Diagnostic Criteria, Clinical Courses, and Rating Scales in MS
Introduction and Objectives

Introduction

- This module will focus on diagnostic tools utilized in randomized clinical trials (RCTs) in MS. Diagnostic criteria that are used to determine whether a person has MS will be reviewed. This module will also review how clinicians use clinical evidence to objectively define the clinical course of a person who is affected by MS, so that uniform cohorts of patients can be enrolled in RCTs. Additionally, this module will discuss the challenges associated with defining the clinical course of MS. Finally, this module will cover how clinical rating scales are used to define whether a person with MS is getting better or worse.

Objectives

- Characterize the need for consistent diagnostic criteria, especially in relation to MS clinical trials
- Understand the range of possible clinical courses experienced by people with MS
- Understand commonly used clinical rating scales
Chapter 1: MS Diagnostic Criteria
• A History of MS Diagnostic Criteria
• McDonald Diagnostic Criteria
• Disease Diagnosis by Magnetic Resonance Imaging (MRI)

Chapter 2: Describing the Different Clinical Courses of MS
• Clinically Isolated Syndrome (CIS) and Radiologically Isolated Syndrome (RIS)
• Relapsing-Remitting MS (RRMS)
• Secondary Progressive MS (SPMS)
• Primary Progressive MS (PPMS)

Chapter 3: Current Clinical Rating Scales and Assessments
• The Need for MS Disease Rating Scales
• The Expanded Disability Status Scale (EDSS)
• The Multiple Sclerosis Functional Composite (MSFC)
• Health-Related Quality of Life (HRQL) Assessments

Summary
Currently, there is no way to prove that a person has MS

- No test to definitively confirm the diagnosis
- Clinicians typically diagnose MS using medical history, physical examination, and laboratory tests
- Diagnosis may include determining if the patient presents with the common and/or atypical symptoms of MS

Formal diagnostic criteria

- Developed to make the diagnostic process more objective and reproducible
- Assist clinicians who are less experienced with the characteristics of MS
- Facilitate the identification of patients with MS for clinical trials

Diagnosis of MS may be considered in part a subjective process that partially relies on interpretation, experience, and opinion

A History of MS Diagnostic Criteria

- Formal MS diagnostic criteria are based on dissemination in space and time
- Early criteria used clinical and laboratory evidence such as attacks or cerebrospinal fluid (CSF) to make a diagnosis of MS
- By the mid-1980s, MRI became widely available, and today most neurologists would not diagnose a patient with MS unless the patient was evaluated by MRI
- The McDonald criteria were developed to incorporate clinical and MRI evidence into MS diagnosis

The McDonald criteria are currently the most widely used diagnostic guidelines

McDonald Criteria: General Requirements for a Diagnosis of MS

Clinical and MRI criteria can be combined to meet dissemination in space (DIS) and dissemination in time (DIT) requirements for diagnosis¹

<table>
<thead>
<tr>
<th>Criteria Type</th>
<th>DIS</th>
<th>DIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical²</strong></td>
<td>Additional attack implicating a different central nervous system (CNS) site</td>
<td>Additional attack</td>
</tr>
<tr>
<td><strong>MRI²</strong></td>
<td>≥1 T2 lesion in at least 2 of 4 areas of the CNS</td>
<td>Simultaneous presence of gadolinium-enhancing and nonenhancing lesions or A new lesion on follow-up MRI with reference to a baseline scan</td>
</tr>
</tbody>
</table>

Positive test results for CSF oligoclonal bands can be used as a substitute for the DIT requirement for diagnosis

A single brain MRI scan that demonstrates both DIS and DIT combined with clinical evidence of an attack is sufficient to diagnose MS¹

2017 McDonald Diagnostic Criteria

2017 Revisions

- Allowed use of oligoclonal bands (OCBs) in CSF to replace DIT in patients with typical CIS who have clinical or MRI evidence of DIS
- Considered both symptomatic and asymptomatic MRI lesions in determining DIS and DIT
- Added cortical lesions for demonstrating DIS
- Recommended determining a provisional disease course at the time of diagnosis, and periodically re-evaluating it based on accumulated evidence

2017 Revised McDonald Criteria

<table>
<thead>
<tr>
<th>Clinical Attack(s)</th>
<th>≥2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions with Objective Clinical Evidence&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥2 or 1 with evidence of DIS from prior attack</td>
<td>1</td>
</tr>
<tr>
<td>Additional Data Needed for Diagnosis</td>
<td>None</td>
<td>DIS&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Objective clinical evidence as determined by an abnormal neurological exam, imaging (MRI or optical coherence tomography), or neurophysiological testing (visual evoked potentials).

