Multiple Sclerosis: New Perspectives on the Patient Journey

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EXECUTIVE SUMMARY

Multiple sclerosis (MS) is a progressive, neurodegenerative, immune-mediated neurological disease that is associated with irreversible physical disability and functional impairment.[1] Approximately 400,000 to 570,000 people in the United States have MS.[2,3] The majority of patients are diagnosed between the ages of 20 and 50 years, during their peak working years.[4] Relapsing-remitting multiple sclerosis (RRMS) comprises the most common initial course of clinical progression, which is highly variable and unpredictable.[5,6] RRMS is up to 3 times more frequent among women than men.[6] Although disease-modifying therapy (DMT) plays an important role in the treatment of relapsing forms of MS,[1,7] due to the heterogeneity of the patient population, treatment in MS is highly individualized.[7,8]

MS is associated with a substantial economic burden, including direct and indirect costs.[9] There has been a correlation between disability level, as measured by the Expanded Disability Status Scale (EDSS), and the total cost in MS.[10] Many neurologic impairments have been linked to higher healthcare costs and/or lost productivity (eg, absenteeism, presenteeism).[11,12] In addition, it has been shown that cognitive decline, fatigue, depression, and anxiety may limit employability, even for patients with MS who have low levels of physical disability.[1]

We analyzed a large administrative database composed of commercial health insurance (ie, insurance not funded by public sources) claims data in a snapshot analysis for the year 2013, as well as in a longitudinal analysis for the years 2003 to 2014. The snapshot analysis highlights that the MS population appears to include patients with diverse resource utilization as exhibited by considerable variations in allowed costs. Broad variations were particularly observed in non-DMT costs (costs associated with medical services and non-DMT prescription drugs), which make up approximately 37% of healthcare costs for patients with MS. In 2013, the unadjusted average monthly non-DMT cost among patients with DMT use was approximately 18% lower than among those without DMT use. Potential confounding factors like age, gender, and disease duration were not adjusted for in this analysis.

Our longitudinal analysis (for the years 2003-2014) identified several tens of thousands of people with MS, and it provides an opportunity to examine disability accumulation, treatment patterns with DMT, and related healthcare costs in newly diagnosed patients over the course of 10 years after diagnosis. Moreover, this paper provides additional information to help understand both the traditional functional impairments that are derived from the EDSS ("EDSS-derived impairments") and related neurologic impairments (eg, pain, fatigue, depression, and cognitive impairment) through use of administrative claims.

This paper uses health insurance claims to show that over the course of the disease, patients have accumulated a growing number of markers of disability and functional impairment. Figure 1 shows that even before diagnosis, people with MS appeared to be diagnosed or treated for many of the impairments associated with MS. It also shows that a very small percentage of people were impairment-free 5 years after diagnosis.

Identified markers included two sets of indicators:

- EDSS-derived disability indicators were captured from medical and/or pharmacy claims and included spasticity, bladder dysfunction, cognitive/behavioral dysfunction (based on medical claims only), visual impairment, and mobility impairments (see Appendix C for specific codes)
- Related neurologic impairment indicators were captured from pharmacy claims and included pain, fatigue, depression, and cognitive impairment (see Appendix C for specific codes)

Figure 1
Cumulative Distribution of Patients With MS by the Combined Number of Indicators for EDSS-Derived Disability and Related Neurologic Impairment During the Course of the Disease

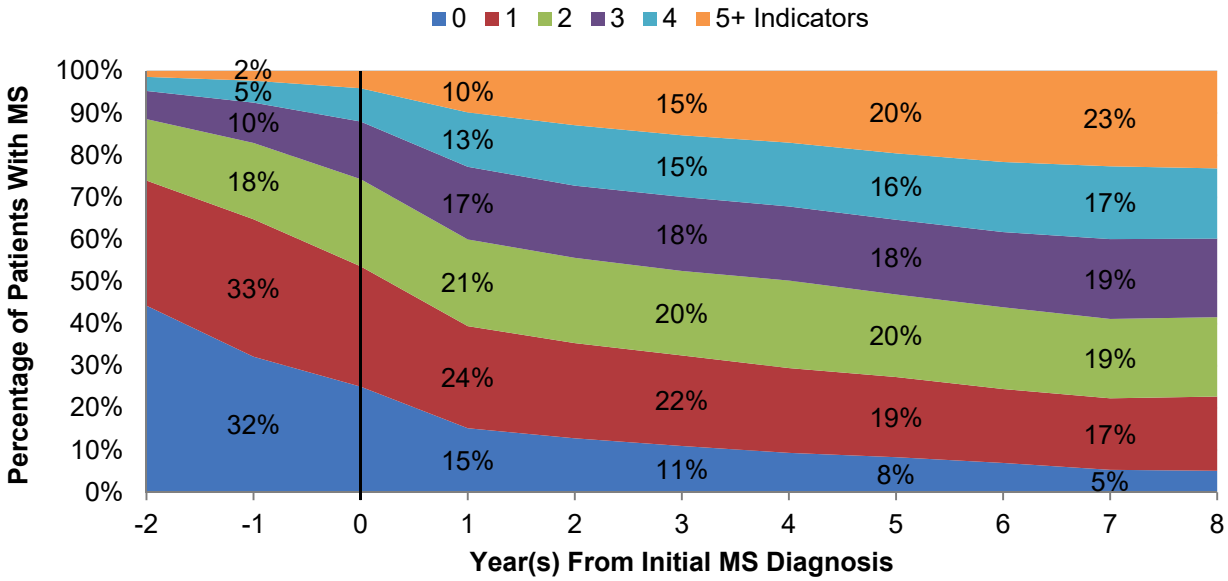

Table 1 highlights important DMT treatment patterns revealed in the longitudinal analysis. Our administrative database suggests that in the first 2 years after diagnosis, about 33% of MS patients did not have claims for DMT, even though experts believe that DMT treatment should be initiated soon after the diagnosis of RRMS is established.[7,13,14] In addition, among patients with one or more claims for DMT, 31% switched therapies.

TABLE 1
DMT TREATMENT PATTERNS FOLLOWING A TWO-YEAR PERIOD FOR PATIENTS NEWLY DIAGNOSED WITH MS IN 2012

Sample Size	1300
DMT Treatment Rate	67% (866/1300)
DMT Switch Rate	31% (270/866)

Thousands of patients with MS can be identified in large administrative databases, and the course of their treatment, health, and impairment can be followed. Important impairments and markers of disease progression may be identified in claims data; patient drug switching, adherence, and nonuse can be identified and flagged for follow-up. The appearance of impairments prior to diagnosis suggests that these findings, along with similar data analyses for other patient populations (including those with neurological conditions unrelated to MS), can be used to explore the feasibility of claims-based predictive modeling for identifying patients at risk for being diagnosed with MS. Furthermore, longitudinal analyses of a large administrative database can help assess the potential cost impact of chronic drug therapies. In our regression model, DMT use was associated with a reduction in non-DMT costs equivalent to approximately 7% of the DMT spend, which corresponded to an estimated 16% reduction in monthly non-DMT costs when adjusted for DMT use in 2013.

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should be reproduced in its entirety, as pieces taken out of context can be misleading. Our analysis of MS patient characteristics, impairment indicators, and utilization of healthcare services and costs is based on historical practice patterns and therapies, which can be expected to change over time. The patient journey is individualized and may differ from patient to patient. Future experience will vary from the estimates presented in this report for many reasons, including random fluctuation. As with any economic or actuarial analysis, it may not be possible to capture all factors that may have significant impact on healthcare utilization and cost. Interpretations of this data may vary. Further, no algorithm for identifying MS patients and relapses will be perfect. Different identification algorithms could produce different results. Because we present national average data, the findings should be interpreted carefully before they are applied to any particular situation since there could be considerable variation among subsets of the population. It is important to note that individual patient characteristics and situations may also vary. Two of the coauthors, Melissa Fredericks and Bruce Pyenson, are members of the American Academy of Actuaries and meet its qualification standards for this work.

INTRODUCTION

Multiple sclerosis (MS) continues to be one of the top specialty management priorities for health plans and pharmacy benefit managers.[15,16] Payers commonly develop metrics for cost, quality, and utilization on a calendar-year basis. However, this "snapshot" approach may miss important elements of both individual and overall patient and treatment dynamics for MS.

The objective of this report is to provide insights into potential patient and treatment dynamics in 2 ways using health insurance claims data:

1. **Snapshot analysis for the year 2013:** includes descriptive statistics to highlight how the MS population appears to be represented in the context of a traditional calendar-year timeframe
2. **Longitudinal analysis for the years 2003-2014:** includes patient-level data capturing patterns of care during a 12-year period

The longitudinal analysis provides information on the potential patient journey during the course of MS, including disease progression after diagnosis, treatment patterns with disease-modifying therapy (DMT), and related healthcare costs. Furthermore, the longitudinal analysis also attempts to capture the information about the disease activity and estimated healthcare costs during the time period leading up to the diagnosis of MS.

These analyses offer additional insights that may supplement currently available evidence to help broaden the understanding of MS among patient advocates and among financial and medical decision-makers within payer organizations, as well as support the value of real-world data to help further research.

BACKGROUND AND HIGHLIGHTS FROM THE LITERATURE

MS is a progressive neurodegenerative, immune-mediated, neurological disease that is associated with irreversible physical disability and functional impairment.[1] The inflammatory process in MS leads to demyelination of nerves and axonal degeneration in the central nervous system (CNS).[17,18] Essentially in MS, the immune system mistakenly attacks and damages the protective myelin sheaths surrounding nerve fibers in the brain, spinal cord, and the optic nerve.[1] Because the disease process can affect any area of the CNS, it has been shown to result in a wide range of fluctuating neurological symptoms, including fatigue, mood and cognitive changes, impaired mobility, pain and other sensory problems, visual disturbances, incontinence, and sexual dysfunction.[1,5,7]

It is estimated that approximately 400,000 to 570,000 people have MS in the United States.[2,3] The majority of patients are diagnosed between the ages of 20 and 50 years, during their peak working years.[4]

MS is associated with a substantial economic burden.[9] Patients with MS have been shown to be high utilizers of healthcare services; they are known to incur significant direct costs. For example, annual healthcare costs were shown to be more than 5 times higher for patients with MS than for those without MS.[1] Furthermore, disability and functional impairment have been associated with significant indirect costs due to lost productivity or inability to work.

