Economic burden of growth hormone deficiency in a US pediatric population

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What is already known about this subject

- Pediatric growth hormone deficiency (GHD) is characterized not only by short stature but also metabolic disorders, impaired musculoskeletal development, and decreased quality of life.
- Current treatment involves daily somatropin injections, but maintaining optimal adherence is difficult.

What this study adds

- This study fills the current gap in knowledge of real-world evidence on the clinical and economic burden of pediatric GHD among patients in the United States, as well as provides real-world data on adherence to and persistence of growth hormone therapy.
- Our findings indicate that untreated GHD is associated with higher non-somatropin health care costs compared with treated GHD, further indicating a need to improve adherence to treatment.

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ABSTRACT

BACKGROUND: Pediatric growth hormone deficiency (GHD) is a rare disorder of short stature that is currently treated with daily injections of somatropin. In addition to short stature, GHD is associated with other comorbidities such as impaired musculoskeletal development, cardiovascular disease, and decreased quality of life.

OBJECTIVE: To analyze somatropin utilization, adherence, and health care costs among children with GHD who had either Medicaid or commercial health insurance.

METHODS: Children (aged <18 years) with a GHD diagnosis between January 1, 2008, and December 31, 2017, were identified in the

IBM MarketScan Commercial and Medicaid databases. Patients with at least 12- and 6-month continuous enrollment pre- and postdiagnosis were eligible. Children with GHD were direct matched (1:3) to controls without GHD (or other short stature-related disorders) on age, gender, plan type, region, and race (Medicaid only). Index date was the date of the first GHD diagnosis during the selection window for GHD patients and using random assignment for controls. Patients were followed until the end of continuous database enrollment or December 31, 2018. Baseline comorbidities and medications were measured during the 12 months pre-index, whereas somatropin treatment patterns along with all-cause and GHD-related health care costs were measured during the variable

follow-up period. Multivariable modeling was used to compare costs between GHD patients and controls and between somatropin-treated and -untreated GHD patients while adjusting for baseline characteristics.

RESULTS: There were 6,820 Medicaid and 14,070 commercial patients with GHD who met the study inclusion criteria. Mean (SD) age at index was 9.5 (4.5) years for Medicaid patients and 11.1 (3.7) years for commercial patients. The majority of patients were male (>65%), and mean follow-up time for all cases and controls was 3-4 years. Overall, 63.2% of Medicaid and 68.4% of commercial GHD patients were treated with somatropin at some point during follow-up. Among Medicaid GHD patients, the treatment rate

was highest among White males and lowest among Black females. Adherence was low as the proportion of days covered was $\geq 80\%$ for only 18.4% of Medicaid patients and 32.3% of commercial patients and 49.1% of treated Medicaid and 24.3% of treated commercial patients discontinued before turning age 13. After adjusting for baseline characteristics, all-cause non-somatropin annualized costs were 5.67 times higher ($\Delta\$19,309$) for Medicaid GHD patients and 5.46 times higher ($\Delta\$12,305$) for commercial GHD patients than matched non-GHD controls. Adjusted all-cause non-somatropin annualized costs were 0.59 times lower ($\Delta\$14,416$) for treated Medicaid patients and 0.69 times lower ($\Delta\$7,650$) for treated commercial patients than for untreated patients.

CONCLUSIONS: Pediatric GHD presents a significant health care burden, and many patients remain untreated or undertreated. Untreated GHD was associated with higher non-somatropin health care costs than treated GHD. Strategies to optimize treatment and improve adherence may reduce the health care burden faced by these patients.

Pediatric growth hormone deficiency (GHD) is characterized by slow growth during childhood due to a lack of growth hormone.¹ Although short stature is the most common manifestation of GHD, other comorbidities include impaired musculoskeletal development, cardiovascular disease, and decreased quality of life.²⁻⁴ GHD has an estimated prevalence of 1.8 to 2.9 per 10,000 children and is more commonly diagnosed in boys.^{5,6}

The current treatment for GHD in children is daily injections of somatropin with the primary objective of correcting the hormone deficiency and reversing symptoms and improving health outcomes. Treatment with somatropin has been associated with improvement in metrics of final height, depression, behavioral issues, and psychosocial evaluations.⁷⁻⁹ In a majority of cases, patients may not require somatropin therapy into adulthood¹⁰; however, some patients will require treatment into adulthood.²

