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THE ICEBERG EFFECT

Subclinical Disease Activity in Multiple Sclerosis

Present in all MS stages and phenotypes—but how do we measure and contain it?

Panel Discussion
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The Iceberg Effect: Subclinical Disease Activity in Multiple Sclerosis

Learning Objectives:

- Analyze clinical and diagnostic factors that guide the diagnosis of progressive multiple sclerosis (MS) across the spectrum of disease.
- Discuss the implications for treatment when a diagnosis of primary progressive MS is suspected.
- Describe methods of assessment for subclinical or asymptomatic progression of MS, including new biomarkers and investigative approaches.
- Discuss the role of patient centered outcomes in the assessment of clinical and subclinical progression in MS.

Introduction

In our understanding of multiple sclerosis (MS), we increasingly recognize the insidious "iceberg" effect that characterizes the disease. Relapses, white matter lesions, measurable disability changes, and patient-reported outcomes lie "above the surface" and may be detectable clinically in the neurologic exam or using tools such as MRI. However, lurking below the surface are undetectable lesions, brain atrophy, and other signs of progressive neurologic degeneration (**Figure 1**).[1-4] This subclinical—and often asymptomatic—progression occurs in all stages of MS, even early in the disease process when functional ability may be near-normal. Damage prevention is critical and, if possible, should be considered as part of the overall treatment plan.

Why is recognition of subclinical progression important? Much of MS care focuses on the findings of the neurologic examination and the patient's description of his or her symptoms. While these are important, we need to learn more about what lies below the surface of the iceberg and how these ongoing changes contribute to long-term disability. As the role of subclinical disease progression in MS becomes more evident, many questions remain about how to effectively measure and treat it. This

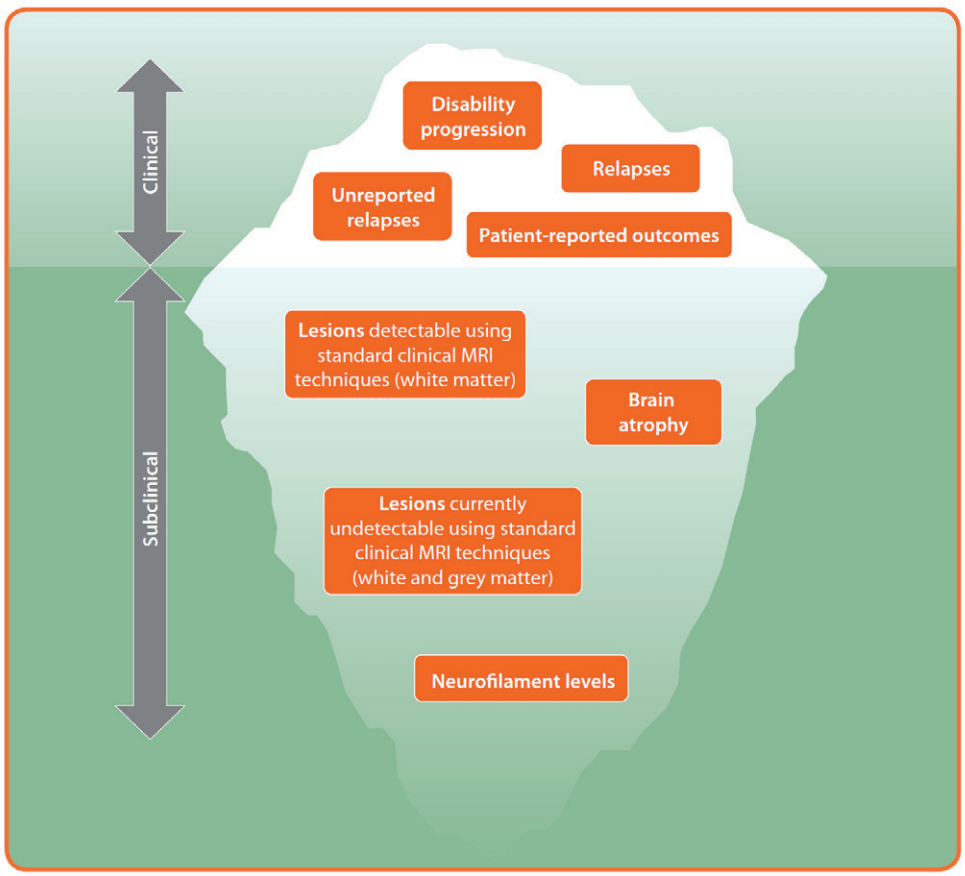

Figure 1. The "Iceberg Effect" of Subclinical Disease Progression[3]

The diagram depicts MS outcomes that are clinically detectable (top) and changes leading to subclinical progression such as brain atrophy that are not easily detectable (bottom). Reprinted from Giovannoni G, et al. *Mult Scler Relat Disord.* 2016 Sep;9 Suppl 1:S5-S48. Open Access.

monograph will cover three critical yet complex questions on the "iceberg" effect:

1. Importance of subclinical activity during early MS
2. Methods for measuring subclinical progression
3. Bridging scientific advances on subclinical progression with "real world" practice

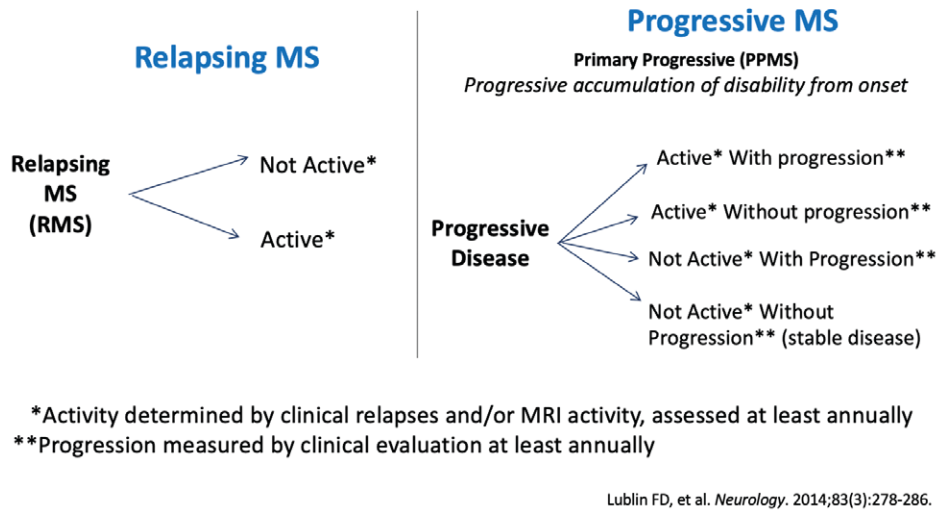

Figure 2. Role of Disease Activity and Progression In Assigning MS Phenotype[9]

How Important is Subclinical Activity Early in the MS Disease Course?