<sup>b</sup>DIS demonstrated by an additional clinical attack implicating a different CNS site or by MRI.

<sup>c</sup>DIT demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific OCBs.

Disease Diagnosis By MRI

MRI in particular can help

- Standardize an approach to diagnosis
- Provide objective information as to whether patients meet the criteria for MS
- Assess the risk of and identify a second attack in patients with CIS, helping to confirm a diagnosis of MS

Incorrect interpretation of MRI scans may lead to misdiagnosing MS

- Occurs when signal changes are falsely interpreted to be caused by MS
- May be due to differences in the protocol for an MRI scan (eg, resolution, slice thickness, magnet strength, head position)

Chapter 2

Describing the Different Clinical Courses of MS
Clinically Isolated Syndrome (CIS) is essentially the first attack of a neurologic deficit that is associated with a demyelinating lesion\textsuperscript{1,2}

- Patients with CIS do not have MS, though they are at high risk for developing MS
- Many people who present with CIS will progress to clinically definite MS
  - Clinical progression can occur within months or years

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CIS: Common Clinical Presentations

Most common clinical presentations of CIS may include:

- **Optic neuritis (ON)**
  - Common first symptom of MS and can also remain an isolated episode\(^1,2\)
  - Typically presents as an abrupt-onset and unilateral loss of vision\(^3\)
  - Contrast enhancement reveals optic nerve lesions on MRI in up to 94% of ON patients\(^3\)
  - Recurrence of ON was also associated with a high risk of developing clinically definite MS (recurrence of ON is not diagnostic of MS)\(^1,2\)

- **Spinal cord syndrome (long tract signs)**\(^1,4\)
  - Suggest lesions in the long nerve fiber tracts of the spinal cord
  - Can include transverse myelitis (TM)

- **Brain dysfunction**\(^1\)
  - Present in approximately 10% of people who present with CIS\(^1\)
  - In a cohort of 23 people with brainstem dysfunction, progression to MS was seen in 57% of people with a brainstem syndrome, after a mean of 14 to 15 months\(^5\)

CIS: Multifocal Abnormality

Multifocal abnormality in patients with CIS suggests that a person experiences more than one sign or symptom, caused by lesions in more than one place

• A study published in 2009 on the predictive value of MRI scans suggested that the time to clinically definite MS was similar to monofocal and multifocal patients
• To determine the risk of developing clinically definite MS, it may be necessary to assess both MRI results and neurologic signs and symptoms

People with CIS can have more than one lesion at initial presentation

Long-term MS prognosis is reported to be affected by several factors at presentation\textsuperscript{1,2}

- Studies indicate that the number of MRI-visible lesions at presentation impacts both conversion to clinically definite MS and development of physical disability\textsuperscript{1,2}

**Features of CIS and Early MS Reported to Affect Prognosis\textsuperscript{1,2}**

**Good Prognosis**
- Normal MRI
- Optic neuritis
- Isolated sensory symptoms
- Long interval to second relapse
- No disability after 5 years

**Bad Prognosis**
- Abnormal MRI with large lesion load
- Efferent systems affected
- Multifocal CIS
- High relapse rate in the first 2-5 years
- Substantial disability after 5 years

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Radiologically Isolated Syndrome (RIS)

RIS is diagnosed in people who have MRI signs of MS but lack clinical symptoms of disease

- Identified with increasing prevalence, as MRI became a common diagnostic tool
- Usually takes the form of T2 demyelinating lesion(s) and/or gadolinium-enhancing lesions with characteristics highly suggestive of MS in an asymptomatic person

Relapsing-Remitting Multiple Sclerosis (RRMS)