Optimal outcomes in final adult height from somatropin treatment are usually achieved when patients are started early, before age 9 years,¹¹ and are highly adherent to treatment, defined in Cutfield et al as missing no more than 1 dose per week.¹² However, maintaining high adherence to daily injections over many years is challenging, and barriers to adherence include injection site pain, perceived inefficacy, lifestyle disruptions, and lack of awareness of the consequences of nonadherence.^{13,14} Suboptimal treatment of GHD can result in outcomes beyond not achieving full adult height potential, such as reduced quality of life and costly clinical mismanagement if nonadherence is hidden from the clinician.^{3,15,16} Multiple long-acting growth hormone

preparations are currently in development intended to help improve treatment adherence.¹⁷

There is a lack of current real-world evidence on the overall burden of GHD among children in the United States. To help address this gap, we examined somatropin utilization and adherence, all-cause health care costs, and GHD-related health care costs among children with a diagnosis of GHD who had either Medicaid or commercial health insurance. Multivariable analysis was used to compare health care costs between patients with GHD and those without GHD and between treated and untreated patients with GHD while adjusting for baseline demographic and clinical differences.

Methods

STUDY DESIGN AND DATA SOURCE

This observational retrospective cohort analysis utilized deidentified US administrative claims data from the IBM MarketScan Commercial Claims and Encounters database (commercial) and MarketScan Multi-State Medicaid Database (Medicaid) for the period from January 1, 2007, to December 31, 2018. The commercial database contains the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents, covered under a variety of fee-for-service and managed care health plans, including exclusive provider organizations, preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations (HMOs). The Medicaid database contains the health care experience (both medical and pharmacy) of Medicaid enrollees from multiple states, including fee-for-service and managed plans. Both databases provide detailed cost, use, and outcomes data for health care services performed in both inpatient and outpatient settings.

All study data were obtained using *International Classification of Diseases, Ninth/Tenth Revisions, Clinical Modification* (ICD-9/10-CM) codes, *Current Procedural Terminology* 4th edition codes, *Healthcare Common Procedure Coding System* (HCPCS) codes, and *National Drug Code* numbers.

All database records are statistically deidentified and certified to be fully compliant with US patient confidentiality requirements set forth in the *Health Insurance Portability and Accountability Act* of 1996. Because this study used only deidentified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from institutional review board approval.

PATIENT SELECTION AND COHORT ASSIGNMENT

From the commercial and Medicaid databases, we identified patients with at least 1 nondiagnostic claim with a diagnosis of GHD between January 1, 2008, and December 31, 2017. Nondiagnostic claims exclude claims for lab tests, imaging services, and other screening procedures, which require a diagnosis code for insurance reimbursement even though the result of the test may rule out the condition as a diagnosis. The index date was set as the date of the first claim with a diagnosis of GHD during the selection window.

Controls were identified from a 25% random sample of the commercial and Medicaid databases. To be eligible for inclusion in the control cohorts, patients were required to be without any claims for GHD, short stature related disorders, or any of the other indications for somatropin therapy approved by the US Food and Drug Administration between January 1, 2007, and December 31, 2018. Short stature-related disorders included idiopathic short stature, Noonan Syndrome, Prader-Willi Syndrome, Turner Syndrome, short bowel syndrome, and a diagnosis of “small for gestational age.” The index date for controls was randomly assigned based on the distribution of index years among GHD patients.

Patients with GHD and controls were required to be aged less than 18 years old on the index date and have continuous enrollment with medical and pharmacy benefits for at least 12 months before (baseline period) and at least 6 months following the index date. This study employed a variable follow-up period extending from the index date until the earliest of the end of continuous enrollment or the end of the study period (December 31, 2018). Random sampling without repetition and direct matching were employed to select controls matched (3:1) to patients with GHD on age, gender, plan type, region, and race. Race data were only available from the Medicaid database and were not used in matching the commercial cohorts.

BASELINE CHARACTERISTICS

Baseline demographic characteristics were measured on the index date and included age, age category (≤ 4 , 5-8, 9-12, 13-17 years), sex, geographic region, health plan type, and race (for Medicaid cohorts). Baseline clinical characteristics were evaluated during the 12-month baseline period and included Deyo-Charlson Comorbidity Index (CCI),¹⁷ endocrine-related conditions, cardiovascular disease, metabolic conditions, anxiety, attention-deficit/hyperactivity disorder (ADHD), bipolar disorders, depression, eating disorders, and sleep disorders (see [Supplementary Tables 5-7](#) for list of ICD-9-CM and ICD-10-CM diagnosis codes used in this study, available in online article). The use of antianxiety medications, attention-deficit/hyperactivity disorder

medications (stimulants and nonstimulants), and antidepressants in the baseline period was also measured.

