

A Clinician's Guide to the

**2021 MAGNIMS–CMSC–NAIMS
Consensus Recommendations on the
use of MRI in Patients with MS**



Presenting Faculty



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Dr. Trabousee has disclosed the following relevant financial relationships:
*Consulting/Advisor/Speaker Fees: Biogen, EMD Serono,
Novartis Pharmaceuticals Corporation, Roche, Sanofi*

Presenting Faculty



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Associate Director, NARCRMS (North American Registry for Care and Research in MS)

University of British Columbia

Dr. Li has disclosed the following relevant financial relationships:

*Consulting/Advisor/Speaker Fees: Biogen, Genzyme,
Novartis Pharmaceuticals Corporation, Sanofi*

Outline

- Introduction to magnetic resonance imaging (MRI) guidelines in multiple sclerosis (MS)
 - Standardized protocols
 - MRI in routine clinical practice
 - Diagnosis and prognosis
 - Monitoring disease activity and treatment safety
- 

Introduction to MRI Guidelines in MS



Anthony (Tony) Traboulee, MD

MRI Is Key to MS Prognosis

- Early intervention in MS is vital
 - Prompt diagnosis
 - Initiate treatment early
 - **MRI plays an important role in an early diagnosis**
- Monitor MS regularly
 - Escalate and change treatment promptly
 - **MRI plays an important role in safety and effectiveness of treatment**

“Early and appropriate treatment can markedly reduce disease activity and accumulation of disability.”

A Brief History of Recent Guidelines

- 2015 and 2016 guidelines from MAGNIMS¹⁻³
- 2006, 2016, and 2018 guidelines from CMSC⁴⁻⁶
- 2021 Consensus Recommendations
 - Jointly endorsed by MAGNIMS, CMSC, and NAIMS
 - Input from neurologists, radiologists, MR technologists, imaging scientists, and MRI manufacturers
 - Survey of members

Need for Updated Consensus Guidelines

- Advances in imaging technology
- New clinical knowledge
- Global alignment of protocols
- Incorporate 2017 revisions to McDonald diagnostic criteria
- Judicious use of gadolinium-containing contrast agents
- Provide guidelines for MRI of pregnant women and pediatric patients

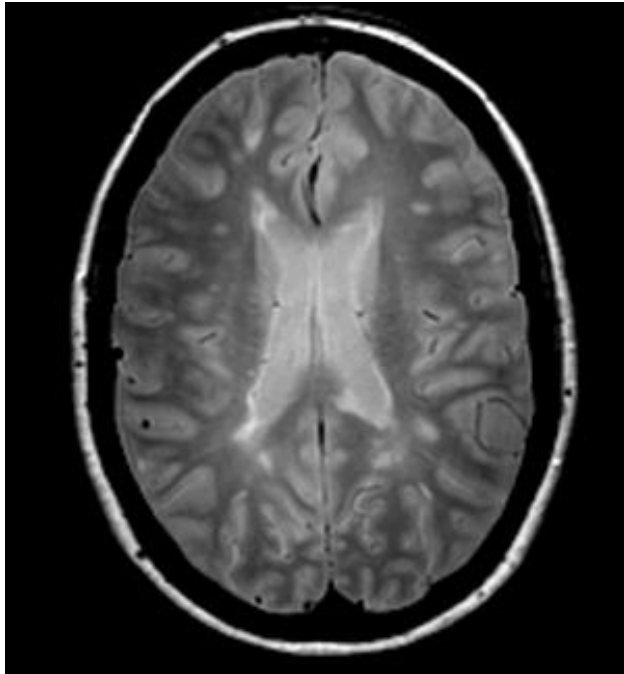
Standardized MRI Protocol in MS for Reliable Detection of Old and New Lesions



David K.B. Li, MD FRCPC

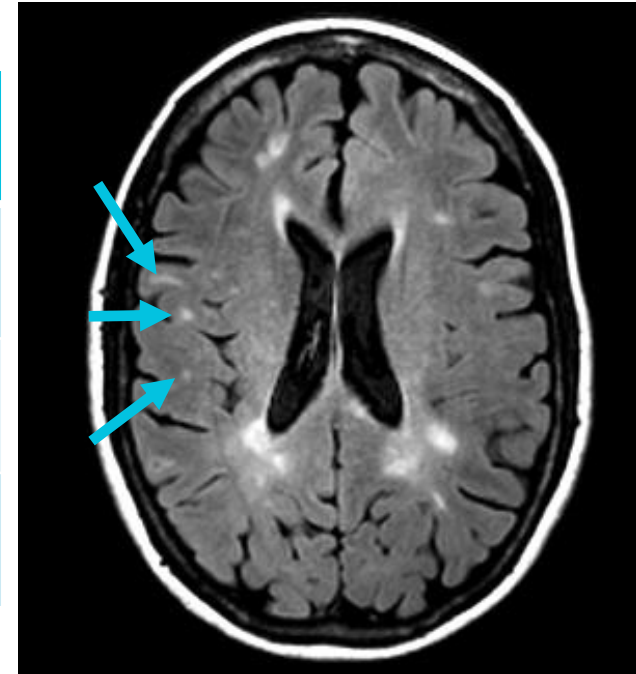
New MS Lesions on MRI – or Not??

Baseline



| MRI Parameters | | |
|----------------|-----------------|-------|
| Proton density | Pulse Sequence | FLAIR |
| 5 mm | Slice Thickness | 3 mm |
| 0.5 mm | Gap | None |

2-Year Follow-Up



Images courtesy of Dr. David Li

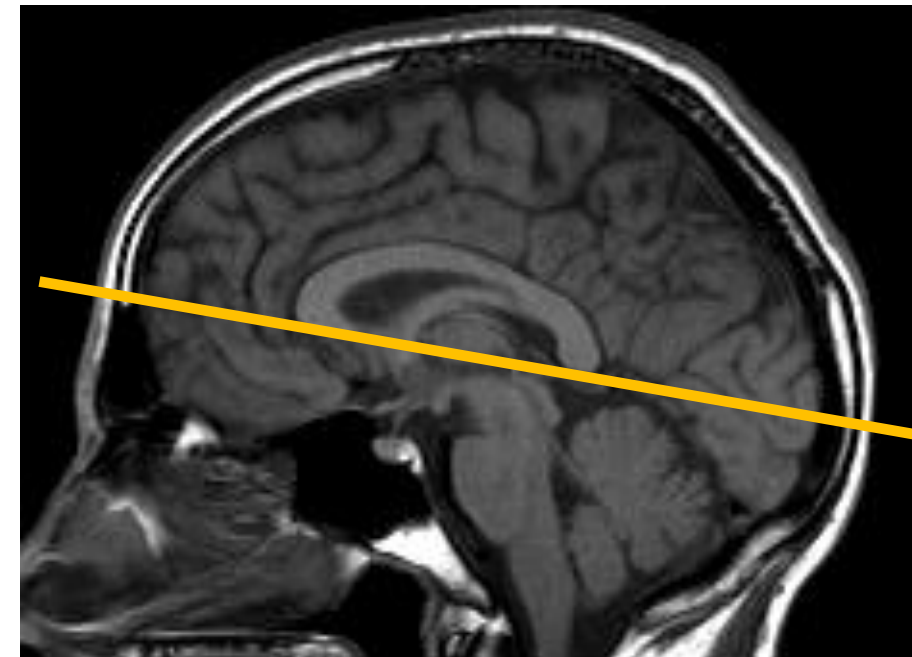
New “lesions” may be not be true lesions but the result of differences in MRI parameters—and NOT evidence of disease activity.