Most common form of MS at diagnosis\(^1,2\)
- Diagnosis of RRMS typically occurs between ages 20 and 50
- Found to be more common in women, with at least a 2:1 female to male ratio

Relapse and progression are considered to be the 2 basic phenomena that constitute MS\(^3\)

1. Clinical relapse is the occurrence, recurrence, or worsening of a neurologic dysfunction that lasts more than 24 hours and eventually resolves either partially or completely
   - If worsening of symptoms is due to fatigue or febrile illness, this is not considered a relapse
   - The interval between apparent relapses must be longer than a month for the symptoms to represent a separate relapse
   - Relapse is the clinical expression of an acute inflammatory lesion in the CNS

2. Progression is defined as the continual worsening of signs and symptoms of MS for at least 6 months, with or without superimposed relapses
   - Progression reflects a gradual accumulation of damage due to axonal demyelination, axonal loss, or gliosis

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RRMS: Typical Disease Course

RRMS can be thought of as a series of relapses interspersed with intervals of partial or complete remission, but without evidence of disease progression between relapses.

- There can be residual deficits upon relapse recovery.
- If and when progression (between relapses) and less recovery between attacks (or none at all) becomes a dominant feature of MS, the patient no longer has RRMS.

Two Representative Clinical Courses for Patients With RRMS

Progression to disability is a critical consideration for every person diagnosed with RRMS

- An observational study of 1844 people with MS (1562 people with RRMS) analyzed the median time to irreversible disability
  - For three disability milestones analyzed, the median time to irreversible disability for people with RRMS is shown below

<table>
<thead>
<tr>
<th>Disability Milestone</th>
<th>Median Time (Years)</th>
<th>Never Reached This Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to walk without aid or rest for more than 500 m</td>
<td>11.4</td>
<td>52%</td>
</tr>
<tr>
<td>Inability to walk with unilateral support for more than 100 m</td>
<td>23.1</td>
<td>73%</td>
</tr>
<tr>
<td>Inability to walk with unilateral support for more than 10 m</td>
<td>33.1</td>
<td>82%</td>
</tr>
</tbody>
</table>

A meta-analysis published in 2006 pooled results from 27 separate published studies of approximately 8600 people with RRMS to determine the best predictors of patient disability

- Factors that were assessed as predictors included the following:
  - Male sex
  - Age at onset
  - Sensory symptoms
  - Longer interval from first to second attack
  - Early relapse frequency
  - Motor symptoms
  - Optic neuritis
  - Brainstem symptoms
  - Cerebellar symptoms
  - Incomplete recovery from the first neurologic attack
  - Sphincter symptoms

Secondary Progressive Multiple Sclerosis (SPMS)

SPMS is diagnosed in people with RRMS when symptoms progress between relapses or when intermittent progression replaces relapses

- Transition from RRMS to SPMS tends to occur at approximately 40 years of age
- Transition from RRMS to SPMS can be difficult to identify
- Natural history studies show that up to 90% of patients with untreated RRMS eventually develop SPMS
- SPMS is characterized by one or all of the following
  - Less recovery following attacks
  - Function persistently worsened during and between attacks
  - Fewer and fewer attacks (or none at all)
  - Intermittent or consistently progressive disability

Neurologic attacks in SPMS can and do remit. The hallmark of SPMS is less frequent relapses, with symptomatic progression between relapses.

Relapse
• Relapses may correspond to immune-mediated demyelination of neurons, accompanied by axonal damage and loss
• Residual symptoms from incomplete recovery may persist indefinitely, contributing to disability progression

Progression
• Progression may represent a neurodegenerative process initiated by earlier episodes of tissue injury
• Neurologic reserve—the ability of the brain to compensate for injury—declines over time as MS damage to CNS tissue accumulates, which may contribute to progression
• Clinical relapses may still occur, especially early in the transition to SPMS

Primary Progressive Multiple Sclerosis (PPMS)

Only 15% of people have PPMS

- PPMS is characterized by the absence of acute attacks and progression of disability from disease onset or with occasional plateaus and temporary minor improvements
- Disease progression starts slowly from the onset without any identifiable relapses