Endocrine-related conditions included GHD, hypopituitarism, adrenal insufficiency, hypothyroidism, diabetes insipidus, and hypogonadism. Cardiovascular disease included ischemic heart disease/coronary heart disease, rheumatic heart disease, congenital heart disease, and other pulmonary and cardiac disorders. Metabolic conditions included diabetes mellitus, hyperlipidemia, hypertension, metabolic syndrome, nonalcoholic fatty liver disease, and obesity.

SOMATROPIN TREATMENT OUTCOMES

Patterns of somatropin utilization during the variable follow-up period were evaluated among those with at least 1 claim for somatropin. The number and percentage of patients with at least 1 outpatient medical or pharmacy claim for somatropin during the follow-up period were calculated. The treatment rate was measured as the number of patients with somatropin treatment during the follow-up period divided by the total person-years and expressed as the rate of treated patients per 100 person-years. Among patients newly initiating treatment (ie, those without claims for somatropin in the baseline period), the time from index to treatment initiation was analyzed. These variables were analyzed by the primary payer, patient sex, and patient race (Medicaid only).

Among patients with at least 1 outpatient pharmacy claim for somatropin, adherence and discontinuation were measured. Patients with outpatient medical (HCPCS) claims for somatropin were excluded from adherence and discontinuation analysis because they represented a minority of patients and their days supply could not be clearly determined from claims records.

Adherence was reported as the proportion of days covered (PDC) defined as the number of days covered by any somatropin medication prescription divided by the number of days in the variable follow-up period. For example, a patient with 365 days of follow-up time who had 180 days covered by any somatropin therapy would have a PDC of 49%. For calculation of the PDC, when the days supply of 2 prescriptions of the same drug overlapped, we appended the days supply, adjusting the prescription start date to be the day after the previous fill ended.

Patients were considered to have discontinued somatropin therapy if there was a continuous gap in treatment greater than 60 days. Medicaid and commercial GHD patients were stratified by age category to report the age at which patients started treatment and the age at which patients ended treatment. The time from treatment start to date of discontinuation was captured and used to calculate

Kaplan-Meier curves of probability of continuation. Time to discontinuation was measured from the index date to the last days supply of any somatropin therapy before a gap in treatment of greater than 60 days, a gap time widely used across claims studies falling into the range of permissible gap times.¹⁸ Patients who did not discontinue were censored at the end of the follow-up period.

HEALTH CARE COSTS

Annualized all-cause health care costs for inpatient admissions; outpatient services (emergency department visits, physician office visits, laboratory tests, and other outpatient services); and outpatient pharmacy services were reported for the 12-month baseline period and the variable follow-up period. Annualized GHD-related health care costs were reported for the variable follow-up period and included any claims with a diagnosis of GHD in any position, as well as claims for somatropin, select laboratory tests, and select imaging studies.

Costs were the paid amounts of fully adjudicated claims, including insurer and health plan payments, as well as patient cost sharing in the form of copayment, deductible, and coinsurance. All costs were reported per person per year and were inflated to 2018 US dollars using the medical care component of the Consumer Price Index.¹⁹

STATISTICAL ANALYSIS

Mean (SD) were reported for continuous variables, whereas frequencies and percentages were reported for categorical variables. All data analyses were conducted using WPS version 4.1 (World Programming).

Multivariable analysis was used to examine index treatment discontinuation and annual all-cause cost outcomes (excluding somatropin outpatient prescription costs) while controlling for baseline demographic and clinical characteristics. Costs were modeled using generalized linear models employing a log link and gamma error distribution. Discontinuation among treated patients was modeled using Cox hazard models. For each primary payer type (commercial and Medicaid), 3 cost models were constructed: (1) modeling costs of GHD patients vs non-GHD patients, (2) modeling costs of treated GHD patients vs nontreated GHD patients, and (3) modeling cost of treated GHD patients who were treatment naive on the index date. Each model adjusted for age, sex, index year, baseline CCI, and duration of follow-up. Models examining all-cause costs excluded somatropin costs. Although it is well accepted that somatropin is a major driver of costs associated with GHD, the intent was to be able to demonstrate the all-cause burden of GHD beyond the cost of treatment, when comparing

to non-GHD controls. Models of commercially insured patients were adjusted for geographic region of residence and health plan type, whereas models of Medicaid-insured patients were adjusted for race. Other control variables for the treated GHD patients vs nontreated GHD patients were based on the literature.^{2-4,7-9} Cost models 2 and 3 also adjusted for baseline clinical characteristics, including the presence of comorbid endocrine-related conditions, pituitary tumors, cardiovascular disease, fractures, hepatic and renal function conditions, metabolic conditions, anxiety, ADHD, depression, and sleep disorders, all conditions associated with treatment and health outcomes of patients with GHD.^{2-4,7-9} The model of index somatropin discontinuation was adjusted for baseline clinical characteristics and the brand name of the first somatropin treatment after index.

