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## Use of Magnetic Resonance Imaging as Well as Clinical Disease Activity in the Clinical Classification of Multiple Sclerosis and Assessment of Its Course

A Report from an International CMSC Consensus Conference, March 5–7, 2010

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*It has recently been suggested that the Lublin-Reingold clinical classification of multiple sclerosis (MS) be modified to include the use of magnetic resonance imaging (MRI). An international consensus conference sponsored by the Consortium of Multiple Sclerosis Centers (CMSC) was held from March 5 to 7, 2010, to review the available evidence on the need for such modification of the Lublin-Reingold criteria and whether the addition of MRI or other biomarkers might lead to a better understanding of MS pathophysiology and disease course over time. The conference participants concluded that evidence of new MRI gadolinium-enhancing (Gd+) T1-weighted lesions and unequivocally new or enlarging T2-weighted lesions (subclinical activity, subclinical relapses) should be added to the clinical classification of MS in distinguishing relapsing inflammatory from progressive forms of the disease. The consensus was that these changes to the classification system would provide more rigorous definitions and categorization of MS course, leading to better insights as to the evolution and treatment of MS. *Int J MS Care.* 2012;14:105–114.*

It was recently suggested by Lincoln et al.<sup>1</sup> that the Lublin-Reingold clinical classification of multiple sclerosis (MS)<sup>2</sup> for the assessment of MS phenotypes and patient evolution over time be modified to include magnetic resonance imaging (MRI). It was

recommended that the classification incorporate the “conventional,” generally available MRI techniques of gadolinium (Gd) T1-weighted sequences and dual-echo and fluid-attenuated inversion recovery (T2-weighted and FLAIR) images (Table 1). It was recognized that

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**Table 1. Definitions of relapse by both clinical and MRI measures<sup>a</sup>**

MS groups	Revised classification	Lublin-Reingold classification <sup>2</sup>
<b>Relapsing forms</b>		
Clinical RR	Clinical relapse with near complete or complete recovery to baseline neurological examination findings	RR MS: "Clearly defined disease relapses [clinical relapse] with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression"
Clinical relapsing-nonremitting	Clinical relapse with minimal if any recovery to baseline neurological examination findings	
Subclinical relapse	As defined below	
<b>Progressive forms</b>		
Secondary progressive	Initial relapsing disease with subsequent progression as defined below; patients may then have continued progression, stability, or recurrent relapse	"Initial RR disease course followed by progression with or without occasional relapses [clinical relapse], minor remissions, and plateaus"
Progressive relapsing	Progression, as defined below, from onset of disease with superimposed clinical or subclinical relapses	"Progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing progression"
Primary progressive	Progression, as defined below, from onset of disease in the absence of either clinical or subclinical relapses	"Disease progression from onset with occasional plateaus and temporary minor improvements allowed"

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Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis; RR, relapsing-remitting.

<sup>a</sup>Magnetic resonance imaging evaluation along with a neurological examination should be performed at regular intervals. "Relapses" include (1) *Clinical relapse*: New or worsening neurological symptoms of central nervous system dysfunction plus 2-grade increase in 1 or more Kurtzke functional scale scores or 1-grade increase in 2 or more functional scale scores in the absence of fever, lasting greater than 24 hours, and preceded by at least 30 days of clinical stability. (2) *Subclinical (MRI) relapse*: Evidence of gadolinium enhancement on routine follow-up MRI of the brain and/or spinal cord in the absence of new symptoms indicates "current subclinical relapse," while evidence of unequivocally new or enlarging T2 lesions should indicate "remote subclinical relapse" occurring at some time since the last MRI. "Progression" is the objective evidence of increased deterioration in neurological examination findings on 2 visits at least 6 months apart in the absence of either clinical or subclinical relapse.

other MRI modalities that are not currently widely available and other validated biomarkers might be added to the classification in the future.

