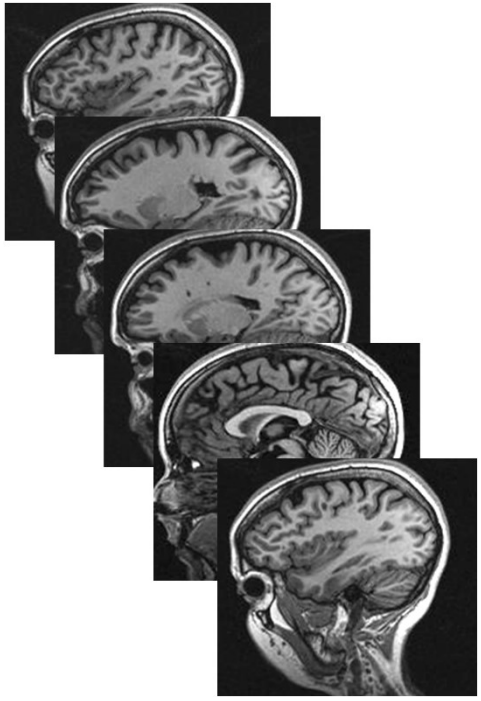
Magnetic field strength: 3T (not mandatory)
Spatial resolution:
2D: 3 mm slice thickness (no gap), in-plane 1x1 mm
3D: isotropic voxelsize 1x1x1 mm

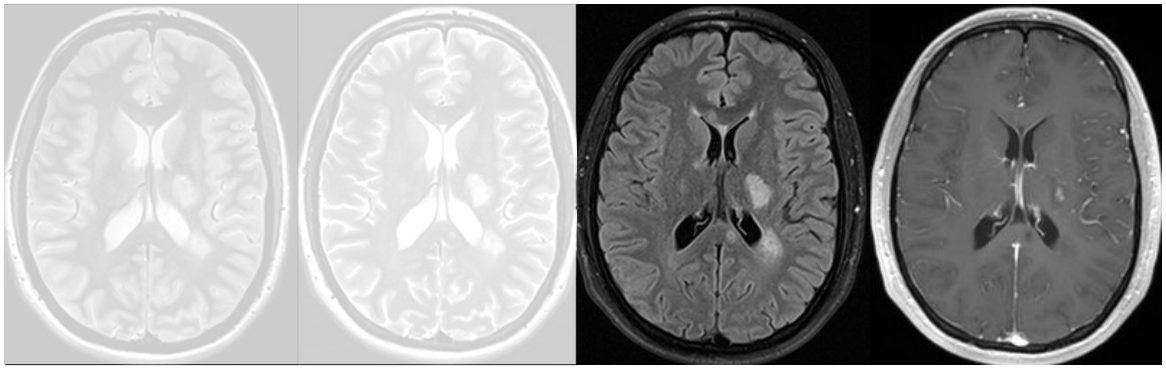
* 2D oder 3D image acquisition

Rovira A et al. *Nat Rev Neurol* 2015;11:471-82
Wattjes MP et al. Nat Rev Neurol 2015; 11: 597-606

PD=Proton density, FLAIR=Fluid attenuated inversion recovery, Gad=Gadolinium, BW=body weight, T=Tesla

Standardized brain MRI protocol: monitoring





0.1 mmol/kg BW Gadolinium (macrocyclic)

delay ≥ 5 minutes

Magnetic field strength: 3T (not mandatory)
Spatial resolution:
2D: 3 mm slice thickness (no gap), in-plane 1x1 mm
3D: isotropic voxelsize 1x1x1 mm

* 2D oder 3D image acquisition

Rovira A et al. *Nat Rev Neurol* 2015;11:471-82
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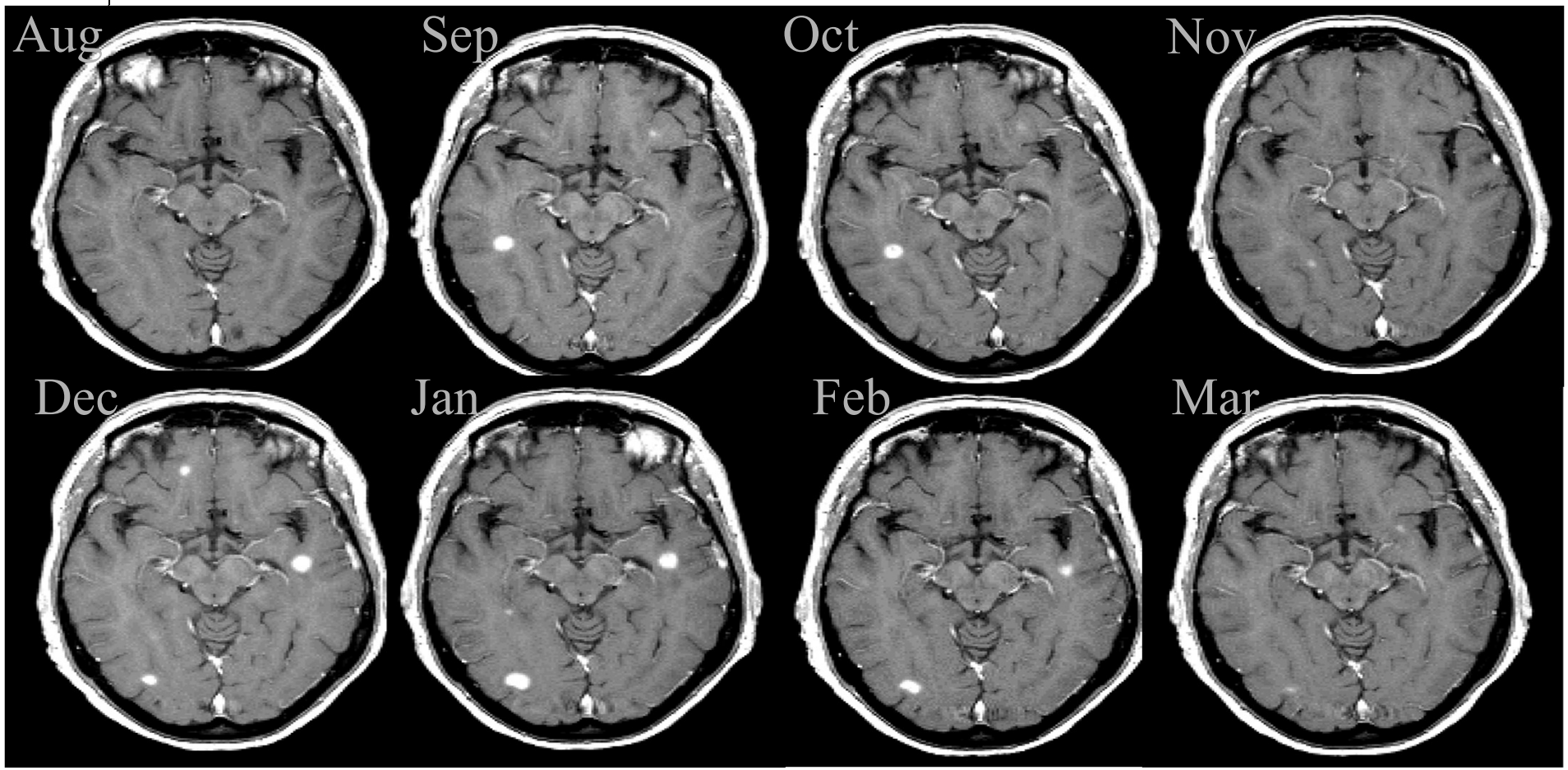
PD=Proton density, FLAIR=Fluid attenuated inversion recovery, Gad=Gadolinium, BW=body weight, T=Tesla

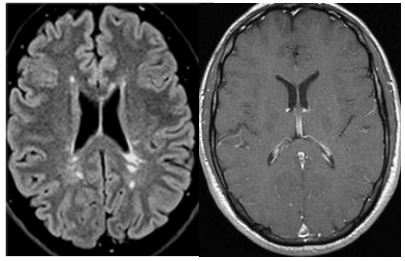
Subclincial Gd-enhancing lesions



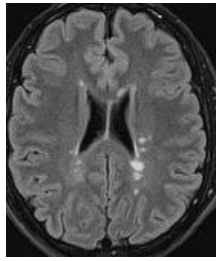
Images courtesy of VU MC Amsterdam

MRI in monitoring MS: revised MAGNIMS guidelines

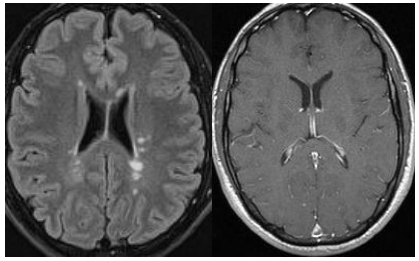
Initial	Re-Baseline	First-follow-up[a,b]	Second follow-up[a, b]	Follow-ups[a, b]
Diagnostic[c] Pre-treatment **Gad** **highly recommended**	3-6 months after treatment onset **Gad optional [e]**	12 months after Re-Baseline **Gad optional [f]**	24 months after Re-Baseline **Gad optional**	Every year[d] **Gad optional[e]**

