Nusinersen Treatment and Healthcare Costs in Spinal Muscular Atrophy

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Abstract

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Importance: Patients with severe forms of Spinal Muscular Atrophy (SMA) depend on costly supportive care interventions. Few studies have evaluated how the clinical effectiveness of nusinersen, the first FDA approved treatment for SMA, affects healthcare costs.

Objective: To assess the effect of nusinersen treatment on healthcare costs in SMA I and SMA Other (SMA types II-IV).

Methods: We conducted a retrospective cohort study using IBM® MarketScan® to identify patients with ≥2 SMA diagnoses ≥30 days apart and ≥30 days of follow-up after their index date. The index date for nusinersen-treated patients was their first nusinersen administration after January 2017, and follow-up ended December 2018. The index date for our historical control group was the first SMA diagnosis after January 2015 and followed through December 2016, before the approval of nusinersen. We used multivariable linear regression to estimate non-nusinersen per member per month (PMPM) costs, adjusting for age category, sex, ventilation support, feeding tube support, Charlson Comorbidity Index score, and region.

Results: 194 patients with SMA I (83 treated, 111 controls) and 510 patients with SMA Other (90 treated, 420 controls) were included in the analytic sample. Nusinersen treatment was associated with a trend toward lower PMPM costs in SMA I compared to controls (-$12,144

[95% Confidence Interval (CI): -$32,123, $7,834]), and in SMA Other was significantly associated with higher healthcare costs ($4,517 [95% CI: $1,225, $7,810]).

Conclusion: Nusinersen treatment may be associated with lower healthcare costs in SMA I, but in contrast appears to be associated with higher costs in SMA Other. Additional studies using larger sample sizes, reliable diagnosis of SMA subtypes, and adjustment to avoid influential confounders are needed to help clarify the impact of SMA treatments in this rare, complex, and costly disease.

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Introduction

Spinal Muscular Atrophy (SMA) is the most common deadly childhood genetic disorder in the US, affecting approximately 1 in 10,000 live births[1]. There are five subtypes of SMA with increasing severity from type 0 to type IV; approximately 60% of patients develop SMA type I (SMA I)[2]. SMA type 0 occurs in neonates with what is believed to be prenatal onset, and most do not survive longer than 6 months[3]. Patients with SMA I develop symptoms before 6 months of age, are never able to sit upright independently, and roughly 50% die before 2 years of age. Patients with SMA type II have delayed motor milestones between 7–18 months of age and are never able to stand independently, but commonly live past 2 years of age. SMA type III is comparably less severe so patients are usually diagnosed at an older age, can stand and walk, and commonly survive to adulthood[4–6]. SMA type IV represents the mildest form of SMA, with patients able to walk independently and most cases presenting above 30 years of age[3].

Patients in SMA types 0 and I (and to a lesser degree, II through IV) depend on costly supportive care interventions including respiratory, nutritional, and orthopedic support due to the progressively worsening pulmonary failure, swallowing dysfunction, and scoliosis which leads to chronic aspiration and failure to thrive[7]. Advances in SMA supportive care from 1980 to 2006 led to a higher proportion of patients receiving ventilation support and gastronomy tube feeding and improved survival[3,6,8,9].

The FDA approved nusinersen (Spinraza™, Biogen) as the first treatment for SMA on December 23rd, 2016. (FDA ref) Given the rarity of SMA and novelty of nusinersen, there are currently studies assessing whether the clinical effectiveness of nusinersen treatment translates to differences in healthcare costs using adjusted models. While it's plausible that improvement in motor milestones, as measured in the clinical trials, would decrease supportive care costs by modifying the natural course of the disease, a claims database analysis can provide insight into

whether nusinersen is associated with decreased health resource costs in the setting of commercially insured patients. The objective of this study was to explore the possibility of an association between nusinersen treatment and changes in health care costs in patients with SMA.

Methods

Overall Approach

We retrospectively evaluated insurance claims data of nusinersen-treated and historical control patients to assess non-nusinersen healthcare costs ('healthcare costs'). We compared nusinersen-treated to historical control patients and used multivariable linear regression to calculate the difference in least squares mean per member per month (PMPM) healthcare costs adjusted for differences between patients in age, gender, clinical status, and region ('adjusted healthcare costs'). We measured costs using PMPM to reflect the variation in follow-up time for each patient.

Data Source

We used the IBM® MarketScan® Research Databases, which are composed of de-identified patient-level health data from more than 255 million unique patients since 1995.[10] Marketscan® includes insurance claims data for individuals with commercial insurance as well as retirees with Medicare supplemental insurance paid by employers. All claims in Marketscan® are fully paid and adjudicated and include claims for inpatient, outpatient, pharmacy, and carve-out care, such as mental health services.

Population

We obtained the final analytic sample from Marketscan® by including patients from 2015 through 2018 with at least one SMA International Classification of Diseases, Tenth Revision (ICD-10, codes available in Appendix table) code for any type of SMA. A visual representation of the study design is available in **Figure 1**, and a flow diagram representing the patient selection process is available in **Supplemental Figure 1**. We excluded patients without at least 2 diagnoses at least 30 days apart of the same SMA ICD-10 codes (grouped into either SMA I or SMA Other (all other SMA types)). We then removed patients with <30 days of follow-up after their respective index dates. We considered SMA Other patients to be misdiagnosed SMA I if they were <2 years of age based on evidence from a claims database analysis of US Department of Defense Military Healthcare System data, which found that clinically similar patients were being diagnosed with different ICD-9 codes for SMA types I-III[5]. Other analyses have used age cutoffs instead of diagnosis codes for SMA[11–13] We considered a patient nusinersen-treated if they had at least one claim with a nusinersen National Drug Code (NDC) or Healthcare Common Procedure Coding System (HCPCS) code at any time during follow-up. We excluded control patients if they had claims for any pregnancy-related ICD-10 code to avoid including results from pregnancy screenings following the methods from Droege et al[12]. Marketscan® datasets are de-identified and not considered protected health information, thus Institutional Review Board (IRB) approval was not required[10,14,15].

Study Period

The index date for nusinersen-treated patients was the first nusinersen administration date after 01/01/2017 and the study period ended on 12/22/2018. The index date for historical controls was the first SMA diagnosis after 01/01/2015, and their study period ended on 12/22/2016, the day before nusinersen was approved by the FDA. We gathered data on patients until the end of clinical follow-up or data availability.

Outcome measure

Our primary and secondary objectives were to assess how nusinersen affects the adjusted healthcare costs of patients with SMA I and SMA Other, respectively. We categorized SMA as SMA I and SMA Other because SMA I represents as much as 60% of SMA cases and because of the extreme variation in the clinical severity and healthcare costs between SMA I and the other SMA types[2,12]. We estimated mean PMPM adjusted healthcare costs in nusinersen-treated patients and historical controls.

We calculated PMPM healthcare costs by taking the sum of total gross payments reported on claims during an individual patient's follow-up and dividing it by the duration of follow-up in months, excluding nusinersen-related costs defined as costs reported on claims with a nusinersen NDC or HCPCS code. We defined a nusinersen episode as the seven days before and after the date of a claim for nusinersen administration HCPCS code.