Importance of Standardized MRI Protocols in MS

- Identify new brain lesions consistent with disease activity over time
 - Facilitates earlier diagnosis
 - Allows for prompt initiation or change of therapy
- Ability to compare images between medical centers
- Reduce the need for unnecessary repeat studies and lower health care resource utilization
- Reduce the need for gadolinium contrast
- Eventually...
 - AI-based lesion detection
 - Third party volumetrics across platforms

2021 MAGNIMS-CMSC-NAIMS Standardized Brain MRI Protocol

| | |
|-------------------------|--|
| Field Strength | ≥ 1.5T (preferably 3T) |
| In-Plane Resolution | ≤ 1 mm x 1 mm |
| Acquisition | 3D preferred; 2D is acceptable |
| Scan Prescription | Axial scan orientation Prescribe/reformat along subcallosal plane |
| Coverage | Whole brain coverage (include as much cervical cord as possible) |
| Slice Thickness and Gap | 3D imaging: 1 mm isotropic is preferred 2D imaging: ≤ 3 mm with no gap DWI ≤ 5 mm with a 10%-30% gap |



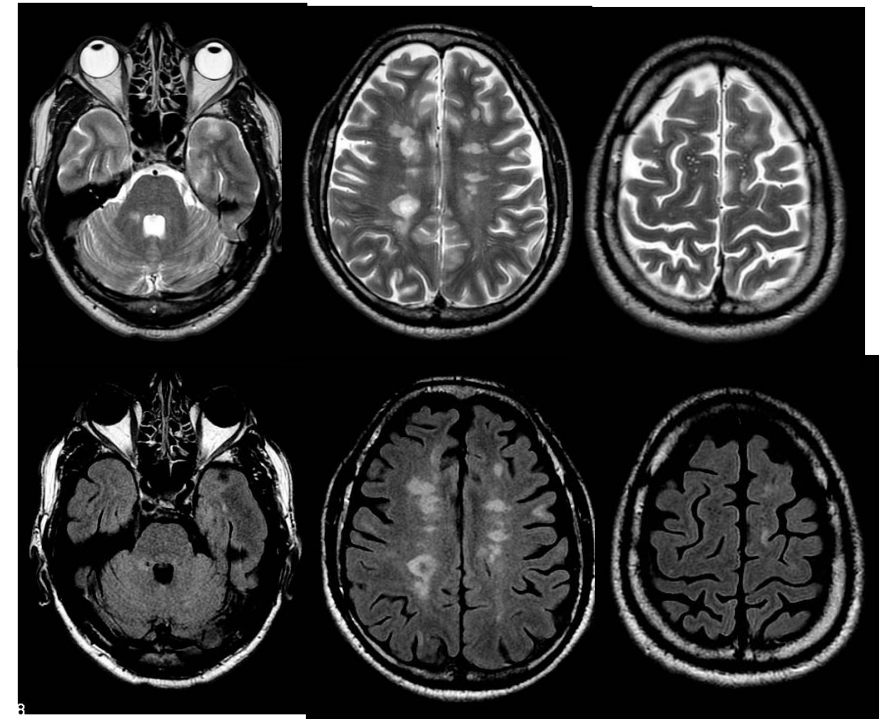
Axial slices oriented to subcallosal plane

2021 MAGNIMS-CMSC-NAIMS Consensus Recommendation on Brain MRI Sequences for Patients With MS: Diagnostic Workup

| MRI Sequences - <u>Brain</u> | Diagnostic Workup |
|---|--|
| Axial T ₂ (TSE or FSE) | Recommended core |
| Sagittal and axial T ₂ FLAIR | Recommended core |
| Post-Gd axial (or 3D sagittal) T ₁ | Recommended core |
| Diffusion-weighted imaging | Optional |
| DIR or PSIR | Optional (for cortical lesions) |
| High-resolution 3D T ₁ | Optional (for brain atrophy monitoring) |
| Susceptibility-weighted imaging | Optional (for central vein sign) |

T₂

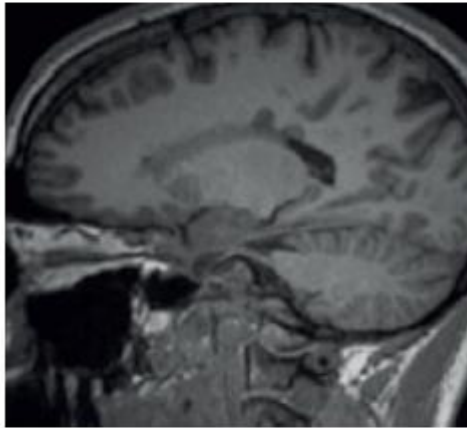
FLAIR



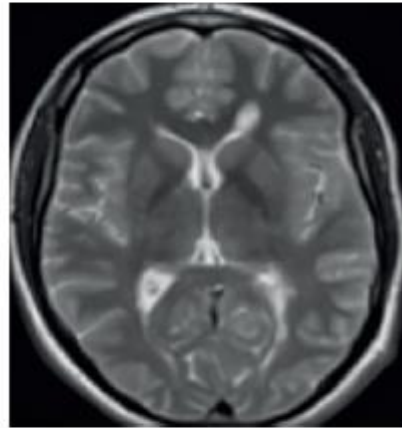
Images courtesy of Dr. David Li.