Results

A total of 6,820 Medicaid-insured and 14,070 commercially insured pediatric patients with GHD met the study inclusion criteria (Figure 1). The majority of patients with GHD were male, and the mean patient age at index was 9.5 years for Medicaid patients and 11.1 years old for commercial patients (Table 1). The mean duration of follow-up was slightly longer for GHD patients (3.7 and 4.0 years for Medicaid and commercial, respectively) than controls (3.3 and 3.5 years for Medicaid and commercial, respectively).

Overall, patients with GHD had a greater comorbid burden than demographically matched patients without GHD (Table 1). A higher percentage of Medicaid patients with GHD than patients without GHD had a recent diagnosis of an endocrine-related condition (22.2% vs 0.3%), cardiovascular disease (7.1% vs 1.2%), a metabolic condition (10.3% vs 4.9%), or a mental health condition (36.7% vs 17.6%). Similar differences were seen among commercial patients: endocrine-related conditions (22.3% vs 0.2%), cardiovascular disease (4.0% vs 0.9%), metabolic conditions (5.5% vs 1.9%), and mental health conditions (22.7% vs 9.6%). Of interest were the higher rate of ADHD diagnosis (Medicaid: 26.5% vs 13.0%; commercial: 15.0% vs 6.1%) and use of stimulants (Medicaid: 25.0% vs 12.0%; commercial: 16.7% vs 6.6%) among patients with GHD compared with patients without GHD. Notably, as patients with GHD were not required to be newly diagnosed or treatment naive at index, 32.6% of children with GHD had at least 1 claim for somatropin during the pre-index period.

TREATMENT PATTERNS

Approximately 68.4% (9,625) of commercial and 63.2% (4,308) of Medicaid patients with GHD received somatropin during the variable follow-up period, whereas 31.6% of

FIGURE 1 Patient Selection

^aIncludes idiopathic short stature, Noonan syndrome, Prader-Willi syndrome, Turner syndrome, diagnosis of "small for gestational age," short-bowel syndrome, chronic kidney disease, human immunodeficiency virus, or short stature homeobox-containing gene deficiency.

^bControls were selected from a 25% random sample of MarketScan patients.

GHD=growth hormone deficiency.

commercial and 36.8% of Medicaid were untreated (Table 2 and [Supplementary Table 1](#), available in online article). The treatment rate was 55.4 treated patients per 100 person-years for commercial patients and 41.5 treated patients per 100 person-years for Medicaid patients. Among treatment-naïve patients who initiated somatropin treatment in the post-index period, the mean (median) time from index to treatment was 131 days (52 days) for commercial patients and 166 days (54 days) for Medicaid patients.

Demographic differences in treatment rate and treatment delays were observed. Treatment rates were higher among males than females, and the time from index to treatment was shorter for males than females (Table 2). Among Medicaid patients, treatment rates were lower among Black patients than White patients (32.1 vs 46.7 per 100 person-years), and the mean time from index to treatment for treatment-naïve patients was longer for Black patients than White patients (193.4 days vs 150.0