In response to the publication of Lincoln et al.,<sup>1</sup> the Consortium of Multiple Sclerosis Centers (CMSC) sponsored an international consensus conference, which was held in Short Hills, New Jersey, from March 5 to 7, 2010. Participating in the conference were 28 invited MS experts from North and South America and Europe who were well versed in clinical trials, the management of MS, biostatistics, neuropathology, neuroimaging, and neuroimmunology. The goal of the meeting was to review the available evidence on the need for modification of the Lublin-Reingold criteria and whether addition of MRI and other biomarkers as proposed by Lincoln et al.<sup>1</sup> would lead to a better understanding of MS pathophysiology and disease

course over time and, in turn, more informed clinical trials and a better understanding of appropriate therapies.

Prior to the meeting, a survey of members of the CMSC was conducted on the need to modify the Lublin-Reingold classification. Over a 1-week period, 141 responses were received, representing 16% of the CMSC members polled. The results were as follows: A total of 70% of respondents indicated that the Lublin-Reingold classification did not sufficiently distinguish the different forms of MS; 87% felt that the Lublin-Reingold classification did not sufficiently distinguish MS disease activity even within a given category of the disease; and 84% indicated that it would be useful to include certain subclinical indices of disease activity in the clinical classification, such as MRI gadolinium-

enhancing (Gd+) T1-weighted lesions or unequivocally new or enlarging T2-weighted lesions. Although this poll reflected the opinions of a relatively small proportion of the CMSC membership over a short period of time, the results supported the concept that changes to the Lublin-Reingold classification should be considered.

Presentations at the meeting included an overview of MRI in various categories of MS, from clinically isolated syndrome (CIS) to primary progressive MS (PPMS) (Li, Arnold); the pathology of MS and of MRI lesions from CIS to PPMS (Moore, Lucchinetti); a historical review of diagnostic and clinical classifications of MS as well as neuromyelitis optica (NMO), radiologically isolated syndrome (RIS), and CIS (Lublin, Kinkel); possible explanations for the so-called MRI-clinical paradox (Miller, Simon); recent evidence supporting a relationship between MRI and clinical endpoints (Sormani, Cutter); the concept of the disease-free state (Giovannoni, Naismith); the status of biomarkers for MS clinical activity (Dhib-Jalbut, Cadavid); and a proposal for modifying the Lublin-Reingold classification (Cook, Lisak). These presentations and reviews with updates are summarized below.

## Background

### Historical Evolution of MS Diagnostic Criteria

Criteria for establishing the diagnosis of MS have evolved considerably over almost 50 years. The Schumacher Committee recommendations issued in 1965 were purely clinical,<sup>3</sup> while the Poser Committee revision of 1983 incorporated laboratory as well as clinical criteria.<sup>4</sup> Most recently, the various iterations of the McDonald Committee criteria (2001, 2005, 2010) used MRI (Gd+ lesions, new T2 lesions) and other laboratory findings in addition to purely clinical criteria for disease diagnosis.<sup>5-7</sup> The occurrence of at least two relapses and dissemination of lesions in space are fundamental to the diagnosis of relapsing-remitting MS (RRMS); however, conventional MRI (Gd+ lesions, new T2 lesions) has become a surrogate for the second relapse and dissemination of disease in space and time. New MRI lesions have expedited the diagnostic evolution of CIS to definite RRMS,<sup>5-7</sup> resulting in earlier diagnosis and treatment of MS.<sup>8,9</sup> Whether MRI can be used as a marker for the first subclinical attack of MS in RIS, as for the second attack in diagnosing MS, is under consideration.<sup>10,11</sup>

### Historical Analysis and Critique of the Lublin-Reingold Criteria

The Lublin-Reingold MS classification has made important contributions to the definition of various MS phenotypes and classical stages on purely clinical grounds. The classification consists of four categories of MS: 1) relapsing-remitting MS (RRMS), characterized by clearly defined episodes of acute neurologic worsening with a variable degree of recovery and a stable course between attacks; 2) secondary progressive MS (SPMS), in which one or more relapses are followed by mainly progressive deterioration, possibly with some plateaus, new relapses, and even slight or transient improvement over time; 3) primary progressive MS (PPMS), consisting of continuous, often slow progression from the onset of symptoms, possibly with some plateauing without obvious relapses; and 4) progressive relapsing MS (PRMS), in which progression occurs from the onset of neurologic symptoms, with occasional relapses thereafter. Whether the latter is really a distinct category or represents a variant of relapsing or another progressive form of MS is unclear. Moreover, it may be the case that each of these categories is actually heterogeneous, with mild clinical or subclinical relapses not being adequately recognized.<sup>1,12-14</sup> Despite these limitations, the Lublin-Reingold classification has facilitated patient selection for enrollment in clinical trials and determination of which patients may be most likely to respond to approved drugs.

