NEW DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS

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2018 Regional MS Summit
30 June 2018
Disclosures

Jeffrey A. Cohen, MD reports for the last year:

- **Personal compensation:**
  - Consultant for Adamas, Convelo, EMD Serono, Novartis, PendoPharm
  - Speaking for Mylan
  - Co-Editor of *Mult Scler J - ETC*

- **Research support paid to his institution:**
  - Celgene, Consortium of MS Centers, Department of Defense, Genentech, Genzyme, Mallinckrodt, NIH, National MS Society, Novartis, Synthon, Teva
Summary of Diagnostic Logic

- Multifocal CNS process – “Dissemination in Space”
  - History, Exam, MRI, OCT, EP

- Evolution over time – “Dissemination in Time”
  - Onset in young adult with a relapsing then progressive course - History
  - New lesions by exam, MRI, OCT, EP

- Inflammatory / immune-mediated process
  - CSF, MRI

- No other better explanation
  - History, exam, MRI, CSF, blood studies, other studies
MS Diagnostic Criteria

- Allison and Millar 1954
- McAlpine 1957, 1965
- Schumacher 1965
- McDonald and Halliday 1977
- Poser 1983
Purposes of MS Diagnostic Criteria

The diagnostic criteria provide formal definitions and successive refinement of:

- Diagnostic categories
- Definitions of relapse and progression
- Criteria for dissemination in space and time
- How imaging and other ancillary tests can be utilized

The 2017 McDonald Criteria are intended for use in both research studies and clinical practice
2016-7 International Panel on Diagnosis of Multiple Sclerosis

• Meetings in Philadelphia 3-5 November 2016 and Berlin 20-21 May 2017

• Organized under the auspices of the International Advisory Committee on Clinical Trials in MS

• Funded by US National MS Society and ECTRIMS
<table>
<thead>
<tr>
<th>Jeffrey Cohen – Co-Chair</th>
<th>Hans-Peter Hartung</th>
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<td>Alan Thompson – Co-Chair</td>
<td>Ludwig Kappos</td>
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<td>Stephen Reingold</td>
<td>Fred Lublin</td>
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<td>Ruth Ann Marrie</td>
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<td>Brenda Banwell</td>
<td>Aaron Miller</td>
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<td>Frederik Barkhof</td>
<td>David Miller</td>
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<td>William Carroll</td>
<td>Xavier Montalban</td>
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<td>Timothy Coetzee</td>
<td>Ellen Mowry</td>
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<td>Giancarlo Comi</td>
<td>Per Soelberg Sorensen</td>
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<td>Jorge Correale</td>
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<td>Franz Fazekas</td>
<td>Anthony Trabousee</td>
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<td>Massimo Filippi</td>
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<td>Mark Freedman</td>
<td>Bernard Uitdehaag</td>
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<td>Kazuo Fujihara</td>
<td>Sandra Vukusic</td>
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<td>Steven Galetta</td>
<td>Emmanuelle Waubant</td>
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<td>Brian Weinshenker</td>
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New Data Motivated Convening the International Panel

• MRI, CSF, and other paraclinical tests
• Performance of the 2010 McDonald Criteria in diverse populations
• Relationship of MS and other diseases with overlapping clinical or imaging features (e.g. NMOSD)
• Challenges making the diagnosis in individuals with non-classical presentations (e.g. RIS)
• Frequency and consequences of misdiagnosis
General Principles in the 2017 Revisions of the McDonald Criteria

• Major changes were not anticipated
• Simplify or clarify components of the 2010 Criteria
• Facilitate earlier diagnosis when MS is likely but not diagnosable with the 2010 Criteria
• Preserve the specificity of the 2010 Criteria and promote appropriate application to reduce misdiagnosis
• Ensure any proposed changes do not weaken the Criteria and are supported by reasonable evidence

Report of the International Panel

• Review of the issue of misdiagnosis, appropriate utilization of the McDonald Criteria, and applicability across diverse populations