TABLE 1 Baseline Patient Characteristics

	Commercial cohort				Medicaid cohort			
	GHD patients n=14,070		Controls n=42,210		GHD patients n=6,820		Controls n=20,460	
Age, mean (SD), years	11.1	(3.7)	11.1	(3.7)	9.5	(4.5)	9.5	(4.5)
Age category, n (%), years								
<4	935	(6.7)	2,805	(6.7)	1,213	(17.8)	3,639	(17.8)
5-8	2,161	(15.4)	6,483	(15.4)	1,418	(20.8)	4,254	(20.8)
9-12	5,048	(35.9)	15,144	(35.9)	2,143	(31.4)	6,429	(31.4)
13-17	5,926	(42.1)	17,778	(42.1)	2,046	(30.0)	6,138	(30.0)
Sex, n (%)								
Male	10,006	(71.1)	30,018	(71.1)	4,497	(65.9)	13,491	(65.9)
Female	4,064	(28.9)	12,192	(28.9)	2,323	(34.1)	6,969	(34.1)
Race/ethnicity, n (%)								
White	NR	(NR)	NR	(NR)	4,212	(61.8)	12,636	(61.8)
Black	NR	(NR)	NR	(NR)	937	(13.7)	2,811	(13.7)
Hispanic	NR	(NR)	NR	(NR)	415	(6.1)	1,245	(6.1)
Other/unknown	NR	(NR)	NR	(NR)	1,256	(18.4)	3,768	(18.4)
Duration of follow-up, mean (SD), years	3.7	(2.7)	3.5	(2.6)	4.0	(2.6)	3.3	(2.1)
Clinical characteristics, n (%)								
Endocrine-related conditions ^a	3,132	(22.3)	94	(0.2)	1,511	(22.2)	69	(0.3)
Cardiovascular disease ^b	561	(4.0)	378	(0.9)	482	(7.1)	240	(1.2)
Metabolic conditions ^c	775	(5.5)	800	(1.9)	702	(10.3)	1,003	(4.9)
Mental health conditions	3,191	(22.7)	4,040	(9.6)	2,503	(36.7)	3,610	(17.6)
Anxiety	915	(6.5)	1,178	(2.8)	488	(7.2)	741	(3.6)
ADHD	2,110	(15.0)	2,566	(6.1)	1,807	(26.5)	2,660	(13.0)
Bipolar disorders	81	(0.6)	97	(0.2)	148	(2.2)	183	(0.9)
Depression	461	(3.3)	670	(1.6)	398	(5.8)	587	(2.9)
Eating disorders	73	(0.5)	32	(0.1)	95	(1.4)	47	(0.2)
Sleep disorders	417	(3.0)	353	(0.8)	550	(8.1)	539	(2.6)

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days). Racial differences persisted when subgroups were examined by sex.

Overall, 97.8% (9,418) of somatropin-treated commercial and 99.7% (4,296) somatropin-treated Medicaid patients with GHD were eligible for inclusion in the discontinuation and adherence analysis. During the variable follow-up period, the mean PDC for commercial patients was 0.59, and 37.1% of patients had a PDC less than 0.5 (Table 3). Only 32.3% of commercial and 18.4% of Medicaid patients had a PDC of 0.8 or greater. Adherence was lower for Medicaid patients as the mean PDC was 0.49, and 50.6% had a PDC less than 0.5. Treatment discontinuation was common

and occurred in 53.6% (5,050) of commercial patients and 71.8% (3,086) of Medicaid patients. Discontinuation was lowest in the group started on somatropin before age 4 years but peaked between the ages of 13 and 17 years in both commercial and Medicaid patients. However, 24.3% (1,227) of commercial and 49.1% (1,515) of Medicaid patients who discontinued somatropin treatment did so before the age of 13 years, presumably before their growth was completed. Models of discontinuation from index somatropin treatment are presented in [Supplementary Figure 1](#) and [Supplementary Table 2](#), available in online article).

TABLE 1 Baseline Patient Characteristics (*continued*)

	Commercial cohort				Medicaid cohort			
	GHD patients n=14,070		Controls n=42,210		GHD patients n=6,820		Controls n=20,460	
Medication utilization, n (%)								
Somatropin ^b	4,582	(32.6)	0	(0)	2,223	(32.6)	0	(0)
ADHD medications								
Stimulants	2,345	(16.7)	2,768	(6.6)	1,705	(25.0)	2,461	(12.0)
Nonstimulants	1,177	(8.4)	738	(1.8)	1,137	(16.7)	1,152	(5.6)
Antidepressants	1,083	(7.7)	903	(2.1)	779	(11.4)	820	(4.0)
Antianxiety medications	745	(5.3)	766	(1.8)	789	(11.6)	836	(4.1)
All-cause health care costs PPPY, mean (SD), USD								
Inpatient costs	4,011	(36,264)	319	(8,452)	8,871	(59,651)	761	(13,463)
Outpatient costs	9,413	(31,407)	1,425	(4,810)	11,039	(25,482)	2,126	(7,538)
Pharmacy costs	11,582	(23,365)	390	(2,807)	9,170	(24,861)	643	(5,82)
Total costs	25,006	(59,790)	2,134	(10,840)	29,081	(76,405)	3,530	(17,451)

^aEndocrine-related conditions included GHD, hypopituitarism, adrenal insufficiency, hypothyroidism, diabetes insipidus, and hypogonadism.

^bCardiovascular disease includes ischemic heart disease/coronary heart disease, rheumatic heart disease, congenital heart disease, hypertensive heart disease, pulmonary heart disease, heart failure, heart valve disease, cardiomyopathy, conduction disorders, cardiac dysrhythmias, endocarditis, myocarditis, pericarditis.

