Introduction

Strategies for Diagnosing MS Early—Avoiding Misdiagnosis

The Evolving Phenotypes of MS

Recent Developments in Disease-Modifying Therapy

CME/CE Post-Test and Evaluation Form

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This continuing education supplement is the second activity in the two-part curriculum, Improving the Diagnosis of MS through Simulation and Peer Benchmarking. Its content was derived from interviews with the faculty and the key teaching points from the previous online activity, Neurology Case Challenges: Critical Decision Points in Accurate Diagnosis, which may be found at: https://tinyurl.com/MSCase17.

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Learning Objectives
At the conclusion of this program, participants should be better able to:
• Discuss the role of radiologically isolated syndromes (RIS) and clinically isolated syndromes (CIS) in diagnosing and monitoring MS
• Describe recent updates to established MS disease phenotypes and discuss their application in clinical practice
• Recognize the importance of early diagnosis and treatment in reducing disability progression
• Identify important risk factors impacting the onset, severity, and progression of MS
• Understand and apply recent discoveries and emerging therapies in the management of patients with MS

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Introduction

In recent years, the treatment options for multiple sclerosis (MS) have increased in number and in efficacy. These new therapies—coupled with our emerging understanding of the nature of the disease state itself—provide clinicians with more options to better control the inflammatory aspects of MS that are often associated with disability.

The benefit from disease-modifying therapies (DMTs) is likely greatest early in the disease course. However, before treatment can begin, a careful, accurate, and timely diagnosis must be made. Despite advances in our understanding of MS and in the tools available for identifying it, misdiagnosis of MS remains a problem.

That challenges exist in the correct identification of MS is not surprising, given that fulfillment of the current (and still-evolving) criteria for the condition can be subjective. These include:

- Demonstration of dissemination of lesions in space (DIS)
- Demonstration of dissemination of lesions in time (DIT)
- Exclusion of alternative diagnoses

Imminent updates to the McDonald diagnostic criteria for MS are likely to refine the ways in which the aforementioned steps can be satisfied. The publication outlining those updates is in press at the time of this writing, in the fall of 2017. However, briefings at the October 2017 meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) indicate that the presence of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) can be substituted for demonstration of DIT to warrant diagnosis of MS in a patient who otherwise might be considered to have clinically isolated syndrome (CIS). While these and other refinements to the criteria will affect clinical practice, the principles that guide early, precise MS diagnosis and the continued emphasis on characteristic clinical symptoms of demyelinating disease will remain in place.

A Note About the 2017 Revisions to the McDonald Criteria

The International Panel on Diagnosis of MS has recommended revisions to the McDonald criteria that are intended to reduce the risk of misdiagnosis while enabling earlier identification of MS. These criteria were awaiting publication as this supplement went to press in December 2017.

First published in 2001, the McDonald criteria apply a three-part formula for the diagnosis of MS: DIS, DIT, and the exclusion of other possible causes. The initial criteria and updates in 2005 and 2010 provided further guidance on how each requirement could be satisfied, as do the 2017 revisions.

Jeffrey A. Cohen, MD, a neurologist with the Cleveland Clinic’s Mellon Center for Multiple Sclerosis Treatment and Research, previewed the revisions at the October 2017 joint ECTRIMS-ACTRIMS meeting in Paris. Key features include:

- Enabling the presence of multiple OCBs restricted to the CSF to warrant the diagnosis of MS in a patient with CIS who has not demonstrated DIT but who has demonstrated DIS clinically or on MRI;
- Allowing both symptomatic and asymptomatic lesions to count toward the criteria for DIT and DIS;
- Considering cortical lesions to be equivalent to juxtacortical lesions when assessing DIS;
- Including symptomatic and asymptomatic cortical lesions when determining whether a patient meets the criteria for primary progressive MS (which remain unchanged); and,
- Recommending that neurologists determine a provisional disease course, in keeping with the clinical courses and phenotypes outlined by a panel of experts in 2014, at diagnosis, and that they periodically review that assessment in light of further evidence.

Dr Cohen said that the panel sought to clarify and simplify the criteria to reflect the latest evidence, reduce the risk of misdiagnosis, and speed the diagnosis of MS.


By the Numbers: Incidence and Prevalence of MS and Related Conditions

MS affects approximately 400,000 people in the United States. The estimated prevalence of MS is 149.2 cases per 100,000 people, and incidence rates as high as 6.2 per 100,000 person-years have been reported. Too often, however, MS is incorrectly diagnosed in patients who have other conditions but whose symptoms mimic MS. As a result, arriving at a true prevalence or incidence rate can be challenging.

As many as 85% of patients with MS first present with a relapse-onset, which can often be categorized as clinically isolated syndrome (CIS), a single demyelinating episode that does not fulfill the diagnostic criteria for MS but that can be predictive of progression to MS. The incidence of CIS ranges from 2.4 to 6.8 per 100,000 person-years.

Other patients who ultimately are diagnosed with MS may first come to medical attention when magnetic resonance imaging (MRI) performed for an unrelated indication reveals brain and spinal lesions suggestive of MS in an individual with no symptoms of the condition. In this situation—known as radiologically isolated syndrome (RIS)—approximately one-third of patients may be diagnosed with MS within about 5 years of the initial MRI findings.

Neuromyelitis optica spectrum disorders (NMOSD) are often mistaken for MS because their clinical and radiographic characteristics can overlap with MS. NMOSD prevalence in the United States is believed to be between 1% and 2% of all MS, which would translate into 4,000 or more patients. Studies conducted in various countries (not including the United States) indicate that incidence ranges between 0.053 and 0.4 per 100,000 person-years. NMOSD incidence is up to 10 times higher in women than in men and is significantly more prevalent in African Americans than in Caucasians.

Morbidity and Mortality

Because MS lesions can develop throughout the brain and spinal cord, nearly any bodily function can be compromised by the condition’s effects on the central nervous system (CNS). Common symptoms of MS range from disabling fatigue, weakness, and dizziness to loss of mobility, spasticity, and numbness or tingling, as well as vision problems and bladder dysfunction.