Predictor Variables

We collected information on potential predictor variables from the MarketScan® claims database using Current Procedural Terminology (CPT), HCPCS, NDC, service subcategory, or provider type codes[10]. We used data from the first recorded claim after index date to create variables for age category (0-2 years, 2-11 years, and 21+ years), sex, Charlson Comorbidity Index (CCI) score (0, 1, and 2+), and region (northeast, north-central, south, west). We measured ventilation or feeding tube support through the presence of related CPT or HCPCS

codes on claims in the 30 days preceding index date to adjust for SMA severity between nusinersen-treated and control patients.

We categorized patients in age categories that were likely SMA type I-II (0-2 years old), type III (>2-21 years old), and type IV (>21-65 years old)[16]. We implemented age at index date as a categorical variable instead of continuous to reflect a more useful comparison between SMA types (since age is closely correlated with SMA type). We categorized CCI scores in groups of 0, 1, and ≥2 because we did not expect the patients in our cohort to develop many of the comorbidities included in the CCI[17].

Analysis

We summarized patient demographics with means for normally distributed continuous variables and medians for non-normal data and compared unadjusted mean costs with descriptive statistics. We performed statistical comparisons on patient demographics with the chi-squared test with continuity correction for categorical variables, one-way ANOVA with equal variance assumption for continuous variables, and the Kruskal-Wallis test by rank for non-normal continuous variables. We inflated all costs to 2019 US dollars using the medical portion of the consumer price index (CPI)[18]. We imputed a cost of zero dollars for any missing cost data.

We used multivariable linear regression to estimate the association between mean PMPM adjusted healthcare costs and the main predictor variable of nusinersen treatment, adjusting for variables that we hypothesized a priori to be potential confounders: age category, sex, ventilation support, feeding tube support, CCI score, and region for comparisons between nusinersen-treated and control patients. We used robust standard errors to account for heteroscedasticity between treatment groups[19]. The β coefficients estimated for predictor

variables are interpreted as the difference in the outcome (adjusted non-nusinersen PMPM or per member per episode costs) between two groups differing by one unit of the predictor variable.

We performed a sensitivity analysis with a log-transformed outcome to account for the heavily right-skewed PMPM healthcare costs in our primary and secondary outcomes.[20] We also conducted an analysis with only patients who were newly diagnosed with SMA, (no SMA ICD-10 codes in the six months before their index date) and one with a control group from the same period as the nusinersen-treated patients to account for potential changes in supportive care from 2015 to 2017). We chose a sensitivity analysis with only newly diagnosed patients because our index dates were based on first treatment versus first diagnosis, in our nusinersen-treated and control groups, respectively. As such, nusinersen-treated patients could have increased healthcare costs compared to control patients at an earlier stage in their disease.

We performed post hoc exploratory analyses with continuous age instead of age categories, and with an interaction term where the effect of nusinersen treatment depended on ventilation or feeding tube support. We also performed a post hoc exploratory analysis in which we defined SMA I as having any SMA diagnosis ≤2 years of age and we defined SMA Other as all patients >2 years old, to replicate the age-based definition of SMA I used in previous research[12].

Inferential statistics for mean adjusted healthcare costs from our multivariable linear regression were done with partial F-tests for individual variables using the uwIntroStats package[21]. Partial F-tests determine statistical significance of a variable by comparing the explanatory power of a regression model with and without the variable. For all statistical comparisons, we used a two-sided 5% significance level. We used SAS version 9.4 (SAS Institute Inc., Cary, NC) to construct the analytic dataset and R version 3.6.3 (R Foundation for Statistical Computing,

Vienna, Austria) was used for all statistical analyses except power calculations. We calculated post hoc statistical power using Stata/MP 16.1 (Stata Corporation, College Station, TX)[22].

Results

Descriptive Analysis

We identified 6,660 unique patients with an SMA ICD-10 code, of which 5,517 were excluded for having <2 SMA diagnoses ≥30 days apart and 1 patient for a missing identification number. We excluded 428 patients for not having any clinical events ≥30 days after their index date, and 29 control patients with pregnancy ICD-10 codes from the remaining 1,142 patients. We thus included 194 patients with SMA I (83 treated, 111 controls) and 510 patients with SMA Other (90 treated, 420 controls) in the final analytic sample. Patient demographics are summarized in **Table 1**. Nusinersen-treated and historical control patients with SMA I differed in age (median: 9 years vs 5 years), the number of patients receiving ventilation (25.2% vs 44.6%), and feeding tube support (4.5% vs 9.3%). Nusinersen-treated and historical control patients with SMA Other differed in age (median: 44 years vs 24 years) but were similar in ventilation (4.4% vs 4.8%) and feeding tube support (3.3% vs 1.9%). The mean duration of follow-up was similar comparing SMA I patients who were nusinersen-treated versus historical controls (11 months vs 10.7 months), but slightly different for SMA Other patients (8.06 months vs 9.44 months).

Nusinersen-treated patients with SMA I had an average of 3.9 nusinersen episodes per patient, with a mean nusinersen-related per member per episode cost of $134,102. Nusinersen-treated patients with SMA Other had an average of 3.2 nusinersen episodes per patient, and a mean nusinersen-related per member per episode cost of $132,468. [**Supplemental Table 4**]

Primary Outcome

Nusinersen treatment was not independently associated with a significant difference in mean PMPM adjusted healthcare costs in SMA I (-$12,144 [95% Confidence Interval (CI): -$32,123, $7,834]) [**Table 2**].

Secondary Outcome

Nusinersen treatment was associated with significantly higher mean PMPM adjusted healthcare costs in SMA Other ($4,517 [95% CI: $1,225, $7,810]) [**Table 2**].

Sensitivity Analyses

Our sensitivity analysis including only patients with newly diagnosed SMA found that nusinersen treatment was not associated with a significant difference in adjusted mean non-nusinersen PMPM costs in SMA I ($34,965 [95% CI: -$89,611, $19,680]) or SMA Other ($5,306 [95% CI: -$2,680, $13,292]). Our sensitivity analysis using controls from the same period as nusinersen-treated patients (2017 – 2018) found no evidence that nusinersen treatment was associated with a significant difference in adjusted mean PMPM costs in SMA I (-$9,775 [95% CI: -$23,103, $3,554]) but did find evidence of an association in SMA Other ($3,646 [95% CI: $414, $6,879]), similar to the results of our primary and secondary outcomes. We also found that the sensitivity analyses using log-transformed costs were similar to the non-transformed results for all primary, secondary, exploratory, and sensitivity analyses in direction (higher or lower costs) except for newly diagnosed SMA Other patients, in which nusinersen treatment was associated with a significant difference in log-transformed adjusted PMPM total costs, but not in the untransformed model. [**Table 2 and Supplemental Table 2**]

Post hoc Exploratory Outcomes

We found that in our exploratory analysis using age as a continuous variable in patients with SMA I, a one-year difference in age was associated with lower mean PMPM adjusted healthcare costs (difference: -$637 [95% CI: -$1,155, -$120.2]). We also found evidence of lower mean PMPM healthcare costs in SMA I with continuous age if a patient required feeding tube support (difference: -$9,025 [95% CI: -$17,982, -$67]) or had a CCI score of 2+ (difference: -$21,603 [95% CI: -$39,080, -$4126]). The only statistically significant covariate we found in SMA Other with a continuous age variable was that the presence of ventilation support was associated with higher mean PMPM adjusted healthcare costs (difference: $12,352 [95% CI: 5229, $19,474]). We found that when SMA I was defined as patients with any SMA diagnosis ≤2 years of age and SMA Other as those >2 years old, the results were similar to those of our primary and secondary outcomes [**Supplemental Table 3**]. None of the interaction terms for ventilation or feeding tube support with nusinersen treatment were statistically significant.