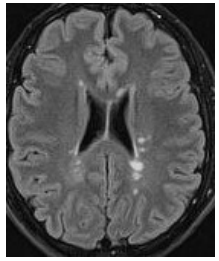


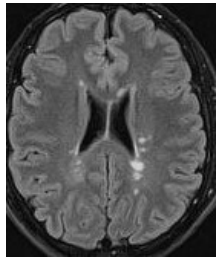
Assess markers of poor prognosis



Active lesions should be ignored (unless associated with clinical activity or unexpected high MRI activity)





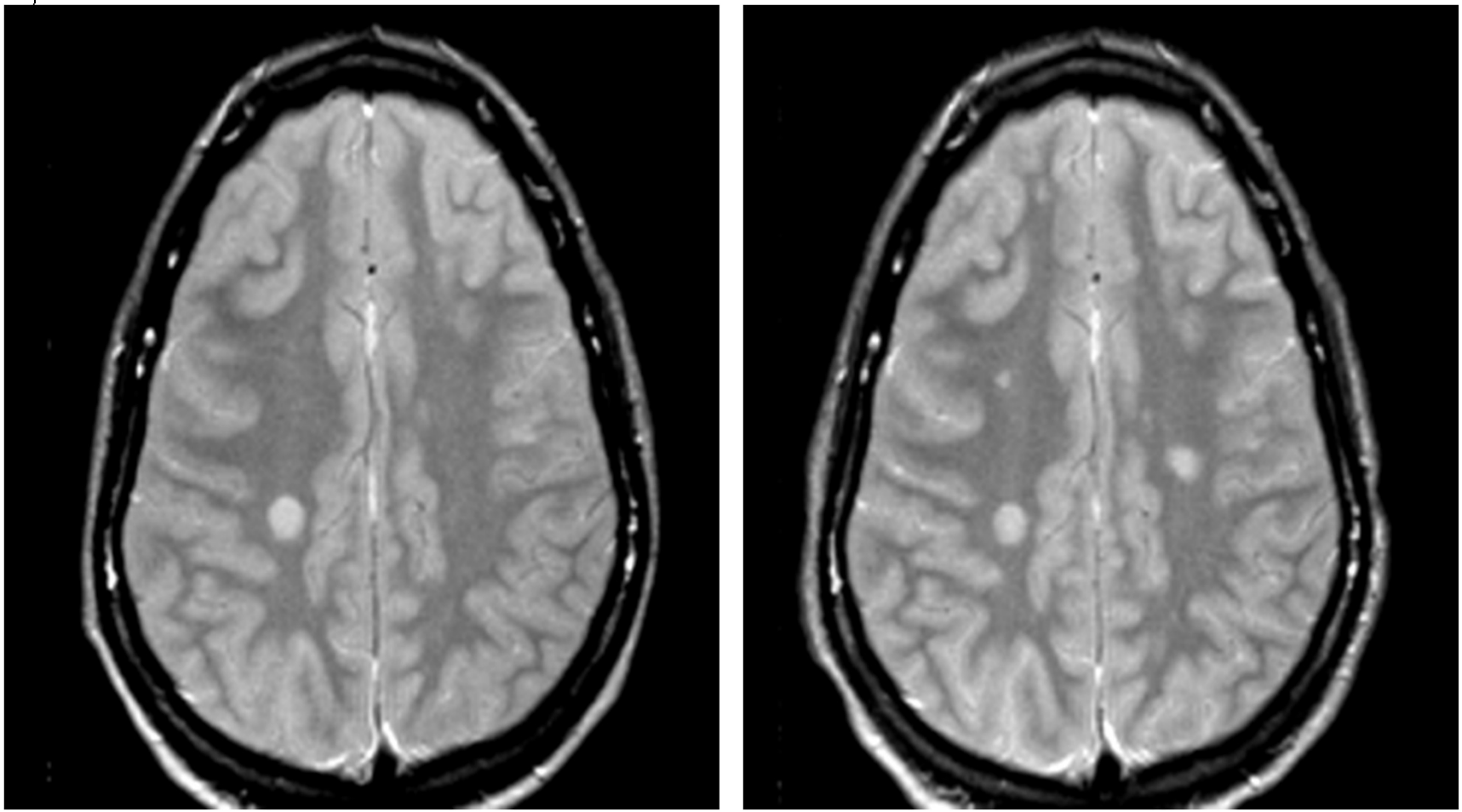


Apply predictive response / prognostic scales /models

[a] Shorter follow-up MRI (6 months) if isolated significantly MRI activity or isolated clinical activity
[b] Add spinal cord MRI to brain MRI if clinically indicated
[C] Add spinal cord MRI to brain MRI for initial diagnosis or if never performed
[d] Less frequent MRIs in clinically stable patients treated with INF or GA
[e] Gad required if clinical activity / progression
[f] Particulary in patients receiving moderate efficacy DMTs

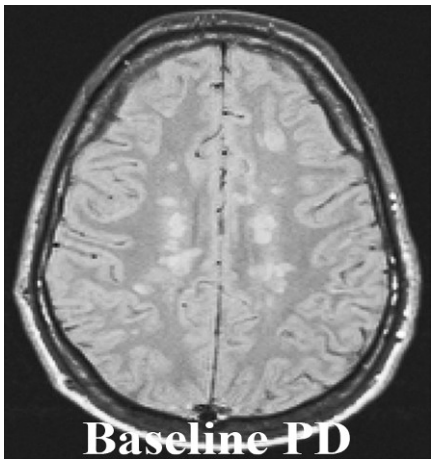
Magnims
Magnetic Resonance Imaging in Multiple Sclerosis

