Medora

La community dei professionisti della salute By Roche

M-IT-00001116

# Clinical presentation and symptoms of MS

# Clinical presentation and symptoms of MS

1. Diagnosis of MS
2. How is MS diagnosed?
3. What are the diagnostic criteria for MS?
4. What changes did the McDonald 2017 update make to the diagnosis of MS?
5. What How do doctors avoid misdiagnosis of MS?
6. Monitoring of patients with MS

# Multiple sclerosis is a chronic, progressive, inflammatory disease of the central nervous system

MS is a chronic, inflammatory, demyelinating disease of the CNS, characterised by ongoing disease activity, with profound effects on patient independence and quality of life[1,2]

- MS is the most common cause of non-traumatic neurological disability in young adults[3,4]
- There is currently no cure for MS and the available therapies only slow disease progression[5]

1. Conway D, Cohen JA. Lancet Neurol 2010;9:299–308; 2. Compston A, Coles A. Lancet 2002;359:1221–31; 3. Multiple Sclerosis International Federation. Atlas of MS 2013. https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf Accessed January 2020; 4. George MF, et al. Neurol Genet 2016;2:e87.

# Symptoms of MS vary and are unpredictable, commonly patients experience fatigue, sensory problems and mobility impairment

Most common symptoms1:

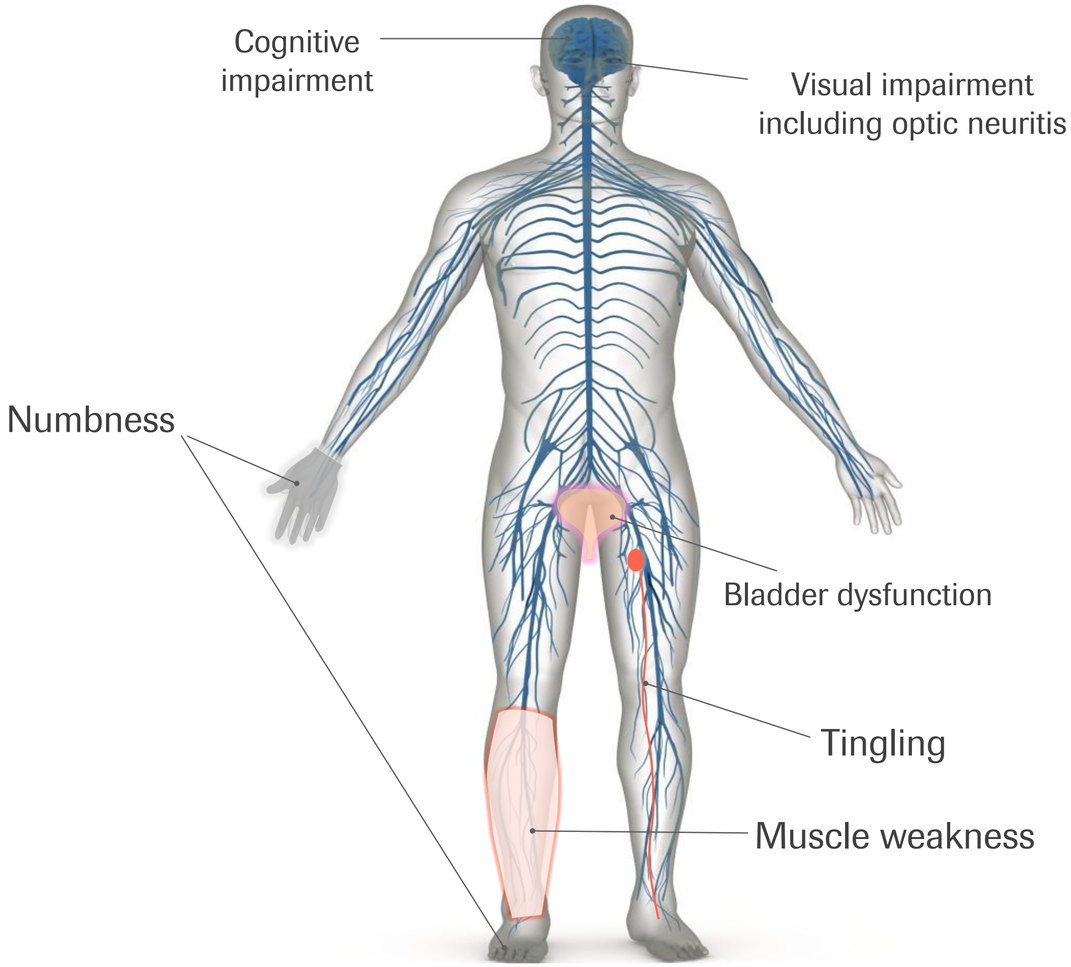
- Mobility impairment and muscle weakness (90%)4
- Sensory problems including visual disturbances, numbness, and tingling (85%)3
- Fatigue (80%)1
- Bladder dysfunction (80%)1
- Walking difficulties and falls (50-70%)1
- Pain (67%)2
- Cognitive changes (50%)1
- Spasticity (44%–84%)4

Less common symptoms1:

- Speech problems (25%–40%)1
- Respiratory problems (20%)2
- Hearing loss (6%) 1
- Seizures (2%–5%) 1

Secondary and tertiary symptoms1:

- Urinary tract infections
- Decreased bone density and loss of muscle tone
- Pressure sores
- Social, vocational, and psychological complications



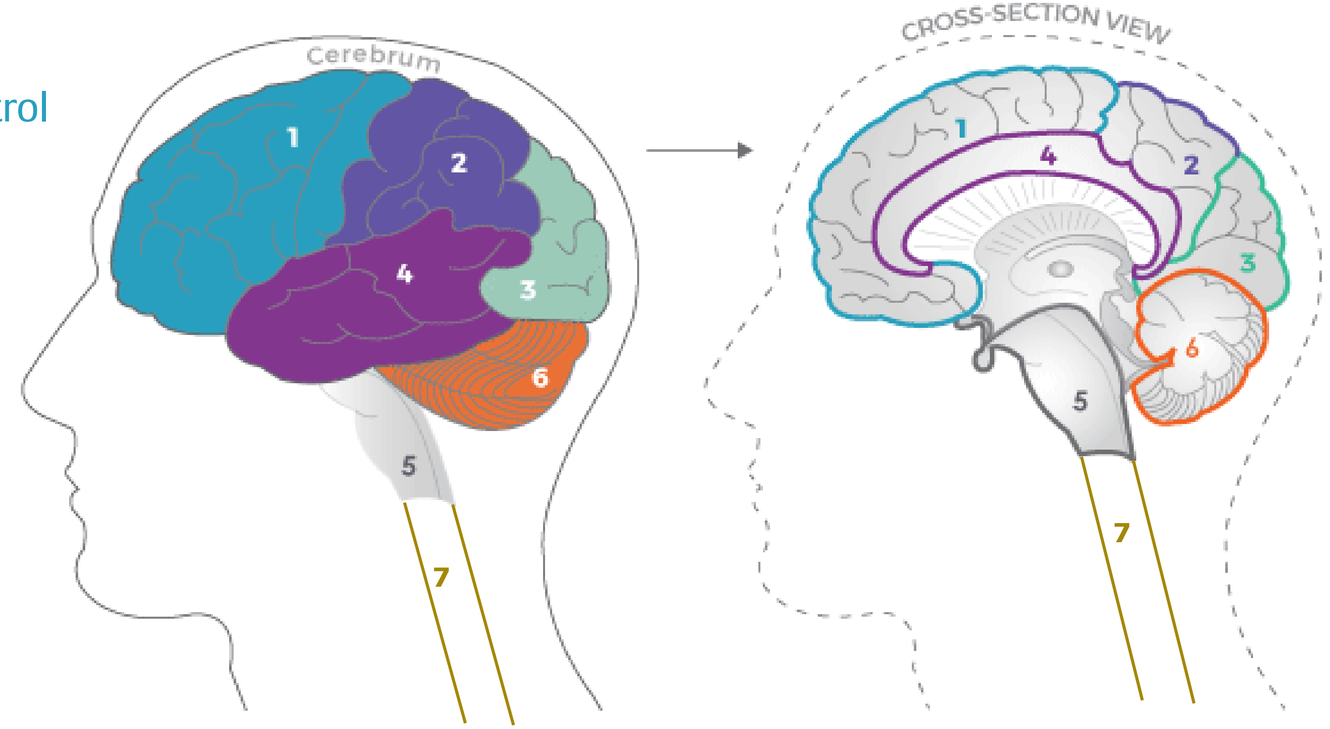

1. National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed January 2020;
2. Rae-Grant AD, et al. Mult Scler 1999:5:179–83; 3. Kister I, et al. Int J MS Care 2013:15:146–56; 4. Zwibel HL. Adv Ther 2009:26:1043–57.

# The heterogeneity of clinical symptoms associated with MS results from damage occurring in different parts of the CNS

**Frontal lobe[1]**
Reduced emotional control
Cognitive issues

**Parietal lobe[1]**
Paraesthesia
Dysesthesia
Cognitive issues

**Occipital lobe[1]**
Visual disturbance




**Temporal lobe[1]**
Cognitive issues

**Brain stem[1,2]**
Diplopia
Vertigo
Dysarthria
Gait ataxia
Genitourinary problems
Lack of proprioception[2]

**Cerebellum[1]**
Tremor
Ataxia
Dysathria
Dysmetria

**Spinal cord[1]**
Spasticity
Sensory symptoms

Image adapted from: https://www.cancer.gov/publishedcontent/syndication/1120672.htm. Accessed January 2020.

1. Miller AE (2001) in Cook SD, et al. Handbook of Multiple Sclerosis. Taylor & Francis Group; 2. National Multiple Sclerosis Society. http://www.nationalmssociety.org/ About-the-Society/News/Looking-at-MS-and-balance-in-a-new-way-An-intervie. Accessed January 2020

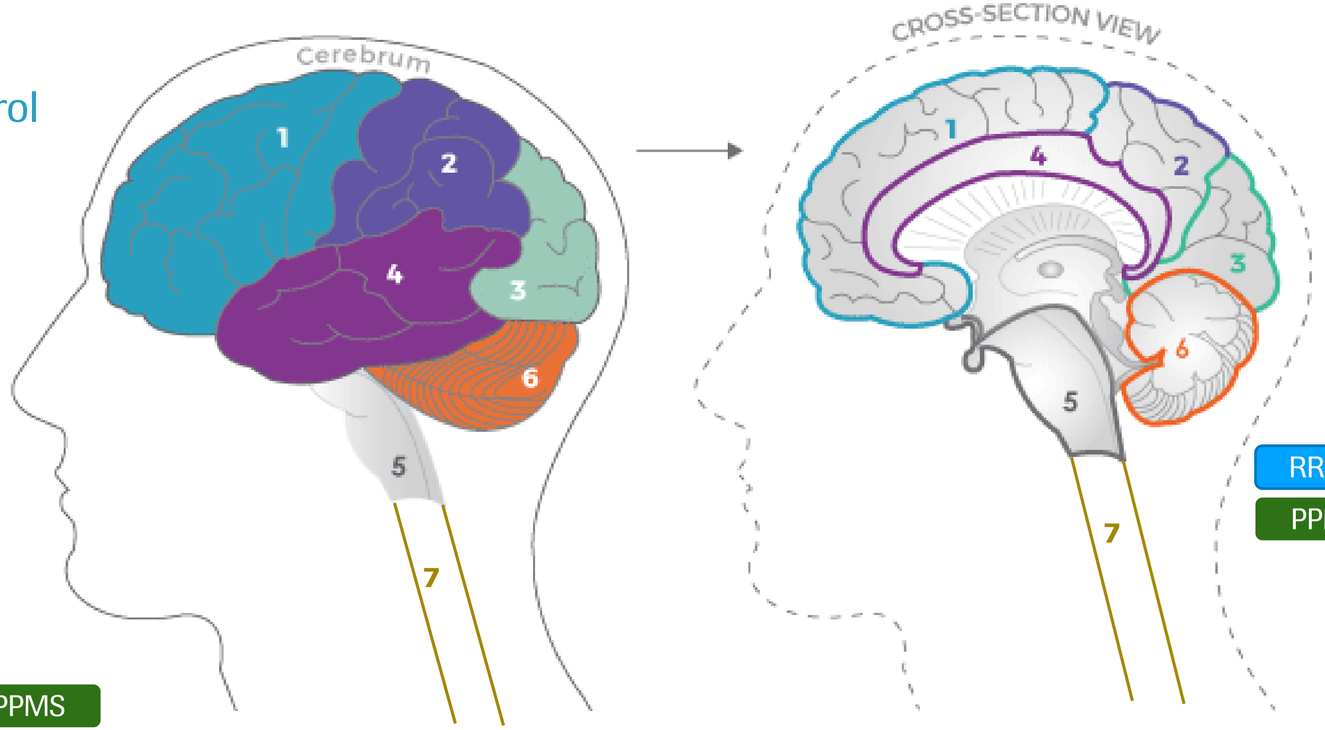
# The heterogeneity of clinical symptoms associated with MS results from damage occurring in different parts of the CNS

Patients with PPMS and RRMS tend to present with different symptoms, though the categories are not mutually exclusive

## Frontal lobe
Reduced emotional control
Cognitive issues

## Parietal lobe
Paraesthesia
Dysesthesia
Cognitive issues

## Occipital lobe
Visual disturbance PPMS




## Temporal lobe
Cognitive issues

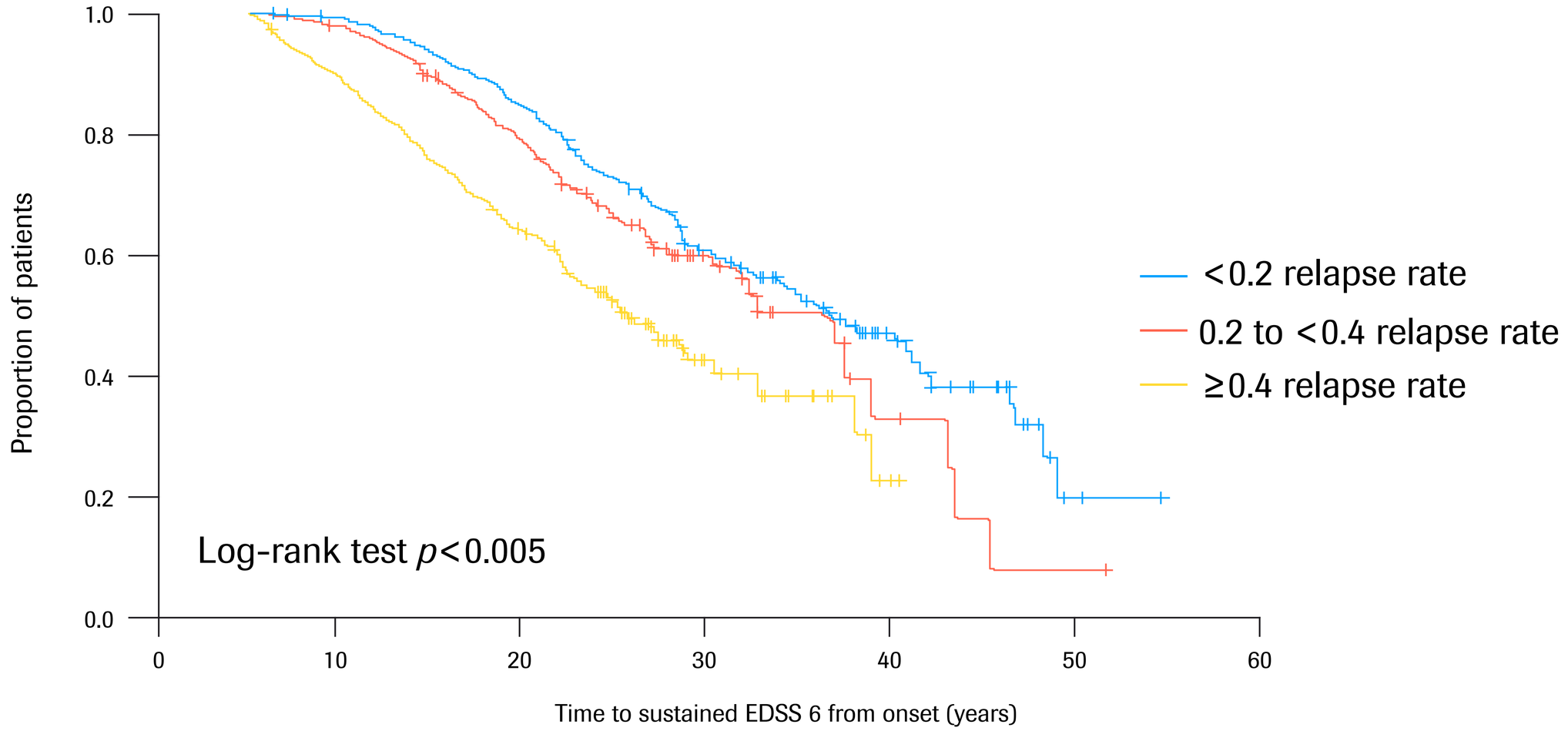
## Brain stem
PPMS Diplopia
PPMS Vertigo
PPMS Dysarthria
RRMS Genitourinary problems
PPMS Lack of proprioception

