Healthcare Utilization and Costs associated with Sickle-cell disease in the United States: A Retrospective Claims Analysis

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Abstract

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Introduction: Sickle cell disease (SCD) is a group of hereditary hematological disorders that are associated with high rate of medical resource utilization and medical costs. In the past few decades, improvement in medical care has contributed to increased survival in individuals with SCD resulting in a growing aging population which will consequently place a huge economic burden on health care resources in upcoming years. Past studies in SCD are either outdated, or focused on individual U.S. states, or focused on specific utilization categories, or had small sample size, or focused primarily on pediatric populations. An updated estimation of healthcare utilization and costs associated with sickle cell disease remedying the aforementioned shortcomings would be important to guide medical resource allocation and would be useful for various payers to anticipate and better plan for the needs of their patients along with appraising value of upcoming novel treatment options. The objective of this study was to measure the economic and healthcare resource burden associated with SCD in the United States.

Methods: A retrospective cross-sectional study using matched cohorts of SCD cases and population controls was conducted using IBM® MarketScan® Commercial Claims and

Encounters database. Eligible patients of all ages within both SCD and control cohorts were included if they had at least 24 months of continuous enrollment within the patient identification period from 1 January 2012 to 31 December 2017. Patients were identified as having SCD if they had at least 3 paid SCD-related claims in a given year. Control patients were obtained from the general population and were required to have no SCD diagnosis or claims during the patient identification period and were matched with SCD cases on age, sex, type of benefit plan, geographic location (state) of residence of the enrollee, and calendar year of eligibility. All-cause health care resource utilization and costs were measured during the 24-months continuous enrollment period for SCD cases and controls. Associations of SCD with cost and utilization were evaluated after adjustment of matching covariates and Charlson comorbidity index through generalized estimating equations using gamma and negative binomial distribution, respectively. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC), STATA SE version 14.2 (StataCorp, College Station, TX) and R version 3.4.3.

Results: A total of 7,446 patients with SCD and an equal number of matched population controls were identified. Nearly, half (44.7%) of the sample comprised of pediatric and adolescent patients aged 0-19. Majority of the patients were female (57.1%), from the southern region of the United States (52.7%), and covered under a Preferred Provider Organization (PPO) health plan (56.7%). SCD patients had significantly more health care resource utilization and incurred higher medical costs than controls across all service categories. After adjusting for age, sex, type of benefit plan, geographic location (state) of the enrollee, calendar year of eligibility, and Charlson Comorbidity Index, SCD patients on average had 83.20 (95%CI: 79.84–86.55), 1.18 (95%CI: 1.14–1.22), and 9.87 (95%CI: 9.08–10.67) greater outpatient visits, inpatient hospitalizations, and prescription drug dispensed than matched controls, respectively. Similarly, after adjusting for the aforementioned set of covariates, we found that SCD patients, on average had $40,657 (95%CI: $37,994 - $43,321) higher total medical costs than matched controls.

Conclusion: We used real-world administrative claims data to measure the burden of SCD in a commercially insured population and found that SCD is associated with high health care resource utilization along with significant direct medical costs. Increased life expectancy among SCD patients in recent decades along with advent of new expensive treatment options like gene therapy will consequently add to the economic burden of SCD.

Introduction and Significance:

Sickle cell disease (SCD) is a group of hereditary hematological disorders that affects approximately 100,000 individuals in the United States[1] and millions worldwide.[2–4] SCD is a lifelong condition characterized by serious acute and chronic multi-organ complications, including pain crises, chronic anemia, stroke, repeated infections, renal failure, pulmonary hypertension, acute chest syndrome, tissue damage, progressive multi-organ failure, and ultimately results in premature death.[2,5–7] Additionally, SCD complications also lead to reduced health-related quality of life.[8–10] SCD is associated with high rate of medical resource utilization[11–14] and treatment costs.[6,11]

In the past few decades, improvement in medical care through efforts involving early diagnosis via implementation of newborn screening[15,16], vaccination programs such as pneumococcal immunizations[17], use of prophylactic antibiotics like penicillins[18], literacy about disease complications[2], introduction of disease-modifying treatments like hydroxyurea[19–22], improved safety in blood transfusions procedures[23,24], transcranial doppler screening to identify children vulnerable to stroke with transfusion[25–27] and intensive hospital-based care[5] coupled with clinician and other medical professionals awareness in dealing with SCD complications have contributed to reduced symptom burden and complexity along with increased survival in individuals with SCD.[2,5,28–30] As a result, a greater proportion of children will live long enough to present for medical attention and thus would generate lifelong healthcare costs.[31] Currently, almost all SCD management strategies focus on treating symptoms and complications and the paucity of cures (presently the only cure is Allogeneic hematopoietic stem cell transplant) available along with the growing aging population of individuals with SCD will consequently place an increasingly large economic burden on health care resources in the upcoming years.[5,31] A reliable estimation of healthcare utilization and direct costs, associated with sickle cell disease

would thus be important to guide medical resource allocation and would be useful for various stakeholders.

Limitations of past studies:

Past studies in the United States which had attempted to measure healthcare utilization and costs in individuals with SCD had several limitations. Some focused on individual states[11,12,14,32–39], or restricted their focus to a specific utilization or cost component such as hospital rates or costs[12,35,39–46], emergency department use[12,37,39,47,48], hematopoietic cell transplantation[49] , or had small sample size[34,40,50], or focused only on a certain age groups such as studying only children[34,38–41,45,49,51–55]) or were antiquated[11,32,56] (operationally defined as a study which had used population databases that were more than 10 years old). Our study would the first in recent times to comprehensively measure inpatient, outpatient, and prescription drug related healthcare utilization and costs in SCD patients of all ages using a multi-state observational database.

Objective:

The objective of this study was to measure the economic and healthcare resource burden associated with SCD in the United States. Our first specific aim was to measure health care resource utilization, namely, outpatient visits, inpatient hospitalizations, and prescription drug dispensed among SCD patients. Our second aim was to measure the direct medical cost of care in SCD patients along with calculating the SCD attributable cost.

