Healthcare utilization and expenditures of parents with and without hemophilia A children

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Abstract

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Background: There is a growing body of evidence characterizing the experience of caring for children with hemophilia A (HA), which includes negative impact on health-related quality of life, emotional stress, and financial burden. Caregiving in general has been shown to also impact physical health and work productivity. How these effects translate to caregivers' utilization of non-mental and mental health services is unknown, and its elicitation can inform future evaluations of interventions that address caregiver burden in this space.

Objective: To understand the impact of caring for HA children on parents' utilization of non-mental health and mental health services by comparing one-year costs and number of medical and pharmacy claims with parents of non-HA children.

Methods: Retrospective matched cohort study using MarketScan® commercial inpatient, outpatient, and drug claims from 2011-2019. HA children were male, age <18, child or dependent policy holders, had ≥1 HA-related medical claim from 2011-2018 (one was randomly chosen to set the index date), and

either a HA-related procedure or drug claim. Parents of HA children (HAP) were adults who were primary and secondary policy holders, shared the same family ID as HA children, continuously enrolled for one year post-index, and for whom comorbidity scores for one year pre-index could be determined. HAP were matched (1:2) with parents of non-HA children on age, sex, beneficiary type, child's age, number of children, index month and year, health plan type, employment status, and region. Primary outcomes were mean non-mental and mental healthcare costs in 2020 US dollars, and secondary outcomes were 1) mean number of non-mental health outpatient claims, 2) utilization of mental health outpatient or drug claim, and 3) all outcomes excluding parents with HA themselves. Outcomes were compared using two-sided, paired t-tests and McNemar's test.

Results: Of 305.8 million enrollees from 2011-2018, 2,246 HAP were identified of which 1,068 met inclusion criteria and were matched to 2,122 control parents. Mean one-year costs for HAP were moderately higher but not statistically significant for both non-mental health services (mean difference of $1,826; 95% CI: -1,000, 4,652; p=0.20) and mental health services (mean difference of $14; 95% CI: -77, 105; p=0.76). Mental health services costs were significantly higher for HAP when parents with HA themselves were excluded, yielding a mean difference of $676 (95% CI: 399, 953; p<0.001). HAP also had more non-mental health outpatient claims with a mean difference of 1.9 (95% CI: -1.1, 4.9; p=0.21) and were 1.2 times (95% CI: 0.99, 1.45; p=0.07) more likely to have a mental health outpatient or drug claim.

Conclusion: HAP had moderately higher healthcare costs and utilization compared to parents of non-HA children; however, these results were not statistically significant. Future studies to better characterize HA disease severity in claims data and assess its impact on caregiver burden or expand caregivers to spouses of adult HA patients may be warranted. Limitations include inability to ascertain severity of HA in children and the use of claims data to capture potentially complex effects on healthcare utilization.

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Introduction

Hemophilia A (HA) is a rare, genetic bleeding disorder caused by a deficiency in factor VIII and occurs predominantly in males.[1] Disease severity depends on factor levels and is associated with frequency of bleeds, which can occur at various places and are sometimes fatal.[1-2] Complications can be long-term and include pain, arthropathy, and negative impact on physical functioning and quality of life.[2] Current prophylaxis and treatment options include injections or factor infusions up to multiple times per week. Gene therapies are currently in development.[3-4]

Diagnosis typically occurs in the first one to three years of life, and parents are thus often the primary caregivers.[5] A body of qualitative evidence informs our current understanding of the experience of parent caregivers. Potential impacts identified through health-related quality of life assessments include financial burden (including decreased productivity), emotional stress and negative impact on mental health (i.e., anxiety and depression), and personal sacrifice of time, own health, or other resources.[6-12] However, how these effects translate to parents' utilization of healthcare is unknown. Additionally, various complex mechanisms may be driving parents' utilization of different healthcare services, specifically mental and non-mental health related, and productivity.