Active T2 lesions

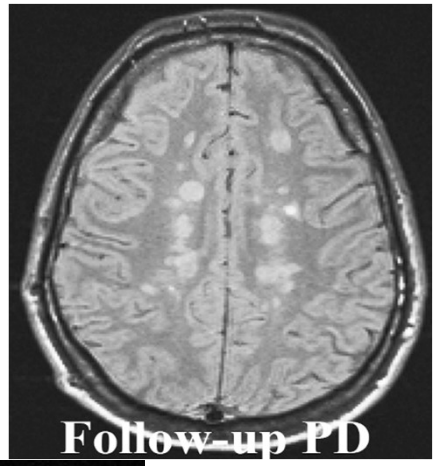


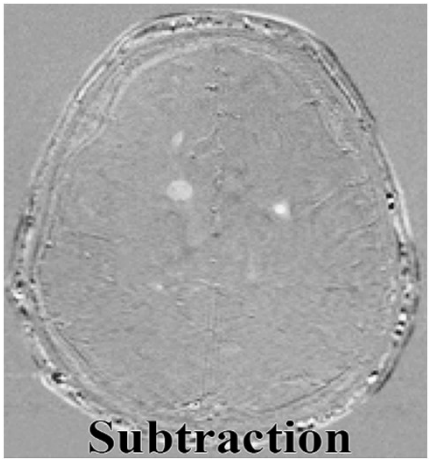
Images courtesy of VU MC Amsterdam

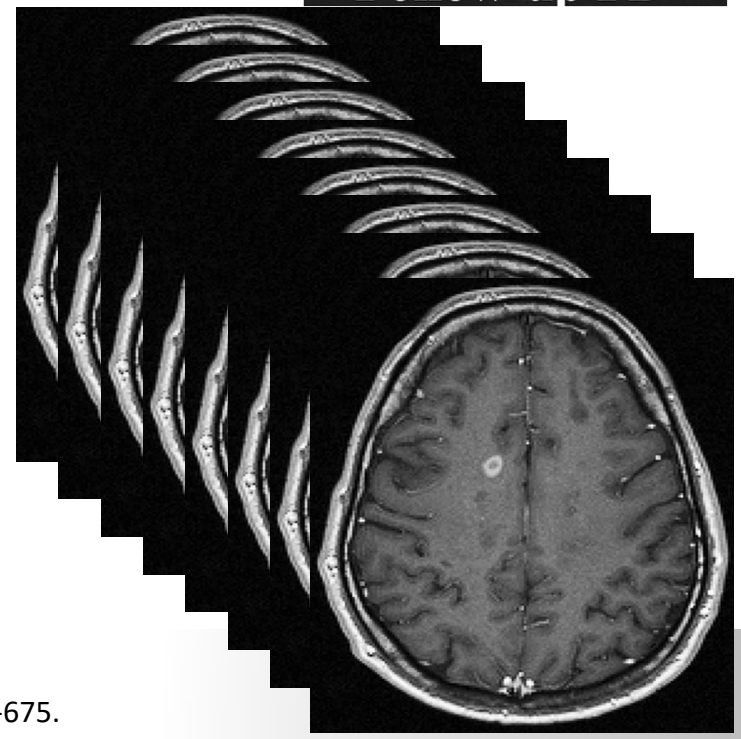
Active T2 lesions: MR subtraction



9 months

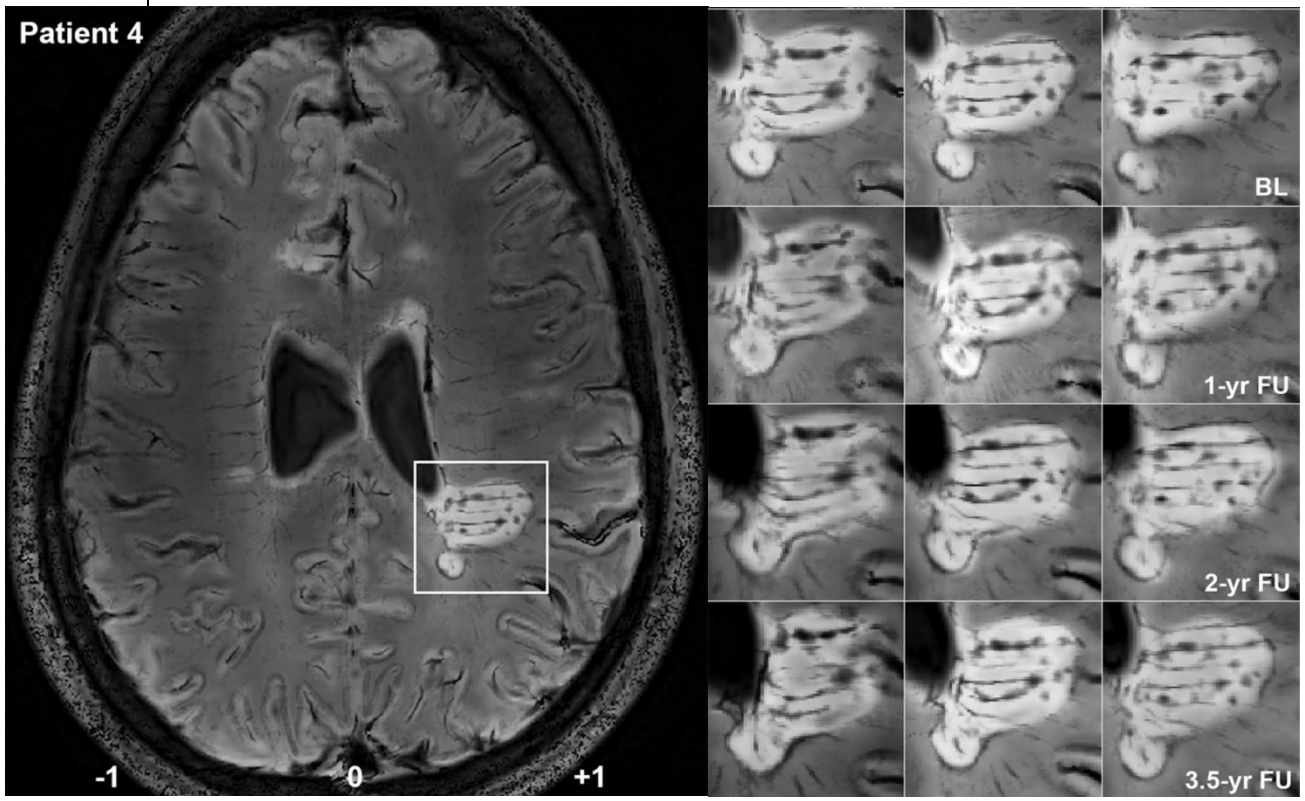


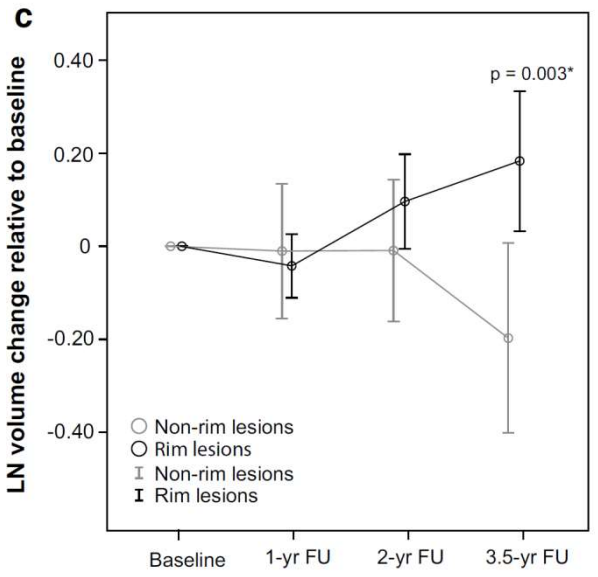




Moraal B et al. *Ann Neurol.* 2010;67:667-675.

Smoldering MS lesions





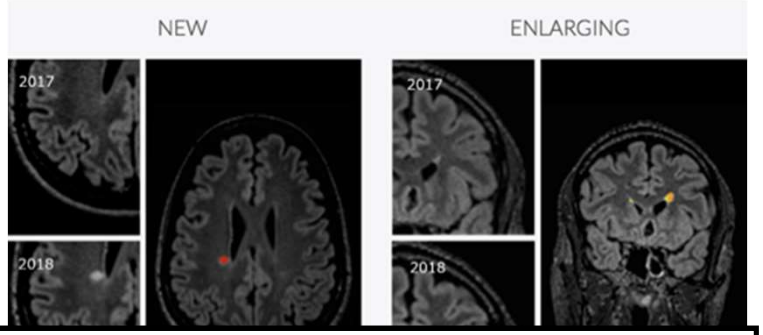
→ Susceptibility weighted imaging (SWI) for the detection of smoldering lesions in progressive MS

Dal-Bianco A et al. *Acta Neuropathol* 2017;133:25-42

Automated segmentation tools

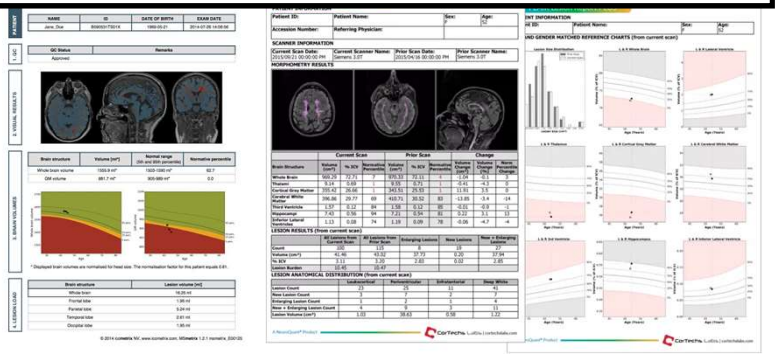
Commercial quantification packages

- Icobrain MS – icometrix
- Lesion Quant – Neuroquant

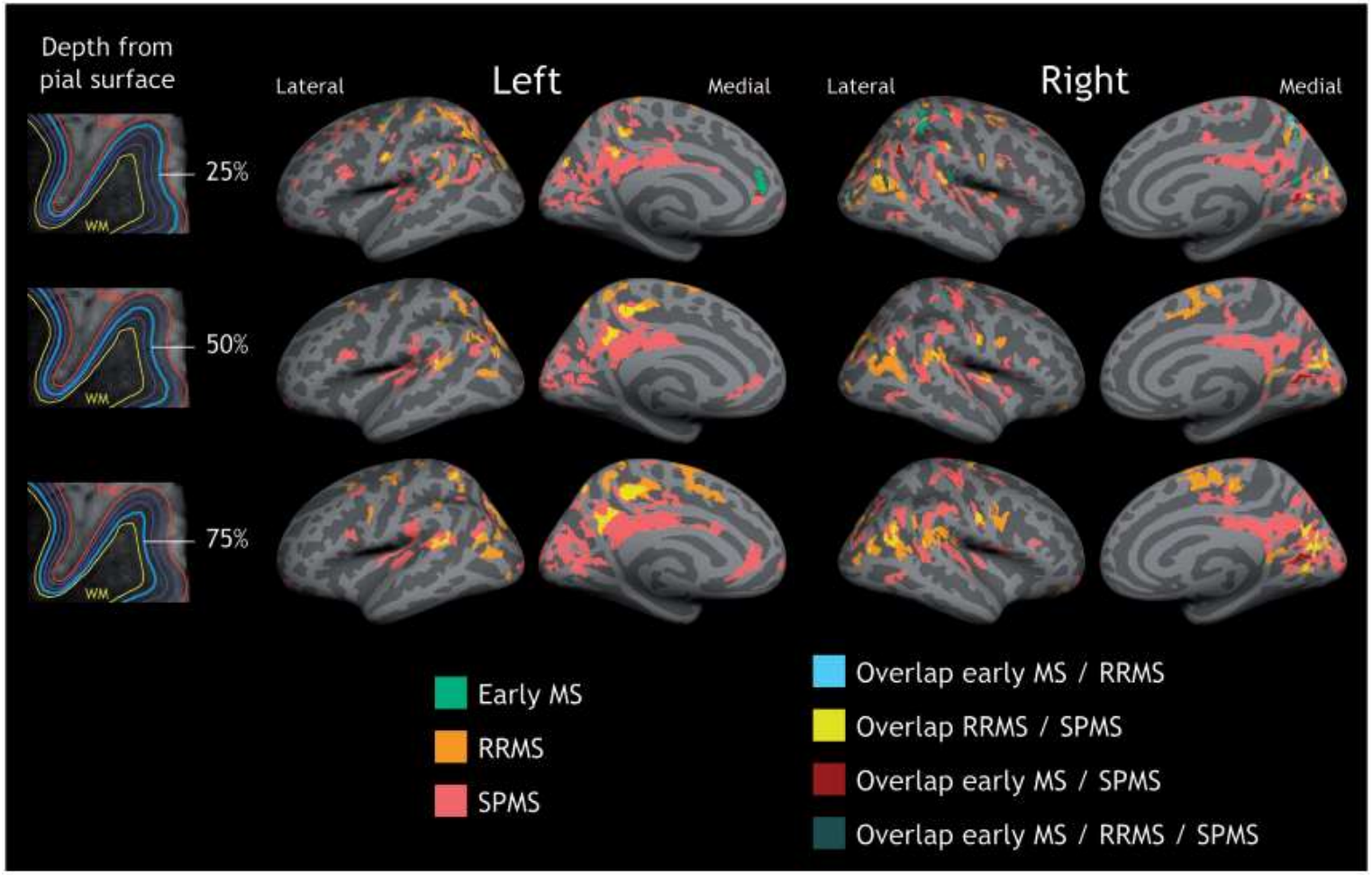


Not recommended for clinical routine use!