Historically, most patients with MS eventually become disabled. MS can shorten life expectancy by 6 to 10 years, with the mean age at time of death being 61 to 65 years. Respiratory infections, urinary tract infections, suicide, and localized infection or sepsis secondary to loss of mobility and skin integrity are common causes of death in MS.

The disease course of NMOSD is marked by devastating relapses that can lead to severe vision impairment, weakness, fatigue, paralysis, paresis, spasticity, loss of bowel or bladder function, and uncontrollable nausea and vomiting. Between 9% and 32% of patients with NMO/NMOSD die during a relapse. African Americans and patients not on preventive therapy at the time of relapse are at highest risk of death, compared with other patient groups.

Balancing Early Intervention With Diagnostic Precision

Early initiation of DMT has been shown to reduce the risk of conversion to MS in patients with CIS. Similarly, in patients diagnosed with MS, starting a DMT soon after diagnosis slows MS progression, extends time to relapse, and forestalls disability. In contrast, delays in diagnosing and treating MS allow the disease’s demyelinating and inflammatory activity to go unchecked, leaving patients vulnerable to advancing disability, impaired cognition, loss of emotional well-being, and a shortened lifespan.

Although the value of early diagnosis and intervention is clear, so is the importance of avoiding attributing symptoms of other conditions to MS. Research has documented the potential for patients with migraine or other neurologic disorders to be misdiagnosed as having MS. Misdiagnosis unnecessarily subjects patients to the documented risks of DMT, which include opportunistic infections, development of other autoimmune conditions, and, in the case of some agents, liver damage. Furthermore, incorrectly diagnosing MS can mean that another serious condition is missed, exposing patients to unnecessary morbidity and, in rare cases, mortality.

Education on the appropriate application of clinical guidelines and interpretation of clinical and paraclinical findings can help clinicians promptly and more accurately identify MS in its early stages.

Classifying MS and Related Conditions

To help neurologists more effectively chart a patient’s disease course and plan treatment, the International Advisory Committee on Clinical Trials in Multiple Sclerosis, a joint committee of the US-based National Multiple Sclerosis Society and ECTRIMS, identified four principal clinical MS phenotypes: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS).

CIS is also part of the MS spectrum, and a subsequent MS phenotype is determined based on clinical follow-up. RIS is not considered an MS phenotype because patients with this syndrome lack clinical signs and symptoms of MS. These patients, however, should be followed prospectively after RIS is identified.
Clinically Isolated Syndrome

CIS refers to an initial demyelinating event with symptoms lasting ≥24 hours. The event is compatible with MS but is isolated in time and may or may not be confined to a single area.18 Optic neuritis, a brain stem or cerebellar syndrome, or a spinal cord syndrome are the most common presentations of CIS in MS patients.18

CIS is recognized as a possible initial presentation of MS.25 As noted in a 2014 consensus paper on clinical phenotypes in MS, patients who present with CIS and have brain lesions on MRI are at high risk for subsequently meeting MS diagnostic criteria.35 Based on definitions operative for the past several years, most patients with CIS meet diagnostic criteria for MS within 12 to 18 months.26 As noted earlier, however, updates to the McDonald diagnostic criteria are forthcoming (see page S4), and those revisions may affect both how the distinction between CIS and MS is made and the period of time from identification of CIS to diagnosis of MS.

Several clinical and demographic characteristics have been shown to increase risk of conversion to MS in patients with CIS. Clinical factors include motor or multifocal symptoms at presentation and a higher Expanded Disability Status Scale (EDSS) score at baseline.18 CIS patients who are of non-Caucasian race, who are younger than 30 years, or who smoke are at increased risk of progression to MS.18

Initiation of a DMT after CIS diagnosis has been shown to reduce the risk of a second event over 2 to 3 years, compared with patients with CIS who are not treated.19,25 For patients with CIS who do develop a successive episode, DMT significantly delays progression to MS.19,25

Taking a thorough patient history is crucial to assessing CIS. Topics to explore include neurologic symptoms such as blurring of vision, double vision, Lhermitte’s sign, numbness, or weakness lasting ≥24 hours, as well as symptoms that may be indicative of other disorders.18 Information on family history of MS, exposure to cigarette smoke, vitamin D consumption, birthplace, and recent travels is also important in considering the risk for demyelinating disease.27-29

The wide range of diseases whose symptoms mimic CIS and MS makes diagnosis challenging. Alternative diagnoses need to be ruled out in the CIS workup; these diagnoses include infection, other inflammatory disorders, metabolic disorders, genetic diseases, neoplasms, and vascular disease.18

Clinicians are also advised to ask about comorbid conditions, including cerebrovascular, cardiovascular, autoimmune, pulmonary, neurologic, metabolic, musculoskeletal, visual, gastrointestinal, mental, and other conditions, as well as cancer. The presence of these comorbidities has been shown to delay MS diagnosis, worsen MS-related disability, and increase the risk of mortality.30-32

Brain MRI with gadolinium is the first paracranial step in the CIS workup.18,33 An MRI of the orbits is needed for patients with optic neuritis; MRI of the cervical or thoracic spinal cord is indicated for patients with a spinal cord syndrome.18,33 The Consortium of Multiple Sclerosis Centers (CMSC) recommends a 3-plane, large area, localized scout view, sagittal fast fluid-attenuated inversion recovery (FLAIR), axial fast spin-echo proton density/T2, axial fast FLAIR, and axial gadolinium-enhanced T1 images to evaluate possible CIS.33

MRI will show one or more clinically silent T2-bright lesions in 50% to 80% of patients with CIS.18 The presence of several clinically silent lesions could predict future development of MS and suggest high-risk CIS, because lesions develop more quickly than do MS symptoms. Clinicians should promptly order a spinal cord MRI if the patient has transverse myelitis or reports symptoms related to the spinal cord, if the patient is older than age 40, or if findings on brain MRI are insufficient for a diagnosis of MS.18,33

To determine DIT and ongoing clinically silent disease, a follow-up brain MRI should be performed 6 to 12 months after the initial brain MRI for patients with high-risk CIS (ie, >2 ovoid lesions on first MRI), or 12 to 24 months later for patients with low-risk CIS (ie, normal brain MRI).26,33