By the time a diagnosis of MS is made, a cascade of inflammatory and neurodegenerative events has already induced changes in the central nervous system (CNS), most of which are thought to be irreversible.[6] The names and definitions of MS phenotypes remain clinical in nature: relapsing MS is defined by relapse activity and progressive disease is defined by clinical progression over time. In the current phenotypic definition (commonly known as the Lublin criteria) whether the disease is active or not active is a key factor (**Figure 2**).[7] However, if one considers silent disease activity, these definitions begin to blur and the process is seen as a continuum with potential for overlapping between the phenotypes.[8,9]

Subclinical progression is one factor that makes it difficult to distinguish between relapsing and progressive MS (PMS). Without the ability to track relapse activity or new MRI lesions, an early diagnosis in a patient suspected of having primary progressive MS (PPMS) can be difficult.[11] For PPMS, the 2017 McDonald diagnostic criteria call for one year of disability progression (retrospectively or prospectively determined) independent of any clinical relapses.[12] However, deciding what constitutes clinical progression and how active the disease course may be are often more nuanced decisions.[9,11,12] Even if measurable disability progression is absent in early disease, the patient is likely to be experiencing subclinical progression.

Similarly, the slowing or cessation of relapse activity in patients with secondary progressive MS (SPMS) make it difficult to gauge how well a disease-modifying therapy (DMT) is working and whether the treatment is still beneficial to the patient in controlling the disease.[13-15]

Evaluating and Measuring Subclinical Progression

There is a substantial unmet need for validated biomarkers to detect subclinical progression in MS.[16,17] Biomarkers can fall into three broad categories:

1. Clinical biomarkers, which include the clinical exam, patient-reported outcomes, and assessment instruments such as the MS Functional Composite (MSFC);
2. Imaging biomarkers, which include standard measurements of white matter lesions as well as brain atrophy, gray matter atrophy, functional MRI, etc.;
3. Biospecimens, including the blood or cerebrospinal fluid markers such as neurofilaments.

Clinical trials showing impact on progression

Current and ongoing clinical trials are evaluating newer biomarkers in all of these categories to determine how MS DMTs affect subclinical progression. The need for additional biomarkers is especially prominent in PMS, due to the relative lack of

outcome measures such as lower relapse rates and reduced accumulation of white matter lesions, relative to RMS. Few clinical trials in PMS have demonstrated that DMTs influence disability progression. This outcome has only recently been demonstrated for the existing DMTs.

The ORATORIO Trial comparing ocrelizumab and placebo in over 700 patients with PPMS showed a favorable impact on the prevention of disability progression among those patients randomized to the active treatment versus placebo.[18] This was the first MS treatment to show a significant effect on disability in patients with PPMS. In a post-hoc analysis from the Phase III open-label extension, this effect was shown to be sustained at 6-year follow-up. Patients who started out on ocrelizumab maintained lower disability levels compared with those who were switched to active treatment during the open-label phase (**Figure 3**).[19] Patients with PPMS who started on active therapy had a 42% reduction in risk for EDSS ≥7.0 (need for wheelchair) compared with patients who were later switched to the active treatment.[19]

Other MS treatments have shown an effect in SPMS, especially in groups who had signs and/or symptoms suggestive of recent active inflammation prior to entry in the study. The Phase 3 EXPAND trial of siponimod versus placebo in SPMS (n=1,645) met its primary endpoint with a 21% reduced risk of 3-month disability progression compared with placebo (*P* = .013).[20] Post hoc analyses of 1,124 patients looked at secondary outcome measures such as cognitive decline, gray matter atrophy, and thalamic atrophy over 5 years and showed a sustained benefit in these measures.[20,21] Those continuing on the active treatment for 5 years had lower risk of 3-month and 6-month confirmed disability progression.

The Phase 2 Sprint-MS Trial evaluated the investigational phosphodiesterase (PDE) inhibitor ibudilast versus placebo in 255 patients, about half with PPMS and half with SPMS for 96 weeks. There was a highly significant 48% decrease in the rate of whole brain atrophy among patients randomized to ibudilast.[22] The rate of change in the brain parenchymal fraction was –0.0010 per year with ibudilast and –0.0019 per year with placebo (difference, 0.0009; 95% confidence interval, 0.00004 to 0.0017; P=0.04), representing approximately 2.5 ml less brain-tissue loss with ibudilast. A larger Phase 3 study is under way in an effort to replicate these findings.[22]

Brain atrophy as a measure of progression

Brain atrophy represents the net effect of the destructive pathogenic processes in MS. Neurons occupy almost half of brain tissue volume. Myelin makes up about 24% while glial and other cells make up about 30%.[6] People with MS lose brain volume at a faster rate than those without MS: a loss of about 0.5% to 1.35% year in untreated MS, versus 0.1% to 0.5% year with normal aging.[5] Accelerated brain atrophy starts early in the course of MS, thus people who only recently developed symptoms may exhibit

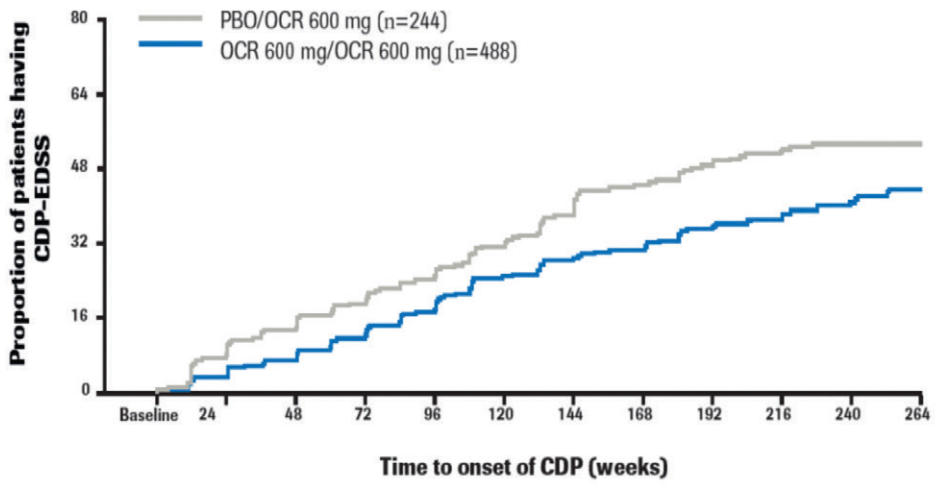

Figure 3. Time to Onset of Clinical Disease Progression (CDP) in Patients With PPMS[19]

Active treatment at start of trial (blue line, n=488) vs placebo switched to active treatment (delayed start; gray line, n=244)

Source: Wolinsky JS, et al. Sustained and durable reduction in confirmed disability progression in patients with primary progressive multiple sclerosis receiving ocrelizumab: findings from the Phase III ORATORIO study extended control period. Presented at: ECTRIMS 2019, Stockholm, Abstract 159.

have a significant degree of brain volume loss. Brain atrophy may be subclinical initially, because loss of function is modulated to some degree by the individual's neurologic reserve, CNS repair mechanisms, and neuroplasticity.[1] At some point, the effects of atrophy overcome this neurologic reserve, resulting in a steep progression over time when the patient is no longer able to compensate for the damage.