- Olea – subtraction module

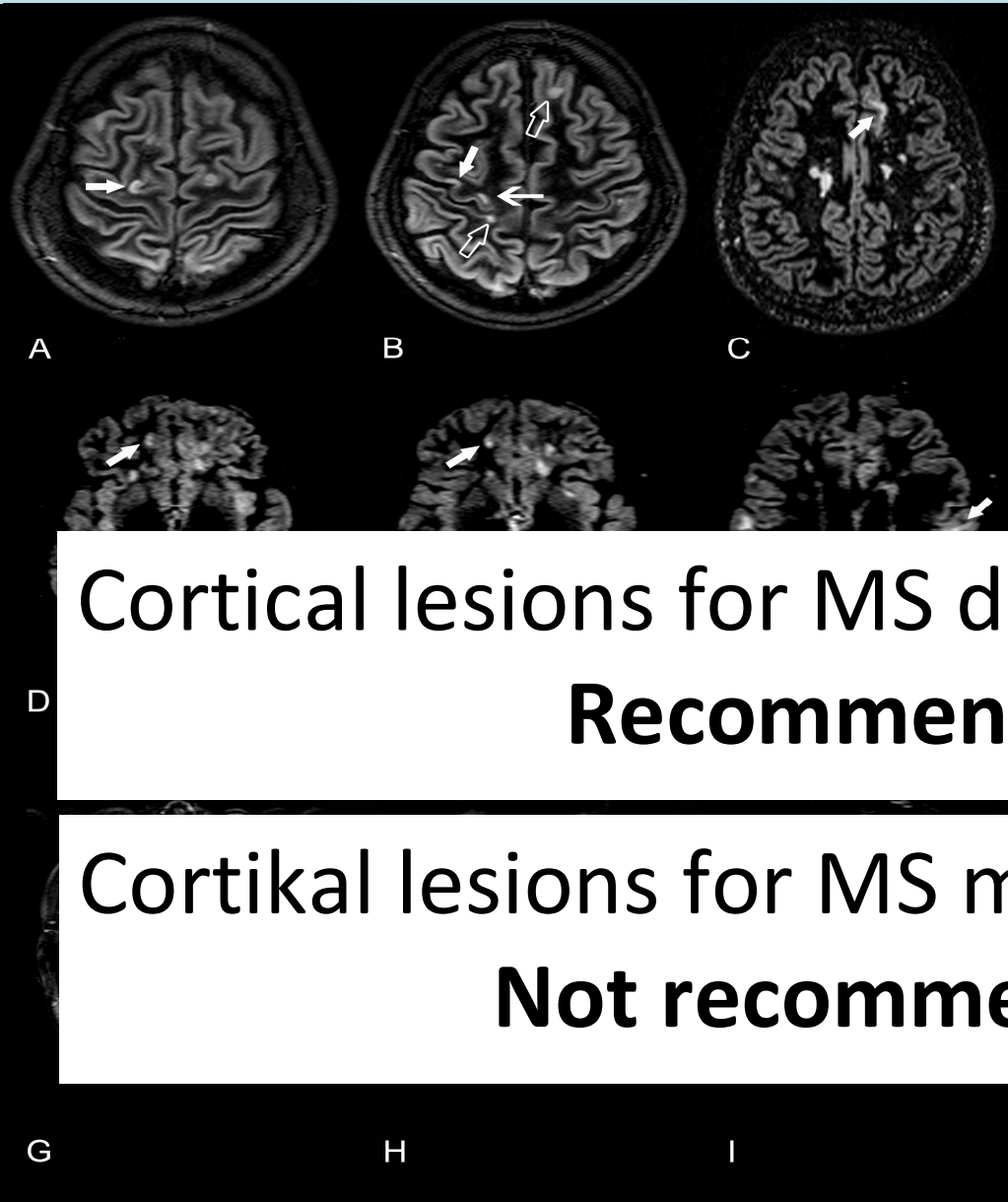


Grey matter demyelinisation in MS



Maneiro C et al. *Brain* 2015;138:932-45.

DIR image analysis consensus meeting



Scoring guidelines

'obligatory criteria'

- **size of lesion (at least 3 pixels)**
- **(hyper)intensity vs. surrounding GM**

'supportive guidelines'

Cortical lesions for MS diagnosis:

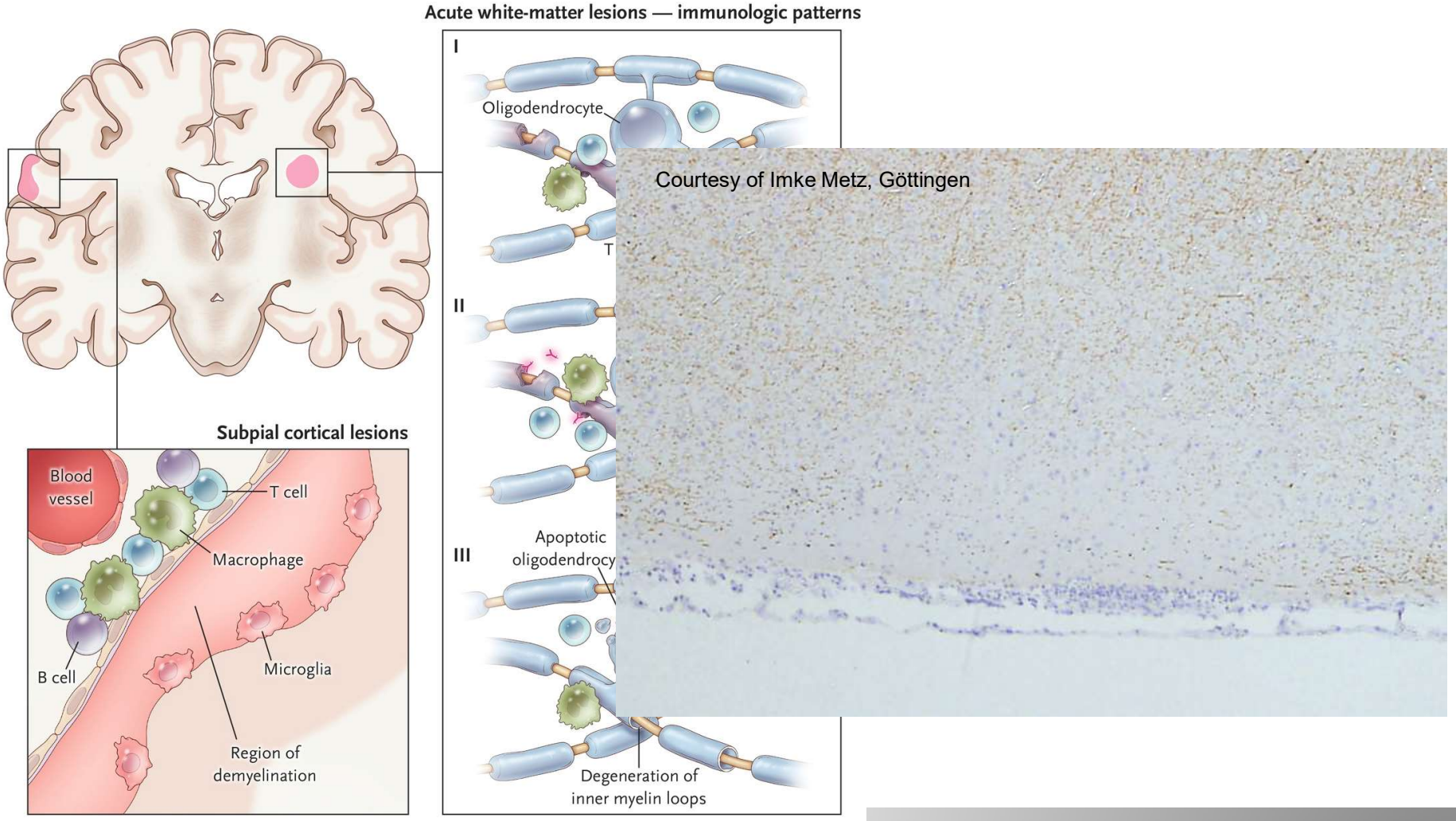
Recommended!

Cortikal lesions for MS monitoring:

Not recommended!

