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CONTEMPORARY MANAGEMENT OF MULTIPLE SCLEROSIS

A STAKEHOLDER INTERCHANGE REPORT

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS). From a managed care perspective, the MS management spectrum is associated with several challenges when it comes to determining benefits design. Moreover, when reviewing efficacy and safety, many variables must be considered beyond treatment cost, as payers determine formulary status or other parts of benefits design using a population-based perspective.

A recent stakeholder interchange from the Institute for Value-Based Medicine and *The American Journal of Managed Care®* convened thought leaders in both the clinical and managed care communities to discuss challenges, opportunities, and future directions in MS, with the goal of assisting stakeholders to optimize outcomes for patients. The interchange reviewed several evolving areas in the MS treatment and research landscape, including advances in pathology, and new emphases on neurological reserve and brain preservation, all of which may help shape efforts to improve benefits design relative to MS.

This article is a summary of key points from the discussion.

DISEASE BACKGROUND AND PHENOTYPES

MS involves a complex combination of genetic susceptibility and nongenetic triggers, such as environmental factors, resulting in a steady or rapid progression of neurological symptoms.[1-4] There are many disease courses in MS. According to a clinician stakeholder, it is likely that MS is not a single disease but rather a syndromic state. Diagnosis of MS is primarily clinical, with assistance from magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid.

There are 4 primary phenotypes of MS[5]:

- **Clinically isolated syndrome (CIS):** a first episode of neurologic symptoms (lasting at least 24 hours) caused by inflammation and demyelination in the CNS. Approximately 50% of patients with CIS have MS, according to 2017 McDonald criteria
- **Relapsing-remitting MS:** the most common disease course (at onset in >85% of patients with MS), characterized by clearly defined attacks of new or increasing neurologic symptoms
- **Secondary progressive MS:** a progressive worsening of neurologic function (accumulation of disability) over time that follows relapsing MS
- **Primary progressive MS:** a worsening neurologic function (accumulation of disability) from the onset of symptoms, without relapses or remissions

Recently, when reviewing and approving therapeutic agents, the FDA broadened its characterizations, according to a clinician stakeholder. Whereas the FDA used to approve with indications for relapsing forms of MS, the characterization of "relapsing" has been revised to include the first attack, which is CIS. Often, from a labeling and indication perspective, a distinction is made between primary progressive MS and the others, noted a clinician stakeholder. Primary progressive MS tends to start out gradually and affects patients who are more advanced in age, noted a clinician stakeholder. Despite the different phenotypes/disease courses and drug approval indications, there is just 1 *International Classification of Diseases, 10th Edition* diagnostic code (G35) for MS. From an MRI and immunology perspective, there are no distinguishing features between these types, which means they represent a pure description of a clinical behavior, observed clinician stakeholders.

MS PATHOLOGY: WHITE MATTER, GRAY MATTER, AND THE SIGNIFICANCE OF NEUROLOGICAL RESERVE

The pathology of MS includes inflammatory demyelination, axonal injury and subsequent loss of neurons, and development of CNS lesions.[1-4] Although the ratio of these pathological features may vary from patient to patient, their interaction produces diffuse, irreversible neurodegeneration.[2,3] Historically, MS has been considered a white matter disease because inflammatory lesions and volume loss have been observed in white matter in patients with MS.[6] Treatment efforts have emphasized prevention of new inflammatory lesions and reduction of atrophy and relapses.[6] More recently, gray matter pathology in the CNS has been shown to play an important role in MS.[7-11] Gray matter lesions have been identified in the earliest phases of disease—even in patients with minimal white matter pathology—with atrophy documented in both cortical and deep gray matter.[7,10]

Gray matter volume is highly associated with long-term clinical outcomes. The results of a 20-year longitudinal study of patients with MS (n = 73) showed significant correlations between total gray matter fraction and disability.[12] Also, in a 3-year prospective study, cortical lesion volume was found to be a strong independent predictor of declining physical disability.[13]

Gray matter lesion visualization is challenging to attain. Gray matter lesions are usually small and have poor contrast resolution. Overall,

MRI sensitivity is much lower than histopathological assessment for gray matter lesions.[6] Conventional MRI methods include T1, T1 gadolinium, and T2/fluid attenuated inversion recovery sequences. However, current technologies are generally limited when it comes to examining the visualization of gray matter pathology because of poor sensitivity and scan quality, as well as low signal-to-noise ratios, according to a clinician stakeholder. Thus, interpretation of MRI scans may be more qualitative than quantitative. Emerging technologies requiring 3T scanners may help address these limitations, potentially allowing for central vein detection, pial enhancement, and cortical and deep gray lesions.