We performed post hoc power calculations for the primary and secondary outcomes using the full-model and semi-partial R_2 (percentage of variation in mean PMPM adjusted healthcare costs explained by predictor variables), comparing the R_2 of two models with and without the nusinersen treatment variable [**Supplemental Table 1**]. We had 5.53% power in SMA I to detect a statistically significant difference in the outcome with a sample size of 194, 12 predictor variables, and a type I error rate (α) of 0.05. We had 91.91% power in SMA Other to detect a statistically significant difference in R_2 with a sample size of 510, 11 predictor variables, and α of 0.05.

We also evaluated what our a priori sample size calculation would have been based on the results of Droege et al. We used the annual healthcare costs Droege et al., reported for nusinersen-treated and overall patients with SMA I and an estimated common standard

deviation using methods from Wan et al. for power and sample size calculations with an α of 0.05 for two independent samples. (Rollin Brandt power calculator, Wan 2014) We calculated an effect size of 48.6% from the mean healthcare costs of Droege et al. when they compared treated versus overall(treated and untreated) SMA I patients, and we expected a larger effect size of at least 55% when comparing treated to untreated patients. Based on a 55% effect size, 80% power, and α of 0.05 for two independent samples, we would have needed 55 patients in both the treated and untreated groups.

Discussion

We conducted a retrospective cohort study of commercial claims data to compare the effect of nusinersen treatment on adjusted healthcare costs in nusinersen-treated patients and historical controls with SMA I or SMA Other. We found evidence that nusinersen was associated with a non-significant trend toward lower adjusted healthcare costs in SMA I. Conversely, we found that nusinersen was significantly associated with higher healthcare costs in SMA Other.

Interpretation of results

There are several possible explanations for our observed results. Confounding by indication, in which nusinersen-treated patients were prescribed nusinersen because they were clinically different compared to untreated patients is of potential concern. This would most likely lead to higher costs in N patients. To address this concern, we used historical control patients from a period before nusinersen's approval and adjusted for comorbidity, ventilation support, and feeding tube support. The effect of nusinersen treatment on healthcare costs may have varied based on the presence of ventilation or feeding tube support, however, we did not detect any statistically significant interactions. Another challenge is that supportive care and other unmeasured healthcare practices may have changed between the two periods of observation

for the control and intervention groups, violating the assumption of clinical equipoise in supportive care between our treated and untreated patients. We performed an exploratory analysis of treated and untreated patients from the same period to address this concern and found similar results to our primary and secondary analyses.

It is also possible nusinersen treatment may have introduced new costs due to complications of intrathecal treatment or adverse events which would have a larger relative effect in patients with SMA Other, who have lower supportive care costs than those with SMA I. It is possible that nusinersen treatment did not reduce supportive care needs for any patients and our sample size of SMA I patients was too small to detect a similar increase in costs. Alternatively, the SMA I sample size might not have been large enough to detect a statistically significant decrease in costs. The possibility remains that the clinical benefits of nusinersen treatment were not apparent in the short term, and that longer-term follow-up could lead us to different results.

Other studies

Droege and colleagues published a claims database analysis of health resource utilization analysis in SMA using a different database[12]. The authors found that non-nusinersen per-patient per-year healthcare costs were substantial in SMA I overall (mean $137,627, including both treated and untreated patients), nusinersen-treated SMA I (mean $92,618), SMA Other overall (mean $49,175,), and nusinersen-treated SMA Other (mean $76,371,). It is important to note that the authors did not conduct a comparative analysis, use a control group, or adjust for potential confounders. Without these steps, the results from Droege et al. may be confounded due to unmeasured adjustment variables (e.g., ventilatory support, age, or other unmeasured confounders that would explain the difference between their results and ours). Our results are

also not directly comparable to those of Droege et al. because we used statistical comparisons between differently defined groups and adjusted for differences in patient characteristics.

In a post hoc analysis defining SMA I as any SMA type ≤2 years old, similar to the approach used by Droege, our unadjusted mean PMPM costs for nusinersen-treated patients with SMA I ($26,838,) and historical control patients ($78204,) had a similar trend as Droege et al. for nusinersen-treated patients ($92,618) and overall ($137,627). (**Supplemental Table 3**) (Droege 2020) Moreover, Goble et al. analyzed per-patient per year healthcare costs for SMA patients who were <2 years of age (mean $159,227), 2-18 years (mean $105,206), and >18 years ($39,355)[23]. The results from Goble et al. support the trend in lower healthcare costs with younger ages we found in our study. Goble et al. followed patients from January 2012 to March 2017 and did not categorize patients by SMA ICD-10 code or motor milestone achievement, which may have led to misclassification of SMA subtypes. Dabbous and colleagues performed a retrospective analysis using a claims database from February 2011 to November 2016 to follow new patients with SMA I for ≥30 to 360 days[11]. The authors concluded that the extrapolated all-cause annual cost per patient in SMA I was $324,751, which is similar to our extrapolated mean estimate of $344,616 per-member per-year for SMA I historical control patients. Although we were unable to find a directly comparable study, our analysis reinforces that costs and healthcare utilization are high for patients with SMA.

In summary, our study found generally higher estimates for monthly healthcare costs than previous analyses, likely due to differences in SMA I definition and study periods. The results from Droege et al. suggest that annual healthcare costs were lower in nusinersen-treated patients, while our study suggests a trend in lower costs for SMA I and a significant increase in costs in SMA Other. However, our analysis was underpowered to detect a difference in SMA I due to our relatively small sample size. Our study paid close attention to potential confounding

by indication by comparing nusinersen-treated patients with a historical control group in addition to adjusting for clinical and demographic differences. We also performed exploratory and sensitivity analyses to assess the impact of our assumptions on study results.

Limitations

The most important limitation of our study was the potential misclassification of patients assigned an SMA I diagnosis. In this manuscript, we have discussed how Armstrong et al. found evidence that clinically similar patients were being assigned different SMA diagnosis codes which suggested that these ICD codes were potentially misclassifying. The definition of SMA subtypes depends on the best motor function milestone achieved, which adds to the uncertainty around the subtype of an SMA diagnosis[3]. We used an age cutoff to identify SMA Other patients <2 years and treated them as SMA I, which includes some patients with the less severe SMA II, despite this method being used in other published analyses[12,16].