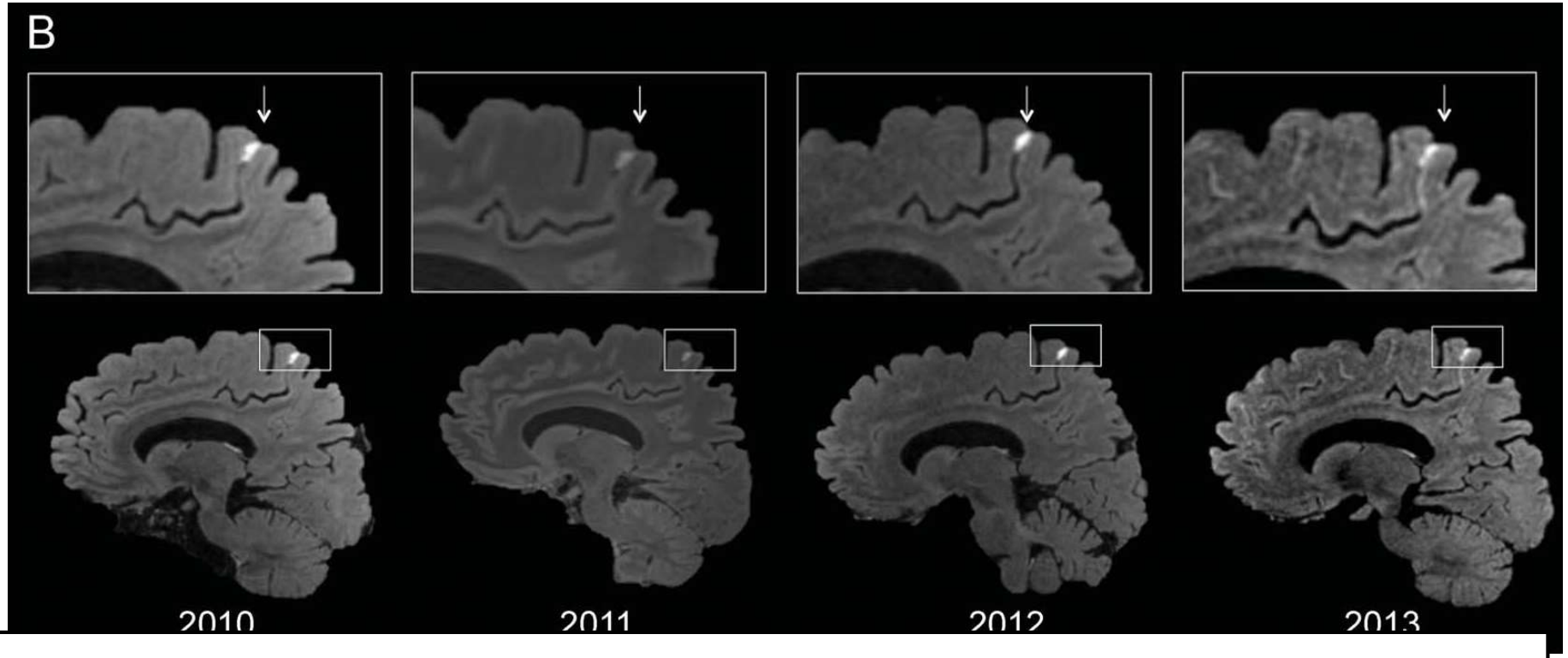
Geurts JJG et al. *Neurology* 2011 ;76:418-24

MS: cortical/leptomenigeal lesions



Reich DS et al. *N Engl J Med* 2018;378:169-180

MS: leptomeningeal enhancement

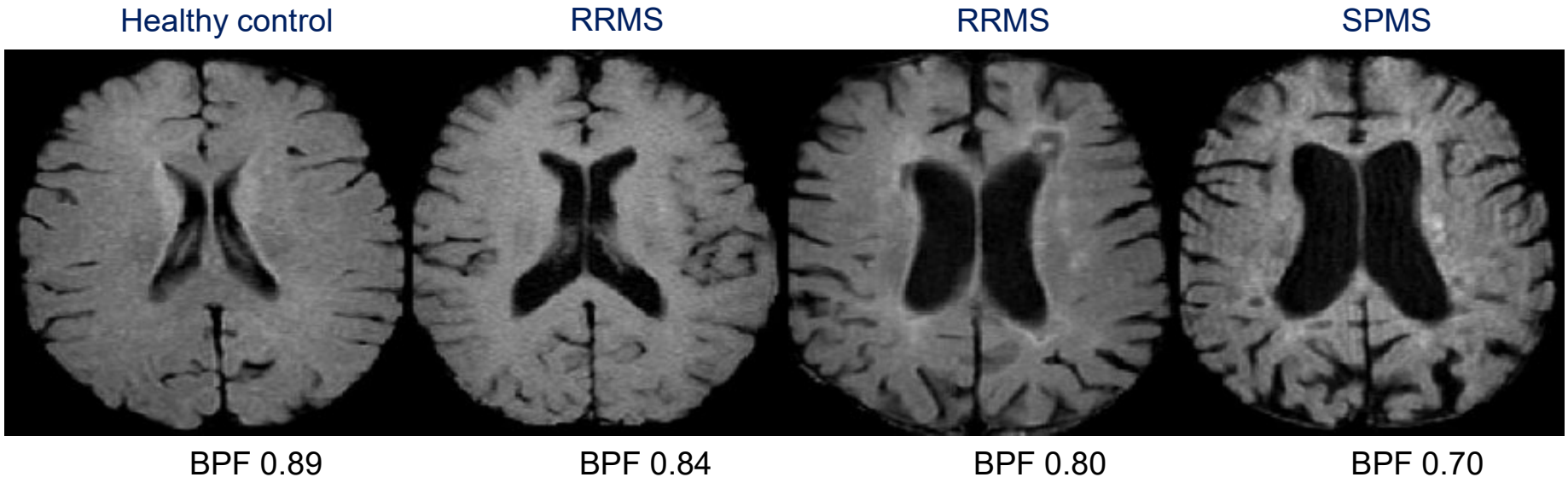


Leptomenigeal lesions as marker for MS diagnosis:
not recommended!

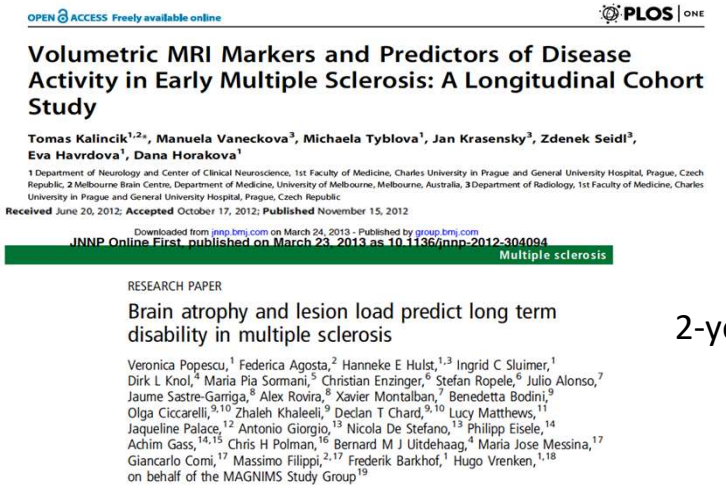
Absinta M et al. *Neurology* 2015;85:18-28

Atrophy measurements

- MRI studies have shown that brain atrophy
  - can be detected in patients with clinically isolated syndrome
  - is progressive during the course of relapsing-remitting MS (RRMS)
  - is more severe in patients with secondary progressive MS (SPMS)



Clinical relevance of atrophy in MS



OPEN ACCESS Freely available online

PLOS ONE

Volumetric MRI Markers and Predictors of Disease Activity in Early Multiple Sclerosis: A Longitudinal Cohort Study

Tomas Kalincik[1,2*], Manuela Vaneckova[3], Michaela Tyblova[1], Jan Krasensky[3], Zdenek Seidl[3], Eva Havrdova[1], Dana Horakova[1]

1 Department of Neurology and Center of Clinical Neuroscience, 1st Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic, 2 Melbourne Brain Centre, Department of Medicine, University of Melbourne, Melbourne, Australia, 3 Department of Radiology, 1st Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Received June 20, 2012; **Accepted** October 17, 2012; **Published** November 15, 2012

JNNP Online First, published on March 23, 2013 as 10.1136/jnnp-2012-304094

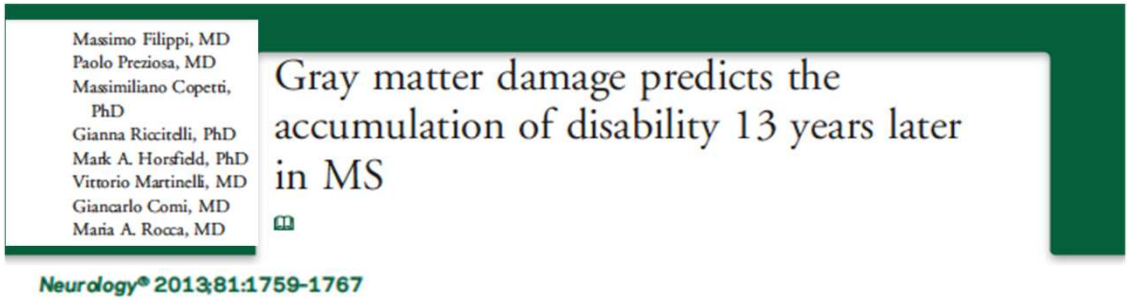
Multiple sclerosis

RESEARCH PAPER

Brain atrophy and lesion load predict long term disability in multiple sclerosis

Veronica Popescu,[1] Federica Agosta,[2] Hanneke E Hulst,[1,3] Ingrid C Sluimer,[1] Dirk L Knol,[4] Maria Pia Sormani,[5] Christian Enzinger,[6] Stefan Ropele,[6] Julio Alonso,[7] Jaume Sastre-Garriga,[8] Alex Rovira,[8] Xavier Montalban,[7] Benedetta Bodini,[9] Olga Ciccarelli,[9,10] Zhaleh Khaleeli,[9] Declan T Chard,[9,10] Lucy Matthews,[11] Jaqueline Palace,[12] Antonio Giorgio,[13] Nicola De Stefano,[13] Philipp Eisele,[14] Achim Gass,[14,15] Chris H Polman,[16] Bernard M J Uitdehaag,[4] Maria Jose Messina,[17] Giancarlo Comi,[17] Massimo Filippi,[2,17] Frederik Barkhof,[1] Hugo Vrenken,[1,18] on behalf of the MAGNIMS Study Group[19]

