

The Evolving Landscape in the Management & Treatment of MULTIPLE SCLEROSIS



Payer Considerations for Providing Support to People with MS and Their Care Partners



Kyle Pinion, Senior Director of Education, Healthcare Relations & Advocacy, MSAA
Alexis Crispino, Director of Education and Healthcare Relations, MSAA

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Introduction

Bridging gaps in communication between managed care decision makers and multiple sclerosis (MS) clinical specialists can contribute to improvements in the overall quality of care delivered to patients with MS. To improve communication and foster collaboration, live meetings (n=4) and webcasts (n=2) were convened by the Multiple Sclerosis Association of America (MSAA) and held between August 2019 and January 2020. Each event featured a panel of payers, physicians, and specialty pharmacy providers. Presentations and subsequent discussions focused on current MS therapies and treatment strategies, the impact of drug cost on access and delivery of care, and the importance of multidisciplinary management of individuals with MS. Discussion yielded recommendations to improve the efficiency of care delivery; enhance multidisciplinary management; reduce barriers between physicians, payers, and specialty pharmacy providers; and improve continuity of care. Incorporating these recommendations has the potential to advance patient outcomes, expand access to appropriate therapy, and increase the overall value of MS care.

RECOMMENDATION

Both payers and providers recommended the formation of a steering committee made up of MS clinical care specialists and managed care decision makers to meet regularly to discuss practical steps to improve the overall value and quality of care delivered to patients with MS. Potential discussion topics include improving the efficiency of care delivery, enhancing multidisciplinary MS care management, reducing barriers between physicians, payers, and specialty pharmacy providers, and improving continuity of care.

Multiple Sclerosis

MS is a chronic inflammatory demyelinating neurodegenerative disease of the central nervous system^{1,2} estimated to affect nearly 1,000,000 individuals in the United States³ with an average age of disease onset between 30 to 35 years.⁴ Due to the relatively early age of onset, patients often live with MS-associated physical, cognitive, and emotional impairment for decades, making it the leading cause of non-traumatic disability in young adults.⁵⁻⁷ Thus, the clinical and economic burden of MS is significant due to its extensive morbidity, and associated comorbidities.⁸ Direct medical costs for health care services are substantially higher in people with MS compared to those without a chronic illness.⁹ For example, a newly diagnosed patient with MS will incur an average of 8 clinic visits annually, nearly 3 times more than an individual without the disease.^{9,10} Furthermore, because the need for medical care often increases as the disease progresses, the cost of care increases over time.⁹ Indirect costs associated with MS can also be substantial, impacting patients as well as their families and caregivers. In fact, decreased productivity resulting from loss of employment or the need to retire early due to the disease may be the largest single factor contributing to the nonmedical financial cost of MS.¹⁰



Disease Modifying Therapy

The management of MS is a clinical success story. Until the mid-1990s, treatment for MS consisted of symptomatic control, usually a short course of high-dose steroids administered during exacerbations. Since then, more than a dozen disease modifying therapies (DMTs) have been proven to slow the course of the disease. Classes of DMTs approved for use by the Food and Drug Administration (FDA) include the interferons (eg, IFN β -1a, IFN β -1b, peginterferon β -1a), the sphingosine 1-phosphate (S1P) receptor modulators (eg, siponimod, fingolimod, ozanimod), monoclonal antibodies (eg, natalizumab, alemtuzumab, ocrelizumab), and immunomodulators (eg, glatiramer, mitoxantrone, teriflunomide, dimethyl fumarate, cladribine, diroximel fumarate, monomethyl fumarate). Fingolimod, siponimod, ozanimod, cladribine, teriflunomide, dimethyl fumarate, diroximel fumarate, and monomethyl fumarate are administered orally; natalizumab, ocrelizumab, and mitoxantrone are administered by intravenous infusion; interferon β -1a (Avonex) is administered by intramuscular injection; and interferon β -1a (Rebif), interferon β -1b, and glatiramer acetate are administered subcutaneously. The significant increase in the number and diversity of DMTs over the last several years suggests increased competition would be reflected in lower drug costs. However, this is not the case as the acquisition price of these agents continues to rise. Despite this, DMTs are widely used to treat MS.