Brain atrophy is useful data to compare across large cohorts of patients, but is not easily measured or monitored clinically in individual patients. Brain atrophy is increasingly used as a marker of disease progression over time, with new MRI techniques able to identify lesions in gray matter and deep brain structures. A barrier to applying these findings to clinical practice is that we don't fully understand the impact of brain volume changes. Why does one person with significant brain atrophy acquire functional impairment earlier than a different person with similar markers?

Grey matter atrophy in MS

Although MS has traditionally been considered a predominantly white-matter disease, more attention is being paid to disease progression in certain regions of the brain's gray matter.[23] Gray matter is made up primarily of neurons, and holds less myelin relative to white matter.[24] Gray matter atrophy is common in MS, but its relationship and weight relative to white matter pathology are largely unknown.[25] Research has suggested that there may be unrecognized phenotypes, such as myelocortical MS, that affect primarily gray matter.[26] Advanced forms of imaging are beginning to shed some light on gray matter deterioration.[27] In addition, some newer and investigational MS DMTs have been shown to affect gray matter atrophy in MS.[28]

Grey matter atrophy is present in early stages of MS.[24] Atrophy in the cerebellum and caudate putamen have been associated with early atrophy in relapsing MS and with later atrophy in PMS. In addition, there are strong correlations between gray matter atrophy and disease duration and disability accumulation in MS. A study by Haider and colleagues illustrated the degree to which gray matter atrophy spreads to involve more brain regions over time. Gray matter involvement was implicated in both relapsing- and progressive-onset disease, with hypothalamic volume loss particularly prominent among patients with PMS (**Figure 4**).[29]

Using advanced imaging techniques, measures of gray matter atrophy could serve as a surrogate biomarker in studies evaluating potential neuroprotective agents. Volume changes in regions of the gray matter such as the thalamus correlate with MS dis-

PANEL DISCUSSION

How do we evaluate progressive disease in the absence of relapses?

Ed Fox: It's important to distinguish between the terminology for "worsening MS" versus "active MS." Active may mean that the patient has had relapses or gadolinium-enhancing lesions on MRI. To evaluate progressive disease, we have to show changes that are not easily explained by relapse activity. I'm hopeful that in the future we will have biomarkers other than MRI to help us determine which patients have an active inflammatory process. By worsening MS, we mean someone who goes from EDSS 3.5 to 5.5. That's very clear-cut worsening—certainly beyond what we would consider to be adequate management of the disease. We have to think of worsening MS as treatment failure, and determine how we are going to manage it.

What is the impact of subclinical progression early in the disease course?

Scott Newsome: This is probably one of the more difficult questions we face on a daily basis. When we treat and follow patients with MS, we want to figure out how we can do better for them, and not look back and wonder if we should have done something differently 5 years ago or even just a few years ago. We know that there is definitely a link between subclinical progression and future disability, in both relapsing-onset MS and progressive-onset MS. It's going to be crucial that we find or develop biomarkers that can identify subclinical progression, especially as it relates to investigating future therapies for neuroprotection and neurorepair.

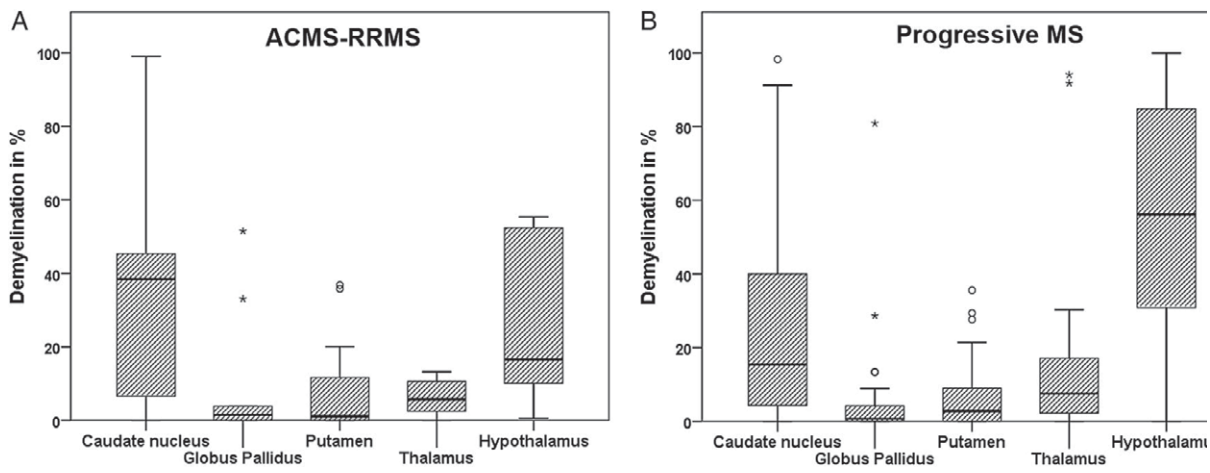

Figure 4. Gray Matter Atrophy in MS[29]

Systematic study in MS deep grey matter from a total sample of 75 MS autopsy patients and 12 controls. Hypothalamic grey matter atrophy is more prevalent in patients with progressive MS. Source: Haider L, et al. *J Neurol Neurosurg Psychiatry.* 2014;85(12):1386-1395. Open Access.

ability measures over time. Thalamic atrophy is a reliable measure that has been seen from the beginning of symptom onset, even in patients presenting with clinically isolated syndrome or radiologically isolated syndrome. A study by Azevedo et al compared rates of thalamic volume decline among people with RMS or progressive-onset MS (n=520) and healthy controls (n=81).[30] As shown in **Figure 5**, thalamic atrophy is present the early stages of MS, with a significantly steeper curve relative to people with no neurologic disease.[30]

Neurofilaments as prognostic markers in progressive MS

Better biomarkers that accurately reflect disease activity and progression in MS would be invaluable for helping to guide treatment decisions and monitor the effects of DMTs. Neurofilaments are emerging as a promising biomarker for MS, due to their correlation with severity and progression of the disease.[31-36] Neurofilaments are polypeptide fibers that are specific to the neurons and especially abundant in the axons. Neurofila-