In addition to the recent emphasis on gray matter in MS research, the concept of neurological reserve has increasingly gained momentum, according to clinician stakeholders. Neurological reserve is the finite capacity of the brain to retain function by remodeling itself following loss of nerve cells, loss of nerve fibers, or atrophy.[14] It provides functional compensation after cumulative damage by MS disease activity. As brain tissue is lost, the ability to respond to subsequent damage diminishes; this process is not only damage related but also age related.[14]

> Neurologic function that is lost cannot be regained; thus, there appears to be a window of opportunity early in the disease stages, noted one of the clinician stakeholders.

Neurological reserve consists of brain reserve and cognitive reserve. Brain reserve (or brain volume) declines as the brain ages.[15] These changes, which are often accelerated in patients with MS, have been associated with disability progression and cognitive impairment.[14,15] The brain actively attempts to cope by using cognitive processing, which allows patients with high cognitive reserve to respond to brain damage better than those with lower cognitive reserve.[16]

Brain reserve and cognitive reserve have also been shown to affect subcortical gray matter in patients with MS. In a longitudinal study involving 71 patients with MS and 23 control patients, all patients underwent an MRI and cognitive assessment at baseline and at a follow-up period of 3 years.[17] Subcortical gray matter volume and cognitive scores were lower in patients with MS compared with the control group. Moreover, low cognitive reserve was associated with a decline in cognitive processing speed in patients with MS.[17]

As scientific inquiries into the role of neurological reserve continue to develop, future findings may help elucidate the underlying pathology of MS.

THE BURDEN OF MS: COMORBIDITIES AND ECONOMIC IMPACT

MS has been associated with several comorbid conditions, the most common being depression, chronic lung disease, hypertension, anxiety, and hyperlipidemia.[18] Additionally, approximately 30% of patients with MS present with autoimmune comorbidities.[19]

The effects of comorbidities on disease course can be significant. For example, patients with MS with 1 or more cardiovascular risk factors have been associated with increased lesion burden and more advanced brain atrophy.[20,21] In a study reviewing 8983 patients, participants who reported at least 1 vascular comorbidity at the time of diagnosis had an increased risk of ambulatory disability.[21] The median time between diagnosis and need for ambulatory assistance was 18.8 years in patients without vascular comorbidities and 12.8 years in patients with vascular comorbidities.[21]

In addition to these comorbidities, depressive disorders have been observed in up to 50% of patients with MS, which is roughly 2 to 3 times higher than that of the general population.[22] It is likely that many depressive disorders remain undiagnosed and untreated in patients with MS. Screening tools should therefore be used to gauge the presence and impact of psychological comorbidities, which could provide clinicians insight into disease impact on quality of life (QOL) so they can tailor a patient's individual treatment accordingly.[18]

There are several consequences to the presence of comorbidities, such as an increased likelihood of relapse, more severe MRI outcomes—including advanced demyelination and neurodegeneration, as well as decreased whole-brain and cortical volumes—accelerated disease progression, and decreased QOL.[19,23] Study findings suggest that patients with 3

or more comorbidities have a 45% increased relapse rate compared with patients with no comorbidities.[23]

In addition to the impact of MS comorbidities on disease course and relapse rates, comorbidities have also been associated with diagnostic delays and increased hospitalizations; these data indicate the substantial economic burden of MS.[11,14,23-25] Moreover, MS ranks second among chronic conditions in direct all-cause medical costs, with an average of $8528 to $54,244 in spending per patient per year.[25]