FDA Indications for Currently Available DMTs ¹²				
Agent	Approval	RRMS	PPMS	SPMS
Interferon b-1b (Betaseron; Extavia)	1993	✓		✓
Interferon b1-a (Avonex)	1996	✓		✓
Glateramer acetate (Copaxone/Glatopa)	1996/2018	✓		✓
Interferon b-1a (Rebif)	1996	✓		✓
Mitoxantrone (Novantrone)	2000	✓		✓
Natalizumab (Tysabri)	2004	✓		✓
Fingolimod (Gilenya)	2010	✓		✓
Teriflunomide (Aubagio)	2012	✓		
Dimethyl fumarate (Tecfidera)	2013	✓		✓
Alemtuzumab (Lemtrada)	2014	✓		
Peginterferon b-1a (Plegridy)	2014	✓		✓
Ocrelizumab (Ocrevus)	2017	✓	✓	✓
Siponimod (Mayzent)	2019	✓		✓
Cladribine (Mavenclad)	2019	✓		✓
Diroximel fumarate (Vumerity)	2019	✓		
Ozanimod (Zeposia)	2020	✓		
Monomethyl fumarate (Bafiertam)	2020	✓		

With the introduction of the wide variety of DMTs, the management of MS has become more complex. Providers are challenged with selecting the most appropriate treatment strategy, especially early in the disease course when it may be possible to maximize the chance of preventing long-term disability. Within 20 years of disease onset, 80% of patients with untreated relapsing MS (RRMS) have accrued substantial disability, and it is at this point in the natural history of MS that patients experience much of the disease's negative physical, psychological, and societal effects.¹³ Thus, there is an urgency to treat in many patients.

The heterogeneity of MS makes it a challenging disease to treat, but treatment can also be hampered by a lack of clear clinical guidelines to direct MS care. The current American Academy of Neurology (AAN) MS treatment guidelines were published in 2018 and provide an extensive review of each DMT rather than specific treatment pathways similar to those established for other disease states (eg, rheumatoid arthritis or oncology).¹⁴ This means the AAN guidelines provide clinicians, patients, and payers minimal guidance on the most appropriate approach to selecting, escalating, and switching DMT treatment. Thus, the treatment decision-making process requires careful evaluation of the results of clinical and post-marketing studies as well as the ability to translate data from clinical studies to patients in everyday clinical practice.

Although the guidelines provide recommendations based on the current clinical evidence, they leave all stakeholders—treating clinicians, patients, and payers—with unanswered questions about how individual patients should be treated. The decision to initiate treatment often occurs after a discussion between the person with MS and the clinician. As is commonly known to providers, patients (and their caregivers) have a variety of views on what is the right treatment for themselves, including different degrees of risk tolerance. Thus, providers must discuss with each patient the available therapeutic options, taking into consideration which therapy the patient is willing to accept, what their comorbidities may be, what their family-planning needs are, the scope of their insurance coverage, and other relevant topics. Understanding these details and incorporating them into the treatment decision can significantly influence treatment outcomes.

RECOMMENDATION

MS providers recommended that the health plan collaborate with MS neurologists and other providers to explore opportunities to apply the latest evidence-based MS treatment guidelines in order to ensure patient access to the most recent therapeutic advances.



