CDI QUALITY INSTITUTE

Provider Led Entity

CDI Quality Institute PLE Multiple Sclerosis (MS) AUC 2020 Update

Appropriateness of advanced imaging procedures* in patients with the following clinical presentations or diagnoses:

12/01/2020

*Including MRI, CT, PET, nuclear medicine, and PET/CT

Abbreviation list:

AAN	American Academy of Neurology
ACR	American College of Radiology
AUC	Appropriate Use Criteria
CIS	Clinically isolated syndrome
CMSC	Consortium of MS Centers
CNS	Central nervous system
CT	Computed tomography
DIS	Disease dissemination in space
DIT	Disease dissemination in time
DMD	Disease-modifying drug
DMT	Disease-modifying treatment / disease-modifying therapy
DWI	Diffusion weighted imaging
EAN	European Academy of Neurology
ECTRIMS	European Committee of Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EFNS	European Federation of Neurological Society
FLAIR	Fluid attenuated inversion recovery
Gd	Gadolinium
IPND	International Panel for NMO Diagnosis
LETM	Longitudinally extensive transverse myelitis
MAGNIMS	Magnetic resonance imaging in multiple sclerosis
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NICE	National Institute for Health and Care Excellence
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorders
PD	Proton density
PLE	Provider Led Entity
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive MS
RIS	Radiologically isolated syndrome
RRMS	Relapsing-remitting multiple sclerosis
SLE	Systemic lupus erythematosus
SPMS	Secondary progressive MS
SS	Sjögren syndrome
SWI	Susceptibility weighted imaging

Appropriate Use Criteria: How to Use this Document

The CDI Quality Institute follows the recommendation framework defined by the Appraisal of Guidelines for Research & Evaluation (AGREE II), AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) and a modified version of the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) to evaluate the strength of recommendations concerning advanced imaging. Considerations used to determine a recommendation are listed below.

Primary recommendation (green): A strong recommendation for initial imaging for this presentation; there is confidence that the desirable effects of imaging outweigh its undesirable effects.

Alternative recommendation (yellow): A conditional recommendation for imaging; the desirable effects of imaging likely outweigh its undesirable effects, although some uncertainty may exist. The individual patient's circumstances, preferences, and values should be considered on a case-by-case basis. This may include: contraindication to the primary recommendation, specific clinical circumstances that require use of the alternative recommendation, or the primary recommendation has results that are inconclusive or incongruent with the patient's clinical diagnosis. Case-by-case indications to consider have been noted in brackets when appropriate.

Recommendation against imaging (red): The undesirable effects of imaging outweigh any desirable effects. Additionally, the recommendation may be impractical or not feasible in the targeted population and/or practice setting(s).

Multiple Sclerosis (MS) AUC Summary:

The diagnosis of MS requires a well-defined acute or subacute clinical episode with symptoms suggesting an inflammatory demyelinating disorder. Up to 85% of MS patients initially present with a clinically isolated syndrome (CIS) which can involve the optic nerve, brainstem, and/or spinal cord (Filippi et al [*EFNS*] 2011). A clinically isolated syndrome is a clinical episode with acute or subacute symptoms and findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS with a duration of at least 24 hours and in the absence of fever or infection in a patient not known to have multiple sclerosis (Thompson et al 2018). In the absence of a clear-cut typical clinically isolated syndrome, caution should be exercised in making the diagnosis of multiple sclerosis, and the diagnosis should be confirmed by further clinical and radiological follow-up (Thompson et al 2018).

The McDonald Criteria are recommended by the National Multiple Sclerosis Society (NMSS) for the diagnosis of MS, which first requires that alternative diagnoses be excluded (Thompson et al 2018). The McDonald Criteria apply primarily to patients presenting with a CIS and define what is needed to satisfy the dissemination in time and dissemination in space requirements for the diagnosis of MS (Thompson et al 2018). The McDonald Criteria have also proven useful in the diagnosis of relapsing-remitting MS (RRMS) (Thompson et al 2018).

The high sensitivity of MRI in the depiction of plaques in the brain and spinal cord has made this technique the most important paraclinical tool for the diagnosis of MS (Rovira et al 2015). An MRI of the brain is recommended as soon as possible in patients presenting with a first episode of neurologic symptoms thought to be caused by inflammation or demyelination of the central nervous system (CNS) (Filippi et al [*EFNS*] 2011; Thompson et al 2018). MRI can satisfy the dissemination in space requirements with the detection of characteristic lesions in two or more anatomic locations (periventricular, cortical/juxtacortical, infratentorial brain regions and the spinal cord). It can show dissemination in time (DIT) with the simultaneous presence of both enhancing and nonenhancing lesions or by the development of new high signal intensity lesion or enhancing lesions on follow-up

scans (Thompson et al 2018). MRI without and with IV contrast can facilitate the early diagnosis and treatment of MS patients.

MRI is also useful in differentiating MS from other demyelinating and inflammatory disorders, such as neuromyelitis optica (NMO) and acute disseminated encephalomyelitis (ADEM), and to exclude other diagnoses. CSF laboratory tests are useful in differentiating MS from other disorders. In patients with a typical clinically isolated syndrome, fulfilment of criteria for DIS, and no better explanation for the clinical presentation, demonstration of CSF oligoclonal bands in the absence of atypical CSF findings allows a diagnosis of MS to be made (Thompson et al 2018). A positive test for AQP4-IgG may confirm the diagnosis of NMO (Thompson et al 2018).

Follow-up brain MRI is required in patients who show clinical and radiological findings suggestive of MS, yet do not fulfil the McDonald Criteria (Rovira et al 2015). In patients with a known diagnosis of MS, clinicians should monitor disease activity to detect accumulation of new lesions in order to better inform treatment decisions (Traboulsee et al 2018). Routine brain MRI and clinical-follow-up after initiation of disease modifying therapies (DMTs) in relapse-remitting MS (RRMS) patients is recommended to identify ongoing inflammatory disease activity (Traboulsee et al 2018). T2-weighted and contrast-enhanced T1-weighted brain MRI are typically the modalities of choice, as they can reveal acute and active inflammation, as well as clinically silent disease progression (Wattjes et al [*MAGNIMS*] 2015). Newer evidence suggests that use of a gadolinium-based contrast agent at follow-up MRI does not change the diagnosis of interval disease progression (Eichinger et al 2019; Sadigh et al 2019; Rudie et al 2019).

The usefulness of CT is typically limited to excluding alternative diagnoses in the workup of MS, and should therefore be reserved only for situations when MRI is not available or is contraindicated for the patient (PLE expert panel consensus opinion).

First episode of neurologic symptoms with clinical suspicion of inflammation and/or demyelination in the central nervous system (clinically isolated syndrome), such as:

- **Optic neuritis or diplopia**
- **Myelopathic symptoms, including bowel and bladder disorders**
- **New ataxia and/or brainstem symptoms**
- **New sensory or motor deficits**

- **Green – MRI brain without and with contrast**
- **Green – MRI orbits without and with contrast**
- **Green – MRI spine (cord/conus medullaris) without and with contrast**

- **Yellow – MRI brain without contrast**
- **Yellow – MRI orbits without contrast**
- **Yellow – MRI spine (cord/conus medullaris) without contrast**
  [patient unable to receive or refuses MRI contrast]

- **Yellow – MRI brain with contrast**
- **Yellow – MRI orbits with contrast**
- **Yellow – MRI spine (cord/conus medullaris) with contrast**
  [patient has undergone recent MRI without contrast]

- **Yellow – CT head with and/or without contrast**
- **Yellow – CT orbits with and/or without contrast**
- **Yellow – CT spine with and/or without contrast**
  [to exclude other diagnoses in patient who cannot undergo MRI]

- **Red – Nuclear medicine; SPECT; PET; PET/CT**

Level of Evidence: MRI brain with and without contrast: high for diagnostic accuracy and yield; MRI brain with or without contrast: moderate; MRI spine (cervical/thoracic) with and without contrast: high for diagnostic accuracy and diagnostic yield with clinical features of cervical cord involvement, moderate for yield with clinical features of brain involvement, very low for sequential vs. simultaneous imaging; MRI spine (cervical/thoracic) with or without contrast: very low; CT: insufficient; MRI spine (lumbar): insufficient; all other modalities: ranging from very low to insufficient

Notes concerning use of contrast: Gadolinium-based contrast agents (GBCAs) do accumulate in the brain. While there is no known CNS toxicity, these agents should be used judiciously, recognizing that gadolinium continues to play an invaluable role in specific circumstances related to the diagnosis and follow-up of individuals with MS (Traboulsee et al [*CMSC*] 2018). The use of GBCA is indispensable in patients presenting with their first clinical attack ("clinically isolated syndrome") as the use of GBCA allows for an earlier diagnosis by demonstrating lesion dissemination in time (GBCA-enhancing lesion) in addition to lesion dissemination in space, the hallmarks for the diagnosis of MS. Early diagnosis leads to early treatment, which may help in preventing disease progression and improve long-term prognosis

(Traboulsee et al [*CMSC*] 2018).