Quantifying caregiver impact and productivity loss as indirect costs to include in economic evaluations becomes increasingly important as prices of health technologies, especially in rare disease spaces, keep increasing and demonstration of incremental value is prioritized.[13] Priority will increase with the imminence of expensive gene therapies as upfront costs will be high and demonstration of non-traditional and novel value elements become more relevant in market access strategies and health technology assessment body considerations.[13-14]

Accordingly, this analysis aims to capture the healthcare burden of a pediatric HA diagnosis on parents of HA children through a retrospective claims database analysis. More specifically, the research question being addressed is: How does a pediatric HA diagnosis affect parents' utilization of non-mental health and mental health related services as well as productivity loss? This information can be used to aid decision makers under budgetary constraints to evaluate and compare new technologies for HA. The primary objectives were to compare mean one-year healthcare costs for parents of children with and without HA for 1) non-mental health and 2) mental health services. The secondary objectives were to compare 1) mean number of non-mental health outpatient services and 2) utilization of mental health outpatient services or drugs. The exploratory objective was to compare work hours lost between parents of children with and without HA children.

2. Methods

2.1 Study Design and Data Source

The study was a retrospective, cross-sectional, matched cohort study using medical and drug claims to compare non-mental and mental healthcare costs and utilization and absenteeism between parents who have children with and without HA.

The IBM® MarketScan® Commercial Claims and Encounters (CCAE) and Health Productivity Management (HPM) databases were used to capture healthcare costs and utilization and absenteeism, respectively. The CCAE database includes de-identified medical and drug claims for a nationally representative sample of individuals with employer-sponsored private health insurance in the United States.[15] The HPM database includes data on workplace absence, short-term and long-term disability, and workers' compensation for a subset of the population in the CCAE database.[15] A Family Identifier field (EFAMID), which links family members enrolled together under a single health insurance policy, was added to the

MarketScan® CCAE database in 2011.[16] Thus, the study period was from January 1, 2011 to December 31, 2019 when latest data were available. Both databases adhered to the Health Insurance Portability and Accountability Act of 1996, and Institutional Review Board approval at the University of Washington was not required as no risk to study participants was involved.[15]

2.2 Sample

HA Children

I used the CCAE database to identify pediatric HA patients who were identified with the following criteria: (1) age <18, (2) male, (3) child or dependent status on the insurance policy (EMPREL = 3 or 4), (4) ≥1 inpatient or outpatient medical claim with a HA diagnosis code (International Classification of Disease, 9th or 10th revision, ICD-9 286.0 or 1CD-10 D66), and (5) either a HA-related medical procedure or drug claim (**Appendix A**). Only males were included in the HA children population because true hemophilia is rare in females, and the optimal approach to identify them is unknown.[17] Females with a HA-related claim are likely carriers, have another coagulation disorder, or were miscoded.[17-18]

Parents of HA Children

Parents of HA children were identified who met the following criteria: (1) primary or secondary policy holder (EMPREL = 1 or 2), (2) shared the same family ID as a HA child, (3) medical data available one-year pre-index, and (3) continuous enrollment one-year post-index (**Figure 6.1**). Primary and secondary beneficiaries under the same insurance policy as HA children were assumed to be parents as well as primary caregivers.[19] One of the child's HA-related medical claims between 2011-2018 was randomly chosen as the parent's index date. I initially thought to set parents' index dates as children's first observed HA-related claims but opted for random selection of claims between 2011-2018 to address calendar year and within year biases. Duplicate parents that arose from families with more than one HA

child were excluded. Parents' medical claims data from the one-year period before the index date was used to calculate their Charlson Comorbidity Index (CCI) as a measure of overall comorbidity burden.

Parents without HA Children

Control parents were identified who met the following criteria: (1) primary or secondary policy holder, (2) shared the same family ID as a child with age <18 and ≥1 non-HA medical claim, (3) medical data available one year pre-index, and (3) continuous enrollment one year post-index. Control parents were excluded if their child had a HA-related medical claim during the same year as the child's non-HA medical claim and the one-year post-index period. Index dates for control parents were randomly assigned in the year of the non-HA child's medical claim, which was also randomly selected from 2011-2018.

Matching

Parents of HA children and control parents were matched one-to-two by the following variables: (1) parent's age (± 5 years), (2) parent sex, (3) parent beneficiary type, (4) child's age (± 3 years), (5) number of children within the family, (6) health insurance plan type (health maintenance organization (HMO) versus preferred provider organization (PPO) versus other), (7) employment status (full-time versus not full-time), (8) CCI, (9) region, (10) index month (± 3 months), and (11) index year.