Finding the right treatment often takes time and requires careful evaluation and monitoring by both physicians and patients. Forcing a patient to switch treatment or denying them access to a medication due to formulary changes or other non-medical reasons, may result in a loss of disease control in previously stable patients. - MS NEUROLOGIST

Treatment Strategy (continued)

There are 2 general approaches to DMT treatment: 1) start with a less aggressive treatment, usually an oral DMT, and escalate gradually if disease activity increases and 2) initiate treatment with a more aggressive therapy (eg, an infused DMT). This first strategy allows slow titration, which may minimize the risk of side effects and thus, positively influence adherence. The downside of this approach is that disease progression may occur during the escalation period, increasing the risk of a loss of central nervous system function and potential irreversible physical and/or mental disability. The more aggressive second approach aims to arrest disease activity quickly after diagnosis, thus preventing permanent loss of function. This strategy has become a favored approach of more and more clinicians in the MS community. There is an expectation that the ideal strategy will be revealed only when data from ongoing and planned clinical trials, as well as real-world registry data, become available.



For newly diagnosed patients who have never been treated, do we start them on an older therapy—either injectables and pills—or do we treat more aggressively with an infusion? In our practice, we start with a more aggressive treatment for most patients. - MS NEUROLOGIST

Although not curative, many patients experience lower long-term risk of MS disease progression with DMT treatment, particularly those with RRMS.¹⁵⁻¹⁹ For example, an analysis of an observational cohort of over 1555 patients with RRMS and a minimum follow-up of four years who were untreated or treated with interferon beta, glatiramer acetate, fingolimod, natalizumab, or alemtuzumab, demonstrated that initial treatment with a DMT was associated with a lower risk of conversion to progressive MS compared with no DMT treatment.¹⁷ Furthermore, risk was lower for patients in whom DMT therapy was initiated within five years of disease onset vs with later treatment.¹⁷ Despite the success observed in patients with RRMS, treatment of primary progressive disease (PPMS), which is characterized by the accumulation of disability in the absence of relapses, remains challenging with only one DMT — ocrelizumab — currently approved to treat this phenotype.

Approach to MS Treatment ²⁰	
Early treatment	• Start treatment with a DMT as early as possible
Early treatment with DMTs	• May limit disability and attenuate secondary progression in patients with active RRMS
Treat-to-target	• Goal is to minimize and/or stop disease activity*
AAN Guidelines Recommendation #14	• Start patients with highly active MS on alemtuzumab, natalizumab, or fingolimod†

* current data on whether this approach improves outcomes is limited

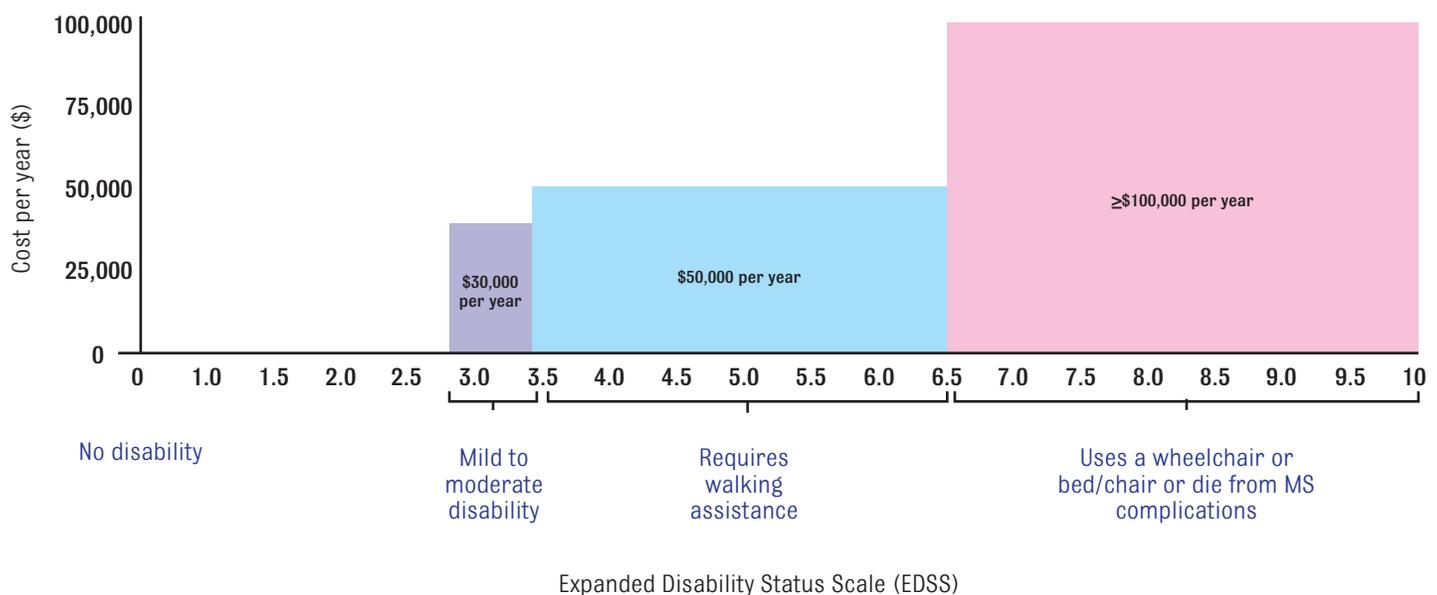
† ocrelizumab was not available at the time of the analysis but would qualify for this indication as well