The unpredictability of MS is another noteworthy burden associated with the disease. Although individuals can go years between attacks, MS produces long-lasting disability. Thus, those with MS often have considerable medical needs over a long period of time, stakeholders noted. Notably, patients at the highest medical cost are often those who have progressed to significant disability and are no longer receiving active therapy for their MS, observed one managed care stakeholder. The disability associated with MS also has a notable impact on QOL, as it can affect employment and take a considerable toll on day-to-day activities, according to stakeholders.[26]

MANAGEMENT CHALLENGES AND OTHER UNMET NEEDS

The management of patients with MS poses several challenges, many of which can be attributed to the complex pathogenesis and the spectrum of comorbid conditions associated with the disease. Importantly, interventions at different points of the disease course do not necessarily confer the same effect, because the disease process may change in character and be less amenable to disease modification.[27,28] Also, neurologic function that is lost cannot be regained; thus, there appears to be a window of opportunity early in the disease stages, noted one of the clinician stakeholders. According to another clinician stakeholder, once a patient has too much disability, neurological reserve has depleted and the ability to recover is significantly diminished. Therefore, it is best to treat after the first attack if a patient meets certain criteria. Strategies to repair the damaged nervous system are under development, but none exist at this time.

The previously noted difficulties associated with MRIs are indicative of a broader challenge regarding the current MS landscape, which is the lack of clear biomarkers. An effective biomarker would allow clinicians to prognosticate which patients should be started on a mechanism of action to garner the greatest therapeutic benefit at the lowest safety risk and cost and monitor treatment response. There is no diagnostic test for MS that can indicate whether a patient is a candidate for a certain modality. Until reliable biomarkers are developed, MS remains a clinical diagnosis. Thus, identifying therapies that can optimize outcomes for patients remains a challenge, according to the clinician stakeholders. One potential biomarker that is being explored is the neurofilament light test, noted a clinician stakeholder. If neurofilament light is high, it means something is wrong in the brain or in the nervous system—although what is wrong remains unknown.

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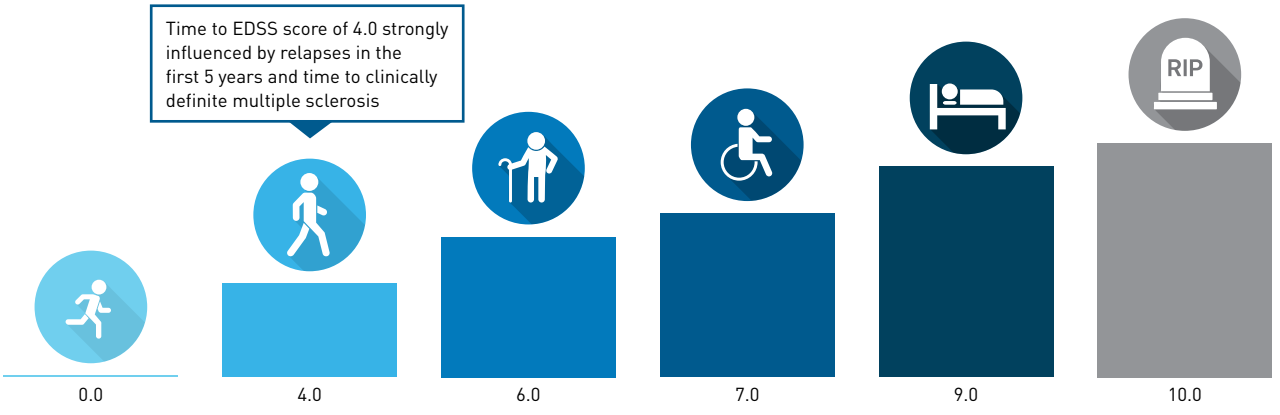
Another clear challenge in MS management is the need for new outcome measures. The currently accepted standard is the Expanded Disability Status Scale (EDSS).[29,30] The EDSS assesses ambulation and motor function (FIGURE).[29] This scale is the only measure outcome the FDA currently allows. Once a patient reaches an EDSS score of

FIGURE. Expanded Disability Status Scale (EDSS)[29]



5.5, there's about an 85% chance that person is no longer gainfully employed.[26] The EDSS has received criticism within the neurological community because it does not assess cognition and memory or indicate what the patient can actually do, according to a clinician stakeholder.