• General recommendations concerning the diagnostic process

• 2017 revisions of the McDonald Criteria

• Recommendations for future studies

Misdiagnosis and Differential Diagnosis

• The potential differential diagnosis of MS is broad
• Misdiagnosis of MS remains an issue in clinical practice \(^1\)-\(^4\)
• In a recent multicenter case series, aside from NMOSD, most often were common conditions with nonspecific symptoms, signs, MRI findings \(^4\)
• Misdiagnosis can have harmful consequences \(^4\)

Applicability of the 2010 McDonald Criteria in Diverse Populations

• The McDonald Criteria were developed and validated with data from academic MS centers, with data from adults age <50 years and of Western European genetic/ethnic origins with a typical CIS

• Overall, the available data support the applicability of the McDonald Criteria in geographically diverse populations, children, older individuals

• Care needs to be taken to address alternative diagnoses, particularly NMOSD, infections, nutritional deficiencies, comorbidities

Neuromyelitis Optica Spectrum Disorders

• Substantial new data have been published since 2010

• 2010 McDonald Criteria and 2015 International Panel for NMO Diagnosis criteria largely distinguish MS and NMOSD though uncertain cases occur

• The possibility of NMOSD should be considered in all patients being evaluated for MS

• Serologic testing for AQP-4 and, when available, MOG
  – Should be performed in all patients with features suggesting NMOSD
  – Considered in groups at higher relative risk for NMOSD

Considerations to Help Avoid Misdiagnosis of MS

• Recognize that the McDonald criteria were developed and validated to identify MS or high likelihood of MS in patients with a typical CIS, not to differentiate MS from other conditions.

• Integration of the history, examination, imaging, and laboratory evidence by a clinician with MS-related expertise remains fundamental in making a reliable diagnosis of MS or an alternative diagnosis.
Considerations to Help Avoid Misdiagnosis of MS

• Besides merely confirming DIS/DIT, diagnostic rigor in the interpretation of clinical data and test results is necessary.

• In the absence of a clear-cut typical CIS:
  – Accept historical events lacking objective corroboration with caution.
  – The diagnosis should be confirmed by additional clinical and radiological follow-up.
  – Consider postponing the diagnosis or institution of therapy to accumulate additional evidence.

Definition of Clinically Isolated Syndrome

• A monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS

• Developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection

• Similar to a typical MS relapse (attack, exacerbation) but in a patient not known to have MS.

• Thus, if the patient subsequently is diagnosed with MS (by fulfilling DIS and DIT and ruling out other diagnoses), the CIS was that patient’s first attack.

Examples of Typical CIS

- Unilateral optic neuritis
- Focal supratentorial syndrome
- Focal brainstem/cerebellar syndrome
- Acute partial myelitis
Examples of Atypical Presentations

• Symptoms that are uncommon in MS
  – Bilateral optic neuritis, complete ophthalmoplegia, complete myelopathy, encephalopathy, alteration of consciousness, meningismus

• Symptoms that are common in MS but nonspecific
  – Fatigue, dizziness, bladder, headache
Considerations to Help Avoid Misdiagnosis of MS

• There should be a low threshold for spinal cord MRI and/or CSF examination:
  – Insufficient clinical and brain MRI evidence supporting MS
  – Non-classical presentation (including progression from onset)
  – With atypical features
  – In populations in which MS is less common

Role of MRI in MS Diagnosis

• Standardized MAGNIMS and CMSC protocols
• Can substitute for clinical findings to determine DIS and DIT
• To look for atypical features
• Brain MRI should be obtained in all patients being considered for an MS diagnosis
• Spine MRI is not mandatory in all cases but is advisable:
  – Presentation suggesting a spinal cord localization
  – When considering MS in a population in which MS is less common
  – When additional data are needed to increase diagnostic confidence
Role of CSF in MS Diagnosis

- OCBs are more useful than IgG Index to demonstrate IT Ab production and sensitivity depends on technical factors.
- CSF examination is not obligatory in all patients under evaluation for MS but there should be a low threshold to increase diagnostic confidence.
- Advised in cases with insufficient evidence to make the diagnosis, atypical features, populations in which MS is less common.
  - The diagnosis of MS should be made with caution with negative OCBs or with findings atypical of MS.