2021 MAGNIMS-CMSC-NAIMS Standardized Brain MRI Sequences

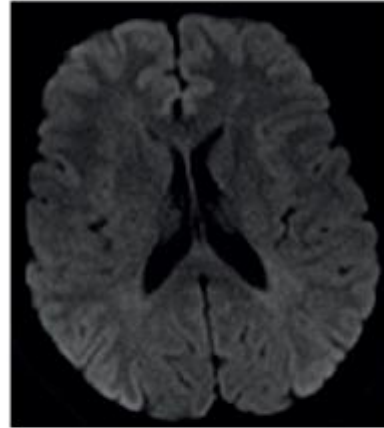
3D T1-weighted
(optional)



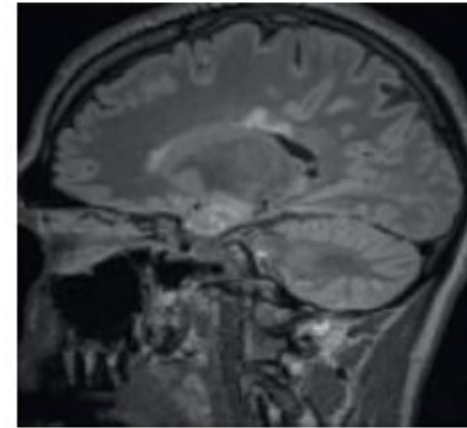
2D turbo spin
echo T2-weighted



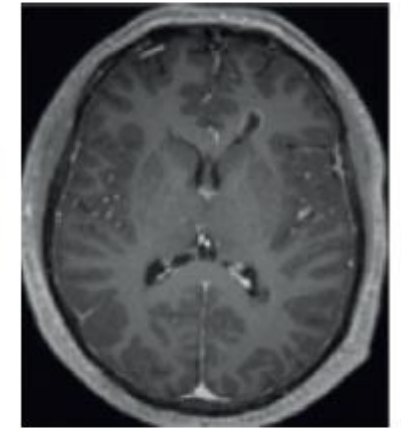
Diffusion-weighted
imaging (optional)



3D T2-weighted
FLAIR:



2D or 3D
contrast-enhanced
T1-weighted
(optional)



Contrast injection in selected cases

↑
Minimum delay 5–10 min
→

2D, 2-dimensional; 3D, 3-dimensional; FLAIR, fluid-attenuated inversion recovery; min, minute.

Clinician's User Manual. <https://mscare.sharefile.com/share/view/saf504881dcad41afb6c1810db720e78a>.

Images reproduced with permission from Wattjes MP, et al. *Lancet Neurol.* 2021;20:653-70.

2021 MAGNIMS-CMSC-NAIMS Standardized Spinal Cord MRI Protocol

| | |
|-------------------------|---|
| Field Strength | ≥ 1.5T |
| In-Plane Resolution | ≤ 1 mm x 1 mm |
| Acquisition | 2D or 3D |
| Scan Prescription | Sagittal Axial scan orientation: perpendicular to the sagittal axis of spinal cord |
| Coverage | Ideally whole cord (cervical, thoracolumbar including conus) |
| Slice Thickness and Gap | Sagittal: ≤ 3 mm, no gap Axial: ≤ 5 mm, no gap |



2021 MAGNIMS-CMSC-NAIMS Consensus Recommendation on Spinal Cord MRI Sequences for Patients With MS: Diagnostic Study

| MRI Sequences – <u>Spinal Cord</u> | Diagnostic Workup |
|---|-------------------------------|
| Sagittal, ≥ 2 of: T₂-weighted (TSE or FSE) Proton-density weighted (TSE or FSE) Short tau inversion recovery | Recommended core |
| Post-Gd Sagittal T₁-weighted (TSE or FSE) | Recommended core |
| Sagittal 3D T ₁ -weighted | Optional |
| Axial T ₂ -weighted or T ₂ * | Optional (through lesions) |
| Pre-Gd Sagittal T ₁ -weighted | Optional |
| Post-Gd Axial T ₁ -weighted | Optional |

Notes

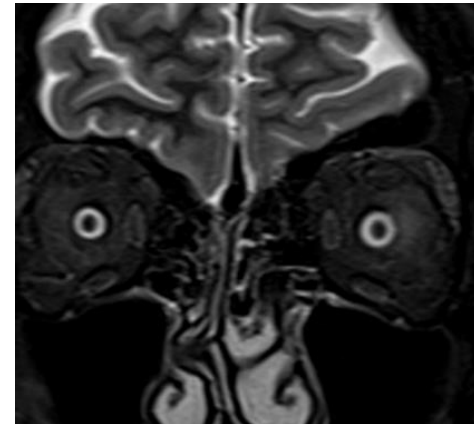
Sagittal 3D T₁-weighted (phase-sensitive inversion recovery or magnetization-prepared rapid acquisition of gradient echoes), an optional sequence for the cervical cord, can substitute for one of the recommended sequences.

No additional Gd needed if spinal cord study immediately follows brain MRI with Gd.

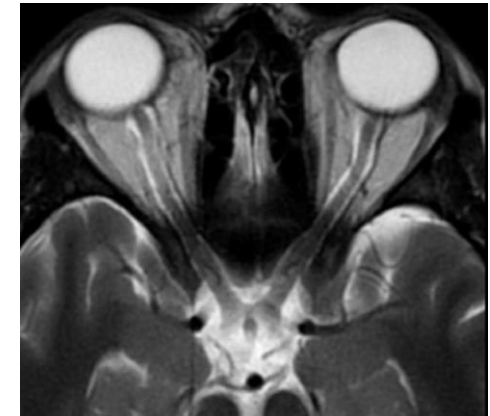
2021 MAGNIMS-CMSC-NAIMS Standardized Optic Nerve MRI Protocol

| | |
|-------------------------|--|
| Field Strength | $\geq 1.5T$ |
| In-Plane Resolution | $\leq 1 \text{ mm} \times 1 \text{ mm}$ |
| Acquisition | 2D or 3D |
| Scan Prescription | Coronal orientation: perpendicular to optic nerve Axial scan orientation: align to optic nerve/chiasm |
| Coverage | Optic nerve and optic chiasm |
| Slice Thickness and Gap | $\leq 2\text{-}3 \text{ mm}$, no gap |