2.3. Outcomes

Primary Outcomes

The primary outcomes of interest were mean one-year costs for all 1) non-mental health services and 2) mental health services. Services included inpatient, outpatient, and drug claims. Mental health services were 1) medical claims coded "mental" in the major diagnostic category field (MDC = 19), which

indicates the body-system or disease related groupings of clinical conditions based on diagnosis codes, or 2) drug claims coded as “antidepressants” (THERCLS = 69) or “anxiolytic/sedative/hypnotic” (THERCLS = 75) in the therapeutic class field, which indicates the therapeutic/pharmacologic category of the drug product.[20] Non-mental health services were all claims not coded for mental health services. Costs were reported in 2020 US dollars using the medical care component of the Consumer Price Index for urban consumers.[21]

Secondary Outcomes

Secondary outcomes were intended to capture the volume of non-mental health services sought by parents and incidence of mental health. Thus, secondary outcomes were 1) mean number of non-mental health medical outpatient claims excluding emergency room (ER) visits (PROCGRP = 111 or 114 or STDPLAC = 23) and 2) utilization of mental health medical outpatient services excluding ER visits or drug claims coded as mental health related during the one-year post-index period.

In another secondary analysis, parents with a HA-related claim were excluded. HA is an inherited disease not captured in the CCI, and some parents of HA children likely have HA themselves.[1] A HA diagnosis in adult populations is associated with higher costs and utilization and could thus, skew study results.[18,22]

Exploratory Outcome

I evaluated workplace productivity loss, defined as hours lost due to absenteeism, during the one-year post-index period for primary beneficiaries in the population. Reported reasons for absence could include sickness, disability, leave, recreational, Family Medical Leave Act, and other.[23]

2.4. Statistical Analysis

Baseline characteristics were summarized using mean and standard deviation (SD) or median and interquartile range for continuous variables and count and percentage for categorical variables. Differences in mental health and HA diagnoses between the two cohorts pre-index were assessed using a two-sided paired t-test with a significance level of 5%. Means and SDs were reported for both primary outcomes, the secondary outcome for non-mental health outpatient services, and exploratory outcome for hours lost. These outcomes were also assessed using a two-sided paired t-test with a significance level of 5%. I used McNemar's test to report an odds ratio (OR) with a 95% confidence interval (95% CI) and p-value for the proportion of parents who utilized mental health services. A sample size providing 900 and 3,879 parent pairs would be required to achieve a power of 80% and level of significance of 5% to detect mean differences of $100 and $1,500, assumed to be meaningful, for mental and non-mental health costs, respectively. Mean costs for the primary outcomes were also stratified by parent beneficiary type and plotted on a histogram to better visualize cost differences between the overall population and beneficiary types. Data sets were constructed in SAS version 9.4 (SAS Institute, Cary, NC), and analyses were performed in RStudio version 1.4.1106 (RStudio, PBC, Boston, MA).

2.5. Sensitivity Analysis

I checked the robustness of the results from the primary analysis by adjusting for the matching variables in an unmatched population. These variables were included in regression models for 1,068 parents of HA children and 4,272 randomly selected control parents (four times the number of matched parents of HA children). A two-part model was chosen to fit the data for mean healthcare costs.

3. Results

3.1. Baseline Characteristics

Of 305.8 million enrollees identified between 2011 and 2018, I identified 1,580 children with HA. These children shared the same family ID as 1,068 unique parents that met inclusion criteria (**Appendix C**). All parents were matched to two controls except 14 parents for a total of 2,122 control parents. Parents were median age 41, mostly female (56%), primary policy holders (55%), had no comorbidities captured by the CCI (85%), and worked full time (67%) (**Table 6.1**). For unmatched baseline characteristics, parents of HA children had more mental health diagnoses (15% vs. 12%; p=0.053) and HA diagnoses (4% vs. 1%; p<0.001) pre-index compared to controls (**Table 6.1**).

3.2. Primary Outcomes

The mean cost for non-mental health services was higher for parents of HA children compared to control parents ($8,154 vs. $6,328), but the mean difference of $1,826 (95% CI: -1,000, 4,652) was not statistically significant (**Table 6.2**). The mean cost for mental health services was higher for parents of HA children compared to control parents ($255 vs. $241), but the mean difference of $14 (95% CI: -77, 105) was not statistically significant (p=0.76) (**Table 6.2**). Mean costs were also reported for primary and secondary beneficiaries separately (**Figures 7.1, 7.2**).