A potential shortcoming of the Lublin-Reingold classification is that it is often difficult to determine the transition from a relapsing to a progressive form of the disease on purely clinical grounds.<sup>15</sup> Using MRI metrics to assess subclinical disease activity, in addition to diagnosing disease, might identify patients with subclinical relapses rather than true progression. A purely clinical classification depends heavily on the patient history, which may not always be a sensitive or accurate measure, particularly over long periods of time. Progression of MS may also be difficult to assess by treating physicians because of inter- and intra-examiner variability, limitations in the accuracy and comprehensiveness of the Expanded Disability Status Scale (EDSS) as a measurement tool, the slow rate of deterioration in some 2-year clinical trials, and other possible factors such as medication side effects, lack of sleep, depression, and time of day.<sup>16-18</sup> Furthermore, even sustained EDSS progression in research studies may reverse after study completion.<sup>19</sup>

Moreover, it is likely that an inflammatory component of disease is present either always or at some time in all stages of MS.<sup>20-24</sup> Indeed, Gd+ lesions, which indicate both an abnormality in blood-brain barrier (BBB) and central nervous system (CNS) inflammation, can occur not only in RRMS but in all Lublin-Reingold forms of MS, including in 14.1% to 42% of patients with PPMS.<sup>12-14</sup> Pathologically inflammatory CNS lesions have also been described in all forms of MS, with or without the presence of Gd+ lesions, although the distribution of inflammatory lesions can vary in location or intensity in different forms of the disease.<sup>20-24</sup>

When sensitive and frequent MRI studies are performed, Gd+ and unequivocally new or enlarging T2 brain lesions (subclinical relapses) can occur much more commonly than clinical symptoms (relapses or progression).<sup>25-28</sup> This may be explained at least in part by several factors: lesions in “eloquent” brain areas such as the optic nerves are more likely to be clinically expressed than lesions in less eloquent pathways; the degree of matrix and axonal destruction may vary; and the potential exists for rapid symptom recovery.<sup>29-38</sup> Even patients with progressive forms of MS, particularly those with Gd+ lesions indicating a subclinical relapse, may respond clinically to disease-modifying therapies (DMTs). For example, in a post hoc analysis of the Olympus trial of rituximab in PPMS, patients with Gd+ lesions had a significantly better response to treatment than those without Gd+ lesions.<sup>13</sup>

In summary, magnetic resonance imaging is the “gold standard” for evaluating drugs in phase 2 trials and is often used by clinicians, along with assessment of the presence of clinical relapses and progression, in making therapeutic decisions. Indeed, “freedom from disease activity” assessed both clinically and using MRI is increasingly regarded as an optimal outcome by which to judge the effectiveness of therapy.<sup>39,40</sup>

### Relationship of MRI to CNS Pathology

A limited number of biopsy and necropsy studies have been carried out involving Gd+ T1-weighted lesions, T2-weighted lesions, and T1 hypointense lesions or “black holes” in an attempt to correlate CNS pathology with identified MRI abnormalities.<sup>41-48</sup> In considering the histologic characteristics of classic MS MRI lesions, it is important to recognize that when frequent, sensitive longitudinal (weekly or monthly)<sup>37,49</sup> MRI studies are performed in RRMS patients, almost

all new T2 lesions (95–100%) as well as acute, transient, and chronic black holes (those lasting for more than 12 months) occur coincidentally with or evolve from Gd+ T1-weighted lesions.<sup>37,49</sup> However, Gd+ lesions evolve into chronic black holes less commonly than they do into T2 lesions or transient black holes.<sup>37</sup> This indicates that unequivocally (not related to technique, positioning, quality of scan, or questionable reader interpretation) new T2 lesions or black holes in RRMS patients had a prior inflammatory phase with alteration of the BBB of a degree sufficient to be detected, even though this may not always be documentable with less frequent or sensitive MRI.<sup>37</sup>

