



## Complete Summary

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### GUIDELINE TITLE

EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis.

### BIBLIOGRAPHIC SOURCE(S)

Filippi M, Rocca MA, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Wolinsky JS. EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis. *Eur J Neurol* 2006 Apr;13(4):313-25. [156 references] [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

The validity of published guidelines will be reviewed by the chairpersons of the Task Force and the relevant Scientist Panel at least every 2 years.

### \*\* REGULATORY ALERT \*\*

### FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse:** This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [May 23, 2007, Gadolinium-based Contrast Agents](#): The addition of a boxed warning and new warnings about the risk of nephrogenic systemic fibrosis (NSF) to the full prescribing information for all gadolinium-based contrast agents (GBCAs).

### COMPLETE SUMMARY CONTENT

\*\* REGULATORY ALERT \*\*

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

## SCOPE

### **DISEASE/CONDITION(S)**

Multiple sclerosis (MS)

### **GUIDELINE CATEGORY**

Diagnosis  
Evaluation  
Technology Assessment

### **CLINICAL SPECIALTY**

Family Practice  
Internal Medicine  
Neurology  
Radiology

### **INTENDED USERS**

Physicians

### **GUIDELINE OBJECTIVE(S)**

- To assist in the use of conventional magnetic resonance imaging (cMRI) for the diagnosis and longitudinal monitoring of patients with multiple sclerosis (MS).
- To provide a foundation for the development of more widespread but rational clinical applications of non-conventional MR-based techniques in studies of MS patients.

### **TARGET POPULATION**

Patients with suspected and definite multiple sclerosis (MS)

### **INTERVENTIONS AND PRACTICES CONSIDERED**

Conventional magnetic resonance imaging (cMRI)

**Note:** Non-conventional MRI techniques (such as magnetization transfer MRI [MT-MRI], diffusion tensor MRI (DT-MRI); functional MRI [fMRI], and MR spectroscopy) were considered but not recommended.

### **MAJOR OUTCOMES CONSIDERED**

Sensitivity, specificity and predictive value of conventional and non-conventional magnetic resonance imaging (MRI) in the management of multiple sclerosis (MS) patients

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Data for this review were identified by searches of Medline and references from relevant articles from 1965 to 2005. The search terms "Multiple Sclerosis", "Magnetic Resonance Imaging", "Diagnosis", "Prognosis", "Atrophy", "Magnetization Transfer MRI", "Diffusion Weighted MRI", "Diffusion Tensor MRI", "Proton Magnetic Resonance Spectroscopy", "Disability", and "Treatment" were used. Only papers published in English were reviewed.

### NUMBER OF SOURCE DOCUMENTS

Not stated

### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

#### Evidence Classification Scheme for a Diagnostic Measure

**Class I:** A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

**Class II:** A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

**Class III:** Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

**Class IV:** Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

## **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses  
Systematic Review

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Not stated

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

The expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS) prepared the guidelines according to EFNS criteria (See "Availability of Companion Documents" field in this summary).

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

### **Rating of Recommendations**

**Level A rating** (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

**Level B rating** (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

**Level C rating** (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

**Good practice point** Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good practice points

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (See "Availability of Companion Document" field in this summary).

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good practice point) are defined at the end of the "Major Recommendations" field.

#### **Magnetic Resonance Imaging (MRI) Assessment of Patients at Presentation with Clinically Isolated Syndromes Suggestive of Multiple Sclerosis (MS)**

In patients at presentation with clinically isolated syndrome (CIS) suggestive of MS (i.e. neurological findings typically seen in the setting of MS) (Frohman et al., 2003) after appropriate exclusion of alternative diagnostic considerations that can mimic MS, the following recommendations should be considered:

1. Conventional MRI (cMRI) of the brain (dual-echo, pre- and post-contrast T1-weighted scans) should be obtained as soon as possible in all patients presenting with an isolated demyelinating syndrome involving the central nervous system (CNS), not only to collect additional evidence for lesion dissemination in space, but also to exclude other possible neurological conditions. As suggested by recent guidelines from the American Academy of Neurology (Frohman et al., 2003) the finding in these patients of three or more T2-hyperintense lesions with the imaging characteristics underlined by the International Panel (IP) guidelines (McDonald et al., 2001) (**Type A recommendation**) and the presence of two or more gadolinium (Gd)-enhancing lesions at baseline are sensitive predictors of the subsequent development of clinically definite MS (CDMS) within the next 7 to 10 years (**Type B recommendation**).
2. The presence of three or more white matter lesions on brain T2-weighted MRI in patients suspected of having MS is not diagnostic, especially when their location and appearance is non-characteristic for demyelination. In this context the IP criteria (McDonald et al., 2001) should be applied. Incidental white matter lesions are not an infrequent observation even in the young normal population. Note that with ageing (at least >50 years) incidental white matter lesions may also show progression (Schmidt et al., 2003; Longstreth et al., 2005) (**good practice point**).
3. In the case of steroids treatment, which is known to dramatically suppress Gd enhancement, one of the possible markers of inflammation, cMRI should be performed before treatment or, at least, 1 month after treatment termination (**good practice point**).
4. cMRI of the spinal cord is useful in those circumstances when brain MRI is normal or equivocal, and in patients with non-specific brain T2-abnormalities (especially when older than 50 years), because, contrary to what happens for the brain, cord lesions rarely develop with ageing *per se* (Kidd et al., 1993). In patients presenting with a spinal cord syndrome, spinal cord MRI is highly

- recommended to rule out other conditions that may mimic MS, such as compressive lesions **(good practice point)**.
5. In patients with acute optic neuritis (ON), MRI of the optic nerve can be useful in ruling out alternative diagnosis. In this case, short-tau inversion recovery (STIR) sequences should be used **(good practice point)**.
  6. Follow-up MRIs are required to demonstrate disease dissemination in time. In this perspective, the appearance of Gd-enhancing lesions 3 months after the clinical episode (and after a baseline MRI assessment) or new T2- or Gd-enhancing lesions 6 months after the clinical episode (and after a baseline MRI assessment) is highly predictive of the subsequent development of definite MS in the near term (Frohman et al., 2003) **(Type A recommendation)**. Follow-up scans need to be performed with the same machinery and scanning parameters and identical slice positions are required for exact comparison.
  7. Repeat scanning beyond the two initial studies need to be considered by individual neurologists considering the clinical circumstances that are appropriate for each patient (is not routinely recommended as the disease becomes more likely to manifest clinically in the longer term (Dalton et al., 2002; Miller et al., 2004) **(good practice point)**).
  8. Even though non-conventional MRI techniques may provide essential and critical information in patients with CIS and their application for monitoring treatment might provide a more accurate assessment of efficacy on inflammation, axonal protection and demyelination/remyelination, their use in clinical practice is, currently, not recommended. All these techniques are yet to be adequately compared with cMRI for sensitivity and specificity in detecting tissue damage in MS and for predicting the development of MS and disability. At present, these quantitative techniques show differences at a group level, but do not allow inferences at an individual level.
  9. In patients with insidious neurological progression suggestive of MS, according to published criteria (Thompson et al., 2000) an abnormal cerebrospinal (CSF) finding with evidence of inflammation and immune abnormality is another important finding to corroborate the diagnostic suspicion.

### **MRI in Patients with Established MS**

In patients with established MS, the following recommendations should be considered:

1. cMRI scans (dual-echo and post-contrast T1-weighted images) should be obtained using standardized protocols and accurate procedures for patients' repositioning in order to facilitate the interpretation of follow-up studies. Post-contrast T1-weighted scans should be acquired after an interval of 5 to 7 min from the injection of contrast material (Fazekas et al., 1999). Considering the weak correlation with clinical finding and the low predictive value of cMRI metrics for the subsequent worsening of clinical disability, the use of surveillance MRI for the purpose of making treatment decisions cannot be generally recommended (Fazekas et al., 1999). Serial MRI scans should be considered when diagnostic issues arise.
2. Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g. mechanical compression) or atypical symptoms develop.