CSF analysis for oligoclonal banding and elevated immunoglobulin G (IgG) can also help determine the risk of conversion to MS in CIS. Between 60% and 70% of patients with CIS have two or more OCBs restricted to the CSF, and the presence of OCBs within 3 months after a CIS attack has been shown to nearly double the risk of a second (demyelinating) attack within 4 to 6 years.18 OCBs are also highly predictive for development of RRMS after CIS.18

Numerous neurologic disorders other than MS are also associated with oligoclonal banding and an elevated IgG index, however, so the differential diagnosis related to CSF analysis is also wide.18 A diagnosis other than MS should be suspected in patients with CSF with >50 white blood cell (WBC) count/mm³ or protein >100 mg/dL, because these findings are unusual in MS (Table 1).18

Radiologically Isolated Syndrome (RIS)

RIS, first identified in 2009, is a diagnosis that applies to patients in whom MRI reveals asymptomatic lesions strongly suggestive of demyelinating pathology.34 RIS is typically discovered in patients who undergo MRI scanning for another medical problem, most commonly migraine or other types of headache.10,35 Trauma, anxiety/depression, and musculoskeletal pain are among other common initial presentations (Table 2).10

RIS carries a risk of conversion to MS. In one study, two-thirds of patients with RIS showed radiologic progression, one-third experienced a clinical event, and about 10% met diagnostic criteria for progressive MS.10

These data illustrate the need to identify patients with RIS who are at elevated risk for conversion to MS. Specific initial MRI findings that are highly suggestive of demyelinating pathology include34:

- Ovoid, well-circumscribed, homogeneous foci with or without involvement of the corpus callosum
- T2 hyperintensities measuring ≥3 mm and fulfilling at least three of four Barkhof criteria for DIS
- Anomalies not following a clear vascular pattern
- Asymptomatic lesions within the cervical or thoracic spinal cord
- Structural neuroimaging abnormalities not explained by another disease process

“[My neurologist] explains himself, he breaks it down so that you can understand what he is trying to tell you. Even though what he talks about is very technical, he makes it so you can understand it at your level, and that’s important. And so after listening, of course, both my wife and I would ask him questions and he would respond so that we could understand and feel comfortable with the information that was being shared back and forth.”

F.F., a 67-year-old retired government worker from Georgia who was diagnosed with RRMS in 2000 after seeking evaluation of sexual dysfunction.
Younger age at initial MRI (<36 years) is also highly predictive, as are lesions within the spinal cord plus additional brain lesions in younger patients. Follow-up MRI is warranted in patients with the findings listed above. Both a spinal cord MRI and a brain MRI should be obtained after an initial brain scan to determine DIS, even if the patient shows no indication of spinal cord symptoms. The CMSC recommends a follow-up MRI 1 to 2 years after the initial scan, although a follow-up scan 6 months after the initial MRI may be warranted in some patients. Brain images should be T1- and T2-weighted spin-echo sequences of the brain in axial, coronal, and sagittal view, with and without gadolinium. Spinal cord images should be T1- and T2-weighted spin-echo sequences, in axial and sagittal planes (with and without gadolinium). CSF in tandem with follow-up MRI should also be ordered to check for oligoclonal banding suggestive of MS.

Although early initiation of DMT has been shown to slow progression after a diagnosis of MS or CIS, it is not known whether beginning DMT after RIS diagnosis will delay progression. Currently no data are available to support the use of DMT after RIS diagnosis, and many researchers recommend a "watch and wait" approach and prompt reconsideration of DMT if the patient develops symptoms compatible with MS.

**MS Diagnostic Strategies**

The patient history can reveal valuable clues to make or rule out a diagnosis of MS. The following information should be obtained:

- Family history of MS
- Medical history
- Recent or current symptoms possibly caused by MS (eg, fatigue, blurred vision, numbness or tingling)
- Environmental exposure (eg, cigarette smoking, vitamin D consumption)
- Birthplace and places of long-term residence (because MS is more prevalent in northern latitudes)

Clinical, laboratory, and paraclinical findings, along with clinical acumen, all come into play when considering an MS diagnosis. MRI scans can help confirm an MS diagnosis by uncovering subclinical lesions or disease progression in the context of clinical findings.

A brain MRI with gadolinium at baseline should be performed. A spinal cord MRI should also be performed if the patient has clinical findings do not support the diagnosis of MS, or in patients aged >40 years with nonspecific brain MRI findings. Orbital MRI should be ordered if symptoms suggest optic neuritis with poor recovery. The 2010 revised McDonald diagnostic criteria for MS should be referred to in order to rule out or pursue an MS diagnosis.

**Table 1. Differential Diagnosis in CSF Analysis During Assessment for CIS**

<table>
<thead>
<tr>
<th>Possible Alternative Diagnosis</th>
<th>Prevalence of Oligoclonal Banding in Patients With Disease's Neurologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenoleukodystrophy</td>
<td>100%</td>
</tr>
<tr>
<td>Rubella encephalitis</td>
<td>100%</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
<td>100%</td>
</tr>
<tr>
<td>Neurosphilis</td>
<td>90%-95%</td>
</tr>
<tr>
<td>Neuroborreliosis</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>75%-90%</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>60%-80%</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>50%-60%</td>
</tr>
<tr>
<td>Neurosarcoidiosis</td>
<td>40%-70%</td>
</tr>
<tr>
<td>Antiglutaminic acid decarboxylase antibody syndromes</td>
<td>40%-70%</td>
</tr>
<tr>
<td>Vogt-Koyanagi-Harada syndrome</td>
<td>30%-60%</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>30%-50%</td>
</tr>
<tr>
<td>Hashimoto's steroid-responsive encephalopathy</td>
<td>25%-35%</td>
</tr>
<tr>
<td>Behçet disease</td>
<td>20%-50%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5%-50%</td>
</tr>
<tr>
<td>Paraneoplastic disorders</td>
<td>5%-25%</td>
</tr>
<tr>
<td>CNS vascular disorders</td>
<td>5%-25%</td>
</tr>
<tr>
<td>Leber hereditary optic atrophy</td>
<td>5%-15%</td>
</tr>
<tr>
<td>CNS masses and structural lesions</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

