

# Healthcare Utilization and Costs associated with Hereditary Hemorrhagic Telangiectasia Patients in a Large US Claims Database

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## Abstract

**Objective:** To assess the health care costs and utilization in patients with hereditary hemorrhagic telangiectasia (HHT) in the United States.

**Patients and Methods:** Retrospective analysis of patients with HHT diagnosed between 2007 and 2017 was performed using deidentified administrative claims data from the OptumLabs Data Warehouse. Adult patients with new (incident) diagnosis of HHT between January 1, 2007, and December 31, 2017, were included. Comparisons were made using the Wilcoxon rank sum test.

**Results:** Three thousand nine hundred seventy-seven patients with a first diagnosis of HHT between 2007 and 2017 were identified, of which 3590 were matched 1:1 to non-HHT patients with similar baseline characteristics and comorbidities. These 3590 patients with HHT were 63.1% female and 83.9% white with a mean age of  $51.1 \pm 18.5$  years, and a mean follow-up period of  $3.2 \pm 2.2$  years (range, 1.0–11.7 years). Compared with the control group, the cumulative 5-year median total health care cost for patients with HHT was 41.4% higher (\$21,118 vs \$14,929;  $P < .001$ ) in those with private commercial insurance and 31.7% higher (\$35,462 vs \$26,925;  $P < .001$ ) in those with Medicare Advantage coverage. The median annual health care costs were significantly higher in patients with HHT with commercial insurance and Medicare Advantage in the first year after diagnosis (\$4,333 vs \$1,804;  $P < .001$ ), and (\$7,322 vs \$5,245;  $P < .001$ ), respectively, and remained higher throughout the duration of follow-up. Further analysis showed that outpatient clinic visits, hospital admission, imaging rates, invasive procedures, iron infusions, and blood transfusions were all significantly higher in the HHT group.

**Conclusion:** Patients with HHT have significantly higher health care costs compared with a matched control group. A better understanding of the reasons underlying these cost differences will provide opportunities for patients, providers, and other stakeholders to better manage this rare condition.

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**H**ereditary hemorrhagic telangiectasia (HHT)—also known as Osler-Weber-Rendu syndrome—is a multisystem vascular disorder with autosomal dominant inheritance that results in disorganized angiogenesis.<sup>1</sup> The prevalence of HHT is between 1:5,000 and 1:8,000 individuals.<sup>2</sup> Disease-causing mutations in HHT involve the transforming growth factor- $\beta$  signaling pathway and most commonly involve the endoglin, activin receptor-like kinase 1, and SMAD4 genes.<sup>3</sup>

Disorganized angiogenesis leads to the formation of arteriovenous malformations (AVMs) that most commonly affect the skin and mucocutaneous membranes and result in the classic cutaneous manifestations of HHT with telangiectasias around the lips, mouth, face, fingers, and oral cavity.<sup>4</sup> These same telangiectasias also involve the nose and the gastrointestinal (GI) tract and can result in severe anemia owing to epistaxis and GI bleeding. In fact, bleeding-related complications are the most common



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reason for hospitalization among patients with HHT.<sup>5</sup>

AVMs in HHT can also involve critical visceral organs leading to a variety of complications, including liver AVMs, which can result in high-output cardiac failure owing to direct shunting between the hepatic arteries and the hepatic veins. Pulmonary AVMs can result in significant hypoxemia and paradoxical embolism resulting in stroke, brain abscess, and hemorrhage, and brain AVMs can result in catastrophic intracranial bleeding.<sup>3,5-8</sup> The multisystem nature of HHT and its propensity to result in serious complications results in the need for a multidisciplinary approach with dedicated providers who have expertise in HHT management. These patients often require specialized procedures such as embolization of pulmonary and brain AVMs, advanced gastrointestinal endoscopies, neurosurgical management of brain AVMs, and treatment of epistaxis by otolaryngologists.

