In this thesis we evaluated different properties of diagnostic guidelines for MS. Our results first suggest that the 2005 McDonald criteria, along with the proposed criteria by Swanton et al. for MS, are indeed specific in discriminating MS from other diagnostically difficult cases, in contrast to criteria as proposed by the American Academy of Neurology (AAN). Secondly, our results suggest that when using the present MS guidelines in the clinical practice of a specialized MS center, only few patients initially not diagnosed with MS, after long term follow up, will turn out to have MS or develop another neurological disease. Thirdly, our results suggest that in multifocal patients, who fulfill criteria for dissemination in space (DIS) on clinical grounds, more MRI parameters are present which are known to represent the pathophysiological burden of the disease, than in monofocal patients. Finally, we demonstrated that in monofocal patients, the presence of $\geq 9$ T2 lesions or enhancement of lesions on MRI, is predictive for the development of CDMS, whereas this is not the case for multifocal patients. In this section the main outcomes will be discussed as well as future perspectives.

**Differentiating MS from other neurological diseases**

We confirmed the specificity of the MRI criteria for DIS (McDonald et al. 121-27; Polman et al. 840-46; Swanton et al.) as incorporated in the diagnostic criteria for MS. As differentiating MS from other diseases is a key issue in clinical practice, it is of great importance to study the performance of the MRI criteria and MS guidelines in patients suspected of MS, yet who are ultimately not diagnosed with MS. Clearly the criteria should not be met in these patients. We investigated (2.1) the ability of the DIS MRI criteria to differentiate MS from other diagnoses in this population and found high specificity for the 2001 McDonald and
2005 Revised McDonald criteria, as well as for criteria as proposed by Swanton et al. Several other papers have reported on specificity of the different diagnostic MRI criteria and found high specificity (Dalton et al. 47-53; Korteweg et al. 221-27; Swanton et al.; Swanton et al. 677-86). Even though, in these papers specificity was calculated in patient groups in whom other diagnoses had been excluded before. Reported specificity in these papers can therefore be perceived as a parameter for disease progression, rather than as an instrument to differentiate between MS and other neurological diseases. Whereas an MS diagnosis requires DIS as well as DIT, we only studied dissemination in space (DIS) criteria. Both have been proven specific for a definite MS diagnosis, but especially the latter component (Swanton et al.) (Dalton et al. 673-76; Swanton et al. 677-86). Therefore, the specificity in our study of the different criteria is likely to be systematically underrated, although is unclear to what extent as there are no other studies investigating DIS and/or DIT in patients suspected of MS, but ultimately diagnosed with another disease. However, it is unlikely that this underestimation would be much larger for the AAN than for the McDonald or Swanton criteria, therefore the difference in specificity will most likely remain (in some measure).

Striving for utmost specificity of (MRI) criteria is one way of avoiding an incorrect MS diagnosis. Consecutive versions of published diagnostic guidelines for MS (McDonald et al. 121-27; Polman et al. 840-46; Polman et al. 292-302; Poser et al. 227-31; Schumacher GA et al. 552-68) demand that: ‘there must be no better explanation for the clinical presentation’. Another similar way to avoid an incorrect MS diagnosis, is to find ‘a better explanation for the clinical picture’ by defining alternative diagnoses of MS, and specific features that positively indicate another diagnosis. We’ve described the alternative diagnoses we found in the retrospective consecutive patient group (chapter 2.1 and 2.4) and in the case report (chapter 2.3). We found that the major differentially diagnostic group comprises of cerebrovascular disease and we found several rarer diagnoses. In the past years two papers (Charil et al. 841-52; Miller et al. 1157-74) have reported on features (‘red flags’) positively indicating other diagnoses. These papers report a consensus view of MS (MRI) specialists, as a first step, on differential diagnoses and an extensive list
of MRI and clinical characteristics that are atypical for MS ('red flags') and characteristic of other diagnoses. A more recent paper by Albertyn et al. (Albertyn et al. 678-84) found that in a general neurology practice those patients who did not meet the diagnostic MS criteria after more than a median of 4 years of follow up, clearly had such red flags, but the presence of these red flags did not lead to other diagnoses. Therefore further defining differentiating characteristics of these alternative diagnoses should be a future goal. Diagnostic practical algorithms further focusing on and prioritizing these most prevalent and important differentially diagnostic diseases, such as cerebrovascular disease, and highlighting the differences of clinical and paraclinical investigations between such other diagnoses and MS, may be helpful. Such an algorithm should be prospectively tested in the appropriate populations. Even though it is unlikely that this process - which is different for each patient - will ever be fully covered by such an algorithm and replace clinical experience.