The Secondary Progressive MS Conundrum

An accurate description of the clinical course of MS helps guide treatment decision making, including selection of an appropriate DMT. Because a majority of the DMT pivotal studies were conducted in individuals with RRMS, FDA approval of these agents was limited to use in patients with relapsing disease. As a result, in clinical practice many patients who progressed from RRMS to secondary progressive MS (SPMS) did not have their status changed in their medical record or on claims forms due to fears that, although the individuals were experiencing clinical success on a particular DMT, it might be denied by payers or pharmacy benefit managers despite the patient experiencing clinical success on that specific therapy. This discrepancy in what patients and clinicians experienced and what was documented caused confusion for patients, families, and clinicians.

In March 2019, siponimod and cladribine were approved for the treatment of patients with both RRMS and *active* SPMS. The incorporation of the term “active” in the approval changed the language used to categorize the MS phenotype. Additionally, the FDA indication for RRMS and active SPMS was also retroactively applied to all available DMTs. The change in FDA guidance provided both physicians and patients more leeway in choosing an appropriate DMT and will likely stimulate changes in payer coverage policies. However, in the case of siponimod, the approval was not based on the clinical trial as designed or the success in meeting the primary endpoint of preventing disability in SPMS,²¹ but rather was based on a subgroup with active SPMS and the category of RRMS, which was not studied in a phase 3 trial.²² There is sufficient reason to think siponimod might be effective in preventing relapses in early MS, but it was not studied in that context. So, despite the indication, clinicians are left with increased complexity and lack of actionable clinical trial guidance, both of which could lead payers to implement further restrictions on approvals.

MS COST OF CARE RISES AS DISABILITY PROGRESSES²³



Medical and Pharmacy DMT Management

Early treatment initiation may reduce total medical cost of care by slowing MS disease progression and minimizing disability, hospitalizations, emergency room visits, and other high-cost interventions;²⁴ however, this strategy may result in higher costs at the pharmacy. While the continual increase in the acquisition price of DMTs has prompted many payers to devise strategies to mitigate the budget impact of steadily increasing drug costs, no payer is interested in withholding a drug proven to be safe and effective and then paying for a hospital visit due to uncontrolled disease activity. Thus, each health plan should conduct a comprehensive review of the total cost of MS care within their system in order to provide insights on the therapeutic approach that provides the greatest value.



We look comprehensively at the total cost of care. We certainly don't want to withhold the drug and then the patient ends up in the hospital and we wind up paying on the medical side... that's absolutely not the goal.