Methods:

Study design and data source:

A retrospective cross-sectional study using matched cohorts of SCD cases and population controls was conducted using IBM® MarketScan® Commercial Claims and Encounters Database. As SCD is a hereditary disorder usually diagnosed in the childhood, the adult patients who would be eligible in our study are more likely to be prevalent cases of SCD rather than having an incident diagnosis of SCD at an advanced age. Hence, use of a cross-sectional study design was preferred over study designs requiring a baseline period with no SCD diagnosis or claim. The IBM® MarketScan® Research Databases provide real-world, Health Insurance Portability and Accountability Act (HIPAA) compliant, de-identified, nationally representative, individual-level healthcare claims data obtained from large employers, government and public organizations, and health plans.[57,58] This study did not qualify under the definition of human subject involvement and was approved under exempt status by the institutional review board at the University of Washington Human Subjects Division.

Patient eligibility

Eligible patients within both SCD and control cohorts were included if they had at least 24 months of continuous enrollment within the patient identification period from 1 January 2012 to 31 December 2017. Patients of all ages were eligible for inclusion. The patient's age at the time of the calendar year of eligibility was calculated based on the natural number year which was non-chronologically closest.

SCD cohort:

Patients were identified as having SCD if they had at least 3 paid SCD claims in any position in a given year irrespective of type of service (inpatient, outpatient or ED). This case definition has been proven to be the most accurate way to identify children with SCD in administrative claims databases.[59] SCD was identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnostic codes in the 2012-2017 claims files. The ICD codes used to identify SCD are provided in Appendix Table 1.

Control cohort:

Control patients were obtained from the general population and were required to have no SCD diagnosis or claims during the patient identification period. Controls were matched with SCD cases on age, sex, type of benefit plan, geographic location (state) of residence of the enrollee, and calendar year of eligibility to improve comparability and minimize differences in baseline characteristics that may have influenced the SCD diagnosis, utilization, and cost. Additionally, to account for potential differences in comorbidities, which could affect healthcare utilization and associated costs, a Charlson Comorbidity Index (CCI) was calculated for each patient. Patients for whom there were no ICD9 or 10 diagnosis codes available to compute a CCI were assigned a value of 0. Patients within our study who did not meet the SCD case definition (had less than 3 paid SCD claims in a given year) were not included in the control group to improve precision while comparing with the SCD cohort.

Assessment of Health Care Resource Utilization and Costs

All-cause health care resource utilization and medical cost were measured during the 2-year continuous enrollment period for SCD cases and controls. Attributable (incremental cost of having SCD) cost of SCD was calculated by deducting the mean total cost in the control cohort from the mean total cost in the SCD cohort. Health care resource utilization was measured by counting the number of inpatient admissions, outpatient visits, and prescription drug claims. For direct medical costs, charges for the aforementioned health care utilization components were calculated for each patient along with providing the total cost. As we required continuous enrollment, patients who had missing data for any of the cost or utilization components were assigned a value of 0 since they hadn't incurred any cost. Average counts of utilization and average costs were calculated for patients of each numeric age along with a global average for all ages.

Statistical Analyses:

Means with corresponding standard deviation and frequencies with corresponding proportions were reported for continuous and categorical variables, respectively. To study the association of SCD diagnosis with healthcare utilization and medical costs, we performed a matched cohort analysis using generalized estimating equation (GEE) adjusting for age, sex, type of benefit plan, geographic location (state) of residence of the enrollee, calendar year of eligibility, and Charlson Comorbidity Index. We used GEE to model utilization and costs in order to account for the correlation between the SCD cases and controls induced from matching on covariates. The costs in our study were heavily right skewed, hence a gamma distribution was chosen. Our healthcare utilization data comprised of over dispersed count outcomes hence a negative binomial link and family was chosen within GEE to model each of the components of health care resource utilization separately, namely, counts of outpatient visit, inpatient admission, and prescription drug use, after

adjusting for the aforementioned set of covariates. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC), STATA SE version 14.2 (StataCorp, College Station, TX) and R version 3.4.3.

Results:

Patient characteristics

A total of 7,446 patients with SCD and an equal number of matched population controls of same age, sex, type of benefit plan, geographic location (state) of residence of the enrollee, and calendar year of eligibility which met the inclusion criteria were identified. Figure 1. shows the SCD case and control identification process after exclusions due to insufficient enrollment period, insufficient matched control availability, or not having met our operational definition of SCD. Among the identified patients, nearly, half (44.7%) of the sample comprised of pediatric and adolescent patients aged 0-19. Majority of the patients were female (57.1%), from the southern region of the United States (52.7%), and covered under a Preferred Provider Organization (PPO) health plan (56.7%). A detailed composition of sample demographics is provided in Table 1. Among our SCD cases and matched control populations, most had no comorbidities (CCI index score of 0 in 63.2% v. 82.4%, respectively); however, there was a greater proportion (5.95%) of SCD cases with a CCI score of 3 and higher compared to matched controls (1.61%). A detailed composition of CCI score among SCD cases and matched controls is provided in Table 2.

Healthcare Utilization

SCD cases had higher healthcare utilization than matched controls for nearly all ages and across all service categories. Among the SCD cases, the mean outpatient visits, inpatient

hospitalizations, and prescription drug dispensed across all the ages were 142.43 (SD: 206.59), 1.40 (SD: 3.04), and 25.92 (SD: 36.16), respectively. Among the matched controls, the mean outpatient visits, inpatient hospitalizations, and prescription drug dispensed across all the ages were 41.38 (SD: 57.16), 0.08 (SD: 0.41), and 13.03 (SD: 24.42), respectively. The mean outpatient visits, inpatient hospitalizations, and prescription drug dispensed for SCD cases and controls during the two-year period are reported by each age year in Table 3.

The unadjusted SCD attributable outpatient visits, inpatient hospitalizations, and prescription drug dispensed were 101.06 (95%CI: 97.69–104.42), 1.32 (95%CI: 1.28–1.36), and 12.89 (95%CI: 12.25–13.53), respectively.