## Cerebellum
RRMS Tremor
RRMS Ataxia
PPMS Dysathria
Dysmetria

## Spinal cord
Spasticity RRMS
Sensory symptoms PPMS

Image adapted from: https://www.cancer.gov/publishedcontent/syndication/1120672.htm

# Patients with higher relapse rates in the first five years after onset of symptoms exhibit greater risk of more rapid worsening to a severe level of disability



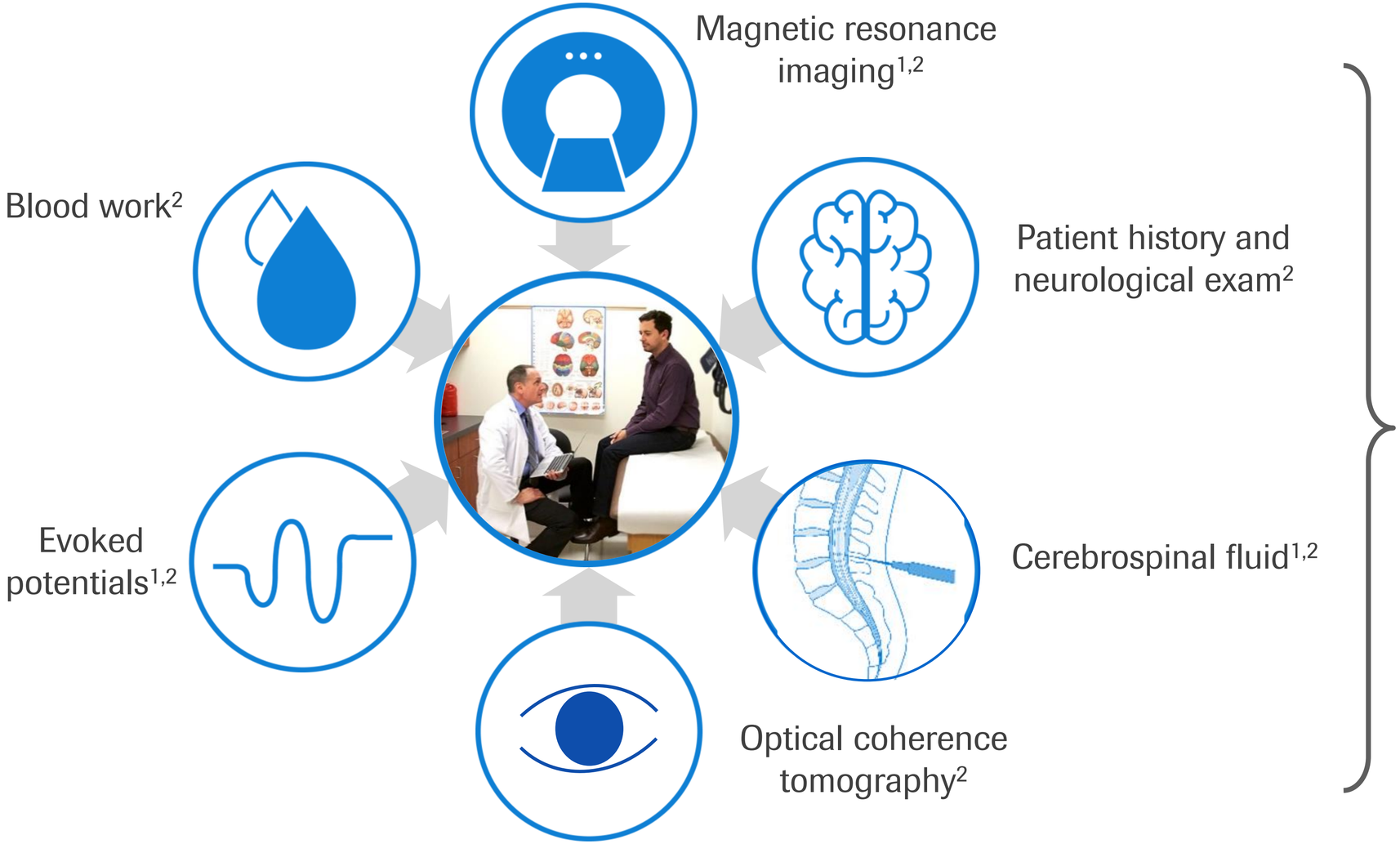

EDSS, Expanded Disability Status Scale.

Tremlett H, et al. Neurology 2009;73:1616–23.

1

# Diagnosis of MS

# Neurologists use a combination of tools to establish a diagnosis of MS




Once the patient is assessed, and the neurologist has their history, examination and any relevant investigation findings, more likely diagnoses are excluded and the McDonald 2017 diagnostic criteria are applied to determine the likelihood of the patient having MS

1. Karussis D. J Autoimmn 2014;48–49:134–42; 2. National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools. Accessed January 2020.

2

# How is MS diagnosed?

# How MS is diagnosed?

## Clinical assessments

## Paraclinical assessments

| Presenting complaint | Foundation for diagnosis of MS[1] | Confirmed by[1] | Supporting investigations[1–3] |
|---|---|---|---|

### Clinical symptoms

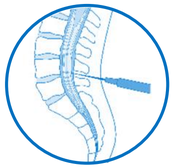
*Patients typically present as the result of clinically overt symptoms during an acute relapse*

### Medical history

### Neurological exam

### MRI

*The patient will only receive an MRI scan if they have a clinically suspicious history and exam*



### Cerebrospinal fluid

### Optical coherence tomography

### Blood tests*

### Evoked potentials

*Primarily used to eliminate other potential conditions, with similar clinical presentations.

1. Gelfand JM, et al. Mult Scler Relat Disord 2014;122:269–90; 2. Kale N. Eye Brain 2016;8:195–202;
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# How MS is diagnosed?

## Clinical assessments

### Presenting complaint

**Clinical symptoms**

*Patients typically present as the result of clinically overt symptoms during an acute relapse*

### Foundation for diagnosis of MS[1]

**Medical history**

**Neurological exam**

## Paraclinical assessments

### Confirmed by[1]



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### Supporting investigations[1–3]



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3. National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools. Accessed January 2020.

# The initial step of MS diagnosis is a comprehensive assessment of patient history and

| Presenting complaint 1,2 | Medical history 1,2 | Systematic enquiry 1,2 | Social history 1,2 | Family history1,3 |
|---|---|---|---|---|
| • Symptoms; onset, duration, triggers, associated symptoms | • Other medical problems<br>• Similar episodes previously? | • Enquire into each body system to identify symptoms suggestive of MS or another disease | • Smoking and drinking habits<br>• Other medications or illicit drugs<br>• Occupational or marital status | • Consider any genetic basis or predisposition |
| **Suggestive of MS** | Numbness/tingling in extremities, visual disturbances, fatigue, heat intolerance, stumbling gait | Visual disturbances that have resolved, previous episodes of numbness/tingling | Bladder control problems, fatigue, pain, dizziness, depression | Difficulty at work due to symptoms, breakdown of social relationships; smoking is a known risk-factor for MS | Approximately 2% of people with a first-degree relative with MS will develop the condition; rates are higher in twins |


1. Neurological history and examination. https://patient.info/doctor/neurological-history-and-examination. Accessed January 2020;
2. MS Symptoms: National Multiple Sclerosis Society. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed January 2020;
3. Developing MS: National Multiple Sclerosis Society. https://www.mstrust.org.uk/a-z/risk-developing-ms. Accessed January 2020.

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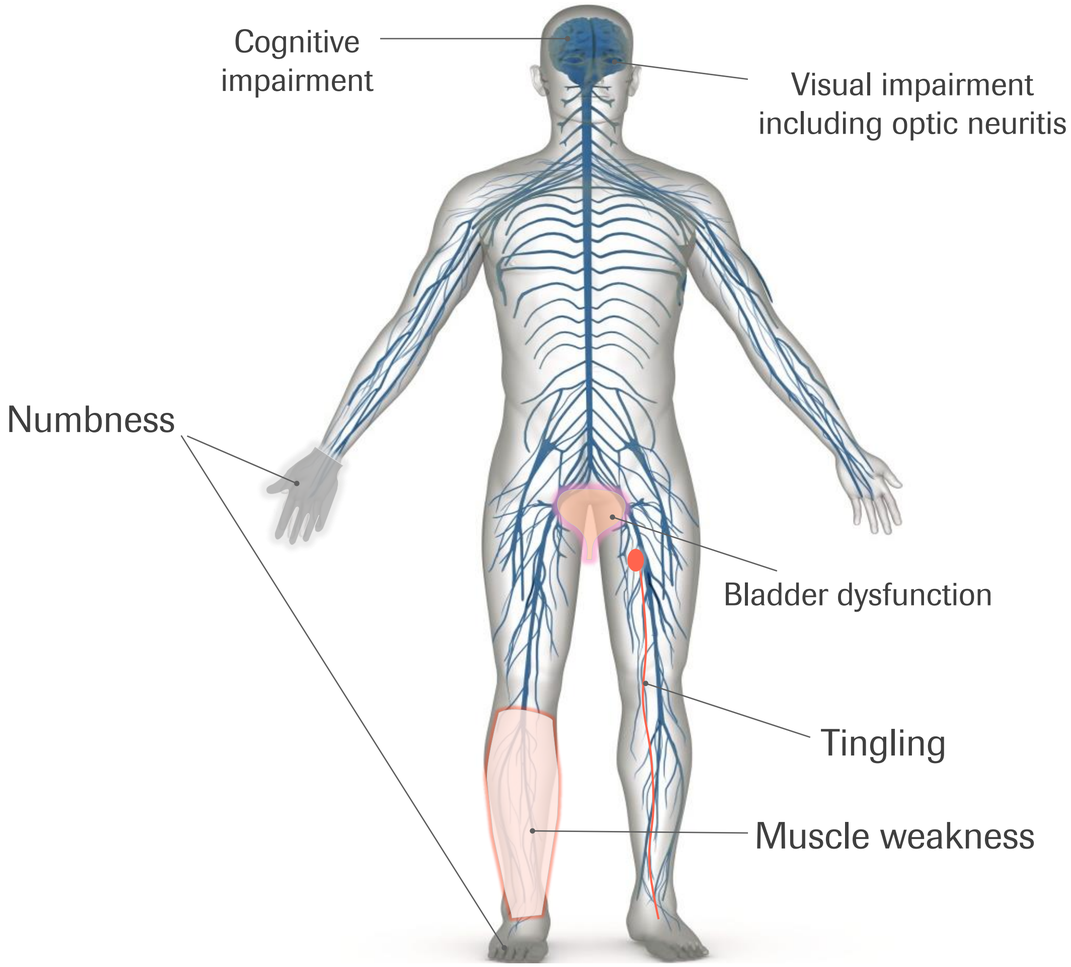


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Presenting complaint → Foundation for diagnosis of MS1 → Confirmed by[1] → Supporting investigations[1–3]

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3. National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools. Accessed January 2020.

# A neurological exam can be key to identifying areas of the CNS that may not be functioning properly


Muscle atrophy, power and tone

Coordination, gait, balance

Posture, motor activity, vital signs

Systematic assessment of nerve responses related to all 12 cranial nerves

Deep tendon reflexes, clonus
Hoffman's response, plantar reflex

Vibration, position, pin prick, temperature, light touch

Orientation, recall, attention, memory, calculations, language

CNS, central nervous system.

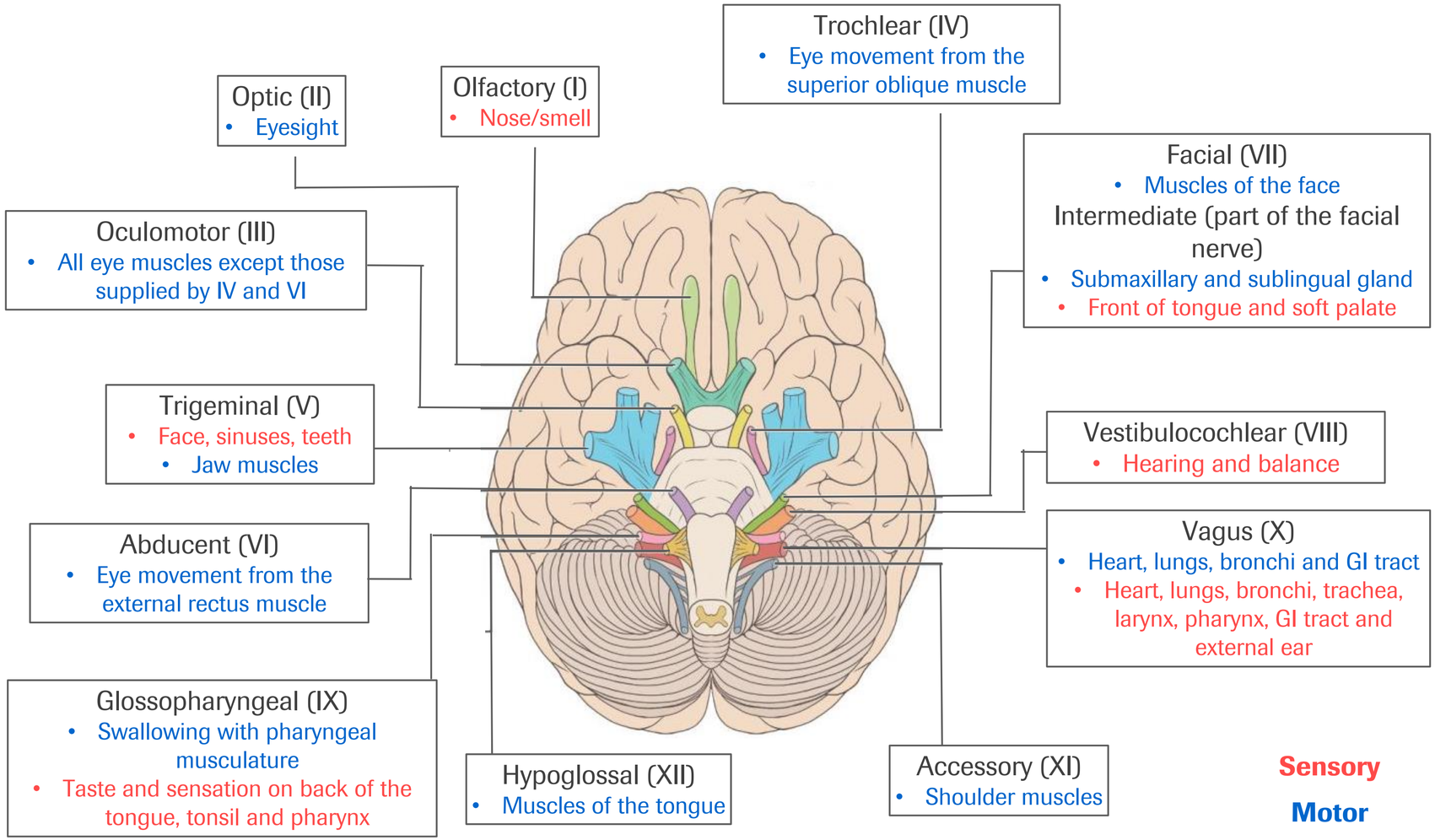
1. New York University School of Medicine. http://informatics.med.nyu.edu/modules/pub/neurosurgery. Accessed January 2020;
2. Brown University. http://www.brown.edu/Courses/BI_278/Other/Clerkship/Didactics/Readings/ THE%20MENTAL%20STATUS%20EXAMINATION.pdf. Accessed January 2020.