Several years ago, the Multiple Sclerosis Society developed the Multiple Sclerosis Functional Composite (MSFC), which measures leg function/ambulation (timed 25-foot walk), arm/hand function (9-hole peg test), and cognitive function (Paced Auditory Serial Addition Test [PASAT]).[31] The MSFC has been used in clinical trials, but it has not been approved by the FDA. According to a clinician stakeholder, it is likely that, at some point, there could be an outcome measure that includes elements of the MSFC, such as the 25-foot walk and the 9-hole peg test, but possibly not the PASAT, which has a very high learning curve.

TREATMENT IMPLICATIONS

Current medications for the treatment of MS aim to restore immunologic balance and control immunity. Despite the lack of biomarkers and the need for new outcome measures, several disease-modifying therapies (DMTs) have reached the market over the past 10 years. These include the oral agents dimethyl fumarate, fingolimod, teriflunomide, and siponimod and a monoclonal antibody delivered by infusion, ocrelizumab. These agents have different mechanisms of action, but given the lack of biomarkers, selection of an appropriate agent can be difficult.

> Current therapies vary in their ability to achieve optimal outcomes, but until there is a clear definition and one can show meaningful differences, there may be a tendency for payers to continue to prefer less expensive products.

Because MS is unpredictable, it is difficult to assess the value of a given therapy, making it difficult to also assess treatment failure or inadequate response. According to a clinician stakeholder, any relapse has roughly a 50% chance of producing residual disability, which can be permanent and irreversible. These variables complicate the managed care spectrum for MS. Often, the first variable payers consider when designing formularies is disease activity. Clinicians typically characterize individuals with relapsing forms of MS based on whether they are active or nonactive. Patients with active disease will experience an attack or new MRI activity in some time frame. Unfortunately, according to a clinician stakeholder, data are lacking regarding the length of time, because of the lack of biomarkers and outcome measures. Thus, according to a managed care stakeholder, without a standard algorithm for disease activity, payers often weigh the intricate interplay of efficacy, comorbidities, risk tolerance, treatment safety, and other factors for each patient. In addition, there are personal issues for each patient, such as family planning and preferences regarding treatment safety/efficacy. Clinicians and patients with MS are frequently engaged in these conversations, but without standard rhythms for payers to construct formularies, treatment selection can be a difficult process.

Several managed care stakeholders also noted the importance for the neurology community that treats MS to define as best they can what they consider optimal outcomes. Current therapies vary in their ability to achieve optimal outcomes, but until there is a clear definition and one can show meaningful differences, there may be a tendency for payers to continue to prefer less expensive products. Further, this inclination toward cost-effective approaches may become more and more problematic once biosimilars and generics become available. If a specific algorithm could be followed, one to suggest a change based on certain clinical and imaging factors, then physicians could consider amending treatment based on that algorithm.

Given the difficulties of MS, clinical and managed care stakeholders agreed that the communication between both sides should be improved. Moreover, it is important for the clinical community to inform the managed care community regarding the importance of both reducing and eliminating the number of relapses. Managed care organizations and clinicians need to emphasize this in their interaction so that consensus can be reached regarding formulary design, treatment selection can be better aligned, and outcomes can be optimized.

BRAIN PRESERVATION AND LIFESTYLE INTERVENTIONS

Given the importance of neurological reserve within the spectrum of MS care, the concept of brain preservation has emerged and gained in relevance. Brain preservation aims to minimize the loss of function and preserve premorbid functioning in all domains of the CNS. The primary goals of brain preservation are to prevent disease progression through neuroprotection and cognitive preservation, as well as limit as much as possible the disease's impact on a patient's daily life. By emphasizing brain preservation in efforts to assess, monitor, and treat MS, clinicians and payers can achieve a better understanding of the effects of interventions on disease progression and develop comprehensive treatment regimens focused on neuroprotection, repair, and prevention of inflammatory activity.