It has been shown that T2 lesions have heterogeneous pathology, with varying degrees of abnormality ranging from edema and inflammation with phagocytosis of myelin, to demyelination, gliosis, and axonal loss, which can be mild to severe.<sup>41-48</sup> However, it is generally recognized that the underlying pathology responsible for enhancement is inflammation with accompanying BBB breakdown. In contrast to T2 lesions, it has been reported that T1 hypointensities or black holes, particularly chronic black holes, correlate better with physical disability, tissue injury including severe demyelination and axonal injury, and brain atrophy.<sup>42,45,50-52</sup> Recent evidence suggests that the size and duration of enhancing lesions, increased radial diffusion on diffusion tensor imaging (DTI), and lower magnetic transfer ratio (MTR) predispose to chronic black holes, matrix destruction, and brain atrophy.<sup>34,45,46,53-60</sup> Some controversy remains as to the degree of inflammation found in MS cortical lesions as compared with white matter lesions on histologic examination, but these differences are probably related to stage of MS (early vs. chronic disease).<sup>61-63</sup>

Newer MRI techniques, currently experimental in nature, are giving us a glimpse of what these modalities may tell us in the future about MRI brain pathology and clinical relevance. These include magnetic transfer imaging (MTI), DTI, proton MRI spectroscopy, functional MRI (fMRI), double inversion recovery (DIR) MRI, subtraction techniques, and ultra-high-field MRI scanners.<sup>64-66</sup> For example, the degree of increase in fMRI activity has been reported to be proportional to the sensitivity of T2 lesion load up to a critical limit, at which time these important compensatory mechanisms (ie, plasticity) fail.<sup>34</sup> Gray matter lesion conspicuity is increased with DIR techniques as well as with ultra-



high-field MRI scanners.<sup>67,68</sup> The latter may even allow one to identify remyelination and distinguish perivenous lesions caused by demyelinating diseases from those caused by other neurologic disorders.<sup>69,70</sup> There is also recent evidence that focal MRI white matter lesions in the optic radiations may lead to retrograde gray matter atrophy in the lateral geniculate nucleus.<sup>71</sup> Even in normal-appearing white matter, abnormalities have been detected with DTI, MTI, and pathologic analysis that may be associated with clinical and cognitive worsening.<sup>72-74</sup>

In summary, a limited number of studies of classic MRI abnormalities show CNS pathology, with virtually all MRI lesions being associated with CNS injury of varying degrees. It is hoped that other easily obtained biomarkers will also emerge over time,<sup>75</sup> particularly as the etiology and pathophysiology of the disease become better understood.

### Relationship Between MRI Disease Activity and MS Clinical Course: The MRI-Clinical Paradox

Although currently Gd+ and new or enlarging T2 lesions are the standard conventional MRI features used in screening for therapeutic efficacy and are important secondary outcome measures in phase 3 trials, their relationship to clinical prognosis has been less robust than anticipated.<sup>76-83</sup> This has led to the concept of a mismatch between MRI findings and clinical outcome, referred to as the “MRI-clinical paradox.” In fact, some researchers have suggested that, given the absence of a clear correlation between presence of Gd+ or T2 lesions and clinical findings, MRI evidence of inflammation may not be of great value as a surrogate for relapses, progression in disability, or the need to reconsider choice of therapeutic drugs.<sup>19,77-83</sup> However, many plausible reasons can be put forward to explain why the MRI-clinical paradox may no longer be the enigma it once was, and indeed the paradigm is now shifting.<sup>31</sup> For example, mild clinical relapses may not be documentable if they do not meet established EDSS or Functional Systems Scale (FSS) criteria, patients do not bring them to medical attention, or they occur in less eloquent brain areas. Subclinical MRI exacerbations are quite common, being detected up to 10 times more frequently than clinical symptoms or findings in RRMS patients.<sup>25-28,49</sup>