# A range of neurological tests are used to assess movement, coordination, vision, balance and reflexes

| | Example tests | Assesses |
|---|---|---|
| **Stance and gait** | • Tightrope or heel-to-toe walk<br>• Romberg test (standing ≥20 seconds with eyes closed) | • Equilibrium and gait stability<br>• Balance |
| **Head and cranial nerves** | • Test sense of smell in each nostril, e.g. using coffee<br>• Finger perimetry or digital confrontation (examiner moves a finger in each visual field quadrant) | • Olfactory function<br>• Visual field defects |
| **Upper limbs** | • Finger–nose test (touching nose with index finger, with eyes closed) | • Motor function and coordination |
| **Trunk** | • Schober tests (measure flexibility of lumbrosacral and thoracic spine) | • Spinal mobility |
| **Lower limbs** | • Heel–knee–shin test (with eyes closed, touching the heel of one leg to the opposite knee, then sliding the heel down to the front of the ankle and back up to the knee) | • Coordination and strength |
| **Autonomic nervous system** | • Ask about possible disturbances e.g. in urination, defaecation, sexual functioning and sweating | • Autonomic nervous system function |

Mumenthaler M, Mattle H (2006). The neurological examination. In: Fundamentals of Neurology 2006;11–43. Thieme.

# A neurological exam should assess the cranial nerve function




GI, gastrointestinal.
Figure adapted from Damodaran O, et al. Clin Anat 2014;27:25–30 and https://www.physio-pedia.com/Facial_nerve.

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## Clinical assessments

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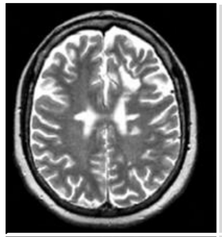
3. National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools. Accessed January 2020.

# MRI is an essential tool for the assessment of patients with MS

- MRI is a technique that allows the neurologist to view high-quality images of the brain
- How does the technology work?[1]
  - Within the scanner is a strong magnetic field that aligns protons found within the patient's cells and surrounding fluid [1]
  - Radio pulses are transmitted in a plane perpendicular to the magnetic field, which energetically excites the protons out of alignment [1]
  - After the radio pulses are ended, the protons return to alignment with the magnetic field by emitting energy, which is converted into an image [1]
- MRI is used for diagnosis of MS and for the assessment of response to disease-modifying therapy in a clinical trial [2]

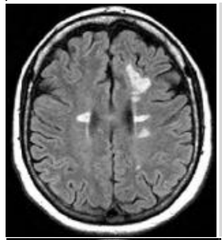

1. Berger A. BMJ 2002;324:35; 2. Sahraian MA, Eshaghi A. Clin Neurol Neurosurg 2010;112:609–15.

# Several different MRI techniques are used to assess brain pathology in MS



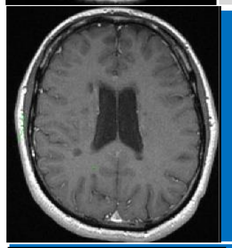
**T2-weighted[1]**

- Sensitive for detecting abnormalities but are not specific for pathology
- Lesions rarely disappear and so serve as a good marker of long-term disease burden



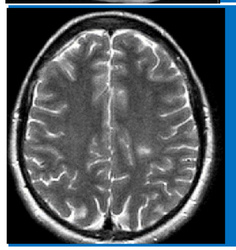
**T2 FLAIR[1]**

- Technique to enhance visibility of lesions in the periventricular and cortical areas



**T1-weighted[2,3]**

- Areas of hypointensity that reflect “black holes” (chronic or persistent T1-hypointense lesions)
- Correlate with disease progression and disability



**T1-weighted with Gd enhancement[1,4]**

- Show disruption of blood-brain barrier and areas of active inflammation
- Tend to be transient

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

1. Sahraian MA, Eshaghi A. Clin Neurol Neurosurg 2010;112:609–15; 2. Ge Y. AJNR Am J Neuroradiol 2006;27:1165–76;
3. Truyen L, et al. Neurology 1996;47:1469–76; 4. Cotton F, et al. Neurology 2003;60:640–6.

# How MS is diagnosed?

## Clinical assessments

## Paraclinical assessments

Presenting complaint → Foundation for diagnosis of MS[1] → Confirmed by[1] → Supporting investigations[1–3]

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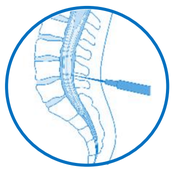


### Cerebrospinal fluid

### Optical coherence tomography

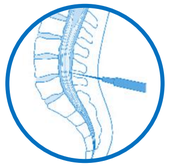
### Blood tests*

### Evoked potentials

*Primarily used to eliminate other potential conditions, with similar clinical presentations.

1. Gelfand JM, et al. Mult Scler Relat Disord 2014;122:269–90; 2. Kale N. Eye Brain 2016;8:195–202;
3. National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools. Accessed January 2020.

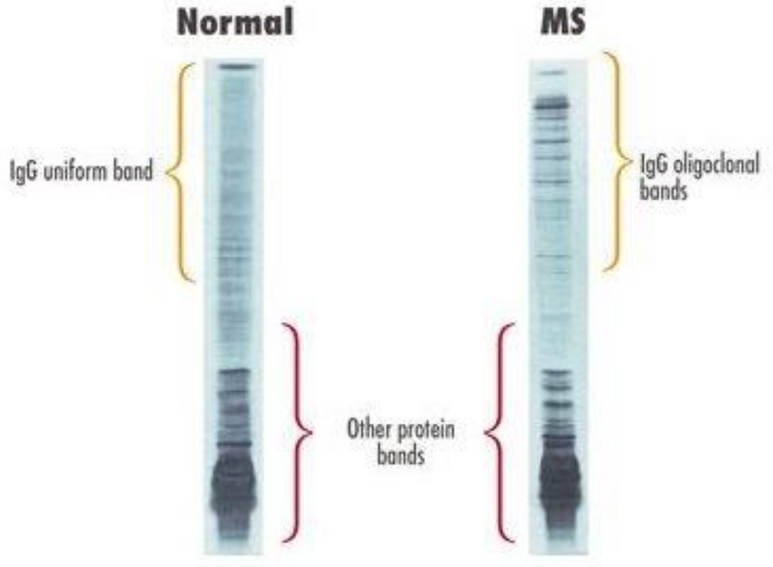
# If MRI findings are inconclusive, analysis of CSF via a lumbar puncture can be a useful diagnostic tool



- A lumbar puncture takes about half an hour under local anaesthetic and must be carried out aseptically. However, this procedure can cause discomfort and increase the risk of headaches and infection in patients[2]
- Analysis of the CSF can show:
- **Increased leukocyte levels** (usually around seven-fold higher in patients with MS, compared with healthy subjects) [2]
- **Oligoclonal bands** indicating high levels of IgG in the CSF[2,3]

Oligoclonal bands are not unique to MS, but provide evidence of intrathecal IgG synthesis

thought to be indicative of compartmentalised CNS humoral immune activation present in MS[4]

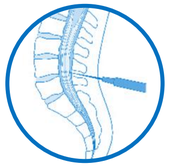



**The gold standard measure of oligoclonal bands is isoelectric focusing on agarose gel followed by immunoblotting or immunofixation for IgG with paired CSF and serum.**
**The sensitivity for detection of OCBs is over 95% using this technique[4]**

CNS, central nervous system; CSF, cerebrospinal fluid; IgG, Immunoglobulin G; OCB, oligoclonal bands.
Image from https://www.mstrust.org.uk/a-z/lumbar-puncture; Accessed January 2020.

1. Awad A, et al. J Neuroimmunol 2010;219:1–7; 2. MS Trust - Lumbar puncture: https://www.mstrust.org.uk/a-z/lumbar-puncture. Accessed January 2020;
3. Link H, Huang YM. J Neuroimmunol 2006;180:17–28. 4. Dobson R, et al. J Neurol Neurosurg Psychiatry 2013;84:909–914.

# Oligoclonal bands are observed in MS and other neurological disorders, in CIS presence of oligoclonal bands positively predicts a conversion to MS



## Frequency of OCB in patients with neurological disorders1*

*CSF database contained 6,825 patients in total; 625 patients had IgG index of >0.6. Diagnostic information available in 460 of these patients

| Diagnosis | Positive OCB, n (%) |
|---|---|
| **Demyelinating diseases** | **241/245 (98.4)** |
| MS | 213/216 (98.6) |
| Transverse myelitis | 12/12 (100) |
| Optic neuritis | 16/17 (94.1) |
| **Inflammatory neurological disease** | **52/76 (68.4)** |
| Meningitis | 23/30 (76.7) |
| Encephalitis | 27/33 (81.8) |
| Radiculitis | 2/3 (66.7) |
| Guillain-Barré syndrome | 0/10 (0) |
| **Other neurological diseases** | **87/123 (70.7)** |
| Vascular | 6/11 (54.5) |
| Degenerative | 4/8 (50) |
| Metabolic | 43/47 (91.5) |
| Psychiatric | 3/5 (60) |
| Neoplastic disorders | 23/29 (79.3) |
| Purine nucleoside phosphorylase | 6/15 (40) |
| Lower back pain | 0/8 (0) |
| **Neuroborreliosis** | **16/16 (100)** |
| **Total** | **396/460 (86.1)** |

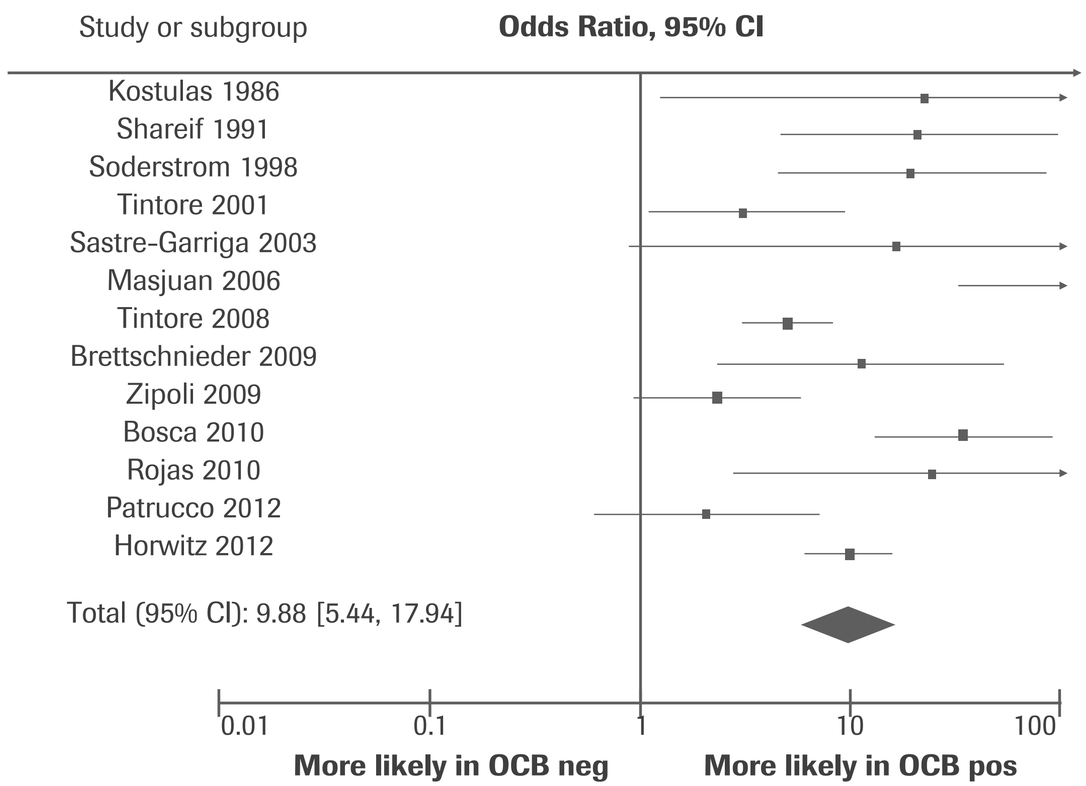
CIS, clinically isolated syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; OCB, oligoclonal bands.