After adjusting for age, sex, type of benefit plan, geographic location (state) of the enrollee, calendar year of eligibility, and CCI, having SCD was associated with significantly ($p<0.05$) higher health care utilization across all service categories. On average, SCD patients had 83.20 (95%CI: 79.84–86.55), 1.18 (95%CI: 1.14–1.22), and 9.87 (95%CI: 9.08–10.67) greater outpatient visits, inpatient hospitalizations, and prescription drug dispensed than matched controls, respectively. In terms of incident rate ratios, SCD cases had a rate of 1.014 (95%CI: 1.013-1.0144), 6.79 (95%CI: 6.28-7.34), and 1.023 (95%CI: 1.021-1.025) times greater outpatient visits, inpatient hospitalizations, and prescription drug dispensed, respectively when compared to matched controls after adjusting for aforementioned covariates.

Healthcare Costs

SCD cases incurred higher healthcare costs than controls for nearly all ages and across all service categories. Among the SCD cases, the mean total, outpatient, inpatient, and prescription drug related costs across all the ages were $52,309 (SD: $124,442), $18,491 (SD: $ 50,487), $ 27,028 (SD: $89,183), and $4,464 (SD: $20,636), respectively. Among the matched controls, the mean

total, outpatient, inpatient, and prescription drug related costs across all the ages were $7,211 (SD: $19,058), $4,091 (SD: $10,863), $1,422 (SD: $9,532), and $1,295 (SD: $6,784), respectively. Mean outpatient, inpatient, prescription drug related, and total costs for SCD cases and controls during the two-year period are reported by each age year in Table 4.

The mean total cost among SCD patients was highest in the West ($85,749) whereas lowest in the South ($46,603). In addition, male SCD cases had higher mean total cost compared to females ($53.115 v. $51,703).

SCD patients incurred more than seven (7.25x) times the total medical cost compared to matched controls. There was a huge variation across total cost among SCD cases with values ranging from $0 - $2,624,478. Similarly, there was also substantial variation across total cost among controls with values ranging from $0 - $554,839. Among all cost categories, inpatient cost accounted for the largest portion whereas prescription drug cost accounted for the smallest portion of total cost for SCD cases. Among, controls, the outpatient cost accounted for the largest portion whereas prescription drug cost accounted for the smallest portion of total cost.

The unadjusted SCD attributable total cost (mean difference) was $ 45,097 (95%CI: $42,083 - $ 48,112). The attributable costs for SCD related outpatient, inpatient, and prescription drug related claims were $14,400 (95%CI: $13,242 - $15,557), $25,606 (95%CI: $22,360 - $28,853), $3,169 (95%CI: $ 2,647 - $3,690), respectively.

After adjusting for age, sex, type of benefit plan, geographic location (state) of the enrollee, calendar year of eligibility, and CCI, having SCD was associated with significantly ($p<0.05$) higher total medical costs (6.1 times higher). On average, SCD patients had $40,657 (95%CI: $37,994 - $43,321) higher total medical costs than matched controls.

Discussion:

We measured the economic and healthcare resource burden associated with SCD in the United States by analyzing administrative claims for a commercially insured population and provided a comparison of direct medical cost and health care resource utilization among SCD patient and population-level controls of the same age, sex, type of benefit plan, geographic location (state) of residence of the enrollee, and calendar year of eligibility.

We found that SCD is associated with considerable health care resource utilization across all service categories after adjusting for age, sex, type of benefit plan, geographic location (state) of the enrollee, calendar year of eligibility, and CCI. When compared with matched controls, SCD cases had a rate of 1.014, 6.79, and 1.023 times higher outpatient visits, inpatient hospitalizations, and prescription drug dispensed, respectively. The alarmingly high rates of inpatient hospitalizations could be mainly due to acute and chronic manifestations of SCD like vaso-occlusive pain crisis, acute chest syndrome, splenic sequestration, and infections among others which might warrant hospital admittance.[12,40,45,60]

SCD is associated with substantial medical costs which have been consistently demonstrated in past economic studies. We found the mean total cost among all ages for two years of enrollment among SCD patients to be $52,309 compared to $7,211 in controls. After adjusting for various matched covariates and CCI, we found that having SCD was, on average, associated with significantly higher (nearly six times greater) total medical costs to the tune of $40,657 compared to matched controls.

Our estimates of medical costs in SCD patients were bit on the higher side when compared to two past economic studies in SCD.[11,52] However, Mvundura et al. 2009 primarily focused on pediatric patients while Kauf et al. 2009 focused on Medicaid eligible patients which could explain their lower cost estimates. Additionally, both these studies identified SCD patients using at least

one inpatient claim or two outpatient claims at least 30 days apart having an ICD-9-CM code for SCD. Our operational definition of at least 3 paid SCD claims in any position in a given year irrespective of type of service was stricter and may have led to inclusion of more serious SCD patients which may have contributed to our higher total estimate of cost. We found that among the cost categories, inpatient cost accounted for the largest portion whereas prescription drug cost accounted for the smallest portion of total cost for SCD patients which was consistent with the findings of previous medical claims studies.[11,52]

Our study has few shortcomings. Firstly, there are few limitations with regards to our choice of dataset. Marketscan claims database are constructed using a large convenience sample which might lack generalizability as it mostly includes patients having an employer sponsored insurance.[58] Additionally, the Marketscan sample is also not nationally representative of the employer sponsored insured population as it gathers data mainly from large employers resulting in underrepresentation of patients employed at small- and medium-sized companies.[58] Another limitation of using a sample of patients having an employer sponsored insurance is the potential for healthy worker bias which results in patients who are healthy enough to be stably employed and receive health insurance benefit. This would cause health care utilization and costs to appear lower for our sample of SCD patients. Additionally, gainfully employed SCD patients are more likely to partake in other healthful activities like exercising or be more conscientious to adhere to treatment, follow-up and seek care, thus raising the concern of healthy-adherer bias and increased cost due to such health-seeking behavior.