Diagnosing PPMS

- Tends to be more challenging than diagnosing relapsing-remitting forms of MS
- Occurs in people who are somewhat older than people diagnosed with RRMS

Treating PPMS

- It is recommended that people with PPMS work with their clinicians to manage symptoms, enhance mobility, promote overall health and wellness, and promote emotional well-being on an ongoing basis

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Several typical courses of PPMS
PPMS: MRI Lesions

There is evidence from MRI that PPMS may be associated with fewer T2 brain lesions than are generally present in people with either RRMS or SPMS\(^1\)

- This finding has been demonstrated with gadolinium-enhancing MRI lesions as well\(^1\)
  - Suggests that there is an early “clinically silent” phase of illness, perhaps for years before the diagnosis of PPMS

Prognostic factors are similar for RRMS and SPMS, but somewhat different for PPMS\(^2\)

1996 MS Clinical Description Subtypes

Relapsing-remitting disease (RRMS)
- With full recovery from relapses
- With sequelae/residual deficit after incomplete recovery

2013 MS Disease Modifiers Phenotypes

Clinically isolated syndrome (CIS)
- Not Active\(^a\)
- Active\(^a,b\)

Clinical relapse and/or MRI activity (Active)\(^a,b\)

Relapsing-remitting disease (RRMS)
- Active\(^a\)
- Not Active\(^a\)

\(^a\) 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."

\(^b\) CIS, if subsequently clinically active and fulfilling current MS diagnostic criteria, becomes RRMS.


1996 vs 2013: Descriptions For Progressive Disease

1996 MS Clinical Description Subtypes

Progressive disease

Primary Progressive
Progressive accumulation of disability from onset with or without temporary plateaus, minor remissions, and improvements

Secondary Progressive
Progressive accumulation of disability from after initial relapsing course, with or without occasional relapses and minor remissions

Progressive Relapsing
Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery

2013 MS Disease Modifiers Phenotypes

Progressive disease

Primary Progressive
Active and with progression

Secondary Progressive
Active but without progression

Not active but with progression

Not active and without progression (stable disease)


Definitions Used in 2013 Recommendations

Active disease

• Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction followed by full or partial recovery, in the absence of fever or infection and/or
• Imaging (MRI): occurrence of contrast-enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions

Progressive disease

• Clinical: steadily increasing objectively documented neurologic dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur)
• Imaging (MRI): imaging measures of progression are not established or standardized and not (yet) useful as phenotype descriptors for individual patients. Under consideration are increasing number and volume of T1 hypointense lesions, brain volume loss, and changes in magnetic transfer imaging and diffusion tensor imaging

Worsening disease

• Documented increase in neurologic dysfunction/disability as a result of relapses or progressive disease, reserving the term disease progression for those solely in a progressive phase of the illness

Confirmed progression or worsening

• Increase of neurologic dysfunction confirmed throughout a defined time interval (eg, 3, 6, or 12 months)
• Because neurologic dysfunction may still improve (especially in relapsing disease), even if progression is confirmed over 6 or 12 months, we recommend abandoning the term sustained

The MS Phenotype Group: 2013 Recommendations

- The core MS phenotype descriptions of relapsing and progressive disease should be retained with some modifications.
- An important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging.
- The second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period.
- The prior category of PRMS can be eliminated since subjects so categorized would now be classified as PP patients with disease activity.
- PPMS is a part of the spectrum of progressive disease and differences from other forms are relative rather than absolute.
- CIS should be included in the spectrum of MS phenotypes. Prospective follow-up of most such patients should determine their subsequent disease phenotype.
- RIS should not be considered a separate MS phenotype, since such patients lack clinical signs and symptoms of the disease. Prospective follow-up is recommended.
- Use of the term worsening is preferable and less confusing than the term progressing to describe a patient in the relapsing phase of disease whose disease is advancing due to frequent relapses and/or incomplete relapse recovery.
- In considering clinical trial or natural history assessment of worsening disease by EDSS or other metrics, use the term confirmed rather than sustained over a defined period of time, either within (more rigorously) the functional system or without considering the specific functional systems in which worsening is detected.
- The terms benign and malignant disease are often misused and should be used with caution.
- Further research is needed to better define the value of imaging and biological markers in assessing, confirming, or revising MS phenotype descriptions.