3.3. Secondary Outcomes

The mean number of non-mental health outpatient claims (excluding ER visits) was higher for parents of HA children compared to control parents (28.3 vs. 26.4), but the mean difference of 1.9 (95% CI: -1.1, 4.9) was not statistically significant (p=0.21) (**Appendix D**). Parents of HA children were 1.2 times more likely to have a mental health outpatient (excluding ER visits) or pharmacy claim compared to control parents (95% CI: 0.99, 1.45; p=0.07) (**Appendix E**).

Parents with HA themselves were excluded in another secondary analysis: 43 parents of HA children and one control parent. Differences in one-year mean cost for non-mental health services ($1,402 (95% CI: -1,430, 4,236; p=0.33)) and number of non-mental health outpatient claims (1.9 (95% CI: -1.6, 3.9; p=0.40)) were not significant between parents of HA children and controls. However, parents of HA children had a significantly higher one-year mean cost for mental health services with a mean difference of $676 (95% CI: 399, 953; p<0.001). Parents of HA children were also 1.2 times more significantly likely to have a mental health outpatient or pharmacy claim (95% CI: 1.01, 1.51; p=0.04).

3.4. Exploratory Outcome

The mean number of hours lost was lower for parents of HA children who were primary beneficiaries compared to control parents who were primary beneficiaries (10.7 vs. 16.9), but the mean difference of -6.4 (95% CI: -13, 0.4) was not statistically significant (**Appendix F**).

3.5. Sensitivity Analysis

Parents of HA children were significantly more likely to have mental health costs (OR 1.20 (95% CI: 1.03, 1.40; p=0.02)) (**Appendix G**). Among parents who did have mental health costs, the cost difference between parents of HA children and control parents was not significant. Likelihood of incurring non-mental health costs (OR 1.12 (95% CI: 0.82, 1.56; p=0.48)) and the cost difference in those who did incur costs were not significantly different between parents of HA children and control parents (**Appendix G**).

4. Discussion

I conducted a retrospective, cross-sectional study using claims data to compare one-year mean healthcare costs and utilization of non-mental and mental health services between parents of children

with and without HA. I hypothesized lower cost and utilization of non-mental health services, potentially driven by parents of HA children seeking less healthcare including preventative services due to financial burden and personal sacrifice of time. I also hypothesized higher cost and utilization for mental health services potentially driven by negative impact on emotional and mental health for parents of HA children. However, non-significant moderately higher healthcare costs and utilization of both service types for parents of HA children were observed. Moreover, when parents with HA themselves were excluded, significant differences were detected in mental health related outcomes. The likelihood of incurring mental health costs was significantly higher in parents of HA children in the sensitivity analysis as well. This suggests mental health utilization in parents may be attributable to a pediatric HA diagnosis in the family. However, this warrants further confirmatory analysis. In addition, parents of HA children lost less work hours due to absenteeism than control parents, but this difference was also not statistically significant.

The inability to detect significant differences in the primary analysis may have been due to insufficient sample size and emphasizes the challenges of evaluating the effects of rare diseases on families using claims data. Primary outcomes for 1,068 parent pairs were reported with a power of 6% and 43% for mental and non-mental mean healthcare costs, respectively. As a result, the current analyses are likely underpowered. In addition, consideration of other study designs for future research in this space may be warranted. Assessing impact on caregivers for patients with severe HA or expanding caregivers to spouses of adult HA patients may yield more meaningful results.

No other analyses to assess healthcare and productivity impacts of a pediatric HA diagnosis on parents have been conducted to compare results. Overall, there is a paucity of evidence detecting significant cost differences between caregivers and their controls. However, in one study for spouse caregivers of

Alzheimer's disease (AD) patients, AD spouses had a significantly greater cost difference between pre- and post-AD diagnosis than control spouses for AD/mental health drugs but not for total costs.[24] Additional analyses of family/caregiver impacts have been conducted in cancer, pediatric Crohn's disease (CD), and pediatric intensive care unit (ICU) hospitalizations. Lower healthcare use and more health diagnoses were observed in spouses of cancer patients.[25] Higher productivity loss was observed for parents of pediatric CD patients.[26] Fewer mental health diagnoses and use of mental healthcare were observed for parents whose children were hospitalized in the ICU.[27] However, comparison between results and those of other analyses is difficult as different healthcare utilization mechanisms may be involved for spouse caregivers, across different patient age groups and conditions, and across acute versus chronic disease management. For example, caregiving for a spouse with cancer may be more expensive, and caregiving for a child hospitalized in the ICU is less of a long-term commitment.