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:

Imaging of clinically isolated syndrome (CIS):

Recommended baseline studies for patients with a CIS and/or suspected MS include (Traboulsee et al [*CMSC*] 2018*):

- Brain MRI protocol with gadolinium at baseline, and to establish dissemination in time
- Spinal cord MRI if myelitis, insufficient features on brain MRI to support diagnosis, or age > 40 with non-specific brain MRI findings [*particularly in patients with hypertension, smoking, vitamin D deficiency, migraines, or diabetes mellitus* (PLE expert panel consensus opinion)]
- A cervical cord MRI performed simultaneously with the brain MRI could have prognostic value in the evaluation of CIS patients with or without myelitis and would reduce the number of patients requiring a subsequent MRI appointment
- Orbital MRI if severe optic neuritis with poor recovery.

MS should not be diagnosed on the basis of MRI findings alone (*NICE* 2019; Thompson et al. 2018**). However, MRI of the brain, when available and not contraindicated, is recommended as soon as possible in all patients presenting with an isolated demyelinating syndrome involving the CNS, not only to collect additional evidence for DIS, but also to exclude other possible neurological conditions (Filippi et al [*EFNS*] 2011; Thompson et al 2018**). Serial imaging may be appropriate at least annually for the first 5 years with close follow-up as an alternative to initiating DMT in people with CIS or relapsing forms of MS who are not currently on DMT, have not had relapses in the preceding 2 years, and do not have active new MRI lesion activity on recent imaging (Rae-Grant, et al [*AAN*] 2018, Level C Recommendation). Available evidence is not sufficient to support the use of advanced MRI - such as proton magnetic resonance spectroscopy, diffusion tensor imaging, magnetization transfer imaging, or myelin mapping - to establish the initial diagnosis or differential diagnosis of MS in patients with CIS (Rovira et al [*MAGNIMS*] 2015).

Imaging of optic neuritis, diplopia or other visual problem:

In patients with suspected optic neuritis, although it will not always be required, MRI of the optic nerve(s) can be useful in ruling out alternative diagnoses. In this case, STIR sequences should be used (Filippi et al [*EFNS*] 2011). Optic neuritis is best assessed with a contrast-enhanced MRI of the orbits and contrast-enhanced MRI of the brain, which are often performed in conjunction with one another (Kennedy et al [*ACR*] 2017). CT imaging and angiography of the head are typically not indicated specifically for the evaluation of a patient with optic neuritis (Kennedy et al [*ACR*] 2017). Visual loss involving the chiasm or post-chiasm is also evaluated with a MRI brain without and with IV contrast. However, a noncontrast MRI of the brain may be appropriate if contrast cannot be given or is refused (Kennedy et al [*ACR*] 2017; PLE expert panel consensus opinion). In patients with diplopia or ophthalmoplegia, contrast-enhanced MRI of the head, contrast-enhanced MRI of the orbits, contrast-enhanced CT of the orbits, or noncontrast MRI of the orbits can be useful. Assessment of the orbits and/or head will depend on suspected anatomic localization and the differential diagnosis related to the patient's specific clinical presentation. (Kennedy et al [*ACR*] 2017).

Imaging of myelopathic symptoms:

Spinal cord MRI should always be performed in patients with spinal cord symptoms at disease onset, mainly to exclude non-demyelinating pathology and/or MS mimics as the cause of the clinical symptoms (Cristiano et al 2018; Rovira et al [*MAGNIMS*] 2015; Filippi et al [*EFNS*] 2011). It is also useful in

circumstances when brain MRI is normal or equivocal, and in patients with non-specific brain T2-abnormalities or findings that suggest radiologically isolated syndrome (RIS) (Rovira et al [*MAGNIMS*] 2015; Filippi et al [*EFNS*] 2011). Spinal cord MRI is advisable when the presentation suggests a spinal cord localization, when there is a primary progressive course, when considering multiple sclerosis in a population in which the disease is less common (e.g., older individuals or non-white populations), or when additional data are needed to increase diagnostic confidence (e.g., when brain MRI findings only fulfil the criteria for DIS) (Thompson et al 2018**; Filippi et al [*MAGNIMS*] 2016). Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g., mechanical compression) or atypical symptoms develop (Filippi et al [*EFNS*] 2011). An MRI of the spine is recommended in patients with symptoms of either acute onset myelopathy or chronic/progressive myelopathy (Agarwal et al [*ACR*] 2020).

Imaging of ataxia and/or brain stem symptoms:
If the disease process is suspected to involve the brain stem, brain, or cisternal segments of the cranial nerves, an MRI of the head without and with contrast including additional small field-of view high-resolution T2-weighted images of the cranial nerves is the preferred imaging modality (Kennedy et al [*ACR*] 2017). MRI of the brain is also usually appropriate for the initial imaging of ataxia in patients without a past history of trauma and with suspected intracranial and/or spinal process. The use of IV contrast for this scenario is preferred (Juliano et al [*ACR*] 2018).

*The *CMSC* Guideline by Traboulsee et al (2018) did not pass the AGREE II rigor of development cutoff. It was included, however, because of its direct relevance to the clinical scenario.

**The guideline by Thompson et al (2018) did not pass the overall AGREE II cutoff. It was included, however, because of its direct relevance to the clinical scenario.

Clinical notes:

- In about 85% of patients with MS, clinical onset of the disease is a *clinically isolated syndrome* (CIS) involving the optic nerve, brainstem, or spinal cord. Approximately 50-80% of these patients have lesions on MRI, consistent with prior disease activity (Filippi et al [*EFNS*] 2011).
- The McDonald criteria should be applied in patients with CIS, defined as a first subacute or acute episode of clinical symptoms suggesting an inflammatory demyelinating disorder (Rovira et al [*MAGNIMS*] 2015).
- 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset (Thompson et al 2018):

	Number of lesions with objective clinical evidence:	Additional data needed for a diagnosis of multiple sclerosis:
≥ 2 clinical attacks	≥ 2	None
≥ 2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None
≥ 2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥ 2	Dissemination in time demonstrated by an additional clinical attack or by MRI OR

		demonstration of CSF-specific oligoclonal bands
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands

- If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis (Thompson et al 2018).
- Brain and spinal cord MRI remain the most useful paraclinical tests to aid the diagnosis of MS and can complement clinical findings in the determination of DIS or DIT in patients with a typical CIS (Thompson et al 2018).
- The diagnostic criteria require exclusion of alternative diagnoses [e.g., collagen vascular disease, sarcoidosis] that can mimic MS either clinically or radiologically (Rovira et al [*MAGNIMS*] 2015). The McDonald criteria were not developed to differentiate MS from other conditions but to identify MS or a high likelihood of disease in patients with a typical CIS once other diagnoses have been deemed unlikely (Thompson et al 2018).
- Both symptomatic and asymptomatic MRI lesions can be used in the determination of DIS and DIT (Thompson et al 2018; Filippi et al [*MAGNIMS*] 2016).
- To help avoid misdiagnosis of MS, the threshold for additional testing should be low, including spinal cord MRI and CSF examination in any of the following situations (Thompson et al 2018):
    - when clinical and MRI evidence is insufficient to support a diagnosis of MS, particularly if initiation of DMTs is being considered
    - when there is a presentation other than a typical CIS, including a progressive course at onset (primary progressive MS)
    - when clinical, imaging, or laboratory features are atypical of MS
    - in populations in which MS is less common (e.g., older individuals).