Chapter 3

Current Clinical Rating Scales and Assessments
MS Disease Rating Scales

Rating scales are used by clinicians in an attempt to assess and to quantify the extent, or severity, of diseases

- Standardized disease ratings are crucial especially during clinical trials when rating scales often measure a treatment’s efficacy in a patient

Several problems inherent to MS make it challenging to develop an effective scale to assess MS disease severity

- Large variety of non-commensurate signs and symptoms in MS
- Difficulty in gaining agreement on the boundaries (levels) for motor strength, coordination, and altered sensation
- Difficulty in developing a scale that allows intra- and inter-rater (observer) reliability

Effective rating scales for MS clinical trials need to be objective and maintain sensitivity and specificity over the full range of disease severity to be examined in the trial¹

- Experts in the field of MS have created a wish list of characteristics for an MS clinical rating scale²
  - Appropriate
  - Valid
  - Accurate
  - Precise
  - Efficient
  - Sensitive
  - Range (comprehensive)

Currently, none of the existing MS rating scales successfully incorporate all of these features²

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Neurologic impairment assessment (rating) system consisting of 8 functional systems and a 10-step disability status scale

• Developed in 1955 by John Kurtzke, MD, as the original Disability Status Scale (DSS)
• To enhance sensitivity of the DSS, in 1983, half-step increments were added between levels 1 and 9 and it became known as the Expanded DSS (EDSS)

To determine a person’s level on the EDSS, neurologic function is first assessed in the following 8 mutually exclusive CNS functional systems

• Pyramidal
• Cerebellar
• Brainstem
• Sensory
• Bowel and bladder
• Visual
• Cerebral (or mental)
• Other functions

Each functional system is evaluated and graded with a score from 0 to 5 or 6

Functional system scores are then collated to determine a level on the EDSS

There are several “milestone” levels within the EDSS.

EDSS steps ≤4.5 refer to patients who are fully ambulatory, and the precise step is defined by the Functional System score(s).

EDSS steps from ≥5 are defined largely or entirely based on ambulation and mobility.

- **Level 4.0** is the first level where there is a severe disability in one of the functional systems.
- **Level 6.0** is where a patient can no longer walk without intermittent or unilateral constant assistance to walk 100 meters.
- At **level 7.0** a person with MS is wheelchair bound but able to self-transfer.

Reported Advantages: EDSS for MS Clinical Trials\textsuperscript{1,2}

- Researchers are familiar, and have experience with, EDSS
- Physicians understand the impairment described by EDSS
- EDSS fosters standardization between trials because clinicians are expected to use the scale in the same way at different study sites
- EDSS covers the whole range of the disease (mild, moderate, and severe disability)
- EDSS does not assume that a person can still walk (as do some other scales)

EDSS is the most frequently utilized rating scale in MS clinical trials

Reported Disadvantages: EDSS for MS Clinical Trials

- Even with rater training, intra- and inter-observer variability of one to two levels\(^1\)
- At the lower end of the scale (scores ≤4.5), EDSS is obtained by rating the severity of impairments determined by neurologic examination of 8 functional systems\(^2\)
  - At this lower range of the scale, the EDSS can be imprecise because of subjectivity in determining these scores and, as a result, some experts believe that the EDSS does not accurately measure disability at the lower end of the scale
- In the middle and upper regions of the scale (scores ≥5.0), the EDSS is almost exclusively dependent on mobility and is less sensitive to other dimensions of MS such as upper extremity function and cognitive function\(^2\)

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Multiple Sclerosis Functional Composite (MSFC)

MSFC consists of three tasks that focus on arm, leg, and cognitive function\(^1\)

<table>
<thead>
<tr>
<th>Clinical Dimension</th>
<th>Test</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>9-hole peg test (9-HPT)</td>
<td>Time to insert and remove 9 pegs with one hand</td>
</tr>
<tr>
<td>Leg</td>
<td>Timed 25-foot walk (T25-FW)</td>
<td>Time to walk 25 feet (8 meters)</td>
</tr>
<tr>
<td>Cognition</td>
<td>Paced Auditory Serial Addition Test (PASAT3)</td>
<td>Number of correct additions</td>
</tr>
</tbody>
</table>