Limitations of claims data encourages consideration of other measures that can help quantify the health burden experienced by parents who provide care in severe pediatric diseases. Further validation of caregiver impact measurement tools, especially on caregivers' health and in the hemophilia space (e.g., Hemophilia Caregiver Impact), needs to be prioritized.[28] These health-related quality of life measurements can be mapped to preference-based utility measures for inclusion in economic evaluations.

Several limitations must be considered when interpreting the results of this research. First, I was unable to ascertain the severity of HA for diagnosed children whose parents were included in the analysis. Inclusion criteria of ≥1 HA-related claim and either a HA-related drug or procedure for HA children captured patients interacting more with the healthcare system and may require more care. This incentivizes future research that better characterizes HA disease severity in claims data as well as

assesses impact on parents caring for very sick HA children (e.g., frequent bleeds or infusions). Second, employment information regarding parents who were secondary policy holders was unknown. Thus, I was unable to match secondary beneficiaries on their employment status and rather matched on their primary beneficiaries' employment status. Third, the study design was cross-sectional in design and thus identified prevalent and not incident HA cases. Thus, I was unable to ascertain parent's involvement at a specific point along a patient's disease course.

5. Conclusion

Parents with HA children were found to have non-significant moderately higher mean costs and utilization of both non-mental and mental health services. Future research exploring other approaches to measure healthcare use and productivity in parent caregivers of HA children is warranted.

6. Tables

6.1. Baseline Characteristics

Characteristic	HAP (n=1068)	COP (n=2122)	p-value
Parent age, median (SD)	41 (7.8)	41 (7.7)	
Parent age group, n (%)			
18-34	238 (22.3%)	471 (22.2%)	
35-44	467 (43.7%)	934 (44.0%)	
45-54	313 (29.3%)	626 (29.5%)	
55-65	50 (4.7%)	91 (4.3%)	
Parent sex, n (%)			
Male	469 (43.9%)	934 (44.0%)	
Female	699 (65.4%)	1188 (56.0%)	
Child's age, median (SD)	10 (5.5)	10 (5.5)	
Number of children, mean (SD)	4 (2.3)	4 (2.2)	
Parent beneficiary type, n (%)			
Primary	591 (55.3%)	1179 (55.6%)	
Secondary	477 (44.7%)	943 (44.4%)	
CCI, n (%)			
0	906 (84.8%)	1807 (85.2%)	
1	119 (11.1%)	237 (11.2%)	
2	27 (2.5%)	52 (2.5%)	
3+	16 (1.5%)	26 (1.2%)	
Parent mental health diagnosis, n (%)	155 (14.5%)	255 (12.0%)	0.053
Parent HA diagnosis, n (%)	43 (4.0%)	1 (0.5%)	<0.001
Health plan type, n (%)			
PPO	633 (59.3%)	1258 (59.3%)	
HMO	150 (14.0%)	298 (14.0%)	
Other	285 (26.7%)	566 (26.7%)	
Employment status of primary, n (%)			
Active full time	713 (66.8%)	1419 (66.9%)	
Other/unknown	355 (33.2)	703 (33.1%)	
Geographic region, n (%)			
Northeast	218 (20.4%)	434 (20.5%)	
North central	247 (23.1%)	492 (23.2%)	
South	386 (36.1%)	765 (36.1%)	
West	207 (19.4%)	411 (19.4%)	
Unknown	10 (0.9%)	20 (0.9%)	

Abbreviations: COP, control parents; HA, hemophilia A; HAP; parents of HA children; SD (standard deviation)