Relapsing-remitting multiple sclerosis (RRMS) comprises the most common initial course of clinical progression, which is highly variable and unpredictable.[5,6] RRMS is up to 3 times more common among women than men.[4] Between 85% and 90% of patients with MS initially exhibit RRMS, where disease activity is characterized by clinical relapses with or without accumulating disability, and functional impairment, along with subclinical signs, including lesions detectable on magnetic resonance imaging (MRI) and brain atrophy.[1,6,7] There is substantial clinical heterogeneity in the relapsing-remitting phase of the disease and the number of relapses, symptom severity, rate of disability progression, and extent of functional impairment

varies considerably within this population.[5,6] However, many people with RRMS will eventually transition to secondary progressive MS (SPMS), where the disease progression may steadily accelerate, with or without relapses.[6,19]

The diagnostic criteria in MS focus on documenting evidence of disease activity disseminated in space and time and require ruling out alternative diagnoses through clinical, radiologic, and laboratory studies.[20] Advances in MRI technology and diagnostic criteria may allow for earlier diagnosis in the course of the disease.[1] Specifically, at least 2 clinical relapses were once required to establish a definitive diagnosis, but the 2010 revised McDonald MS diagnostic criteria allow supplementing clinical findings with data from MRI scans.[1,20] For example, a person can be diagnosed with MS on the basis of a single relapse and relevant MRI findings. Revisions to MS diagnostic criteria may result in a decline in the number of people diagnosed with clinically isolated syndrome (ie, the first clinical presentation of disease) because many of those patients are being diagnosed with RRMS based on meeting diagnostic criteria with a single MRI scan.[19] However, despite recent changes in diagnostic criteria, diagnosis is still often delayed in MS because patients may postpone seeking diagnosis or may not see an MS specialist promptly.[1] By the time diagnosis is established, patients may have sustained functional impairment due to unrecognized disease activity.[1] For instance, there is emerging evidence that patients may experience cognitive impairment before other clinical symptoms of MS appear.[21]

During the course of the disease, symptom burden may increase as irreversible damage in the CNS accumulates.[1] Specifically, MS patients may manifest a variety of markers of disability and functional impairment.[1,22] Traditionally in clinical trials, disability in MS has been assessed using the Expanded Disability Status Scale (EDSS), which assigns values from 0 (normal neurological functioning) to 10 (death due to MS) (Table 2).[23] The EDSS score is based on the assessment of multiple functional systems (ie, pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral), but it is largely affected by physical ability and mobility.[1,19,23] Because the EDSS is a nonlinear scale, a small increase in EDSS can reflect a significant change in a patient's functionality and daily activities. There has been a correlation associated with EDSS-derived disability level and the total cost in MS, including healthcare and productivity costs.[10]

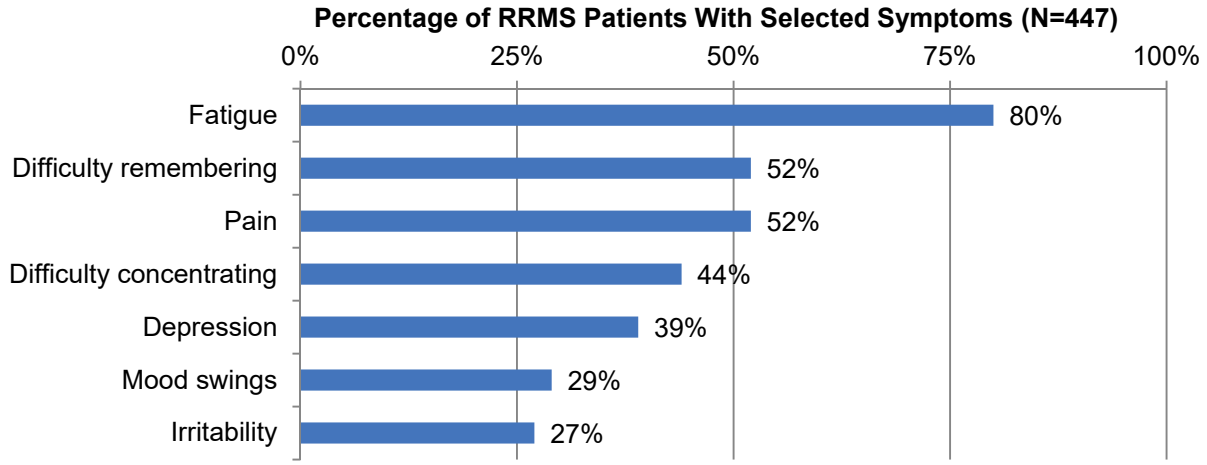
The EDSS score is largely affected by physical mobility, but it may underrepresent common functional impairments in MS, including cognitive impairment, fatigue, pain, and depression.[1,24] It may be helpful to supplement EDSS-based disability data with the findings regarding these neurological problems because they are highly prevalent among MS patients. For instance, a recent national survey presents self-reported symptoms associated with at least 1 neurologic impairment (Figure 2).[22] Many neurologic impairments have been linked to higher healthcare costs and/or lost productivity (eg, absenteeism, presenteeism).[11,12] For example, cognitive decline, fatigue, depression, and anxiety may limit employability even for MS patients with low levels of physical disability.[1] EDSS emphasizes functional impairment, which is the basis of traditional eligibility for disability insurance. Some studies have found physical disabilities, especially impaired ambulation, to have the greatest impact on quality of life, while other authors report pain and depression to be the most burdensome aspects of the disease.[22,25]

TABLE 2
DISABILITY PROGRESSION BASED ON THE EDSS[23]

EDSS Score	Level of Disability
0.0	Normal neurologic exam
1.0	No disability[a]
2.0	Minimal disability[a]
3.0	Moderate disability[a]
4.0	Relatively severe disability; able to walk without assistance for 500 meters
5.0	Disability affects daily routine, able to walk without assistance for 200 meters
6.0	Assistance required to walk
7.0	Restricted to wheelchair
8.0	Restricted to bed or wheelchair
9.0	Confined to bed
10.0	Death due to MS

[a]For EDSS scores of 1.0, 2.0, and 3.0, the disability refers to the maximum impairment in a single functional system. It is possible for such individuals to qualify for disability benefits due to other factors or to combinations of factors.

Figure 2
Patient-Reported Symptoms of Neurologic Impairment[22]



DMT is thought to play an important role, as these therapies are currently approved and indicated for the treatment of relapsing forms of MS.[1,7] According to the consensus paper updated by the MS Coalition in 2015, typically the goal of treatment with DMT is to reduce the early clinical and subclinical disease activity that is thought to contribute to long-term disability.[1] There is a consensus among a panel of MS specialists in the United States that all patients with RRMS should be treated with DMT soon after diagnosis.[13,14] In clinical trials, DMTs have been shown to provide reduction in MRI lesions, reduced relapse frequency, and delayed physical disability progression.[7] Use of DMT has also been associated with reductions in healthcare resource utilization, particularly hospitalizations and emergency room (ER) visits.[26] Among DMT-treated patients, improvements in persistence and adherence have been also associated with lower rates of hospitalization and ER visits, as well as reduced direct nonpharmaceutical costs and indirect costs.[27,28] We note that only limited long-term studies are available on the impact of DMTs on MS[29,30] and to our knowledge there are no published studies examining long-term impact of DMTs on resource utilization.

Treatment in MS is individualized based on numerous factors, including disease activity, prior treatment, and risk tolerance.[7,8] Due in part to the heterogeneity of the patient population, treatment guidelines in MS do not endorse a specific treatment algorithm.[7,8,31] DMTs offer diverse treatment options, but there is still lack of consensus on the choice of DMT in initial treatment of relapsing MS.[7,13,14] DMT utilization patterns demonstrate relatively frequent transitioning or discontinuation among DMT agents.[32,33]

SNAPSHOT ANALYSIS (2013 DATA)

This analysis includes descriptive statistics to highlight how the MS population is represented in the context of a traditional calendar year (ie, 2013). Please see Appendices A, B, and C for detailed descriptions of the data sources, methodology, and code sets.

PREVALENCE

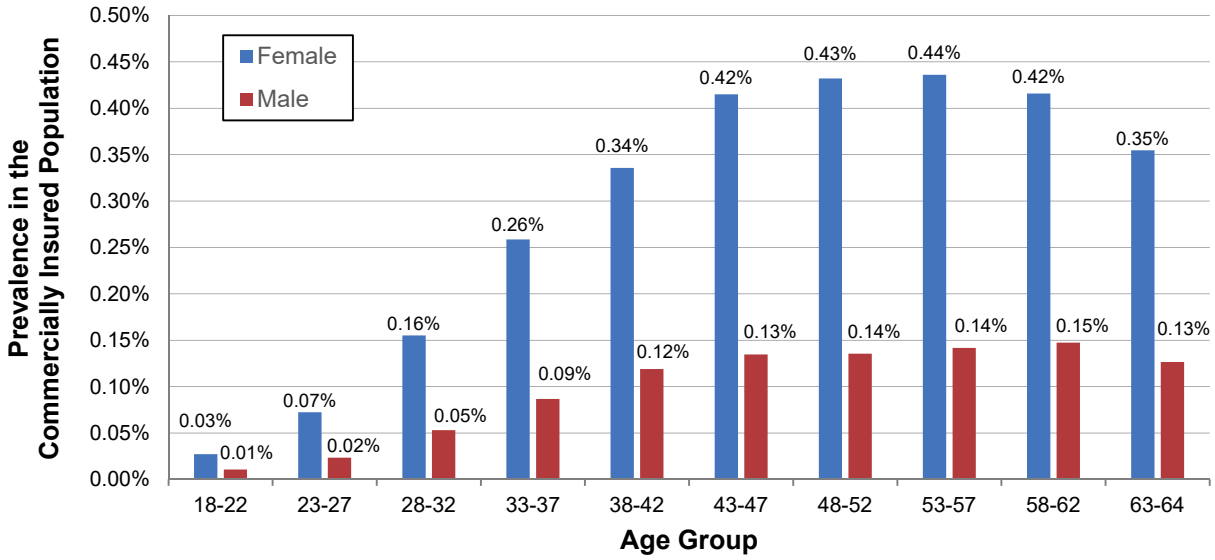
Prevalence data for 2013 show that MS affected 0.15% of people within a commercially insured population (Table 3). In this patient population, the average age was approximately 48 years and a large majority were women. These statistics are consistent with prior published studies using commercial claims data.[34,35]

TABLE 3
PREVALENT CASES OF MS IN 2013

Prevalence Rate	151.2 per 100,000
Average Age	47.7 years old
Proportion of Females	77%

Figure 3 shows that for both women and men, MS prevalence continued to rise with increasing age until rates peaked and started to decline around the ages of late 50s to early 60s. This decline is consistent with the loss of active commercial insurance coverage that would be expected for patients with a debilitating disease such as MS. The fact that the MS prevalence rate is declining for later age groups suggests that patients with MS are exiting (for any reason) faster than the general commercial population of the same age.

Figure 3
MS Prevalence by Age Group and Gender in 2013



MS prevalence in the commercial population peaked at 53 to 57 years for women and 58 to 62 years for men.

INCIDENCE

Newly diagnosed MS patients were identified through a look-back process whereby patients were identified as newly diagnosed if they did not have any claims indicating MS diagnosis or DMT use in the previous 24 months.

New cases of MS were identified in 0.015% of the commercially insured sample. Table 4 shows the average age for the 24-month continuous enrollment criteria needed to identify new MS patients. As seen in large claims databases, commercial health plans have a greater turnover rate for younger patients. Thus, there are proportionately fewer members meeting the 24-month continuous enrollment criterion. This may dampen the number of newly diagnosed patients who are identified at the younger age range. As a result, prevalent and incident cases may appear to have the same average age, which was in fact reported by other investigators.[35] However, after normalizing the data, the average age of newly diagnosed patients was approximately 43 years for females and males, or about 5 years lower than for prevalent cases. Additional details on the normalization process used in this analysis are included in Appendix B.

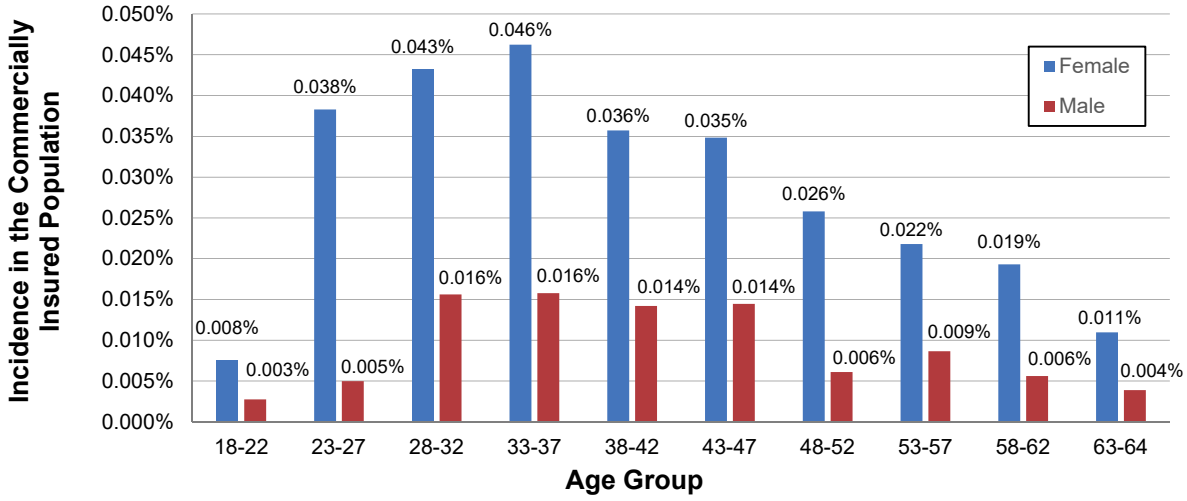
While no algorithm will consistently and accurately identify all initial MS diagnoses, our normalization methodology may help researchers who use administrative claims databases to identify newly diagnosed patients with MS and can be considered by insurers who analyze their own data.