1. Mayringer I, et al. Eur J Neurol 2005;12:527–30; 2. Dobson R, et al. J Neurol Neurosurg Psychiatry 2013;84:909–14.

# Oligoclonal bands are observed in MS and other neurological disorders, in CIS presence of oligoclonal bands positively predicts a conversion to MS

## Relationship between oligoclonal band status and conversion to MS in CIS[2]

The presence of oligoclonal bands positivity strongly predicts conversion from CIS to MS[2]

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# The collection and analysis of peripheral blood enables neurologists to exclude other conditions

- Peripheral blood tests are commonly done during the MS diagnostic process
- These tests may be helpful in **excluding** other diseases or clinical disturbances that may mimic MS, including:

- Vitamin and mineral deficiencies
- Systemic lupus erythematosus
- Sjögrens syndrome
- Rare hereditary diseases
- NMOSD

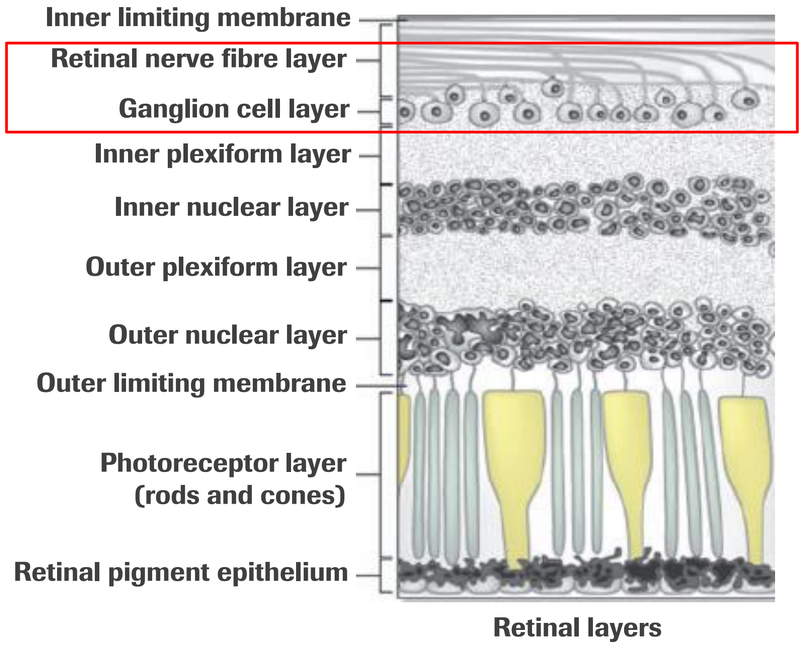
**These conditions may all be confused for MS at initial presentation, and vice-versa, therefore peripheral blood testing as part of a differential diagnosis is essential for accurately identifying the patient's condition**

NMOSD, neuromyelitis optica spectrum disorder

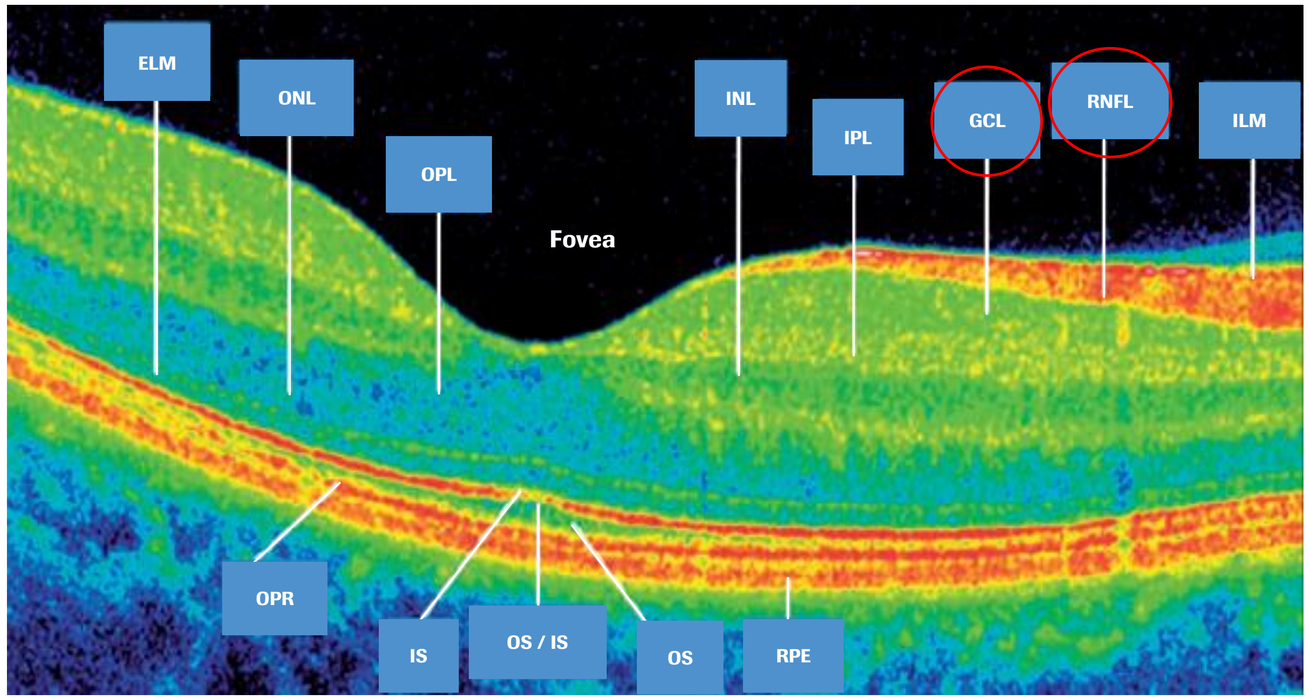
National Multiple Sclerosis Society. http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools. Accessed January 2020.

# Optical coherence tomography assessment of the retinal nerve fibre layer can aid assessment of disease severity and progression in MS

- Optical coherence tomography (OCT) is a noninvasive high-resolution imaging technique that allows for the quantification of retinal layers[1,2]
- The retinal nerve fibre layer (RNFL) has no myelin[2]
- RNFL thickness decreased with normal ageing but MS patients have a higher reduction [3]
- Thinning of the RNFL and ganglion cell layer (GCL) in MS indicates neuronal injury2



Retinal layers



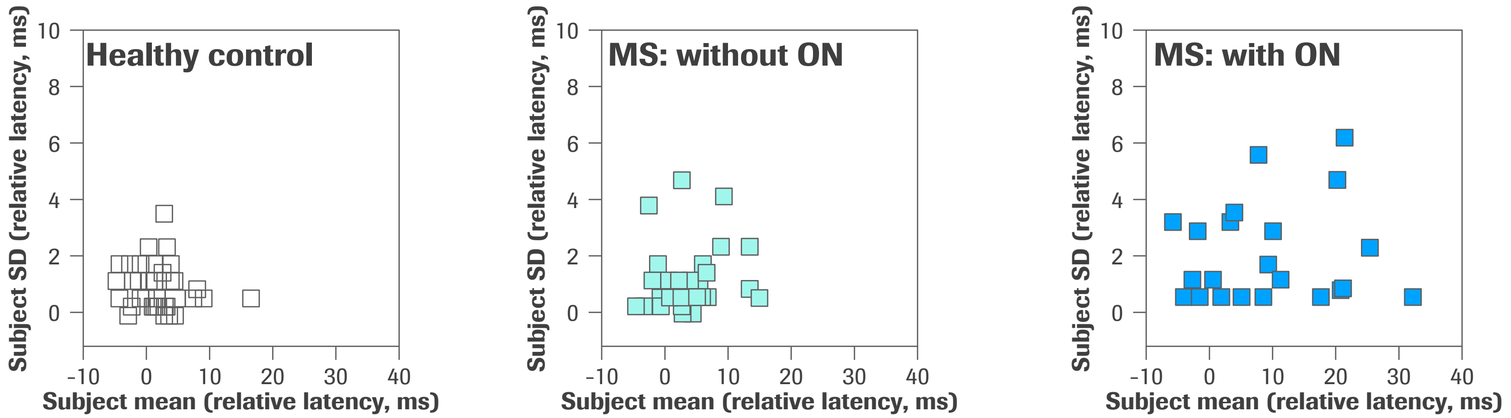

ELM, external limiting membrane; GCL, ganglion cell layer; ILM, inner limiting membrane; INL, inner nuclear layer; IPL, inner plexiform layer; IS, inner photoreceptor segments; OCT, optical coherence tomography; ONL, outer nuclear layers; OPL, outer plexiform layer; OPR, outer photoreceptors; OS, outer photoreceptor segment; RNFL, retinal nerve fibre layer; RPE, retinal pigment epithelium.

1. Saidha S, et al. Ann Neurol 2015;78:801–13; 2. Syc SB, et al. Brain 2012;135:521–33; 3. Satue M, et al. J Ophthalmol 2016;2016:8503859.

# Evoked potentials are tests that measure the electrical response of the brain to sensory stimulation

- An evoked potentials test measures the speed of nerve conduction, and may therefore detect the slowing of electrical conduction caused by demyelination1
- The latency of nerves to respond to stimulation and the amplitude of the response are typically measured2,3
- 60–70% of MS patients exhibit abnormalities in evoked potentials4
- Common evoked potentials pathologic in patients with MS are2–4:
  - **Visual** – patient views alternating checkerboard patterns
  - **Brainstem auditory** – patient hears auditory stimuli through headphones, such as clicks
  - **Somatosensory** – nerves of the arms or legs are stimulated by small electrical impulses delivered through electrodes on the skin

**Comparison of delayed latency in visual-evoked potentials in healthy controls and MS patients with or without ON[3]**




ON, optic neuritis.

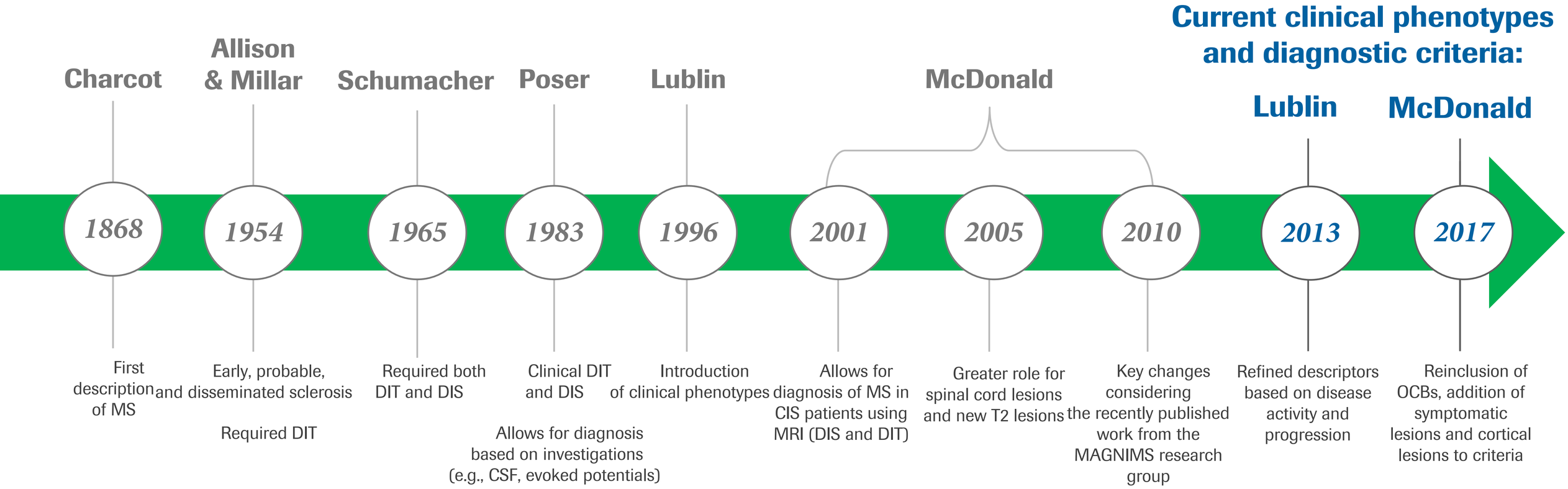
1. National Multiple Sclerosis Society http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools. Accessed January 2020;
2. Sand T, et al. Tidsskr Nor Laegeforen 2013;133:960–5; 3. Narayanan D, et al. Doc Ophthalmol 2015;130:31–41; 4. Karussis D. J Autoimmun 2014;48–49:134–42.

3

# What are the diagnostic criteria for MS?

# Ongoing evolution of MS diagnostic criteria and MS phenotype definitions

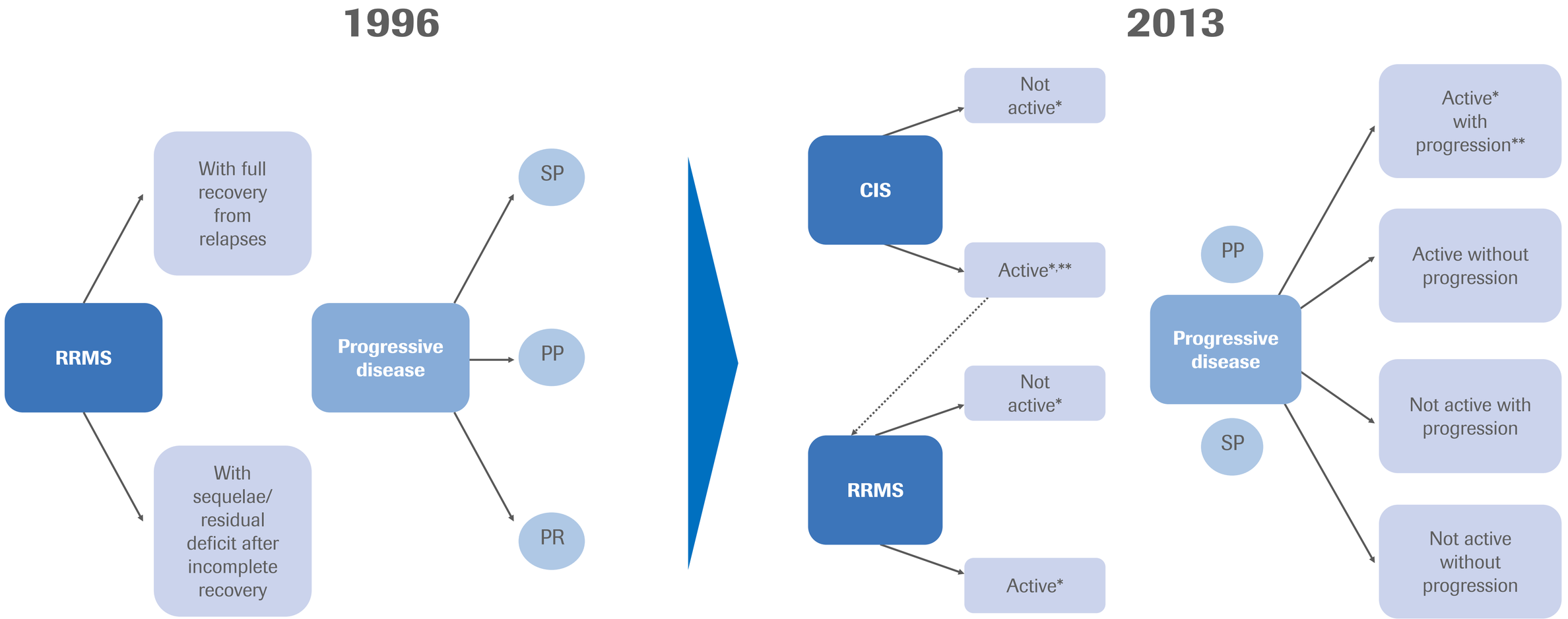
**As MS is inherently difficult to diagnose, a series of diagnostic criteria have been developed to aid clinicians, the most recent of which have emphasised the use of MRI to confirm the diagnosis**




CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; OCBs, oligoclonal bands.