Unfortunately, the lack of familiarity with HHT and its rarity often result in delayed diagnosis for many years or even decades until the occurrence of severe complications. The effect of this diagnostic delay on costs and HHT-related complications has not been systematically studied in a large nationwide scale.<sup>9</sup> An understanding of the overall costs (including all inpatient and outpatient costs) and HHT-related disease burden is essential given the rare nature of HHT and the multisystem nature of organ involvement seen in this disease.

## PATIENTS AND METHODS

### Data Collection

We conducted a retrospective cohort analysis using deidentified administrative claims data from the OptumLabs Data Warehouse (OLDW). OptumLabs is an open, collaborative research and innovation center founded in 2013 as a partnership between Optum and Mayo Clinic with its core linked data assets in the OLDW. The database contains deidentified, longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities, and geographical regions across the United States. The claims data in OLDW includes medical and pharmacy claims, and enrollment records for commercial and Medicare Advantage enrollees.<sup>10,11</sup> This study

involved analysis of pre-existing, deidentified data; therefore, it was exempt from institutional review board approval.

### Patient Population

We aimed to identify all patients with a new (incident) diagnosis of HHT, defined by at least one documented primary or secondary diagnosis based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 448.0 or *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code I78.0 between January 1, 2007, and December 31, 2017. Additional details regarding diagnosis and procedure codes are provided in [Supplemental Table 1](#) (available online at <http://mcpiqjournal.org>). Upon data review, a period of 1 year without the diagnosis of HHT was required for all patients to confirm incident diagnosis. Furthermore, continuous medical and pharmacy coverage was also required for at least 12 months before and after HHT diagnosis (index date). A control cohort was assembled by identifying enrollees with at least one medical claim for an office visit and no diagnosis of HHT during the time-frame (2007-2017). The index date for controls was based on a randomly selected office visit. Like the cases, controls were required to have at least 12 months of continuous medical and pharmacy coverage before and after the index date. Enrollees were exclusively covered by either a commercial or Medicare Advantage health plan during our study time-frame. For those who transitioned from one health plan to the other, follow-up ended at coverage termination of the initial health plan. The controls were then matched 1:1 with cases on age, sex, comorbidities (hypertension, diabetes, hyperlipidemia, and cardiovascular disease), length of follow-up, year of diagnosis, race, census region, and health plan. All variables were exact matched except for age ( $\pm 5$  years) and length of follow-up ( $\pm 90$  days).

### Independent Variables

We assessed demographic and clinical characteristics within 12 months before the index date (baseline). Patient characteristics included age, sex, race (Asian, Black, Hispanic, non-Hispanic white, Other/Unknown), region

(Midwest, Northeast, South, West), health plan (Commercial, Medicare Advantage), year of index date, and length of follow-up. Comorbidities associated with HHT, hypertension, diabetes, hyperlipidemia, and cardiovascular disease were identified by ICD-9-CM and ICD-10-CM diagnosis codes during baseline (Supplemental Appendix, available online at <http://mcpiqjournal.org>).

### Outcomes of Interest

Outcomes assessed include the median annual total cost of care and utilization rates for outpatient office visits, emergency department visits, hospital admissions, imaging (including abdominal ultrasonography, magnetic resonance imaging [MRI] and computed tomography [CT], chest CT and MRI, brain CT and MRI, head CT, transthoracic echocardiography and cerebral angiography), procedures (including GI endoscopy and brain and lung embolization), iron infusion, and blood transfusion. Total cost of care included medical and surgical (inpatient and outpatient) and outpatient pharmacy claims. Costs were adjusted to 2017 US dollars using the Consumer Price Index.<sup>12</sup> All outcomes were assessed 1 year before and each year 1 to 5 years after HHT diagnosis.

### Statistical Analysis

Baseline characteristics were described using counts and percentages for categorical variables and mean  $\pm$  standard deviation for continuous variables. Unadjusted utilization rates (number of events per 1000 patients) and total cost of care were compared between HHT cases and controls. Cost and utilization comparisons were tested using Wilcoxon rank sum test. Rate ratios were also used to compare utilization rates. Data for Medicare Advantage and privately insured patients were reported separately. Statistical analyses were performed in SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

## RESULTS

Three thousand nine hundred seventy-seven patients with a new (incident) diagnosis of HHT between 2007 and 2017 were identified. From these 3977 newly diagnosed HHT cases, 3590 patients were matched 1:1 to non-HHT patients (controls). The final cohort comprised 7180 patients with mean age of  $51 \pm 18.4$

years; 63.1% of which were female and 83.9% were white. The median length of follow-up was  $3.2 \pm 2.2$  years (range, 1.0–11.7 years). Baseline characteristics are summarized in Table.