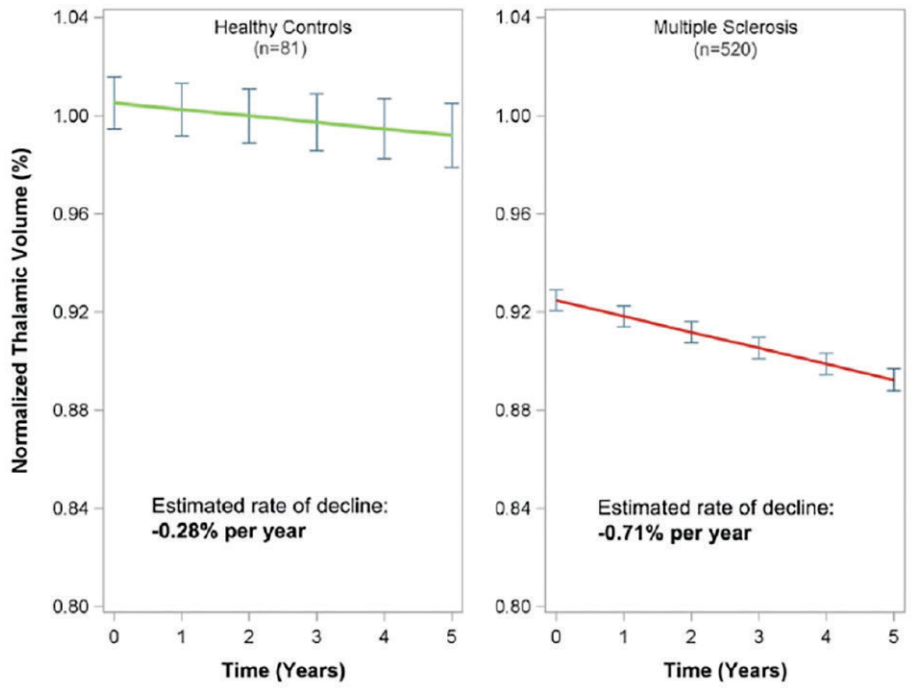

Figure 5. Thalamic Atrophy in MS[30]

Study of thalamic atrophy comparing healthy controls and persons with MS shows significantly greater thalamic volume loss among persons with MS. Source: Azevedo CJ, et al. *Ann Neurol.* 2018;83(2):223-234. Reprinted with permission.

ments play a role in early cell development for radial growth as well as in maintaining the diameter of the axon.[37-39] During neurodegeneration, however, light chain (NFL) and heavy chain (NFH) neurofilaments are released from CNS parenchymal cells and into the cerebrospinal fluid (CSF) and serum.[40] Until recently, neurofilaments could be measured only in CSF, but using newer, highly sensitive assays they can now be reliably quantified in the blood.[41,42]

NFL is the neurofilament protein that appears to be the most promising biomarker of neurodegeneration. Increased NFL levels have been associated with a number of outcomes in MS, including:[36,43]

- Early conversion from clinically isolated syndrome to definite MS
- MS relapses
- Appearance of contrast-enhancing lesions
- Change from onset of MS versus long-term follow up
- Assessing the efficacy of DMTs

Elevated neurofilament levels in serum are indicative of neuronal breakdown, but they are not specific to MS. Elevated NFL levels have been observed in other neurologic degenerative conditions such as HIV-associated dementia and amyotrophic lateral sclerosis (**Figure 6**).[35,44,45] More information is needed about variations in NFL levels among individuals, the potential effects of aging and comorbidities, and how to best study factors specific to MS.[17]

Relevance of myelocortical MS in progression

Myelocortical MS, a novel phenotype that suggests evidence of neurodegeneration without prior evidence of inflammation, was identified in 2018 by Trapp et al.[26] While examining pathologic samples of brain tissue from people with MS, the researchers found that white matter demyelination was absent in 12% of individuals, despite a confirmed MS diagnosis. These samples were compared with more typical MS samples and brain tissue from controls who did not have neurologic disease. Myelocortical MS was characterized by a significant decrease in the quantity and density of neurons in the cerebral cortex. Axonal death appeared to occur in the absence of cerebral white matter demyelination, although there was spinal cord demyelination. These findings were the first to show pathological evidence that neuronal degeneration in MS can occur without brain white matter demyelination. This suggests that neurodegeneration and demyelination may be independent events. These findings help put into context how continued neurodegeneration in MS appears to occur by a separate mechanism independent of inflammation.[26] So far, there are no proven theories as to what causes these different patterns of neurodegeneration. The next stages of research will involve the use of advanced imaging techniques in an attempt to identify myelocortical patterns of damage in living patients with MS. Therapeutic strategies could potentially be developed to protect neurons with myelinated axons.

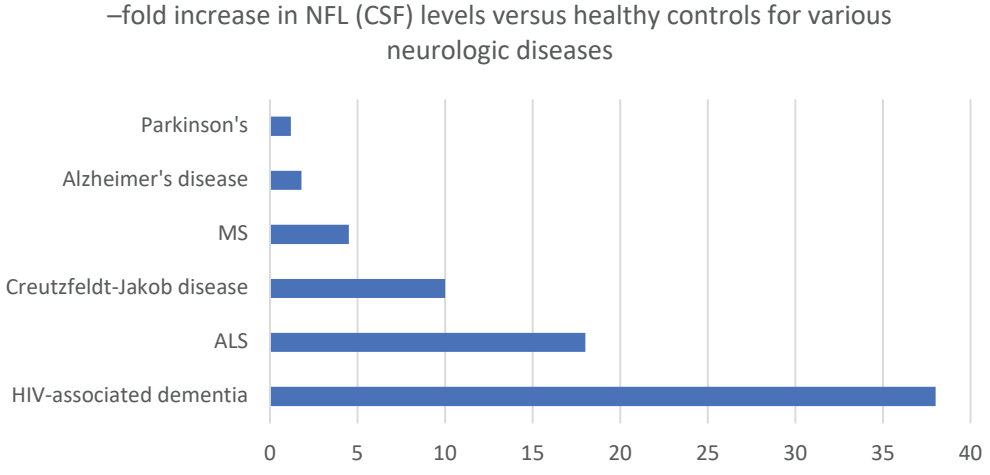

Figure 6. CSF Neurofilament Light Chain Levels in Neurologic Disease[31]

ALS=amyotrophic lateral sclerosis; CJD: Creutzfeldt-Jakob disease; MS=multiple sclerosis; MSA=multiple system atrophy. Data adapted from: Gaetani L, et al. *J Neurol Neurosurg Psychiatry.* 2019;90:870-881.

Other biomarkers of interest

A number of other promising biomarkers could be useful in trying to identify the subclinical progression in MS:[46-49]

- Glial fibrillary acidic protein (GFAP) is a filament that forms the astrocyte cytoskeleton. The astrocytes play a role inducing the

PANEL DISCUSSION

Is it possible to use brain atrophy measurements to determine subclinical progression in an individual patient with MS?