The age of the SMA I patients in our nusinersen-treated and historical control cohorts (median 5 years and 9 years, respectively) are much older than in the analyses referenced above, due to their use of age cutoffs when defining SMA I[11,12,16,23]. Of our SMA I sample, only 30% of nusinersen-treated and 32% of historical controls were <2 years of age, which may explain the variation between our results and those in the published literature. However, our post hoc exploratory analysis using a stricter SMA I definition of <2 years for our SMA I cohort found similar results to the primary outcome model. It should be noted that among patients with SMA I, a registry survey by Oskoui et al. found that of patients born between 1995 to 2006, two-year survival was 50.3%, a marked improvement from the 24.6% those born between 1980 and 1994 due to advances in supportive care[6]. Researchers should consider that assuming the true two-year survival probability in SMA I is 50%, excluding patients <2 years would exclude a sizeable

portion of SMA I patients. Thus, as imperfect as SMA I ICD-10 codes are, the age cutoff method also has limitations.

One limitation of using insurance claims databases is the inability to identify newly diagnosed patients, since the availability of long-term medical history is sporadic. Differential time since diagnosis could have led to higher costs in nusinersen-treated patients because they had more advanced disease. We performed a sensitivity analysis with a 6-month washout period to include more newly diagnosed patients and did not find significant differences in healthcare costs in either SMA I or SMA Other. The estimated difference in mean adjusted healthcare costs for SMA I patients was larger in the newly diagnosed cohort (-$34,965) than our primary outcome cohort (-$12,144). We found that when we only included newly diagnosed patients with SMA Other, nusinersen treatment was no longer associated with a difference in mean adjusted healthcare costs, as it was in our secondary outcome. One possible explanation for this difference is an improved clinical response to nusinersen treatment early after diagnosis[24].

Importantly, we did not have enough statistical power to detect a difference in PMPM healthcare costs in SMA I due to the small amount of variation in healthcare costs that was explained by nusinersen treatment. We would have needed a sample size of 32,789 patients to achieve 80% power with the same difference in R_2, number of predictor variables, and α. Thus, while we did not identify a statistically significant difference in healthcare costs for SMA I, confounding may have led to diminished effect size and our study was underpowered.

Another limitation is the method of categorizing SMA types II-IV as SMA Other. Droege et al. used the same definition of SMA Other and found that, in a post hoc analysis, there were differences in mean non-nusinersen per-patient per-year healthcare costs between SMA type II ($82,799), SMA type III ($54,923), and SMA type IV ($34,451)[12]. We decided that commercial

claims data did not provide enough clinical data to reliably differentiate between SMA types II-IV given the absence of specific ICD-10 codes.

We chose to not apply age cutoffs to our patients with SMA I ICD-10 codes because SMA type I has a unique ICD-10 code unlike SMA 0, II, or IV, it represents the majority of SMA cases, and we wanted to ensure a sufficiently large sample size for our multivariable linear regression. Despite our efforts, the sample size of our analytic sample was still small (as few as 83 patients in our SMA I nusinersen cohort) owing to the rarity of SMA, which makes it more difficult to accurately estimate and model from our analytic sample.

We may not have been observing a sample generalizable to all SMA patients since Marketscan® is not a randomly sampled population, and unmeasured confounding may have influenced the results. We used age categories to isolate differences based on likely SMA subtype, but since it may have masked the effects of nusinersen, we performed a post hoc exploratory analysis with age as a continuous variable. The results with age as a continuous variable were similar to our primary and secondary outcomes. The SMA Other cohort included SMA types II-IV, which would have masked the differences in treatment effect by SMA type. Future research should focus more on the differences between SMA types II-IV, due to significant heterogeneity between SMA subtypes.

Future studies with larger patient cohorts and more accurate diagnoses from medical records (e.g, chart reviews) could provide more information on nusinersen treatment's effect on healthcare costs in patients with SMA I. Future analyses could compare the effect of nusinersen on differences in specific types of supportive care utilization with micro-costing instead of our more general approach. Research using longitudinal data may also reveal treatment effects that

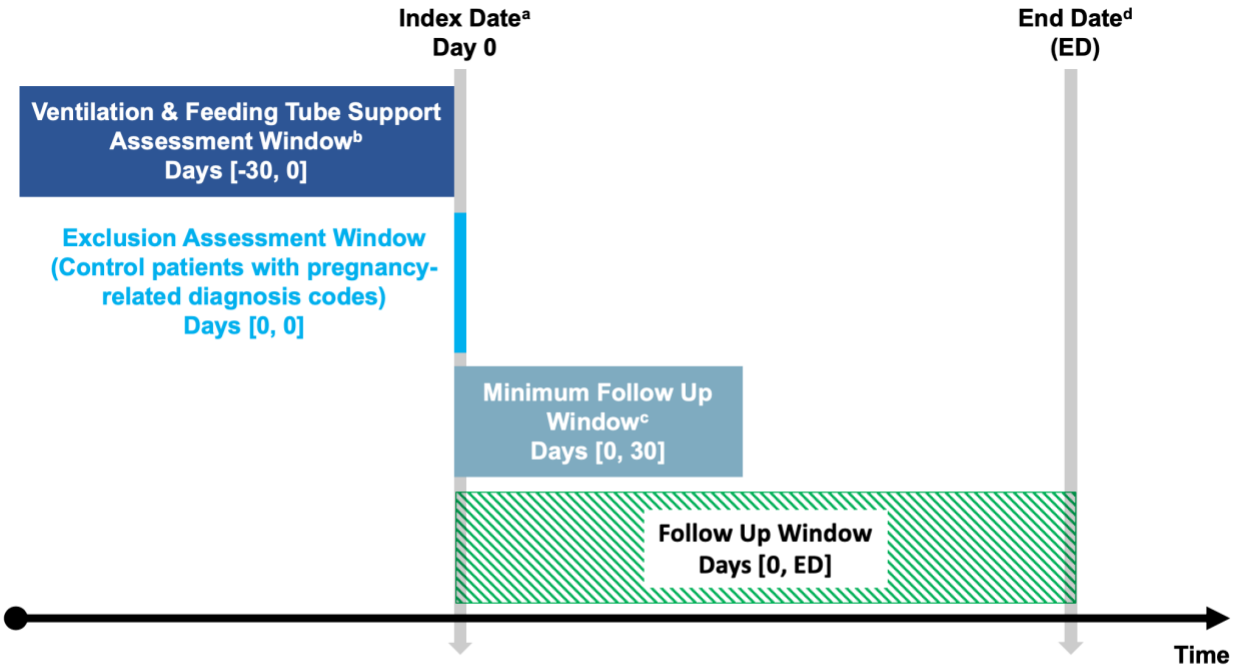
were unobserved in our relatively short study period, or more accurately identify newly diagnosed patients.