Allison RS & Millar JHD. Ulster Med J 1954;23:5–27; Schumacher GA, et al. Ann New York Acad Sci 1965;122:552–68; Poser CM, et al. Ann Neurol 1983;13:227–31; McDonald WI, et al. Ann Neurol 2001;50:121–27; Polman CH, et al. Ann Neurol 2011;69:292–302; Polman CH, et al. Ann Neurol. 2005;58:840–6; Gafson A, et al. Mult Scler Relat Disord 2012;1:9–14; Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# The 2013 revised Lublin classification now provides guidance on categorising disease based on both progression and activity



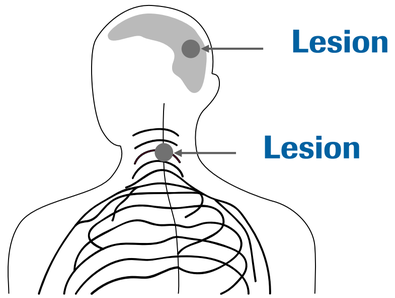

*Activity determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually); if assessments are not available, activity is "indeterminate." **CIS, if subsequently clinically active and fulfilling current multiple sclerosis (MS) diagnostic criteria, becomes relapsing-remitting MS (RRMS).
PP, primary progressive; PR, progressive remitting; SP, secondary progressive
Adapted from: Lublin FD, et al. Neurology 2014;83:278-286.

# 2017 McDonald Criteria are the key criteria for diagnosing MS

## To make a diagnosis of MS using these criteria the neurologist has to demonstrate <u>three</u> things:

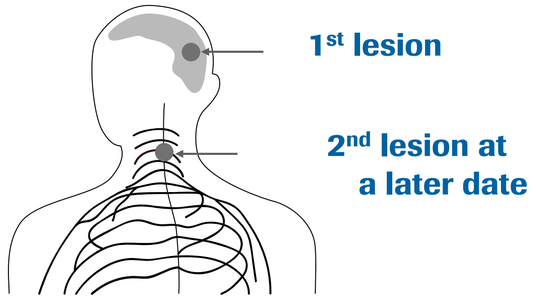
### Dissemination in space (DIS)

The development of lesions in distinct anatomical locations within the CNS – i.e. indicating a multifocal CNS process



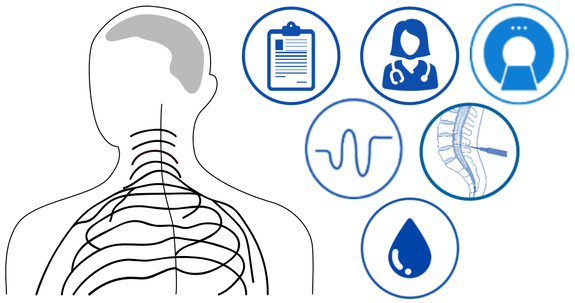

### Dissemination in time (DIT)

The development or appearance of new CNS lesions over time, separate to the initial lesion(s)




### No better explanation for the clinical presentation

Other possible causes of the patient's neurological symptoms must be ruled out



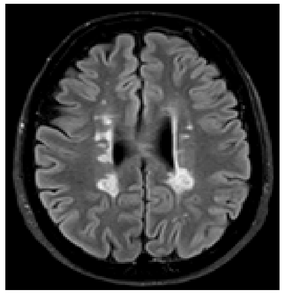
CNS, central nervous system.

Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

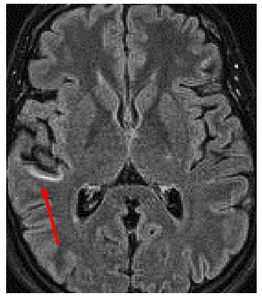
# The neurologist must use clinical and paraclinical assessments to establish DIS and DIT

## Dissemination of lesions in space

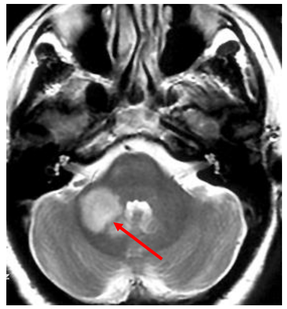
≥1 T2 lesions in at least two of four areas of the CNS



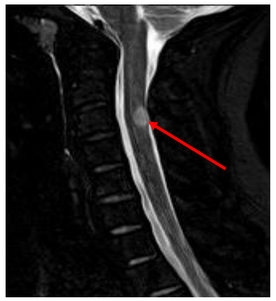
Periventricular



Cortical or juxtacortical



Infratentorial

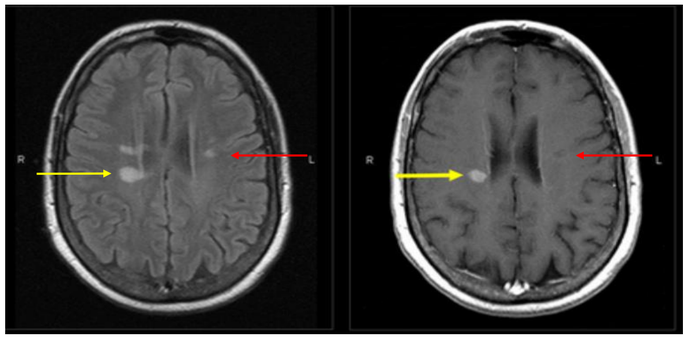


Spinal cord

**DIS can also be demonstrated by an additional clinical attack at a different CNS site**

## Dissemination of lesions in time

Simultaneous presence of Gd+ and Gd- lesions at any time



T2 FLAIR

T1 post-Gd

**OR**

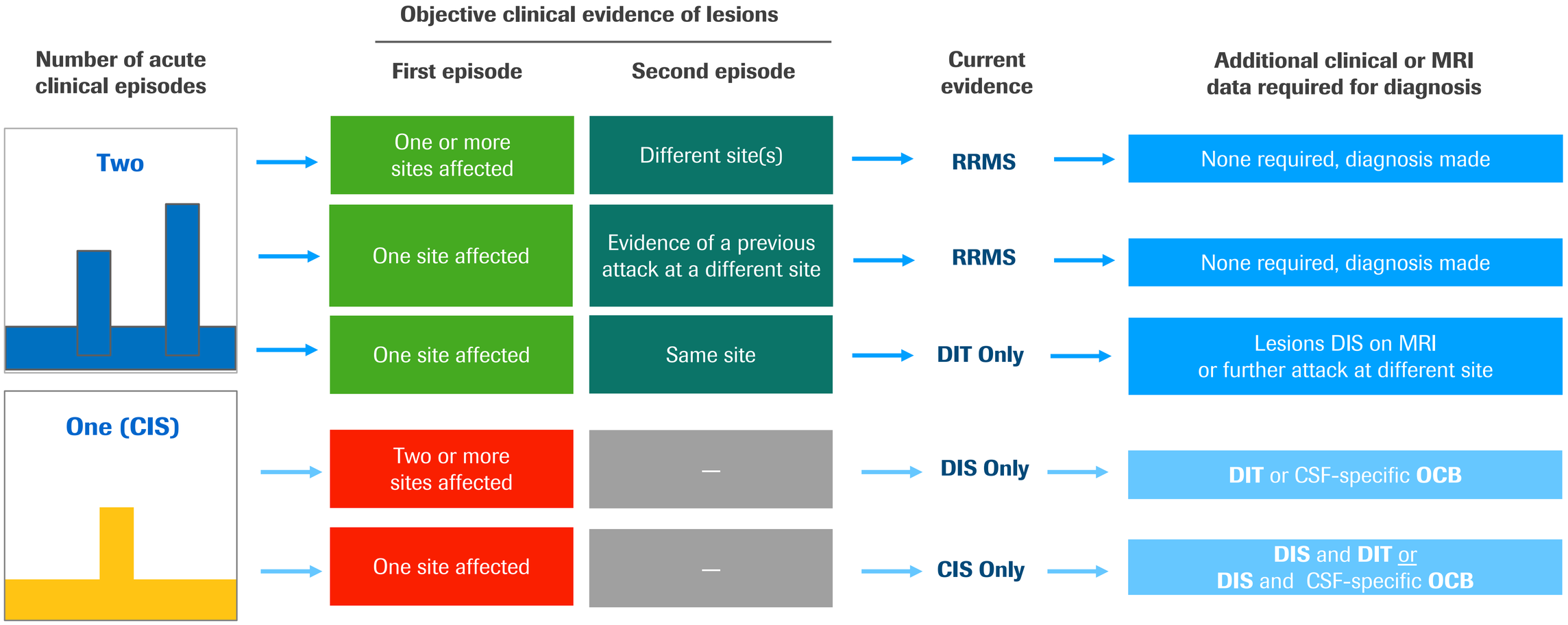
A new T2-hyperintense or Gd+ lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline scan

**DIT can also be demonstrated by an additional clinical attack**

CNS, central nervous system; Gd+, gadolinium-enhancing; Gd-, gadolinium-non-enhancing; PML, progressive multifocal leukoencephalopathy.

Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# Diagnosis following an acute episode may also require additional data




CNS, central nervous system; CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; DIS, dissemination of lesions in space; DIT, dissemination of lesions in time; OCB, oligoclonal bands; RRMS, relapsing remitting MS.

Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

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# What changes did the McDonald 2017 update make to the diagnosis of MS?

# McDonald 2010 criteria were updated in 2017 to take into account the availability of new evidence in several key areas

The decision to revise the criteria was motivated by the availability of new data in the following areas:

- Performance of the 2010 McDonald criteria in diverse populations
- Challenges in making the diagnosis in individuals with presentations other than a typical CIS
- Acknowledgement via new data that OCBs are predictive and helpful to substantiate the diagnosis of MS
- Distinction between MS and other diseases with potentially overlapping clinical and imaging features, such as NMOSDs
- Frequency and consequences of misdiagnosis
- Revisions to MAGNIMS MRI criteria for the diagnosis of MS

**Recommended revisions are expected to speed up the diagnostic process and reduce the chance of misdiagnosis**

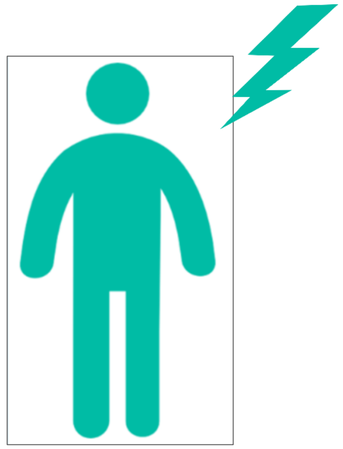
CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; MAGNIMS, Magnetic Resonance Imaging in Multiple Sclerosis; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal bands.

Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# McDonald 2017: What remains the same as 2010?

MS is best diagnosed by a clinician with MS-related expertise with support of imaging and other tests

The need to ensure there is no better explanation for the individual's symptoms

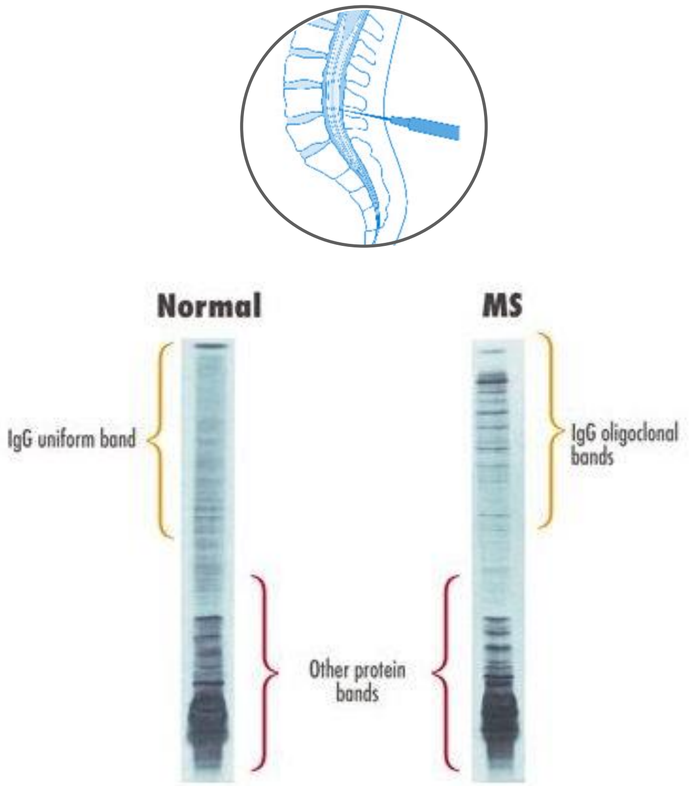


The McDonald Diagnostic Criteria apply to individuals experiencing a typical CIS

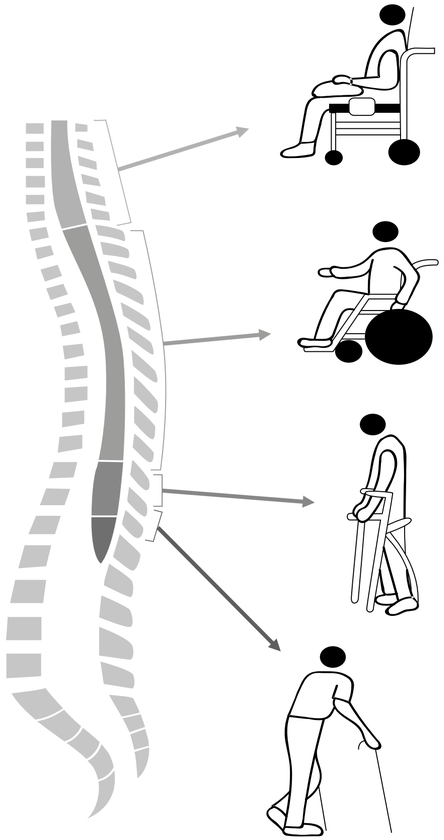
CIS, clinically isolated syndrome.
Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# Overview of the primary changes in McDonald 2017

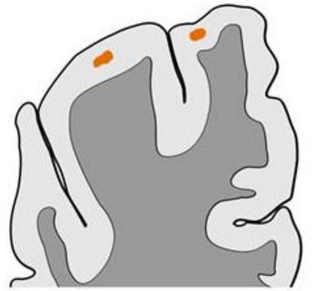
## Recognition of utility of CSF oligoclonal bands



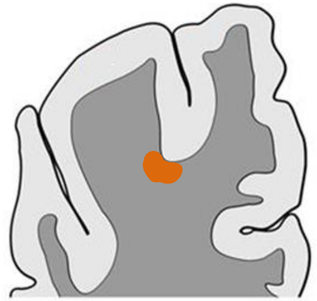

## Symptomatic lesions as evidence for DIS and DIT



## Cortical lesions equivalent to juxtacortical lesions



Intracortical lesion examples

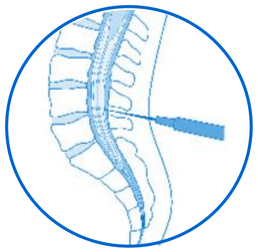


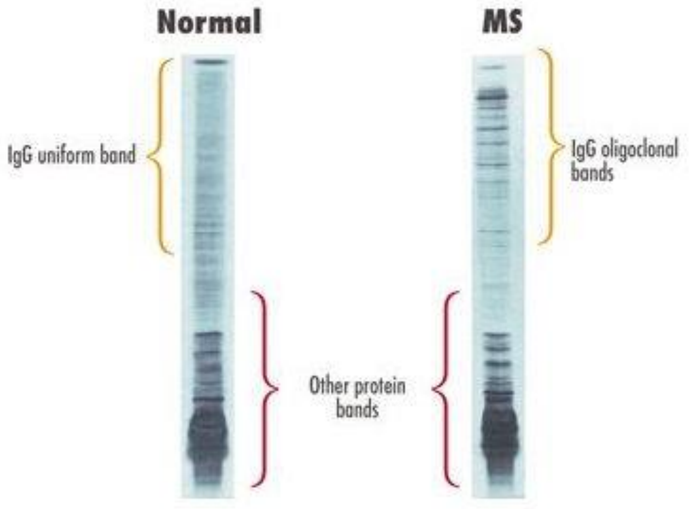
Juxtacortical lesion examples

CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time.
Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

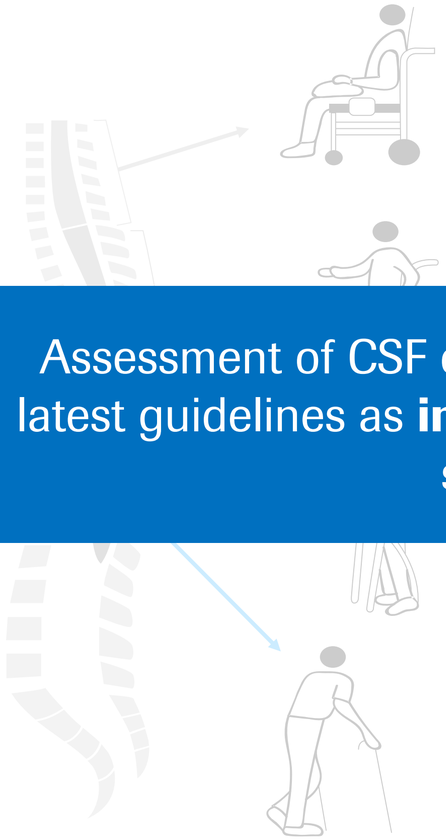
# CSF oligoclonal bands can now be used as an alternative to evidence of DIT for those with CIS

## Recognition of utility of CSF oligoclonal bands






## Symptomatic lesions as evidence for DIS and DIT



## Cortical lesions equivalent to juxtacortical lesions

Intracortical lesion examples

Juxtacortical lesion examples

Assessment of CSF oligoclonal bands are recognised by the latest guidelines as **independent predictors of the risk of a second MS attack**

CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time.