### Healthcare Cost in Patients with HHT

The median annual total health care cost of HHT compared to matched controls is outlined in Figure 1. Overall, patients with HHT (both in commercial and Medicare Advantage plans) had significantly higher overall cost of care with the highest cost of care in the first year after establishing the diagnosis of HHT.

The median annual total health care cost in patients with HHT and commercial insurance was higher in the HHT group 1 year after the diagnosis (\$4333 vs \$1804;  $P < .001$ ) with an increase of 47.4% from a median of \$2939 one year before the diagnosis. This cost remained higher in the HHT group throughout the duration of follow-up. Similarly, the median annual total health care cost in patients with HHT and Medicare Advantage was higher in the HHT group 1 year after the diagnosis (\$7322 vs \$5245;  $P < .001$ ) with an increase of 17.6% from a median of \$6228 one year before the diagnosis; it also remained higher throughout the duration of follow-up.

The 1-year increase in health care cost in the control group was less pronounced, with an increase of 16.2% (\$1553 to \$1804) and 12.8% (\$4650 to \$5245) in those with private commercial and Medicare Advantage coverage, respectively. Further increase in the annual health care cost 1 year or more after the initial diagnosis was less than the immediate increase noted in the first year immediately following diagnosis in both groups. Compared with the control group, the cumulative 5-year median total health care cost for patients with HHT was 41.4% higher (\$21,118 vs \$14,929;  $P < .001$ ) in those with private commercial insurance and 31.7% higher (\$35,462 vs \$26,925;  $P < .001$ ) in those with Medicare Advantage coverage.

### Factors Contributing to Health Care Cost and Healthcare Utilization in Patients With HHT

Further analysis elucidated factors accounting for the increase in health care cost among these patients with newly diagnosed HHT. This analysis was performed in a similar

**TABLE. Baseline Patient Characteristics of Patients with Hereditary Hemorrhagic Telangiectasia and Matched Controls<sup>a</sup>**

Characteristics	Control group (N = 3590)	HHT (N = 3590)
Mean age, years (SD)	51.0 (18.4)	51.0 (18.5)
Female sex, n (%)	2267 (63.1%)	2267 (63.1%)
Race, n (%)		
Asian	63 (1.8%)	63 (1.8%)
Black	175 (4.9%)	175 (4.9%)
Hispanic	251 (7.0%)	251 (7.0%)
White	3012 (83.9%)	3012 (83.9%)
Other/unknown	89 (2.5%)	89 (2.5%)
Region of residence, n (%)		
Midwest	680 (18.9%)	680 (18.9%)
Northeast	510 (14.2%)	510 (14.2%)
South	1844 (51.4%)	1844 (51.4%)
North	556 (15.5%)	556 (15.5%)
Insurance plan, n (%)		
Commercial	2712 (75.5%)	2712 (75.5%)
Medicare Advantage	878 (24.5%)	878 (24.5%)
Index year, n (%) <sup>b</sup>		
2007	239 (6.7%)	239 (6.7%)
2008	278 (7.7%)	278 (7.7%)
2009	252 (7.0%)	252 (7.0%)
2010	265 (7.4%)	265 (7.4%)
2011	270 (7.5%)	270 (7.5%)
2012	259 (7.2%)	259 (7.2%)
2013	206 (5.7%)	206 (5.7%)
2014	198 (5.5%)	198 (5.5%)
2015	353 (9.8%)	353 (9.8%)
2016	716 (19.9%)	716 (19.9%)
2017	554 (15.4%)	554 (15.4%)
Length of follow-up, years		
Mean (SD)	3.2 (2.2)	3.2 (2.2)
Range	1.0-11.7	1.0-11.7
Comorbidities, n (%)		
Hypertension	1170 (32.6%)	1170 (32.6%)
Diabetes mellitus	376 (10.5%)	376 (10.5%)
Hyperlipidemia	1295 (36.1%)	1295 (36.1%)
Cardiovascular disease	710 (19.8%)	710 (19.8%)

<sup>a</sup>HHT = hereditary hemorrhagic telangiectasia; SD = standard deviation.