Sarah Morrow: I think it can be. You need a neuroradiologist on board who is willing to follow it. However, with atrophy measurements, it's like closing the barn door after the horse is already gone. By the time we are able to see significant atrophy, it is most likely irreversible. Despite scientific advances, it is unrealistic that the next generation of therapies is going to be capable of completely regenerating CNS tissues that have been damaged by inflammation and astrocyte overgrowth and the scarring present in these chronic lesions. So measuring brain atrophy is like everything else we do in MS; we need to have serial measurements to detect and report on the atrophy prior to it becoming so devastating that no intervention can make an impact.

Scott Newsome: Once we get into the realm of obtaining automated evaluations or measurements, this may help speed up the time for looking at atrophy, especially in regions like the thalamus. The biggest challenge that I have right now is, even if I have a measure of whole-brain atrophy, I don't know what to do with that information right now. I can't make a treatment decision based on one time point. Even if we see a change in the rate of atrophy that is greater than expected, do we know whether the treatments we have today actually make a clinically relevant impact on brain atrophy?

Ed Fox: At this time, brain atrophy may be helpful in aggregate data in large numbers to compare different groups, but it is too variable on an individual level. It can be influenced by the type of equipment and software being used, and also by patient-specific factors such as hydration or time of day. We may find that there is too much individual variability for whole brain atrophy to be used as a measure of whether a medication is working to slow subclinical progression.

How far are we away from using neurofilament biomarkers in clinical practice for our patients with MS?

Sarah Morrow: Part of the problem is that we still don't know what constitutes a normal level. It may be like vitamin D, where it's not the same from one lab to the next. Or that other factors influence NFL levels outside of just MS. There could be many different companies licensing this test, and there may be varying levels of normal ranges. So that's part of the holdup. Can the test be done? Absolutely. They are being done routinely, but they're not licensed because we have no standards right now.

Scott Newsome: I agree. Probably within the next couple of years, we will have the ability to obtain NFL levels commercially. That doesn't necessarily mean we will be in a position to make treatment decisions based solely on NFL. We have to look at the whole picture: relapses, MRI activity, bedside exam, and maybe NFL if available. It's exciting that in a short time we may have a biomarker that measures degeneration behind the scenes. This may actually provide a hint about subclinical progression that we can't measure right now.

What can we learn from other neurologic conditions about the significance of NFL?

Ed Fox: At AAN 2019 there was an overflow room with six screens showing different slides. All these trials had a different outlook on how it could be used clinically. In patients with stroke, a small study looked at NFL levels during hospitalization and showed that those with rapidly increasing levels had worse outcomes even after rehabilitation. In Alzheimer's, this biomarker is being used to speed up research in order to screen a lot of different medications over a short time period. When we go back in clinical trial data that have gone on 10 years, the people with the lowest NFL levels initially had better outcomes. But more importantly, this biomarker can be used to show that DMT can have a very rapid effect on NFL levels and normalize them.

death of neurons at oligodendrocytes, the myelin-producing cells of the CNS. GFAP can be measured in CSF and potentially in serum.

- Chitinase-3-like protein 1 is a non-glial cell-related protein in activated macrophages. High levels of this marker have been associated with early MS progression.
- Glutamate, one of the most prevalent neurotransmitters in the brain, may be another potential biomarker in MS. In the normal CNS, glutamate acts as an excitatory neurotransmitter essential for neuronal signaling. However, excess glutamate activity can be toxic, causing apoptosis in neurons and oligodendrocytes.[50] Because glutamate is released in large quantities by activated immune cells, it is suspected to have a role in MS pathology.
- N-acetylaspartate (NAA) is a marker associated with neuronal health and viability. Studies suggest that it may play a role in neuronal energy metabolism.[51] As with glutamate, NAA concentration can be estimated in vivo by using 1H-MR spectroscopy. Chronic reduction in NAA and high levels of glutamate have been shown to precede brain atrophy.[52]
- Biomarkers derived from optical coherence tomography (OCT) include measures of the retinal nerve fiber layer (RNFL) and ganglion cell layer with inner plexiform layer (GCIP). Studies show a strong correlation with both these biomarkers in differentiating MS subtypes—with or without optic neuritis—as well as subclinical thinning that occurs within these layers. OCT is being utilized in clinical trial programs, looking at novel remyelination agents.

Bridging Scientific Advances in Subclinical Progression with "Real World" MS Patient Care

As scientific advances continue to accumulate rapidly in many areas of MS, translating research findings to real world practice is always a challenge. Studies in MS need to become more patient-oriented in order to address the issues that truly matter to the person with MS. This philosophy forms the basis of patient-centered outcome measures, or PROMs. PROMs are defined as "outcomes that capture effects of disease and treatment on everyday life from the patient's perspective, without intervention from others."[53] This issue is receiving attention and funding from international healthcare and regulatory bodies, but in order to be worthwhile the research findings must also translate into patient-centered care.

The Patient-Centered Outcomes Research Institute (PCORI) is a government-sponsored program that aims to incorporate meaningful patient outcomes into research design. Three studies with a combina-

Table 1. PCORI Studies Measuring Outcomes Related to MS Subclinical Progression[57]

Trial Name	Primary Center Study Design
DELIVER MS "Determining the Effectiveness of Early Intensive versus Escalation Approaches for the Treatment of Relapsing-Remitting Multiple Sclerosis"	**Cleveland Clinic** 800 patients with RRMS. Compare early intensive therapy vs escalation, 36 months. Primary outcome: brain volume loss
TREAT MS "TRaditional versus Early Aggressive Therapy for Multiple Sclerosis"	**Johns Hopkins** 900 patients w RRMS (~45 sites) stratified by high-risk and low-risk for disability. Compare early-aggressive vs traditional therapy in both groups (approx 60 months). Primary outcome: disability progression (EDSS plus).
DISCO-MS "Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis"	**University of Colorado Denver** 260 patients age ≥55 with no relapses (5 yrs) or new lesions (3 yrs). Compare DMT vs no DMT for 2 years.

Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for RRMS (DELIVER-MS). ClinicalTrials.gov. NCT03535298; Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS). ClinicalTrials.gov. NCT03500328; Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS) (DISCOMS). ClinicalTrials.gov. NCT03073603.

tion of approximately 2,000 patients with MS are looking at long-term relevant to subclinical disease (**Table 1**).[54-57] The DELIVER MS and TREAT MS trials are collectively enrolling well over 1,000 treatment-naive patients with MS to shed light on the "induction versus escalation" debate. Is it better to initiate therapy with an aggressive or intensive approach and then ease off, or to start conservatively for most patients and then advance as needed? The DELIVER MS trial based at Cleveland Clinic is comparing early intensive therapy versus escalation (starting with an injectable or oral medication and going to an IV therapy due to breakthrough disease activity) over 36 months, with a primary outcome of reduced brain volume loss. The TREAT MS Trial at Johns Hopkins is comparing whether early aggressive treatment versus traditional therapy, has a differential impact on long-term disability. Patients are stratified prior to randomization into groups according to risk (high or low) for disability progression. The primary outcome is disability progression (EDSS plus) over 60 months.