2017 Revisions to the McDonald Criteria

1. In a patient with a typical CIS and fulfillment of clinical or MRI criteria for DIS and no better explanation for the clinical presentation, demonstration of CSF-specific OCBs allows an MS diagnosis to be made.

   — *Addition to the 2010 McDonald Criteria*

2017 Revisions to the McDonald Criteria

2. Symptomatic and asymptomatic MRI lesions can be considered in the determination of DIS or DIT.
   - In the 2010 McDonald Criteria, the symptomatic lesion in a patient presenting with a brainstem or spinal cord CIS could not be included as MRI evidence of DIS or DIT
2017 Revisions to the McDonald Criteria

3. Cortical and juxtacortical lesions can be used in fulfilling MRI criteria for DIS

   - In the 2010 McDonald Criteria, cortical lesions could not be used in fulfilling MRI criteria for DIS

2017 Revisions to the McDonald Criteria

4. The diagnostic criteria for primary-progressive MS are the same in the 2017 McDonald Criteria as in the 2010 McDonald Criteria

   – Aside from the removal of the distinction between symptomatic and asymptomatic lesions and that cortical lesions can be used
5. At the time of diagnosis, a provisional disease course\textsuperscript{a} should be specified and periodically re-evaluated based on accumulated information

— Addition to the 2010 McDonald Criteria

\textsuperscript{a} Lublin FD, et al. Neurology. 2014;83:278-286
Revision of MS Phenotypes

• Consensus meeting held October 2012 under the auspices of International Advisory Committee on Clinical Trials in MS (sponsored by US National MS Society and ECTRIMS)

• Readdressed the 1996 Lublin-Reingold classification

• Maintained distinction between relapsing from onset vs progressive from onset
  – Dropped Progressive Relapsing

• Additional categorization based on presence/absence of:
  – Recent inflammatory activity determined by clinical relapses and/or MRI lesion activity to both relapsing and progressive disease
  – Progression (for progressive disease)

Lublin FD et al. Neurology 2014;83:278-286
MS Phenotypes

- Relapsing Remitting
- Secondary Progressive
- Primary Progressive
- Progressive Relapsing

Revision of MS Phenotypes

Lublin FD et al. Neurology 2014;83:278-286
Revision of MS Phenotypes

1996
MS clinical description
Subtypes

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

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

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

2013
MS disease modifiers
Phenotypes

- Progressive accumulation of disability from onset
  Active* and with progression**
  (PP)

- Progressive accumulation of disability after initial relapsing course
  Active but without progression
  Not active but with progression
  Not active and without progression (stable disease)
  (SP)

Lublin FD et al. Neurology 2014;83:278-286
Motivation for Revised Phenotypes

• The intent is to periodically re-assess disease phenotype e.g. annually

• Activity
  – RRMS: Need to initiate or change anti-inflammatory disease therapy
  – Progressive MS: Likelihood that anti-inflammatory therapy will be helpful (both in practice and in clinical trials)

• Progression
  – As additional effective therapies for progressive disease emerge, to determine the need for disease therapy and response to therapy

Lublin FD et al. Neurology 2014;83:278-286
OLYMPUS Trial of Rituximab in PPMS

3-month confirmed EDSS worsening

Hawker K et al. Ann Neurol 2009;66:460-71
**ORATORIO Trial of Ocrelizumab in PPMS**

Table 3: Time to onset of disability progression confirmed after ≥12 and ≥24 weeks in patients with/without T1 Gd+ lesions at baseline