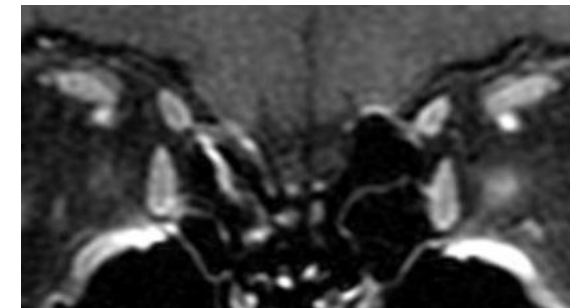
Coronal STIR



Axial Fat-Sat T₂



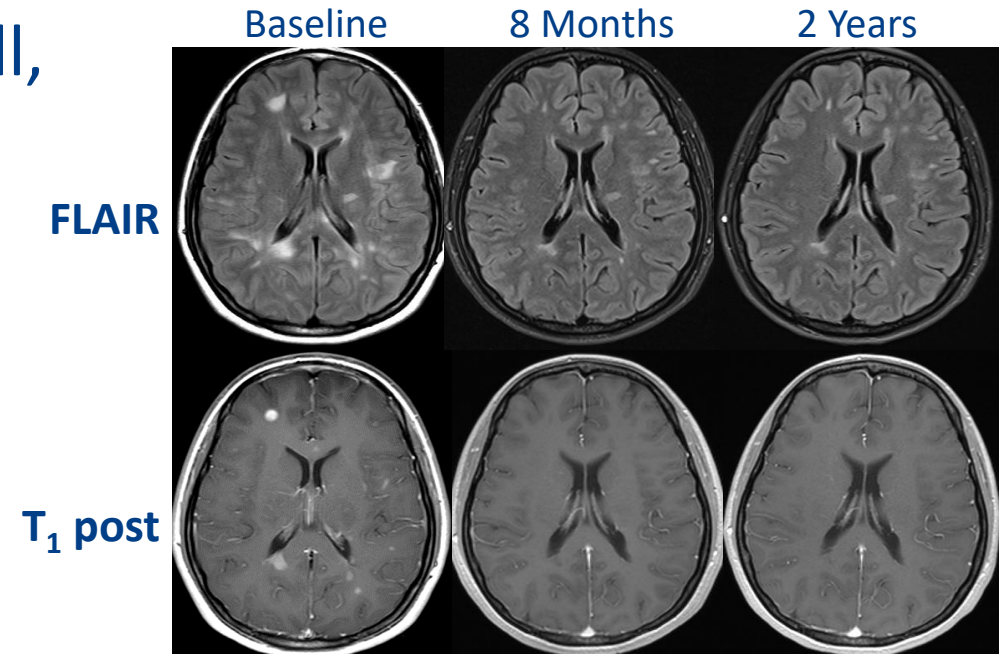
Coronal Fat-Sat Post-Gd T₁



Images courtesy of Dr. David Li.

Tips on When to Use Gadolinium-Based Contrast Agents

- All Gd-based contrast agents deposit a small, dose-dependent amount of Gd in brain
 - Macrocyclic agents show less deposition than linear agents
- Use Gd-based contrast agents at diagnosis for:
 - Showing dissemination in time
 - Differential diagnosis
 - Predicting disease activity and possibly disease progression
 - Phenotyping patients with progressive disease



Standard dose of 0.1 mmol/kg body weight
Macrocyclic Gd chelates only;
Minimum delay of 5 to 10 min

Images courtesy of Dr. David Li.

MRI in Routine Clinical Practice:

- Diagnosis and Prognosis
- Monitoring Treatment and Safety



Anthony (Tony) Traboulee, MD

Recommendations for Clinical Practice: Why, What, When

- Diagnostic workup
 - Initial: brain and cord with Gd
 - Follow-up: brain only in 6 to 12 months if needed for dissemination in time
- Routine RMS monitoring
 - Brain, no Gd needed
 - Every 12 to 24 months
- Safety monitoring if JCV+ on natalizumab ≥ 2 years
 - Brain PML protocol
 - Every 3 to 4 months
- Re-baseline
 - Brain (with Gd in some cases)
 - Before and 3 to 6 months after starting treatment

2017 Revision of McDonald Diagnostic Criteria in MS

Brain and Cord MRI With Gadolinium

- Dissemination of CNS lesions on MRI **in space (brain and cord)**
 - In ≥ 2 areas:
 - Periventricular
 - Cortical and/or juxtacortical
 - Infratentorial
 - Spinal cord
- Dissemination of CNS lesions on MRI **in time (brain MRI only)**
 - Simultaneous presence of Gd-enhancing and non-enhancing lesions at baseline
 - New brain lesion on follow-up MRI
 - T₂-hyperintense or Gd-enhancing
 - At any time after baseline

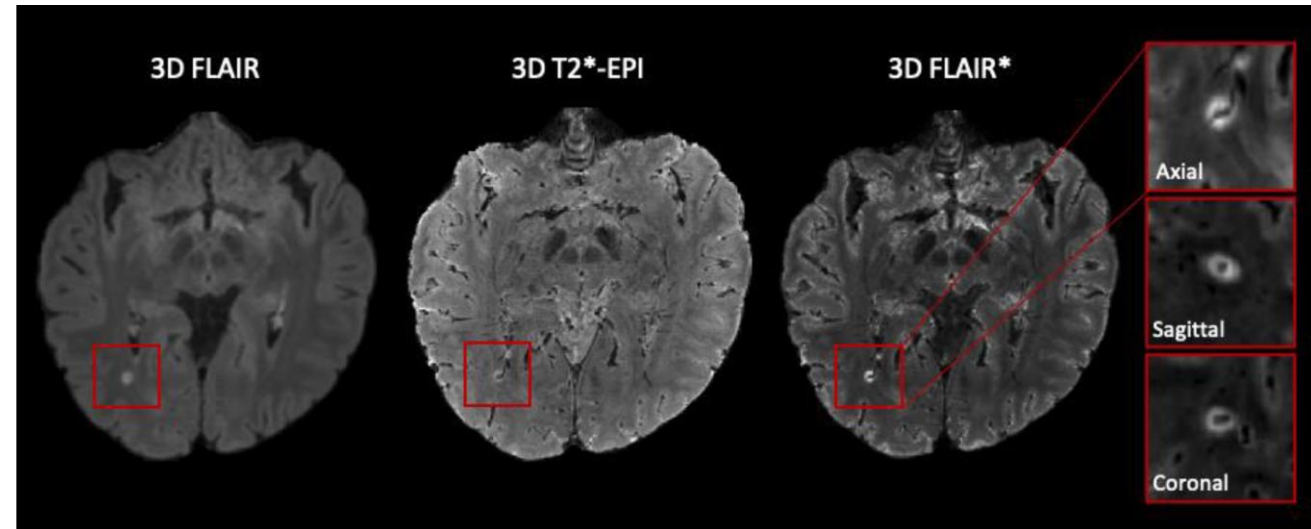
Both symptomatic and asymptomatic MRI lesions can serve as evidence.