**Table 2. Common Presentations in Patients Who Ultimately Receive a Diagnosis of RIS**

<table>
<thead>
<tr>
<th>Presentation That Prompted MRI</th>
<th>Percentage of RIS Patients (N=451) ±1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine or other headache</td>
<td>42.1%</td>
</tr>
<tr>
<td>Trauma</td>
<td>8.4%</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>5.5%</td>
</tr>
<tr>
<td>Spells of unknown etiology</td>
<td>5.5%</td>
</tr>
<tr>
<td>Pain (musculoskeletal, radiculalgia, other)</td>
<td>4.4%</td>
</tr>
<tr>
<td>MS family history</td>
<td>3.3%</td>
</tr>
<tr>
<td>Presyncope/syncope</td>
<td>3.3%</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>3.1%</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>3.1%</td>
</tr>
<tr>
<td>Tumor screen/surveillance</td>
<td>2.2%</td>
</tr>
<tr>
<td>Vascular events (eg, CVA, TIA)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Galactorrhea/hyperprolactinemia</td>
<td>1.6%</td>
</tr>
<tr>
<td>Amenorrhea/dysmenorrhea</td>
<td>1.3%</td>
</tr>
<tr>
<td>Other presentations*</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*Acromegaly, allergies, aneurysm screen, angioma, anosmia, Arnold-Chiari malformation, asymptomatic quadranopia, blepharospasm, cervical rib, ear discomfort with air travel, endocrinopathy, essential tremor, facial dystonia, fatigue, hypersomnolence, hypertension, ill-defined sensory complaint, infertiltiy evaluation, (focal) itching, Meniere disease, mesial temporal sclerosis, mononeuropathy, motion sickness, multiple atypical neurologic symptoms, narcolepsy, neuroleptic-induced tremor, nonspecific paresthesia, olfactory alterations after diving, orthostasis, otosclerosis, peripheral 7th nerve palsy, peripheral sensorinal hearing loss, personality changes, pituitary adenoma, positional paresthesias, psychiatric disorder/ unconciousness, tardive dyskinesia, ulnar neuropathy, uveits, vasovagal symptoms, visual abnormality.

CVA=cerebrovascular accident; MRI=magnetic resonance imaging; MS=multiple sclerosis; RIS=radiologically-isolated syndrome; TIA=transient ischemic attack.

Source: Okuda DT, et al.β

Source: Marcus JF, et al.
Four principal clinical phenotypes of MS were described in 2014 (Figure 1).25

1. Relapsing-remitting MS (RRMS), which is characterized by clearly defined exacerbations of new or increasing neurologic symptoms. Each exacerbation is followed by a full or incomplete recovery that leaves in its wake potentially disabling sequelae or residual deficits.25

2. Secondary progressive MS (SPMS). RRMS is marked by a pattern of severe exacerbations and disabling symptoms that worsen with each relapse. SPMS, in contrast, is characterized by gradual worsening after an initial relapsing disease course, with or without acute exacerbations during progression.25

3. Primary progressive MS (PPMS) is pathologically similar to relapsing forms of MS and worsens at a similar rate compared with SPMS. However, exacerbations before clinical worsening are absent in PPMS.25

4. Progressive relapsing MS (PRMS) is characterized by progressive accumulation of disability from onset but with clear, acute attacks throughout the disease course. Full recovery may or may not follow each attack.25

MS can be classified as relapsing or progressive based on worsening of disability, disease activity detected after a clinical relapse, or the presence of gadolinium-enhancing lesions or new or unequivocally enlarging T2 lesions.25 MS subtype should be determined based on current status and patient history but should be reassessed as the disease course progresses. For example, RRMS could evolve into a secondary remitting subtype.25

When determining MS disease course, clinicians should supplement current medical status and history with information on disease activity. This information can be obtained from clinical relapses, progression of disability, and presence of gadolinium-enhancing or unequivocally enlarging T2 lesions.25

Neuromyelitis Optica Spectrum Disorder

NMOSD is an inflammatory CNS disorder characterized by severe, immune-mediated demyelination and axonal damage in the optic nerves and spinal cord.12 NMOSD can be mistaken for MS because of their often overlapping clinical and radiographic characteristics. Until the early 2000s, NMOSD and MS were thought to be the same disease. Unlike MS, however, in NMOSD, necrosis and cavitation are found in both gray and white matter.12 NMOSD also disproportionally affects Asians, African Americans, and Native Americans relative to Caucasians.41

The following clinical findings should raise suspicion that a patient may have NMOSD and not MS12:

- Optic neuritis that is simultaneously bilateral, involves the optic chiasm, causes an altitudinal visual field defect, or causes severe residual visual loss
- Longitudinally extensive transverse myelitis (see NMOSD diagnostic criteria for details)
- Complete (not partial) spinal cord syndrome, especially with paroxysmal tonic spasms
- An area postrema clinical syndrome consisting of intractable hiccups, nausea, or vomiting

The presence of aquaporin-4 (AQP4) IgG antibodies in serum or CSF may confirm NMOSD in the context of the clinical presentations described above. CSF OCBs typically are not present in NMOSD, whereas they usually are present in MS.12

The patient should also be asked about recent nausea and vomiting as part of the patient history, as these symptoms are hallmarks of NMOSD.12
The Topographical Model of MS

By envisioning the CNS as a pool with a shallow end and a deep end, the topographical model of MS proposes that lesions in different areas of the nervous system are more or less likely to cross the clinical threshold, and that as functional reserve decreases over time, more of the underlying disease topography is revealed (Figure 2).

Figure 2. The Topographical Model of MS

(A) Clinical view: Water is opaque; only above-threshold peaks are visible. (a) Above-threshold topographical peaks depict relapses and quantified EDSS/functional system disability measures. Each peak yields localizable clinical findings; this topographical distribution defines the clinical picture for an individual patient. (b) Water level at outset reflects baseline functional capacity and may be estimated by baseline brain volume. (c) Water level decline reflects loss of functional reserve and may be estimated by metrics of annualized brain atrophy. (B) Subclinical view: Water is translucent; both clinical signs and subthreshold lesions are visible. (d) Subthreshold topographical peaks depict T2 lesion number and volume. (e) The tallest peaks (ie, the most destructive) in the cerebral hemispheres are shown in black as T1 black holes.