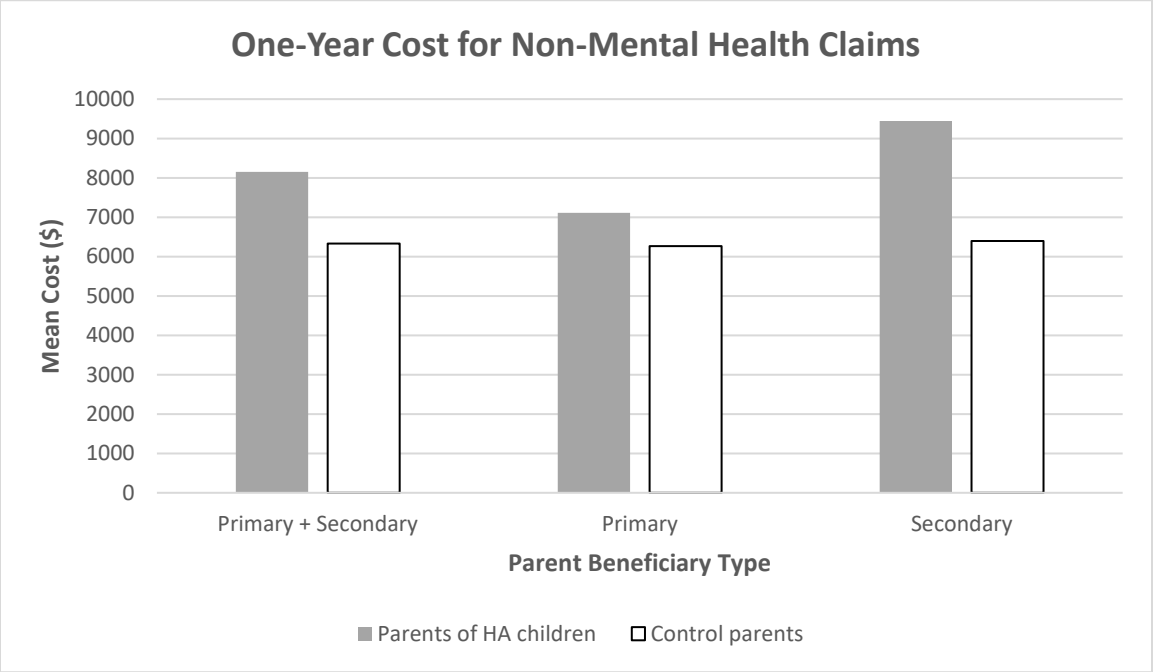
6.2. Mean One-Year Costs for Non-Mental and Mental Health Services

Primary Outcomes		HAP (n=1068)	COP (n=2122)	p-value
Non-Mental Health Cost	Mean ± SD	$8154 ± 45563	$6328 ± 12129	
	Median (IQR)	$2014 (590, 6015)	$2661 (1110, 6984)	
	Mean difference (95% CI)	$1826 (-1000, 4652)		0.20
Mental Health Cost	Mean ± SD	$255 ± 1222	$241 ± 905	
	Median (IQR)	$0 (0, 21)	$0 (0, 100)	
	Mean difference (95% CI)	$14 (-77, 105)		0.76

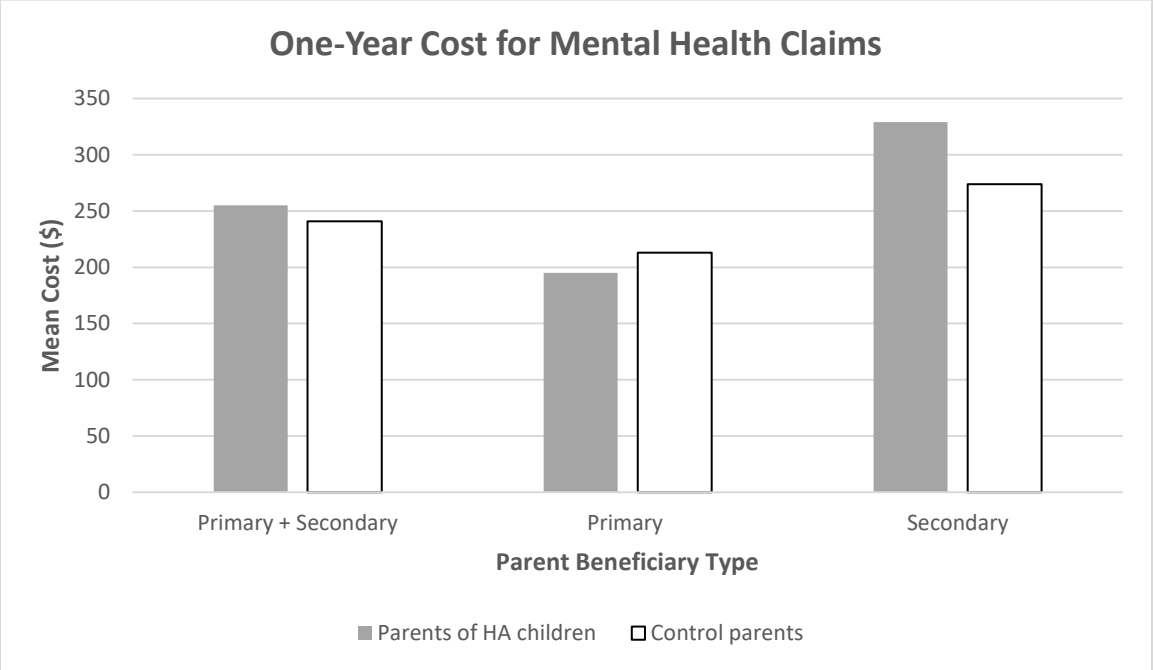
Abbreviations: CI, confidence interval; COP, control parents; HAP, parents of hemophilia A children; IQR, interquartile range; SD, standard deviation