Conclusion

We conducted a retrospective cohort study using claims data and identified a trend in lower mean PMPM adjusted healthcare costs in patients with SMA I, although statistical significance was not achieved. Among patients with SMA Other, nusinersen-treated patients had statistically significantly higher non-nusinersen PMPM costs. Additional studies using larger sample sizes, reliable diagnosis of SMA subtypes, and adjustment to avoid influential confounders are needed to help clarify the impact of SMA treatments in this rare, complex, and costly disease.

Tables & Figures

Figure 1. Study Design[25]

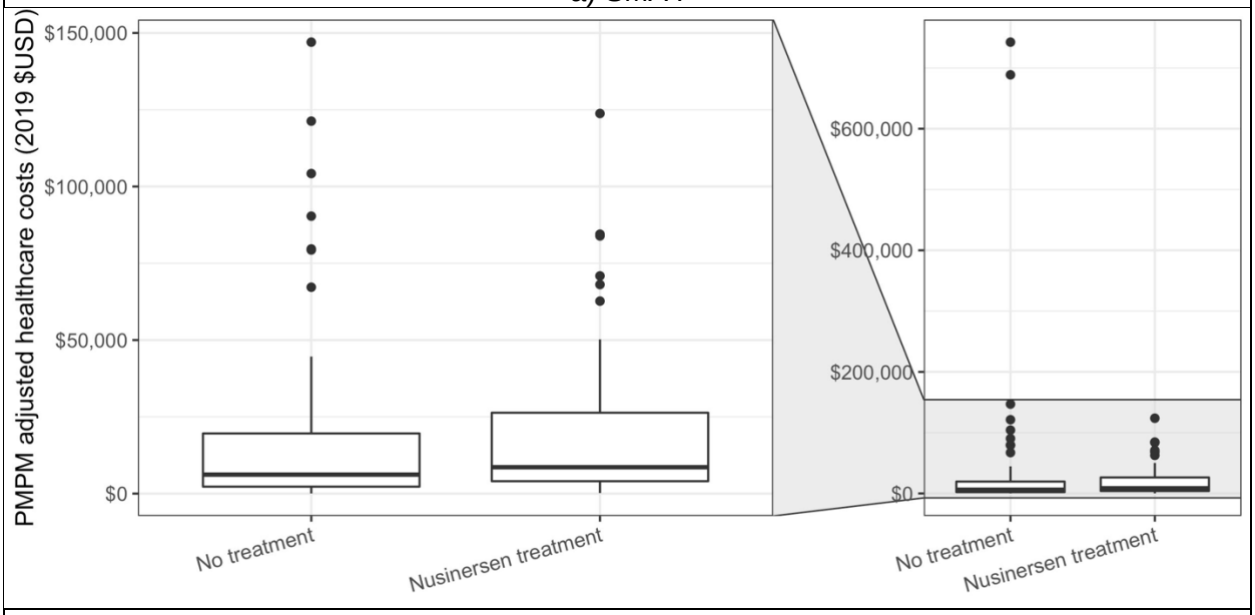


a. Historical control patients: Date of claim with first SMA diagnosis after January 1st, 2015.
Nusinersen patients: Date of nusinersen initiation after January 1st, 2017.
b. Ventilation or feeding tube support defined using claims with corresponding CPT or HCPCS codes
c. Patients were required to have ≥1 clinical event ≥30 days after index date, and ≥2 claims with an SMA diagnosis ≥30 days apart
d. Earliest of end of clinical follow up or data availability (December 22nd, 2016 for historical control patients, December 22nd, 2018 for nusinersen patients

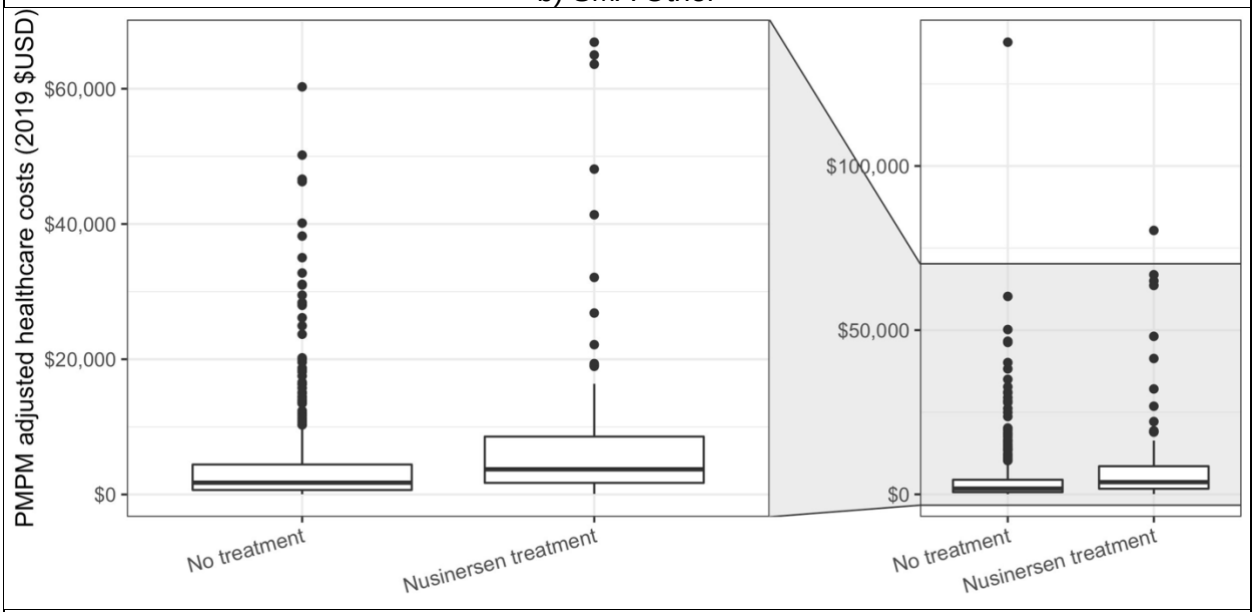
SMA = Spinal Muscular Atrophy, CPT = Current Procedural Terminology, HCPCS = Healthcare Common Procedure Coding System

Figure 2. Mean PMPM Adjusted Healthcare Costs in SMA I & SMA Other by Treatment Group‡

a) SMA I



b) SMA Other



‡: Adjusted for age category, sex, ventilation support, feeding tube support, Charlson Comorbidity Index score, and region.
SMA I: Spinal Muscular Atrophy Type I, SMA Other: Spinal Muscular Atrophy Types II-IV, USD: United States Dollars, PMPM: Per member per month

Table 1. Sample baseline patient characteristics for the primary and secondary outcomes