Spinal Cord MRI at Baseline Is Also a Prognostic Indicator

- Radiologically isolated syndrome
 - On spinal cord MRI, detection of asymptomatic lesions
 - Predicts development of MS
 - Suggest repeat brain MRI every 6 to 12 months
- Clinically isolated syndrome or early MS
 - Spinal cord lesions predict future disability and SPMS
 - Detection of active lesions on follow-up cord MRI not helpful for establishing DIT
 - Suggest repeat brain MRI every 6 to 12 months

Future of MRI in Diagnosis of MS: Improving Specificity

- “Central vein sign”
 - Presence of central vessel in MS lesion¹⁻³
 - Used to distinguish MS lesions from lesions with other etiologies
 - 3 CVS lesion criteria + 35% CVS threshold was highly specific to MS vs non-MS⁴
 - **Promising biomarker, but not yet recommended**



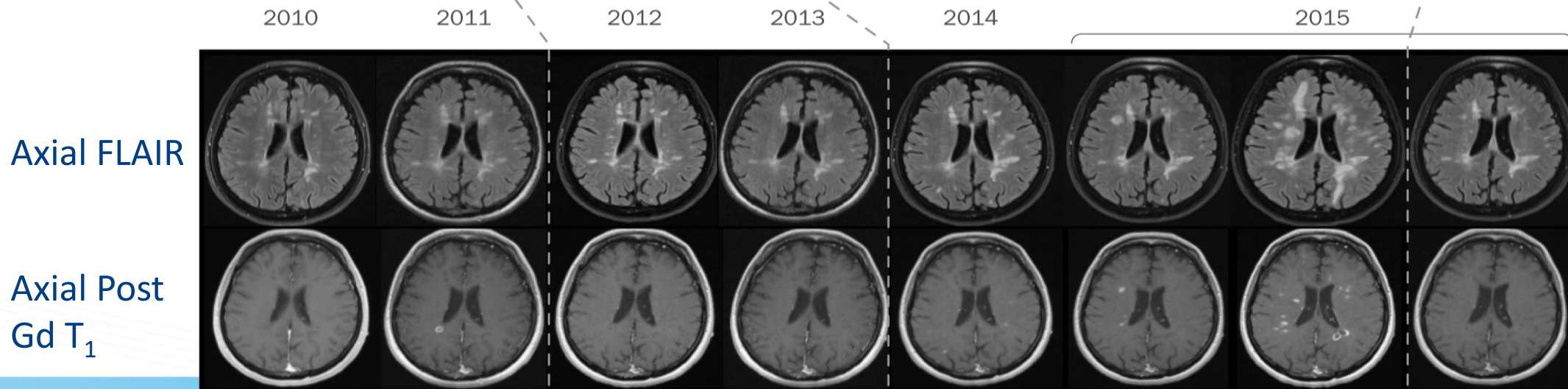
A central vein running through a lesion visible in the 3 planes (zoomed-in boxes) in a 3D FLAIR* obtained combining FLAIR and T2*-EPI acquisitions at 3T.

Image reproduced from La Rosa, et al. under [CC-BY license](#).⁵

Recommendations for Clinical Practice: Why, What, When

- Diagnostic workup
 - Initial: brain and cord with Gd
 - Follow-up: brain only in 6 to 12 months if needed for dissemination in time
- **Routine RMS monitoring**
 - **Brain, no Gd needed**
 - **Every 12 to 24 months**
- Safety monitoring if JCV+ on natalizumab ≥ 2 years
 - Brain PML protocol
 - Every 3 to 6 months
- **Re-baseline**
 - **Brain (with Gd in some cases)**
 - **Before and 3 to 6 months after starting treatment**

When to Perform Brain MRI in Adults With Relapsing MS



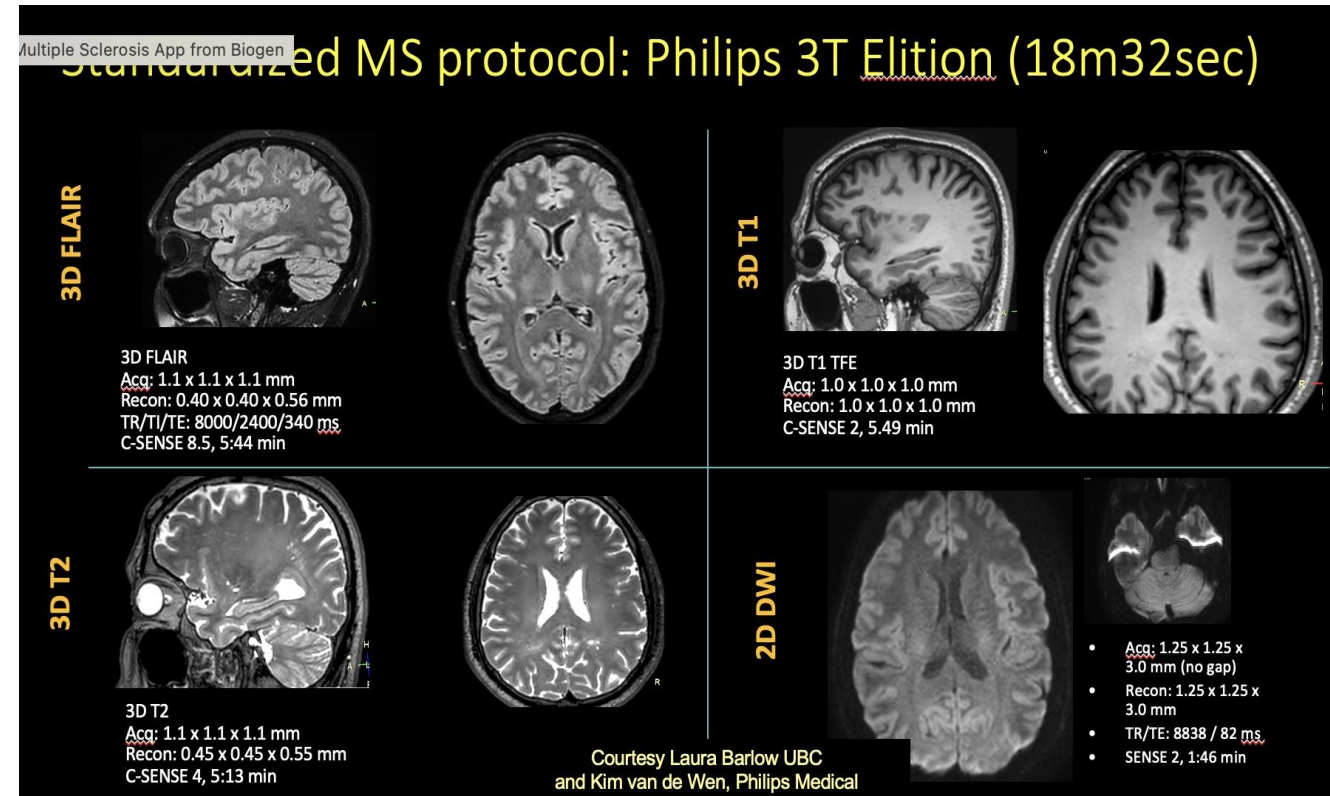
FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium.