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Placebo (n=244)</th>
<th>Ocrelizumab (n=488)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>Events</td>
<td>n</td>
<td>Events</td>
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<tr>
<td>CDP ≥ 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Overall population</td>
<td>731</td>
<td>244</td>
<td>96</td>
<td>487</td>
<td>160</td>
</tr>
<tr>
<td>T1 Gd+ lesions</td>
<td>193</td>
<td>60</td>
<td>27</td>
<td>133</td>
<td>43</td>
</tr>
<tr>
<td>No T1 Gd+ lesions</td>
<td>533</td>
<td>183</td>
<td>68</td>
<td>350</td>
<td>115</td>
</tr>
<tr>
<td>CDP ≥ 24 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall population</td>
<td>731</td>
<td>244</td>
<td>87</td>
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<tr>
<td>T1 Gd+ lesions</td>
<td>193</td>
<td>60</td>
<td>23</td>
<td>133</td>
<td>39</td>
</tr>
<tr>
<td>No T1 Gd+ lesions</td>
<td>533</td>
<td>183</td>
<td>63</td>
<td>350</td>
<td>103</td>
</tr>
</tbody>
</table>

Analysis based on ITT population; p-values are based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression. CDP, confirmed disability progression; Gd+, gadolinium-enhancing; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent to treat.
## Baseline Characteristics in PPMS Trials

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PROMiSe (N=943)</th>
<th>OLYMPUS (N=439)</th>
<th>INFORMS (N=823)</th>
<th>ORATORIO (N=732)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, N (%)</td>
<td>460 (48.8)</td>
<td>218 (49.7)</td>
<td>425 (51.6)</td>
<td>120 (49.1)</td>
</tr>
<tr>
<td>Age, years</td>
<td>50.4 (8.3)</td>
<td>49.9 (8.9)</td>
<td>48.5 (8.4)</td>
<td>44.4 (8.3)</td>
</tr>
<tr>
<td>Caucasian, N (%)</td>
<td>747 (89.8)</td>
<td>402 (91.6)</td>
<td>791 (96.1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>PROMiSe (N=943)</th>
<th>OLYMPUS (N=439)</th>
<th>INFORMS (N=823)</th>
<th>ORATORIO (N=732)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years from symptom onset</td>
<td>10.9 (7.5)</td>
<td>9.1 (6.6)</td>
<td>5.8 (2.4)</td>
<td>6.1 (3.6)</td>
</tr>
<tr>
<td>Years from diagnosis</td>
<td>5.0 (5.1)</td>
<td>4.0 (4.2)</td>
<td>NA</td>
<td>2.8 (3.3)</td>
</tr>
<tr>
<td>EDSS score</td>
<td>4.9 (1.2)</td>
<td>4.8 (1.4)</td>
<td>4.7 (1.0)</td>
<td>4.7 (1.2)</td>
</tr>
<tr>
<td>Prior use of DMT, N (%)</td>
<td>NA</td>
<td>154 (35.1)</td>
<td>179 (22)</td>
<td>30 (12.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI characteristics</th>
<th>PROMiSe (N=943)</th>
<th>OLYMPUS (N=439)</th>
<th>INFORMS (N=823)</th>
<th>ORATORIO (N=732)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Gd+ lesions</td>
<td>14.1</td>
<td>24.5</td>
<td>13.4</td>
<td>24.7</td>
</tr>
<tr>
<td>Number of Gd+ lesions</td>
<td>0.45 (2.7)</td>
<td>NA</td>
<td>0.3 (1.06)</td>
<td>0.6 (1.6)</td>
</tr>
<tr>
<td>Total T2 lesion volume, cm³</td>
<td>8.4</td>
<td>9.2 (13.1)</td>
<td>9.8 (11.9)</td>
<td>10.9 (13.0)</td>
</tr>
<tr>
<td>Normalized brain volume, cm³</td>
<td>0.86a</td>
<td>1206 (123)</td>
<td>1491 (86)</td>
<td>1470 (89)</td>
</tr>
</tbody>
</table>

NA: not available; EDSS: Expanded Disability Status Scale; DMT: disease-modifying therapy; MRI: magnetic resonance imaging.