TABLE 4
INCIDENT CASES OF MS IN 2013

Prevalence Rate	14.6 per 100,000
Average Age	42.6 years old
Proportion of Females	77%

Figure 4 shows that, unlike prevalence trends presented above, most incident cases were observed among those who are in their late 20s to late 40s.

Figure 4
MS Incidence by Age Group and Gender in 2013

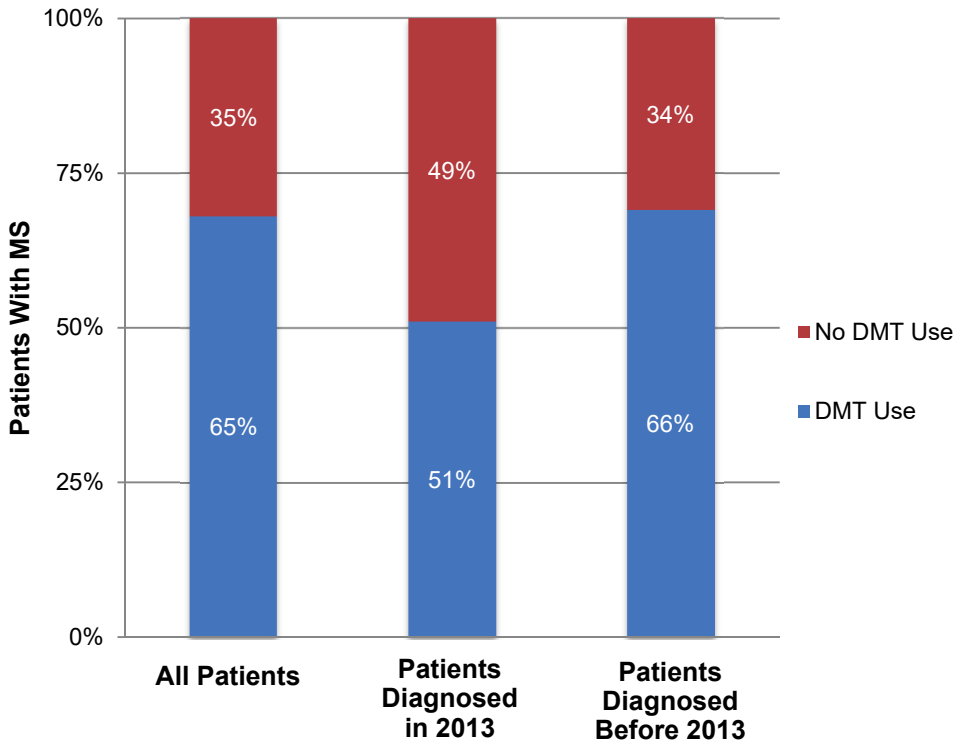


In 2013, approximately 10% of MS patients in a commercial population were newly diagnosed.

DMT TREATMENT RATE

Among patients with MS, 65% had at least 1 or more claim for DMT during the 12-month period in 2013. This DMT treatment rate was somewhat higher than the previously reported rates of 53% to 58%.[11,34] Figure 5 illustrates that among patients newly diagnosed with MS in 2013, 51% had claims for DMT treatment. However, this may be an underestimation because we are only capturing 1 year's worth of data and may be missing patients who initiated treatment early in the next calendar year. Specifically, it is possible that patients diagnosed at the end of 2013 may have started treatment in the beginning of 2014.

Figure 5
DMT Treatment Rate Among Patients With MS in 2013

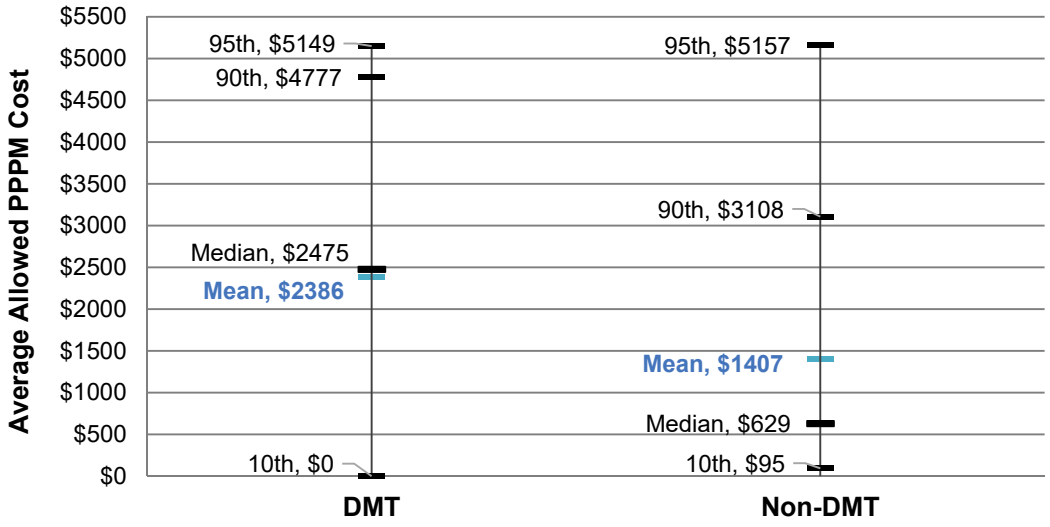


About 1 out of 3 patients with MS did not receive DMT treatment in the year 2013.

HEALTHCARE COSTS

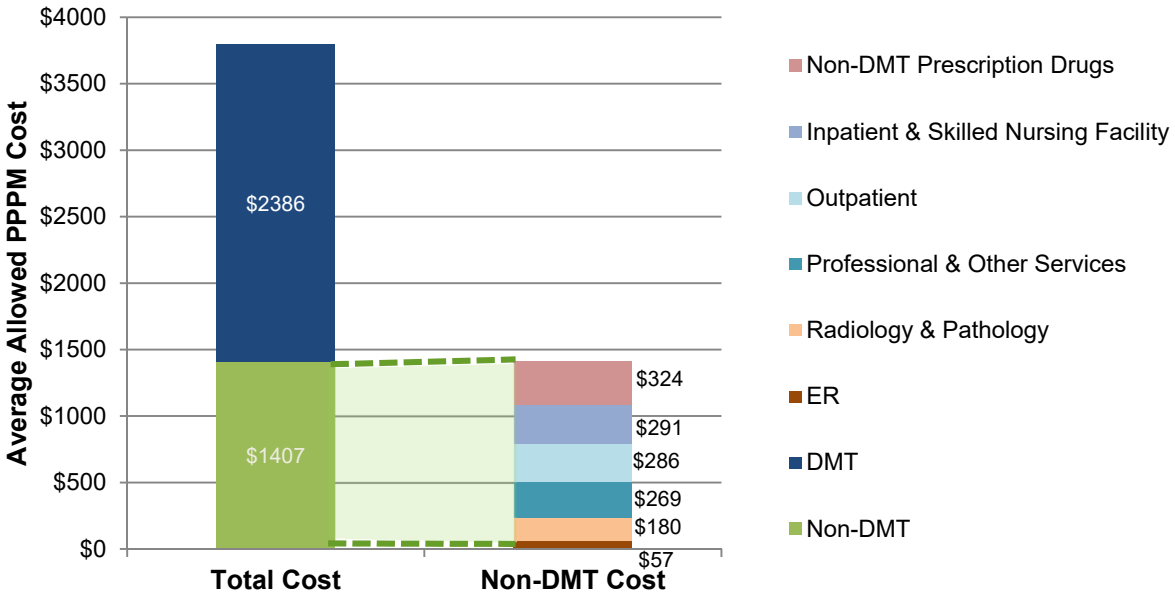
Per-patient per-month (PPPM) claim costs were evaluated for all database patients with MS in 2013 and included both insurer-paid and patient cost-sharing amounts. The average allowed PPPM claim cost in this patient population was $3793, which was substantially greater than approximately $400 per member per month for the entire commercially insured population in the database. Figure 6 depicts considerable variations in allowed costs for patients with MS, particularly for claim costs associated with medical services and non-DMT prescription drugs (ie, non-DMT costs). For example, for non-DMT items and services, the 95th percentile PPPM claim cost ($5157) was more than 3 times the mean ($1407). This finding demonstrates that the MS population included patients with diverse resource utilization.

Figure 6
Percentile Distribution of Allowed PPPM Claim Costs for Patients With MS in 2013



DMTs made up 63% of the average allowed cost, while the remaining 37% was attributed to all other costs, including inpatient and outpatient care, ER visits, durable medical equipment (DME) supplies, and non-DMT prescription drugs (Figure 7). Hospitalizations, skilled nursing facility (SNF) stays, and ER visits made up nearly 25% of non-DMT costs. A previously published analysis of claim costs among patients with MS reported a similar distribution of healthcare costs across these service categories.[34]

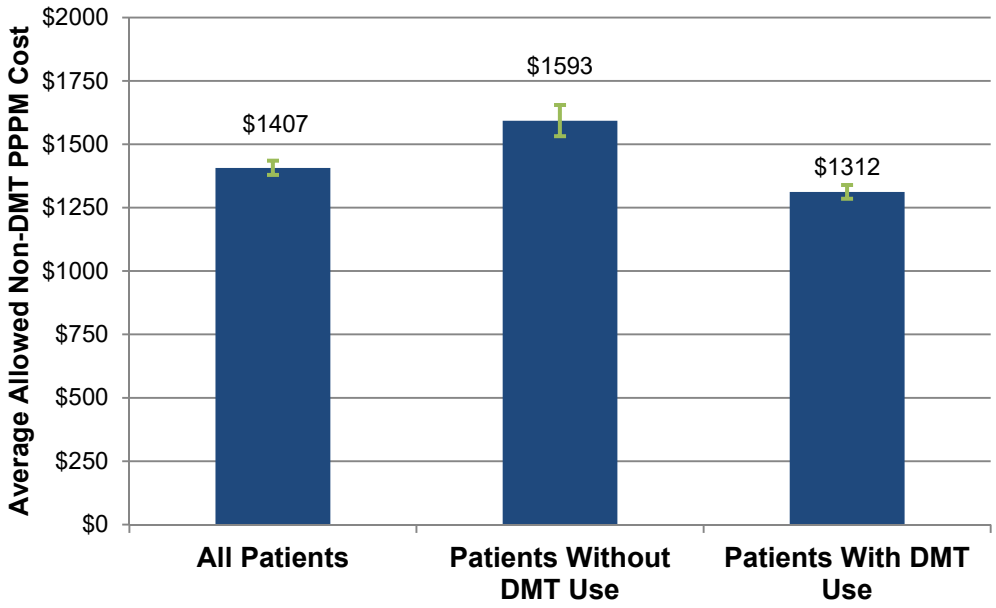
Figure 7
Allowed PPPM Claim Costs by Service Category for Patients With MS in 2013



37% of healthcare spending for patients with MS was attributed to non-DMT costs.