<u>Imaging notes:</u>

- For patients with CIS, the recommended brain MR protocol includes axial 2D or 3D T2 fluid attenuated inversion recovery (FLAIR), axial T2 fast spin echo (FSE), sagittal 2D or 3D T2-FLAIR, DWI and SWI, and pre- and post-Gd 2D or 3D T1 weighted sequences. The T1 post-Gd sequence should be obtained at least 10 minutes after the injection of contrast. 3D sequences should be used, if possible, to get multiplanar views, and to save time (PLE expert panel consensus opinion).
- For patients with CIS, the recommended spine MR protocol includes sagittal T1, sagittal T2 FSE, sagittal STIR or T2 fat saturation, axial T1 and axial T2 (FSE and GRE). T1 sagittal and axial post-Gd images should be obtained if high signal intensity cord lesions are seen on T2 or STIR images (PLE expert panel consensus opinion).
- For patients with CIS, the recommended orbital MR protocol includes 2-3 mm axial and coronal T2- fat saturation or STIR images, and T1 axial and coronal pre- and post-Gd images (PLE expert panel consensus opinion).
- In a patient with CIS, dissemination in space can be demonstrated by one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in two or more of four areas of the CNS: periventricular, cortical or juxtacortical, infratentorial brain regions, and the spinal cord (Thompson et al 2018).

- In a patient with CIS, dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI (Thompson et al 2018).
- Symptomatic and asymptomatic MRI lesions can be considered in the determination of DIS or DIT. MRI lesions in the optic nerve in a patient presenting with optic neuritis remain an exception and, owing to insufficient evidence, cannot be used in fulfilling the McDonald criteria (Thompson et al 2018).
- Cortical and juxtacortical lesions can be used to fulfil MRI criteria for DIS (Thompson et al 2018).
- For some patients—e.g., older individuals or with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions (Thompson et al 2018).
- Spinal cord MRI should be carried out on systems with a minimum field strength of 1.5 T (Rovira et al [*MAGNIMS*] 2015). In patients with severe claustrophobia and in patients with large body habitus, consideration might be given to high field strength (1.2T) open MRI imaging (PLE expert panel consensus opinion).

Evidence update (2014-present):

Chung et al (2020), in a prospective study, sought to determine long-term outcomes in MS, and identify early prognostic features. A total of 132 patients presenting with a clinically isolated syndrome (CIS) were followed-up clinically and radiologically 1, 5, 10, 14, 20, and 30 years later. All available notes and MRI scans were reviewed, and MS was defined according to 2010 McDonald criteria. All data was available for 120 patients; 80 were known to have developed MS by 30 years. Expanded Disability Status Scale (EDSS) scores were available for 107 patients, 77 whom had MS; 32 (42%) remained fully ambulatory (EDSS scores ≤ 3.5), and MS contributed to death in 16 (20%). Of those with MS, 11 received DMT. The strongest early predictors (within 5 years of presentation) of secondary progressive MS at 30 years were presence of baseline infratentorial lesions and deep white matter lesions at 1 year. The authors conclude that, after 30 years, there was a divergence of MS outcomes; some accrued substantial disability early on; others ran a more favorable long-term course (low level of evidence).

Rahn et al (2019), in a systematic review, assessed the prognostic value of MRI for disability following a CIS. Cohort studies were included if they reported associations of MRI and disability following a CIS, included $\geq$ 50 people with a CIS at baseline, had $\geq$ 5 years of follow-up, and obtained at least one structural MRI measurement (T1 lesions, T2 lesions, T1 contrast-enhancing lesions, or brain atrophy). A total of 13 studies were identified. T2 brain lesion number determined soon after the occurrence of a CIS was associated with disability progression after 5-7 years, with an increased risk when $\geq$ 10 lesions were present. Additionally, the authors found that intfratentorial lesions were associated with a higher risk of subsequent disability (moderate level of evidence).

Brownlee et al (2019), in a multicenter prospective study, evaluated 178 patients with clinically isolated syndrome (CIS) to identify early MRI predictors of long-term outcomes in relapse-onset MS. All patients had MRI scans around initial presentation, and follow-up MRI scans at 1 and 3 years. Patients were then followed-up clinically after ~15 years to determine disease course and disability. After 15 years, 166 (93%) patients were assessed clinically: 119 (72%) had MS [94 (57%) RRMS, 25 (15%) secondary progressive], 45 (27%) remained CIS, and two (1%) developed other disorders. Physical disability was overall low in MS patients; 71% were untreated. Baseline gadolinium-enhancing (OR 3.16, $P < 0.01$) and spinal cord lesions (OR 4.71, $P < 0.01$) were independently associated with secondary progressive MS at 15 years. Baseline gadolinium-enhancing ($b = 1.32$, $P < 0.01$) and spinal cord lesions ($b = 1.53$, $P < 0.01$) showed a consistent association with Expanded Disability Status Scale at 15 years. The authors conclude

that MRI abnormalities seen around time of presentation with CIS and over the first few years after disease onset predict development of long-term outcomes in relapse-onset MS (low level of evidence).

Brownlee et al (2017) conducted an observational study to investigate longitudinal changes in spinal cord lesions and atrophy in patients with a non-spinal CIS, and how they relate to disability development (measured by EDSS). A total of 131 patients had brain and spinal cord imaging at time of CIS and at 5-year follow-up. During follow-up, 93 (71%) patients were diagnosed with MS. Baseline spinal cord lesion number, change in spinal cord lesion number, and change in upper cervical cord cross-sectional area (UCCA) were found to be independent predictors of worsened EDSS. The authors conclude that asymptomatic spinal cord lesions and atrophy contribute to the development of MS-related disability over the first 5 years after a non-spinal CIS (moderate level of evidence).

Tintore et al (2016) conducted an observational study of a CIS cohort of 1,107 patients to study the contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. Eligible patients (n = 954) were divided into 4 groups according to baseline MRI: normal MRI (n = 290); single asymptomatic lesion (n = 18); single cord/brainstem symptomatic lesion (n = 35); and > 1 lesion (n = 611). Risk of second attack was studied for each group. Results found those with a cord/brainstem single symptomatic lesion have a higher risk of second attack and disability accumulation than those with 0 lesions, but a similar risk compared to patients with 1 asymptomatic lesion. The authors conclude that symptomatic lesions should be taken into account when considering the diagnosis and prognosis of patients with CIS (high level of evidence).

Kuhle et al (2015) retrospectively assessed which clinical and environmental variables predict risk of conversion from adult CIS to clinically definite MS (CDMS). A total of 1,047 CIS cases with at least two years of follow-up were included. Age, sex, clinical presentation, T2-hyperintense lesions, cerebrospinal fluid (CSF) oligoclonal bands (OCBs), CSF IgG index, CSF cell count, serum 25-hydroxyvitamin D3 (25-OH-D), cotinine and IgG titres against Epstein-Barr nuclear antigen 1 (EBNA-1) and cytomegalovirus were tested for association with risk of CDMS. Results found that, at median follow-up of 4.31 years, 623 CIS cases (59.5%) converted to CDMS. Predictors of conversion were OCB (HR = 2.18, 95% CI = 1.71–2.77, $p < 0.001$), number of T2 lesions (2-9 lesions vs 0/1 lesions: HR = 1.97, 95% CI = 1.52–2.55, $p < 0.001$; > 9 lesions vs 0/1 lesions: HR = 2.74, 95% CI = 2.04–3.68, $p < 0.001$) and age at CIS (HR per year inverse increase = 0.98, 95% CI = 0.98–0.99, $p < 0.001$). The authors conclude that MRI lesion load, OCB and age at CIS are strongest independent predictors of conversion to CDMS (moderate level of evidence).

Nazerian et al (2014) prospectively evaluated the prevalence of different diseases causing diplopia and role of medical history, clinical exam, and unenhanced head CT (UHCT) in the identification of secondary diplopia among 260 ED patients. Secondary diplopia was diagnosed in 35.8% diplopic patients with the most frequent diagnoses as stroke (45.2%), MS (18.3%), and brain tumor (11.8%). Among 118 (45.4%) patients without associated neurological signs/symptoms (isolated diplopia), secondary diplopia was diagnosed in 13 (11%); UHCT was negative in all. Sensitivity of CT for secondary causes (including MS) was 0%. Eighty of 142 (56.3%) patients with associated signs/symptoms had secondary diplopia. The presence of signs/symptoms associated with diplopia showed sensitivity of 87% (95% CI: 80-92%) and specificity of 63% (95% CI: 59-66%) for diagnosis of secondary diplopia. In this group, UHCT identified 30/80 (37.5%) cases, increasing specificity to 98% (95% CI: 96-99%). The authors conclude that one-third of diplopic patients had secondary diplopia and in patients with associated neurological signs / symptoms, prevalence of secondary diplopia was high and UHCT showed incremental diagnostic value (moderate level of evidence).