	SMA 1			SMA Other		
Characteristic	Historical Control n = 111	Nusinersen n = 83	p-values§	Historical Control n = 420	Nusinersen n = 90	p-values§
Follow up time‡, mean months (SD)	10.7 (4.4)	11.0 (6.0)	0.734	9.44 (3.86)	8.06 (4.25)	0.003
Female, n (%)	50 (45.0)	38 (45.8)	1.000	211 (50.2)	39 (43.3)	0.283
Age, median years [IQR]	9.0 [2.0, 26.5]	5.0 [2.5, 13.0]	0.051	44.0 [23.0, 61.0]	24.0 [13.0, 37.0]	<0.001
Age category, n (%)			<0.001			<0.001
0-2 years (likely SMA I-II)	39 (35.1)	25 (30.1)		0 (0)	0 (0)	
2-21 years (likely SMA III)	39 (35.1)	52 (62.7)		96 (22.9)	39 (43.3)	
21+ years (likely SMA IV)	33 (29.7)	6 (7.2)		324 (77.1)	51 (56.7)	
Ventilation support, n (%)	37 (44.6)	28 (25.2)	0.008	20 (4.8)	4 (4.4)	1.000
Feeding tube support, n (%)	16 (9.3)	5 (4.5)	0.002	8 (1.9)	3 (3.3)	0.655
CCI Score, n (%)			0.582			0.013
0	74 (66.7)	62 (74.7)		289 (68.8)	76 (84.4)	
1	24 (21.6)	15 (18.1)		72 (17.1)	11 (12.2)	
2	7 (6.3)	4 (4.8)		33 (7.9)	1 (1.1)	
2+	6 (5.4)	2 (2.4)		26 (6.2)	2 (2.2)	
Region, n (%)			0.297			0.065
Northeast	20 (18.0)	19 (22.9)		86 (20.5)	16 (17.8)	
North Central	20 (18.0)	17 (20.5)		93 (22.1)	28 (31.1)	
South	51 (45.9)	27 (32.5)		173 (41.2)	26 (28.9)	
West	20 (18.0)	20 (24.1)		68 (16.2)	20 (22.2)	
Plan type, n (%)			0.208			0.114
PPO	68 (61.3)	39 (47.0)		251 (59.8)	43 (47.8)	
HMO	8 (7.2)	6 (7.2)		35 (8.3)	7 (7.8)	
POS	10 (9.0)	9 (10.8)		38 (9.0)	9 (10.0)	
Other	25 (22.5)	29 (34.9)		96 (22.9)	31 (34.4)	

§: Chi-squared test with continuity correction for categorical variables, one-way ANOVA with equal variance assumption for continuous variables, and Kruskal-Wallis test by rank for non-normal continuous variables

‡: Historical controls were indexed on date of claim with first SMA diagnosis after January 1st, 2015 and followed until December 22nd, 2016 , versus nusinersen treated patients who were indexed on date of first nusinersen initiation after January 1st, 2017 and followed until December 22nd, 2018.

SMA: Spinal Muscular Atrophy, **CCI**: Charlson Comorbidity Index, **PPO**: Preferred Provider Organization, **HMO**: Health Maintenance Organization, **POS**: Point of Service plan

Table 2: Primary Multivariable Linear Regression Predictors of adjusted mean PMPM Total Costs for All Analyses§

	Difference in Non-Nusinersen PMPM Costs, 2019 USD†			
	Nusinersen vs control, unadjusted		Nusinersen vs control, adjusted††	
Primary Outcome	**β Coefficient**	**95% CI**	**β Coefficient**	**95% CI**
SMA I, historical controls‡	-9375	-28181, 9466	-12144	-32123, 7834
Secondary Outcome				
SMA Other, historical controls‡	4507**	1161, 7853	4517**	1225, 7810
Sensitivity Analyses				
Newly diagnosed SMA I (26 treated, 111 controls)	-3279	-24039, 17482	-34965	-89611, 19680
Newly diagnosed SMA Other (6 treated, 420 controls)	5246	-2492, 12984	5306	-2680, 13292
SMA I, 2017 controls¶ (83 treated, 99 controls)	-3647	-15003, 7739	-9775	-23103, 3554
SMA Other, 2017 controls¶ (90 treated, 466 controls)	3873*	579, 7167	3646*	414, 6879

§: PMPM costs represent all costs divided by months of follow up for each patient, excluding claims with a nusinersen NDC or HCPCS code

†: Coefficients from linear regressions represent the difference in PMPM costs between two groups that differ by one unit of each predictor.

‡: Historical controls were indexed on date of claim with first SMA diagnosis after January 1st, 2015 and followed until December 22nd, 2016, versus nusinersen treated patients who were indexed on date of first nusinersen initiation after January 1st, 2017 and followed until December 22nd, 2018.

¶: 2017 controls were indexed on date of claim with first SMA diagnosis after January 1st, 2017 and followed until December 22nd, 2018, the same time period as the nusinersen treated patients.

††: Adjusted for age category, sex, ventilation support, feeding tube support, Charlson Comorbidity Index score, and region.

*: p <0.05, **: p<0.01, ***: p<0.001,

Table 3: Mean Non-Nusinersen PMPM and Supportive Care Costs in Primary and Secondary Outcome populations§

	PMPM Costs, 2019 USD			
	SMA I		SMA Other	
Cost type	**Historical Control n = 111**	**Nusinersen n = 83**	**Historical Control n = 420**	**Nusinersen n = 90**
Healthcare Cost†,				
mean (SD)	28718 (96897)	19361 (23031)	4752 (10092)	9258 (15521)
median [IQR]	6188 [2263, 19597]	8597 [4045, 26337]	1742 [664, 4434]	3721 [1716, 8564]
Other Drug Cost‡,				
Utilization, n (%)	47 (42%)	73 (88%)	149 (35%)	74 (82%)
Mean $ (SD)	4696 (11774)	42262 (115005)	1791(12825)	25374 (106206)
Median $ [IQR]	0 [0, 884]	1384 [437, 6116]	0 [0, 87]	811 [256, 1985]

	PMPM Healthcare Costs¶			
Cost type	**Historical Control n = 111**	**Nusinersen n = 83**	**Historical Control n = 420**	**Nusinersen n = 90**
Respiratory Support,				
Utilization, n (%)	60 (54%)	47 (57%)	53 (13%)	13 (14%)
Mean $ (SD)	4899 (18732)	2546 (3317)	942 (977)	1213 (2109)
Median $ [IQR]	1043 [333, 2190]	1577 [928, 2575]	706 [126, 1514]	556 [68, 1106]
DME,				
Utilization, n (%)	94 (85%)	74 (89%)	177 (42%)	45 (50%)
Mean $ (SD)	1540 (1619)	1894 (2044)	782 (1413)	3010 (7297)
Median $ [IQR]	1065 [344, 1895]	1308 [535, 2535]	181 [53, 960]	701 [214, 2774]
Orthopedic Surgery,				
Utilization, n (%)	27 (35%)	23 (28%)	84 (20%)	15 (17%)
Mean $ (SD)	182 (390)	327 (774)	584 (2796)	100 (119)
Median $ [IQR]	26 [17, 176]	15 [8, 153]	47 [17, 180]	60 [28, 118]
Orthotics/Orthoses,				
Utilization, n (%)	13 (12%)	18 (22%)	3 (1%)	4 (4%)
Mean $ (SD)	88 (88)	149 (213)	135 (48)	177 (191)
Median $ [IQR]	78 [11, 137]	76 [35, 161]	154 [117, 163]	141 [20, 297]
PT/OT/Speech Therapy,				
Utilization, n (%)	69 (62%)	70 (84%)	206 (49%)	45 (50%)
Mean $ (SD)	495 (809)	591 (628)	286 (427)	380 (421)
Median $ [IQR]	256 [110, 564]	470 [115, 755]	140 [44, 307]	204 [93, 645]

§: PMPM costs represent all costs divided by months of follow up for each patient, For the primary and secondary outcomes, historical controls were indexed on date of claim with first SMA diagnosis after January 1st, 2015 and followed until December 22nd, 2016, versus nusinersen treated patients who were indexed on date of first nusinersen initiation after January 1st, 2017 and followed until December 22nd, 2018.