The manual for the MSFC recommends that the MSFC tests be performed in the following specific order\(^2\)

1. T25-FW
2. T25-FW
3. 9-HPT, dominant hand
4. 9-HPT, dominant hand
5. 9-HPT, non-dominant hand
6. 9-HPT, non-dominant hand
7. PASAT3

Calculating the MSFC Score

Scores for these three dimensions—arm, leg, and cognitive function—are combined to create a single score that can then be utilized to identify change over time in a group of MS patients

• This can be done by creating z-scores for each component of the MSFC and averaging them to create an overall composite score known as the MSFC score

There are three scoring components to the MSFC

1. The average scores from the four trials on the 9-HPT
2. The average scores of two 25-Foot Timed Walk trials
3. The number correct from the PASAT3

The MSFC score is the average of the 3 z-scores:

\[
\text{MSFC score} = \frac{[z_{\text{arm}, \text{average}} + z_{\text{leg}, \text{average}} + z_{\text{cognitive}}]}{3.0}
\]
Reported Advantages: MSFC for MS Clinical Trials

- The MSFC can be administered by a trained technician (does not require a neurologist)\(^1\)
- The MSFC provides a quantitative method to measure disease severity\(^1\)
- Studies suggest that the MSFC is more sensitive to changes in impairment than the EDSS, especially for patients who have a low level of disease severity (impairment)\(^1\)
- The MSFC is very precise and highly reproducible\(^2\)
- Very little inter- and intra-observer variability has been identified\(^2\)

Reported Disadvantages: MSFC for MS Clinical Trials

- Long-term prognostic value of the MSFC may be no better than that of the EDSS\textsuperscript{1}
- MSFC does not cover the whole range of disease (it becomes non-informative once the patient is unable to ambulate 25 feet or complete the 9-HPT)\textsuperscript{2}
- Lacks a measure of visual function\textsuperscript{3}
- It requires initial patient training to minimize practice effects with the PASAT3 and 9-HPT (study participants could appear to be in remission when they are actually improving performance through practice effect)\textsuperscript{1}
- Scoring requires averaging the baseline values of study participants and determining the standard deviation in each patient cohort to obtain a base z-score against which change is measured\textsuperscript{3}
- Clinical interpretation of the MSFC z-score and individual component z-score changes can be difficult\textsuperscript{1}
- Conducting the MSFC tests requires equipment (9-hole peg board and pegs, stopwatch, PASAT recording and player, recording sheets)\textsuperscript{3}
- Conducting the MSFC requires a 25-foot straight hallway\textsuperscript{4}

Health-Related Quality of Life (HRQL) Assessments

This section covers information related to Quality of Life Scales for MS studies. QOL results data are not currently included in any disease-modifying agent’s prescribing information and therefore it is not appropriate to discuss Quality of Life results data with anyone outside of Novartis Pharmaceuticals.

HRQL assessments are designed to evaluate people regarding their
  • Overall health and physical functioning
  • Psychological and social/role functioning

HRQL assessments are available as both generic and disease-specific documents
  • Health Status Questionnaire (SF-36)
    o Generic questionnaire; therefore, results may be compared across different diseases
  • Multiple Sclerosis Quality of Life-54 (MSQOL-54)
    o Self-administered, 54-item scale based on SF-36, but adds 18 disease-specific items that aim to make the scale more appropriate for MS patients
  • Multiple Sclerosis Quality of Life inventory (MSQLI)
    o Covers some patient concerns in more depth than does the MSQOL-54, so subscales may be more useful for tracking certain features of MS
  • Multiple Sclerosis Impact Scale (MSIS-29)
    o 29-item, self-administered assessment that measures the physical and psychological impact of MS from the patient’s perspective

Summary

Diagnosis of MS
• Currently, there is no test to definitively confirm a diagnosis of MS
• Neurologists combine features of the patient’s medical history, physical examination, and laboratory tests, including MRI, to conclude with confidence that a patient does have MS