Secondly, the Marketscan database doesn't include out-of-pocket costs and direct non-medical cost e. g. transportation costs and paid caregiver cost. Pain in SCD patients is a major complain and could necessitate regular use of OTC pain medications such as aspirin, ibuprofen, and naproxen which can be obtained at a cheaper price than paying the required copayments to access these via insurance. Also, indirect cost consisting of reduced productivity and work

absences along with intangible costs comprising of emotional pain and suffering were not measured. Thus, the economic burden of SCD would be considerably higher if out-of-pocket costs, direct non-medical cost, indirect costs, and intangible cost were accounted for our patients.

Thirdly, during SCD identification phase, we excluded patients who didn't meet the SCD case definition (had less than 3 paid SCD claims in a given year) or were intermittently insured. Excluding these uncertain SCD patients from SCD cohort will lead to decreased overall utilization and cost burden but will improve precision of attributable cost while comparing SCD cohort with controls.

Finally, misclassification due to overlap between SCD symptomatology and other non-sickle hematologic conditions along with over-reliance on ICD codes which lack sufficient specificity to ascertain SCD status can resulted in false positive identification of SCD and inaccurate coding by medical professionals which limits the accuracy of our results.[61,62] However, our strategy to define SCD using at least 3 claims in a year ensures sufficient accuracy.

The strengths of our study include a large sample size along with use of real-world medical claims dataset to characterize all types of medical utilizations along with their corresponding costs in all age groups. Also, this is the first study in the SCD cost literature space to use ICD-10 diagnosis codes which have improved specificity compared to ICD-9. In the U.S., SCD is more common in people of African descent. Our sample demographics is congruous and shows that more than half of our SCD patients came from the South which is historically a black-dominated region according to the U.S. Census Bureau Annual estimates of regional distribution of black population[63]. This improves the confidence in our dataset to measure utilization and cost that can be extrapolated nationally.

Our updated SCD utilization and cost estimates could be useful for multiple audiences/stakeholders and serve various purposes. Evaluating the economic burden of SCD

could assists payer organizations in anticipating and better planning for the needs of their patients along with appraising value of newer treatment strategies[11]. The cost estimates provided could be used as inputs in budget impact and cost-effectiveness analyses. In the SCD space, there are currently two drugs approved to treat patients. Hydroxyurea which was originally approved in 1998 for treating adults with SCD had a label extension in December 2017 to include pediatric patients. Endari (L-glutamine oral powder) was approved in July 2017 to reduce complications associated with SCD in pediatric and adult patients. Additionally, there are various gene therapy trials currently ongoing which offer great promise. However, based on the pricing for the first gene therapy to be approved in the U.S., voretigene neparvovec (Luxturna), for degenerative blindness, it would be safe to surmise that these novel therapies for SCD are going to be extremely expensive.[64] Additionally, the advent of increasingly expensive and effective cures for SCD in the near future would offset other direct medical costs (inpatient admission and outpatient visit costs) in the long-term with short-term drug related cost. Thus, a role reversal is anticipated where prescription drug cost which currently contributes to a small percentage of total cost would gradually evolve to form a major portion of total medical cost for SCD.

The increased life expectancy among SCD patients in recent decades has led to development of various age-related non-sickle complications which have contributed to existing SCD morbidity.[65] This, along with the emergence of novel treatment options in pipeline has sparked an interest in the economic burden of SCD. Our timely and updated estimates of health care resource utilization and cost would bolster this discussion.

Conclusion:

We used real-world administrative claims data to measure the economic burden of SCD in a commercially insured population and found that SCD is associated with high health care resource

utilization along with significant direct medical costs. The brunt of this burden, although mostly borne by payers, is further compounded by reduced health-related quality of life in patients along with unmeasured cost associated with poor employee engagement and lost productivity for employers. Increased life expectancy among SCD patients in recent decades due to improvement in medical care along with advent of new expensive treatment options like gene therapy will consequently add to the economic burden of SCD.