†: Total costs excluding claims with a nusinersen NDC or HCPCS code.

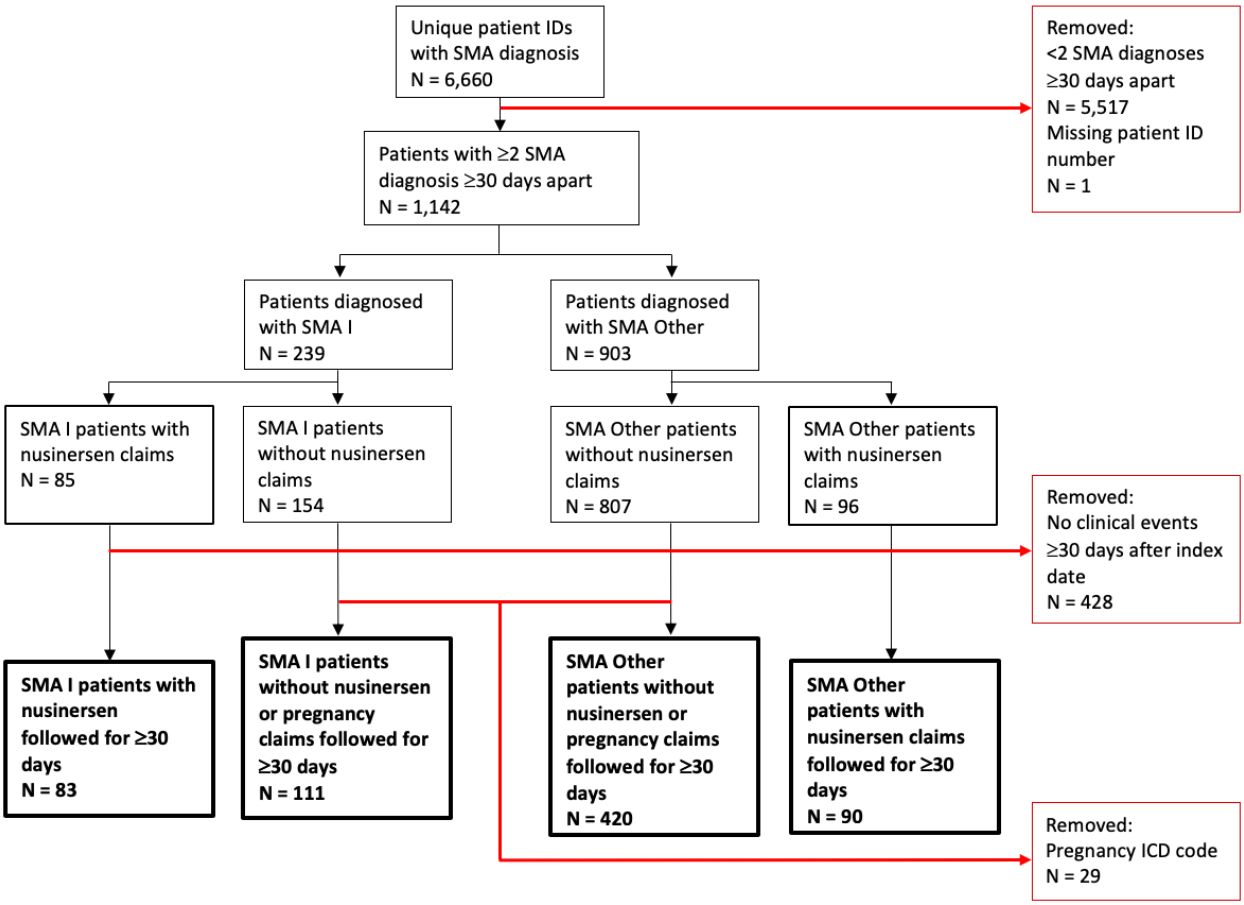
‡: Inpatient and outpatient drug costs excluding claims with a nusinersen NDC or HCPCS code.

¶: Mean and median costs calculated from patients with at least 1 claim of the corresponding type.

DME: Durable medical equipment, PT: Physical therapy, OT: Occupational therapy

Supplemental Information/Appendix

Supplemental Figure 1: Patient flow diagram



Supplemental Table 1: All Multivariable Linear Regression Predictors of Non-Nusinersen PMPM Costs for Primary & Secondary Outcomes§

	Difference in PMPM Costs, 2019 USD†			
	SMA I		SMA Other	
Predictor	**β Coefficient**	**95% CI**	**β Coefficient**	**95% CI**
Nusinersen treatment, unadjusted	-9375	-28181, 9466	4507**	1161, 7853
Nusinersen treatment, adjusted‡	-12144	-32123, 7834	4517**	1225, 7810
Female sex	-5119	-24023, 13785	-1343	-3282, 595
Age category				
0-2 years (likely SMA I-II)	Reference	Reference	--	--
2-21 years (likely SMA III)	-29151*	-56947, -1355	Reference	Reference
21+ years (likely SMA IV)	-40283*	-74450, -6116	-465	-2660, 1729
Ventilation support	14740**	4305, 25175	12008**	4651, 19366
Feeding tube support	-8383	-18899, 2132	4264	-2882, 11410
CCI Score				
0	Reference	Reference	Reference	Reference
1	-12084	-26633, 2464	-1.4	-2089, 2086
2	-5569	-26832, 15695	-208.7	-2422, 2004
2+	-22306*	-41858, -2754	4408*	31, 8785
Region				
Northeast	Reference	Reference	Reference	Reference
North Central	-10316	-43410, 22778	3237	-419, 6892
South	-12997	-48555, 22602	1259	-1218, 3735
West	1416	-39170, 42002	700.8	-1517, 2918

	SMA I		SMA Other	
Model	**R^2**	**Adjusted R^2**	**R^2**	**Adjusted R^2**
Unadjusted Model	0.00385	-0.00134	0.0229	0.0210
Adjusted Model‡	0.0637	0.00169	0.108	0.0886