EDSS=Expanded Disability Status Scale.
Source: Krieger SC, et al.39
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That is how one the authors of this supplement Stephen C. Krieger, MD, views the evolution of MS from early-stage demyelination to relapse and remission and, ultimately, progressive MS. In a 2016 article, Krieger and colleagues presented the topographical model of MS, a model that they believe helps to clarify the dynamic continuum between RIS, CIS, RRMS, and ultimately, progressive MS.39 Distinguishing between relapsing and progressive MS can be challenging, because atrophy begins early in the disease course and inflammation continues in the late stages, often leading to overlapping clinical symptomatology.39 Existing MS phenotypes have been defined based on clinical manifestations but do not directly represent diversity of symptoms, relapse severity, or accumulation of disability.39 The exact point at which relapsing MS becomes progressive is unclear; the authors identified a mean 4.3-year period of diagnostic uncertainty between RRMS and SPMS.40

The topographical model—which builds on the International Advisory Committee on Clinical Trials in Multiple Sclerosis 2013 definition of MS phenotypes25—is designed to illustrate the interplay of relapse and progression across the spectrum of MS.39 The model is based on the premise that MS progression clinically recapitulates a patient’s prior relapse symptoms and unmask previously clinically silent lesions.39

In this topographical model, the CNS is symbolized as a pool divided into three basic anatomical regions with different levels of functional reserve. The water represents neurologic functional capacity, which compensates for regions of damage by keeping them “submerged” and asymptomatic. The shallow end of the pool represents the spinal cord and optic nerves, with the least amount of functional compensatory reserve. The deep end illustrates the cerebral hemispheres, regions with the greatest capacity to compensate for lesions.39 Levels of functional reserve fluctuate throughout the MS disease course (during fever or concurrent illness, for example) and decline over the long term as MS progresses.39 Correspondingly, in the MS topographical model, the water surface depicts the clinical threshold. Peaks that cross above the threshold upon formation cause relapses; those that are below the threshold are clinically silent, such as lesions identified in RIS, where by definition there have been no clinically-apparent MS symptoms.39

As the model is further tested and validated, it has the potential to enhance patient care by facilitating a more clinically nuanced and individualized representation of the disease course, which would help clinicians identify progressive MS sooner.39 The model could also be used for patient education (a free patient-education app, "MS Topography," is available for the iPad® mobile digital device from the Apple App Store®) and in the future could inform the design of clinical trials in MS.39
A Current Practice Snapshot of MS Diagnosis: Where We Are and Where We Need to Be

This infographic was developed based on data from scientific sources combined with insights from the program’s faculty and learner data from a currently available online CME/CE simulation activity designed to educate clinicians about the challenges of timely diagnosis of multiple sclerosis (MS).

1. Making a Timely Diagnosis of MS Is an Ongoing Challenge

   Patients wait an average of nearly 6 years between the onset of symptoms and receiving a diagnosis of MS.¹

   ![Diagram showing the timeline of MS diagnosis and treatment stages.]


2. The Variety of Presenting Symptoms Can Contribute to Delayed Diagnosis...

   The wide array of initial symptoms seen in MS can make timely diagnosis a challenge. MS can first manifest in various ways.¹,²

   **Presenting symptoms of MS**
   - Sensory disturbances of the face: 2.8%
   - Vision loss: 15.9%
   - Vertigo: 1.0%
   - Diplopia: 6.8%
   - Motor (acute/subacute): 4.3%/8.9%
   - Acute transverse myelopathy: 0.7%
   - Lhermitte’s phenomenon: 1.8%
   - Sensory disturbances in limbs: 30.7%
   - Limb ataxia: 1.0%
   - Bladder disturbance: 1.0%
   - Gait disturbance: 4.8%
   - Balance problems: 2.9%
   - Other
     - Pain: 0.5%
     - Polysymptomatic onset, acute: 13.7%
     - Unclassified: 2.5%


3. …As Can the Broad Differential Diagnosis

   The presenting symptoms of MS might indicate any number of conditions, ranging from infectious diseases to genetic syndromes.³

   **Alternative diagnoses for MS: A partial list**
   - Anatomic
   - Autoimmune
   - Genetic
   - Infectious
   - Inflammatory
   - Metabolic
   - Neoplastic
   - Other MS mimics
   - Vascular

   *NMSS. Differential diagnosis. *Diagnostic categories are listed alphabetically.

4. Suboptimal Use of MRI May Delay Diagnosis

   In a recent CME/CE activity, clinicians were asked which neurologic-focused study they would order first in evaluating the patients presented in 2 case simulations. Only somewhat more than half of participants made the optimal choice: MRI.

   **In exploring possible neurologic causes for this patient’s symptoms, which one of the following tests would you order first?**

   **When MRI of the thoracic spinal cord is indicated**
   - Presentation: 54-year-old man; 5-year history of weakness in right leg with increasing severity, accompanying numbness, and difficulty walking up stairs
   - Evoked potentials study: 12%
   - CSF analysis: 8%
   - MRI of the thoracic spinal cord: 54%
   - EMG: 26%
   - N=242 responses

   **When MRI of the brain is indicated**
   - Presentation: 28-year-old woman; intermittent dizziness; initial findings suggesting central vestibular disorder
   - Evoked potentials study: 1%
   - Holter monitoring: 18%
   - Electronystagmogram: 23%
   - MRI of the brain: 58%
   - N=93 responses
5 CSF Analysis Is Increasingly Important in MS Diagnosis

Oligoclonal bands (OCBs) restricted to cerebrospinal fluid (CSF) support a diagnosis of MS. However, only 70% of participants in a CME/CE activity identified CSF analysis as the one best test to assess risk of conversion from clinically isolated syndrome (CIS) to clinically definite multiple sclerosis (CDMS). CSF analysis is now part of the McDonald criteria (2017) but clinicians may be unaware of the value of CSF analysis.