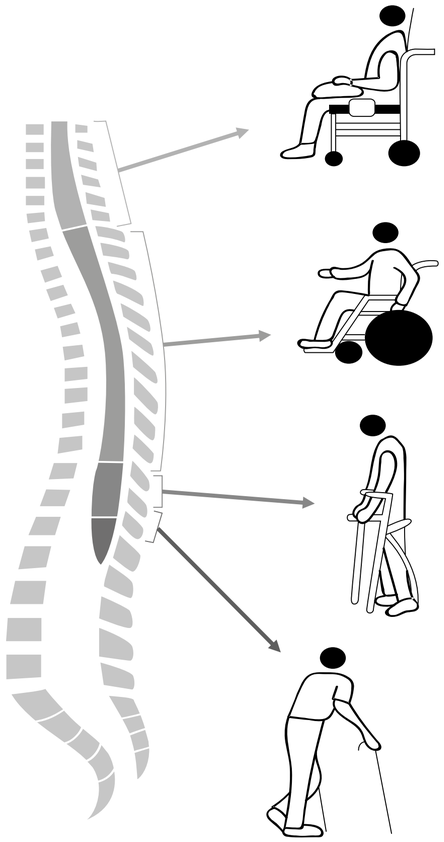
Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# Symptomatic lesions can now be used as evidence for DIS and DIT

## Recognition of utility of CSF oligoclonal bands




## Symptomatic lesions as evidence for DIS and DIT



## Cortical lesions equivalent to juxtacortical lesions

- Symptomatic lesions can be used to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome
- Symptomatic lesions are lesions that align with an acute clinical deficit



lesion examples

CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time.

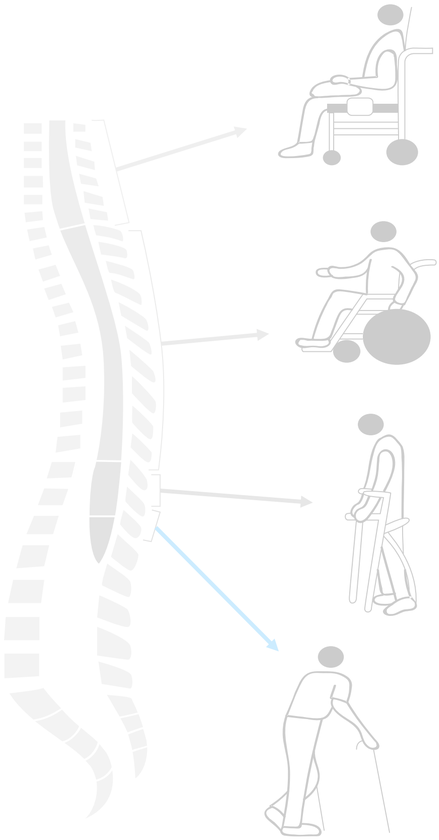
Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# In addition to juxtacortical lesions, cortical lesions can now be used to fulfil MRI criteria for DIS

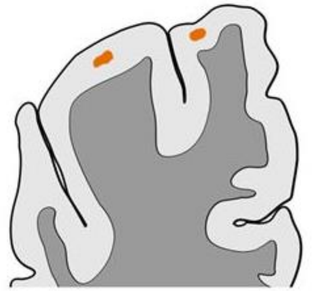
## Recognition of utility of CSF oligoclonal bands



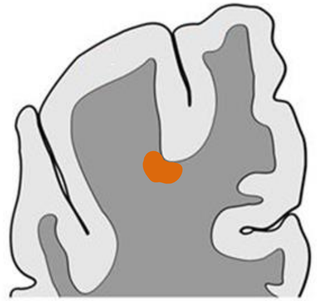

## Symptomatic lesions as evidence for DIS and DIT



## Cortical lesions equivalent to juxtacortical lesions



Intracortical lesion examples



Juxtacortical lesion examples

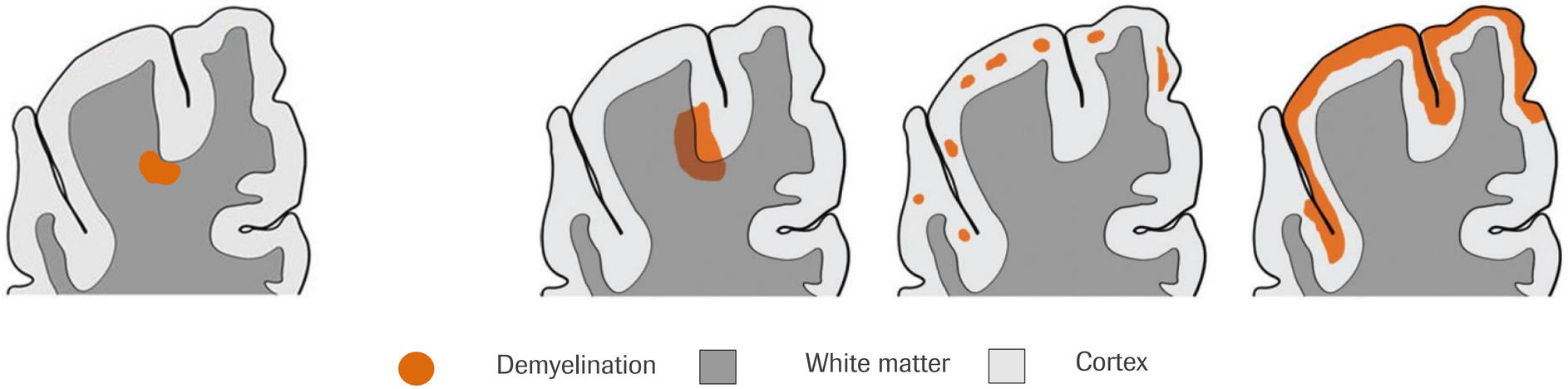
CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time.

Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# In addition to juxtacortical lesions, cortical lesions can now be used to fulfil MRI criteria for DIS

**Juxtacortical lesions were already included in the previous criteria[2]**

**Cortical lesions can now also be considered as evidence of dissemination in space[1]:**




With the development of improved techniques to identify cortical lesions, their potential to contribute to diagnosis has been appreciated[2]

1. Adapted from Peterson JW, et al (2005). In: Multiple Sclerosis as a Neuronal Disease. (pp. 165–84). Elsevier Academic Press.
2. Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# Diagnostic criteria for PPMS were also updated slightly in the latest McDonald update

## Primary progressive multiple sclerosis can be diagnosed in patients with:

- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

## Plus two of the following criteria:

- One or more T2-hyperintense lesion characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions in the spinal cord
- Presence of CSF-specific oligoclonal bands

Unlike the 2010 criteria, no distinction between symptomatic and asymptomatic MRI lesions is required

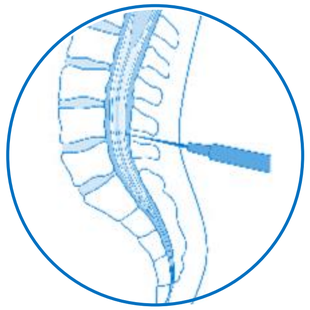
CSF, cerebrospinal fluid; PPMS, primary progressive MS.
Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# McDonald 2017 criteria included several other key recommendations

## MRI

**Brain MRI** should be obtained during the MS diagnostic process, unless not possible. Spinal MRI should be obtained when additional data are needed to confirm the diagnosis

## CSF



When spinal fluid is used as part of the diagnostic process, **paired serum and CSF samples** should be analysed to confirm that oligoclonal bands are unique to the CSF

## Disease course


At the time of diagnosis, the **MS course** should be indicated, and whether the course is **active or not**, and **progressive or not**; and the type and course of MS should be **re-evaluated periodically** as the disease evolves

CSF, cerebrospinal fluid.

Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# The authors of the revised McDonald criteria highlight several key considerations to help avoid misdiagnosis of MS

- Recognise that the McDonald criteria were not developed to differentiate MS from other conditions
- The MS diagnosis should be made by a clinician with MS expertise
- Diagnostic caution should be exercised in the absence of clear-cut CIS
- Caution should be taken in accepting a historical event as an attack in the absence of objective evidence
- The threshold for additional testing should be low, including for spinal cord MRI or CSF examination

CIS, clinically isolated syndrome; CSF, cerebrospinal fluid.

Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

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# What How do doctors avoid misdiagnosis of MS?

# Several other conditions have similar characteristics and symptoms to MS

**METABOLIC DISORDERS[1]**

Disorders of B12 metabolism, leukodystrophies

**NEOPLASTIC DISEASES[1]**

Spinal cord tumours, CNS lymphoma, paraneoplastic disorders

**PYSCHIATRIC DISORDERS[2]**

Conversion reaction, malingering

**AUTOIMMUNE DISEASES[1]**

Sjögren's syndrome, systemic lupus erythematosus, Behçet's disease, sarcoidosis, antiphospholipid–antibody syndrome

**VARIANTS OF MS[1]**

Optic neuritis, isolated brain-stem syndrome, transverse myelitis, ADEM, Marburg disease, NMOSD

**INFECTIOUS DISEASES[1]**

HIV-associated myelopathy and HTLV-1-associated myelopathy, Lyme disease, meningovascular syphilis, Eales disease, PML

**VASCULAR DISORDERS[1]**

Spinal dural arteriovenous fistula, cavernous hemangiomata,
CNS vasculitis, CADASIL

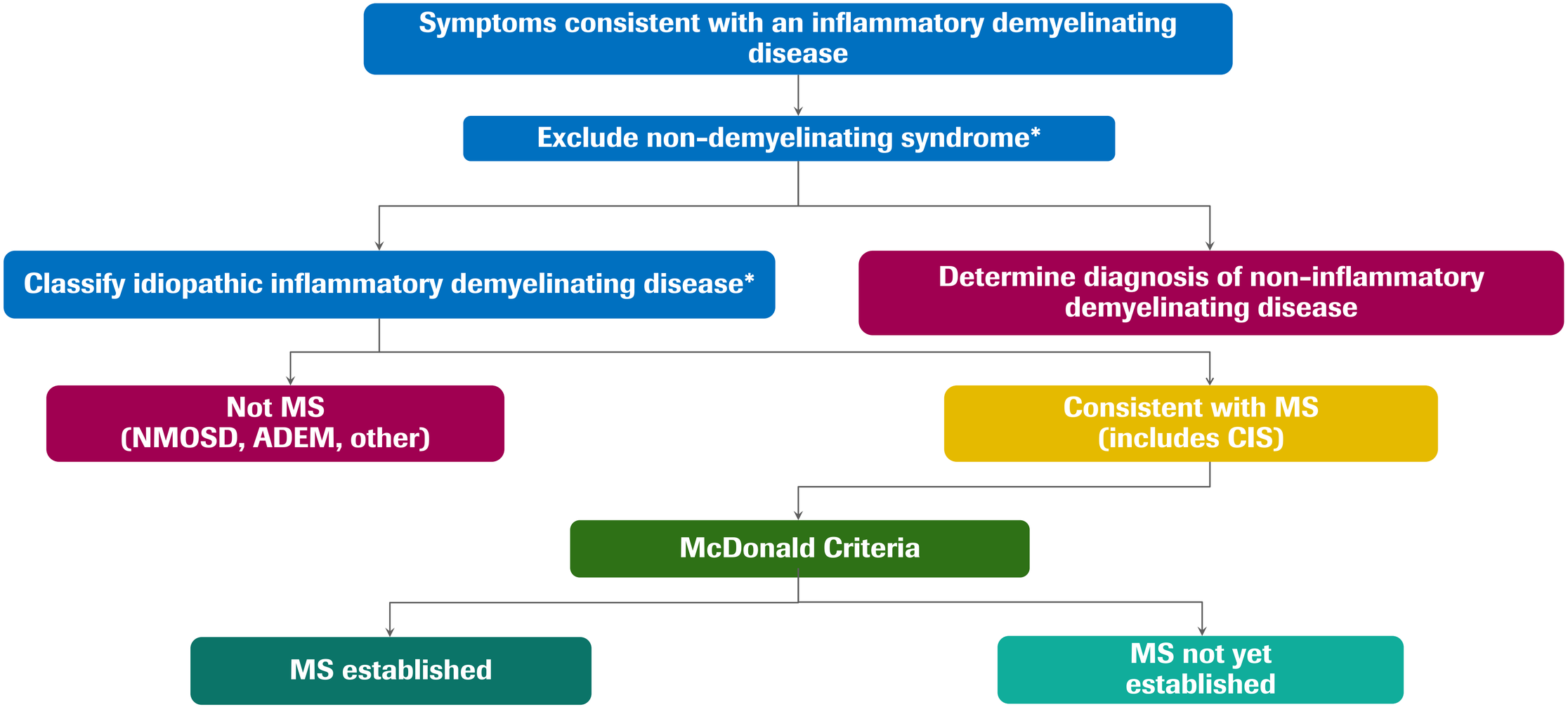
**GENETIC DISORDERS[1,2]**

Hereditary ataxias and hereditary paraplegias, Leber's optic atrophy

ADEM, acute disseminated encephalomyelitis; CADASIL, human T-cell lymphotropic virus; CNS, central nervous system; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; NMOSD, neuromyelitis optica spectrum disorder; PML, progressive multifocal leukoencephaolopathy.