In addition to DMTs, the MS treatment spectrum encompasses the consideration of lifestyle interventions as part of the growing emphasis on overall preservation of long-term brain health.[32,33] A comprehensive approach to health in MS includes lifestyle changes to manage comorbidities that can affect disease activity and potentially improve QOL in patients with MS. Adherence to lifestyle interventions, much like adherence to therapeutics regimens, is key to their potential benefits.[33] Patients must be willing to practice healthy

habits, such as reducing or eliminating tobacco/alcohol use, maintaining a healthy weight through a healthy diet and physical activity, increasing sleep time, and taking measures to reduce stress.

Diet has been shown to play a role in inflammation and MS. Because obesity is inherently inflammatory, it is important for patients to maintain a healthy weight.[33] In addition to taking in omega-3 polyunsaturated fatty acids, which diminish inflammation, patients should exercise regularly, which can reduce fatigue and have a positive benefit on brain health and the CNS.[33]

In addition to maintaining physical health, psychological wellness can play an important role in brain preservation. For instance, meditation can reduce stress levels, improve well-being and QOL, and decrease morbidity.[34] Mindfulness practices potentially confer similar benefits and may even improve certain aspects of physical health.[35]

MANAGED CARE CONSIDERATIONS AND FUTURE DIRECTIONS

Brain preservation and the increasing emphasis on lifestyle interventions add a new dimension to evolving perspectives on ambulation, relapse, and disability with respect to MS treatment selection and formulary design. It is difficult to translate lifestyles into a measurable benefit regarding MS and treatment selection. Nevertheless, establishing metrics that can be measured in relation to brain preservation would allow clinicians and payers to gain a better grasp of the importance of brain preservation.

A managed care stakeholder noted that the development of a stratification tool for patients with MS would allow those in the clinical and managed care community to follow them and learn more about how their disease is affecting them. Such a tool could monitor emergency department visits and collate MRI findings to potentially quantify certain data points, which would allow everyone to better understand how treatments are deployed in individual neurology practices. This may be particularly helpful for patients with MS, given the individual factors that may affect their disease course and likelihood of relapse.

The stakeholders agreed that the changing treatment landscape and recent emphasis on brain preservation have shed new light on the notion of the window of opportunity for effective interventions. Given the many unknown variables regarding MS pathology, the neurology community has not defined specific standards for treatment outcomes. Ongoing and future efforts regarding the development of new biomarkers and a new generation of DMTs may enable improved outcomes with agents that exert neuroprotective effects, stimulate remyelination, and help recovery by enhancing neuronal plasticity. Moreover, novel meaningful outcome measures may facilitate evidence-based practice and allow claims to be better established.

As development of biomarkers, outcome measures, and new treatments continues, an urgent need remains for payers and clinicians to consider new solutions regarding management of MS, particularly when it comes to how value (regarding risk/benefit) is understood. The managed care stakeholders agreed that improved standardization by the clinical community in its approach to management of these patients will likely lead to more effective partnerships with the managed care community in aligning with their efforts. Additionally, those in the managed care community would benefit from increased awareness regarding the importance of relapse prevention, as well as brain preservation and neurological reserve.

> Although health plans tend to focus on populations and the cost of the loss of functionality, clinicians usually focus on the individuals and keeping them functional. Ultimately, according to the managed care stakeholder, these sensibilities go hand in hand, and the more the 2 sides can work together, the more likely they can foster an environment in which patients are gaining the most clinically- and cost-effective care.

The expense of MS goes far beyond dollars and cents; MS is expensive emotionally and takes a financial toll on families, one managed care stakeholder observed. Although health plans tend to focus on populations and the cost of the loss of functionality, clinicians usually focus on the individuals and keeping them functional. Ultimately, according to the managed care stakeholder, these sensibilities go hand in hand, and the more the 2 sides can work together, the more likely they can foster an environment in which patients are gaining the most clinically- and cost-effective care. As one managed care stakeholder noted, "The solution is us working together to help shape a population approach that can be individualized, rather than the approach to the population as individual." •

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FOR ADDITIONAL INSIGHTS

into managed care implications of MS, see the March 2019 publication *The Role of Brain Preservation in the Management of Multiple Sclerosis*, available at: **ajmc.com/link/4220**.

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