Unadjusted average allowed non-DMT costs were also compared among patients with MS based on the presence of DMT claims (ie, patients without DMT claims versus those with at least one DMT claim in 2013). As shown in Figure 8, the average monthly non-DMT cost among patients with DMT use ($1312) was approximately 18% lower than among those without DMT use ($1593). It is important to note that in addition to DMT treatment, other factors such as age, gender, and disease duration might have contributed to this difference; however, it was not possible to control for these factors due to the limitations associated with a snapshot analysis.

Figure 8
Allowed Non-DMT PPPM Claim Costs by DMT Use for Patients With MS in 2013
(Including 95% confidence intervals)



In 2013, the unadjusted average monthly non-DMT cost among patients with DMT use was approximately 18% lower than among those without DMT use. Potential confounding factors like age, gender, and disease duration were not adjusted for in this analysis.

LONGITUDINAL ANALYSIS (2003-2014 DATA)

This analysis includes patient-level data capturing patterns of care during a 12-year period (for the years 2003-2014). This longitudinal analysis provides an opportunity to examine disease progression, treatment patterns with DMT, and related healthcare costs in newly diagnosed patients over the course of 10 years. The core focus of this analysis was on the identification of disability and functional impairment during the course of MS because this aspect of disease activity, to our knowledge, has not been evaluated previously through claims data. Assessments of disease activity in previously published claims analyses have been generally limited to the identification of relapse rates.[35]

Please see Appendices A, B, and C for detailed descriptions of the data sources, methodology, and code sets. In addition, Appendix D includes supplemental data with detailed description of allowed claim costs and annual relapse rates.

DISABILITY MARKERS

Claims data can be used to track some aspects of disability and functional impairment. Even though insurance claims do not capture all clinical details needed to assess functional systems for EDSS scoring (which is frequently used in clinical trials), claims data may capture disability indicators that can be approximately analogous to several of those used in the EDSS, such as mobility and visual impairments, spasticity, bladder dysfunction, and cognitive or behavioral dysfunction. Claims data may also track neurologic impairment indicators that are often related to MS. This approach can supplement the information identified by the EDSS-derived disability indicators.

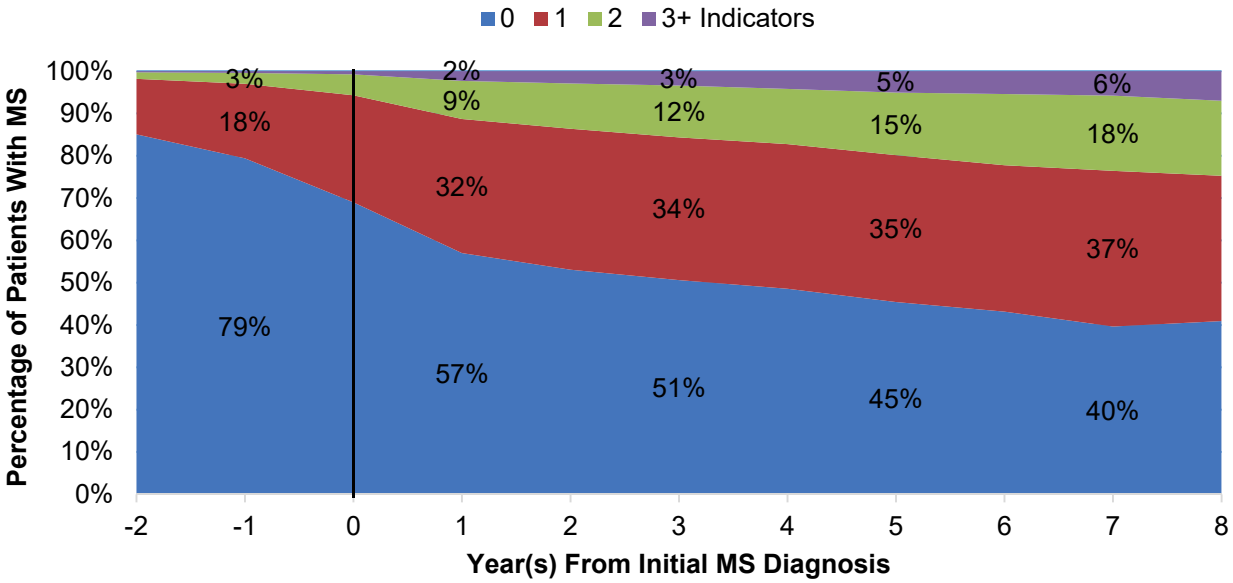
In this analysis, health insurance claims of newly diagnosed MS patients were used to identify the presence and progression of both sets of indicators. A patient flagged for any of these disability and functional impairment indicators continued to be flagged for the remainder of the observation.

EDSS-Derived Disability Indicators *(identified through diagnosis codes and/or non-DMT prescription drug treatment)*	**Related Neurologic Impairment Indicators** *(identified through non-DMT prescription drug treatment)*
• Spasticity • Bladder dysfunction • Cognitive/behavioral dysfunction[a] • Visual impairment • Mobility impairments requiring cane, walker, wheelchair, or specialty bed	• Pain • Fatigue • Depression • Cognitive impairment[b]

[a]Identified through medical claims with relevant diagnosis codes (eg, ICD-9 codes for dementia, mild cognitive impairment, pseudobulbar affect, etc).
[b]Identified through pharmacy claims for relevant non-DMT prescription drug therapies (eg, acetylcholinesterase inhibitors for the treatment of dementia).

EDSS-derived disability indicators were observed in up to 30% of patients by the date of diagnosis (Figure 9). During the course of the disease, more patients became affected and the number of indicators had grown. For instance, by 5 years after diagnosis, at least 1 EDSS-derived disability indicator was identified for 55% of patients. Moreover, at 5 years, 1 in 5 patients were identified as having 2 or more EDSS-derived disability indicators.

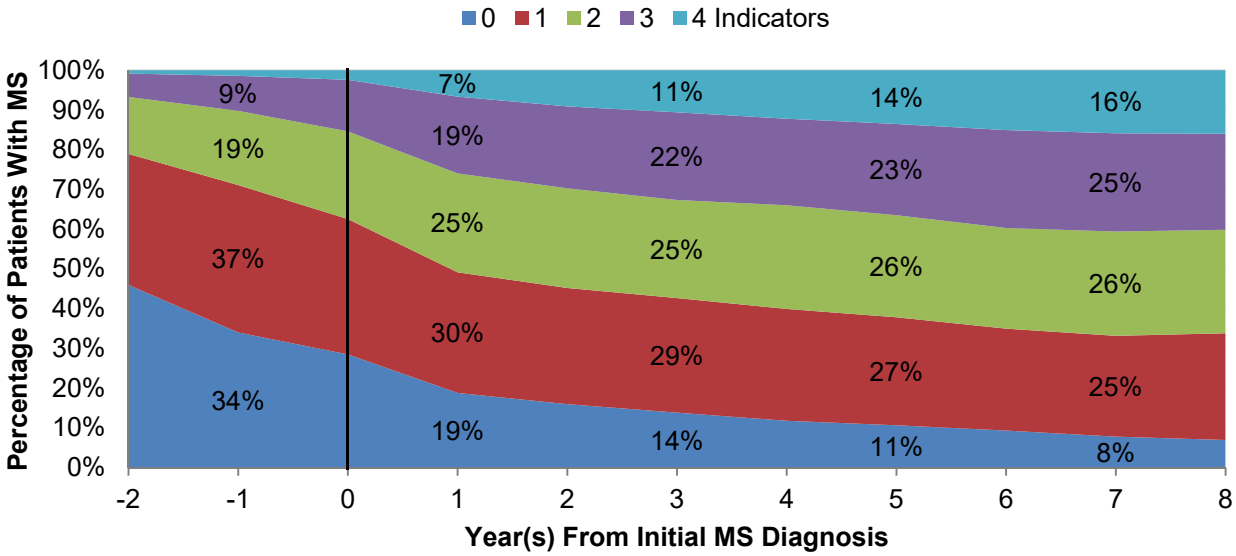
Figure 9
Cumulative Distribution of Patients With MS by the Number of EDSS-Derived Disability Indicators During the Course of the Disease



Identification of patients with related neurologic impairment indicators that include pain, fatigue, depression, and cognitive impairment may offer additional insights into the patient journey and the burden associated with MS disease activity. Related neurologic impairment indicators for individual MS patients were defined by the presence of a single claim in the particular non-DMT drug classes shown in Appendix C. Figure 10 shows that more than 50% of patients filled at least 1 prescription in classes generally used to treat pain, fatigue, depression, or cognitive impairment, by 2 years before MS diagnosis was identified. By 1 year after diagnosis, this percentage increased to approximately 80%. Almost 90% of patients filled 1 or more prescriptions for the drug classes by 5 years after MS diagnosis; most of them filled prescriptions in 2 or more of the classes.

Whether the use of such medication was for an MS-related symptom or a nonrelated condition was not determined. This may result in overlaps between both sets of indicators; therefore, Figure 10 should be a consideration—indicating the increase in impairments—rather than a definitive statement of the prevalence or incidence of impairments. Our data support previously published findings that these neurologic impairments are commonly reported among patients with MS and may manifest early in the disease course.[1,21,22,36] These findings may have important health management implications because neurologic impairments such as fatigue, pain, depression, and cognitive impairment have been shown to impact healthcare costs, productivity, and loss of employment.[1,11,12]

Figure 10
Cumulative Distribution of Patients With MS by the Number of Related Neurologic Impairment Indicators[a] During the Course of the Disease

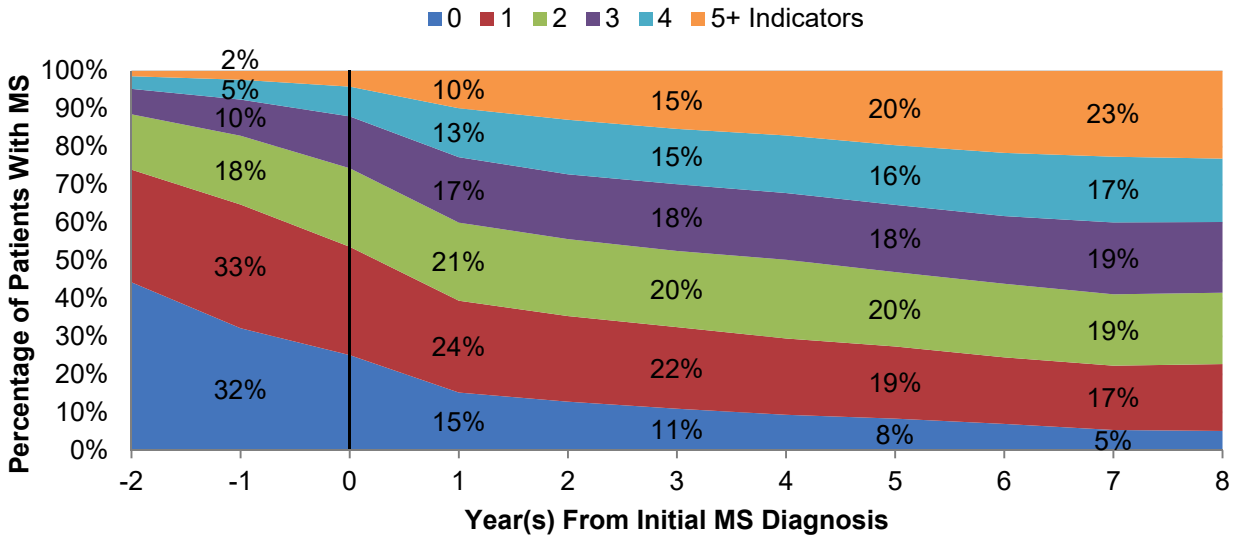


[a]Identified by prescriptions filled for particular drug classes.

