SUPPLEMENTARY MATERIAL

Patterns of Healthcare Utilization and Expenditure across Multiple Sclerosis Disease-Modifying Therapies: A Retrospective Cohort Study Using Claims Data from a Commercially Insured Population in the United States, 2010-2019

Wen Zhu, MD, MS[1], Xiaoyu Tang, MS[2], Rock A. Heyman, MD[1], Tianxi Cai, ScD[3, 4], Kangho Suh, PharmD, PhD[5], John D. Seeger, PharmD, DrPH[6], Zongqi Xia, MD, PhD[1]

1. Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA
2. Department of Biostatistics, Boston University, Boston, MA, USA
3. Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA
4. Department of Biostatics, Harvard T. H. Chan School of Public Health, Boston, MA, USA
5. Department of Pharmacy and Therapeutics, University of Pittsburgh, Pittsburgh, PA, USA
6. Optum Epidemiology, Boston, MA, USA

Corresponding Author:

Zongqi Xia, MD, PhD

Department of Neurology, University of Pittsburgh

Biomedical Science Tower 3, Suite 7014, 3501 5th Avenue, Pittsburgh, PA USA 15260

Phone: 412-383-5377; Fax: 412-648-7233; Email: zxia1@post.harvard.edu

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SUPPLEMENTARY METHODS

For healthcare expenditure in each category, we calculated two types of charges: total charges and out-of-pocket charges, the latter by summing copayments, coinsurance, and deductible payments. **Total charge** was the amount that providers requested to be reimbursed for the service provided. **Copayment** was the fixed amount that insured members paid for a specific service as defined in their benefit plan. **Coinsurance** was the amount (usually calculated as a percent of the provider's submitted charges) that insured members paid for a specific service as defined in their benefit plan. **Deductible** was the fixed amount that insured members paid for services until reaching a specified limit (usually defined on an annual basis). After reaching such limit, insurance typically pays 100% of the cost of services.

SUPPLEMENTARY RESULTS

1. Demographics

From 2010 to 2019, we identified 99,403 people who met the MS case definition from a commercially insured population of >54 million people in the United States **(Figure 1)**. To assess MS prevalence and DMT prescription pattern, we used this MS main cohort in which the estimated cumulative 10-year MS prevalence was 183 (95% CI 165-201) per 100,000 people. The Northeast region had the highest percentage of MS cases in this insured population (0.25%), with the states of Connecticut and Vermont having the highest percentage (0.33%) (**Figure S1A, Table S1**).

To analyze healthcare utilization and expenditure, we identified from the MS main cohort a subset of 25,932 people with MS (pwMS) who additionally had continuous enrollment for both medical and pharmacy benefits for at least 3-months preceding and at least 12-months after the index date, forming the MS sub cohort (**Figure 1**). The MS sub cohort shared similar characteristics as the MS main cohort, except for the higher percentage of untreated pwMS in the sub cohort than the main cohort (**Table 1**). In the MS sub cohort, untreated pwMS were the oldest, followed by pwMS treated with high-efficacy and then standard-efficacy DMTs, while pwMS on high-efficacy DMTs had the longest MS cohort duration.

2. DMT Prescription Pattern

When examining the prescription pattern of the FDA-approved DMTs in the MS main cohort between 2010 and 2019 (**Figure S1B**), we found a significant decrease in the percentage of DMT-prescribed pwMS (-0.76% per year, p=.010). Injectable DMTs (interferon-beta and glatiramer acetate) represented the largest proportion of DMT prescriptions. The percentage of pwMS on injectable DMTs decreased during the study period (-1.75% per year, p<.001). Among the oral DMTs, prescription of S1P-R modulator (predominantly fingolimod as it received approval in 2010 while siponimod was only approved in 2019) remained stable (0.14% per year, p=.096). Prescription of teriflunomide (0.82% per year, p<.001) increased, while prescription of dimethyl fumarate (-0.85% per year, p<.001) decreased, after receiving FDA approval in late 2012 and early 2013, respectively. Because cladribine received FDA approval in 2019, this data set contained insufficient information to calculate its prescription trend. Among the infused DMTs, prescription of natalizumab remained stable throughout the study period (-0.01% per year, p=.053). Prescription of B-cell depletion therapy (ocrelizumab, which received approval in 2017; rituximab, which has been used off-label) remained stable throughout the study period (-

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0.6% per year, p=.485). Among all DMTs, interferon-beta had the longest median duration of

prescription (530 days) unsurprisingly since this is the oldest class of DMTs **(Figure S1C)**.