Table 2. "No Evidence of Disease Activity" (NEDA) Definitions[59]

NEDA 3	NEDA 4	Future Criteria for NEDA 5 or 6?
• No sustained disability after 3 months	• No sustained disability after 3 months	• Neurofilament light chain (NFL)
• No relapses	• No relapses	• Other biomarkers for microscopic neurodegeneration
• No MRI activity (new/enlarging T2 or Gd+ lesions)	• No MRI activity	• Advanced imaging
	• No added brain volume loss (>0.4% annual)	

Data adapted from: Lu G, et al. *Mult Scler Relat Disord.* 2018;20:231-238.

In patients with SPMS, a prevailing question is whether their DMT should be discontinued when relapse activity and change MRI white matter lesions have slowed. If the DMT may be helping to prevent subclinical progression to some degree, is it better to err on the side of caution? Another PCORI trial is in progress to help answer this question. DISCO-MS is a 2-year trial with 300 subjects age 55 years and over.[58] At enrollment, subjects exhibited no MS disease activity for 5 years (no clinical attacks or new MRI lesions) but did have worsening disability. Trial participants were randomly assigned to two groups: a group who remained on their current DMT and a group who discontinued therapy. This study will compare changes in disease progression and relapse activity in both populations.

Is "NEDA" achievable?

Most patients with MS want to know, "How do I know if my DMT is working?" This is an especially difficult question when considering subclinical progression. "No evidence of disease activity" or NEDA may seem like an ideal goal, but it has been called a poor measure of therapeutic response, in part because it fails to distinguish between clinically measurable changes and subclinical activity.[59] Current definitions of NEDA are shown in **Table 2**. There is debate about how "no disease activity," should be defined, and whether absence of these markers is sufficient to signify "remission" or control of MS. While NEDA can be a useful outcome measure in research, trying to achieve NEDA in clinical practice may be unrealistic, and may result in excessive switching between agents.[60,61] A more realistic view might be MEDA or "minimal evidence of disease activity," which reinforces treatment goals (**Table 3**)[5] while acknowledging a higher standard for controlling the disease.

Treatment goals include understanding the patient's priorities. With an initial appointment, it is helpful to learn about the person's perceptions and if they know other people who have MS. For example, if the person had a relative who died at an early age from MS, their fear of the disease is often tremendous. On the other hand, they might know an individual with very minimal disease or who has used alternative treatments only. These early perceptions can strongly influence the conversation.

Most available evidence suggests that patients who receive earlier intervention with a DMT have long-term advantages in terms of delays in reaching certain disability milestones, such as transitioning to certain EDSS markers or to SPMS. Even those patients who get a late start—due to delayed diagnosis, inadequate treatment or nonadherence, or in a delayed treatment arm of a clinical trial, do not reach the level of disability seen with untreated MS.

Table 3. Treatment Goals and Principles of Shared Decision Making[5]

Treatment Goals

- Treat early: what is lost is hard to regain
  - Treatment initiation criteria may lag behind diagnostic criteria

o Initial treatment options may be restricted

- Goals of treatment
  - Maximize neurologic reserve
  - Maximize cognitive and physical functioning
  - Reduce disease activity
- Regular monitoring (clinical and subclinical) is central to managing MS
  - Monitoring can improve adherence to DMTs
  - Increased engagement is more likely with regular monitoring

Shared Decision making

Shared decision making refers to proactive collaboration between person with MS and healthcare team. DMT decisions should be shared and well informed:

- Align prescribing guidelines with latest accepted diagnostic criteria
  - Start treatment/support at time of diagnosis
- Take time to educate patients about disease-management strategies
  - Benefits of early treatment
  - Likely consequences of inadequate, suboptimal, or discontinued treatment
- Full range of therapies should be available to patients with relapsing MS, regardless of treatment history
  - Speed up adoption of most appropriate strategy

Among communication barriers, patients may not report breakthrough of the disease or understand the difference between daily MS symptoms and progression. It can be difficult for the patient to discern the difference between loss of strength due to deconditioning versus the disease process itself. There is also wide interpersonal variation in how patients might perceive and define fatigue, relapse symptoms, cognition, and other experiences associated with MS. The following principles apply to patient-centered care and communication:[62]

- Communication, understanding of disease is key in improving patient satisfaction, adherence, and outcomes;
- MS clinicians should be able to speak the patient's language, and help them to understand the language used in MS care;
- Barriers to these discussions include: stigma associated with progression and communication challenges;
- Patients' communication preferences vary widely. Health care professionals should personalize communication when possible;
- Communicate in clear and understandable language, acknowledge and discuss the role "invisible" symptoms play in patients' experience, and in the understanding of disease progression.

References

1. Krieger SC, Sumowski J. New Insights into Multiple Sclerosis Clinical Course from the Topographical Model and Functional Reserve. *Neurol Clin.* 2018;36(1):13-25.
2. Krieger SC, Cook K, De Nino S, et al. The topographical model of multiple sclerosis: A dynamic visualization of disease course. *Neurol Neuroimmunol Neuroinflamm.* 2016;3(5):e279.
3. Giovannoni G, Tomic D, Bright JR, et al. "No evident disease activity": The use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler.* 2017;23(9):1179-1187.
4. Giovannoni G, Turner B, Gnanapavan S, et al. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? *Mult Scler Relat Disord.* 2015;4(4):329-333.
5. Giovannoni G, Butzkueven H, Dhib-Jalbut S, et al. Brain health: time matters in multiple sclerosis. *Mult Scler Relat Disord.* 2016;9:S5-48.
6. Andravizou A, Dardiotis E, Artemiadis A, et al. Brain atrophy in multiple sclerosis: mechanisms, clinical relevance and treatment options. *Auto Immun Highlights.* 2019;10(1):7.
7. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014;83(3):278-286.
8. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. *Curr Opin Neurol.* 2018;31(6):752-759.
9. Kantarci OH. Phases and Phenotypes of Multiple Sclerosis. *Continuum (Minneap Minn).* 2019;25(3):636-654.
10. Havrdova E, Arnold DL, Bar-Or A, et al. No evidence of disease activity (NEDA) analysis by epochs in patients with relapsing multiple sclerosis treated with ocrelizumab vs interferon beta-1a. *Mult Scler J Exp Transl Clin.* 2018;4(1):2055217318760642.
11. Ontaneda D, Fox RJ, Chataway J. Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives. *Lancet Neurol.* 2015;14(2):208-223.
12. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162-173.
13. Hua LH, Fan TH, Conway D, et al. Discontinuation of disease-modifying therapy in patients with multiple sclerosis over age 60. *Mult Scler.* 2018:1352458518765656.
14. Tobin WO, Weinshenker BG. Disease-modifying therapies can be safely discontinued in an individual with stable relapsing-remitting MS - NO. *Mult Scler.* 2017;23(9):1190-1192.