Although with different versions of the McDonald criteria (McDonald et al. 121-27) (Polman et al. 840-46) accuracy has improved and an MS diagnosis can be made earlier, the criteria have been shown complex in clinical use (Hawkes and Giovannoni; Korteweg et al. 67-71; McHugh, Galvin, and Murphy 81-85). This is probably due to the complexity of the MRI guidelines (Korteweg et al. 67-71), the complexity of the clinical scheme to be followed, and ambiguous clinical definitions (Hawkes and Giovannoni). In patients suspected of MS in a general neurology practice,

**Table 1** criteria for DIS as incorporated in the McDonald criteria 2010 based on Swanton et al. 677-86

<table>
<thead>
<tr>
<th>DIS Can Be Demonstrated by ⇒1 T2 Lesion(^a) in at Least 2 of 4 Areas of the CNS:</th>
</tr>
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<tbody>
<tr>
<td>Periventricular</td>
</tr>
<tr>
<td>Juxtaglomerular</td>
</tr>
<tr>
<td>Infratentorial</td>
</tr>
<tr>
<td>Spinal cord(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Gadolinium enhancement of lesions is not required for DIS
\(^b\) If a subject has a brainstem or spinal cord syndrome these lesions are excluded from the Criteria and do not contribute to the lesion count
<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
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<tbody>
<tr>
<td>≥ 2 attacks(^{a}); objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack(^{b})</td>
<td>None(^{c})</td>
</tr>
</tbody>
</table>
| ≥ 2 attacks\(^{a}\); objective clinical evidence of 1 lesion                        | Dissemination in space, demonstrated by: 
> 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)\(^{d}\); or Await a further clinical attack\(^{e}\) implicating a different CNS site |
| 1 attack\(^{a}\); objective clinical evidence of ≥ 2 lesions                        | Dissemination in time, demonstrated by: 
Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack\(^{e}\) |
| 1 attack\(^{a}\); objective clinical evidence of 1 lesion (clinically isolated syndrome) | Dissemination in space and time, demonstrated by: 
For DIS: 
≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)\(^{d}\); or 
Await a second clinical attack\(^{e}\) implicating a different CNS site; and 
For DIT: 
Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or 
A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or 
Await a second clinical attack\(^{e}\) |
| Insidious neurological progression suggestive of MS (PPMS)                           | 1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria\(^{e}\): |
1. Evidence for DIS in the brain based on ≥ 1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions
2. Evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord
3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is “MS”; if suspicious, but the Criteria are not completely met, the diagnosis is “possible MS”; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is “not MS.”

* An attack (relapse, exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

* Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

* No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

* Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DI = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.
an MS diagnosis was frequently made even though DIT was not present and an MRI was frequently not repeated (McHugh, Galvin, and Murphy 81-85). To improve accuracy and to simplify the diagnostic process, diagnostic criteria were proposed by Swanton et al. It was proposed to diminish the number of lesions, while retaining their specific locations as evidence for DIS (table 1). In these criteria at least 1 T2 lesion is required in at least 2 out of 4 for MS typical locations (periventricular, juxtacortical, infratentorial and spinal cord). In chapter 2.3 we compared the specificity of the (revised) McDonald MRI criteria to these Swanton criteria (Swanton et al.) and found comparable specificity. In a large multicenter study of CIS patients (Swanton et al. 677-86) these criteria were found to be simpler than the former criteria without compromising specificity while slightly increasing sensitivity. The criteria as proposed by Swanton et al. were then incorporated in the revised 2010 McDonald criteria (Polman et al. 292-302) (Table 2).

Several other revisions have been made in this latest version of the diagnostic criteria: In the 2005 McDonald criteria DIT was defined as a new T2 lesion appearing on MRI at least 30 days after a reference scan. Tur et al. (Tur et al. 631-35) found unchanged specificity when defining DIT as a new T2 lesion appearing at any time, as compared to appearing within 30 days after the reference. Additionally, it was demonstrated (Rovira et al. 587-92) that a single brain MRI could be sufficient to prove DIT: the presence of both enhancing and non-enhancing lesions at the same time was shown to be highly specific for CDMS. Furthermore the MRI criteria for primary progressive MS (PP-MS) have been adapted: DIS can now be accomplished by the presence of ≥1 T2 lesion in a for MS characteristic region (periventricular, infratentorial or juxtacortical), therefore the criteria have become more similar to those for relapsing MS. This modification results from a study that found a high fulfillment in PP MS patients of the DIS criteria as used for RR MS patients, thereby suggesting that similar criteria for these two groups of patients are feasible (Montalban et al. 1459-65).

Further modifications concern different subgroups: Neuromyelitis optica (NMO) is now recognized as a separate entity because of its different clinical course, prognosis, pathophysiology and response to
therapy compared to MS. There is consensus in the 2010 revisions that the criteria probably also serve well for pediatric patients that present as CIS, but this should still be confirmed in a prospective fashion. Recently, the McDonald 2001 MRI criteria were compared to modified criteria that require fewer total, fewer periventricular lesions and that omit juxtacortical lesions in pediatric patients. These modified criteria were found to be somewhat more sensitive than the 2001 McDonald criteria while also being highly specific (Callen et al. 961-67).