Clinician's User Manual. <https://mscare.sharefile.com/share/view/saf504881dcad41afb6c1810db720e78a>.

Images reproduced with permission from Wattjes MP, et al. *Lancet Neurol.* 2021;20:653-70.

2021 MAGNIMS-CMSC-NAIMS Consensus Recommendation on MRI in Patients With MS: Follow-Up

| MRI Sequences - <u>Brain</u> | Follow-up |
|---|---|
| Axial T ₂ (TSE or FSE) | Recommended core Optional if 3D FLAIR acquired |
| Sagittal and axial T ₂ FLAIR | Recommended core |
| Post-Gd axial (or 3D sagittal) T ₁ | Optional |
| Diffusion-weighted imaging | Optional |
| DIR or PSIR | Optional |
| High-resolution 3D T ₁ | Optional |
| Susceptibility-weighted imaging | Not required |

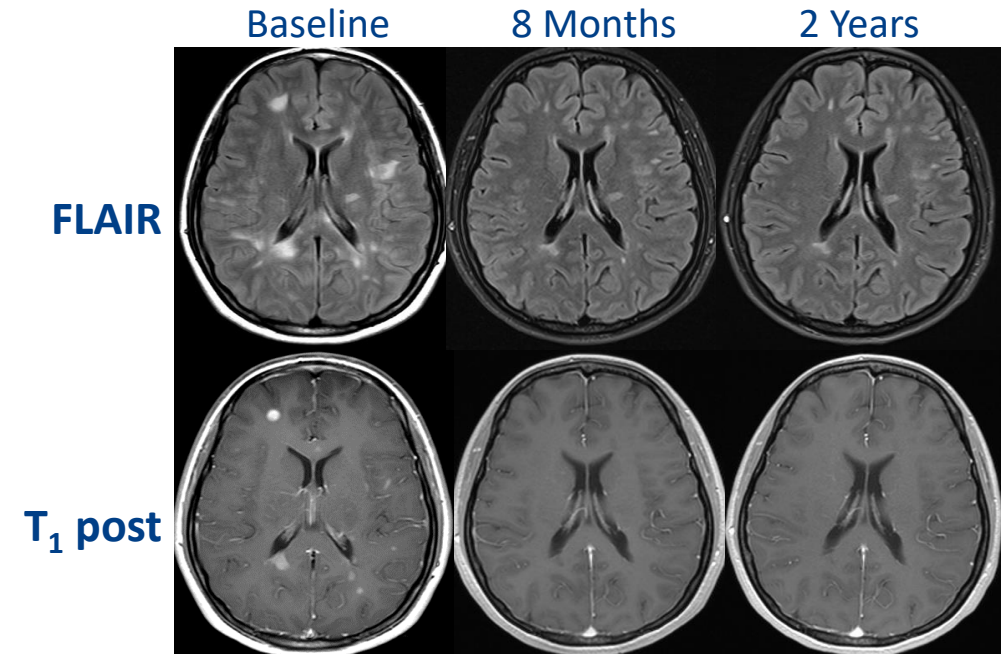


3D, 3-dimensional; acq, acquisition; C-SENSE, compressed sensitivity encoding; DIR, double inversion recovery; FLAIR, fluid-attenuated inversion recovery; FSE, fast spin echo; Gd, gadolinium; min, minute; mm, millimeter; PSIR, phase-sensitive inversion recovery; recon, reconstruction; TSE, turbo spin echo.

Clinician's User Manual. <https://mscare.sharefile.com/share/view/saf504881dcad41afb6c1810db720e78a>; Wattjes MP, et al. *Lancet Neurol.* 2021;20:653-70.

Tips on When to Use Gadolinium-Based Contrast Agents

- Use Gd-based contrast agents at follow-up:
 - If new baseline MRI was not obtained 3 to 6 months after treatment initiation, perform Gd-enhanced scan within first year
 - For detection or confirmation of clinical disease activity in patients without recent brain scan
 - If showing disease activity with Gd is necessary to initiate or change DMT
 - For patients with diffuse and confluent chronic MS lesions



Majority of patients (>93%) show NO Gd-enhancing lesions on routine follow-up (one year)

Images courtesy of Dr. David Li.

2021 MAGNIMS-CMSC-NAIMS Consensus Recommendation on Spinal Cord MRI in Patients With MS: Follow Up as Needed

- Significant clinical worsening with little-to-no change on brain MRI
- New spinal cord lesions could affect treatment decisions
- Patient has predominant spinal cord phenotype
- Rule out alternate cause for progressive myelopathy

Image removed due to
copyright restrictions

Follow-Up MRI in PPMS or SPMS

- Patients with PPMS or SPMS often do not need annual brain MRI
 - Less likely to develop new T₂ lesions or Gd-enhancing lesions
- Follow-up brain MRI recommended:
 - To detect clinically silent disease activity when deciding to initiate DMT
 - Gd may be required
 - To re-evaluate unexpected decline or rate of decline



Image courtesy of Dr. Anthony Traboulsee.

Recommendations on MRI in Pediatrics and Antepartum

| | |
|---------------------------------|---|
| Pediatric – Diagnosis | <ul style="list-style-type: none">- Brain and full spinal cord with Gd- Optic nerve when MOG/NMOSD under consideration |
| Pediatric – Follow-Up | <ul style="list-style-type: none">- Follow adult recommendations for follow-up and safety monitoring- For highly active disease, repeat every 6 months- MRI with Gd-based contrast agents optional for monitoring |
| Pregnancy | <ul style="list-style-type: none">- Assessed on case-by-case basis (eg, unexpected disease activity)- Use standardized protocols, 1.5T- No Gd-based contrast agents (contraindicated) |
| Postpartum and Lactation | <ul style="list-style-type: none">- New baseline brain MRI at 2 to 3 months postpartum- Gd-based contrast agents used only if highly necessary |