Surveillance of suspected (relapsing-remitting) MS not fulfilling all diagnostic criteria in patients with no new clinical symptoms:

- Green – **MRI brain without and with contrast**
- Yellow – **MRI brain without contrast**
  [patient unable to receive or refuses MRI contrast]
- Yellow – **MRI brain with contrast**
  [patient has undergone recent MRI without contrast]
- Red – **CT; MRI orbits; MRI spine; Nuclear medicine; SPECT; PET; PET/CT**

Level of Evidence: MRI brain with and without contrast: high for diagnostic accuracy, very low for surveillance interval; MRI brain with or without contrast: moderate; MRI spine (cervical/thoracic): very low; CT: insufficient; MRI spine (lumbar): insufficient; all other modalities: ranging from very low to insufficient

Notes concerning use of contrast: Gadolinium-based contrast agents do accumulate in the brain. While there is no known CNS toxicity, these agents should be used judiciously, recognizing that gadolinium continues to play an invaluable role in specific circumstances related to the diagnosis and follow-up of individuals with MS (Traboulsee et al [*CMSC*] 2018). MS gadolinium-based contrast agent (GBCA) is essential when there is concern regarding an alternative diagnosis other than MS (Traboulsee et al [*CMSC*] 2018).

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:

Follow-up imaging of CIS and/or suspected MS

A follow-up brain MRI protocol for patients with CIS and/or suspected MS to look for evidence of dissemination in time (i.e., new T2 lesions or gadolinium-enhancing lesions) has been recommended at ≥ 6 months for high risk CIS, and ≥ 12 months for low risk CIS (Traboulsee et al [*CMSC*] 2018*). The PLE expert panel consensus was that a follow-up brain MRI scan is appropriate after a six-month period for MS patients with no new symptoms, irrespective of number of lesions (PLE expert panel consensus opinion). Serial imaging may be appropriate (at least annually for the first 5 years with close follow-up) as an alternative to initiating DMT in people with CIS or relapsing forms of MS who are not currently on DMT, have not had relapses in the preceding 2 years, and do not have active new MRI lesion activity on recent imaging (Rae-Grant, et al [*AAN*] 2018, Level C Recommendation). Follow-up MRIs may be needed to demonstrate DIT, which may be established with the appearance of new Gadolinium-enhancing lesions 3 months after the clinical episode, or with the detection of new T2 lesion(s) compared to a reference scan done ≥ 30 days after the clinical episode (Filippi et al. [*EFNS*] 2011). Follow-up brain imaging 3-6 months after baseline scan is recommended in patients with CIS who have an abnormal baseline MRI scan, but do not fulfil the 2010 McDonald diagnostic criteria. If the second brain scan is inconclusive, a third can be acquired 6-12 months later (Rovira et al. [*MAGNIMS*] 2015). Follow-up spinal cord MRI in patients with CIS, to demonstrate DIS and DIT, seems to have limited value and should not be routinely performed (Rovira et al. [*MAGNIMS*] 2015).

Follow-up imaging of radiologically isolated syndrome (RIS)

Radiologically isolated syndrome involves a subset of individuals with MRI findings that are strongly

suggestive of MS lesions but have no neurological manifestations or other clear-cut explanation (Thompson et al 2018). Identical DIS and DIT MRI criteria used in MS should be applied for the evaluation of RIS. In patients with RIS, a follow-up brain scan 3-6 months after the initial MRI is recommended (Rovira et al [*MAGNIMS*] 2015).

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**The guideline by Thompson et al. (2018) did not pass the overall AGREE II cutoff. It was included, however, because of its direct relevance to the clinical scenario.

Clinical notes (Thompson et al 2018):

- In the absence of a clear-cut typical clinically isolated syndrome, caution should be exercised in making the diagnosis of MS, and the diagnosis should be confirmed by further clinical and radiological follow-up. In such cases, the clinician should consider postponing making a definitive diagnosis and initiation of long-term disease-modifying therapies, pending longer follow-up to accumulate additional evidence supporting the diagnosis.
- *Solitary sclerosis*: rare patients have an inflammatory lesion of the cerebral white matter, cervicomedullary junction, or spinal cord and develop progressive disability that is clinically indistinguishable from progressive forms of multiple sclerosis and who might have CSF-specific oligoclonal bands but have no clinical or radiological evidence of new lesion formation-a condition that has been termed progressive solitary sclerosis syndrome.
- *Radiologically isolated syndrome*: a subset of individuals has MRI findings that are strongly suggestive of MS lesions but no neurological manifestations or other clear-cut explanation. Approximately a third of individuals with radiologically isolated syndrome are diagnosed with multiple sclerosis within 5 years of presentation, most often with a relapsing- remitting course, but occasionally with a primary progressive course. Factors that correlate with the subsequent development of MS include younger age, higher cerebral lesion load, asymptomatic infratentorial or spinal cord lesions, Gd-enhancing lesion, CSF-specific oligoclonal bands, and abnormal visual evoked potentials.
    - When a clinical attack occurs in RIS-DIT positive subjects (who, by definition, have DIS), a diagnosis of MS can be made (Filippi et al [*MAGNIMS*] 2016).
- *Possible multiple sclerosis*: defined as suspicion of multiple sclerosis (i.e., a patient with a clinically isolated syndrome but not meeting the full criteria).
- To help avoid misdiagnosis of MS, the threshold for additional testing should be low, including spinal cord MRI and CSF examination in any of the following situations:
    - when clinical and MRI evidence is insufficient to support a diagnosis of MS, particularly if initiation of DMTs is being considered
    - when there is a presentation other than a typical CIS, including a progressive course at onset (primary progressive MS)
    - when clinical, imaging, or laboratory features are atypical of MS
    - in populations in which MS is less common (e.g., older individuals).
- Although the absence of CSF oligoclonal bands does not rule out MS, particularly early in the condition and in children, caution should be exercised in making this diagnosis when CSF oligoclonal bands are not detected and, certainly, in the presence of atypical clinical, imaging, or CSF findings syndrome.
- Although MS typically presents between the ages 20-50 years, approximately 0.5% of adults with this disease have symptom onset at age $\geq$ 60 years. Careful attention to alternative

diagnoses and particularly comorbidities is necessary.

Imaging notes:

- Follow-up MRI scans should be performed with the same machinery and scanning parameters, and identical slice positions are required for exact comparison (Filippi et al [*EFNS*] 2011).
- For patients with suspected MS, the recommended follow-up brain MR should include axial 2D or 3D T2 fluid attenuated inversion recovery (FLAIR), axial T2 fast spin echo (FSE), sagittal 2D or 3D T2-FLAIR, DWI and SWI, and pre- and post-Gd 2D or 3D T1 weighted sequences. The T1 post-Gd sequence should be obtained at least 10 minutes after the injection of contrast. 3D sequences should be used, if possible, to get multiplanar views, and to save time (PLE expert panel consensus opinion).
- In a patient with CIS, dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI (Thompson et al 2018).

Evidence update (2014-present):

Solomon et al (2016) conducted a cross-sectional analysis to characterize patients misdiagnosed with MS. Of 110 patients, 51 (46%) were classified as “definite” and 59 (54%) “probable” misdiagnoses. Alternate diagnoses included migraine alone or in combination with other diagnoses (22%), fibromyalgia (15%), nonspecific or nonlocalizing neurologic symptoms with abnormal MRI (12%), conversion or psychogenic disorders (11%), and neuromyelitis optica spectrum disorder (6%). Duration of misdiagnosis was $\geq$ 10 years in 36 (33%) and an earlier opportunity to make a correct diagnosis was identified for 79 patients (72%). The authors conclude that misdiagnosis of MS leads to unnecessary and potentially harmful risks to patients. Misinterpretation and misapplication of MS clinical and radiographic diagnostic criteria are important contemporary contributors to misdiagnosis (low level of evidence).

