

GLOBAL HEALTH

Health Services Utilization and Cost of Retinitis Pigmentosa

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Objective: To estimate annual per-patient health services utilization and costs of retinitis pigmentosa (RP) in the United States.

Methods: A retrospective claims analysis of patients with RP (N = 2990) and a 1:1 exactly matched cohort of non-RP patients was conducted using the MarketScan Commercial and Medicare Supplemental Databases. Individuals were continuously enrolled in a commercial health plan or employer-sponsored health insurance for at least 1 year. The following annual outcomes were analyzed using non-linear multivariate models: inpatient hospital admissions, inpatient hospital days, emergency department visits, outpatient physician visits, and prescription drug refills and inpatient and outpatient medical, pharmacy, and total health care costs.

Results: Patients with RP had 0.04 more hospital admissions ($P < .001$), 0.19 more inpatient hospital days ($P < .02$), 0.05 more emergency department visits

($P < .01$), 2.74 more outpatient visits ($P < .001$), and 2.18 additional prescription drug fills ($P < .001$) annually compared with their non-RP counterparts. Health care expenditures were significantly higher for patients with RP, who cost \$894, \$4855, and \$452 more for inpatient, outpatient, and pharmacy services, respectively ($P < .001$). Overall health care costs were \$7317 more per patient per year in the RP cohort, with expenditures varying considerably by age.

Conclusions: Patients with RP consume substantially greater amounts of health services with significantly higher health care costs.

Clinical Relevance: Treatments that slow, halt, or possibly restore RP-related vision loss may prove cost-effective for payers and society.

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RETINAL DYSTROPHIES ARE characterized by degeneration of photoreceptor and retinal pigment epithelium cells and are the major cause of incurable hereditary blindness in the Western world.¹ Retinitis pigmentosa (RP) is the most frequent cause of inherited visual impairment (VI), with a prevalence of 1:4000, and is estimated to affect 50 000 to 100 000 people in the United States and approximately 1.5 million people worldwide.^{2,3} Manifesting initially with a deficiency in night vision, the course of RP is characterized by deterioration of specialized light-absorbing cells in the retina, leading to progressive loss of peripheral and day vision and, over decades, in most cases, severe VI or blindness. Age at onset can vary from early childhood to adulthood, with photoreceptor degeneration often present several years before a patient reports visual symptoms.⁴ Approximately 45 causal genes have been identified in RP, and these account for

two-thirds of cases. In general, RP is a progressive disease, with exponential decline in the visual field area of approximately 9% per year and in cone electroretinographic amplitude of 10% per year.^{3,5-9}

There is no therapy that stops disease evolution or restores vision for RP, and, hence, the prognosis is poor. These conditions are largely deemed incurable diseases, with the resultant VI managed primarily through low-vision rehabilitation to offset reduced visual function and health-related quality of life as VI manifestations progress over time.¹⁰ The therapeutic approach aims to restrict the degenerative process via light protection and vitamin and antioxidant therapy, address complications, and help patients cope with the psychological impact of vision loss.^{11,12} Significant scientific advances are leading to potentially promising therapies, including ocular gene therapy,^{13,14} retinal microimplants,^{15,16} oral retinoid pharmacotherapy, retinal transplants,¹⁷ neu-

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rotrophic factors,¹⁸ and sustained drug delivery systems.¹⁹

A wide range of adverse physical and psychological outcomes has been reported in patients with partial or totally blinding VI, including RP. These challenges include higher risk of injury,²⁰⁻²² problems with timely access to health care,²³ greater dependency and increased rates of admission to institutional facilities,^{22,24,25} and reduced mental well-being.²⁵⁻²⁷ Patients with RP commonly report headaches,²⁸ and sleep disturbances arising from lack of photic input occur in as many as 76% of patients, increasing the risk of cardiovascular, metabolic, and psychiatric disorders.²⁹ Retinitis pigmentosa is also associated with difficulty performing daily activities³⁰ and increased rates of depression.³¹ Productivity losses for patients with VI³²⁻³⁴ are likely to be amplified in patients with RP because of the early age at onset, vision challenges at school, and loss of visual function without some type of rehabilitation during prime working years.