SUPPLEMENTARY FIGURES AND TABLES

Figure S1. MS main cohort characteristics. A. Percentage of MS cases among this commercially insured population between 2010 and 2019 in each state or territory. B. Percentage of people with MS receiving no DMT, any DMT, or a specific DMT monotherapy, from 2010 to 2019. C. Median treatment duration (with IQR) for each DMT.
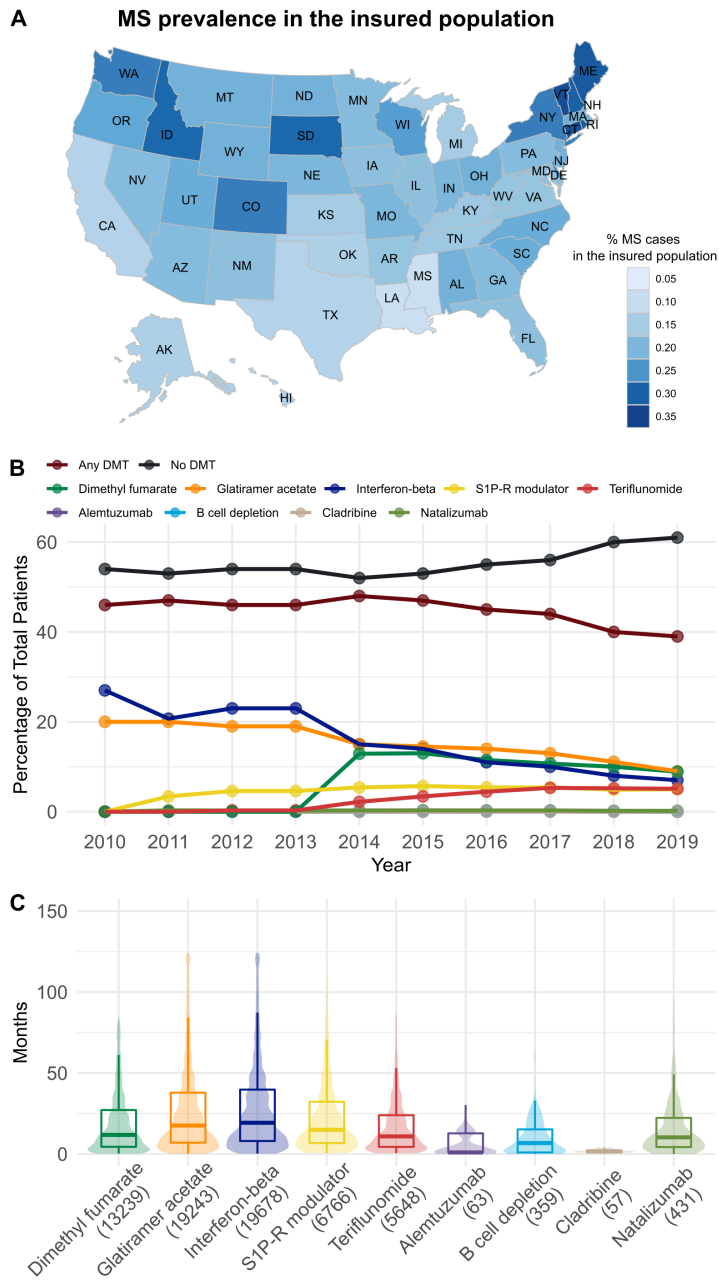
Table S1. MS case prevalence in a large commercially insured population in the United States from 2010 to 2019 according to state and region.