15. Kister I, Spelman T, Alroughani R, et al. Discontinuing disease-modifying therapy in MS after a prolonged relapse-free period: a propensity score-matched study. *J Neurol Neurosurg Psychiatry.* 2016;87(10):1133-1137.
16. Rotstein D, Montalban X. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. *Nat Rev Neurol.* 2019;15(5):287-300.
17. Varhaug KN, Torkildsen Ø, Myhr KM, et al. Neurofilament Light Chain as a Biomarker in Multiple Sclerosis. *Front Neurol.* 2019;10:338.
18. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med.* 2017;376(3):209-220.
19. Wolinsky JS, Montalban X, Hauser SL, et al. Sustained and durable reduction in confirmed disability progression in patients with primary progressive multiple sclerosis receiving ocrelizumab: findings from the Phase III ORATORIO study extended control period. Presented at: ECTRIMS 2019, Stockholm, Abstract 159.
20. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 2018;391(10127):1263-1273.
21. Kappos L, et al. Long-term Efficacy and Safety of Siponimod in Patients with SPMS: EXPAND Extension Analysis up to 5 Years. *Neurology*. 2020; 94 (15 Suppl): 4128.
22. Fox RJ, Coffey CS, Conwit R, et al. Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis. *N Engl J Med.* 2018;379(9):846-855.
23. Eshaghi A, Marinescu RV, Young AL, et al. Progression of regional grey matter atrophy in multiple sclerosis. *Brain.* 2018;141(6):1665-1677.
24. Chard DT, Griffin CM, Parker GJ, et al. Brain atrophy in clinically early relapsing-remitting multiple sclerosis. *Brain.* 2002;125(Pt 2):327-337.
25. Steenwijk MD, Daams M, Pouwels PJ, et al. Unraveling the relationship between regional gray matter atrophy and pathology in connected white matter tracts in long-standing multiple sclerosis. *Hum Brain Mapp.* 2015;36(5):1796-1807.
26. Trapp BD, Vignos M, Dudman J, et al. Cortical neuronal densities and cerebral white matter demyelination in multiple sclerosis: a retrospective study. *Lancet Neurol.* 2018;17(10):870-884.
27. Calabrese M, Castellaro M. Cortical Gray Matter MR Imaging in Multiple Sclerosis. *Neuroimaging Clin N Am.* 2017;27(2):301-312.
28. Rasche L, Paul F. Ozanimod for the treatment of relapsing remitting multiple sclerosis. *Expert Opin Pharmacother.* 2018:1-14.
29. Haider L, Simeonidou C, Steinberger G, et al. Multiple sclerosis deep grey matter: the relation between demyelination, neurodegeneration, inflammation and iron. *J Neurol Neurosurg Psychiatry.* 2014;85(12):1386-1395.
30. Azevedo CJ, Cen SY, Khadka S, et al. Thalamic atrophy in multiple sclerosis: A magnetic resonance imaging marker of neurodegeneration throughout disease. *Ann Neurol.* 2018;83(2):223-234.
31. Gaetani L, Blennow K, Calabresi P, et al. Neurofilament light chain as a biomarker in neurological disorders. *J Neurol Neurosurg Psychiatry.* 2019;90(8):870-881.
32. Gaetani L, Eusebi P, Mancini A, et al. Cerebrospinal fluid neurofilament light chain predicts disease activity after the first demyelinating event suggestive of multiple sclerosis. *Mult Scler Relat Disord.* 2019;35:228-232.
33. Yang Z, Zhu T, Mondello S, et al. Serum-Based Phospho-Neurofilament-Heavy Protein as Theranostic Biomarker in Three Models of Traumatic Brain Injury: An Operation Brain Trauma Therapy Study. *J Neurotrauma.* 2019;36(2):348-359.
34. Thouvenot E, Demattei C, Lehmann S, et al. Serum neurofilament light chain at time of diagnosis is an independent prognostic factor of survival in amyotrophic lateral sclerosis. *Eur J Neurol.* 2019.
35. Kuhle J, Plavina T, Barro C, et al. Neurofilament light levels are associated with long-term outcomes in multiple sclerosis. *Mult Scler.* 2019:1352458519885613.
36. Novakova L, Axelsson M, Khademi M, et al. Cerebrospinal fluid biomarkers as a measure of disease activity and treatment efficacy in relapsing-remitting multiple sclerosis. *J Neurochem.* 2017;141(2):296-304.
37. Eyer J, Peterson A. Neurofilament-deficient axons and perikaryal aggregates in viable transgenic mice expressing a neurofilament-beta-galactosidase fusion protein. *Neuron.* 1994;12(2):389-405.
38. Yum SW, Zhang J, Mo K, et al. A novel recessive Nefl mutation causes a severe, early-onset axonal neuropathy. *Ann Neurol.* 2009;66(6):759-770.
39. Zhu Q, Couillard-Despres S, Julien JP. Delayed maturation of regenerating myelinated axons in mice lacking neurofilaments. *Exp Neurol.* 1997;148(1):299-316.
40. Olsson B, Portelius E, Cullen NC, et al. Association of Cerebrospinal Fluid Neurofilament Light Protein Levels With Cognition in Patients With Dementia, Motor Neuron Disease, and Movement Disorders. *JAMA Neurol.* 2019;76(3):318-325.
41. Kuhle J, Barro C, Andreasson U, et al. Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and Simoa. *Clin Chem Lab Med.* 2016;54(10):1655-1661.
42. Gisslen M, Price RW, Andreasson U, et al. Plasma Concentration of the Neurofilament Light Protein (NFL) is a Biomarker of CNS Injury in HIV Infection: A Cross-Sectional Study. *EBioMedicine.* 2016;3:135-140.
43. COMparison Between All immunoTherapies for Multiple Sclerosis. (COMBAT-MS). NCT03193866.
44. Olsson B, Portelius E, Cullen NC, et al. Association of Cerebrospinal Fluid Neurofilament Light Protein Levels With Cognition in Patients With Dementia, Motor Neuron Disease, and Movement Disorders. *JAMA Neurol.* 2019;76(3):318-325.
45. Yuan A, Rao MV, Veeranna, et al. Neurofilaments at a glance. *J Cell Sci.* 2012;125(Pt 14):3257-3263.
46. Van Schependom J, Guldolf K, D'Hooghe M B, et al. Detecting neurodegenerative pathology in multiple sclerosis before irreversible brain tissue loss sets in. *Transl Neurodegener.* 2019;8:37.
47. Gil-Perotin S, Castillo-Villalba J, Cubas-Nunez L, et al. Combined Cerebrospinal Fluid Neurofilament Light Chain Protein and Chitinase-3 Like-1 Levels in Defining Disease Course and Prognosis in Multiple Sclerosis. *Front Neurol.* 2019;10:1008.
48. Abdelhak A, Huss A, Kassubek J, et al. Serum GFAP as a biomarker for disease severity in multiple sclerosis. *Sci Rep.* 2018;8(1):14798.
49. Cortese R, Collorone S, Ciccarelli O, et al. Advances in brain imaging in multiple sclerosis. *Ther Adv Neurol Disord.* 2019;12:1756286419859722.
50. Pitt D, Werner P, Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. *Nat Med.* 2000;6(1):67-70.
51. Criste GA, Trapp BD. N-acetyl-L-aspartate in multiple sclerosis. *Adv Exp Med Biol.* 2006;576:199-214; discussion 361-193.
52. Lee JY, Taghian K, Petratos S. Axonal degeneration in multiple sclerosis: can we predict and prevent permanent disability? *Acta Neuropathol Commun.* 2014;2:97.
53. Finlayson, M. PROMS: Supporting patient-centred care. Presented at ECTRIMS 2019. Stockholm, Sept 12, 2019. Available at: https://onlinelibrary.ectrims-congress.eu/ectrims/2019/stockholm/279485/marcia.finlayson.proms.supporting.patient-centred.care.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dfinlayson.
54. World Health Organization (WHO). Effective Public Education. Available at: http://archives.who.int/PRDUC2004/RDUCD/Session_Guides/effective_public_education.htm.
55. National Health Information Center (NHIC). Available at: https://health.gov/nhic/.
56. Office of Disease Prevention and Health Promotion. HealthyPeople.gov. https://www.healthypeople.gov/.
57. Patient-Centered Outcomes Research Institute (PCORI). Multiple Sclerosis Topic Spotlight. Updated August 2019. Available at: https://www.pcori.org/topics/multiple-sclerosis.
58. ClinicalTrials.gov. Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS) (DISCOMS). NCT03073603.
59. Lu G, Beadnall HN, Barton J, et al. The evolution of "No Evidence of Disease Activity" in multiple sclerosis. *Mult Scler Relat Disord.* 2018;20:231-238.
60. Rotstein DL, Healy BC, Malik MT, et al. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol.* 2015;72(2):152-158.
61. Freedman MS. Are we in need of NEDA? *Mult Scler.* 2016;22(1):5-6.
62. Vermersch P, Shanahan J, Langdon D, et al. Knowledge Is Power, but Is Ignorance Bliss? Optimising Conversations About Disease Progression in Multiple Sclerosis. *Neurol Ther.* 2020;9(1):1-10.