- HEALTH PLAN MEDICAL DIRECTOR

Due to the progressive nature of MS, it is critical providers have an historical perspective of the disease course in each patient in order to guide selection of appropriate therapy. The need for historical perspective is also true for payers who rely on claims data to tell them what was covered in the past and provide insights on treatment patterns over time. For example, historical information on whether the patient has been hospitalized, seen in the emergency department, or treated with another medication can inform treatment selection. However, the current payer often lacks the continuity and understanding of the patient's entire therapeutic journey because the average length of enrollment for most members in a commercial plan is 12 to 18 months. This becomes a significant issue when a provider calls the payer to justify aggressive therapy for a patient due to an increase in disease activity. However, the payer may not have historical records with imaging test results or an inventory of prior treatments and may deny the claim. Hence, providers and payers must work together to communicate the disease and therapeutic history of the patient including level of disease activity, outcomes of prior therapeutic interventions, and patient adherence to therapy.

On the whole, health plans are committed to helping providers focus on delivering care. It is in the health plan's best interest to quickly get patients on the right therapy and keep them on appropriate therapy for as long as possible, particularly when uncontrolled disease activity is associated with a high risk for disability and excessive cost. Although plans are motivated to get patients to the right therapy as soon as possible, barriers do exist and must be navigated and negotiated by the plan, providers, and patients.

Medical and Pharmacy DMT Management (continued)

Value-based benefit design is one strategy used by health plans to manage costs associated with MS therapies.²⁵ Value-based designs, or those that encourage utilization of services that provide significant clinical benefits relative to costs, have been well-documented in the reduction of the use of nondrug health care services, thus offsetting the costs associated with additional use of drugs.²⁶ While many healthcare systems are revamping their infrastructures to promote the value-based payment model, inefficient data management capabilities make it difficult for many plans to successfully achieve value-based care goals. The volume of electronic health record data necessary to compute “value” can overwhelm providers who often find themselves with inconsistent performance reports, differences in performance measures, poor relationships with payers, and a lack of transparency. The use of value-based design for MS is also complicated due to a relative lack of head-to-head clinical trials of DMTs. Furthermore, the highly unpredictable nature of MS results in challenges when assessing cost estimates associated with no treatment or undertreatment.



We're not just looking at the cost of the drug...if data is available that shows there's cost benefit to a drug, then that's potentially the one we're going to select.

- HEALTH PLAN MEDICAL DIRECTOR

Payers have other tools to manage the cost of therapy. Cost-effectiveness reports generated by the Institute for Clinical and Economic Review (ICER) are often used by payers to inform formulary inclusion and positioning decisions for DMTs.²⁷ It should be noted that payers frequently utilize ICER findings as just one of many data points to determine the cost-effectiveness of DMTs due to limitations in methodology, failure to include the full range of available DMTs, and economic assumptions that often do not apply to specific payers.

Other tools utilized to manage drug costs include placing preferred agents in a favored position on the formulary or incentivizing use of specific agents via tiered copays. This strategy has been enabled by the rapid introduction of new medications over the last several years providing payers with more opportunities to select among competing agents in certain classes. Utilization management techniques, such as prior authorization, are also frequently utilized to ensure that an appropriate diagnosis (eg, phenotype of the disease) has been made or a specific patient functional status is present (eg, non-ambulatory, cognitive impairment) prior to granting access to a DMT. A requirement for use of a specific first-line medication before second- or third-line therapies can be accessed (eg, step therapy) is also a common practice. Step therapy becomes a particular concern when health plans require a patient to “fail” a less aggressive or less convenient first-line therapy prior to becoming eligible for a second-line agent; a situation that becomes a waste of time, money, and effort if the new therapy is ineffective, inconvenient to administer, or associated adverse events—all of which contribute to poor adherence. Other tools include quantity and day supply limits to prevent waste of medications by either limiting to an FDA approved dose per day, week, or month, or limiting each fill to a certain day supply at a time and proper distribution channel selection, which can provide payers an opportunity to secure a preferred cost per unit on medications. Since many MS therapies are infused or injectable, payers can consider the pros and cons of placing the therapy in either the medical or pharmacy benefit.

RECOMMENDATION

MS neurologists recommended that health plans structure the pharmacy benefit to minimize disruptions in care created by changes in the formulary status of a drug. One approach to implement this recommendation is for the health plan to regularly engage providers to assess the impact of formulary changes on continuity of care.