6 The Flip Side of the Coin: Mistaking Other Conditions for MS

In addition to the delayed or missed diagnosis of MS, incorrectly attributing symptoms of other conditions to MS is a significant problem. In one survey of MS specialists, 95% had seen at least 1 patient within the past year who previously had been diagnosed incorrectly as having MS.

Clinicians who see patients misdiagnosed as having MS (%)

- >10 misdiagnosed patients 17%
- 6-10 misdiagnosed patients 17%
- 3-5 misdiagnosed patients 40%
- 1-2 misdiagnosed patients 26%

7 MS Misdiagnosis Poses Serious Consequences

In a 2016 study of 110 patients with a definite (46%) or probable (54%) misdiagnosis of MS, most received disease modifying therapy (DMT), and one-third experienced unnecessary morbidity due to the misdiagnosis.

Of 110 patients misdiagnosed with MS...

- 33% had lived with a misdiagnosis for ≥10 years
- 70% received unnecessary DMT for MS
- 31% had unnecessary morbidity, including adverse effects of treatment, due to misdiagnosis

8 A Systematic Approach to Evaluation Is Essential

Considering several key questions in a step-wise fashion can help the clinician determine which tests or studies are warranted, and which conditions deserve further investigation or may be ruled out.

Step 1 > Step 2 > Step 3 > Step 4a > Step 4b

9 Paying Close Attention to Clinical Features Can Help Guide the Evaluation

Making the correct diagnosis requires remaining alert to features suggestive of MS, as well as to the red flags that indicate MS might be a less likely cause of a patient’s symptoms.

10 Increasing MS Prevalence and an Expanded Role for DMTs Provide New Urgency for Making a Timely, Accurate Diagnosis

The prevalence of MS may be twice as high as previously reported; 2017 revisions to McDonald criteria may increase this number even further. New treatments are available to treat the spectrum of MS phenotypes, including primary progressive MS (PPMS). This data set was created to highlight key points from an educational activity, “Neurology Case Challenges: Critical Decision Points in Accurate Diagnosis.” The complete interactive version of this Infographic, with additional learner data, can be found at the following link: https://www.globalacademycme.com/cme/neurology/current-snapshot-ms-diagnosis-where-we-are-and-current-snapshot-ms-diagnosis-infographic and via this QR code.
Recent Developments in Disease-Modifying Therapy

Expanding the Armamentarium

Recent advances in DMT have greatly expanded neurologists’ options for slowing progression of MS, preserving function, and improving patients’ quality of life. Although these agents have varying routes of administration and different side effect profiles and mechanisms of action, all were developed with a view toward halting or slowing demyelination and MS progression.

Neurologists now have more than a dozen DMTs to draw upon in individualizing care, including two approved in 2016 and 2017. The two new agents, described briefly below, are both monoclonal antibodies that powerfully affect the immune system.

Ocrelizumab, a CD20-directed cytolytic antibody, was approved by the US Food and Drug Administration (FDA) in March 2017 for patients with relapsing or primary progressive forms of MS. The agent, administerpres through intravenous infusion, promotes immunosuppression by targeting the CD20 marker on B lymphocytes. Ocrelizumab is the first therapy specifically approved to treat primary progressive MS.

In two identical randomized trials that followed a total of 1,656 patients with relapsing MS, the annualized relapse rate was 46% lower among patients who received ocrelizumab 600 mg every 24 weeks, compared with those who received subcutaneous interferon beta-1a, 44 mcg 3 times weekly for 96 weeks. Lower incidence of disability progression, higher Multiple Sclerosis Functional Composite scores, and fewer gadolinium-enhancing lesions per T1-weighted MRI scan were reported in the ocrelizumab groups.

In a third randomized clinical trial that followed 732 patients with PPMS, ocrelizumab was associated with lower rates of disability progression at 12 weeks (32.9% of patients in the treatment group vs 39.3% with placebo) and 24 weeks (29.6% vs 35.7%). Total volume of brain lesions on T2-weighted MRI decreased 3.4% among the ocrelizumab group and increased 7.4% with placebo. Brain volume loss and decline in timed 25-foot walk performance were also lower in the ocrelizumab group.

Infusion site reactions occurred in 33% to 40% of patients in the three trials and were significantly more prevalent in the treatment groups versus the comparison groups. Most of these reactions were mild to moderate. Upper respiratory tract infections were reported in 15.2% of patients in the two identical trials evaluating ocrelizumab in relapsing MS and in 10.9% of patients in the PPMS trial. An increased risk of malignancy may also exist with ocrelizumab.

Daclizumab, a subcutaneous interleukin (IL)-2 receptor blocking antibody, was approved by the FDA in 2016 for adult patients with relapsing forms of MS. Daclizumab inhibits some T-cell inflammatory activity by blocking the IL-2 receptor.

In a trial that tracked 1,841 RRMS patients ages 18 to 55 years over 96 weeks, more patients in the daclizumab group (n=919) showed clinically meaningful improvement in Symbol Digit Modalities Test scores and significantly fewer showed clinical worsening, compared with patients who received intramuscular interferon beta-1a, 30 mcg/weekly (n=922). Clinical assessments occurred every 12 weeks and after a relapse, and MRI scans were performed at 24 and 96 weeks.

In a second controlled trial, patients who received daclizumab 150 or 300 mg every 4 weeks (n=208) had fewer gadolinium-enhancing lesions after 24 weeks or after 4 to 20 weeks that evolved into T1 black holes at week 52, compared with patients receiving placebo (n=204). Daclizumab also reduced the percentage of gadolinium-enhancing lesions that evolved into black holes compared with placebo.

Daclizumab carries a black box warning that the agent can cause severe and sometimes fatal liver injury, including autoimmune hepatitis and liver failure. The agent is contraindicated in patients with preexisting hepatic disease or hepatic impairment. Neurologists are advised to monitor transaminase and bilirubin levels monthly and up to 6 months after the last dose.

The warning also states that immune-mediated disorders, including skin reactions, lymphadenopathy, immune-mediated colitis, and other disorders can occur with daclizumab. Because of the drug’s safety profile, its prescribing information includes guidance that daclizumab should generally be reserved for patients who have responded inadequately to two or more DMTs.