State/Territory	n, MS Cohort	% MS Main Cohort	n, Total Insured Cohort	% Total Insured Cohort	% MS Cases in the Total Insured Cohort
AK = Alaska	33	0.03	24341	0.04	0.14
AL = Alabama	1222	1.23	575387	1.06	0.21
AR = Arkansas	794	0.80	457337	0.84	0.17
AZ = Arizona	3509	3.53	1837285	3.39	0.19
CA = California	5867	5.90	4573921	8.44	0.13
CO = Colorado	4396	4.42	1644276	3.03	0.27
CT = Connecticut	1769	1.78	535843	0.99	0.33
DC = District of Columbia	200	0.20	135721	0.25	0.15
DE = Delaware	169	0.17	66938	0.12	0.25
FL = Florida	8996	9.05	4894895	9.03	0.18
GA = Georgia	4668	4.70	2504818	4.62	0.19
HI = Hawaii	84	0.08	65066	0.12	0.13
IA = Iowa	966	0.97	543350	1.00	0.18
ID = Idaho	486	0.49	165429	0.31	0.29
IL = Illinois	3707	3.73	2042150	3.77	0.18
IN = Indiana	2312	2.33	1139396	2.10	0.20
KS = Kansas	648	0.65	434189	0.80	0.15
KY = Kentucky	856	0.86	524926	0.97	0.16
LA = Louisiana	718	0.72	787563	1.45	0.09
MA = Massachusetts	1255	1.26	611517	1.13	0.21
MD = Maryland	1870	1.88	1046879	1.93	0.18
ME = Maine	309	0.31	98922	0.18	0.31
MI = Michigan	986	0.99	636389	1.17	0.15
MN = Minnesota	3216	3.24	1652571	3.05	0.19
MO = Missouri	3222	3.24	1582155	2.92	0.20
MS = Mississippi	333	0.33	391656	0.72	0.09
MT = Montana	113	0.11	53820	0.10	0.21
NC = North Carolina	4500	4.53	2089186	3.86	0.22
ND = North Dakota	279	0.28	131122	0.24	0.21

	n, MS Cohort	% MS Cohort	n, Total Insured Cohort	% Total Cohort	% MS Cases in the Total Insured Cohort
NE = Nebraska	996	1.00	488743	0.90	0.20
NH = New Hampshire	393	0.40	131736	0.24	0.30
NJ = New Jersey	2182	2.20	1028169	1.90	0.21
NM = New Mexico	467	0.47	258129	0.48	0.18
NV = Nevada	709	0.71	371951	0.69	0.19
NY = New York	4648	4.68	1739105	3.21	0.27
OH = Ohio	4695	4.72	2225097	4.11	0.21
OK = Oklahoma	947	0.95	683264	1.26	0.14
OR = Oregon	1260	1.27	542468	1.00	0.23
PA = Pennsylvania	2030	2.04	1054841	1.95	0.19
PR = Puerto Rico	3	0.00	2814	0.01	0.11
RI = Rhode Island	946	0.95	308762	0.57	0.31
SC = South Carolina	1417	1.43	638577	1.18	0.22
SD = South Dakota	248	0.25	85967	0.16	0.29
TN = Tennessee	1594	1.60	1005305	1.86	0.16
TX = Texas	8753	8.81	6882752	12.70	0.13
UT = Utah	1499	1.51	681656	1.26	0.22
VA = Virginia	2213	2.23	1268776	2.34	0.17
VT = Vermont	110	0.11	33659	0.06	0.33
WA = Washington	2666	2.68	977755	1.80	0.27
WI = Wisconsin	3710	3.73	1543241	2.85	0.24
WV = West Virginia	214	0.22	129410	0.24	0.17
WY = Wyoming	130	0.13	60584	0.11	0.21
Unknown	90	0.09	801700	1.48	0.01

Region [1]	n, MS Cohort	% MS Cohort	n, Total Insured Cohort	% Total Cohort	% MS Cases in the Total Insured Cohort
Northeast	13642	13.72	5542554	10.23	0.25
South	39464	39.70	24083390	44.46	0.16
Midwest	24985	25.14	12504370	23.08	0.20
West	21219	21.35	11235462	20.74	0.19
Unknown	93	0.09	804514	1.49	0.01

Note:

1. Regions were defined according to the United States Census Bureau

   (https://www.census.gov/geographies/reference-maps/2010/geo/2010-census-regions-

   and-divisions-of-the-united-states.html).