Clinical definition of dissemination in space, relation to MRI and prognostic evidence

In spite of an increasing role for MRI in diagnosing MS, clinical data remain essential. In contrast to the interpretation of MRI, no clinical classification existed up until now. Therefore a classification system to define dissemination in space in more detail was proposed to provide further guidance on this subject. In chapter 3.1 we justified this classification system by showing that multifocal patients have significantly more T2 hyperintense and T1 hypointense (‘black holes’) lesions than monofocal patients. Accordingly ‘clinically multifocal’ is associated with more lesions on MRI. In chapter 3.2 we investigated the prognostic value of the classification system. We found that the initial presence of at least nine T2 lesions or at least one Gadolinium-enhancing lesion, was predictive for time to CDMS in monofocal but not in multifocal patients. Therefore in CIS patients with monofocal, but not with multifocal clinical presentation, these MRI findings seem to have prognostic value. Possibly more pronounced subclinical disease dissemination in monofocal CIS patients reflects more active disease, whereas similar findings in multifocal patients may be more indicative of prolonged subclinical disease evolution. MRI might contribute less information in these latter patients. In addition, we hypothesized that signs not accompanied by symptoms from the same location (for example an extensor plantar reflex not accompanied by leg motor symptoms) might be due to a past episode of inflammation that has not fully recovered. In these patients one might assume a longer subclinical disease history. Aside from prognostic information, a different treatment response in mono and
multifocal patients might help in deciding which patients to treat. In the same trial, a treatment effect was found for interferon in both groups. This effect was more pronounced yet not significant in the monofocal group. This treatment effect was especially present in monofocal patients with ≥9 T2 lesions, compared to monofocal patients with less lesions in whom the treatment effect was lower and not significant (Polman et al. 480-87). However, all these findings are the result of post hoc analysis and still need confirmation. The clinical relevance, with regard to both prognosis and treatment effect of the clinical classification system, need to be investigated prospective with a longer follow up.

Future diagnostic criteria may benefit from new MRI techniques and different cerebral lesion features. Cortical lesions are not usually seen on conventional MR images, even though they contain a large amount of lesions. With double inversion recovery (DIR), an MRI technique where the signal from white matter as well as from cerebrospinal fluid is suppressed, cortical lesions can be more accurately depicted (Filippi and Rocca 659-81). These lesions were present in 30% of a group of typical CIS patients. It was shown in this same study that the presence of an intracortical lesion is an independent predictor of CDMS, increasing specificity in comparison to the present criteria (Filippi et al. 1988-94). Another future MRI characteristic that seems to be associated with conversion to MS and that might have additional value to the Swanton criteria, is a lesion in the corpus callosum. This was shown recently (Jafari et al. 1837-41) in a group of 158 CIS patients that was followed for 39 months. These findings should be further investigated in larger multicenter groups of CIS patients, but suggest that the incorporation of cortical and corpus callosum lesions in the diagnostic criteria could be useful. Another promising MRI technique is scanning with high-field strength. Present criteria have been investigated with 1.0 or 1.5 Tesla field strength, however scanning with as much as 7.0 Tesla is now possible, even though this is not commonly available. Higher field strength has been shown to improve infratentorial lesion detection (Wattjes et al. 1159-63). Although 3 Tesla scanning resulted in little improvement in meeting criteria for dissemination in space in CIS patients in one
study (Wattjes et al. 54-59), higher field strength scanning should be prospectively evaluated in modified criteria in cohorts of CIS patients.

Alternatively, the development of specific biomarkers should have additional value in future diagnostic criteria. Such biomarkers should clearly have (additional) diagnostic value, yet should ideally also have clinicopathological correlations. An exemplary biomarker is NMO- IgG, an antibody that selectively targets the aquaporine-4 water channel. This antibody is not only able to distinguish neuromyelitis optica (NMO) from MS (Lennon et al. 473-77), but is also implicated in the pathophysiology of NMO (Jarius et al. 3072-80; Roemer et al. 1194-205; Takahashi et al. 1235-43).

Issues remain for patients who present in a less typical manner (Rudick 234-36). Some patients are being investigated for other reasons than suspected MS, when MRI shows lesions that are highly suspicious of the disease. One cannot diagnose MS in these patients due to the absence of MS like symptoms. However, a substantial number of these develop disease defining symptoms at follow up, and some seem to be at high risk for disease progression (Okuda et al. 800-05; Okuda et al. 686-92). Other patients presenting with a CIS have had previous symptoms regarded as atypical. The predictive value for MS diagnosis and disease progression in these subjects should be studied further and incorporated in future diagnostic criteria.