7. Figures

7.1. Mean One-Year Cost for Non-Mental Health Claims in Primary and Secondary Parent Beneficiaries



7.2. Mean One-Year Cost for Mental Health Claims in Primary and Secondary Parent Beneficiaries



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APPENDICES

Appendix A. Hemophilia A-related Drug and Procedure Codes

HA-related drug code (NDC)	genme like 'Antihem%
HA-related procedure (HCPCS)	C9136, C9137, C9140, C9141, C9267, J2597, J7170, J7182, J7183, J7184, J7185, J7186, J7187, J7188, J7189, J7190, J7191, J7192, J7198, J7199, J7205, J7207, J7208, J7209, J7210, J7211, Q9975, Q9995

Appendix B. Diagnosis Codes for Charlson Comorbidity Index

Comorbidities	Deyo's ICD-9-CM +	ICD-10 *	Enhanced ICD-9-CM *
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2	410.x, 412.x
Congestive heart failure	428.x	I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Peripheral vascular disease	443.9, 441.x, 785.4, V43.4 Procedure 38.48	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular disease	430.x-438.x	G45.x, G46.x, H34.0, I60.x-I69.x	362.34, 430.x-438.x
Dementia	290.x	F00.x-F03.x, F05.1, G30.x, G31.1	290.x, 294.1, 331.2
Chronic pulmonary disease	490.x-505.x, 506.4	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Rheumatic disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x
Peptic ulcer disease	531.x-534.x	K25.x-K28.x	531.x-534.x
Mild liver disease	571.2, 571.4-571.6	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Diabetes without chronic complication	250.0-250.3, 250.7	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	250.0-250.3, 250.8, 250.9
Diabetes with chronic complication	250.4-250.6	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7,	250.4-250.7

		E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	
Hemiplegia or paraplegia	344.1, 342.x	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9	334.1, 342.x, 343.x, 344.0-344.6, 344.9
Renal disease	582.x, 583-583.7, 585.x, 586.x, 588.x	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	140.x-172.x, 174.x-195.8, 200.x-208.x	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6
Moderate or severe liver disease	456.0-456.21, 572.2-572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	456.0-456.2, 572.2-572.8
Metastatic solid tumor	196.x-199.1	C77.x-C80.x	196.x-199.x
AIDS/HIV	042.x-044.x	B20.x-B22.x, B24.x	042.x-044.x

Sources:

+ Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992; 45: 613-9.

***** Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining Comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005 Nov; 43(11): 1130-9.