<sup>b</sup>Index year refers to the year diagnosis was established in the HHT group versus a randomly selected office visit for the control group.

fashion to health care cost estimates discussed above with analysis done at 1 year before and 1-5 years after the diagnosis of HHT.

### Outpatient Office Visits

The rate of office visits per 1000 patients was significantly higher in the HHT groups in both patients with commercial and Medicare Advantage plans in the 1 year preceding diagnosis and at 1-5 years after diagnosis (Figure 2). For example, the rate of office visits in patients

with commercial insurance increased from 5607 (vs 3980 in controls;  $P < .001$ ) in the HHT group 1 year before diagnosis to 6999 (vs 4136;  $P < .001$ ) 1 year after diagnosis, and the difference remained statistically significant even at 5 years (5233 vs 4081;  $P = .001$ ). In a similar way, office visit rates in those with Medicare Advantage insurance increased from 9962 in the HHT group (vs 7464 in controls;  $P < .001$ ) 1 year before diagnosis to 11,215 (vs 7628;  $P < .001$ ) 1 year after diagnosis. The

difference remained statistically significant 5 years after diagnosis (8705 vs 5807;  $P = .004$ ). Overall, outpatient visits with primary care accounted for the majority of office visits in both groups of patients with private insurance and Medicare Advantage. On the other hand, hematology and pulmonology office visits accounted for a small proportion of outpatient office visits, with only 2.3% and 1.5% for patients with private insurance and 0.1% and 1.4% for those with Medicare Advantage coverage, respectively.

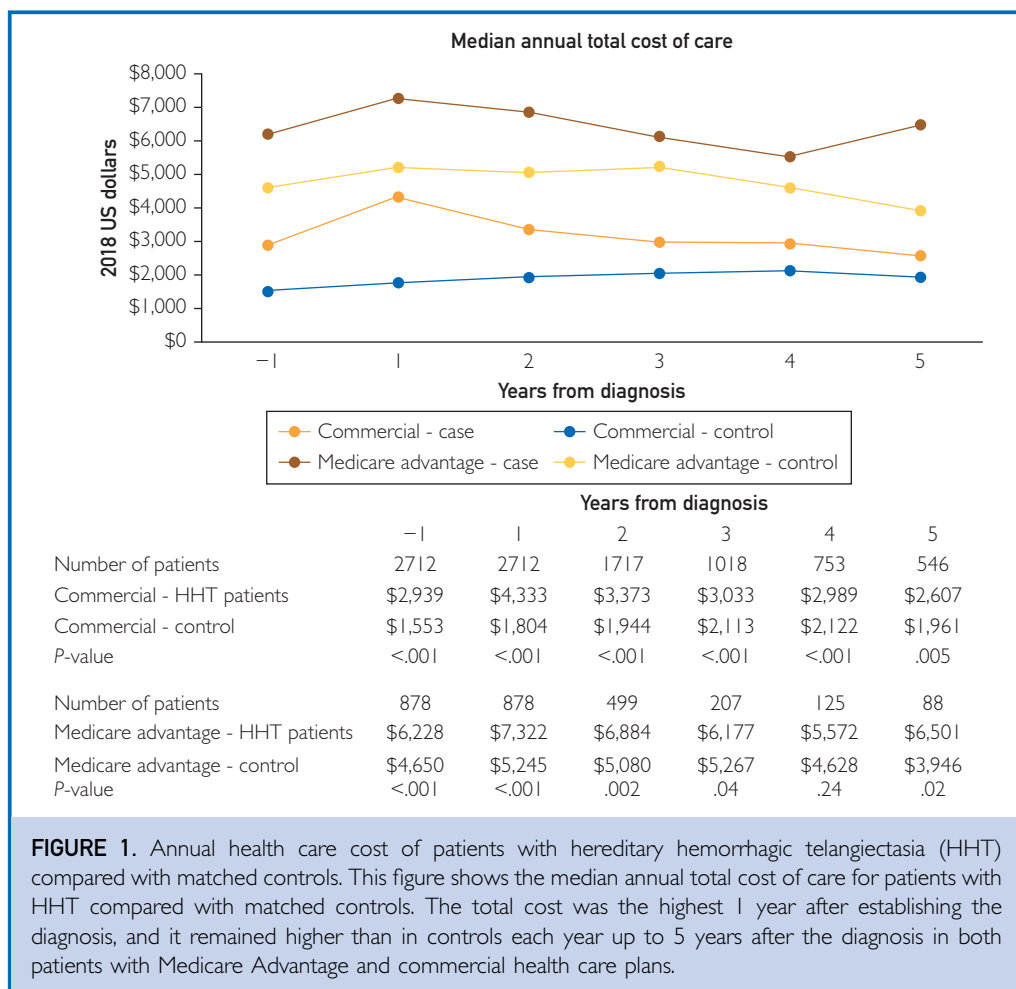
### Hospitalization Rates and Emergency Department Visits