6-month callosal atrophy and greater baseline T2LV predicted conversion to CDMS within 2 years



Massimo Filippi, MD
Paolo Preziosa, MD
Massimiliano Copetti, PhD
Gianna Riccitelli, PhD
Mark A. Horsfield, PhD
Vittorio Martinelli, MD
Giancarlo Comi, MD
Maria A. Rocca, MD

Gray matter damage predicts the accumulation of disability 13 years later in MS

Neurology® 2013;81:1759-1767

2-year central atrophy and lesion volume change as MRI predictors of 10-year EDSS

baseline GM fraction as the only predictc of worsening of disability at 13 years

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–7

DOI: 10.1177/1352458513494958
msj.sagepub.com

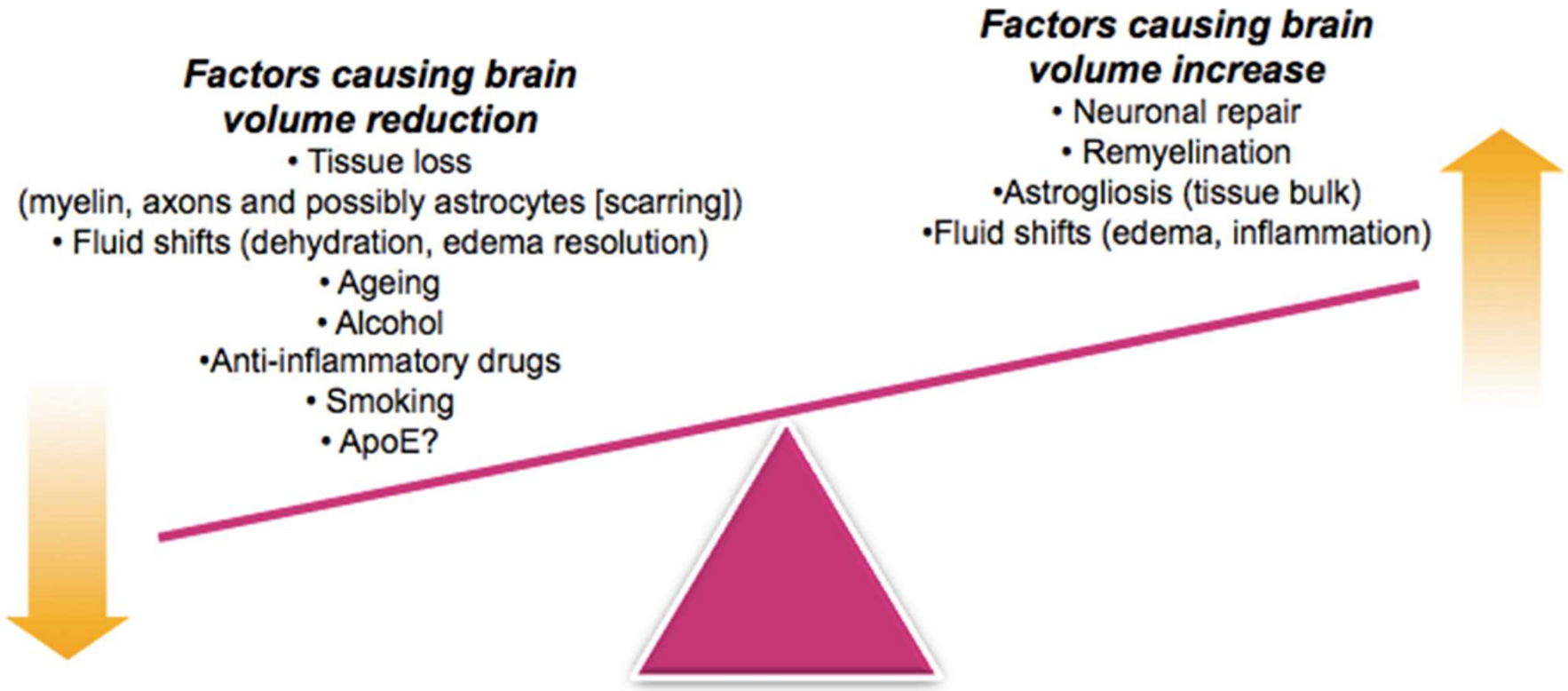
SAGE

Clinical and magnetic resonance imaging predictors of disease progression in multiple sclerosis: a nine-year follow-up study

L Lavorgna[1], S Bonavita[1,2], D Ippolito[1], R Lanzillo[3], G Salemi[4], F Patti[5], P Valentino[6], G Coniglio[7], M Buccafusca[8], D Paolicelli[9], A d'Ambrosio[1], V Bresciamorra[3], G Savettieri[4], M Zappia[5], B Alfano[10], A Gallo[1], IL Simone[9] and G Tedeschi[1,2]

baseline GM volume and EDSS as the best predictors of disease progression (conversion to SP, achievement of EDSS 4) after 9 years in RRMS

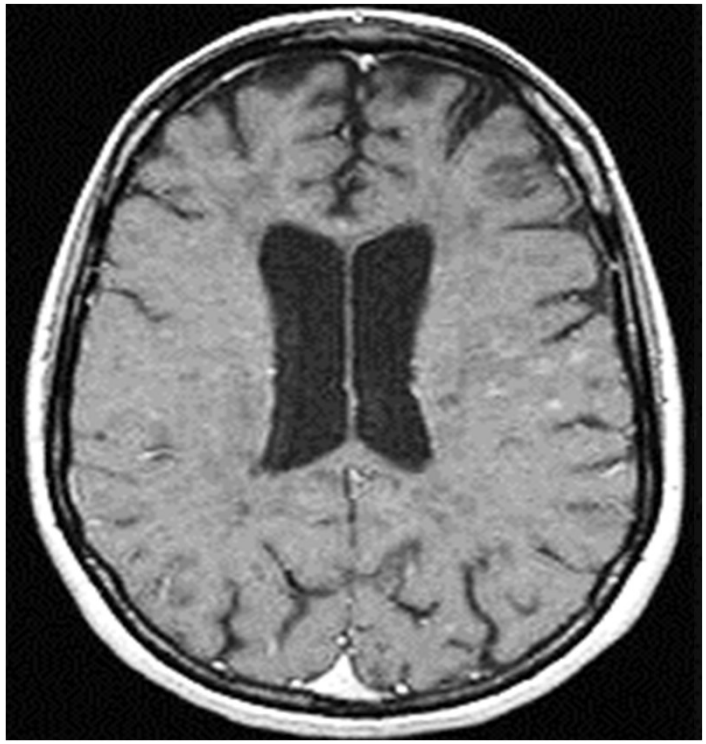
Interpretation of atrophy measurements



ApoE=apolipoprotein E

Simon JH. *Mult Scler.* 2006;12:679-687
Barkhof F et al. *Nat Rev Neurol.* 2009 ;5:256-266
De Stefano N et al. *CNS Drugs.* 2014;28:147-156

Pseudoatrophy during DMT

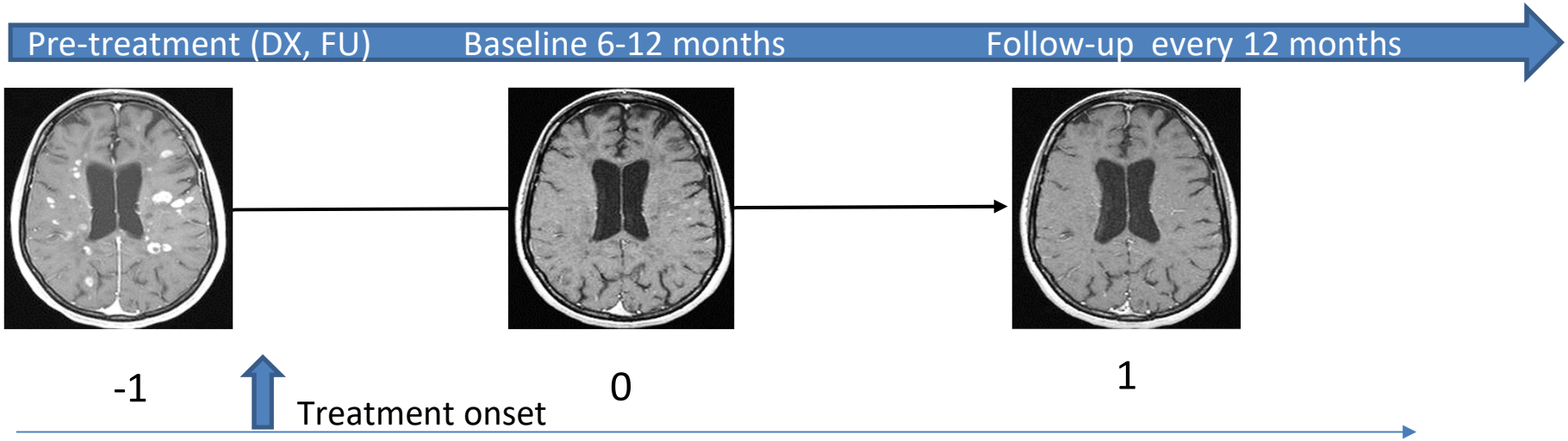


Courtesy of Alex Rovira

Vall d'Hebron Hospital

Minimize Pseudoatrophy during DMT

- **Exclude brain atrophy changes during the first months after treatment onset**