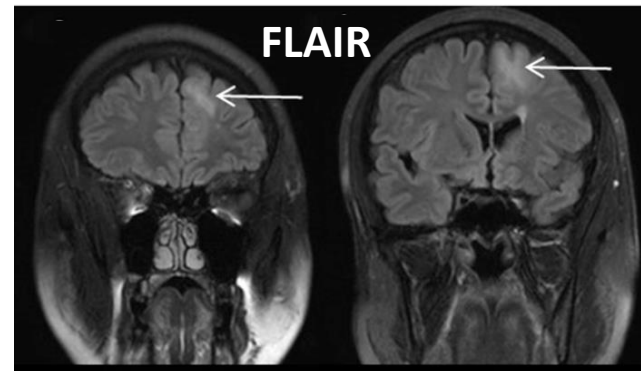
Recommendations for Clinical Practice: Why, What, When

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 - Brain PML protocol
 - Every 3 to 4 months
- Re-baseline
 - Brain (with Gd in some cases)
 - Before and 3 to 6 months after starting treatment

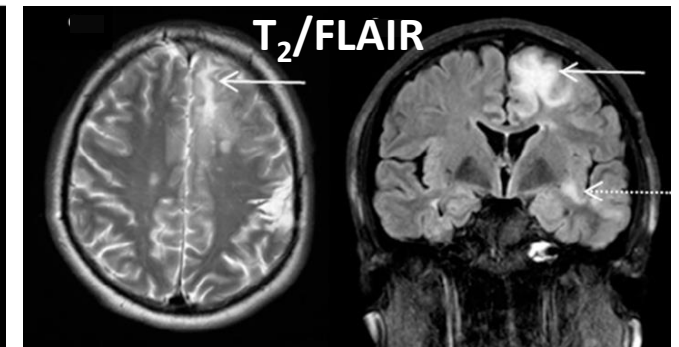
2021 MAGNIMS-CMSC-NAIMS Consensus Recommendation on MRI in Patients With MS: Safety Monitoring

| MRI Sequences - <u>Brain</u> | Follow-up |
|---|---|
| Axial T₂ (TSE or FSE) | Recommended core Optional if 3D FLAIR acquired |
| Sagittal and axial T₂ FLAIR | Recommended core |
| Post-Gd axial (or 3D sagittal) T ₁ | Optional |
| Diffusion-weighted imaging | Recommended core (for PML detection) |
| DIR or PSIR | Optional |
| High-resolution 3D T ₁ | Not required |
| Susceptibility-weighted imaging | Not required |

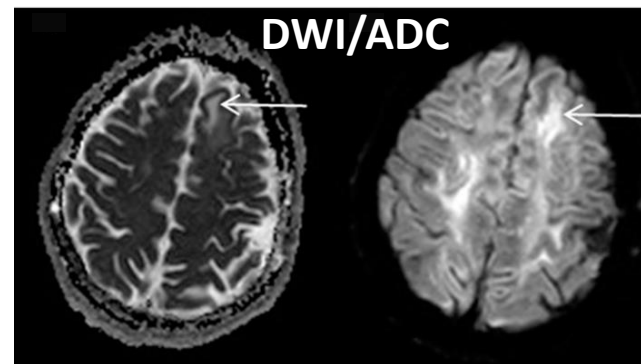
PML Diagnosis



6 Weeks Later



Enlargement of the pre-existing left frontal lobe lesion (solid arrows).



Ill-defined focus of high signal without restricted diffusion on DWI/ADC (solid arrows).

Findings consistent with PML in a patient with MS treated with natalizumab who presented with progressive changes in behavior. Images reproduced from Igra MS, et al. with permission.

3D, 3-dimensional; ADC, apparent diffusion coefficient; DIR, double inversion recovery; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; FSE, fast spin echo; Gd, gadolinium; PML, progressive multifocal leukoencephalopathy; PSIR, phase-sensitive inversion recovery; TSE, turbo spin echo.

Wattjes MP, et al. *Lancet Neurol.* 2021;20:653-70; Clinician's User Manual. <https://mscare.sharefile.com/share/view/saf504881dcad41afb6c1810db720e78a>; Igra MS, et al. *Br J Radiol.* 2017;90:20160721.

2021 MAGNIMS-CMSC-NAIMS Consensus Recommendation on MRI in Patients with MS – Safety Monitoring

- For patients treated with natalizumab who have high risk of PML
 - Seropositive for JCV, treated with natalizumab \geq 18 months
 - High anti-JCV antibody index values
 - Previously treated with immunosuppressive therapies
- Consider continuous lesion enlargement and typical PML-immune reconstitution inflammatory syndrome on MRI as supportive of PML
 - Even if JCV DNA not detected

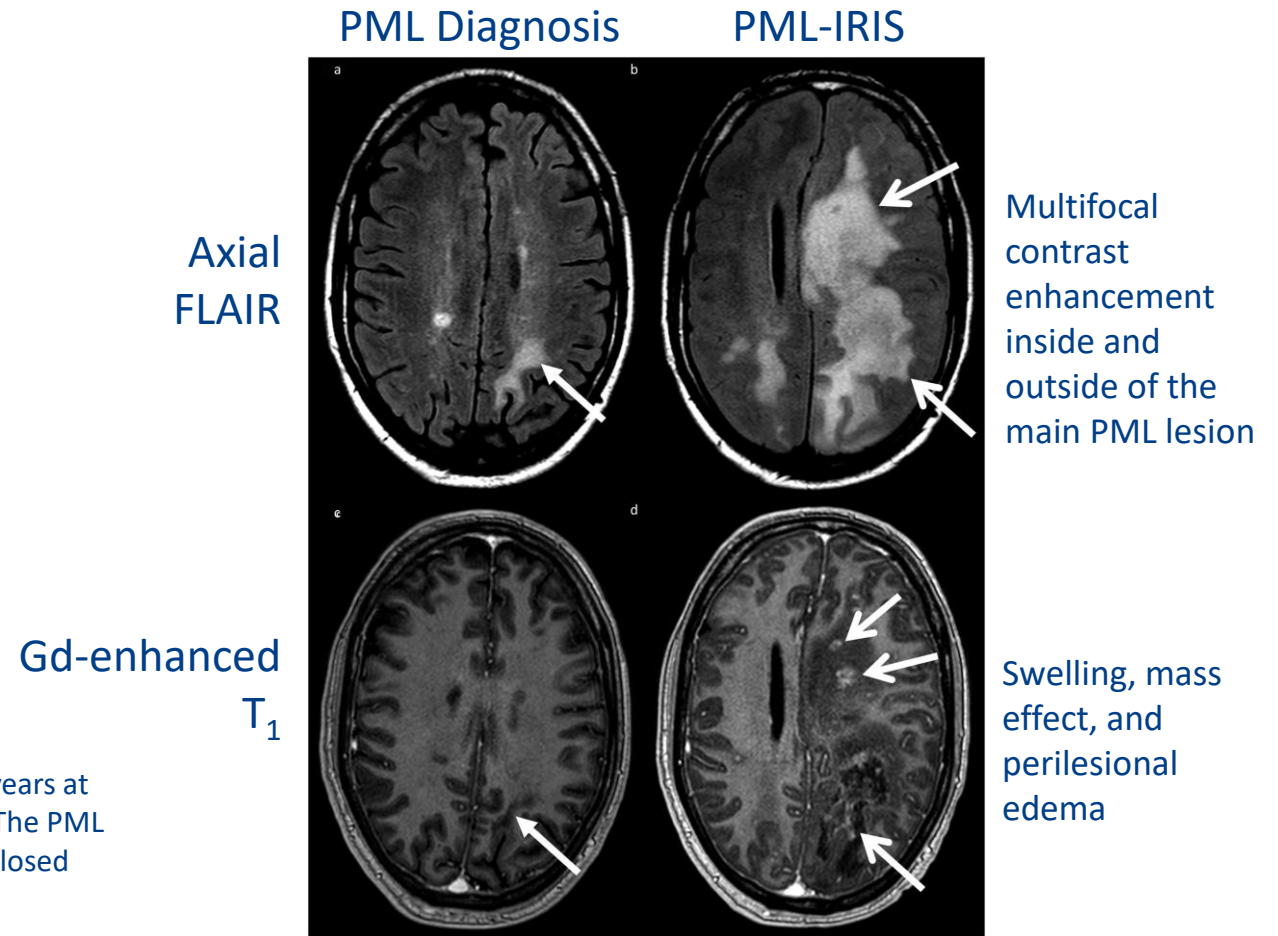
When to Perform Brain MRI in Adults at Risk for PML