Guaranteeing continuity of care, minimizing delays in access to treatment, and avoiding unexpected changes in treatment—particularly when a patient is experiencing beneficial results on established therapy—are crucial to preventing deleterious health consequences, including irreversible accumulation of disability. Consequently, many individuals with MS carefully review the coverage provided by competing health insurance plans in their local markets and make choices based on coverage of medically necessary services and prescriptions. Despite this, payers are permitted to make changes to coverage without regard to a patient’s stability or what expert providers recommend as the best course of treatment in a process referred to as “non-medical switching.” Changes that can be made by payers include moving a prescription to a higher cost-sharing tier; increasing out-of-pocket costs by moving from co-pay to co-insurance; adding utilization review requirements,

such as step therapy or prior authorization; or removing a prescription from a drug formulary completely. Similarly, providers may instigate a non-medical switch when a patient changes to an insurance plan that does not provide coverage for the patient’s preferred DMT. In this case, unbeknownst to the patient, the provider may not even consider offering the patient the preferred DMT because they know the chance of it being approved by the payer is unlikely or will involve a significant amount of work.

There are reports in the literature that suggest switching patients who are clinically stable to alternative DMTs for non-medical reasons is associated with higher risk of relapse,²⁸ adverse medical outcomes, decreased satisfaction with the provider and health care system,²⁹ and poor adherence.³⁰ Given these reports, formulary decision makers must evaluate the trade-offs of any potential cost savings of switching stable patients.



Our biggest concern is when a patient is doing well on a drug, but their insurance changes and the agent is no longer on formulary...that's where we have our biggest problem.

- MS NEUROLOGIST

The heterogeneity of MS makes it a challenging disease to treat—a one-size-fits-all approach to care is not applicable to a majority of patients with MS. In addition to highly variable presentation, multiple comorbid conditions, including depression, spasticity, fatigue, and bladder dysfunction, make MS management extraordinarily complex. As a result of this complexity, many patients are dissatisfied with varying levels of access, quality, and availability of care, frequent and avoidable complications, insufficient psychological counseling, and too little education. Successful management of patients with MS often depends on the coordinated efforts of a multidisciplinary care team consisting of specialists who manage the entire MS care plan including not only therapeutic interventions, but also the social, emotional, educational, and economic needs of the patient and their families. Multidisciplinary care ensures that the direction and goals of treatment are consistent, rational, and progressive and facilitates coordination and continuity of services while avoiding duplication and fragmentation of care. Although the exact makeup of the MS care team varies across settings, it usually consists of a core group of specialists such as MS neurologists, nurses, rehabilitation specialists, social workers, dietitians, psychologists, psychiatrists, primary care providers, physical therapists, radiology/imaging specialists, and pharmacists. The person with MS and their caregiver is also an integral member of the care team and should be an active participant in planning and implementing healthcare and self-care activities.



In my plan, we have case management for diabetes, cerebrovascular disease, and other complex conditions but we have nothing for MS—we just don't have the bandwidth.

- HEALTH PLAN MEDICAL DIRECTOR

Specialty pharmacy providers can also play an important role in managing the patient experience, particularly as it relates to facilitating drug access and reimbursement, setting patient expectations about a therapy, providing education on the safety and efficacy of the agent, encouraging and assessing adherence, and generally being available to answer patient questions and address concerns. The frequent interaction between the specialty pharmacy and patient also provides an excellent opportunity to collect data on clinical outcomes, side effects, adherence, and patient-reported outcomes, which can be used by the payer to develop and/or inform the formulary strategy as well as care management opportunities on both an individual or population level.

While many health plans provide multidisciplinary care management for more common chronic diseases such as diabetes and cerebrovascular disease, few provide comprehensive care for MS despite its high cost and high impact. Specific reasons for the lack of comprehensive care programs for MS vary by plans, but many plans lack the information technology bandwidth necessary to integrate and analyze data from the diverse array of providers that interface with a patient with MS. The lack of data contributes to an inability of plans to assess the budget impact of a comprehensive MS care management program. Because health plan budgets typically encompass only one year, they do not provide a line of sight on the longitudinal cost of health care. Thus, because the economic benefits of an MS care management program often accrue over a long period of time, plans have no way of easily realizing the economic benefit of these programs.