^cMetabolic conditions included diabetes mellitus, hyperlipidemia, hypertension, metabolic syndrome, nonalcoholic fatty liver disease, and obesity.

^dBased on outpatient pharmacy prescriptions and excluded medical claims for somatropin.

ADHD = attention-deficit/hyperactivity disorder; GHD = growth hormone deficiency; NR = not reported; PPPY = per person per year; USD = US dollars.

HEALTH CARE COSTS

When comparing patients with and without GHD, mean unadjusted annual all-cause health care costs were 10.8 times greater (\$37,392 vs \$3,472) for Medicaid patients with GHD and 16.7 times greater (\$40,265 vs \$2,405) for commercial patients with GHD (Table 4 and [Supplementary Table 3](#), available in online article). Outpatient prescription expenditures were a major cost driver among patients with GHD. Prescription medication costs were 26.1 times greater (\$16,042 vs \$615) for Medicaid patients with GHD and 60.3 times greater (\$26,581 vs \$441) for commercial patients with GHD compared with patients without GHD. Costs for inpatient admissions were 11.3 times greater (\$11,034 vs \$976) for Medicaid patients with GHD and 12.6 times greater (\$4,923 vs \$391) for commercial patients with GHD compared with patients without GHD.

Average unadjusted annual GHD-related costs were \$18,069 for Medicaid-insured patients with GHD and \$27,893 for commercially insured patients with GHD (Table 4). Among Medicaid patients with GHD, 66% of total GHD-related costs were for somatropin medications, whereas, among commercial patients with GHD, 86% of total GHD-related costs were for somatropin medications. Outpatient pharmacy costs for somatropin were twice as high among

commercial patients vs Medicaid patients, though this did not adjust for differences in treatment rates and adherence, which were lower among Medicaid patients.

After adjusting for baseline demographic differences, estimated all-cause costs excluding somatropin costs were 5.46 times higher for patients with GHD compared with patients without GHD (\$15,068 vs \$2,762) in the commercial population and 5.67 times higher for patients with GHD compared with patients without GHD (\$23,447 vs \$4,138) in the Medicaid population ([Supplementary Figure 2](#), available in online article). After adjusting for baseline demographic and clinical differences, and excluding somatropin costs, somatropin-treated patients had significantly lower all-cause costs than untreated patients with GHD. The adjusted cost ratio between treated and untreated GHD was 0.69 (\$17,187 vs \$24,837) for commercial patients and 0.59 (\$20,569 vs \$34,986) for Medicaid patients ([Supplementary Figure 3](#), available in online article).

Among commercially insured treatment-naïve patients who were treated with somatropin, the lowest PDC was associated with the highest costs, and each additional month of delay in treatment from the diagnosis date was associated with a slight increase in costs ([Supplementary Table 4](#), available in online article). The trends were in the

TABLE 2 Treatment Rates Among Patients With Growth Hormone Deficiency

Payer	Race/ ethnicity	Sex	n	All treated patients		Treatment rate per 100 person- years	Treatment-naïve patients ^a		Days from index to treatment ^b		
				n	%		n	%	Mean	SD	Median
Commercial	All ^c	All	14,070	9,625	68.4	55.4	5,157	36.7	131.3	233.4	52.0
		Male	10,006	7,125	71.2	62.7	3,850	38.5	126.1	222.9	50.0
		Female	4,064	2,500	61.5	41.7	1,307	32.2	146.6	261.3	56.0
Medicaid	All ^c	All	6,820	4,308	63.2	41.5	2,205	32.3	166.1	317.8	54.0
		Male	4,497	2,934	65.2	45.9	1,538	34.2	154.7	302.1	52.0
		Female	2,323	1,374	59.1	34.4	667	28.7	192.5	350.3	58.0
	White	All	4,212	2,764	65.6	46.7	1,430	34.0	150.0	283.4	52.0
		Male	2,823	1,916	67.9	51.5	1,018	36.1	138.0	250.5	50.0
		Female	1,389	848	61.1	38.6	412	29.7	179.6	350.3	55.0
	Black	All	937	518	55.3	32.1	265	28.3	193.4	320.7	65.0
		Male	623	357	57.3	36.8	185	29.7	181.8	308.4	65.0
		Female	314	161	51.3	25.0	80	25.5	220.1	348.2	65.5
	Hispanic	All	415	259	62.4	45.1	140	33.7	159.1	340.5	55.0
		Male	246	158	64.2	49.2	86	35.0	140.8	339.8	50.5
		Female	169	101	59.8	39.8	54	32.0	188.2	342.7	58.5

^aTreatment-naïve patients who received somatropin treatment during the variable follow-up period.^bAmong treatment-naïve patients who received somatropin treatment.^cIncludes White, Black, Hispanic, other race/ethnicity, and unknown.

same direction for the Medicaid cohort, but the differences were not statistically significant.