3. Although preliminary work based on clinical trial data has suggested that presence (Giugni et al., 2003) and amount (Rudick et al., 2004) of MRI-detected disease activity may identify interferon (IFN)-beta response status in terms of relapse rate and accumulated disability (Rudick et al., 2004) in MS patients at a group level, there are no validated methods for monitoring disease-modifying therapy in individual patients.
4. Metrics derived from cMRI are not enough to provide a complete picture of the MS pathological process. Although cMRI has undoubtedly improved our ability to assess the efficacy of experimental MS therapies and, at least partially, our understanding of MS evolution, it provides only limited information on MS pathology in terms of accuracy and specificity and it has limited correlations with clinical metrics. This implies that the ability of a given treatment to modify metrics derived from cMRI does not mean that the treatment will necessarily be able to prevent the progressive accumulation of clinical disability, especially at an individual patient level.
5. Measurements of T1-hypointense lesions loads and brain and cord atrophy in clinical practice continue to be considered at a preliminary stage of development, as they need to be standardized in terms of acquisition and post-processing. Conversely, these metrics should be included as an end-point in disease-modifying agents trials (Miller et al., 2002) in order to further elucidate the mechanisms responsible for disability.
6. The application of non-conventional MRI techniques in monitoring patients with established MS in clinical practice is, at the moment, not advisable. All these techniques still need to be evaluated for sensitivity and specificity in detecting tissue damage in MS and its changes over time.
7. Magnetization transfer (MT) MT-MRI should be incorporated into new clinical trials to gain additional insights into disease pathophysiology and into the value of this technique in the assessment of MS. The performance and contribution of diffusion tensor MRI (DT-MRI) and MR spectroscopy (<sup>1</sup>H-MRS) in multicenter trials still have to be evaluated.

### **Definitions:**

#### **Evidence Classification Scheme for a Diagnostic Measure**

**Class I:** A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

**Class II:** A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

**Class III:** Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

**Class IV:** Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

## Rating of Recommendations

**Level A rating** (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

**Level B rating** (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

**Level C rating** (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

**Good practice point** Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good practice points.

## CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate use of neuroimaging in the management of multiple sclerosis (MS)

### POTENTIAL HARMS

Not stated

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

### IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Filippi M, Rocca MA, Arnold DL, Bakshi R, Barkhof F, De Stefano N, Fazekas F, Frohman E, Wolinsky JS. EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis. Eur J Neurol 2006 Apr;13(4):313-25. [156 references] [PubMed](#)

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2006 Apr

### GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

## **SOURCE(S) OF FUNDING**

European Federation of Neurological Societies

## **GUIDELINE COMMITTEE**

European Federation of Neurological Societies Task Force on the Use of Neuroimaging in the Management of Multiple Sclerosis

## **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

These guidelines are provided as an educational service of the EFNS task force. It is based on current scientific and clinical information.

## **GUIDELINE STATUS**

This is the current release of the guideline.

The validity of published guidelines will be reviewed by the chairpersons of the Task Force and the relevant Scientist Panel at least every 2 years.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available to registered users from the [European Federation of Neurological Societies Web site](#).

Print copies: Available from M. Filippi, Neuroimaging Research Unit, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy; Phone: 39-02-26433032; Fax: 39-02-26433054; E-mail: [filippi.massimo@hsr.it](mailto:filippi.massimo@hsr.it).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the [European Federation of Neurological Societies Web site](#).
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the [European Federation of Neurological Societies Web site](#).
- Continuing Medical Education questions available from the [European Journal of Neurology Web site](#).

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI on March 20, 2007. The information was verified by the guideline developer on May 3, 2007. This summary was updated by ECRI Institute on June 20, 2007 following the U.S. Food and Drug Administration (FDA) advisory on gadolinium-based contrast agents.

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