The Iceberg Effect: Subclinical Disease Activity in Multiple Sclerosis

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PLEASE SELECT THE BEST ANSWER

1. A 38-year-old woman with progressive MS presents for follow-up. Since her last evaluation six months ago, she has had one relapse. Her Expanded Disability Status Scale (EDSS) score is stable. MRI shows one new contrast enhancing lesion. How would you characterize her MS at this time?

A. Active with progression
B. Active without progression
C. Not active with progression
D. Not active without progression

2. A patient in your practice has increasing MS symptoms and over the course of 1 year her EDSS score has gone from 3.5 to 5.5. The appropriate terminology for this change in disease course is:

A. Progressive MS
B. Transitional MS
C. Active MS
D. Worsening MS

3. In "no evidence of disease activity" or NEDA, what outcome measure is added toNEDA-3 to constitute the basis for NEDA-4?

A. No activity on magnetic resonance spectroscopy
B. No additional brain volume loss
C. No detectable serum neurofilament
D. No neurological deficit on clinical exam

4. What is the potential benefit for measuring neurofilament light chain (NFL) levels in patients with MS?

A. NFL is a marker of inflammation that correlates with MRI
B. NFL is a blood biomarker that may serve as an early detector of MS relapse
C. NFL is found only in cerebrospinal fluid (CSF) and can identify spinal involvement in MS
D. NFL in blood or CSF is a marker of axonal breakdown correlating with disability and progression.

5. Which of the following approaches to disease-modifying therapy (DMT) is most likely to result in the best long-term outcome for a patient with MS?

A. Allowing the patient to decide when to begin treatment
B. Beginning DMT early in the disease course
C. Delaying DMT until disability (shown by a sustained increase of 1 point or more in EDSS score)
D. Delaying DMT until the second clinical relapse

6. Which of the following statements is accurate regarding gray matter atrophy in multiple sclerosis:

A. Is present in advanced disease and indicative of severe brain volume loss
B. Has primarily been measured in post-mortem tissue samples from people with MS
C. Can be detected at all stages of MS and correlates with disability and disease duration
D. Present mainly in patients who have primary progressive or secondary progressive MS

Evaluation Form

The Iceberg Effect: Subclinical Disease Activity in Multiple Sclerosis

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent to Which Program Activities Met the Identified Objectives: *After completing this activity, participants should be better able to:*

1) Analyze clinical and diagnostic factors that guide the diagnosis of progressive multiple sclerosis (MS) across the spectrum of disease. 5 4 3 2 1
2) Discuss the implications for treatment when a diagnosis of primary progressive MS is suspected. 5 4 3 2 1
3) Describe methods of assessment for subclinical or asymptomatic progression of MS, including new biomarkers and investigative approaches. 5 4 3 2 1
4) Discuss the role of patient centered outcomes in the assessment of clinical and subclinical progression in MS. 5 4 3 2 1

To what extent was the content:

5) Well-organized and clearly presented 5 4 3 2 1
6) Current and relevant to your area of professional interest..... 5 4 3 2 1
7) Free of commercial bias 5 4 3 2 1
8) Clear in providing disclosure information 5 4 3 2 1

General Comments

9) As a result of this continuing education activity (check only one):

❒ I will modify my practice. (If you checked this box, how do you plan to modify your practice?) _____

_____

❒ I will wait for more information before modifying my practice.
❒ The program reinforces my current practice.
❒ No, I will not modify my practice.

Please indicate any barriers you perceive in implementing these changes:

❒ Cost
❒ Lack of time to assess/counsel patients
❒ Lack of administrative support
❒ Cultural or language barriers
❒ Reimbursement/insurance issues
❒ Concerns about patient safety/well being

10) This activity will assist in the improvement of my (check all that apply):

❒ Competence ❒ Performance ❒ Patient outcomes

Suggestions for future topics/additional comments: _____

_____

Follow-up

As part of our continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please check one:

❒ Yes, I would be interested in participating in a follow-up survey.
❒ No, I would not be interested in participating in a follow-up survey.

There is no fee for this educational activity.

Post-test Answer Key	1	2	3	4	5	6

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