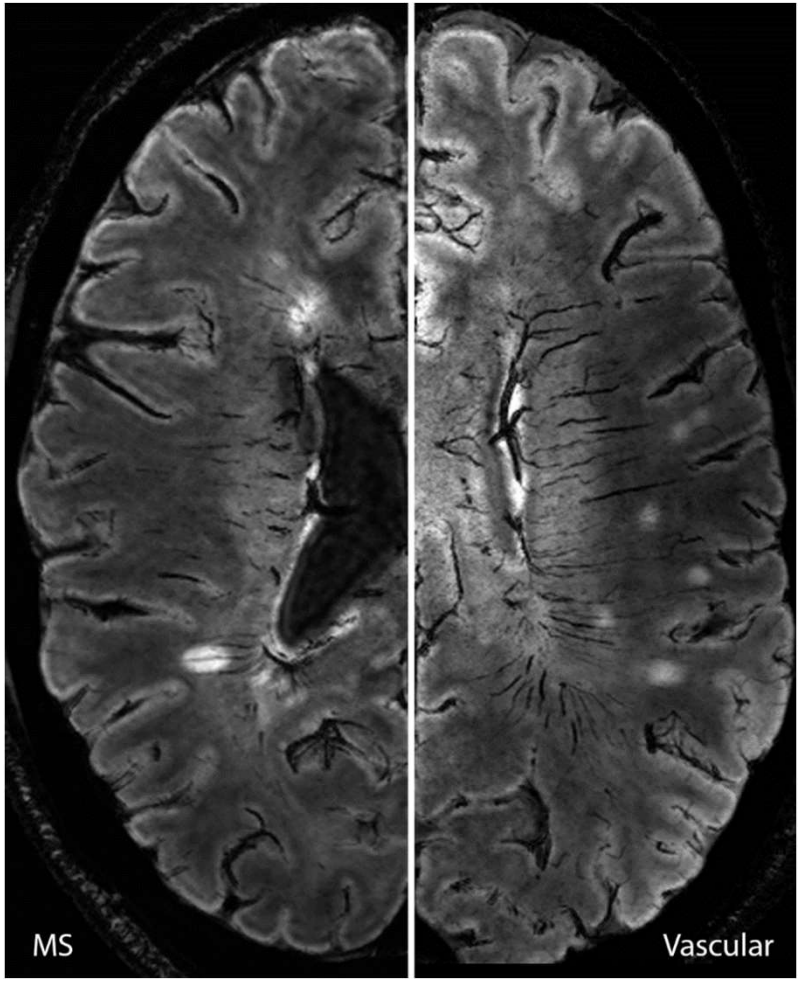


Courtesy of Alex Rovira

Vall d'Hebron Hospital

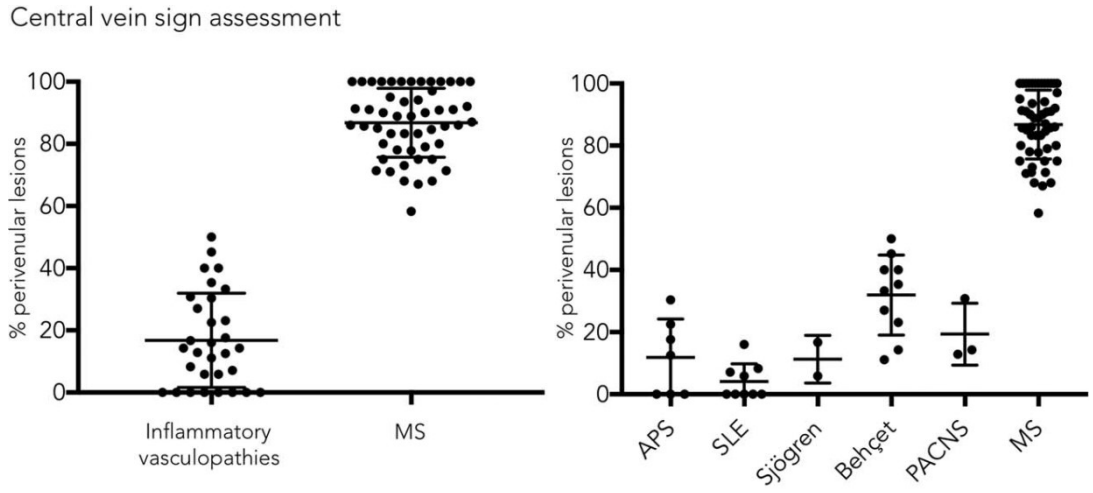
Medizinische Hochschule Hannover

“Central vein sign” for lesion differentiation



Kilsdonk ID, Wattjes MP, Lopez-Soriano A et al. *Eur Radiol* 2014;24:841-9

„Central vein sign“: lesion differentiation



Central vein sign not recommended for clinical routine!

Central vein sign can be used for certain indications!

- high standardization image acquisition/reading
- High level of expertise

Maggi P et al. *Ann Neurol* 2018;83:283-294

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Predcitive value of brain MRI at disease onset

<u>MRI markers</u>

- Number of brain lesions
- Lesion distribution
  - Posterior fossa (e.g. brain stem)
- Contrast-enhancing lesions

Standardized brain MRI (including contrast) is crucial at the stage of MS diagnosis !

- ➢ Long-term disability
- ➢ Disability progression
- ➢ Development of secondary progressive MS

Fisniku LK et al. Brain 2008;131:808-17; Swanton JK et al. Neurology 2009;72:542-50; Swanton JK et al. *Mult Scler* 2010;16:156-65.Tintoré M et al. Neurology 2010;75:1933-8; Brownlee WJ etal. *Brain* 2019; 142:2276-2287

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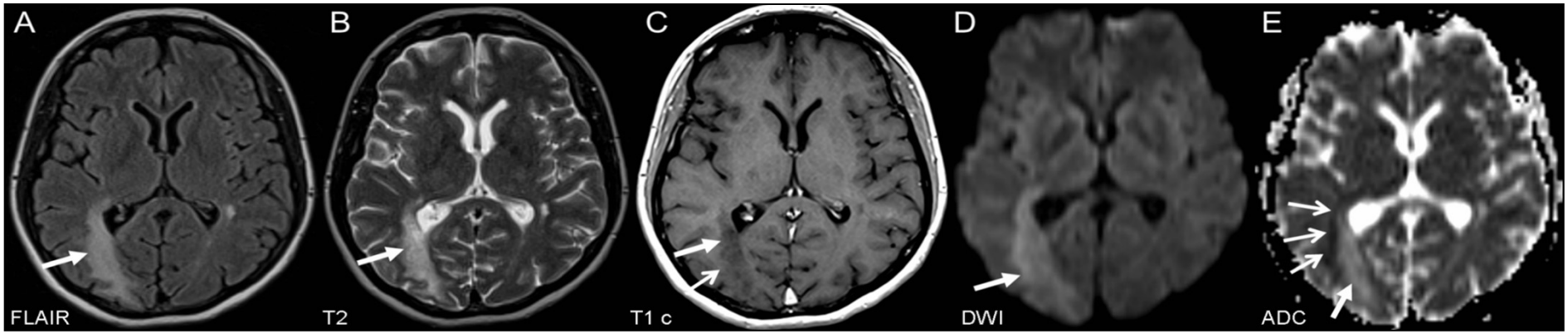
MRI protocol for PML detection

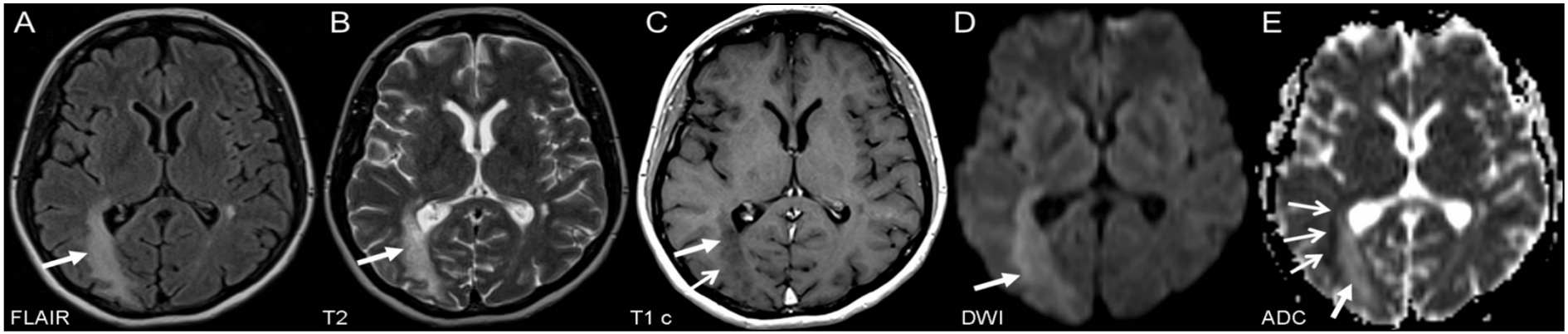


- FLAIR: Highest sensitivity in the detection of PML
- T2W: Detection of vacuoles, microcysts (‘punctate pattern’)
- T1W Gd: Degree of demyelination, inflammation
- DWI: Acute and active infection

DWI=diffusion-weighted imaging; FLAIR=fluid-attenuated inversion recovery; c=contrast; T2W=T2 weighted; T1W=T1 weighted.