Further, as previously indicated, progression can be difficult to assess.<sup>16-18</sup> The rate of deterioration in patients with established disability may be slow, in

both relapsing and progressive forms of MS<sup>18,19,31</sup>; the EDSS is a relatively insensitive barometer of progression; and pseudoprogession may occur, making it difficult to accurately assess stability, worsening, or even mild improvement over the short term.<sup>16,17,19</sup> Progression of cognitive dysfunction is more problematic to clearly document, by either routine clinical or routine imaging metrics. Mild-to-moderate cognitive impairment may not be readily detected even by competent physicians or on EDSS testing, which is insensitive to such changes,<sup>16-18</sup> nor can cortical gray matter lesions be easily detected with conventional MRI techniques.<sup>67,68</sup> However, cortical lesions are much more commonly detected pathologically and on MRI with DIR and high-field scans and documented much more easily with neuropsychological testing, even early in the patient’s course.<sup>18,74,84-86</sup>

Furthermore, in both clinical practice and study trials, neither frequent brain MRI scans nor even infrequent spinal cord MRI scans are regularly obtained, so that many overt MRI lesions in the neuraxis can be missed, and previously hypointense or hyperintense lesions can become isointense and be difficult to detect unless prior MRI studies have been done.<sup>18,87,88</sup> In such instances, structural damage may still be identified with DTI or MTI in former T2 lesions or black holes that have subsequently become isointense.<sup>87,88</sup>

Lastly, although most if not all focal Gd+, T2, and T1 hypointense lesions may cause damage to the brain parenchyma, there may be sufficient reserves in neural pathways—with redundancies in critical thresholds of axonal function, or even compensatory mechanisms including plasticity and regeneration (particularly early in the course of MS)—so that new neurologic deficits or progression in disability may not be readily seen.<sup>19,31,89</sup> Ultimately, however, sufficient axonal loss may accumulate over time (albeit at a unique rate in each patient) so that deterioration occurs, even when overt new MRI lesions are not identified.<sup>89</sup>

All of the above could decrease MRI lesion conspicuity on conventional scanning and affect the correlation of MRI lesions with clinical phenotypes, relapses, and progression.

### Evidence That the MS MRI-Clinical Paradox Is Disappearing

#### Individual MRI-Clinical Studies

The relevance of MRI-clinical relationships has changed remarkably in recent years.<sup>31</sup> A large and grow-

ing number of reports from observational, retrospective, randomized, and prospective studies show a much stronger correlation than was found previously between MS MRI and clinical disease activity.<sup>18,59,90-100</sup> For example, RRMS and CIS patients with elevated Gd+ and T2 lesion activity, in terms of number or volume of lesions before or after therapy, have a greater likelihood of subsequent clinical relapses, disability progression, cognitive impairment, decreased quality of life, and even death as compared with patients with lower or absent MRI activity.<sup>18,59,90-100</sup> Although most of these studies have been relatively short term, some have followed study cohorts for 20 or more years.<sup>100-102</sup>

### Patterns of MRI Activity and Clinical Course

In the BECOME study, a sensitive monthly (for up to 24 months) MRI technique (3-T scanner, up to a 40-minute delay in postcontrast imaging, and triple-dose Gd administration, all of which increase lesion conspicuity)<sup>102-105</sup> was used along with periodic clinical and cognitive assessments to study patients with early MS and CIS randomized to interferon beta-1b (IFN $\beta$ -1b) or glatiramer acetate (GA).<sup>18,26,37</sup> Scans were obtained at baseline before patients were started on IFN $\beta$ -1b or GA and regularly thereafter. On post hoc analysis, three categories of MRI patterns were apparent.<sup>18</sup> One patient group never had Gd+ or new T2 lesions (23.2%); another group had continuous Gd+ or new T2 lesions with the exception of at most 1 inactive month between active MRI months (30.4%); and a third group had an intermediate pattern of MRI monthly activity (46.4%). Overall, no clinical relationship was found in this relatively small number of study patients between MRI pattern and drug treatment. However, subset analysis showed that patients with active MRI patterns had a higher relapse rate, greater sustained worsening in the Timed 25-Foot Walk, and more cognitive impairment—the latter both at baseline and subsequently during the study—than those without active MRIs. This is the first time that such clinical outcomes have been so clearly related to MRI patterns; moreover, it is remarkable that this could be seen with so few patients, all of whom were on therapy. In addition, 75% to 80% of patients had MRI activity at some point during the BECOME study.<sup>26</sup> This reinforces that what we see in clinical practice or during clinical trials using infrequent, less sensitive MRIs represents just a fraction of what is actually occurring in the neuraxis.