The rate of hospital admissions per 1000 patients in patients with HHT and commercial insurance was higher 1 year after the diagnosis

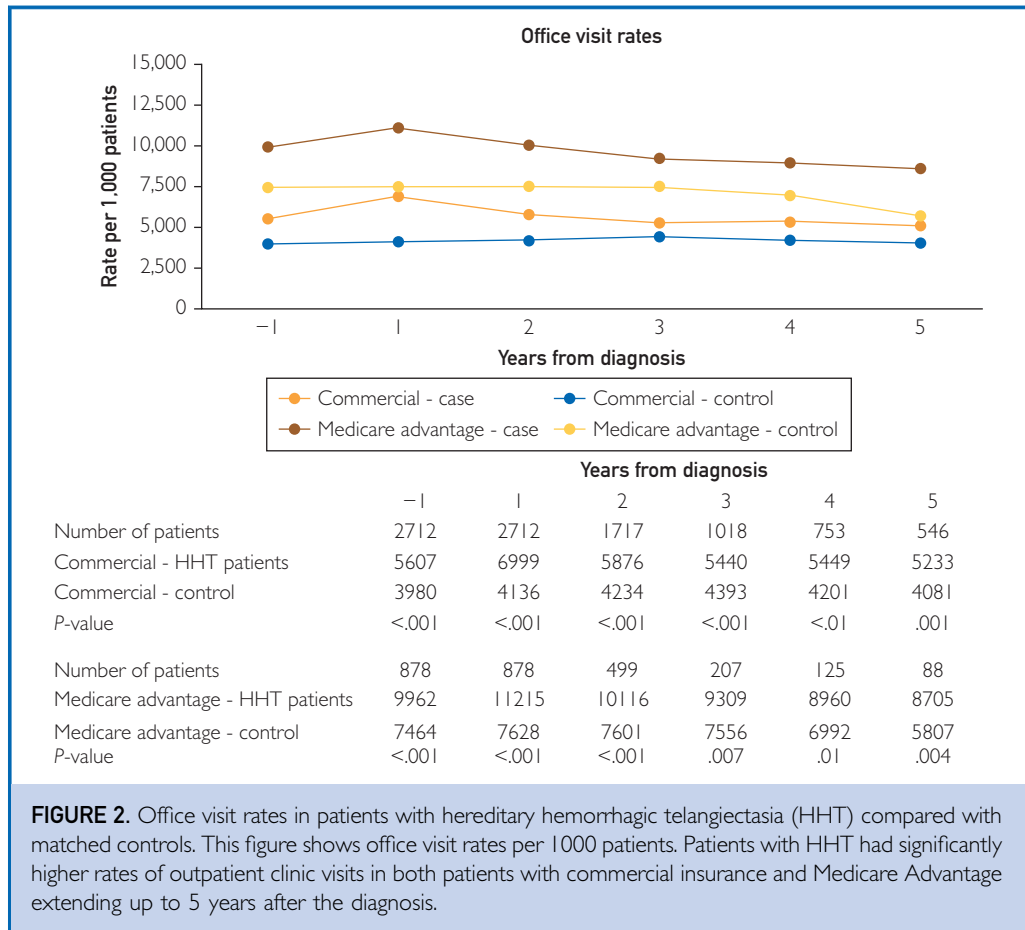
( $P = .01$ ). On the other hand, this rate was higher 1 year before the diagnosis in patients with HHT and Medicare Advantage coverage. No statistically significant difference was noted at other time points. There was no statistically significant difference in the rate of emergency department visits in either commercial or Medicare Advantage patients as compared with controls.