Multidisciplinary Care

Beyond the impaired mobility that is a salient example of MS-related disability, patients with MS potentially have to contend with a host of other important signs and symptoms that can be disabling, including vision loss, dizziness/vertigo, bladder/bowel incontinence, sexual dysfunction, depression, emotional problems, and cognitive changes.

Neurologists thus are an integral part of an MS multidisciplinary team that also includes a primary care physician and (as needed) a urologist, neuropsychologist, psychiatrist, speech therapist, physical/recreational/occupational therapist, social worker/counselor, support staff, and nurses specializing in MS care, among others. Neurologists are the “point people” who select treatment, address symptoms, and monitor disease progression. Neurologists also play a crucial role in explaining to patients how other team members’ skills can help them deal with various manifestations of MS.

As coordinators of the patient’s imaging needs, neurologists should follow a uniform procedure for providing imaging and other information from the patient history, so that other specialists can quickly interpret the findings. The CMSC recommends including in each communication:

- The rationale for diagnosis and treatment
- Relevant clinical history and physical examination findings
- MS medication history
- Date and location of previous examinations, if known

The CMSC also recommends that radiologists and others use standardized nomenclature and terminology to describe imaging findings, so that all team specialists can easily interpret reports.

The report should include:

- A description of the findings, which should include the lesion type, location, size, shape, character, and number of lesions
- A comparison of lesions and atrophy found in previous examinations
- An interpretation (ie, typical for MS, atypical for MS, not MS) and differential diagnosis, if applicable
Follow-up MRI should be performed for patients with suspected MS or in whom CIS has been diagnosed. The second scan should be performed if:

- 6 to 2 months later for patients with high-risk CIS (e.g., ≥2 ovoid lesions on first MRI)
- 12 to 24 months later for low-risk CIS (i.e., normal brain MRI findings) or for an uncertain clinical syndrome with suspicious brain MRI features, such as RIS

Once a diagnosis of MS is established, brain MRI with gadolinium should be performed if one or more of these situations exist:

- If no prior images are available (e.g., for a patient new to your practice)
- Postpartum, to establish a new baseline
- Before starting or switching a DMT
- Approximately 6 months after switching starting DMT to establish a new baseline, after the therapy has reached its therapeutic potential
- Every 1 to 2 years during DMT to monitor response and assess subclinical disease activity
- In response to unexpected clinical deterioration
- To reassess the original diagnosis

Further, follow-up brain MRI at 3T magnetic strength may reveal increased lesion load if prior images were taken at 1.5T. CSF analysis, performed in tandem with MRI and clinical examination, is also helpful in confirming or ruling out an MS diagnosis. The presence of oligoclonal banding (≥2 bands) in the setting of 2 MRI-detected lesions is sufficient to meet MS diagnostic criteria. Conversely, absence of oligoclonal banding should raise suspicion of an alternative diagnosis.

Clinicians, however, need to consider all tests in the CSF panel, including cell count, protein, glucose, and lactate levels. For example, while a higher-than-normal WBC count (>5 x 10⁶/L) is found in one-third of MS cases, an extremely high WBC count (>50 x 10⁶/L) is rare in MS. Low CSF glucose would suggest an infection or neoplastic process.

**MS Misdiagnosis**

The diagnosis of MS can be challenging. Its presentation is heterogeneous, and the neurologic and clinical symptoms suggestive of MS could also indicate a wide range of other diseases. The lack of a CSF or serum biomarker to definitively confirm the MS diagnosis adds to the challenge, and neurologists must rely on clinical and radiographic results, plus their own acumen. Not surprisingly, data suggest that misdiagnosis of MS is alarmingly common.

Among 122 surveyed neurologists specializing in MS, 95% said they had assessed one or more patients over the previous year who they strongly believed had been misdiagnosed with MS. Two-thirds of respondents said they had seen six or more such patients. In another study, investigators identified 110 patients from four academic MS centers who MS specialists believed had been misdiagnosed. One-third of these patients had lived with an incorrect MS diagnosis for 10 years or longer, and one-third experienced unnecessary morbidity because of misdiagnosis. Of those 110 patients, 70% had received one or more immunomodulatory therapies for MS, 24% received two such therapies, and 7% received four or five therapies.

Aside from the disease's widely varying presentations and broad differential diagnosis, common causes of MS misdiagnosis include:

- Overreliance on MRI abnormalities meeting DIS criteria in the context of clinical syndromes with nonspecific symptoms or symptoms not typical of MS
- A desire by neurologists to make a presumptive diagnosis of MS and start treatment promptly, rather than pursue additional clinical and radiographic monitoring to confirm the diagnosis over time
- Inappropriate application of diagnostic criteria for neurologic symptoms atypical for a demyelinating attack
- Inappropriate application of diagnostic criteria for a historical episode of neurologic dysfunction without corroborating objective evidence of a lesion

Atypical symptoms for a demyelinating attack contributed to MS misdiagnosis in two-thirds of the 110 patients, suggesting that stricter adherence to MS clinical and radiologic guidelines may reduce the prevalence of misdiagnosis. Although the benefits of prompt MS diagnosis have been well documented, a “watch and wait” approach using serial clinical and radiologic monitoring may be prudent in patients with atypical clinical presentations or with nonspecific MRI abnormalities.
Making an accurate diagnosis of MS remains challenging, but by taking a thorough approach, following evidence-based assessment strategies, and giving due consideration to clinical, paraclinical, laboratory, and imaging findings, neurologists can bridge the gap between where we are with MS diagnosis and where we need to be.
A Current Snapshot of MS Diagnosis: Where We Are and Where We Need to Be Post-Test

Original Release Date: December 31, 2017 • Expiration Date: December 31, 2018 • Estimated Time to Complete Activity: 1.0 hour

To get instant CME/CE credits online, go to https://tinyurl.com/SnapshotMS17. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. If you have any questions or difficulties, please contact: Global Academy for Medical Education at info@globalacademycme.com or (973) 290-8225.