Figure 1: SCD case and control identification

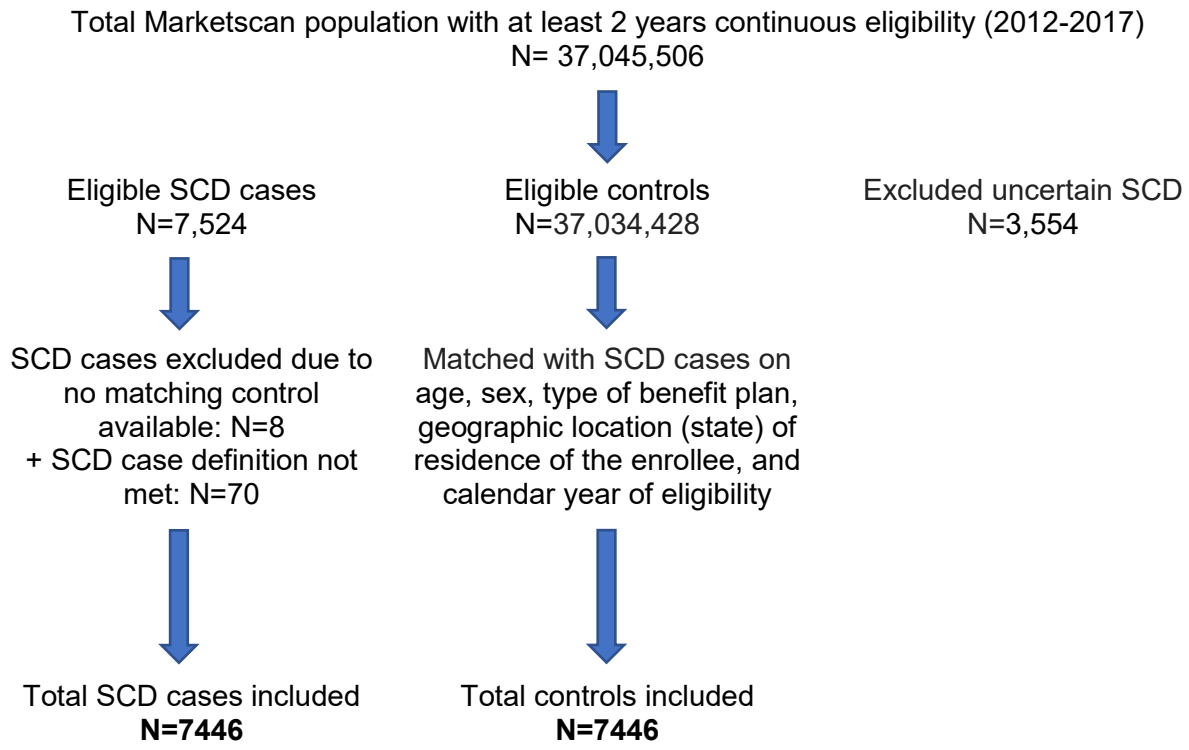

Table 1: Matched pair demographics

Variable	Number (n=7446)	Proportion (%)
Age (years)		
00-09	1,512	20.31
10-19	1,819	24.43
20-29	1,169	15.70
30-39	1,140	15.31
40-49	992	13.32
50-59	677	9.09
60-65	137	1.84
Start Year		
2012	4,432	59.52
2013	1,764	23.69
2014	604	8.11
2015	495	6.65
2016	151	2.03
Sex		
Male	3,195	42.91
Female	4,251	57.09
Plan type		
Comprehensive	150	2.01
EPO	154	2.07
HMO	1,383	18.57
POS	798	10.72
PPO	4,221	56.69
POS with capitation	60	0.81
CDHP	445	5.98
HDHP	235	3.16
Region		
North East	1,757	23.60
North Central	1,015	13.63
South	3,922	52.67
West	590	7.92
Unknown	162	2.18

Table 2: Charlson Comorbidity Index distribution in SCD cases and matched controls

	Cases		Control	
CCI Index	Number (n=7446)	Proportion (%)	Number (n=7446)	Proportion (%)
0	4,707	63.22	6,133	82.37
1	2,073	27.84	1,093	14.68
2	223	2.99	100	1.34
3+	443	5.95	120	1.61

Table 3: Mean outpatient visits, inpatient hospitalizations, and prescription drug dispensed by Age in SCD cases and matched controls

		SCD CASES						MATCHED CONTROLS					
Age	N	Mean OU	SD	Mean IU	SD	Mean RxU	SD	Mean OU	SD	Mean IU	SD	Mean RxU	SD
0	281	123.84	137.06	1.26	2.22	24.33	25.44	57.32	33.79	0.05	0.22	7.40	9.61
1	144	114.02	112.02	1.58	2.13	27.24	28.33	33.31	50.16	0.03	0.22	5.69	7.17
2	127	124.67	200.22	1.31	2.27	25.37	28.96	30.65	35.84	0.02	0.15	5.01	7.09
3	111	115.62	240.96	1.23	1.84	27.12	32.61	27.17	22.82	0.01	0.09	5.55	9.05
4	136	116.93	136.36	1.09	1.52	20.95	25.25	30.46	34.32	0.05	0.22	5.59	7.39
5	147	122.27	176.88	0.87	1.46	18.73	25.09	21.06	28.25	0.06	0.39	6.25	14.43
6	129	145.01	215.20	0.95	1.41	19.92	25.53	20.78	24.98	0.02	0.12	5.65	10.30
7	160	126.73	220.66	0.81	1.51	16.98	25.66	28.49	71.74	0.02	0.24	4.41	9.21
8	136	130.43	170.56	0.94	1.93	19.07	24.43	20.95	22.36	0.01	0.09	4.74	8.22
9	141	154.65	239.33	1.32	3.62	18.52	23.38	24.28	39.23	0.08	0.55	5.67	11.52
10	142	130.65	191.29	1.01	2.23	18.57	22.79	22.77	25.44	0.04	0.23	5.46	18.34
11	173	172.03	285.64	1.54	2.24	19.96	31.82	21.50	25.35	0.02	0.17	3.66	7.43
12	163	121.09	164.36	1.37	2.65	19.20	25.20	25.17	31.40	0.03	0.17	6.39	18.74
13	155	146.59	204.02	1.53	2.94	18.28	24.23	27.57	32.19	0.02	0.14	5.97	12.09
14	181	122.72	183.41	1.33	3.27	16.31	21.26	28.44	45.07	0.05	0.28	6.69	12.24
15	192	123.95	171.33	0.99	2.01	16.38	20.54	33.26	47.46	0.06	0.27	7.30	11.62
16	218	113.06	158.05	1.14	2.40	14.39	24.26	29.06	45.40	0.05	0.34	7.84	15.71
17	232	113.08	150.53	1.75	4.26	16.04	24.64	24.22	28.65	0.03	0.17	8.43	14.11