### Imaging Utilization

Imaging utilization rates were analyzed for abdominal ultrasonography, MRI, CT, echocardiography, and cerebral angiography. In general, patients with HHT had higher utilization rates of imaging; however, the difference was more pronounced in the HHT and control groups with commercial insurance.



**FIGURE 1.** Annual health care cost of patients with hereditary hemorrhagic telangiectasia (HHT) compared with matched controls. This figure shows the median annual total cost of care for patients with HHT compared with matched controls. The total cost was the highest 1 year after establishing the diagnosis, and it remained higher than in controls each year up to 5 years after the diagnosis in both patients with Medicare Advantage and commercial health care plans.



Patients with HHT and commercial insurance (compared with controls) had higher rates (per 1000 patients) for the following imaging tests: abdominal ultrasonography 5 years following diagnosis (62.3 vs 33.0;  $P = .04$ ); CT scans (including head, chest, abdomen and pelvic CTs) 1 year after diagnosis (101.0 vs 184.7;  $P < .001$ ); MRI (including head, chest, abdomen and pelvic MRIs) 1, 2, and 4 years after diagnosis (106.6 vs 32.8,  $P < .001$ ; 48.9 vs 32,  $P = .04$ ; and 53.1 vs 23.9,  $P = .009$ , respectively), and echocardiography 1, 2, 4, and 5 years after diagnosis (91.1 vs 47.2,  $P < .001$ ; 64.7 vs 42.5,  $P < .001$ ; 63.8 vs 35.9,  $P = .03$ ; and 95.2 vs 51.3,  $P = .01$ , respectively). The difference was less pronounced in those with Medicare Advantage insurance where HHT patients compared with controls had

higher rates of abdominal sonography 2 years after diagnosis (84.2 vs 50.1;  $P = .04$ ), CT scans (including head, chest, abdomen and pelvic CTs) 2 years after the diagnosis (430.9 vs 300.6;  $P = .02$ ), and echocardiography 1 year after diagnosis (296.3 vs 224.4;  $P = .007$ ).

### Invasive Procedures, Iron Infusion, and Blood Transfusion Rates

Invasive procedures of interest included GI endoscopy (upper and lower) and brain or lung embolization. Similar to imaging utilization, procedure rates were significantly higher among patients with HHT and commercial insurance compared with the control group.

Patients with HHT (compared with controls) and commercial insurance had higher rates of GI endoscopic procedures 1 year after diagnosis



(133.5 vs 76.3;  $P < .001$ ), brain or lung embolization 1 year after the diagnosis ( $P < .001$ ),\* iron infusions up to 5 years after diagnosis ( $P = .03$ ), and blood transfusions 1 and 2 years after diagnosis ( $P = .002$  and  $P = .02$ , respectively).\*

Similarly, those with Medicare Advantage coverage had higher rates of GI endoscopic procedures at 1 (284.7 vs 156.0;  $P < .001$ ), 2 (210.4 vs 134.3;  $P = .005$ ) and 5 years ( $P = .01$ )\* after diagnosis, iron infusion rates at 3 years after diagnosis ( $P = .05$ ),\* and blood transfusions 2 ( $P = .02$ )\* and 3 ( $P = .04$ )\* years after diagnosis.

### Use of Antiangiogenic Medications

There was no statistically significant difference between the HHT and control group in both patients with private and Medicare Advantage insurance throughout the study period. The same holds true when intravenous bevacizumab was analyzed separately.