*aReported as brain parenchyma as a fraction of intracranial contents.
### 2017 McDonald Criteria: Attack Onset

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Number of Lesions with Objective Clinical Evidence</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 clinical attacks</td>
<td>&gt;2</td>
<td>None</td>
</tr>
<tr>
<td>&gt;2 clinical attacks</td>
<td>1</td>
<td>DIS demonstrated by an additional clinical attack implicating a different CNS site OR by MRI</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>&gt;2</td>
<td>DIT demonstrated by an additional clinical attack OR by MRI OR CSF-specific oligoclonal bands</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>1</td>
<td>DIS demonstrated by an additional clinical attack implicating a different CNS site OR by MRI OR DIT demonstrated by an additional clinical attack OR by MRI OR CSF-specific oligoclonal bands</td>
</tr>
</tbody>
</table>

2017 McDonald Criteria for Demonstration of DIS by MRI

**DIS:** \( \geq 1 \) T2 lesions in \( \geq 2 \) locations

**Changes from the 2010 McDonald Criteria:**
- No distinction between symptomatic and asymptomatic lesions
- Both cortical and juxtacortical lesions can be utilized

2017 McDonald Criteria for Demonstration of DIT by MRI

DIT can be demonstrated by:

• Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time

OR

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

Change from the 2010 McDonald Criteria: No distinction between symptomatic and asymptomatic lesions

2017 McDonald Criteria: DIT

A new clinical relapse
2017 McDonald Criteria: DIT

A new T2 lesion on followup MRI compared to baseline scan, irrespective of the timing of the baseline scan.

Clinical threshold
2017 McDonald Criteria: DIT

Simultaneous presence of GdE and non-GdE lesions at any time
2017 McDonald Criteria: DIT

Simultaneous presence of GdE and non-GdE lesions at any time, including at the time of CIS
2017 McDonald Criteria

CIS
+ Clinical or MRI demonstration of DIS
+ CSF-specific OCBs *

* Similar to Poser laboratory-supported definite MS
2017 McDonald Criteria: Progression From Onset

**Primary Progressive MS** can be diagnosed with:

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

**Plus 2 of 3** of the following:

- \( \geq 1 \) T2-hyperintense lesions in \( \geq 1 \) areas in the brain characteristic of MS (periventricular, cortical/juxtacortical, or infratentorial)

- \( \geq 2 \) T2-hyperintense lesions in the spinal cord

- Demonstration of CSF-specific OCBs

Key Proposals That Were Discussed but Felt to Require Further Evidence

- Number of periventricular lesions (i.e. more than 1?)
- How to incorporate involvement of the anterior visual system in the diagnostic criteria
- How to handle nonclassical presentations
  - Radiologically isolated syndrome
  - Solitary sclerosis
  - Possible MS

Other High Priority Areas of Research

Validation of the 2017 McDonald Criteria is needed in diverse populations:

• Asia, Latin America, Middle East, Africa
• Pediatric and late-onset
• With comorbidities
• Non-specialty and general practice

Other High Priority Areas of Research

MRI

• Validation of the 2016 MAGNIMS Criteria in aggregate
• Methods to evaluate chronicity of lesions
• Methods to detect gray matter pathology
• Techniques to distinguish MS lesions from other pathologies
• Role of higher field strength (7T) MRI

Other High Priority Areas of Research

- Diagnostic utility of anti-MOG antibodies
- Diagnostic non-imaging biomarkers for MS
- Utility on evoked potentials other than VEP

Conclusions

- The 2017 revisions further refine the well established McDonald Criteria with an appropriate tradeoff between sensitivity and specificity
- Appropriate application of the McDonald Criteria criteria is necessary to avoid misdiagnosis
- MS remains a clinical diagnosis, requiring rigorous synthesis of clinical, imaging, and laboratory data by a clinician with MS-related expertise