Clinical courses of MS
• CIS is essentially the first attack of a neurologic deficit that is associated with a demyelinating lesion
• RIS is diagnosed in people who have MRI signs of MS but lack clinical symptoms of disease
• RRMS is the most common form of MS at diagnosis
• SPMS is diagnosed in people with RRMS when symptoms progress between relapses or when intermittent progression replaces relapses
• PPMS is characterized by the absence of acute attacks and progression of disability from disease onset or with occasional plateaus and temporary minor improvements

MS disease rating scales
• EDSS is the most frequently utilized rating scale in MS clinical trials
• MSFC is a new multidimensional clinical outcome measure for MS clinical trials, consisting of three tasks that focus on arm, leg, and cognitive function
• HRQL assessments are designed to assess overall health, physical functioning, and psychological and social/role functioning
Additional Information
### Functional Scale (FS) Definitions for the EDSS: Pyramidal Function

<table>
<thead>
<tr>
<th>FS1 - Pyramidal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

**Functional Scale (FS) Definitions for the EDSS: Cerebellar Function**

**FS2 - Cerebellar function**

Use finger-to-nose, heel-to-shin test, rapid alternating movements, and gait. You are testing cerebellar functions of trunk and limbs – not weakness. If one or more limbs cannot be tested for cerebellar dysfunction (eg, paraplegia or hemiplegia) but the remaining limbs can be tested, score only the remaining limbs.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal – no evidence of cerebellar dysfunction. This may be used if one or more limbs are uncoordinated due to weakness, apraxia, or sensory loss but not due to cerebellar dysfunction</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal signs without disability – slight abnormality on formal testing but does not interfere with activities of daily living</td>
</tr>
<tr>
<td>2</td>
<td>Mild ataxia - limb or gait ataxia in any limbs adequate to noticeably interfere with function when the targeted function is stressed, including stressed gait hopping, toes, heels; physical or mechanical adaptation of the targeted activity is not necessary</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ataxia - use this if there is moderate ataxia in any or all limbs, in gait or stressed gait. This is also used if there is severe ataxia in one limb. It requires some physical or mechanical adjustment for the targeted activity to be completed (eg, the patient must hold the wall to hop or be steadied by the examiner)</td>
</tr>
<tr>
<td>4</td>
<td>Severe ataxia - more than 2 limbs for routine activities and/or routine gait, but still functional, albeit with difficulty (eg, may still be able to walk with aids and feeds self)</td>
</tr>
<tr>
<td>5</td>
<td>Unable to perform coordinated limb or routine gait movements due to ataxia</td>
</tr>
<tr>
<td>7</td>
<td>Not testable</td>
</tr>
<tr>
<td>8</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### Functional Scale (FS) Definitions for the EDSS: Brainstem Function

<table>
<thead>
<tr>
<th>FS3 - Brainstem Function</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Signs only (unsustained nystagmus, detectable impairment of saccadic pursuit or ocular dysmetria)</td>
</tr>
<tr>
<td>2</td>
<td>Sustained conjugate nystagmus, incomplete internuclear ophthalmoplegia, or other mild disability</td>
</tr>
<tr>
<td>3</td>
<td>Dysconjugate nystagmus (internuclear ophthalmoplegia) or severe extraocular weakness, or moderate disability of other cranial nerves</td>
</tr>
<tr>
<td>4</td>
<td>Severe <em>dysarthria</em> or other severe disability of the cranial nerves</td>
</tr>
<tr>
<td>5</td>
<td>Inability to swallow or speak</td>
</tr>
<tr>
<td>6</td>
<td>Not testable</td>
</tr>
<tr>
<td>7</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### Functional Scale (FS) Definitions for the EDSS: Sensory Function

<table>
<thead>
<tr>
<th>FS4 - Sensory Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