In all models, a higher comorbidity burden at baseline, as measured by CCI, was associated with higher costs in both commercial and Medicaid patients. Among Medicaid patients, Black patients had lower costs compared with White patients in the model comparing patients with GHD to patients without GHD; however, in the model of treated vs untreated GHD patients, Black patients had higher costs compared with White patients. In contrast, Hispanic patients had higher costs compared with White patients in the model comparing patients with GHD to patients without GHD, and in the model of treated vs untreated GHD patients, Hispanic patients had similar costs compared with White patients.

Discussion

The results of this retrospective cohort study showed that there is a substantial health care burden associated with GHD in the pediatric population. Compared with patients without GHD, adjusted annualized all-cause costs, excluding

somatropin costs, were \$12,305 higher for commercial patients with GHD and \$19,309 higher for Medicaid patients with GHD. Overall, baseline clinical conditions were strong predictors of GHD-related medical costs in both commercially and Medicaid-insured GHD populations. However, treated patients had lower costs, suggesting that improved adherence may further lower health care costs. This study demonstrated there is a need for interventions aimed at improving somatropin adherence and treating GHD-related conditions in order to reduce costs, clinical burden, and consequences of GHD, which go beyond short stature.

Although nonprescription health care costs were lower among treated patients, in both commercial and Medicaid patients, adherence to somatropin was low, and discontinuation was high. In addition, treatment rates and treatment delays varied by payer, sex, and race. In the Medicaid population, White males had the highest treatment rate (51.5 per 100 person-years) and the shortest mean time from diagnosis to treatment initiation (138 days). By comparison, Black females had the lowest treatment rate (25.0 per 100 person-years) and the longest time from diagnosis to treatment initiation (220 days). Male and female patients

TABLE 3 Treatment Patterns Among Patients Who Received Somatropin Therapy^a

	Commercial cohort n = 9,418	Medicaid cohort n = 4,296
Adherence to somatropin		
PDC, mean (SD)	0.59 (0.29)	0.49 (0.28)
Median	0.63	0.48
PDC categories, n (%)		
0-0.49	3,496 (37.1)	2,174 (50.6)
0.50-0.59	827 (8.8)	436 (10.2)
0.60-0.69	899 (9.6)	430 (10.0)
0.70-0.79	1,149 (12.2)	469 (10.9)
0.80-0.89	1,442 (15.3)	436 (10.2)
0.90-1.00	1,605 (17.0)	351 (8.2)
Discontinuation from somatropin, n (%)		
5,050 (53.6)	3,086 (71.8)	
Age categories at treatment start (among treatment-naïve patients who discontinued), years, n (%)		
0-4	83 (3.6)	208 (13.7)
5-8	290 (12.6)	334 (22.0)
9-12	870 (37.8)	541 (35.7)
13-17	1,042 (45.3)	424 (28.0)
18+	17 (0.7)	10 (0.7)
Age categories at time of discontinuation of any somatropin (among all treated patients who discontinued), years, n (%)		
0-4	53 (1.1)	215 (7.0)
5-8	325 (6.4)	458 (14.8)
9-12	849 (16.8)	842 (27.3)
13-17	3,300 (65.4)	1,398 (45.3)
18+	523 (10.4)	173 (5.6)

^aExcludes patients with medical claims for somatropin and patients with claims whose days supply was less than 0.

PDC = proportion of days covered.

with commercial insurance had higher treatment rates and shorter times to treatment than male and female Medicaid patients, but the data could not be examined by race. These findings are consistent with earlier research, which has reported treatment disparities across sex and race, as boys and White children are more often diagnosed and referred for treatment compared with their female and minority counterparts.^{12,20,21}

The mean annualized somatropin outpatient pharmacy costs for commercial patients were twice as high as costs for Medicaid patients. The data available in claims records includes the paid amounts of adjudicated claims, including health plan payments and patient out-of-pocket costs, but it may not capture all discounts, rebates, or patient assistance programs available to insurers or patients.²² As a result, the true financial burden from high-cost medications like somatropin may

be overestimated in claims data, particularly for commercial plans where there is less cost transparency and negotiated prices may vary highly between plans.²³