1. Eckstein C, et al. J Neurol 2012;259:801–16; 2. Scolding N, et al. J Neurol Neurosurg Psychiatry 2001:Sii9–15.

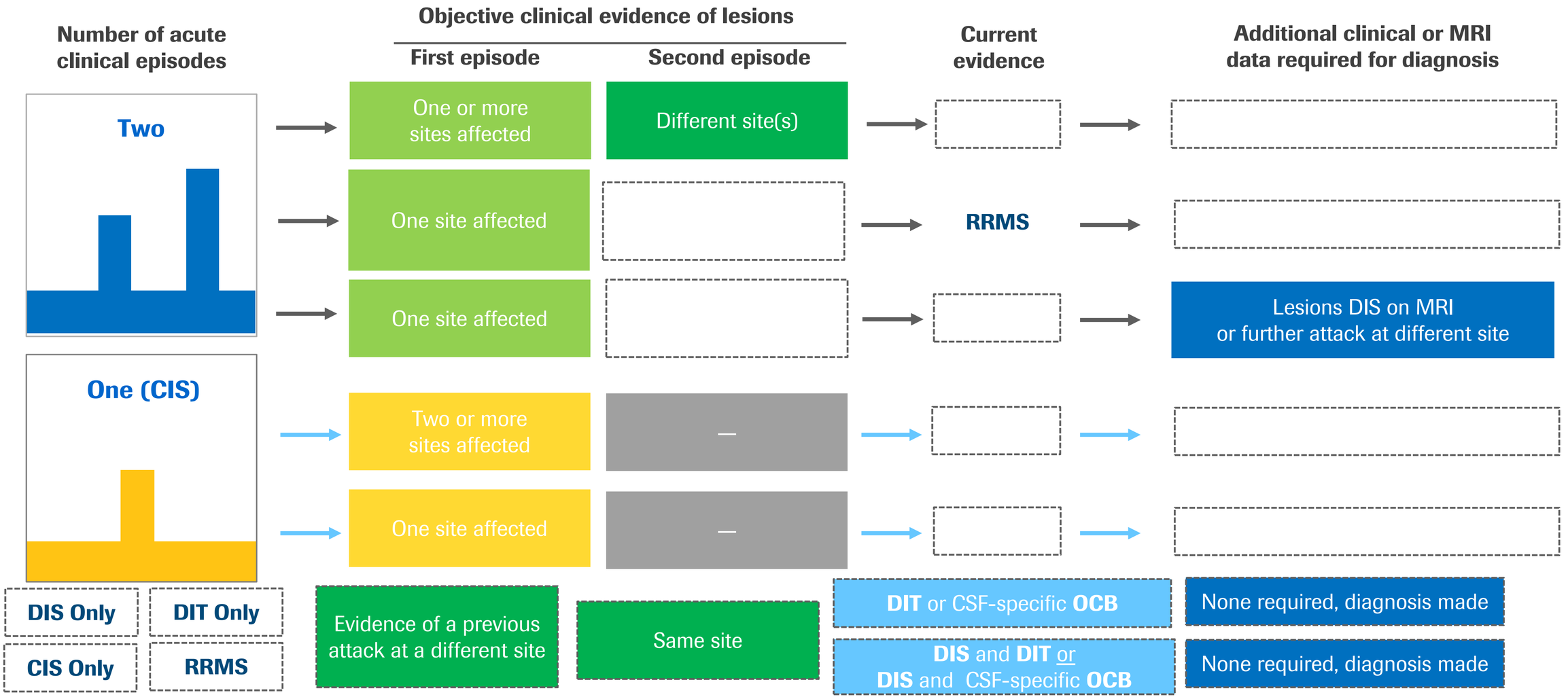
# Key steps in the differential diagnosis of MS




*Based on demographics, clinical course, specific symptoms and signs, radiology, lab tests.
ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; NMOSD, neuromyelitis optica spectrum disorder.
Miller DH, et al. Mult Scler 2008;14:1157–74.

# Diagnosis of MS

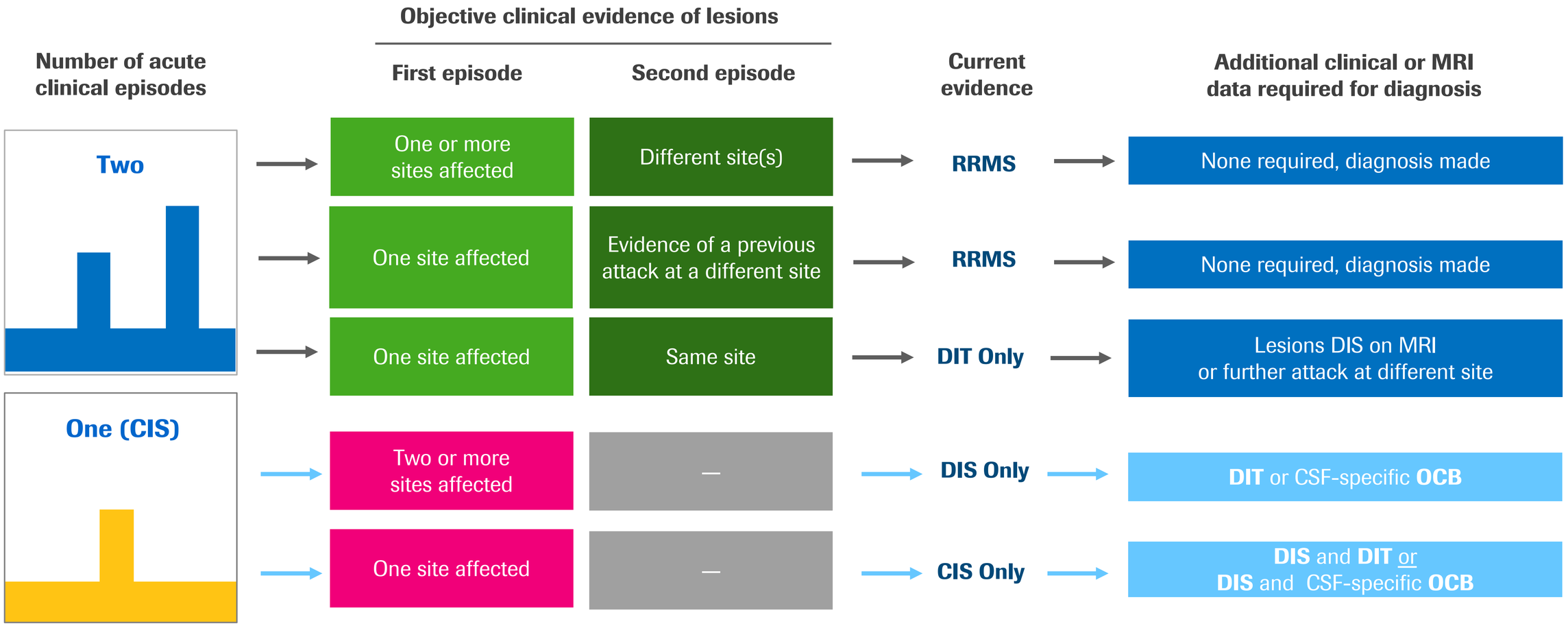
*Quiz – repopulate the diagram below*




CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; DIS, dissemination of lesions in space; DIT, dissemination of lesions in time; OCB, oligoclonal bands; RRMS, relapsing remitting MS.
Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

# Diagnosis of MS

*Quiz answers – repopulate the diagram below*

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Thompson AJ, et al. Lancet Neurol 2018;17:162–73.

6

# Monitoring of patients with MS

# The MS appointment – The patient and the healthcare team

## Regular appointments with HCPs are critical to appropriately assess and manage the course of the patient's MS[1]

- The members of a patient's team may vary depending on the patient's presenting symptoms[1,2]
  - This team can include: a neurologist, general practitioner, nurse, and other specialised healthcare professionals such as physical therapists, psychologists or ophthalmologists

- Typically, routine appointments last approximately 10 to 30 minutes[1], though the time can vary between countries
  - Dependent on the HCP that is being seen and the tests that are required, many tests for disability are not frequently performed

HCP, healthcare professional.

1. Multiple Sclerosis Trust. https://www.mstrust.org.uk/understanding-ms/ms-symptoms-and-treatments/making-most-appointments. Accessed January 2020;
2. Gallien P, et al. Eur Neurol 2014;72:20–5.

# All clinicians are limited by time, resource, and technology restrictions

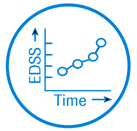
## Idealised MS routine monitoring protocol (~3–6 monthly)

Consultation with full medical history (~30mins)

Range of MRI sequences (brain and spine)

Full neurological exam

Assessment of upper and lower limb function




EDSS assessment

Medication adherence and routine labs

Pain assessment

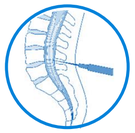
Questionnaire to assess mood and mental health

Speech and swallowing assessment

Assessment of cognition (e.g. SDMT or BICAMS)

PRO measures

Multi-disciplinary team review of patient case



Fluid biomarker assessment

Vision assessment by an ophthalmologist

## A more realistic typical monitoring protocol (~6–12 monthly)

Consultation with full medical history (~10mins)

Yearly MRI, may not follow guidelines (due to equipment)

Partial functional assessment by practice nurse (uncommon)

Partial neurological exam and routine labs

9HPT, 9-Hole Peg Test; BICAMS, Brief International Cognitive Assessment for MS; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FBC, full blood count; LFT, liver function test; MRI, magnetic resonance imaging; NfL, neurofilament light; PRO, patient reported outcomes; QoL, quality of life; SDMT, Symbol Digit Modalities Test; T25FW, timed 25-foot walk.

Ziemssen T, et al. BMC Neurology 2016; MS Brain Health Report; Gelfand JM, et al. Mult Scler Relat Disord 2014122:269–290; Kale N. Eye Brain 2016;8:195–202

# Monitoring the impact and progression of MS is complex and requires use of multiple tools and techniques

- The complexity and unpredictable course of the signs and symptoms of MS make assessing the impact of the disease complex, requiring the use of a variety of outcome measures

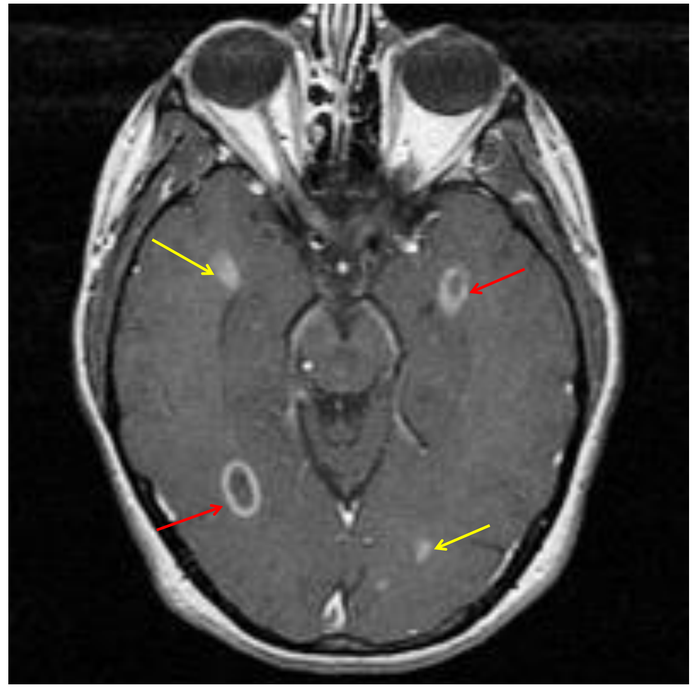
| Impact | Measurements | Clinically apparent? |
|---|---|---|
| **Neurological pathology** | MRI measures of lesion burden and grey and white matter volumes | Not necessarily (subclinical) |
| **Relapse** | Annualised relapse rate, time to first relapse, probability of freedom from relapse | Yes (clinical) |
| **Disability** | EDSS (ambulation), MSFC (ambulation, dexterity and cognitive function) | Yes (clinical) |
| **Symptoms** | Specific scales for pain, fatigue, visual acuity, depression, cognition | Yes (clinical) |
| **QoL** | Generic or MS-specific QoL scales | Yes (clinical) |

EDSS, Expanded Disability Status Scale; MSFC, MS Functional Composite; QoL, quality of life.

Foley JF, Brandes DW. Neurology 2009;72:S1–11.

# Assessing the incidence of acute relapses can be clarified by MRI

- Sometimes it can be difficult for a neurologist (or patient) to determine if symptoms indicate acute relapse, because they may be[1]:
  - **New** symptoms of MS
  - **Former** symptoms recurring
  - **Worsening** of symptoms because of disease progression
- MRI can help to clarify the diagnosis of acute relapse*
  - The number and volume of Gd-enhancing† lesions are higher during acute relapse than during remission (before or after relapse) [2]



Gd-enhanced $T_1$-weighted MRI scan allows detection of two ring-enhancing (red arrows) and several more nodular-enhancing lesions (yellow arrows)

*MRI is not necessary or sufficient to diagnose an acute relapse;
†Gd is an element that, when attached to an organic molecule, can be given intravenously as a contrast agent. Gd, gadolinium.
1. Managing Relapses: Multiple Sclerosis Trust https://www.mstrust.org.uk/about-ms/ms-symptoms/managing-relapses. Accessed January 2020;
2. Rovaris M, et al. Eur Neurol 1999;41:123–7.

# Neurological disease activity in MS is typically measured using MRI

There is debate over how MRI should be used in clinical assessments of MS[1]:

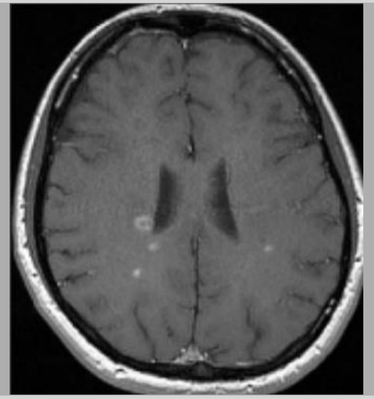
1. MRIs should be performed routinely on all patients with MS[1]

-or-

2. MRIs should be performed for diagnosis, to monitor effects of treatment, when treatment changes are under consideration, or when a patient has very active MS[1,2]

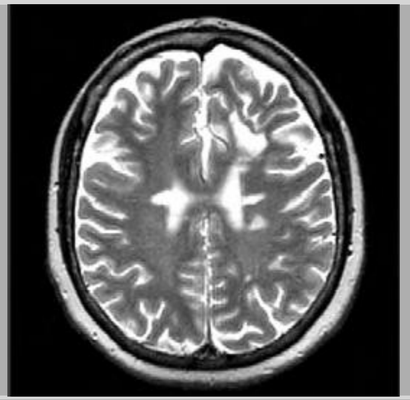
## Gd-enhanced T1 lesions

Tend to be transient, serve as a marker of active inflammation[3,4]



## New or enlarging T2 lesions

Rarely disappear, serve as a marker of long-term disease burden[4,5]



Reprinted from Sahraian MA, Eshaghi A. *Clin Neurol Neurosurg* 2010;112(7):609–15. Copyright 2010, with permission from Elsevier.

Gd, gadolinium.

1. Arnold D, Stone L. Int MS J 2011;17:58–62;
2. Cleveland Clinic. http://my.clevelandclinic.org/ccf/media/Files/Neurological-Institute/mellen-center/13-neu-539-mri-fact-sheet.pdf. Accessed 14 September, 2015;
3. Cotton F, et al. Neurology 2003;60:640–6; 4. Sahraian MA, Eshaghi A. Clin Neurol Neurosurg 2010;112:609–15;
5. Ge Y. AJNR Am J Neuroradiol 2006;27:1165–76.