## DISCUSSION

We present results from the first nationwide study in the United States that provides detailed information about inpatient and outpatient health care costs associated with newly diagnosed HHT in a large commercial insurance database. Our data seem to confirm a significant diagnostic delay for patients with HHT and a mean age of 51 years at the time of diagnosis. Similar to previous studies, there appears to be a female predominance in our cohort as well, with 63% female subjects. Patients with newly diagnosed HHT in our cohort have significantly higher health care costs as compared with a carefully matched control cohort. The cumulative median annual total health care cost over 5 years was 41.4% higher for patients with HHT and commercial insurance than in the commercially insured non-HHT control group with similar demographics and comorbidities and 31.7% higher in patients with Medicare Advantage coverage. These higher health care costs were noted for patients with private insurance or Medicare Advantage coverage with significantly higher rates of imaging studies, invasive procedures, iron infusions, and blood transfusions in the HHT cohort.

These costs peak 1 year after establishing the diagnosis of HHT, with annual costs of \$4333 and \$7322 per patient for those with commercial and Medicare Advantage coverage, respectively. Although there have been previous HHT studies

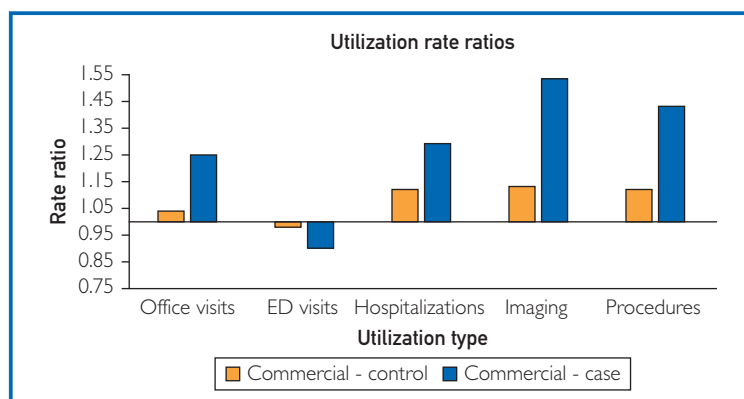
on large, population-based cohorts, the number of studies available remains small, and none of the previous reports focused on the full spectrum of health care costs spread across both the inpatient and outpatient settings simultaneously.<sup>5,13-15</sup>

It is known that AVMs in patients with HHT require advanced imaging modalities for diagnosis and management. Telangiectasias in the nose and intestinal tract can lead to severe bleeding complications, including life-threatening epistaxis and GI bleeding. In addition, lung and brain AVMs can result in catastrophic infectious, bleeding, and thrombotic complications.<sup>5,16-20</sup> Our study confirms that the increase in health care costs is driven by an increase in the rates of advanced imaging, invasive procedures, iron infusions, and blood transfusions. This is particularly true for patients with private or commercial insurance who had a significant increase in utilization rates for these interventions shortly after the diagnosis of HHT (Figure 3).

### Low Rates of Specialist Involvement in the Outpatient–Office Setting

One interesting finding in our study was the low rate of subspecialty involvement in the care of patients with HHT. HHT is a complex disorder that requires a multidisciplinary team approach,

\*The number of events per 1000 patients was not available in accordance with OptumLabs policy, where analyses with counts less than 11 are suppressed to protect patient confidentiality.



**FIGURE 3.** Increased utilization rate ratios in the peri-diagnosis period in patients with hereditary hemorrhagic telangiectasia (HHT) and commercial insurance compared with matched controls. This figure shows utilization rate ratios for patients with HHT and matched controls with private insurance in the peri-diagnosis period (calculated as rates 1 year after diagnosis divided by rates 1 year before diagnosis). This figure shows a significant increase in utilization of outpatient office visits, hospitalizations, imaging, and procedures (including iron and blood transfusions).