Monitoring of treatment response in patients with known (relapsing-remitting) MS:

- Green – **MRI brain without and with contrast** or **MRI brain without contrast**
- Yellow – **MRI brain with contrast**
  [patient has undergone recent MRI without contrast]
- Yellow –**MRI spine (cord/conus medullaris) without and/or with contrast**
  [follow known prior involvement of spinal cord; or suspicion of new cord lesion(s)]
- Yellow –**MRI orbits without and/or with contrast**
  [follow known prior involvement of optic nerves; or suspicion of new visual symptoms]
- Red – **CT; Nuclear medicine; SPECT; PET; PET/CT**

Level of Evidence: MRI brain with and without contrast: low for impact of monitoring on patient management or outcome, very low for timing of follow-up; MRI brain with or without contrast: low; MRI spine (cervical/thoracic) with and without contrast: insufficient; MRI spine (cervical/thoracic) with or without contrast: very low; CT: insufficient; MRI spine (lumbar): insufficient; all other modalities: ranging from very low to insufficient

Notes concerning use of contrast: Gadolinium-based contrast agents do accumulate in the brain. While there is no known CNS toxicity, these agents should be used judiciously, recognizing that gadolinium continues to play an invaluable role in specific circumstances related to the diagnosis and follow-up of individuals with MS (Traboulsee et al [*CMSC*] 2018). MS gadolinium-based contrast agents (GBCA) are optional for the follow-up monitoring of patients with MS to detect subclinical disease activity which could lead to a change in therapy. The use of GBCA may be helpful within the first two years of treatment onset but is not required because new T2 MS lesions can be identified on well-performed MRI using a standardized protocol unless there is a large T2 lesion burden (Traboulsee et al [*CMSC*] 2018).

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
Brain MRI
Timing of brain MRI protocol for patients with an established diagnosis of MS (Traboulsee et al [*CMSC*] 2018*):

- Prior to starting or switching disease-modifying therapy
- Approximately 6-12 months after switching disease-modifying therapy to establish a new baseline on the new therapy

Every 1-2 years while on disease modifying therapy to assess for subclinical disease activity (i.e., new T2 lesions or gadolinium enhancing lesions). Less frequent MRI scans required in clinically stable patients after 2-3 years of stable treatment (gadolinium-based contrast optional)*The PLE expert panel agreed that stable, low-risk patients may not need long term yearly surveillance with MRI* (PLE expert panel consensus opinion).

Clinicians should monitor disease activity from the clinical onset to detect the accumulation of new lesions in order to inform treatment decisions in people with MS (Rae-Grant, et al [*AAN*] 2018, Level B Recommendation). Routine brain MR and clinical-follow-up of patients after treatment initiation of disease modifying therapies (DMTs) in relapse-remitting MS (RRMS) patients is recommended to

identify ongoing inflammatory disease activity (Cristiano et al 2018; Montalban et al [*ECTRIMS/EAN*] 2018, weak recommendation). T2-weighted and contrast-enhanced T1-weighted brain MRI are the modalities of choice, as they can reveal acute and active inflammation, as well as clinically silent disease progression (Wattjes et al [*MAGNIMS*] 2015). When monitoring treatment response in patients treated with DMTs, a standardized reference brain MRI should usually be performed within 6 months of treatment onset and compared with a brain MRI performed typically 12 months after starting treatment. Additionally, pseudoatrophy effects mostly occur within the first 6-12 months from treatment initiation with any anti-inflammatory therapy, and a re-baseline MRI at 6-12 months after initiation of any therapy is recommended to mitigate the impact of pseudoatrophy on outcome measures (Sastre-Garriga et al [*MAGNIMS*] 2020). The timing of such follow-up MRI intervals can be adjusted, and should be dependent on pharmacodynamics (onset of action) of the specific DMT used, as well as disease activity (including clinical and MRI features) (Montalban et al [*ECTRIMS/EAN*] 2018, consensus statement; Cristiano et al 2018; Montalban et al [*ECTRIMS/EAN*] 2018; PLE expert panel consensus opinion). MRI should also be included in drug surveillance programs to screen for opportunistic infections (PML), unexpected disease activity (including paradoxical reactions), and comorbidities (Wattjes et al [*MAGNIMS*] 2015).

Spinal cord MRI

The use of spinal cord MRI in addition to brain MRI is not recommended for routing monitoring, and should be limited to certain clinical situations (such as unexplained and/or unexpected spinal cord symptoms) (Wattjes et al [*MAGNIMS*] 2015; Cristiano et al 2018). Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g., mechanical compression) or atypical symptoms develop (Filippi et al [*EFNS*] 2011).

Advanced MRI methods

The use of advanced MRI methods (proton magnetic resonance spectroscopy, diffusion tensor imaging, magnetization transfer imaging, myelin mapping) for MS disease monitoring is promising but has not been well investigated; their value is potentially limited by a lack of standardization, and advanced MRI is, therefore, not recommended for routine clinical use (Wattjes et al [*MAGNIMS*] 2015).

*The *CMSC* Guideline by Traboulsee et al (2018) did not pass the AGREE II rigor of development cutoff. It was included, however, because of its direct relevance to the clinical scenario.

<u>Clinical notes:</u>

- When monitoring treatment response in patients treated with DMDs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method supplemented by GAD enhancing lesions for monitoring treatment response (Montalban et al [*ECTRIMS/EAN*] 2018, consensus statement).
- The presence of new MR lesions in patients with RRMS, after at least 6 months of correct DMT use, is indicative of persistence of disease activity (Cristiano et al 2018).

<u>Imaging notes:</u>

- A standardized MR protocol at follow-up should be applied to RRMS patients. For surveillance of patients on DMT, follow-up brain MR exams should include axial 2D or 3D T2 fluid attenuated inversion recovery (FLAIR), axial T2 fast spin echo (FSE), sagittal 2D or 3D T2-FLAIR, DWI and SWI, and pre- and post-Gd 2D or 3D T1 weighted sequences. The T1 post-Gd sequence should be obtained at least 10 minutes after the injection of contrast. 3D sequences should be used, if possible, to get multiplanar views, and to save time (PLE expert panel consensus opinion).

Evidence update (2014-present):
Narayana et al (2020), in a prospective study, evaluated whether deep learning can predict enhancing lesions obtained on MRI scans without the use of contrast material. Scans from 1,008 RRMS patients were analyzed. A convolutional neural network was used for classification of enhancing lesions on unenhanced MRI scans; this classification was performed for each slice, and the slice scores were combined by using a fully connected network to produce participant-wise predictions. Enhanced lesions on postcontrast T1-weighted images served as the ground truth, and network performance was assessed by using fivefold cross-validation. At least one enhancing lesion was observed in 519 participants. The sensitivity and specificity averaged across the five test sets were 78% +/- 4.3 and 73% +/- 2.7, respectively, for slice-wise prediction. The corresponding participant-wise values were 72% +/- 9.0 and 70% +/- 6.3. The diagnostic performances (AUCs) were 0.82 +/- 0.02 and 0.75 +/- 0.03 for slice-wise and participant-wise enhancement prediction, respectively. The authors conclude that deep learning used with conventional MRI identified enhanced lesions in MS from unenhanced multiparametric MRI images with moderate to high accuracy (moderate level of evidence).

Sadigh et al (2019), in a retrospective study, evaluated whether enhancing MS lesions on follow-up MRI can be detected by visual assessment of unenhanced double inversion recovery and FLAIR sequences. A total of 252 consecutive MRIs in 172 adult patients with known MS were reviewed. The co-presence or absence of associated double inversion recovery and FLAIR signal abnormality within contrast-enhancing lesions was recorded by 3 neuroradiologists. A total of 34 of 252 MRIs (13%) demonstrated 55 enhancing lesions, of which 52 (95%) had corresponding hyperintensity on double inversion recovery and FLAIR. All lesions were concordant between double inversion recovery and FLAIR, and the 3 enhancing lesions not visible on either sequence were small (<2 mm) and cortical/subcortical (n = 2) or periventricular (n = 1). The authors conclude that there was a high concordance between enhancing lesions and hyperintensity on either double inversion recovery or FLAIR (low level of evidence).