Wattjes MP et al. *Mult Scler* 2013;19:1826-40; Wattjes MP, Barkhof F. Curr Opin Neurol 2014;27:260-270

MRI protocol for PML detection



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- T2W: Detection of vacuoles, microcysts ('punctate pattern')
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PML Screening

DWI=diffusion-weighted imaging; FLAIR=fluid-attenuated inversion recovery; c=contrast; T2W=T2 weighted; T1W=T1 weighted.

* Availability of high quality 3D FLAIR

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Expert panel pharmacovigilance guidelines

Publication Author, Year	Country/ Region	High Risk Patient Definition	MRI Testing Frequency
MAGNIMS (Wattjes et al, 2015[1]	Europe	JCV+, >18 months therapy	3–4 months
Fernandez/Montalban, 2015[2]	Spain	• Low risk = JCV+ • Moderate risk = JCV+ and (>2 years therapy or prior IS+) • High risk = all 3 factors	• Low risk = yearly MRI • Moderate risk = 6 months • High risk = 3–4 months
Svenningsson (Swedish MS Association Guidelines), 2014[3]	Sweden	JCV+ and index >0.9	3–6 months for JCV+ (the higher the index, the more frequent the MRIs)
McGuigan et al, 2016[4]	UK/Ireland	JCV+, index ≤1.5, >18 months therapy JCV+, index >1.5, >18 months therapy	6 months 3–4 months

Physicians are performing MRIs more frequently than once yearly (ranging from every 3–6 months) to screen for PML in high risk patients as part of clinical practice

1. Wattjes MP et al. *Nat Rev Neurol*. 2015;11:597-606; 2. Fernández O et al. *Neurologia*. 2015;30:302-314; 3. Svenningsson A et al. Swedish MS Association Guidelines | Risk Assessment of Natalizumab-associated PML. http://www.mssallskapet.se/SMSS%20info%20om%20Tysabri.pdf Accessed 23 June 2017; 4. McGuigan C et al. *J Neurol Neurosurg Psychiatry* 2016;87:117-125.

Natalizumab extended interval dosing

ARTICLE CLASS OF EVIDENCE

Personalized extended interval dosing of natalizumab in MS

A prospective multicenter trial

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Standard MRI safety monitoring protocol and risk stratification recommended!

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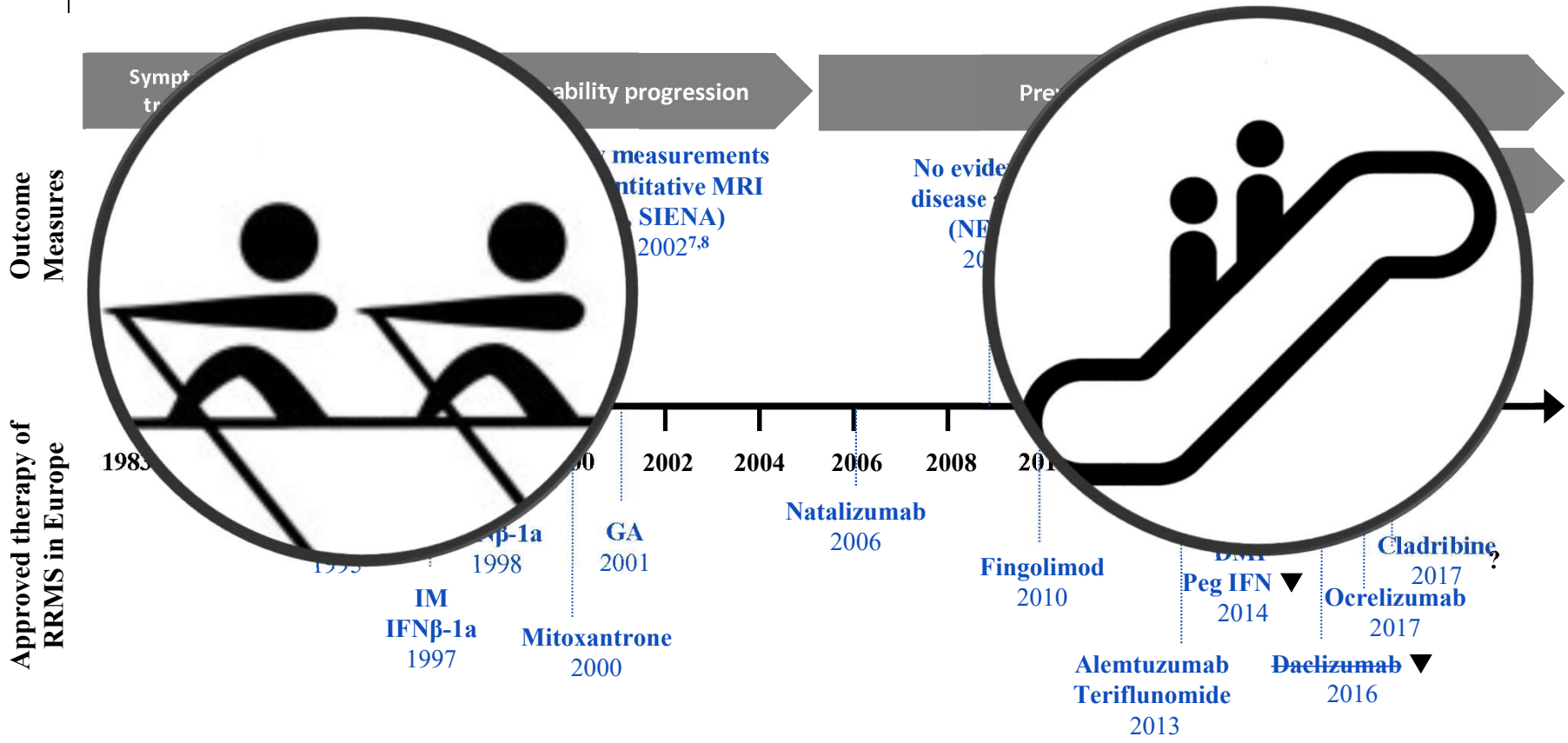
Van Kempen et al. *Neurology* 2020 Jul 20, online ahead of print; Ryerson LZ et al. *Neurology* 2019;93(15)e1452-e1462

Spectrum of MS therapies in Europe



RRMS=relapsing-remitting MS; EDSS=Expanded Disability Status Scale; MRI=magnetic resonance imaging; Gd+=gadolinium-enhancing; MSFC=Multiple Sclerosis Functional Composite; MTR=magnetic transfer ratio; SIENA=Structural Image Evaluation, using Normalisation, of Atrophy; SC=subcutaneous; IFNβ=interferon beta; GA=glatiramer acetate; DMF=dimethyl fumarate; Peg IFN=pegylated interferon beta-1a; DAC HYP=daclizumab HYP; S1PR1=sphingosine-1-phosphate receptor 1.

1. Kurtzke J. *Neurology.* 1983;33:1444-1452; 2. The IFNβ Multiple Sclerosis Study Group. *Neurology*. 1993;43:655-661; 3. Miller DH et al. *Ann Neurol.* 1996;39:6-16; 4. Miller DM et al. *Arch Neurol*. 2000;57:1319-1324; 5. Havrdová E et al. *Lancet Neurol*. 2009;8:254-260; 6. Phillips J et al. *Mult Scler.* 2011;17:970-979; 7. Smith SM, De Stefano N. In: *Proc Int Soc of Magnetic Resonance in Medicine*, 2002; 8. Smith SM et al. *J Comp Assisted Tomography*. 2001;25:466-475.

MRI during/after treatment switch

Requirement	Recommendations for MRI monitoring
To assess inflammation and development of new enlarging lesions	Contrast-enhanced T1W scans and T2W scans
Patients at risk of serious treatment-related AEs, such as PML	T2-FLAIR and DWI (plus T2W imaging), every 3–4 months
Patients at low-risk of PML (JCV sero-negative)	Annual MRI
Patients at high-risk of OI who are switching DMTs	**MRI at the time current treatment is discontinued and after new treatment is started**
Patients switched from natalizumab to other therapies*	**MRI every 3–4 months for up to 12 months**

*Including alemtuzumab, dimethyl fumarate, and fingolimod. DWI=diffusion weighted imaging; FLAIR=fluid attenuation inversion recovery; MRI=magnetic resonance imaging; OI=opportunistic infections; PML=progressive multifocal leukoencephalopathy; T1W=T1-weighted; T2W=T2-weighted

Wattjes M et al. *Nat Rev Neurol.* 2015;11:597–606

Conclusions

- **Standardized brain acquisition is crucial**

Gd optional and not mandatory!

Preferably 3T but not mandatory!

- **Standard outcome measures (Gd-anhancing, active T2 lesions) are important!**
- **Rates of change in brain volume and other advanced MRI methods are not recommended as a marker of disease progression** in individual patients
- **New MRI markers (cortical, smoldering lesions) need to be validated**
- **Established safety protocols for natalizumab also applicable for extended dosing schemes**

Thank you for your attention!