§: PMPM costs represent all costs divided by months of follow up for each patient, excluding claims with a nusinersen NDC or HCPCS code. For the primary and secondary outcomes, historical controls were indexed on date of claim with first SMA diagnosis after January 1st, 2015 and followed until December 22nd, 2016, versus nusinersen treated patients who were indexed on date of first nusinersen initiation after January 1st, 2017 and followed until December 22nd, 2018.
†: Coefficients from linear regressions represent the difference in PMPM costs between two groups that differ by one unit of each predictor.
‡: Adjusted for all listed variables, --: Patients age <2 years were categorized as SMA I
*: p <0.05, **: p<0.01, ***: p<0.001
R^2: Proportion of variance in the outcome that can be explained by the linear regression formula.
Adjusted R^2: R^2 adjusted for the number of explanatory variables and sample size

Supplemental Table 2: Transformed Multivariable Linear Regression Predictors of Log Non-Nusinersen PMPM Costs for Primary & Secondary Outcomes§

	Relative Difference in PMPM Costs†			
	SMA I		SMA Other	
Predictor	**Transformed β Coefficient**	**95% CI**	**Transformed β Coefficient**	**95% CI**
Nusinersen treatment, unadjusted	1.55*	1.23, 2.34	2.24***	1.64, 3.04
Nusinersen treatment, adjusted‡	1.13	0.74, 1.74	2.36***	1.73, 3.21
Female sex	1.14	0.73, 1.78	0.99	0.78, 1.25
Age category				
0-2 years (likely SMA I-II)	Reference	Reference	--	--
2-21 years (likely SMA III)	0.51**	0.32, 1.17	Reference	Reference
21+ years (likely SMA IV)	0.30***	0.16, 0.55	0.90	0.68, 1.18
Ventilation support	3.30***	2.18, 4.98	5.37***	3.68, 7.83
Feeding tube support	0.89	0.57, 1.39	1.84**	1.16, 2.90
CCI Score				
0	Reference	Reference	Reference	Reference
1	0.70	-57, 1.13	1.25	0.93, 1.69
2	0.65	-75, 1.70	1.76**	1.16, 2.66
2+	0.80	-51, 1.29	2.86***	1.74, 4.68
Region				
Northeast	Reference	Reference	Reference	Reference
North Central	1.23	-33, 2.24	1.54*	1.06, 2.22
South	1.25	-36, 2.43	1.05	0.74, 1.48
West	1.27	-29, 2.27	1.15	0.62, 1.18

	SMA I		SMA Other	
Model	**R_2**	**Adjusted R_2**	**R_2**	**Adjusted R_2**
Unadjusted Model	0.0203	0.01524	0.0450	0.0431
Adjusted Model‡	0.224	0.172	0.187	0.169

§: PMPM costs represent all costs divided by months of follow up for each patient, excluding claims with a nusinersen NDC or HCPCS code. For the primary and secondary outcomes, historical controls were indexed on date of claim with first SMA diagnosis after January 1st, 2015 and followed until December 22nd, 2016, versus nusinersen treated patients who were indexed on date of first nusinersen initiation after January 1st, 2017 and followed until December 22nd, 2018.

†: Transformed coefficients from linear regressions with a log transformed outcome represent the multiplicative difference in PMPM costs between two groups that differ by one unit of each predictor. Transformed β coefficients above one represent increases, coefficients below one represent decreases.

‡: Adjusted for all listed variables, --: Patients age <2 years were categorized as SMA I

*: p <0.05, **: p<0.01, ***: p<0.001

R_2: Proportion of variance in the outcome that can be explained by the linear regression formula. Adjusted R_2: R_2 adjusted for the number of explanatory variables and sample size

Supplemental Table 3: Primary Multivariable Linear Regression Predictors for Exploratory Analyses

	Difference in Non-Nusinersen PMPM Costs, 2019 USD§†			
	Nusinersen vs control, unadjusted		Nusinersen vs control, adjusted††	
Exploratory Analyses	**β Coefficient**	**95% CI**	**β Coefficient**	**95% CI**
SMA I, Interaction term	-9357	-28181, 9466	-20466	-50735, 9803
SMA Other, Interaction term	1305**	1161, 7853	3946*	909, 6983
SMA I, Age as continuous	-9357	-28181, 9466	-16826	-40242, 6590
SMA Other, Age as continuous	1305**	1161, 7853	5048**	1850, 8245
SMA I, Any SMA <2 (24 treated, 28 controls)	-51366	-121882,19151	-59356	-152178, 33466
SMA Other, Any SMA >2 (166 treated, 520 controls)	6295***	3337, 9253	4117**	1115, 7119

§: PMPM costs represent all costs divided by months of follow up for each patient, excluding claims with a nusinersen NDC or HCPCS code

†: Coefficients from linear regressions represent the difference in costs between two groups that differ by one unit of each predictor.

‡: Adjusted for age category, sex, Charlson Comorbidity Index score, and region.

¶: Mean cost per episode of care for each patient. Episode of care defined as the 7 days before and after nusinersen administration date.

‡‡: Nusinersen-related costs included. Adjusted for age category, sex, ventilation support, feeding tube support, Charlson Comorbidity Index score, and region.

††: Adjusted for age category, sex, ventilation support, feeding tube support, Charlson Comorbidity Index score, and region

*: p <0.05, **: p<0.01, ***: p<0.001

Supplemental Table 4: Cost Per Member Per Nusinersen Episode in Primary and Secondary Outcome by Claim Type§

	Cost Per Episode, 2019 USD	
Descriptor	**SMA I N = 320 episodes**	**SMA Other N = 290 episodes**
Episodes per patient Mean (SD)	3.9 (2.1)	3.2 (1.6)
Cost per episode Mean $ (SD) Median $ [IQR]	147620 (70395) 134102 [128265, 149321]	146551 (97758) 132468 [127730, 154212]
Nusinersen-related cost per episode† Mean $ (SD) Median $ [IQR]	142786 (66003) 135734 [129565, 141857]	145105 (102371) 134936 [129951, 153715]
	Supportive care cost per episode¶	
Descriptor	**SMA I N = 320 episodes**	**SMA Other N = 290 episodes**
Drug cost‡ Episodes, n (%) Mean $ (SD) Median $ [IQR]	162 (51%) 4083 (22429) 305 [146, 600]	169 (58%) 4687 (23256) 250 [182, 697]
Anesthesiology claims Episodes, n (%) Mean $ (SD) Median $ [IQR]	74 (23%) 782 (510) 717 [478, 922]	59 (20%) 582 (432) 540 [217, 843]
Radiology claims Episodes, n (%) Mean $ (SD) Median $ [IQR]	92 (28%) 331 (606) 150 [91, 425]	99 (34%) 349 (304) 209 [146, 527]

§: Cost per episode represents all costs accrued in the 7 days before and after nusinersen administration. Nusinersen treated patients were indexed on date of first nusinersen initiation after January 1st, 2017 and followed until December 22nd, 2018.
†: Defined as all costs reported on claims with a nusinersen NDC or HCPCS code.
‡: Inpatient and outpatient drug costs excluding claims with a nusinersen NDC or HCPCS code.
¶: Sum of gross total payments per episode from episodes with at least 1 claim of the corresponding type.

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