Although poor growth velocity is the primary clinical feature in the majority of cases of idiopathic GHD, it is not diagnostically definitive without confirmation of inadequate GH secretion; however, this confirmation can be difficult to obtain due to inconsistencies in laboratory assays and uncertainty in how to account for confounding variables like obesity.^{8,24} As a result, there is the potential for misdiagnosis of GHD among patients with short stature due to other conditions. For example, we observed that a higher proportion of patients with GHD had a diagnosis of ADHD and had claims for stimulants in the baseline period. The use of stimulants can impact growth and can make it more likely that a patient may present with short stature and be diagnosed with GHD though the underlying cause may be a medication adverse event.^{25,26}

LIMITATIONS

This study has some limitations. One limitation is that we had no information as to why somatropin was discontinued during the study period in such a large proportion of patients. We did not analyze patients who restarted somatropin treatment after discontinuing treatment as part of the discontinuation models. For the group started at age 4 years or younger, persistence with treatment was high as expected, in part due to age and likely because patients diagnosed at a young age tend to have more severe GHD. For patients started on treatment at ages 13-17 years, a high rate of discontinuation likely reflects the fact that during late puberty, growth typically slows as the growth plates close. Other patients may discontinue treatment with somatropin when they

TABLE 4 Annualized All-Cause and GHD-Related Health Care Costs in the Variable Follow-Up Period

	Commercial cohort		Medicaid cohort	
	GHD patients n=14,070	Controls n=42,210	GHD patients n=6,820	Controls n=20,460
All-cause costs, mean (SD), USD				
Inpatient costs	4,923 (44,166)	391 (8,304)	11,034 (94,177)	976 (20,644)
Outpatient costs	8,761 (23,567)	1,573 (5,342)	10,317 (25,288)	1,881 (6,237)
Pharmacy costs	26,581 (29,555)	441 (3,599)	16,042 (29,937)	615 (6,136)
Total costs	40,265 (63,351)	2,405 (11,921)	37,392 (107,868)	3,472 (23,897)
GHD-related costs, mean (SD), USD				
Inpatient costs	1,934 (23,557)		5,471 (77,243)	
Outpatient costs	1,829 (5,621)		647 (3,267)	
Somatropin outpatient pharmacy costs	24,130 (27,308)		11,951 (18,534)	
Total costs	27,893 (35,760)		18,069 (79,119)	

GHD=growth hormone deficiency; USD=US dollars.

reach a satisfactory height even if it is shorter than their genetic height potential. Another factor leading to nonpersistence may be families tiring of the regimen of daily injections and frequent office visits to monitor therapy, while families moving or changing insurance are other factors we had no way of assessing.

This study has further limitations. First, it was limited to only those individuals with commercial health coverage or Medicaid coverage for selected states within the United States. Consequently, the results of this analysis will not be generalizable to GHD patients with other insurance or without health insurance coverage.

Second, there is a potential for misclassification of GHD, covariates, or study outcomes as patients were identified through administrative claims data as opposed to medical records, as administrative claims data are subject to data coding limitations and data entry error.

Third, medication adherence was based on filled prescriptions. Patients

were assumed to have filed insurance claims for all prescriptions and taken the medications as prescribed, but we were not able to confirm how patients received or consistently took the medications.

Fourth, this study reported a longer continuous enrollment period in the group with GHD compared with the group without GHD, which may reflect the fact that patients with chronic conditions retain their health insurance carrier longer. This study calculated annualized metrics in order to adjust for differing lengths of follow-up, and all regression models included length of follow-up as a covariate.

Finally, there may be systematic differences between the study cohorts that account for differences found in health care costs and utilization. Differences between cohorts were controlled for by matching and multivariable regressions, but this adjustment was limited to those characteristics that could be measured from administrative claims.

Conclusions

Health care costs are high among patients with GHD but are lower among the subset of patients treated with somatropin when the cost of medication is excluded. Poor adherence and nonpersistence with somatropin therapy, along with a high percentage of untreated patients, particularly among female and Black patients, suggests that there is an opportunity to improve outcomes through new interventions.

DISCLOSURES

This study was funded by Ascendis Pharma, Inc. Smith and Pitukcheewanont are employed by Ascendis Pharma, Inc. Manjelievskaia, Lopez-Gonzalez, and Morrow are employed by IBM Watson Health, which received funding from Ascendis Pharma, Inc., to conduct this study. Kaplowitz is a paid consultant of Ascendis Pharma, Inc.

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