18	152	116.64	170.43	1.91	3.25	17.63	25.78	35.20	66.50	0.08	0.36	9.33	13.36
19	211	116.91	154.66	1.82	3.43	17.25	30.56	23.28	39.16	0.08	0.37	9.10	14.80
20	171	153.63	259.55	2.17	4.70	19.24	29.43	26.12	34.46	0.08	0.27	7.78	14.28
21	156	151.69	189.30	2.10	3.96	17.35	21.54	33.28	46.15	0.13	0.38	9.75	15.07
22	160	171.34	390.70	2.39	3.94	22.77	38.99	28.16	44.58	0.09	0.36	8.68	14.97
23	136	127.32	165.55	3.15	5.54	23.59	37.68	27.29	40.47	0.12	0.40	7.09	12.76
24	67	187.87	212.16	2.61	6.08	30.99	41.08	34.25	40.72	0.04	0.21	9.15	13.84
25	73	127.10	139.63	1.08	1.95	23.53	38.32	33.00	31.05	0.14	0.42	11.73	14.76
26	90	150.26	204.91	1.81	3.93	26.98	35.32	32.86	40.34	0.17	0.43	9.79	17.99
27	120	165.73	269.51	2.24	4.49	30.62	46.62	47.70	73.77	0.28	1.75	12.53	26.85
28	94	120.14	148.39	1.33	3.17	25.07	39.81	35.86	37.00	0.13	0.37	10.99	17.55
29	102	209.22	347.30	2.62	4.55	31.79	40.31	42.28	43.47	0.24	0.45	14.16	18.26
30	101	112.89	134.38	1.21	1.90	22.91	39.58	47.46	62.56	0.12	0.35	14.97	24.71
31	104	96.36	92.81	1.14	1.81	20.57	30.00	49.41	61.20	0.18	0.46	15.30	23.20
32	144	126.56	141.69	1.12	1.96	25.75	33.60	42.85	53.80	0.15	0.37	12.19	18.49
33	125	121.03	140.14	1.54	2.44	26.50	35.15	38.57	53.10	0.11	0.32	12.85	19.50
34	97	184.95	230.45	1.74	3.87	32.73	41.98	37.63	53.57	0.12	0.36	12.35	21.87
35	129	146.78	182.74	1.93	3.98	32.91	41.34	54.29	70.31	0.16	0.50	15.71	20.62
36	122	146.84	193.88	1.01	2.02	30.32	40.73	45.96	49.18	0.07	0.31	20.90	32.19
37	103	130.37	151.98	1.11	1.79	28.74	33.74	50.11	62.09	0.09	0.28	15.84	26.28
38	106	168.88	218.46	1.53	3.21	32.05	44.62	62.58	75.02	0.08	0.30	19.36	33.46
39	109	157.48	246.60	1.05	2.39	29.58	38.86	60.41	92.07	0.07	0.30	18.84	26.93
40	123	134.67	168.82	0.88	1.87	27.82	35.27	60.77	64.25	0.04	0.20	20.28	26.94
41	127	153.19	242.78	1.57	5.17	28.72	34.25	52.44	71.28	0.08	0.30	15.98	21.87
42	93	185.01	243.60	1.51	4.62	35.10	43.46	59.23	76.56	0.05	0.23	16.38	18.03
43	119	172.98	371.01	0.93	1.77	30.32	35.25	52.14	58.07	0.08	0.30	21.50	36.40
44	82	117.78	111.04	0.99	2.04	27.61	34.86	50.71	56.70	0.12	0.89	17.50	29.33
45	85	152.54	168.88	1.86	4.68	28.02	32.67	57.20	71.33	0.04	0.19	20.12	31.28
46	92	136.87	171.68	0.66	1.89	31.99	36.32	61.95	73.42	0.12	0.44	25.55	38.48
47	106	131.60	147.54	0.69	1.30	34.87	44.59	47.81	62.04	0.05	0.25	17.91	23.10
48	81	198.02	233.12	0.86	1.60	38.79	54.04	64.48	67.92	0.14	0.74	30.86	47.17
49	84	167.77	289.52	0.99	2.99	30.57	36.84	67.74	93.23	0.08	0.42	25.35	40.17
50	87	168.25	212.49	1.21	3.01	40.29	51.42	58.06	59.78	0.05	0.21	22.36	33.18
51	71	143.58	150.66	0.77	1.43	34.27	45.91	58.25	54.98	0.20	0.99	23.90	40.38

52	77	170.23	191.42	1.32	2.66	52.34	65.42	83.64	94.00	0.03	0.16	27.14	33.43
53	74	202.88	212.38	1.46	2.79	39.28	41.95	58.27	56.47	0.14	0.34	28.07	37.62
54	75	156.19	167.19	1.15	1.68	40.12	47.26	67.13	59.52	0.15	0.43	26.91	35.36
55	63	157.81	144.39	1.10	2.59	49.70	55.28	80.76	72.89	0.17	0.46	27.52	26.98
56	61	138.39	131.96	0.80	1.56	43.82	48.97	73.87	69.54	0.23	0.56	32.98	47.68
57	53	193.25	322.36	0.75	1.04	44.58	55.38	98.30	157.06	0.09	0.30	38.19	45.10
58	48	267.56	326.86	1.27	2.06	47.15	46.71	58.75	50.47	0.10	0.37	26.38	32.06
59	68	179.82	207.82	0.99	2.09	60.32	56.06	77.57	66.60	0.06	0.24	30.18	43.59
60	48	181.54	220.58	1.13	1.54	52.25	58.96	91.46	81.41	0.17	0.43	42.46	47.99
61	49	220.49	244.49	1.55	2.53	58.59	60.32	67.08	67.78	0.10	0.42	53.31	58.68
62	39	159.03	126.47	0.41	0.75	33.41	40.60	94.77	108.06	0.26	0.75	41.49	53.30
63	1	393.00	-	3.00	-	48.00	-	153.00	-	0.00	-	10.00	-
All	7446	142.43	206.59	1.40	3.04	25.92	36.16	41.38	57.16	0.08	0.41	13.03	24.42

N is the number of pairs of case and control matched on age, sex, type of benefit plan, geographic location (state) of residence of the enrollee, and calendar year of eligibility.
OU: Outpatient visits; IU: Inpatient hospitalizations; RxU: Prescription drug dispensed

Table 4: Mean total cost, outpatient cost, inpatient cost, prescription drug cost by Age in SCD cases and matched controls

		SCD CASES								MATCHED CONTROLS							
Age	**N**	**Mean TC**	**SD**	**Mean OC**	**SD**	**Mean IPC**	**SD**	**Mean RxC**	**SD**	**Mean TC**	**SD**	**Mean OC**	**SD**	**Mean IPC**	**SD**	**Mean RxC**	**SD**
0	281	31,828	73,264	11,488	24,656	17,487	50,494	964	4,760	6,519	9,944	4,617	5,020	867	5,801	333	682
1	144	38,366	55,620	13,071	22,895	21,721	37,571	982	3,732	3,198	4,609	2,176	2,866	395	2,610	226	438
2	127	41,926	94,497	17,994	57,583	20,764	47,316	1,321	5,315	3,745	5,352	2,880	4,714	68	474	229	504
3	111	53,757	254,928	15,467	64,440	34,665	185,559	1,577	7,253	2,518	3,187	1,894	2,345	51	538	303	797
4	136	31,915	46,583	14,853	32,354	12,275	20,139	2,330	8,790	4,340	9,613	2,565	5,666	1,178	6,178	325	729
5	147	29,417	47,050	14,767	31,565	11,543	22,959	1,604	5,212	2,980	7,856	1,644	3,978	577	4,361	402	1,678
6	129	50,804	166,907	17,195	30,689	28,082	139,927	4,187	12,526	2,488	4,689	1,611	2,842	129	1,036	506	1,704
7	160	39,548	102,133	16,180	41,177	17,457	65,354	4,590	35,056	4,487	16,096	3,715	15,670	137	1,739	342	935