Patients with these neurologic impairment indicators for MS were compared with the general 2013 commercial population (aged 18 to 64 years as described in Appendix A). In 2013, approximately 68% (SD 47%) of patients with MS had 1 or more non-DMT prescriptions that were filled and related to MS neurologic impairment indicators, compared with 38% (SD 48%) for the general commercial population.

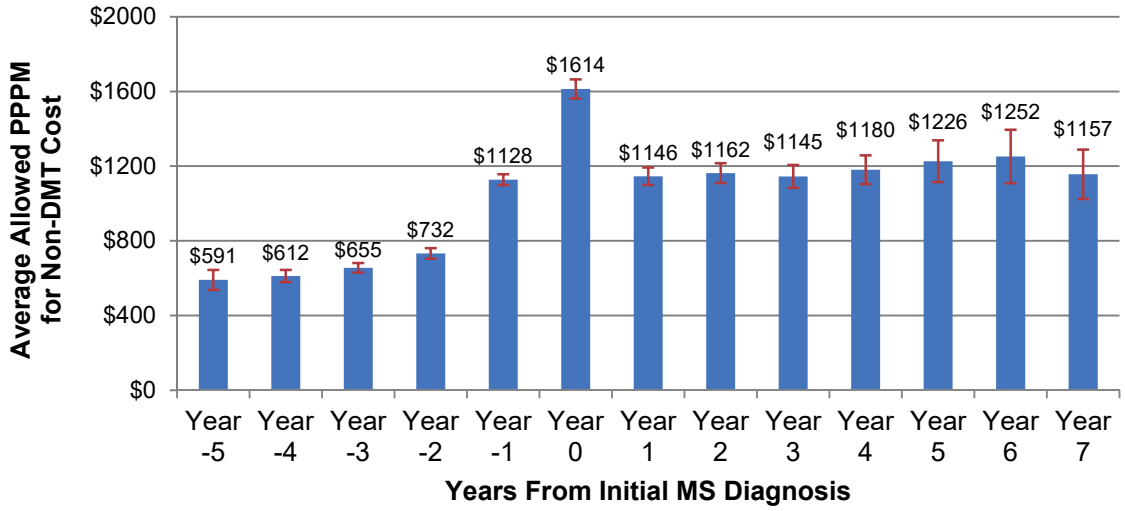
Combining the indicators of EDSS-derived disability and related neurologic impairment showed that MS patients can be affected by many different conditions (Figure 11). During the course of the disease, patients tend to accumulate a growing number of markers of disability progression and functional impairment.

Figure 11
Cumulative Distribution of Patients With MS by the Combined Number of Indicators for EDSS-Derived Disability and Related Neurologic Impairment During the Course of the Disease



Results indicated that this accumulation of impairments often begins years before patients are diagnosed. Non-DMT costs appeared to increase above the prior year's level in the second and first years before diagnosis. Costs appeared to peak in the year following MS diagnosis and were reduced somewhat thereafter (Figure 12).

Figure 12
Allowed PPPM Costs Associated With Non-DMT Services During the Course of the Disease (including 95% confidence intervals and trended to 2015)



Indicators of disability and functional impairment were evident in claims for many patients before MS diagnosis was established and appeared to increase during the course of disease.

DMT TREATMENT INITIATION

To examine treatment initiation dynamics, a cohort of patients who were newly diagnosed in 2012 and had 24 months of continuous enrollment following diagnosis was identified. A total of 33% of these newly diagnosed patients did not have claims for DMT treatment in the 2 years after diagnosis.

One-third of newly diagnosed patients with MS had no claims for DMTs in the 2 years after diagnosis.

DMT IMPACT

In light of the differences in non-DMT costs identified in the snapshot analysis, a regression model was used to identify key factors that influence non-DMT claim costs for MS patients. The dependent variables considered in this analysis were age, gender, DMT use, MS patient status (new or established), calendar year, and duration of disease (from diagnosis [Year 0] to Year 10).

Patient characteristics such as age, gender, and health status of the underlying sample population in each year of data used were accounted for in the regression analysis. However, because this study is longitudinal, patients entered and left the database at different times, and therefore, it was not feasible to display the patient characteristics for each year. For example, a patient could be in our study for as long as 10 years and the characteristics of this patient would be different in each of the 10 years.

The regression analysis showed that non-DMT claim costs appeared to increase with age for both females and males, but with large variation, as shown in Appendix B. Calendar year did not appear to be a significant driver of non-DMT claim costs or relapse rates and thus was excluded from the final regression model. The final regression model and summary charts are shown in Appendix B. A detailed exhibit of estimated claim costs by duration for MS patients is included in Appendix D.

In our regression analysis, DMT use was associated with a reduction in non-DMT costs equivalent to approximately 7% of the DMT spend. In a hypothetical example, an estimated savings of $4550 in non-DMT claim costs may occur for a patient who incurs DMT claim costs of approximately $65,000 in a given year. This is an important finding that may warrant further studies of the potential impact of DMT on non-DMT utilization and cost, especially among patients with similar or matched baseline characteristics. Previously, DMT use has been shown to be associated with significant reductions in hospitalizations, length of stay, and ER visits.[26]

In addition, findings from the regression analysis were used to adjust the average monthly non-DMT cost among patients with DMT use in 2013. Considering that DMT use was associated with a reduction in non-DMT costs equivalent to approximately 7% of the DMT spend, it was determined that the adjusted average monthly non-DMT cost among patients with DMT use was an estimated 16% lower than among those without DMT use (Table 5).

TABLE 5
REDUCTION IN ALLOWED NON-DMT PPPM CLAIM COSTS ASSOCIATED WITH DMT USE FOR PATIENTS WITH MS IN 2013

	Average Non-DMT PPPM Claim Cost		%
	Patients Without DMT Use	Patients With DMT Use	Difference
Unadjusted for DMT Use	$1593	$1312	18%
Adjusted for DMT Use	$1593	$1336	16%

In the regression model, DMT use was associated with a reduction in non-DMT costs equivalent to approximately 7% of the DMT spend, which corresponded to an estimated 16% reduction in monthly non-DMT costs when adjusted for DMT use in 2013.

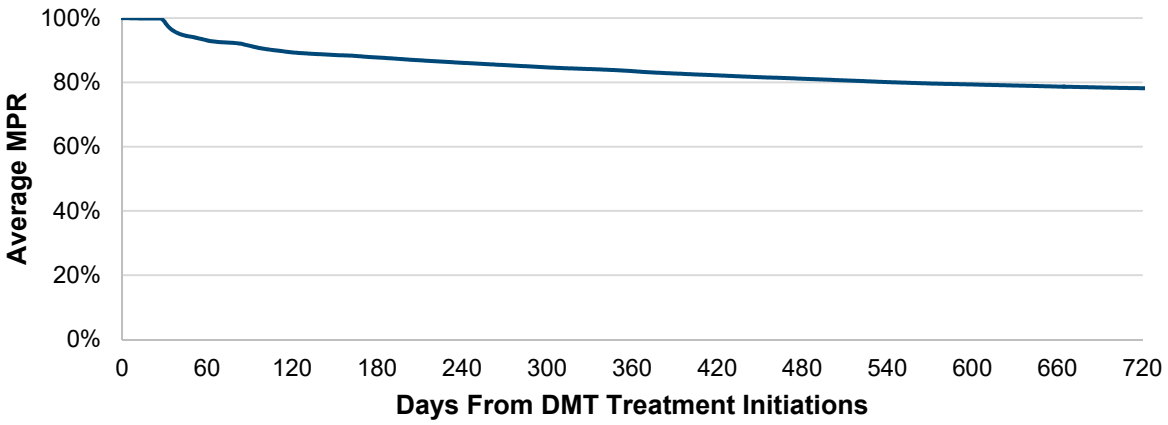
DMT USE PATTERNS

DMT-switching patterns and treatment adherence were evaluated in a cohort of patients who were newly diagnosed in 2012 and had 24 months of continuous enrollment following diagnosis.

A total of 31% of patients switched to another DMT option within 2 years of initiating treatment. This finding reflects the dynamic nature of DMT use and is somewhat higher than the 19% switch rate reported in a previously published study, which included patients who initiated DMT between 2007 and 2009.[33] This discrepancy might be due in part to the evolving therapeutic landscape in MS. It is possible that patients included in our analysis switched treatment more frequently because they had access to more DMT options than those treated before 2012. It has been suggested that patients may switch to another DMT option due to breakthrough disease activity, intolerance, safety concerns, or suboptimal adherence.[7,32,37] It has been reported in one study that patients who switch DMT treatment tend to have higher costs than those who remain on initial therapy.[32]

Figure 13 shows the average medication possession ratio (MPR) for patients who had 24 months of continuous enrollment following diagnosis in 2012 (starting with each patient's first day of therapy). MPR is a standard measure of prescription drug compliance. Overall, adherence steadily declined during the first 2 years of treatment, with the average MPR falling below 80% at around 18 months. It has been reported that lack of DMT adherence may lead to increased resource utilization, along with higher healthcare and productivity costs.[27,28]

Figure 13
Average MPR During a 2-Year Period After DMT Initiation in Newly Diagnosed Patients



Approximately 1 out of 3 patients switched to a different DMT within 2 years after initiating treatment.

POTENTIAL IMPLICATIONS FOR PAYERS

Up to 12 years of commercial insurance claims were analyzed to help provide additional insights on the patient journey in MS, including disease progression after diagnosis, treatment patterns with DMT, and related healthcare costs. These insights may supplement currently available evidence and may encourage payer organizations to explore their own data.

The findings underscore 3 potential important implications for payer organizations:

Potential Implications	Relevant Findings
Claims data may be a useful source for insurers to help understand the patterns and progression of MS and its impairments.	• Important impairments and markers of disease progression have been identified in claims data • Patient drug switching, adherence, and nonuse can be identified • The appearance of impairments prior to diagnosis suggests that these findings, along with similar data analyses for other patient populations (including those with neurologic conditions unrelated to MS), can be used to explore the feasibility of claims-based predictive modeling for identifying patients at risk for being diagnosed with MS
Disease burden in MS can be assessed through various markers of disease progression and functional impairment.	• Use of disability indicators approximately analogous to those used in EDSS, along with related neurologic impairment indicators, may be useful in assessing disease burden in MS
Longitudinal analyses of a large administrative database may help assess the potential cost impact of chronic drug therapies.	• DMT use was associated with apparent differences in non-DMT costs ○ In the snapshot analysis, the *unadjusted* average monthly non-DMT cost among patients with DMT use was approximately18% lower than among those without DMT use ○ In the regression model, DMT use was associated with a reduction in non-DMT costs equivalent to approximately 7% of the DMT spend, which corresponded to an estimated 16% reduction in monthly non-DMT costs when adjusted for DMT use in 2013

In addition, the data may be relevant to aspects of current expert opinion in the treatment of MS:

Expert Opinions	Relevant Findings
It has been suggested that DMT treatment should be initiated soon after the diagnosis of RRMS is established.[7,13,14]	• Approximately one-third of patients with MS remained untreated within 2 years after diagnosis
Due to the heterogeneity of patients with RRMS, access to a broad range of DMT options is important.[7,8]	• MS population includes patients with diverse resource utilization as exhibited by considerable variations in allowed costs • Approximately 1 out of 3 patients switched to a different DMT within 2 years after initiating treatment

APPENDIX A: DATA SOURCES

The Truven Health Analytics MarketScan® Commercial Databases (2003-2014) were used in preparing the results found in this memo.