Eichinger et al (2019), in a retrospective study, investigated whether use of contrast material has an effect on detection of new or enlarged MS lesions and, consequently, assessment of interval progression. A total of 507 follow-up MR images obtained from 359 patients with MS (88% with RRMS; 10% with CIS) were evaluated. With use of subtraction maps, nonenhanced images (double inversion recovery [DIR], fluid-attenuated inversion recovery [FLAIR]) and contrast material–enhanced (gadoterate meglumine, 0.1 mmol/kg) T1-weighted images were separately assessed for new or enlarged lesions in independent readings by two readers blinded to each other's findings and to clinical information. New or enlarged lesions were identified on 264 of the 507 follow-up images. Four lesions were detected on only nonenhanced images, corresponding to 1.9% (4/207) of the enhancing and 0.2% (4/1992) of all new or enlarged lesions. Nine enhancing lesions were not detected on FLAIR-based subtraction maps (9/1442, 0.6%). In none of the 507 images did the contrast-enhanced sequences reveal interval progression that was missed in the readouts of the nonenhanced sequences, with use of either DIR- or FLAIR-based subtraction maps. Interrater agreement was high for all three measures, with intraclass correlation coefficients of 0.91 with FLAIR, 0.94 with DIR, and 0.99 with contrast-enhanced T1-weighted imaging. The authors conclude that, at 3.0 T, use of a gadolinium-based contrast agent at follow-up MRI did not change the diagnosis of interval disease progression in patients with MS (low level of evidence).

Rudie et al (2019), implemented a prospective quality improvement project to reserve use of IV contrast only for MS patients with evidence of new disease activity on noncontrast imaging. The project sought to make the decision of whether patients had new disease activity in "real-time" while still on the MRI scanner table. To do so, the project utilized a routine in-house computer assisted detection (CAD)

software for evaluating changes in MS FLAIR MRs. Prior to implementation, multidisciplinary meetings were held with clinical staff regarding implementation. During the 2-month trial, 153 patients were imaged under the new protocol. Technologists using the CAD software were able to identify patients with new or enlarging lesions on FLAIR images with 95% accuracy and 97% negative predictive value relative to final neuroradiologist interpretations. This allowed avoidance of contrast and additional imaging sequences in 87% of patients (low level of evidence).

Eden et al (2019), in a prospective study, explored the spatial distribution of MS lesions in the cervical spinal cord among 642 suspected or confirmed MS patients (31 CIS; 416 RRMS; 84 secondary progressive; and 73 PPMS) from 13 clinical sites). Cervical spine lesions were manually delineated on T2- and T2*-weighted axial and sagittal MRI scans acquired at 3 or 7 T. No cervical spine lesions were identified in 22.58% (n = 7) of CIS patients, 9.62% (n = 40) of RRMS patients, 4.76% (n = 4) of SPMS patients, and 1.37% (n = 1) of PPMS patients. Overall, inter-rater agreement was good with Dice kappa of 0.63 +/- 0.21, lesion positive predictive value of 0.79 +/- 0.16 and lesion sensitivity of 0.69 +/- 0.16. Lesions appearing in the lateral funiculi and central cord area were significantly correlated with Expanded Disability Status Scale score ($P < 0.001$). The authors conclude that high lesion frequencies were observed in patients with a more aggressive disease course, rather than long disease duration, and that this work shows the added value of cervical spine lesions (moderate level of evidence).

Barisano et al (2019), in a retrospective study, assessed the effects of linear gadolinium-based contrast agents on T1 signal intensity of 3 cerebral areas (dentate nucleus, globus pallidus, and substantia nigra) and the cervical spinal cord in 100 patients with RRMS. Over a 13-year period, patients underwent between 2-16 contrast-enhanced MRIs: 50 patients received $\leq$ 5 linear gadolinium injections, and 50 had $\geq$ 6 injections. Analysis of signal intensity changes was independently performed by 2 readers on first and last MRI scan. Results found an increase of globus pallidus-to-thalamus, dentate nucleus-to-middle cerebellar peduncle, and substantia nigra-to-midbrain signal intensity ratios after multiple administrations of linear gadolinium-based contrast agents. These changes were significantly higher in patients who received $\geq$ 6 injections ($P < .001$) and positively correlated with the number of injections and the accumulated dose of contrast. No significant changes were detected in the spinal cord ($P = .400$) (low level of evidence).

Granella et al (2019), in a retrospective study, investigated the frequency of asymptomatic spinal cord combined unique activity (SC-CUA), defined as occurrence of new/enlarging T2 or gadolinium-positive (Gd+) spinal cord lesions (SCLs) on MRI in 230 patients diagnosed with CIS (6%) or RRMS (94%). In a total of 340 scans, SC-CUA was asymptomatic in 31.2%; 12.1% had neither clinical activity nor brain radiological activity (44.5% and 25.4%, respectively). Asymptomatic SC-CUAs were associated with older age at onset, non-spinal onset, lower EDSS at MRI, and lower number of Gd+ SCLs, compared to symptomatic SC-CUAs. The authors conclude that a substantial proportion of patients had SC-CUA without clinical symptoms and/or without concomitant brain MRI activity. This suggests that regular SC-MRI follow-up is required for reliable assessment of radiological activity (low level of evidence).

Uher et al (2017) conducted an observational cohort study of patients with RRMS (n = 177) who participated in the original Avonex-Steroids-Azathioprine (ASA) 2-year randomized double-blind, placebo-controlled trial. The authors examined accuracy of early prediction of 12-year disability outcomes using clinical and MRI parameters. Patients underwent 3-mo clinical follow-ups; associations were modeled between clinical and MRI markers at baseline or after 12 mo with sustained disability progression (SDP) over the 12-year observational period. Results found that, at baseline, T2 lesion number, T1 and T2 lesion volumes, corpus callosum (CC), and thalamic fraction were best predictors of

SDP (HR = 1.7-4.6; $p \leq 0.001$-0.012). At 12 mo, Expanded Disability Status Scale (EDSS) and its change, number of new or enlarging T2 lesions, and CC volume % change were best predictors of SDP over follow-up (HR = 1.7–3.5; $p \leq 0.001$–0.017). The authors conclude that the combination of established MRI and clinical indices with MRI volumetric predictors improved prediction of SDP over long-term follow-up and may provide valuable information for therapeutic decisions (high level of evidence).

Zecca et al (2016) conducted a retrospective study to assess the prognostic value of asymptomatic spinal cord lesions (a-SL) in predicting MS course. A total of 103 RRMS patients who received serial MRI (brain and spinal) at baseline (t1) and within 12-36 months (t2) during clinical stability, and had a follow-up (t2-t3) $\geq$ 24 mo were included. Relapses and disability progression were evaluated between t2 and t3. When compared to the overall cohort, relapse risk was significantly increased in patients with asymptomatic spine and brain lesions (HR = 2.3). 9% of patients with MS had asymptomatic progression in the spine, but not the brain. There were no differences in the risk of disability progression as measured by EDSS when compared to patients without asymptomatic lesions. The authors conclude that a-SL occur in one-quarter of clinically stable RRMS, and combined with asymptomatic brain lesions (a-BL) contribute significantly in predicting future disease course (low level of evidence).

Hua et al (2016) conducted a cross-sectional analysis to determine whether cervical spinal cord lesions predict presence of thoracic cord lesions in MS patients. The study cohort was 126 patients fulfilling 2010 McDonald criteria for MS. MRI studies of the brain, cervical, and thoracic spine were acquired. There was an overall odds ratio (OR) increase of thoracic spine involvement when any cervical spine lesion was present (OR=6.08, 95% CI (2.21–16.68), P=0.001). A substantial and significant increase was found in the odds of thoracic spine involvement when more than two cervical spine lesions were present, two lesions (OR 4.44, (0.91–21.60), P=0.06), three lesions (OR 19.76, (3.51–111.17), P=0.001), four or more lesions (OR 20.49, (1.97–213.23), P=0.012) and diffuse lesions (OR 71.94, (5.28–979.88), P=0.001), when adjusting for significant covariates. The authors conclude that thoracic spinal cord lesions appear to be predicated on the degree of cervical spine involvement in patients with MS, a risk that appears to be independent of brain findings or clinical features (low level of evidence).