The annual cost of adult vision problems in the United States has been estimated to be \$51.4 billion.³⁵ Frick et al³⁶ estimated average annual medical care and informal care costs (1996-2002) for adults 40 years or older with VI to be \$5.5 billion, with higher total health care expenditures for vision-impaired and blind individuals relative to sighted individuals. Of note, non-eye-related medical costs are also significantly increased with VI.²⁵ An article from the United Kingdom estimated 2.5 times higher community costs for RP than for adult retinal diseases because of the number of years of blindness experienced.²

Despite the recent focus on blindness and VI in general, the specific economic consequences of RP have not been investigated. Economic data obtained from earlier studies in patients with VI cannot be applied to RP because of differences in patient populations and comorbidities and longitudinal changes in treatment and costs. As new, and presumably more costly, interventions become available for RP, economic evaluations will be needed to establish the cost-effectiveness of competing therapies, to assess the benefits of treatment, and to make informed coverage decisions. The objective of this study was to examine health services utilization and costs of patients with RP with commercial health insurance compared with those without VI, exactly matched on 4 characteristics.

METHODS

STUDY SAMPLES

This study was a cross-sectional retrospective claims analysis of individuals with RP compared with matched individuals without RP. Data for the 5-year period, January 1, 2005, to December 31, 2009, from the MarketScan Commercial and Medicare Supplemental Databases were used. These databases include insurance enrollment information with integrated inpatient, outpatient, and pharmacy data on 115 million covered lives encompassing 150 employers and 130 carriers.³⁷

For each of the 5 calendar years in the data set, we first excluded individuals without continuous insurance enrollment for the entire year. Next, we selected patients diagnosed as having RP during a calendar year if they had at least 1 inpatient claim or 2 outpatient medical claims on different dates with *International Classification of Diseases, Ninth Revision*, code

362.74 in the primary or secondary diagnosis position. Then, all the insurance claims for a patient's qualifying calendar year were included in the ensuing analysis. Finally, a 1:1 exactly matched comparison group was selected from a 5% random sample of the full MarketScan database. The pool of possible control subjects excluded those with a diagnosis of RP, although other eye disorders were allowed. Each RP cohort member was exactly matched to 1 individual from the control pool on the following variables: age (in 3-year bands), sex, geographic region, and Charlson Comorbidity Index, a composite measure of general health status that does not capture conditions of the eye.³⁸⁻⁴⁰

HEALTH SERVICES UTILIZATION AND COST MEASURES

For the calendar year during which a participant met the inclusion criteria, health services utilization and cost variables were constructed. Utilization measures included (1) number of inpatient hospital admissions, (2) number of inpatient hospital days, (3) number of emergency department visits, (4) number of outpatient physician visits, and (5) number of prescription drug fills (in 30-day equivalents). The cost analysis was conducted from the all-payer perspective. Using insurance-allowed amounts (ie, plan sponsor plus patient-paid amounts, including coordination of benefits information), costs were categorized as inpatient, outpatient, pharmacy, and total (sum of the 3 components).

COMORBIDITIES

In addition to the Charlson Comorbidity Index, differences in the prevalence of other health conditions across the 2 cohorts were assessed using the Healthcare Cost and Utilization Project's Clinical Classification Software.^{41,42} Moreover, the presence of 1 or more prescriptions for antidepressants, opioid/analgesic medications, or both was examined given the mental health and pain issues reported in the RP literature.^{22,28,43,44}

ECONOMETRIC ANALYSES

Statistically significant differences in independent and dependent variable means across the RP and control groups were tested using the nonparametric Kruskal-Wallis equality-of-populations rank test.⁴⁵ In addition to these bivariate analyses, multivariate models were estimated to control for additional covariates not used in the matching process. These variables included insurance plan sponsor (employer vs health plan), insurance plan type, and cohort calendar year (to control for underlying secular trends in health services utilization and cost).