8	136	50,949	114,178	18,731	34,839	27,261	88,598	3,247	13,054	3,078	10,200	1,662	2,907	14	165	1,136	9,024
9	141	68,053	241,142	22,925	63,154	37,365	189,742	6,270	20,768	4,144	12,345	1,961	5,483	1,265	7,357	674	2,380
10	142	40,318	70,524	14,793	30,321	16,256	40,614	7,836	27,416	5,085	24,969	3,704	21,111	607	3,701	623	3,200
11	173	79,988	213,370	30,975	111,654	38,369	115,661	8,737	45,986	4,941	25,412	1,846	3,301	1,647	19,978	1,140	10,597
12	163	42,285	71,563	14,947	31,193	19,730	42,869	6,217	31,544	4,179	14,023	2,070	3,585	1,151	12,232	645	2,364
13	155	58,747	104,182	20,336	39,969	30,346	66,106	5,714	20,893	3,335	6,239	2,341	5,247	262	2,244	545	1,410
14	181	51,441	96,378	17,557	40,647	27,456	70,249	5,194	21,183	4,145	9,546	2,522	4,895	757	4,938	482	1,133
15	192	40,738	78,823	14,989	29,166	15,137	38,871	9,306	36,678	5,563	14,594	2,705	5,249	532	2,624	1,983	12,973
16	218	49,518	166,299	15,694	37,224	27,786	135,732	4,431	21,233	4,483	9,869	2,650	5,519	619	4,032	925	3,697
17	232	63,624	198,599	13,876	30,944	42,886	186,414	4,218	22,557	3,267	4,845	1,843	2,606	281	1,630	752	2,618
18	152	57,406	106,081	20,079	55,518	33,226	77,296	1,779	6,530	6,584	15,812	3,993	10,597	1,046	5,405	988	2,440
19	211	77,087	219,078	17,115	41,264	53,383	186,590	4,321	23,848	4,361	11,458	2,030	4,552	1,184	7,992	678	2,039
20	171	65,276	127,826	19,002	42,029	38,671	90,554	2,726	9,934	3,635	5,560	1,983	3,167	751	2,815	394	909
21	156	59,414	87,052	19,057	35,140	30,905	64,375	5,437	22,303	6,624	15,633	2,998	6,231	2,582	10,128	483	949
22	160	67,602	172,196	24,234	119,705	37,042	69,703	2,341	7,421	5,514	14,106	2,800	5,651	975	4,524	1,305	10,415
23	136	85,862	165,739	17,560	51,053	61,199	122,718	3,054	10,337	6,679	17,708	2,958	6,838	1,962	9,205	1,473	11,663
24	67	79,557	128,165	26,142	60,841	40,153	90,117	7,531	25,383	4,309	6,776	2,541	4,007	408	1,957	1,172	4,122
25	73	37,930	57,384	13,295	25,233	19,779	39,262	2,582	9,194	6,525	12,835	2,800	5,433	1,580	5,273	1,706	5,649
26	90	58,914	101,931	17,865	40,981	28,009	59,409	6,815	29,389	6,680	16,427	3,107	9,330	2,453	7,857	746	2,054
27	120	68,079	112,626	20,942	46,207	38,702	81,616	4,412	18,586	9,499	28,435	4,111	9,261	3,203	18,475	1,422	5,520
28	94	40,840	79,713	16,967	55,051	19,406	48,577	2,144	6,962	5,823	8,131	3,512	5,826	1,448	4,437	496	1,079
29	102	73,503	120,111	24,029	60,387	38,447	67,529	7,276	25,929	7,935	10,932	3,453	5,601	3,413	7,344	742	1,510
30	101	37,032	65,912	11,235	25,842	18,086	36,810	5,878	30,845	6,773	10,827	4,114	6,818	1,433	4,638	854	2,010
31	104	30,968	43,005	10,379	17,336	17,262	30,094	1,729	6,119	9,730	18,215	5,287	10,086	2,465	7,747	1,495	5,001
32	144	37,457	58,389	13,787	24,092	16,962	34,110	4,086	22,162	6,879	10,968	4,248	8,454	1,875	5,208	480	1,029
33	125	44,317	68,801	11,373	18,753	25,388	48,665	3,779	15,577	6,296	11,795	3,618	8,108	1,407	4,195	911	2,688
34	97	78,483	163,105	28,526	62,664	42,025	123,237	5,263	19,560	6,656	11,211	3,415	5,702	1,686	5,321	1,227	4,487
35	129	63,038	125,232	20,276	59,209	36,544	96,361	2,970	9,620	9,048	17,321	4,669	9,184	3,060	11,200	912	1,946
36	122	53,108	107,414	21,895	61,380	23,169	69,920	6,270	23,850	7,572	14,389	3,996	5,007	824	3,937	2,103	10,802
37	103	43,055	65,713	14,432	22,892	18,780	39,816	8,080	37,180	7,805	15,931	5,092	13,112	1,329	5,563	1,238	3,692
38	106	75,650	194,930	31,347	125,470	34,037	108,093	7,441	42,903	12,323	22,405	7,743	14,843	1,626	7,695	2,106	6,031
39	109	51,420	106,690	24,138	61,737	19,858	60,118	5,292	13,904	11,389	25,736	7,025	18,498	1,538	7,131	2,129	8,026
40	123	36,195	66,039	13,953	26,484	15,967	41,789	4,678	18,375	8,167	10,989	5,901	8,609	466	2,596	1,448	2,732