# CMSC and MAGNIMS provide guidance on the use of MRI in the ongoing monitoring of MS

- When to use the CMSC brain MRI protocol (with Gd) for patients with an established diagnosis of MS:[1]

- No recent prior imaging available (e.g. new patient)
- Postpartum to establish a new baseline
- Prior to starting or switching DMT
- Approximately 6 months after switching DMT to establish a new baseline on the new therapy
- Every 1–2 years while on DMT to assess subclinical disease activity
- Unexpected clinical deterioration or reassessment of original diagnosis

THE CONSORTIUM OF MULTIPLE SCLEROSIS CENTERS

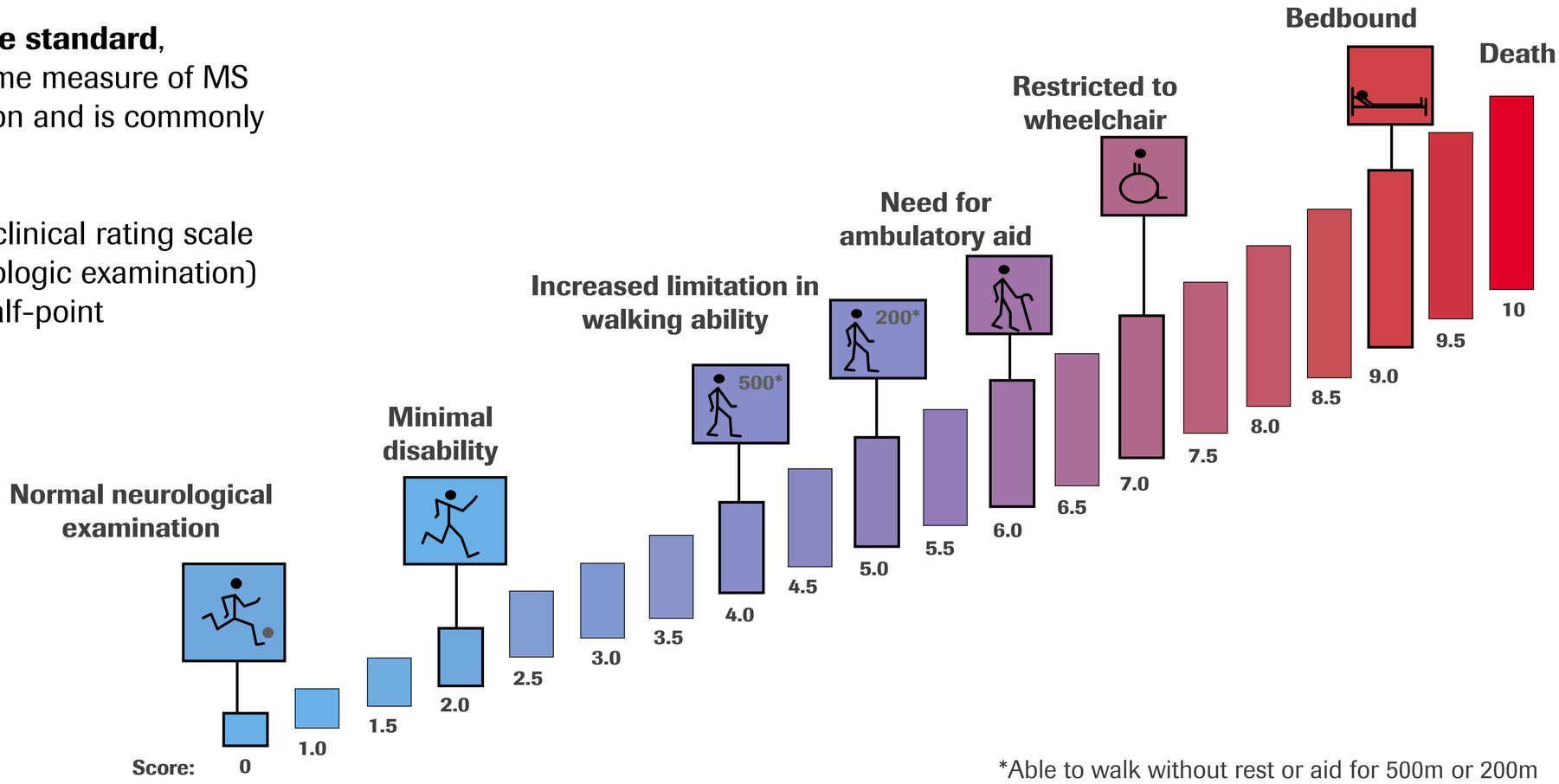
| Category | CMSC recommendation*[1] |
|---|---|
| **Field strength** | Scans should be of good quality, with adequate signal to noise ratio (SNR) |
| **Slice thickness** | ≤3 mm, whole brain, subcallosal plane |
| **Spatial resolution** | ≤1 x 1 mm |
| **Brain MRI** | Axial and sagittal 2D/3D FLAIR;<br>axial 2D/3D T2;<br>3D IR-prep GE T1;<br>axial 2D DWI;<br>axial 2D or 3D contrast-enhanced T1 |
| **Optional brain MRI** | Axial PD;<br>pre- or post-Gd 2D/3D axial T1 SWI |

**MAGNIMS** guidance on the use of MRI for monitoring treatment efficacy in MS is similar, with scans recommended 6–12 months after treatment initiation, and yearly thereafter[2]

*CMSC recommends a separate protocol for spinal cord imaging.
CMSC, Consortium of Multiple Sclerosis Centers; DMT, disease modifying therapy; DWI, diffusion-weighted imaging; Gd, gadolinium; MAGNIMS, Magnetic Resonance Imaging in MS; PD, proton density; SWI, susceptibility weighted imaging.
1. Traboulsee A, et al. AJNR Am J Neuroradiol 2016;37:394–401; 2. Wattjes M, et al. Nat Rev Neurol 2015;11:597□606.

# The Expanded Disability Status Scale (EDSS) is used to quantify disability and measure disease progression

- **The EDSS is considered the standard**, objective neurological-outcome measure of MS disease status and progression and is commonly used in clinical trials[1,2]
- It is comprised of an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments[1,2]




*Able to walk without rest or aid for 500m or 200m

EDSS, Expanded Disability Status Scale.

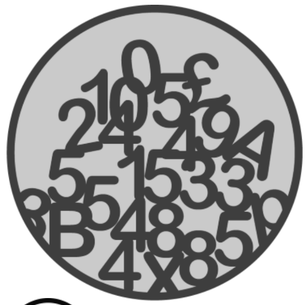
1. Kurtzke JF. Neurology 1983;33:1444–52; 2. Orme M, et al. Value Health 2007;10:54–60.

# The brief international cognitive assessment for MS (BICAMS) is a validated measuring tool to assess cognitive disability

- BICAMS is a brief test that can be given to a patient during every visit
  - Not intended to replace full neuropsychological assessment
  - Optimal for centres where a neuropsychologist may not be present
  - Can be performed by other HCPs such as a neurologist or nurse

## SDMT

To measure information processing speed, patients must match numbers with corresponding symbols



5 minutes

## CVLT-II T1-5

Patients' verbal memory is tested through recalling as many words from a 16-word list that is read aloud to them

5–10 minutes

## BVMTR T1-3

To measure visual memory, patients must draw an array of shapes correctly and in the correct position from memory

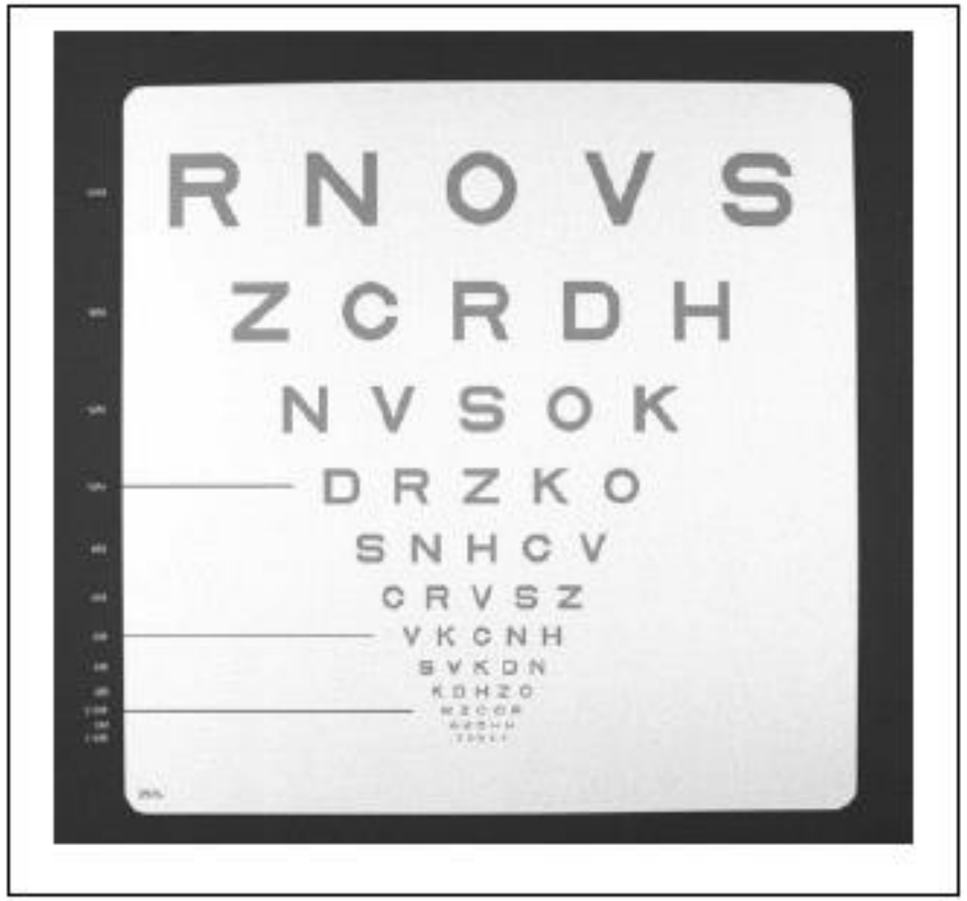
>30 seconds, variable

BVMTR T1-3, Brief Visuospatial Memory Test Revised, trials 1-3; CVLT-II T1-5, California Verbal Learning Test II, trials 1–5; HCP, healthcare professional; SDMT, Symbol Digit Modalities Test.

Langdon DW, et al. Mult Scler 2012;18:891–8.

# Low contrast visual acuity (LCVA) is a method of assessing visual dysfunction

- A majority of patients with MS experience visual dysfunction; optic neuritis is the presenting symptom in many patients[1,2]
- Low-contrast visual acuity test examines[3]:
  - How well patients can distinguish objects from similarly coloured or shaded backgrounds
  - What size of progressively smaller letters can still be read at particular levels of contrast




1. Ma SL, et al. Am J Ophthalmol 2002;133:686–92; 2. Sørensen TL, et al. Neurology 1999;53:473–8; 3. Balcer LJ, et al. Mult Scler 2017;23:734–47.

# Remote monitoring can aid our understanding and treatment of MS

Evaluating patients continually, rather than in cross-sectional clinical visits, to allow for more individualised treatment decisions and speedier treatment adjustments

Improving access to health services otherwise limited by mobility, fatigue or travel costs

Increasing patient engagement and treatment adherence

Generating longitudinal real-world data that may yield valuable insights into MS disease progression

Capturing information on social and QoL aspects of the disease not captured using traditional clinical outcomes

QoL, quality of life.

Marziniak M, et al. JMIR Rehabil Assist Technol 2018;5:e5.

# Digital technologies may aid remote monitoring of patients with MS

- **Advantages of these digital outcomes:**
  - Largely **independent** of human examinations, and therefore not prone to bias
  - Can monitor patients over **extended periods** of time
  - **Non-invasive**

Inertial measurement technologies can provide a sensitive measurement of a patient's gait and balance over time[1]

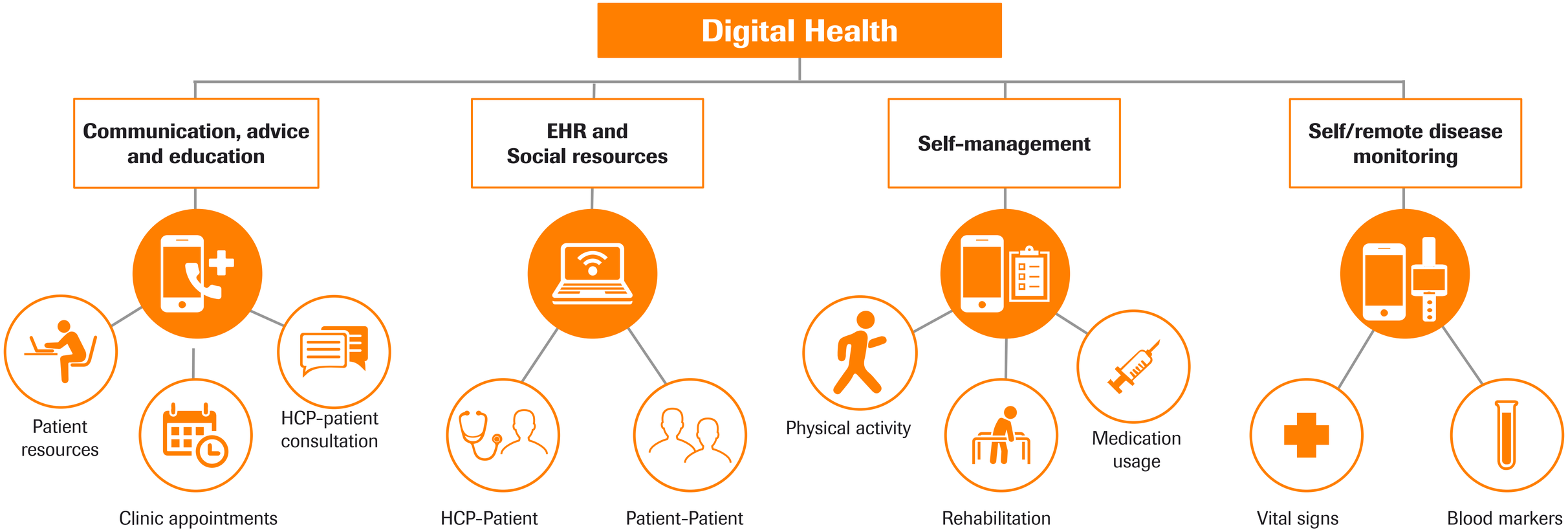
Smartphones/tablets can be used to assess cognition and patient-reported outcomes[2]

Wrist-worn devices can measure fatigue[3]

- **Floodlight™** is a smartphone sensor-based tool designed by Roche for active and passive remote monitoring of patients with MS[2]

1. Sun R, et al. Digit Biomark 2018;2:1–10; 2. Midaglia L, et al. J Med Internet Res 2019;21:e14863;
3. Kim E. et al. J Rehabil Res Dev 2010;47:477–84.

# A number of digital solutions are already being implemented in MS care




HER, electronic health record; HCP, healthcare professional; MS, multiple sclerosis.
Marziniak M, et al. JMIR Rehabil Assist Technol 2018;5:e5.

Medora

# Il futuro della medicina, l’avanguardia di noi medici.

La community dei professionisti della salute By Roche