MarketScan databases contain all paid claims generated for millions of commercially insured lives. The 2014 MarketScan database currently contains about 40 million lives. The MarketScan database represents the inpatient and outpatient healthcare service use of individuals nationwide who are covered by the benefit plans of large employers, health plans, government, and public organizations. The data include diagnosis codes, procedure codes, diagnosis-related group codes, and national drug codes (NDCs), along with site of service information and the amounts paid by commercial insurers. The MarketScan database links paid claims and encounter data to detailed patient information across sites, types of providers, and over time. The annual medical database includes private sector health data from approximately 100 payers.

Please note that the contributors to MarketScan may vary from year to year; therefore, whether a member continues in the database depends on the member continuing coverage in a health plan that continues to contribute its data to MarketScan. A member may not appear in MarketScan because the member has stopped or switched coverage or because the member's health plan has stopped contributing.

In developing non-DMT cost trends, reports of Medical Care CPI-U were used from the US Bureau of Labor Statistics. For DMT cost trends, Wolters Kluwer's Medi-Span database was used to identify average wholesale price (AWP) unit prices for all DMT drugs. Medi-Span is a comprehensive drug data source that contains brand and generic drug names, NDCs, generic product identifiers, manufacturer information, and various price metrics for close to 200,000 drug products.

APPENDIX B: METHODOLOGY

Denominator Population

The denominator population for the 2013 snapshot analysis of prevalence, incidence, and costs included members who were identified with MS in 2013 or any previous year, while excluding months for members with the following characteristics:

- Aged 65 years or older
- Enrolled in unknown or capitated plan types
- Employment status of part-time or seasonal; Medicare-eligible retiree; or long-term disability
- No prescription drug coverage

MS Identification

Patients with MS in the MarketScan databases were identified using the following: 2 inpatient (IP) stays or outpatient (OP) claims (including observation, ED, or evaluation and management [E&M]) with MS ICD-9 diagnosis code 340 at any time during the claim, and 30 or more days apart, but no greater than 12 months apart. Patients younger than 18 years or older than 65 years were excluded from this analysis. The index date (unless modified as described below) was set as the incurral date of the claim according to this logic.

Newly Diagnosed Patient Identification

Newly diagnosed MS patients were identified as having 24 months of continuous enrollment prior to first MS diagnosis date with no earlier MS identification possible. The index date was reset to the incurral date of the first DMT script if earlier than the first MS diagnosis date.

Commercial health plans have greater turnover of younger patients. Thus, there are proportionately fewer members meeting the 24-month continuous enrollment criteria at younger ages than at older ages. This dampens the number of newly diagnosed patients who are identified at the younger age ranges. As a result, prevalent and incident cases may appear to have the same average age, which was also reported by other investigators.

Consequently, the denominator for MS incidence was determined as the number of people in each age group with 24-month continuous enrollment. After making this modification to the normal incidence rate calculation, the average age of newly diagnosed patients was approximately 43 years for females and for males, or about 5 years lower than for prevalent cases.

Duration Year

For each member, duration year, year(n), is defined as the nth year before or after the 12-month period starting with the member's initial diagnosis date (or index date). The initial diagnosis date begins year (0). The following table illustrates our assignment of years for year(-4) through year(4).

Year(-2)	Year(-1)	Year(0)	Year(1)	Year(2)
2 full years before initial diagnosis	1 full year before initial diagnosis	1st full year after initial diagnosis, day 1 of Year(0)	2nd full year after initial diagnosis (1 full year after initial diagnosis year)	3rd full year after initial diagnosis (2 full years after initial diagnosis year)

Trending of Allowed Claim Costs

Allowed claim costs were trended from the incurral month of the claim to July 1, 2015, using the following trend rates:

- Non-DMT claim costs: based on the change in Medical Care CPI-U
- DMT claim costs: based on annual change in AWP, weighted by the utilization by drug for each year

The resulting trend rates are as follows:

Year[a]	Annual Trend Rate	
	Non-DMT	DMT
2003	N/A	N/A
2004	N/A	N/A
2005	4.0%	2.8%
2006	4.4%	5.5%
2007	3.7%	9.9%
2008	3.2%	16.7%
2009	3.4%	10.4%
2010	3.0%	16.1%
2011	3.7%	14.8%
2012	2.5%	17.2%
2013	2.4%	9.7%
2014	2.6%	12.1%

[a]The trend from 2004 to 2005 is shown in the 2005 row.

Regression Analyses

Non-DMT Claim Costs Model

A normal linear regression was chosen to estimate non-DMT claim costs, which is most accurate when compared with other linear regression models based on the Akaike information criterion (AIC), a measure of the relative quality of statistical models for a given dataset.

The regression model-dependent variable is non-DMT claim costs of MS patients. The model explanatory variables were age, gender, DMT use, MS patient status (new or established), and duration from index date.

The non-DMT claim cost regression model output is the marginal allowed non-DMT per-patient-per-year (PPPY) claim costs by explanatory variable. Marginal costs refer to the change in cost from the "base" scenario when changing the parameter variables. The base scenario is represented by the parameters with the lowest marginal non-DMT costs—a newly diagnosed male, aged 18 to 35 at duration Year(2).

The model formula is:
$Y = intercept + age/gender + (DMT\ PPPY\ x\ coefficient) + duration\ year + MS\ status$

Claim Cost Regression—Marginal Allowed Non-DMT PPPY Claim Costs

Parameter	Estimate Diagnosed	95% Confidence Interval
Intercept	*$14,025*	*$13,096 – $14,955*
Female Aged 18-35	$1245	$378 – $2113
Female Aged 36-45	$2075	$1247 – $2903
Female Aged 46-55	$4120	$3303 – $4937
Female Aged 56+	$8058	$7183 – $8933
Male Aged 18-35	*$0*	*$0*
Male Aged 36-45	$638	-$334 – $1609
Male Aged 46-55	$5491	$4556 – $6426
Male Aged 56+	$8264	$7194 – $9335
Duration Year(0)	$3452	$2990 – $3935
Duration Year(1)	$20	-$494 – $534
Duration Year(2)	*$0*	*$0*
Duration Year(3)	$154	-$477 – $785
Duration Year(4)	$484	-$224 – $1192
Duration Year(5)	$875	$43 – $1707
Duration Year(6)	$1432	$444 – $2420
Duration Year(7)	$1300	$123 – $2477
Duration Year(8)	$740	-$710 – $2190
Duration Year(9)	$487	-$1481 – $2454
Duration Year(10)	$563	-$2642 – $3767
Established	$2607	$2192 – $3022
Newly Diagnosed	*$0*	*$0*
DMT PPPY	-$0.07	-$0.07 – $0.06

Notes:
The “base” scenario, as reflected in the intercept, represents an established male MS patient aged 18-35 years in duration Year(2) (highlighted rows in table).

Duration Year(n) is defined as the nth year before or after the 12-month period starting with the member’s initial diagnosis date (or index date). The initial diagnosis date begins Year(0).

For example, if the annual allowed DMT claim costs of a newly diagnosed female aged 40 were $20,000 in the index year, year(0), the model predicts that her annual allowed non-DMT claim costs in duration year(1) would be $14,720, or $1400 less than a similar person not using DMT.

Non-DMT PPPY (F40, Year(1) = $14,025 + $2075 + ($20,000 x -$0.07) + $20 + $0 = $14,720

Kaplan-Meier Survival Analysis of Functional Impairment

The progression of the various functional impairments experienced by MS patients was measured using a Kaplan-Meier (KM) survival approach, a standard technique used to estimate survival functions for populations with incomplete data. Health insurance claims of newly diagnosed MS patients were analyzed for the presence and progression of various indicators of functional impairment. Impairment indicators were tabulated for MS patients identified from MarketScan as newly diagnosed from several years before their diagnosis for up to 10 years after. Each year, these patients were flagged as having 1 or more of the following functional impairment indicators segmented into EDSS-derived impairments and MS-related CNS impairments. For purposes of the survival analysis, it was assumed that a patient's impairment, once identified, persisted through the remaining observation years. Due to the limitations associated with claims data, it is not possible to determine definitively when a condition identified by one of these indicators has improved or resolved. For instance, a patient who has discontinued antidepressant therapy might continue to suffer from depression.

EDSS-derived disability indicators (identified through diagnosis and/or drug treatment):

- Spasticity
- Bladder dysfunction
- Cognitive/behavioral dysfunction
- Visual impairment
- Mobility impairments requiring:
    - Cane
    - Walker
    - Wheelchair
    - Specialty bed

Related neurologic impairment indicators (identified through drug treatment):

- Pain
- Fatigue
- Depression
- Cognitive impairment

Drugs used for neurologic impairments were grouped by their common classification; however, the use of many of these drugs for MS patients may vary from their common classifications. For example, depression medications may have been used to treat pain. For this reason, the potential overlap between functional impairment indicators was not attempted.

A description of the identification criteria for these markers is shown in Appendix C. A patient flagged for any of these functional impairment indicators was flagged for the remainder of the observation.

DMT Patterns and Adherence

DMT Brands

Prescriptions filled for the following DMT drugs were included in the analysis: Aubagio (teriflunomide), Avonex (interferon beta-1a), Betaseron (interferon beta-1b), Copaxone (glatiramer acetate), Extavia (interferon beta-1b), Gilenya (fingolimod), Glatopa (glatiramer acetate), Plegridy (peginterferon beta-1a), Rebif (interferon beta-1a), and Tecfidera (dimethyl fumarate). Visits coded with the following DMT treatments were included in the analysis: Lemtrada (alemtuzumab) and Tysabri (natalizumab).

We use the following conventions to define 30-day supplies of Lemtrada and Tysabri: A Lemtrada CPT code is equivalent to 12 thirty-day supplies. A Tysabri CPT code is equivalent to 28/30 thirty-day supplies.

Medication Possession Ratio (MPR)

Medication possession ratio (MPR) is typically calculated based on a single prescription medication. The MPR concept was adapted because the analysis included people who may have prescriptions for multiple DMT drugs. Overlaps in different drugs were ignored. Each newly diagnosed patient (as described in cohort descriptions) with DMT use in the 24-month period following the index date, and with full eligibility in the 24 months following the first use of DMT, is captured in the graph. For each patient, every eligible day from the date of first use of DMT up to 24 months after was evaluated. If a day fell in this range for a DMT drug (incurred date to incurred date + day supply), then the patient was said to be using DMT on this day.

The date of first DMT use was called Day 0. For each Day x, $0 \leq x \leq 729$ and each patient, a variant of MPR was calculated on the interval Day 0 to Day x as follows:

$$MPR = (\#\ days\ patient\ possesses\ DMT)/(x+1)$$

The average value across patients was taken for each Day (x).