Known MS with new or recurrent neurological symptoms (MS exacerbation or relapse):

- Green – **MRI brain without and with contrast**

- Yellow – **MRI spine (cord/conus medullaris) without and with contrast**
  [follow known prior involvement of spinal cord; or suspicion of new cord lesion(s)]
- Yellow – **MRI orbits without and with contrast**
  [follow known prior involvement of optic nerves; or suspicion of new visual symptoms]

- Yellow – **MRI brain without contrast**
- Yellow – **MRI orbits without contrast**
- Yellow – **MRI spine (cord/conus medullaris) without contrast**
  [patient unable to receive or refuses MRI contrast]

- Yellow – **MRI brain with contrast**
- Yellow – **MRI orbits with contrast**
- Yellow – **MRI spine (cord/conus medullaris) with contrast**
  [patient has undergone recent MRI without contrast]

- Yellow – **CT head with and/or without contrast**
- Yellow – **CT orbits with and/or without contrast**
- Yellow – **CT spine with and/or without contrast**
  [to exclude other diagnoses in patient who cannot undergo MRI]

- Red – **Nuclear medicine; SPECT; PET; PET/CT**

Level of Evidence: MRI brain with and without contrast: high for diagnostic accuracy and yield; MRI brain with or without contrast: moderate; MRI spine (cervical/thoracic) with and without contrast: high for diagnostic accuracy and diagnostic yield with clinical features of cord involvement; MRI spine (cervical/thoracic) with or without contrast: very low; CT: insufficient; MRI spine (lumbar): insufficient; all other modalities: ranging from very low to insufficient

Notes concerning use of contrast: Gadolinium-based contrast agents do accumulate in the brain. While there is no known CNS toxicity, these agents should be used judiciously, recognizing that gadolinium continues to play an invaluable role in specific circumstances related to the diagnosis and follow-up of individuals with MS (Traboulsee et al [*CMSC*] 2018). MS GBCA is essential for following a patient with highly active disease, or when there is unexplained/unexpected clinical worsening (Traboulsee et al [*CMSC*] 2018).

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
MRI protocol for patients with an established diagnosis of MS includes unexpected clinical deterioration or reassessment of original diagnosis (Traboulsee et al [*CMSC*] 2018*). Patients should be further evaluated with MRI after each unexpected clinical presentation that might be related to MS (such as

unexplained or atypical symptoms of disease activity), or is not typical of MS (e.g., suspected comorbidity such as vascular or neoplastic disease, or adverse effects of treatments) (Wattjes et al [*MAGNIMS*] 2015). Treatment with DMTs should be offered to patients with active relapsing-remitting MS, as defined by clinical relapses and/or MRI activity (such as active lesions, contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually) (Rae-Grant et al [AAN] 2018, level B recommendation; Montalban et al [*ECTRIMS/EAN*] 2018, strong recommendation). The use of spinal cord MRI in addition to brain MRI is not recommended for routine monitoring, and should be limited to certain clinical situations (such as unexplained and/or unexpected spinal cord symptoms) (Wattjes et al [*MAGNIMS*] 2015). Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g., mechanical compression) or atypical symptoms develop (Filippi et al [*EFNS*] 2011).

*The *CMSC* Guideline by Traboulsee et al (2018) did not pass the AGREE II rigor of development cutoff. It was included, however, because of its direct relevance to the clinical scenario.

Clinical notes:

- Diagnose a relapse of MS if the person develops new symptoms or has worsening of existing symptoms and these last for more than 24 hours in the absence of infection or any other cause after a stable period of at least one month (*NICE* 2019).

Imaging notes:

- A standardized MR protocol should be applied to RRMS patients with new or recurrent symptoms. The follow-up brain MR exam should include axial 2D or 3D T2 fluid attenuated inversion recovery (FLAIR), axial T2 fast spin echo (FSE), sagittal 2D or 3D T2-FLAIR, DWI and SWI, and pre- and post-Gd 2D or 3D T1 weighted sequences. The T1 post-Gd sequence should be obtained at least 10 minutes after the injection of contrast. 3D sequences should be used, if possible, to get multiplanar views, and to save time (PLE expert panel consensus opinion).
- For patients with new or recurrent symptoms, the recommended spine MR protocol includes sagittal T1, sagittal T2 FSE, sagittal STIR or T2 fat saturation, axial T1 and axial T2 (FSE and GRE). T1 sagittal and axial post-Gd images should be obtained if high signal intensity cord lesions are seen on T2 or STIR images (PLE expert panel consensus opinion).
- For patients with new or recurrent symptoms, the recommended orbital MR protocol includes 2-3 mm axial and coronal T2- fat saturation or STIR images, and T1 axial and coronal pre- and post-Gd images (PLE expert panel consensus opinion).

Evidence update (2014-present):

Treaba et al (2014) conducted a retrospective study to identify imaging characteristics on conventional MRI that could predict MS brain lesion activity without contrast media administration among MS patients with symptoms or signs on neurologic examination suggestive of new disease activity. MR data sets of 42 patients with RRMS were reviewed. Results found that, on T2-weighted images, only the pattern consisting of a thin border of decreased intensity compared with the lesion's center and perifocal edema (Type II) reached diagnostic accuracy in terms of its relationship with gadolinium enhancement (P = 0.006). Sensitivity was 0.461 and specificity was 0.698. The authors conclude that assessment of MS lesion activity should include a careful evaluation of T2-weighted images in addition to contrast enhancement assessment (low level of evidence).

Optic neuritis and/or myelopathic symptoms suspicious for neuromyelitis optica spectrum disorders (NMOSDs):

- Green – **MRI orbits without and with contrast**
- Green – **MRI brain without and with contrast**
- Green – **MRI spine (cord) without and with contrast**

- Yellow – **MRI brain without contrast**
- Yellow – **MRI orbits without contrast**
- Yellow – **MRI spine (cord/conus medullaris) without contrast**
  [patient unable to receive or refuses MRI contrast]

- Yellow – **MRI brain with contrast**
- Yellow – **MRI orbits with contrast**
- Yellow – **MRI spine (cord/conus medullaris) with contrast**
  [patient has undergone recent MRI without contrast]

- Yellow – **CT head with and/or without contrast**
- Yellow – **CT orbits with and/or without contrast**
- Yellow – **CT spine with and/or without contrast**
  [to exclude other diagnoses in patient who cannot undergo MRI]

- Red – **Nuclear medicine; SPECT; PET; PET/CT**

Level of Evidence: MRI brain with and without contrast: high for diagnostic accuracy and yield; MRI brain with or without contrast: moderate; MRI spine (cervical/thoracic) with and without contrast: high for diagnostic accuracy and diagnostic yield with clinical features of cervical cord involvement, moderate for yield with clinical features of brain involvement, very low for sequential vs. simultaneous imaging; MRI spine (cervical/thoracic) with or without contrast: very low; CT: insufficient; MRI spine (lumbar): insufficient; all other modalities: ranging from very low to insufficient

Notes concerning use of contrast: Gadolinium-based contrast agents do accumulate in the brain. While there is no known CNS toxicity, these agents should be used judiciously, recognizing that gadolinium continues to play an invaluable role in specific circumstances related to the diagnosis and follow-up of individuals with MS (Traboulsee et al [*CMSC*] 2018).

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
Neuromyelitis optica is a demyelinating condition that typically affects the optic nerves and spinal cord and is best assessed with MRI (Kennedy et al [*ACR*] 2017). Serum and cerebrospinal fluid laboratory tests are also useful in differentiating between multiple sclerosis and neuromyelitis optica (Kennedy et al [*ACR*] 2017). Brain MRI is a mainstay in the work-up and may display gadolinium-enhancement of the optic nerve and both symptomatic and asymptomatic brain lesions (Sellner et al [*EFNS*] 2010). MRI lesion patterns are a major arbiter of CNS demyelinating disease differential diagnosis. Several brain, optic nerve, and spinal cord patterns are characteristic or highly suggestive of NMOSD (Wingerchuk et al

[*IPND*] 2015). MRI appearance of spinal cord lesions also plays a central role in the diagnosis of neuromyelitis optica (Sellner et al [*EFNS*] 2010). Optic neuritis is best assessed with a contrast-enhanced MRI of the orbits and contrast-enhanced MRI of the brain, which are often performed in conjunction with one another (Kennedy et al [*ACR*] 2017).