including care from otolaryngologists, pulmonologists, cardiologists, gastroenterologists, hematologists, neurologists, geneticists, and interventional radiologists.<sup>5</sup> However, we found that the vast majority of cases in this study were managed by primary care providers, with primary care visits accounting for the vast majority of the office visits. Interestingly, outpatient visits with hematologists and pulmonologists accounted for only a small proportion of outpatient office visits, with only 2.3% and 1.5% for patients with private insurance and 0.1% and 1.4% for those with Medicare Advantage coverage, respectively. The lack of more significant subspecialty involvement in patients with HHT is an interesting observation with a number of possible explanations, including a lack of awareness of the role of these specialists in the management of these patients or lack of access to these specialists locally or to specialists at the various HHT Centers of Excellence located nationwide. Another possibility is that these patients had a mild HHT phenotype that did not merit consultation with these subspecialists. However, the high health care costs and high rates of iron infusions, blood transfusions, and imaging studies would argue against this explanation. Another important finding is that the mean age at the time of diagnosis was  $51.0 \pm 18.4$  years. Although this diagnostic delay has been noted in previous studies,<sup>5,13</sup> it is still higher than in some prior reports, suggesting a lag in diagnosis after the onset of symptoms of HHT.<sup>9</sup> Finally, although we expected higher utilization rates of antiangiogenic medications in the HHT group given their increased use for the treatment of HHT-related complications,<sup>6,21-24</sup> there was no statistically significant difference in their use compared with the control group. This result could be related to the fact that the majority of patients in this study were managed by primary care providers, who do not commonly prescribe these medications as often as hematologists and pulmonologists who care for patients with HHT. Another possibility is that antiangiogenic medications are commonly used for the treatment of several cancers, and this might have elevated the utilization rates in the control group and masked any apparent differences between the groups.

The high cost of care and increased utilization rates of various diagnostic and therapeutic interventions along with the advanced age at

the time of diagnosis highlight the importance of spreading awareness on the diagnosis and treatment of HHT among primary care providers.<sup>9,14,22,25</sup> The question of whether HHT-related health care costs could be reduced with earlier diagnosis as well as proactive screening of HHT patients for anemia and other visceral AVMs (as is recommended in current guidelines) is an intriguing one. For example, one could argue that early detection of HHT related anemia could potentially avoid the use of expensive interventions like iron infusions and blood transfusions. Given the availability of effective antiangiogenic therapy for HHT-related bleeding complications; this proactive screening approach should become the norm for all patients with HHT.<sup>6,21-23</sup> Similarly, the detection of pulmonary AVMs by proactive screening with a contrast echocardiogram could detect these lesions before they result in catastrophic complications, such as stroke or brain abscess.

The present study has limitations. First, the OLDW database does not include patients with regular Medicare insurance (without supplementary Medicare Advantage plans), patients with Medicaid, and those who lack insurance coverage. The inclusion of these groups could likely alter some of our study results; however, the large number of patients in our study and their nationwide distribution lead us to believe that we have a representative sample of the US population in general. Another limitation is the use of ICD-9 and -10 codes for the identification and inclusion of patients with HHT without actually reviewing individual medical records to confirm the diagnosis. This is a shortcoming of all database studies of this nature, and it is likely that some patients with HHT might have been included or excluded incorrectly. Given that the vast majority of visits were with primary care, we believe that it would be less likely that primary care providers would label patients with HHT and code this into their medical record in the absence of supporting evidence, considering the complexity and specificity of this diagnosis.

## CONCLUSION

In this large nationwide study, we found that patients with HHT have significantly higher costs of care along with increased utilization of diagnostic and therapeutic modalities and invasive procedures. The advanced age at



HHT diagnosis and the lack of significant subspecialty involvement raise a number of important questions, including the general awareness (or lack thereof) about HHT among medical practitioners and actual utilization rates of current HHT screening and management guidelines among clinicians.

### SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://mcpiqjournal.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** **AVM** = arteriovenous malformation; **CT** = computed tomography; **GI** = gastrointestinal; **HHT** = hereditary hemorrhagic telangiectasia; **ICD** = International Classification of Diseases; **MRI** = magnetic resonance imaging; **OLDW** = OptumLabs Data Warehouse

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