### Functional Scale (FS) Definitions for the EDSS: Bladder and Bowel Function

**FS5 - Bladder and Bowel Function - Ask about both bladder and bowel; score the worst, as follows**

<table>
<thead>
<tr>
<th>Bladder</th>
<th>Bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal bladder function</td>
<td>0 Normal bowel function</td>
</tr>
<tr>
<td>1 Bladder symptoms but no incontinence</td>
<td>1 Mild constipation but no incontinence</td>
</tr>
<tr>
<td>2 Incontinence less than once per week</td>
<td>2 Severe constipation but no incontinence</td>
</tr>
<tr>
<td>3 Incontinence more than once per week but less than daily</td>
<td>3 Rare (once per week) bowel incontinence</td>
</tr>
<tr>
<td>4 More than daily incontinence</td>
<td>4 Frequent (more than weekly but less than daily) bowel incontinence</td>
</tr>
<tr>
<td>5 Indwelling bladder catheter</td>
<td>5 No bowel control</td>
</tr>
<tr>
<td>6 Grade 5 bladder function plus grade 5 bowel function</td>
<td>6 Grade 5 bladder function plus grade 5 bowel function</td>
</tr>
<tr>
<td>7 Not testable</td>
<td>7 Not testable</td>
</tr>
<tr>
<td>8 Unknown</td>
<td>8 Unknown</td>
</tr>
</tbody>
</table>

# Functional Scale (FS) Definitions for the EDSS: Visual Function

<table>
<thead>
<tr>
<th>FS6 - Visual Function (all visual acuity is best corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>
### Functional Scale (FS) Definitions for the EDSS: Cerebral Function

<table>
<thead>
<tr>
<th>FS7 - Cerebral (or Mental) Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

### Functional Scale (FS) Definitions for the EDSS: Other Functions

#### FS8 - Other Functions (Any other neurologic findings attributable to multiple sclerosis)

<table>
<thead>
<tr>
<th>Siblingtity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild (detectable only)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (minor interference with function)</td>
</tr>
<tr>
<td>3</td>
<td>Severe (major interference with function)</td>
</tr>
<tr>
<td>4</td>
<td>Not testable</td>
</tr>
<tr>
<td>5</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>
**EDSS steps ≤4.5 refer to patients who are fully ambulatory, and the precise step is defined by the Functional System score(s)**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>Normal neurological exam (all grade 0 in all Functional System (FS) scores*)</td>
</tr>
<tr>
<td>1.0</td>
<td>No disability, minimal signs in one FS* (ie, grade 1)</td>
</tr>
<tr>
<td>1.5</td>
<td>No disability, minimal signs in more than one FS* (more than 1 FS grade 1)</td>
</tr>
<tr>
<td>2.0</td>
<td>Minimal disability in one FS (one FS grade 2, others 0 or 1)</td>
</tr>
<tr>
<td>2.5</td>
<td>Minimal disability in two FS (two FS grade 2, others 0 or 1)</td>
</tr>
<tr>
<td>3.0</td>
<td>Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory</td>
</tr>
<tr>
<td>3.5</td>
<td>Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1)</td>
</tr>
<tr>
<td>4.0</td>
<td>Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters</td>
</tr>
<tr>
<td>4.5</td>
<td>Fully ambulatory without aide, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters</td>
</tr>
</tbody>
</table>

*Excludes cerebral function grade 1.

### Kurtzke Expanded Disability Status Scale: Steps ≥5

**EDSS steps ≥5 are defined largely or entirely based on ambulation and mobility**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)</td>
</tr>
<tr>
<td>5.5</td>
<td>Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0)</td>
</tr>
<tr>
<td>6.0</td>
<td>Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+)</td>
</tr>
<tr>
<td>6.5</td>
<td>Constant bilateral assistance (cane, crutches, braces) required to walk about 200 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+)</td>
</tr>
<tr>
<td>7.0</td>
<td>Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone)</td>
</tr>
<tr>
<td>7.5</td>
<td>Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+)</td>
</tr>
<tr>
<td>8.0</td>
<td>Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems)</td>
</tr>
<tr>
<td>8.5</td>
<td>Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems)</td>
</tr>
<tr>
<td>9.0</td>
<td>Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+)</td>
</tr>
<tr>
<td>9.5</td>
<td>Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+)</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
</tr>
</tbody>
</table>

*Note: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. National Multiple Sclerosis Society. Kurtzke Expanded Disability Status Scale. http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/10-2-3-29-EDSS_Form.pdf. Accessed March 20, 2018.*