POST-TEST CME/CE QUESTIONS

1. The diagnosis of multiple sclerosis (MS) requires all but which one of the following criteria?
   A. Dissemination in space (DIS)
   B. Dissemination in time (DIT)
   C. Expanded Disability Status Scale (EDSS) score ≥4
   D. Exclusion of alternative diagnoses

2. Multiple symptoms (eg, blurred vision and numbness in the right leg) during an initial demyelinating event consistent with MS precludes the diagnosis of clinically isolated syndrome (CIS):
   A. True
   B. False

3. A patient being evaluated for headache reports no other neurologic symptoms and has an unremarkable neurologic examination. When brain magnetic resonance imaging (MRI) reveals lesions consistent with MS, the most appropriate characterization of that finding would be:
   A. Early-stage MS
   B. MS, with migraine phenotype
   C. CIS
   D. Radiologically isolated syndrome (RIS)

4. What percentage of people ultimately diagnosed with MS first present with CIS—a single demyelinating episode that does not meet the full diagnostic criteria for MS?
   A. Up to 50%
   B. Up to 65%
   C. Up to 75%
   D. Up to 85%

5. Demographic factors shown to contribute to risk for conversion for CIS to MS include:
   A. Age <30 years
   B. Current smoking
   C. Non-Caucasian race
   D. All of the above

6. In patients with CIS, all of the following findings are consistent with elevated risk for a second demyelinating episode and/or conversion to MS except:
   A. Presence of two or more oligoclonal bands restricted to the cerebrospinal fluid (CSF) at the time of the initial demyelinating episode
   B. Presence of oligoclonal bands within 3 months after a CIS episode
   C. Elevated immunoglobulin G index
   D. Presence of ≥50 white blood cell count/mm³ in the CSF sample

7. The Consortium of Multiple Sclerosis Centers (CMSC) 2016 updated guidelines on use of MRI in MS recommend that in patients who have been diagnosed with MS, clinicians should order a brain MRI with gadolinium:
   A. If no prior images are available (eg, for a patient new to your practice)
   B. Before starting or switching a disease-modifying therapy (DMT)
   C. Every 1 to 2 years during DMT to monitor response and assess subclinical disease activity
   D. All of the above

8. A 2016 study of patients who had been misdiagnosed with MS found that common causes of misdiagnosis included all of the following except:
   A. Failure to order spinal cord imaging
   B. Inappropriate attribution of symptoms to demyelinating disease
   C. Overreliance on MRI abnormalities in patients with syndromes atypical for MS to satisfy diagnostic criteria
   D. Reliance on historical symptoms without corroborating objective evidence of a lesion

9. Which statement best summarizes the evidence regarding the use of DMT in CIS?
   A. DMT can reduce the risk of a second event for 2 to 3 years but does not reduce risk of conversion to MS
   B. DMT does not reduce the risk of a second event but does reduce the risk of conversion to MS
   C. DMT can reduce the risk of a second event for 2 to 3 years and the risk of conversion to MS
   D. DMT does not reduce the risk of a second event for 2 to 3 years or the risk of conversion to MS

10. Which of the following statements best describes the treatment armamentarium for primary progressive multiple sclerosis (PPMS)(as of December 2017)?
    A. There are no US Food and Drug Administration (FDA)-approved therapies to treat PPMS
    B. There are several FDA-approved therapies to treat PPMS
    C. There is an FDA-approved intravenously administered therapy to treat PPMS
    D. There is an FDA-approval orally administered therapy to treat PPMS
A Current Snapshot of MS Diagnosis: Where We Are and Where We Need to Be Evaluation Form

Original Release Date: December 31, 2017 • Expiration Date: December 31, 2018 • Estimated Time to Complete Activity: 1.0 hour

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: https://tinyurl.com/SnapshotMS17.

Please indicate your profession/background:

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Student ☐ Resident/Fellow Researcher
☐ Administrator ☐ Other; specify _________________________________________________________________________

LEARNING OBJECTIVES: Having completed this activity, you are able to:

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss the role of radiologically isolated syndromes (RIS) and clinically isolated syndromes (CIS) in diagnosing and monitoring MS</td>
<td>☐ 5</td>
<td>☐ 4</td>
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<tr>
<td>Describe recent updates to established MS disease phenotypes and discuss their application in clinical practice</td>
<td>☐ 5</td>
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</tr>
<tr>
<td>Recognize the importance of early diagnosis and treatment in reducing disability progression</td>
<td>☐ 5</td>
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<td>Identify important risk factors impacting the onset, severity, and progression of MS</td>
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<td>Understand and apply recent discoveries and emerging therapies in the management of patients with MS</td>
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If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.
__________________________________________________________________
__________________________________________________________________

Based on the content of this activity, what will you do differently in the care of your patient(s)/regarding your professional responsibilities? (check one)

☐ Implement a change in my practice/workplace.
☐ Seek additional information on this topic.
☐ Implement a change in my practice/workplace and seek additional information on this topic.
☐ Do nothing differently. Content was not convincing.
☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.
__________________________________________________________________
__________________________________________________________________

OVERALL EVALUATION

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The information presented increased my awareness/understanding of the subject.</td>
<td>☐ 5</td>
<td>☐ 4</td>
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<tr>
<td>The information presented will influence how I practice/do my job.</td>
<td>☐ 5</td>
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<tr>
<td>The information presented will help me improve patient care/my job performance.</td>
<td>☐ 5</td>
<td>☐ 4</td>
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<tr>
<td>The program was educationally sound and scientifically balanced.</td>
<td>☐ 5</td>
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<tr>
<td>Overall, the program met my expectations.</td>
<td>☐ 5</td>
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</tr>
<tr>
<td>I would recommend this program to my colleagues.</td>
<td>☐ 5</td>
<td>☐ 4</td>
<td>☐ 3</td>
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Stephen Krieger, MD
- Demonstrated current knowledge of the topic.
- Was organized in the written materials.

Andrew J. Solomon, MD
- Demonstrated current knowledge of the topic.
- Was organized in the written materials.

What issue(s) are you experiencing in your practice/regarding your professional responsibilities that could be addressed in future programming?
__________________________________________________________________
__________________________________________________________________

Please provide additional comments pertaining to this activity and any suggestions for improvement.
__________________________________________________________________
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The Global Education Group thanks you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.
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