Table S2. Analysis of healthcare expenditure across multiple sclerosis disease-modifying therapy (DMT) efficacy groups.

		6 Months							
		Total Charges (USD) [3]				Out-of-pocket Charges (USD) [3]			
Cost Category [1]	Treatment Group [2]	Mean	95% CI		Adjusted-P [4]	Mean	95% CI		Adjusted-P [4]
Medical Costs	No DMT	$35,583	$28,038	$45,158		$607	$593	$621	
	Standard-efficacy DMT	$14,418	$13,593	$15,293	<.001	$399	$381	$418	<.001
	High-efficacy DMT	$21,089	$13,454	$33,056	.541	$241	$118	$493	0.275
Pharmacy Costs	No DMT	$1,977	$1,725	$2,266		$233	$214	$255	
	Standard-efficacy DMT	$31,167	$27,760	$34,992	<.001	$1,155	$1,056	$1,264	<.001
	High-efficacy DMT	$36,604	$31,810	$42,119	<.001	$1,240	$994	$1,547	<.001
DMT Costs	Standard-efficacy DMT	$30,589	$27,832	$33,620	NA	$978	$945	$1,012	NA
	High-efficacy DMT	$36,101	$32,226	$40,442	NA	$1,085	$778	$1,513	NA
Overall Healthcare Costs	No DMT	$41,870	$35,520	$49,356		$840	$823	$858	
	Standard-efficacy DMT	$54,606	$52,429	$56,872	<.001	$1,554	$1,506	$1,605	<.001
	High-efficacy DMT	$66,878	$49,041	$91,202	.074	$1,481	$1,146	$1,915	<.001
		12 Months							
		Total Charges (USD) [3]				Out-of-pocket Charges (USD) [3]			
Cost Category [1]	Treatment Group [2]	Mean	95% CI		Adjusted-P [4]	Mean	95% CI		Adjusted-P [4]
Medical Costs	No DMT	$68,204	$55,216	$84,248		$988	$968	$1,009	
	Standard-efficacy DMT	$34,575	$32,815	$36,429	<.001	$827	$798	$857	<.001
	High-efficacy DMT	$51,115	$34,318	$76,134	1.000	$452	$258	$791	.148
Pharmacy Costs	No DMT	$3,475	$3,057	$3,950		$444	$415	$475	
	Standard-efficacy DMT	$49,232	$44,336	$54,668	<.001	$1,829	$1,706	$1,962	<.001
	High-efficacy DMT	$48,962	$42,535	$56,360	<.001	$1,822	$1,473	$2,253	<.001
DMT Costs	Standard-efficacy DMT	$42,022	$37,633	$46,923	NA	$1,453	$1,406	$1,502	NA
	High-efficacy DMT	$46,523	$40,108	$53,964	NA	$1,459	$1,027	$2,071	NA
Overall Healthcare Costs	No DMT	$70,399	$60,363	$82,104		$1,432	$1,406	$1,458	
	Standard-efficacy DMT	$100,910	$97,144	$104,821	<.001	$2,656	$2,585	$2,730	<.001
	High-efficacy DMT	$115,470	$86,397	$154,327	.020	$2,274	$1,822	$2,837	.001

Note:

1. Using study index date (for the untreated patients) or DMT initiation date (for the DMT-treated patients) as the reference date, we obtained three categories of healthcare expenditure (in US dollars): medical costs, pharmacy costs and overall healthcare costs (combination of medical costs and pharmacy costs) (in US dollars per person) at 6 months and 12 months.

2. We compared the differences in healthcare costs among patients on high-efficacy DMTs (HE), standard-efficacy DMTs (SE) or no DMT (ND) during the study period, using ND as the reference group.

3. For each cost category, we calculated two types of charges: total charges and out-of-pocket charges, the latter by summing copayments, coinsurance and deductible payments. All healthcare expenditure was inflation-adjusted to 2019 dollars using the medical care component of the Consumer Price Index.

4. Adjusted-P = Bonferroni-adjusted p-value for 16 independent outcomes with 2 comparisons per outcome.