Appendix C. Attrition of Parents with HA Children

Description	N	% of Prior Step
MarketScan enrollees (2011-2018)	305,799,312	
Enrollees with ≥1 encounter with HA diagnosis code	29,487	0.01%
Male, age < 18, child/dependent beneficiary status	6,854	23.2%
HA-related drug or procedure	3,725	54.3%
Unique across all years (randomly selected claim)	1,580	42.4%
Parents matched by family ID	2,246	--
Continuous enrollment one-year post-index	1,332	59.3%
Unique parents (allow only 1 HA child per family)	1,270	95.3%
Data available to calculate CCI and number of children	1,127	88.7%
Random selection of parents across years	1,087	96.5%
Matched parents	1,068	98.3%

Abbreviations: CCI, Charlson Comorbidity Index; HA, hemophilia A

Appendix D. Mean Number of Non-Mental Health Outpatient Claims

Number of Non-Mental Health Outpatient Claim	HAP (n=1068)	COP (n=2122)	p-value
Non-mental health outpatient claim, mean ± SD	28.3 ± 44.1	26.4 ± 44.3	
Mean difference (95% CI)	1.9 (-1.1, 4.9)		0.21

Abbreviations: CI, confidence interval; COP, control parents; HAP, parents of hemophilia A children; SD, standard deviation

Appendix E. Utilization of Mental Health Outpatient or Drug Claim

Use of Mental Health Service		**Control Parents**		
		Use	No use	Total
Parents of HA Children	Use	75	**226**	301
	No use	**189**	578	767
	Total	264	804	1068

Appendix F. Absenteeism in Primary Beneficiaries

Lost Work Hours in Primary Beneficiaries	**HAP (n=1068)**	**COP (n=1068)**	**p-value**
Number of hours absent, mean ± SD	10.7 ± 54.1	16.9 ± 65.8	
Mean difference (95% CI)	-6.4 (-13, 0.4)		0.06

Abbreviations: CI, confidence interval; COP, control parents; HAP, parents of hemophilia A children; SD, standard deviation

Appendix G. Sensitivity Analysis Results for Likelihood of Incurring Healthcare Costs

Non-Mental Health Cost				
Parameter	Odds Ratio	Standard Error	95% CI	p-value
Parent of HA child	1.12	0.18	0.82, 1.56	0.478
Age	1.06	0.01	1.04, 1.08	<0.001
Female	2.36	0.32	1.81, 3.09	<0.001
Secondary beneficiary	1.12	0.16	0.86, 1.47	0.415
Child's age	0.99	0.01	0.96, 1.02	0.409
Number of children	0.99	0.03	0.93, 1.05	0.718
Index month	0.94	0.02	0.90, 0.97	<0.001
Insurance type, HMO*	1.76	0.41	1.14, 2.85	0.016
Insurance type, other*	1.25	0.18	0.95, 1.68	0.120
CCI	2.24	0.49	1.51, 3.60	<0.001
Region, north central≡	0.79	0.15	0.54, 1.14	0.213
Region, south≡	1.15	0.21	0.79, 1.65	0.451
Region, west≡	0.87	0.18	0.58, 1.30	0.501
Region, unknown≡	0.41	0.17	0.19, 0.99	0.032
Full-time employment≠	1.27	0.18	0.97, 1.67	0.082
Index year	0.90	0.02	0.86, 0.95	<0.001
Mental Health Cost				
Parameter	Odds Ratio	Standard Error	95% CI	p-value
Parent of HA child	1.20	0.09	1.03, 1.40	0.018
Age	1.00	5.33e-03	0.99, 1.01	0.550
Female	1.72	0.12	1.50, 1.98	<0.001
Secondary beneficiary	1.04	0.07	0.91, 1.19	0.597
Child's age	1.00	7.45e-03	0.99, 1.02	0.524
Number of children	1.01	0.02	0.98, 1.04	0.740
Index month	1.00	9.35e-03	0.98, 1.02	0.753
Insurance type, HMO*	0.86	0.09	0.70, 1.05	0.134
Insurance type, other*	0.84	0.06	0.72, 0.97	0.018
CCI	1.13	0.05	1.03, 1.23	0.008
Region, north central≡	1.39	0.14	1.15, 1.70	<0.001
Region, south≡	1.22	0.11	1.02, 1.47	0.030
Region, west≡	1.13	0.12	0.92, 1.39	0.249
Region, unknown≡	1.00	0.29	0.54, 1.74	0.998
Full-time employment≠	1.23	0.09	1.07, 1.42	0.004
Index year	1.01	0.01	0.98, 1.04	0.451

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HA, hemophilia A; HMO, health maintenance organization

*Reference group = preferred provider organization

≠Reference group = northeast region

≡Reference group = not full-time employment