### Meta-analysis of Large Randomized MS Trials

Until recently, attempts to show that conventional MRI is a surrogate for clinical relapses and progression were limited and not very robust.<sup>76-82</sup> This situation started to change when it was shown that MRI reflected not only pathology but also clinical prognosis and response to therapy. Subsequently, a meta-analysis of all large randomized placebo-controlled studies of patients with RRMS was carried out by Sormani et al.<sup>106-109</sup> In the initial study, 23 trials involving 6591 patients were analyzed. It was demonstrated that the therapeutic response effect on new MRI T2 lesions correlated strongly with the effect of drugs on relapses (adjusted  $R^2 = 0.81$ ). In a second study, these investigators carried out a similar analysis of 11 trials involving 10,009 patients with complete data on MRI and disability progression. This meta-analysis also showed a significant correlation of MRI response to therapy with effect on disability progression (adjusted  $R^2 = 0.57$ ) over the 2 to 3 years of the study. These and two subsequent studies based on individual patient analysis showed that MRI markers satisfy the rigorous Prentice criteria for consideration as a valid surrogate marker in group studies of RRMS.<sup>108-110</sup> In considering the impact of these studies, it is important to remember that while one may not always see a robust relationship between MRI and clinical course in individual study patients, neither does one always see a robust effect of treatment with a drug that has been proven clinically effective in a cohort of patients in all individual members of the cohort.

At present, sophisticated research MRI studies such as fMRI, MTI, DTI, spectroscopy, and the use of stronger magnets or other MRI outcomes are not being considered for incorporation into the current Lublin-Reingold clinical classification because they are not generally available for use in clinical practice and do not show clear differences in MRI subclinical relapses, including alteration of BBB and inflammation, between Lublin-Reingold patient categories. For the same reasons, we did not take into consideration data on brain atrophy for this discussion on clinical classification.

### Discussion

After the presentations further group discussions were held (Durelli, Trabousee), as well as a final discussion to review the evidence available and assess the desirability of incorporating standard MRI metrics into the current Lublin-Reingold criteria for MS disease classification.

There was general agreement that conventional MRI activity including Gd+ lesions or unequivocally new or enlarging T2 lesions (activity not due to marginally enlarging lesions or related to technique, positioning, quality of scan, or questionable reader interpretation) indicates contemporary or prior inflammation, respectively, associated with CNS tissue damage; that the effect of therapy on new lesions correlates with the effect on relapses in RRMS; and that MRI is a surrogate for relapses in these studies. It was agreed that conventional MRI is readily available and should be performed according to consensus guidelines.<sup>111</sup> Lastly, it was also agreed that the clinical classification for distinguishing between relapsing and progressive forms of MS should be supplemented with MRI findings.

## Conclusion

At the end of the meeting, it was unanimously recommended that evidence of new MRI Gd+ lesions, and probably unequivocally new or enlarging T2 lesions (subclinical activity), should be added to the clinical classification of MS disease types, as suggested by Lincoln et al.<sup>1</sup> There was also a strong consensus that Gd+ lesions and possibly unequivocally new or enlarging T2 lesions should be recognized as contemporary or prior subclinical relapses, respectively. It was felt that these changes would lead to a better understanding of the evolution of MS, with more rigorous definitions and categorization of MS course.

Further, it was felt that at the present time no available biomarker was superior to MRI in combination with clinical criteria for use in disease classification or distinguishing between relapsing and progressive forms

of MS, although it was hoped that this situation would change in the future. Moreover, there was a consensus that, as with MS diagnostic criteria, the clinical classification likely would undergo periodic modification, particularly as metrics based on currently experimental quantitative measures become generally available and relevant. □

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## Practice Points

- The widely used Lublin-Reingold classification of MS disease course is based purely on clinical measures of disease activity.
- An increasing body of literature shows a much stronger correlation between magnetic resonance imaging and MS clinical disease activity than was found in previous studies.
- Thus magnetic resonance imaging should be used in the clinical classification of MS, particularly to distinguish inflammatory relapsing forms, which might be amenable to treatment, from progressive forms.



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## Call for Abstracts



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