Relapse Identification

"Relapse episodes" were identified as:

- An acute IP admission with MS diagnosis code 340 in the primary position of the claim at least 30 days from earliest MS diagnosis date

OR

- An ED or E&M claim with MS diagnosis code 340 in any position of the claim at least 30 days from earliest MS diagnosis date and a relapse drug treatment claim or script within 7 days of the qualifying ED/E&M claim. Note that the relapse drug treatment claim and the ED/E&M claim could be the same claim

To prevent counting the same relapse episode more than once, the following algorithm was applied at the patient level to the above criteria:

- Identify the earliest relapse episode occurring more than 30 days from the earliest MS diagnosis date. This qualifies as a relapse in our analysis
- Identify the next relapse episode occurring at least 30 days from the most recent qualifying relapse and continue this way until all relapses are identified for each patient

APPENDIX C: CODE SETS

DMT Drugs
EXTAVIA (interferon beta-1b)
GILENYA (fingolimod)
COPAXONE (glatiramer acetate)
GLATOPA (glatiramer acetate)
REBIF (interferon beta-1a)
REBIF REBIDOSE TITRATION
REBIF REBIDOSE
REBIF TITRATION PACK
BETASERON (interferon beta-1b)
LEMTRADA (alemtuzumab)
AUBAGIO (teriflunomide)
TYSABRI (natalizumab)
AVONEX (interferon beta-1a)
AVONEX PEN
TECFIDERA (dimethyl fumarate)
TECFIDERA STARTER PACK
PLEGRIDY (peginterferon beta-1a)
PLEGRIDY STARTER PACK

DMT Procedures
LEMTRADA (alemtuzumab)
COPAXONE (glatiramer acetate)
GLATOPA (glatiramer acetate)
AVONEX (interferon beta-1a)
AVONEX PEN
REBIF (interferon beta-1a)
REBIF REBIDOSE
REBIF REBIDOSE TITRATION
REBIF TITRATION PACK
BETASERON (interferon beta-1b)
TYSABRI (natalizumab)

Non-DMT Relapse Drugs
SOLU-MEDROL
A-METHAPRED
METHYLPREDNISOLONE SODIUM SUCCINATE
PREDNISONE

Relapse Procedures
INTRAVENOUS METHYLPREDNISOLONE
ACTHAR GEL

CODES AND NON-DMT DRUG THERAPIES USED FOR THE IDENTIFICATION OF EDSS-DERIVED DISABILITY INDICATORS:

Cognitive/Behavioral Dysfunction Diagnosis Codes	Description
29410	DEMENTIA W/O BEHAV DIST
29411	DEMENTIA W BEHAVIOR DIST
3101	PERSONALITY CHG OTH DIS
31081	PSEUDOBULBAR AFFECT
33183	MILD COGNITIVE IMPAIREMT

Visual Impairment Diagnosis Codes	Description
36900	BOTH EYES BLIND-WHO DEF
36901	TOT IMPAIRMENT-BOTH EYES
36902	ONE EYE-NEAR TOT/OTH-NOS
36903	ONE EYE-NEAR TOT/OTH-TOT
36904	NEAR-TOT IMPAIR-BOTH EYE
36914	ONE EYE-SEV/OTH-PRFND
36915	ONE EYE-MOD/OTH-BLIND
36916	ONE EYE-MODERATE/OTH-TOT
36917	ONE EYE-MOD/OTH-NEAR TOT
36918	ONE EYE-MOD/OTH-PROFOUND
36920	LOW VISION, 2 EYES NOS
36921	ONE EYE-SEVERE/OTH-NOS
36922	SEVERE IMPAIR-BOTH EYES
36923	ONE EYE-MODERATE/OTH-NOS
36924	ONE EYE-MODERATE/OTH-SEV
36925	MODERATE IMPAIR-BOTH EYE
3693	BLINDNESS NOS, BOTH EYES
3694	LEGAL BLINDNESS-USA DEF
36960	BLINDNESS, ONE EYE
36961	ONE EYE-TOTAL/OTH-UNKNWN
36962	ONE EYE-TOT/OTH-NEAR NOR
36963	ONE EYE-TOTAL/OTH-NORMAL
36964	ONE EYE-NEAR TOT/OTH-NOS
36965	NEAR-TOT IMP/NEAR-NORMAL
36966	NEAR-TOTAL IMPAIR/NORMAL
36967	ONE EYE-PRFOUND/OTH-UNKN
36968	PROFND IMPAIR/NEAR NORM
36969	PROFOUND IMPAIR/NORMAL
36970	LOW VISION, ONE EYE
36971	ONE EYE-SEVERE/OTH-UNKNW
36972	ONE EYE-SEV/OTH-NR NORM
36973	ONE EYE-SEVERE/OTH-NORM
36974	ONE EYE-MOD/OTHER-UNKNWN
36975	ONE EYE-MOD/OTH-NR NORM
36976	ONE EYE-MOD/OTH NORMAL
3698	VISUAL LOSS, ONE EYE NOS
3699	VISUAL LOSS NOS

Bladder Dysfunction Drugs
Botox (onabotulinumtoxinA)
DDAVP Nasal Spray (desmopressin)
Detrol (tolterodine)
Ditropan (oxybutynin), Ditropan XL
Enablex (darifenacin)
Flomax (tamsulosin)
Hytrin (terazosin)
Minipress (prazosin)
Oxytrol (oxybutynin)
Pro-Banthine (propantheline)
Sanctura (trospium chloride)
Tofranil (imipramine)
Vesicare (solifenacin succinate)

Spasticity Drugs
Dantrium (dantrolene)
Gablofen (baclofen [intrathecal])
Klonopin (clonazepam)
Lioresal (baclofen)
Valium (diazepam)
Zanaflex (tizanidine)

Mobility Impairment Type	HCPCS Code	Description
Specialty bed	E0250	Hosp bed fixed ht w/mattress
Specialty bed	E0251	Hosp bed fixed ht w/o mattress
Specialty bed	E0255	Hosp bed var ht w/ mattress
Specialty bed	E0256	Hosp bed var ht w/o mattress
Specialty bed	E0260	Hosp bed semi-electr w/ mattress
Specialty bed	E0261	Hosp bed semi-electr w/o mattress
Specialty bed	E0265	Hosp bed total electr w/mattress
Specialty bed	E0266	Hosp bed total electr w/o mattress
Specialty bed	E0270	Hosp bed institutional t
Specialty bed	E0271	Mattress innerspring
Specialty bed	E0272	Mattress foam rubber
Specialty bed	E0273	Bed board
Specialty bed	E0274	Over-bed table
Specialty bed	E0275	Bed pan standard
Specialty bed	E0276	Bed pan fracture
Specialty bed	E0277	Powered pres-redu air mattress
Specialty bed	E0280	Bed cradle
Specialty bed	E0290	Hosp bed fx ht w/o rails w/m
Specialty bed	E0291	Hosp bed fx ht w/o rail w/o
Specialty bed	E0292	Hosp bed var ht w/o rail w/o
Specialty bed	E0293	Hosp bed var ht w/o rail w/
Specialty bed	E0294	Hosp bed semi-elect w/mattress
Specialty bed	E0295	Hosp bed semi-elect w/o mattress
Specialty bed	E0296	Hosp bed total elect w/mattress
Specialty bed	E0297	Hosp bed total elect w/o mattress
Specialty bed	E0300	Enclosed ped crib hosp grade
Specialty bed	E0301	HD hosp bed, 350-600 lbs
Specialty bed	E0302	Ex HD hosp bed >600 lbs

Mobility Impairment Type	HCPCS Code	Description
Specialty bed	E0303	Hosp bed hvy dty xtra wide
Specialty bed	E0304	Hosp bed xtra hvy dty xtra wide
Specialty bed	E0305	Rails bed side half length
Specialty bed	E0310	Rails bed side full length
Specialty bed	E0315	Bed accessory brd/tbl/support
Specialty bed	E0316	Bed safety enclosure
Wheelchair	E0950	Tray
Wheelchair	E0951	Loop heel
Wheelchair	E0952	Toe loop/holder, each
Wheelchair	E0955	Cushioned headrest
Wheelchair	E0956	W/c lateral trunk/hip support
Wheelchair	E0957	W/c medial thigh support
Wheelchair	E0958	Whlchr att- conv 1 arm drive
Wheelchair	E0959	Amputee adapter
Wheelchair	E0960	W/c shoulder harness/straps
Wheelchair	E0961	Wheelchair brake extension
Wheelchair	E0966	Wheelchair head rest extension
Wheelchair	E0967	Manual wc hand rim w project
Wheelchair	E0968	Wheelchair commode seat
Wheelchair	E0969	Wheelchair narrowing device
Wheelchair	E0970	Wheelchair no. 2 footplates
Wheelchair	E0971	Wheelchair anti-tipping device
Wheelchair	E0973	Wheelchair access det adj armrest
Wheelchair	E0974	Wheelchair access anti-rollback
Wheelchair	E0978	Wheelchair access safety belt pelv strap
Wheelchair	E0980	Wheelchair safety vest
Wheelchair	E0981	Seat upholstery, replacement
Wheelchair	E0982	Back upholstery, replacement
Wheelchair	E0983	Add power joystick
Wheelchair	E0984	Add power tiller
Wheelchair	E0985	Wheelchair seat lift mechanism
Wheelchair	E0986	Man wheelchair push-rim power system
Wheelchair	E0988	Lever-activated wheel drive
Wheelchair	E0990	Wheelchair elevating leg res
Wheelchair	E0992	Wheelchair solid seat insert
Wheelchair	E0994	Wheelchair arm rest
Wheelchair	E0995	Wheelchair calf rest
Wheelchair	E1002	Power seat tilt
Wheelchair	E1003	Power seat recline
Wheelchair	E1004	Power seat recline mech
Wheelchair	E1005	Power seat recline power
Wheelchair	E1006	Power seat combo w/o shear
Wheelchair	E1007	Power seat combo w/shear
Wheelchair	E1008	Power seat combo power shear
Wheelchair	E1009	Add mech leg elevation
Wheelchair	E1010	Add power leg elevation
Wheelchair	E1011	Ped wheelchair modify width adjustm
Wheelchair	E1014	Reclining back add ped wheelchair
Wheelchair	E1015	Shock absorber for man wheelchair
Wheelchair	E1016	Shock absorber for power wheelchair
Wheelchair	E1017	HD shock absorber for hd man wheelchair

Mobility Impairment Type	HCPCS Code	Description
Wheelchair	E1018	HD shock absorber for hd power wheelchair
Wheelchair	E1020	Residual limb support system
Wheelchair	E1028	Wheelchair manual swingaway
Wheelchair	E1029	Wheelchair vent tray fixed
Wheelchair	E1030	Wheelchair vent tray gimbaled
Wheelchair	E1031	Rollabout chair with casters
Wheelchair	E1035	Patient transfer system <300
Wheelchair	E1036	Patient transfer system >300
Wheelchair	E1037	Transport chair, ped size
Wheelchair	E1038	Transport chair pt wt<=300lb
Wheelchair	E1039	Transport chair pt wt >300lb
Wheelchair	E1050	Wheelchair fxd full length arms
Wheelchair	E1060	Wheelchair detachable arms
Wheelchair	E1070	Wheelchair detachable foot r
Wheelchair	E1083	Hemi-wheelchair fixed arms
Wheelchair	E1084	Hemi-wheelchair detachable a
Wheelchair	E1085	Hemi-wheelchair fixed arms
Wheelchair	E1086	Hemi-wheelchair detachable a
Wheelchair	E1087	Wheelchair lightwt fixed arm
Wheelchair	E1088	Wheelchair lightweight det a
Wheelchair	E1089	Wheelchair lightwt fixed arm
Wheelchair	E1090	Wheelchair lightweight det a
Wheelchair	E1092	Wheelchair wide w/leg rests
Wheelchair	E1093	Wheelchair wide w/foot rest
Wheelchair	E1100	Wheelchair s-recl fxd arm leg res
Wheelchair	E1110	Wheelchair semi-recl detachable
Wheelchair	E1130	Wheelchair stand fxd arm ft rest
Wheelchair	E1140	Wheelchair standard detach a
Wheelchair	E1150	Wheelchair standard w/leg r
Wheelchair	E1160	Wheelchair fixed arms
Wheelchair	E1161	Manual adult wheelchair w tiltin spac
Wheelchair	E1170	Wheelchair amputee fxd arm leg rest
Wheelchair	E1171	Wheelchair amputee w/o leg r
Wheelchair	E1172	Wheelchair amputee detachable ar
Wheelchair	E1180	Wheelchair amputee w/ foot r
Wheelchair	E1190	Wheelchair amputee w/ leg re
Wheelchair	E1195	Wheelchair amputee heavy duty
Wheelchair	E1200	Wheelchair amputee fixed arm
Wheelchair	E1220	Wheelchair special size/constrc
Wheelchair	E1221	Wheelchair spec size w foot
Wheelchair	E1222	Wheelchair spec size w/leg
Wheelchair	E1223	Wheelchair spec size w/foot
Wheelchair	E1224	Wheelchair spec size w/leg
Wheelchair	E1225	Manual semi-reclining back
Wheelchair	E1226	Manual fully reclining back
Wheelchair	E1227	Wheelchair spec sz spec ht a
Wheelchair	E1228	Wheelchair spec sz spec ht b
Wheelchair	E1229	Pediatric wheelchair NOS
Wheelchair	E1230	Power-operated vehicle
Wheelchair	E1231	Rigid ped wheelchair tilt-in-space
Wheelchair	E1232	Folding ped wheelchair tilt-in-space