41	127	51,432	105,433	18,959	36,730	26,852	81,533	3,798	10,113	8,439	16,125	5,202	10,682	977	3,672	1,807	6,652
42	93	55,708	104,731	18,107	23,949	28,672	85,651	6,547	22,800	10,067	17,854	5,989	8,895	1,803	10,404	1,882	8,989
43	119	43,461	93,884	20,450	55,315	17,812	44,326	3,012	7,940	10,049	16,165	5,049	8,002	1,836	8,403	2,717	8,391
44	82	38,544	73,547	13,461	23,865	20,859	56,836	2,263	5,661	9,602	21,009	5,303	9,517	2,239	13,801	1,585	6,178
45	85	53,471	106,180	14,818	21,631	32,330	87,740	3,833	14,289	7,301	10,000	5,590	9,053	449	2,785	1,003	1,864
46	92	44,729	98,587	26,053	79,087	14,172	48,642	3,391	8,974	10,110	16,833	5,126	8,209	2,270	10,373	2,095	6,612
47	106	37,433	58,625	15,324	25,161	17,458	40,439	3,221	7,895	7,643	16,172	3,946	5,782	1,103	8,180	2,253	12,563
48	81	43,752	60,288	20,824	31,275	16,428	33,507	3,124	6,409	12,877	23,344	7,093	12,541	2,681	12,783	2,742	6,058
49	84	47,220	110,771	20,163	42,708	19,322	60,109	3,824	15,254	15,165	61,880	9,715	39,011	2,334	15,240	2,981	10,589
50	87	46,034	76,198	19,415	33,047	20,155	46,599	4,037	11,763	9,737	14,789	6,672	11,334	873	4,300	1,829	4,218
51	71	39,099	82,513	21,231	63,703	14,661	31,986	1,772	3,426	13,786	29,125	6,418	9,381	4,472	25,319	2,213	5,157
52	77	70,810	137,035	27,793	66,580	35,206	80,902	5,731	14,055	12,219	17,692	7,930	10,971	396	2,649	3,420	11,033
53	74	63,030	94,978	28,384	43,982	27,575	57,775	5,319	18,203	9,869	12,547	5,326	7,147	2,207	6,625	1,698	3,332
54	75	48,878	76,603	17,104	25,292	23,947	54,151	6,351	21,657	18,404	40,936	11,620	33,935	4,749	20,174	1,640	2,609
55	63	49,084	102,032	16,689	23,157	24,959	74,663	6,386	15,302	12,586	14,172	8,308	10,216	2,327	6,596	1,765	2,421
56	61	47,675	90,295	21,045	57,496	21,601	53,531	4,269	12,070	23,494	51,957	12,043	30,719	5,111	18,401	6,012	20,082
57	53	39,627	64,169	18,758	43,149	13,194	21,277	6,400	18,227	16,033	33,818	9,494	17,742	1,019	3,574	4,833	16,924
58	48	82,667	136,905	41,858	75,398	32,141	65,761	6,158	10,912	10,504	17,934	6,120	14,620	2,235	8,593	1,729	3,000
59	68	54,191	85,442	21,199	34,838	21,102	47,130	11,118	34,823	17,552	39,017	7,459	8,684	2,775	17,019	7,139	28,920
60	48	47,533	57,957	17,021	21,311	22,639	38,635	5,465	11,387	24,098	39,320	15,404	33,761	4,318	14,349	4,120	12,068
61	49	79,571	148,429	37,749	93,769	30,479	63,674	8,232	14,795	14,529	26,511	6,776	12,229	2,750	15,383	4,344	6,224
62	39	29,719	44,561	17,679	27,441	8,423	16,472	2,645	6,672	31,819	73,365	11,992	20,349	14,673	60,714	4,750	12,559
63	1	119,633	-	32,874	-	70,495	-	2,186	-	25,378	-	22,364	-	0	-	1,933	-
All	7,446	52,309	124,442	18,491	50,487	27,028	89,183	4,464	20,636	7,211	19,058	4,091	10,863	1,422	9,532	1,295	6,784

N is the number of pairs of case and control matched on age, sex, type of benefit plan, geographic location (state) of residence of the enrollee, and calendar year of eligibility.
TC: Total cost; OC: Outpatient cost; IPC: Inpatient cost; RxC: Prescription drug cost

Appendix Table 1: ICD codes for SCD

ICD 9	ICD 10
282.6 Sickle-cell disease	D57 Sickle-cell Disorders
282.60 Sickle-cell disease, unspecified	D57.0 Hb-SS disease with crisis
282.61 Hb-SS disease without crisis	D57.00 Hb-SS disease with crisis, unspecified
282.62 Hb-SS disease with crisis	D57.01 Hb-SS disease with acute chest syndrome
282.63 Sickle-cell/Hb-C disease without crisis	D57.02 Hb-SS disease with splenic sequestration
282.64 Sickle-cell/HB-C disease with crisis	D57.1 Sickle-cell disease without crisis
282.68 Other sickle-cell disease without crisis	D57.2 Sickle-cell/Hb-C disease
282.69 Other sickle-cell disease with crisis	D57.20 Sickle-cell/Hb-C disease without crisis
282.41 Sickle-cell thalassemia without crisis	D57.21 Sickle-cell/Hb-C disease with crisis
282.42 Thlassemia Hb-S w crisis	D57.211 Sickle-cell/Hb-C disease with acute chest syndrome
	D57.212 Sickle-cell/Hb-C disease with splenic sequestration
	D57.219 Sickle-cell/Hb-C disease with crisis, unspecified
	D57.4 Sickle-cell thalassemia
	D57.40 Sickle-cell thalassemia without crisis
	D57.41 Sickle-cell thalassemia with crisis
	D57.411 Sickle-cell thalassemia with acute chest syndrome
	D57.412 Sickle-cell thalassemia with splenic sequestration
	D57.419 Sickle-cell thalassemia with crisis, unspecified
	D57.8 Other sickle-cell disorders
	D57.80 Other sickle-cell disorders without crisis
	D57.81 Other sickle-cell disorders with crisis
	D57.811 Other sickle-cell disorders with acute chest syndrome
	D57.812 Other sickle-cell disorders with splenic sequestration
	D57.819 Other sickle-cell disorders with crisis, unspecified

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