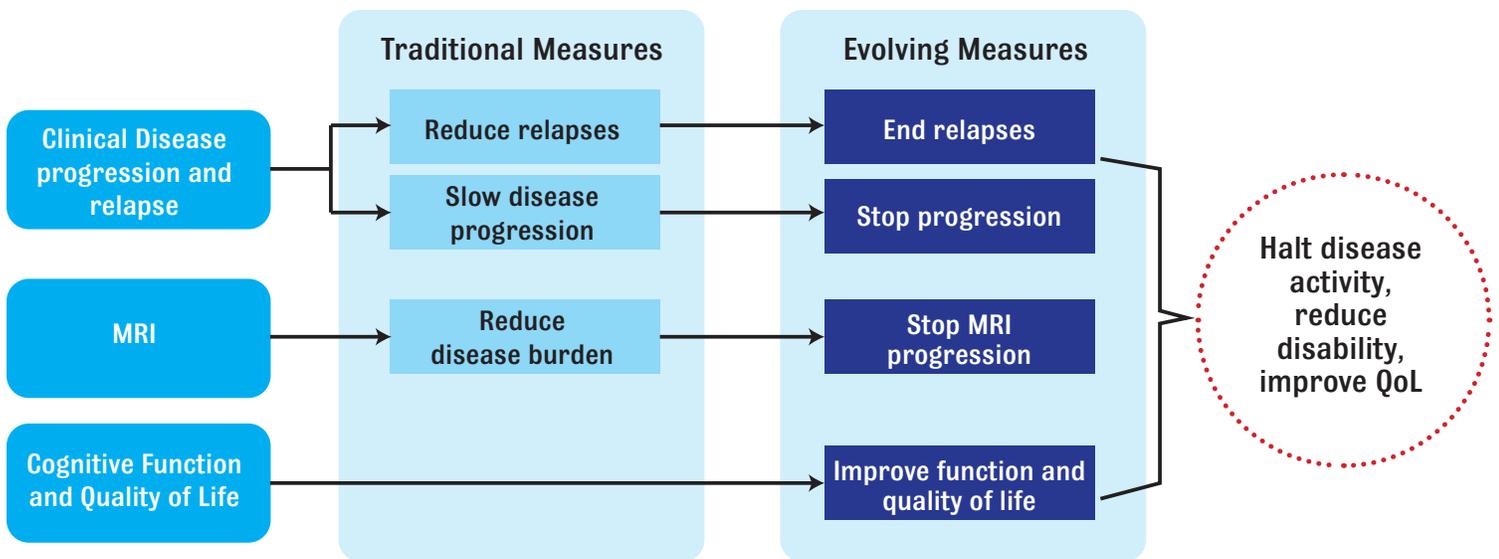
Summary

MS care is currently in a paradoxical position; there are now more than twenty DMTs available and more in the pipeline. Despite the beneficial impact of DMTs, there is less appreciation for the impact of access barriers to DMTs and the deleterious effect of poorly coordinated care delivery on MS treatment outcomes. Bridging gaps in communication between managed care decision makers and MS clinical specialists can contribute to improving the overall quality of care for patients with MS. Recommendations from a panel of physicians, payers, and specialty pharmacy providers include the need to apply the latest clinical guidelines to the treatment of patients with MS and to lower barriers to DMT access. Incorporation of these recommendations into clinical and administrative practice have the potential to advance patient health, well-being, and treatment outcomes by expanding access to appropriate MS care.

RECOMMENDATION

Specialty Pharmacy providers recommended creating opportunities for them to share clinical, safety, and adherence data with the providers of MS care within the health plan on a regular basis.

GOALS OF TREATMENT³¹



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MSAA'S MISSION

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