Clinical notes:

- Neuromyelitis optica (NMO) is an inflammatory CNS syndrome distinct from MS that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) (Wingerchuk et al [*IPND*] 2015).
- Core clinical characteristics for NMOSD are (Wingerchuk et al [*IPND*] 2015):
    - Optic neuritis particularly if it is simultaneously bilateral, involves the optic chiasm, causes an altitudinal visual field defect, or causes severe residual visual loss
    - Acute myelitis particularly with complete (rather than partial) spinal cord syndrome and paroxysmal tonic spasms
    - Area postrema syndrome (16-43% incidence) consisting of intractable hiccups or nausea and vomiting
    - Acute brainstem syndrome
    - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
    - Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- Diagnostic criteria for NMOSD with AQP4-IgG (Wingerchuk et al [*IPND*] 2015):
    - At least one core clinical characteristic
    - Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
    - Exclusion of alternative diagnoses.
- Diagnostic criteria for NMOSD without AQP4-IgG and for NMOSD with unknown AQP4-IgG status include at least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements (Wingerchuk et al [*IPND*] 2015):
    - At least one episode consistent with optic neuritis, acute myelitis with LETM, or area postrema syndrome
    - Dissemination in space (2 or more different core clinical characteristics)
    - Fulfillment of additional MRI requirements, as applicable
    - Negative tests for AQP4-IgG using best available detection method, or testing unavailable
    - Exclusion of alternative diagnoses.
- Additional MRI requirements for NMOSD without AQP4-IgG and for NMOSD with unknown AQP4-IgG status include (Wingerchuk et al [*IPND*] 2015):
    - Acute optic neuritis with brain MRI showing
        - normal findings or only nonspecific white matter lesions, OR
        - optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over > 1/2 optic nerve length or involving optic chiasm
    - Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
    - Area postrema syndrome with associated dorsal medulla/area postrema lesions
    - Acute brainstem syndrome with associated periependymal brainstem lesions on MRI.

- The majority of patients [with neuromyelitis optica] suffer from a recurrent course (80-90%) while monophasic (10-20%) and primary or secondary progressive courses are rare (Sellner et al [*EFNS*] 2010).
- Most relapses of neuromyelitis optica worsen over several days and then slowly improve in the weeks or months after the maximum clinical deficit is reached (Sellner et al [*EFNS*] 2010).
- NMOSD diagnosis is not warranted in asymptomatic patients with NMOSD-compatible MRI lesions because the expected clinical course in such individuals is unknown (Wingerchuk et al [*IPND*] 2015).
- Systemic lupus erythematosus (SLE), Sjögren syndrome (SS) or myasthenia gravis may coexist with NMOSD clinical syndromes in AQP4-IgG-seropositive patients, and in fact their presence supports the diagnosis of NMOSD (Wingerchuk et al [*IPND*] 2015).
- Sarcoidosis, cancer and chronic infection (e.g. HIV or syphilis) may present with neurologic syndromes that mimic NMOSD (Wingerchuk et al [*IPND*] 2015).
- Although the clinical, imaging, and CSF features of multiple sclerosis and NMOSDs can overlap, these disorders are now understood to be distinct with the diagnosis of NMOSDs facilitated by the development and use of serological testing for antibodies reactive with the AQP4 water channel and the validation of the antibodies not only as markers of NMOSDs but also as pathogenic factors (Thompson et al 2018).
- Because the treatments for multiple sclerosis and NMOSDs are different, the *International Panel on Diagnosis of Multiple Sclerosis* recommended that NMOSDs should be considered in any patient being evaluated for multiple sclerosis. Serological testing for AQP4 and for MOG should be done in all patients with features suggesting NMOSDs (Thompson et al 2018).

<u>Imaging notes:</u>

- For patients with a suspected NMOSD, the recommended brain MR protocol includes axial 2D or 3D T2 fluid attenuated inversion recovery (FLAIR), axial T2 fast spin echo (FSE), sagittal 2D or 3D T2-FLAIR, DWI and SWI, and pre- and post-Gd 2D or 3D T1 weighted sequences. The T1 post-Gd sequence should be obtained at least 10 minutes after the injection of contrast. 3D sequences should be used, if possible, to get multiplanar views, and to save time (PLE expert panel consensus opinion).
- For patients with a suspected NMOSD, the recommended spine MR protocol includes sagittal T1, sagittal T2 FSE, sagittal STIR or T2 fat saturation, axial T1 and axial T2 (FSE and GRE). T1 sagittal and axial post-Gd images should be obtained if high signal intensity cord lesions are seen on T2 or STIR images (PLE expert panel consensus opinion).
- For patients with a suspected NMOSD, the recommended orbital MR protocol includes 2-3 mm axial and coronal T2- fat saturation or STIR images, and T1 axial and coronal pre- and post-Gd images (PLE expert panel consensus opinion).
- Spinal cord lesions extending over three or more vertebral segments are the most reliable finding for the diagnosis of NMO (Sellner et al [*EFNS*] 2010, Class IV).
- Acute spinal cord lesions tend to occupy most of the cross-sectional area of an affected segment and are associated with swelling and Gd-enhancement (Sellner et al [*EFNS*] 2010, Class IV).
- A LETM spinal cord lesion associated with acute myelitis is the most specific neuroimaging characteristic of NMOSD and is very uncommon in adult MS. 7%–14% of initial and 8% of subsequent myelitis attacks in AQP4-IgG-seropositive patients do not meet the LETM definition. Therefore, NMOSD must be considered in the differential diagnosis in patients presenting with short myelitis lesions (Wingerchuk et al [*IPND*] 2015; Sellner et al [*EFNS*] 2010, Class IV).

- Patients with optic neuritis may show increased signal within the optic nerve on fat-suppressed T2-weighted orbital MRI sequences, enhancement of the optic nerves with gadolinium on T1-weighted sequences, bilateral optic nerve involvement, posterior nerve predominance (with extension into the optic chiasm), or extensive involvement of the optic nerve (more than half of its length) (Wingerchuk et al [*IPND*] 2015).
- Patients with NMOSD may show high signal intensity lesions on T2-weighted images involving the dorsal medulla (especially the area postrema), periependymal surfaces of the fourth ventricle, hypothalamus, thalamus, or periependymal surfaces of the third ventricle. They may also show large, confluent, unilateral, or bilateral subcortical or deep white matter lesions; long diffuse, heterogeneous, or edematous corpus callosum lesion; long unilateral or bilateral corticospinal tract lesions involving internal capsule and cerebral peduncle; or extensive periependymal brain lesions, often with gadolinium enhancement (Wingerchuk et al [*IPND*] 2015).
- A normal brain MRI or the detection of nonspecific white matter lesions is a key supportive criterion, however as many as 10-16% of patients with NMOSD will have MRI white matter lesions consistent with MS (Wingerchuk et al [*IPND*] 2015; Sellner et al [*EFNS*] 2010, Class IV).

<u>Evidence update (2014-present):</u>
Kim et al (2016) conducted a retrospective study to investigate the frequency of asymptomatic acute brain MRI abnormalities accompanying optic neuritis (ON) or myelitis in neuromyelitis optica spectrum disorder (NMOSD) patients with aquaporin-4 antibodies (AQP4-Ab). A total of 324 brain MRI scans were obtained during acute attacks of ON or myelitis in 165 patients. Acute asymptomatic NMOSD-typical brain lesions accompanied 27 (8%) acute attacks of ON or myelitis in 24 (15%) patients. The most common asymptomatic brain abnormalities included edematous corpus callosum lesions (n = 17), followed by lesions on the internal capsule and/or cerebral peduncle lesions (n = 9), periependymal surfaces of the fourth ventricle (n = 5), large deep white matter lesions (n = 4), and periependymal cerebral lesions surrounding the lateral ventricles (n = 3). The authors conclude that asymptomatic acute NMOSD-typical brain lesions can be accompanied by an acute attack of ON or myelitis. Identifying these asymptomatic brain lesions may help facilitate earlier diagnosis of NMOSD (low level of evidence).

Guideline exclusions:

- Primary progressive MS (PPMS)
- Other demyelinating diseases
- Pregnant patients
- Pediatric patients

AUC Revision History:

Revision Date:	New AUC Clinical Scenario(s):	Posting Date:	Approved By:
12/01/2020	n/a	12/08/2020	CDI Quality Institute's Multidisciplinary Committee

Information on our evidence development process, including our conflicts of interest policy is available on our website at **https://www.mycdi.com/ple**