Mobility Impairment Type	HCPCS Code	Description
Wheelchair	E1233	Rig ped wheelchair tltn spc w/o seat
Wheelchair	E1234	Fld ped wheelchair tltn spc w/o seat
Wheelchair	E1235	Rigid ped wheelchair adj
Wheelchair	E1236	Folding ped wheelchair adj
Wheelchair	E1237	Rgd ped wheelchair adj w/o seat
Wheelchair	E1238	Folding ped wheelchair ad w/o seat
Wheelchair	E1239	Ped power wheelchair NOS
Wheelchair	E1240	Wheelchair lightweight det arm leg rest
Wheelchair	E1250	Wheelchair lightweight fixed arm
Wheelchair	E1260	Wheelchair lightweight foot rest
Wheelchair	E1270	Wheelchair lightweight leg r
Wheelchair	E1280	Wheelchair heavy-duty det arm leg res
Wheelchair	E1285	Wheelchair heavy-duty fixed
Wheelchair	E1290	Wheelchair heavy-duty detachable a
Wheelchair	E1295	Wheelchair heavy-duty fixed
Wheelchair	E1296	Wheelchair special seat height
Wheelchair	E1297	Wheelchair special seat depth
Wheelchair	E1298	Wheelchair spec seat depth/w
Walker	E0130	Walker rigid adj/fixed height
Walker	E0135	Walker folding adj/fixed
Walker	E0140	Walker w/trunk support
Walker	E0141	Rigid wheeled walker adj/fix
Walker	E0143	Walker folding wheeled w/o s
Walker	E0144	Enclosed walker w/rear seat
Walker	E0147	Walker variable wheel resist
Walker	E0148	Heavy-duty walker no wheels
Walker	E0149	Heavy-duty wheeled walker
Walker	E0153	Forearm crutch platform attach
Walker	E0154	Walker platform attach
Walker	E0155	Walker wheel attach,pair
Walker	E0156	Walker seat attach
Walker	E0157	Walker crutch attach
Walker	E0158	Walker leg extenders - set of 4
Walker	E0159	Brake for wheeled walker
Cane	E0100	Cane adj/fixed with tip
Cane	E0105	Cane adj/fixed quad/3 pro

NON-DMT DRUG THERAPIES USED FOR THE IDENTIFICATION OF RELATED NEUROLOGIC IMPAIRMENT INDICATORS:

Anticonvulsants
Carbamazepine
Divalproex sodium
Valproate sodium
Valproic acid
Gabapentin
Levetiracetam

Analgesics
Meperidine
Morphine
Oxycodone
Acetaminophen with codeine
Ibuprofen
Flurbiprofen
Fenoprofen
Nabumetone
Ketoprofen
Naproxen
Indomethacin
Salicylates
Celecoxib
Rofecoxib
Valdecoxib

Fatigue Drugs
Modafinil
Amantadine
Amphetamine
Armodafinil
Dextroamphetamine
Dexmethylphenidate
Methamphetamine
Lisdexamfetamine
Methylphenidate
Pemoline
Amphetamine + Dextroamphetamine

Antidepressants
Mirtazapine
Venlafaxine
Duloxetine
Desvenlafaxine
Desipramine
Nortriptyline
Protriptyline
Amitriptyline
Clomipramine
Doxepin
Imipramine
Trimipramine
Amoxapine
Fluoxetine HCl
Paroxetine HCl
Sertraline HCl
Citalopram Hydrobromide
Fluvoxamine Maleate
Escitalopram Oxalate
Paroxetine Mesylate

Cognition Drugs
Donepezil HCl
Donepezil HCl (ER)
Galantamine
Memantine HCl
Rivastigmine
Tacrine

APPENDIX D: SUPPLEMENTAL DATA

TABLE 6
ALLOWED PPPM COSTS FOR NEWLY DIAGNOSED MS PATIENTS DURING THE COURSE OF THE DISEASE (trended to 2015)[a]

Service Line	Year (-10)	Year (-9)	Year (-8)	Year (-7)	Year (-6)	Year (-5)	Year (-4)	Year (-3)	Year (-2)	Year (-1)	Year (0)	Year (1)	Year (2)	Year (3)	Year (4)	Year (5)	Year (6)	Year (7)	Year (8)	Year (9)
Member Months	2265	5971	11,631	19,662	31,262	49,074	76,807	121,171	159,900	170,467	173,100	128,698	95,097	68,833	50,087	34,501	23,316	15,502	9350	4367
Patients	317	737	1330	2131	3342	5285	8076	12,872	13,854	15,821	15,876	12,528	9298	6706	4902	3415	2328	1547	989	486
IP Facility & Professional	$183	$115	$76	$114	$105	$134	$129	$134	$152	$206	$478	$213	$233	$215	$242	$270	$319	$248	$199	$148
Skilled Nursing Facility	$0	$0	$0	$0	$0	$1	$2	$2	$2	$4	$11	$7	$6	$7	$7	$17	$4	$10	$14	$15
Home Health	$0	$0	$0	$0	$1	$0	$1	$4	$3	$5	$11	$16	$15	$12	$18	$25	$16	$5	$3	$5
Hospice	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$1	$2	$2	$2	$3	$2	$1	$0	$0
Emergency Department	$18	$23	$20	$27	$29	$28	$32	$37	$41	$77	$67	$46	$45	$39	$44	$36	$39	$36	$32	$36
Lab & Pathology[1]	$17	$18	$19	$19	$21	$21	$22	$25	$27	$46	$49	$33	$31	$30	$29	$30	$26	$25	$27	$26
Radiology - Advanced Imaging[1]	$28	$20	$22	$22	$24	$28	$28	$34	$43	$168	$165	$103	$95	$86	$79	$76	$72	$61	$55	$63
Radiology - Other[1]	$19	$16	$20	$19	$20	$21	$21	$21	$24	$27	$30	$25	$23	$27	$25	$24	$35	$27	$19	$17
Physical/ Occupational/ Speech Therapy[1]	$10	$9	$7	$10	$10	$11	$10	$12	$15	$18	$31	$19	$19	$18	$18	$19	$21	$20	$22	$23
Outpatient Other[2]	$97	$113	$102	$97	$121	$113	$124	$135	$149	$235	$277	$234	$232	$251	$251	$249	$246	$268	$223	$159
DME/ Supplies	$4	$4	$4	$7	$9	$8	$8	$8	$12	$12	$21	$20	$19	$19	$19	$19	$20	$21	$23	$48
Professional Other[3]	$78	$87	$85	$88	$94	$98	$103	$113	$128	$177	$242	$187	$187	$182	$192	$185	$171	$150	$156	$146
Drug - Relapse[4]	$0	$0	$0	$0	$0	$0	$0	$0	$0	$1	$5	$2	$1	$2	$3	$1	$1	$1	$1	$0
Drug - Other[5]	$110	$117	$126	$123	$129	$128	$131	$130	$136	$151	$228	$239	$253	$255	$252	$274	$279	$284	$305	$314
Subtotal – Non-DMT	**$565**	**$522**	**$480**	**$526**	**$563**	**$591**	**$612**	**$655**	**$732**	**$1128**	**$1614**	**$1146**	**$1162**	**$1145**	**$1180**	**$1226**	**$1252**	**$1157**	**$1078**	**$1001**
Standard Deviation	$1193	$1399	$961	$1106	$1293	$1993	$1488	$1480	$1688	$1858	$3307	$2647	$2605	$2566	$2749	$3327	$3511	$2652	$2144	$1547
Lower 95% CI	$433	$421	$428	$479	$519	$537	$579	$629	$704	$1099	$1562	$1099	$1109	$1083	$1103	$1114	$1109	$1024	$944	$863

Service Line	Year (-10)	Year (-9)	Year (-8)	Year (-7)	Year (-6)	Year (-5)	Year (-4)	Year (-3)	Year (-2)	Year (-1)	Year (0)	Year (1)	Year (2)	Year (3)	Year (4)	Year (5)	Year (6)	Year (7)	Year (8)	Year (9)
Member Months	2265	5971	11,631	19,662	31,262	49,074	76,807	121,171	159,900	170,467	173,100	128,698	95,097	68,833	50,087	34,501	23,316	15,502	9350	4367
Patients	317	737	1330	2131	3342	5285	8076	12,872	13,854	15,821	15,876	12,528	9298	6706	4902	3415	2328	1547	989	486
Upper 95% CI	$697	$623	$531	$573	$607	$644	$644	$681	$761	$1157	$1665	$1192	$1215	$1207	$1258	$1338	$1394	$1289	$1212	$1139
DMT Drugs[4]	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$2803**	**$2801**	**$2856**	**$2883**	**$2887**	**$2849**	**$2880**	**$2903**	**$2993**	**$3043**
Standard Deviation	$10	$5	$3	$2	$4	$54	$28	$89	$96	$85	$2502	$2556	$2558	$2546	$2620	$2623	$2677	$2658	$2729	$2647
Total - All Costs	**$565**	**$522**	**$480**	**$526**	**$563**	**$591**	**$612**	**$655**	**$732**	**$1128**	**$4417**	**$3946**	**$4019**	**$4028**	**$4067**	**$4075**	**$4131**	**$4059**	**$4072**	**$4043**
Standard Deviation	$1194	$1399	$961	$1106	$1293	$1994	$1489	$1493	$1702	$1861	$3936	$3573	$3525	$3538	$3654	$4110	$4343	$3735	$3491	$3039

[a]Notes:
Based on Milliman's analysis of MarketScan commercial databases, 2003-2014.
Allowed claim costs trended to 2015.
Year(0) is the 12-month period beginning on the earliest claim contributing to an MS diagnosis (index date).Year(n) is the 12-month period (+/-) from the index date.
1. Includes facility and professional.
2. Includes services such as outpatient surgery and psychiatric. Facility costs only.
3. Includes professional services not otherwise listed such as surgery and office visits.
4. Includes both medical drugs and prescription drugs.
5. Includes prescription drugs only.

TABLE 7
AVERAGE ANNUAL RELAPSE RATE FOR NEWLY DIAGNOSED MS PATIENTS DURING THE COURSE OF THE DISEASE[a]

	Year (0)	Year (1)	Year (2)	Year (3)	Year (4)	Year (5)	Year (6)	Year (7)	Year (8)	Year (9)	Year (10)
Number of Patients	15,876	12,528	9298	6706	4902	3415	2328	1547	989	486	165
Number of Relapses per Patient per Year	0.10	0.07	0.06	0.06	0.06	0.05	0.05	0.05	0.03	0.06	0.05

[a]Notes:
Based on Milliman's analysis of MarketScan commercial databases, 2003-2014.
Year (0) is the 12-month period beginning on the earliest claim contributing to an MS diagnosis (index date); Year(n) is the 12-month period (+/-) from the index date.

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