Tips on When to Use Gadolinium-Based Contrast Agents

- Use contrast agents for safety monitoring¹⁻²:
 - For PML evaluation when a suspicious lesion is detected on a PML-screening MRI
 - To monitor PML
 - To detect and monitor PML-immune reconstitution inflammatory syndrome

54-year-old patient with relapsing-remitting MS being treated with natalizumab ≥ 3 years at the time of PML diagnosis (left column) and at the time of PML-IRIS (right column). The PML lesion shows typical characteristics without any mass effect or perilesional edema (closed head arrows). Images reproduced from Igra MS, et al. with permission.³



FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium; IRIS, immune reconstitution inflammatory syndrome; PML, progressive multifocal leukoencephalopathy.

1. Wattjes MP, et al. *Lancet Neurol.* 2021;20:653-70; 2. Clinician's User Manual. <https://mscare.sharefile.com/share/view/saf504881dcad41afb6c1810db720e78a>;

3. Igra MS, et al. *Br J Radiol.* 2017;90:20160721.

Tips for Success: MRI Requisition

- Clinical question must be included in MRI order
 - Diagnosis
 - Monitoring for management decision
- Relevant clinical history and physical exam findings
- Current MS DMT, and JCV status if on natalizumab
- Date and place of previous studies, if known

Tips for Success: MRI Report

- Universal nomenclature/terminology
 - Eg, periventricular, juxtacortical, infratentorial
- Description of findings
 - Lesion type, location, size, shape, character, number for diagnostic scan
 - CIS diagnostic scan: does it meet current DIS or DIT criteria?
 - Qualitative assessment of brain volume/atrophy
- MS monitoring or CIS follow-up: comparison with previous studies
- Interpretation and differential diagnosis, if appropriate
 - Eg, typical for MS, atypical for MS

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2021 MAGNIMS-CMSC-NAIMS STANDARDIZED MRI PROTOCOL

Magnims

Magnetic Resonance Imaging in Multiple Sclerosis



THE CONSORTIUM OF
MULTIPLE SCLEROSIS CENTERS

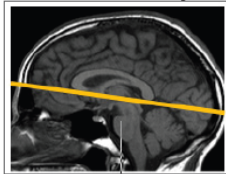


NAIMS

North American Imaging in MS Cooperative

Lancet Neurology 20: 653-670, 2021



| | BRAIN | SPINAL CORD | OPTIC NERVE |
|--|---|---|--|
| FIELD STRENGTH | ≥1.5 T (preferably 3T) | ≥1.5 T | ≥1.5 T |
| ACQUISITION | 3D (preferred) or 2D | 2D or 3D | 2D or 3D |
| SLICE THICKNESS | 3D: 1mm isotropic ¹ 2D: ≤3mm, no gap ² | Sagittal ≤3mm, no gap Axial ≤5mm, no gap | ≤2-3mm, no gap |
| IN-PLANE RESOLUTION | ≤1mm x 1mm | ≤1mm x 1mm | ≤1mm x 1mm |
| COVERAGE | Whole brain (include as much of cervical cord as possible) | Whole cord (cervical, thoracolumbar including conus) | Optic nerve & chiasm |
| AXIAL SCAN ORIENTATION (2D ACQUISITION OR 3D RECONSTRUCTION) | Subcallosal plane  | Perpendicular to sagittal axis of cord | Align to optic nerve/ chiasm orientation |

T = tesla; 3D = 3 dimensional; 2D = 2 dimensional

¹ Isotropic preferred; if over-contiguous (through-plane and in-plane), not ≥ 1.5 mm with 0.75 mm overlap

² Diffusion-weighted imaging: slice thickness should be ≤ 5mm with no more than a 10–30% slice gap

Thank you to Lori Saslow & Rachelle Ramirez for their help.

Download and order copies from
www.mscares.org/MRI

Summary and Conclusions

- Standardized MRI protocols are critical for:
 - Facilitating early diagnosis of MS
 - Identifying new MS lesions over time
 - Detecting treatment-associated PML in high-risk patients
 - Minimizing the need for gadolinium-based contrast
 - Comparing images between medical centers/scanners
- MRI can aid prognostication, especially with spinal cord imaging at baseline
- At MS diagnosis, imaging should include the brain and spinal cord, with optional optic nerve MRI
- In relapsing MS, brain MRI should be performed before initiation of treatment, 3 to 6 months after new treatment (new baseline), annually on treatment, and as clinically indicated
- Ensure optimal interdisciplinary communication
 - Include the clinical question and relevant information in MRI order
 - Use universal nomenclature/terminology to describe findings in MRI report
- Download or order copies of the MRI summary card at https://www.mscares.org/page/MRI_protocol

THANK YOU