As is common in health services research, health care costs were not normally distributed (ie, they were highly right skewed, alternatively referred to as *positively skewed*). Therefore, to obtain an unbiased estimate, generalized linear modeling with gamma family and log link was the selected multivariate method, a nonlinear technique that was suggested by leading health econometricians.⁴⁶ Because many individuals in the data set did not have any hospitalizations, a 2-part model was estimated for inpatient costs. Part 1 of this type of model was a logistic regression predicting whether any inpatient costs were incurred. Part 2 was the generalized linear modeling gamma/log technique previously described in which the dependent variable was positive inpatient costs. For ease of presentation and interpretation, marginal effects were estimated at the mean of all right-hand-side variables. All the analyses were conducted using a commercially available software program.⁴⁷

DESCRIPTION OF POPULATION

Characteristics of the RP and control cohorts are given in **Table 1**. The 2 groups each comprised 2990 patients, with a slightly higher proportion of women (56.4% vs 43.6% men) and a mean age of 48.2 years. Approximately 10% of patients were 18 years or younger, 13% were aged 18 to 34 years, 58% were aged 35 to 64 years, and 19% were 65 years or older. Most patients (55.5% of patients with RP and 54.3% of controls) were enrolled in a preferred provider organization plan ($P = .52$), and more than two-thirds of the insurance was employer sponsored ($P = .13$). No significant differences ($P > .01$) in mean values across the 2 groups in the variables used in the matching process or in the other characteristics presented.

HEALTH SERVICES UTILIZATION

Per-person annual health services utilization averages are presented in **Table 2**. The number of inpatient hospital admissions ($P = .02$) and days and the number of emergency department visits ($P = .12$) did not differ significantly between patients with RP and controls ($P = .38$). Patients with RP, however, had significantly ($P < .001$) more outpatient physician/clinic visits (mean, 7.81; median, 6.00) compared with control individuals (mean, 5.28; median, 4.00) ($P < .001$). The number of prescriptions filled was also significantly higher in the RP group (mean [median]: 19.30 [12.00] vs 17.70 [10.00]; $P < .001$).

Table 2 also provides estimates of the average marginal effect of RP from the multivariate models of annual health services utilization. After adjusting for all the covariates, patients with RP had 0.04 more inpatient hospital admissions ($P < .001$), 0.19 more inpatient hospital days ($P < .01$), 0.05 more emergency department visits ($P < .01$), 2.74 more outpatient physician/clinic visits ($P < .001$), and 2.18 more prescriptions filled ($P < .001$).

HEALTH SERVICES COSTS

Average annual total health care costs were significantly greater for the RP group (mean, \$14 988; median, \$4973) compared with the control group (mean, \$9965; median, \$2778) ($P < .001$). Outpatient costs composed 68% to 71% of total expenditures in both cohorts but differed significantly in magnitude across the groups ($P < .001$). Pharmacy costs were also significantly higher in the RP group ($P < .001$), although no significant differences in inpatient costs were detected ($P > .11$).

In all econometric health services cost models, the average marginal effect of RP was positive and significant ($P < .001$). After controlling for other covariates, as previously noted, patients with RP had annual costs that were higher by \$894 for inpatient, \$4855 for outpatient, \$452 for pharmacy, and \$7317 for total health care costs.

To examine whether the impact of having RP varied with age, the total health care cost model was reestimated on each of 10 age group subsamples. The RP mar-

Table 1. Sample Characteristics^a

Characteristic	RP Group (n = 2990)	Non-RP Group (n = 2990)
Characteristics Used in Matching		
Male sex	0.436 (0.496)	0.436 (0.496)
Age, y ^b	48.244 (19.711)	48.244 (19.752)
0-12	0.057 (0.232)	0.057 (0.232)
13-17	0.043 (0.202)	0.042 (0.202)
18-24	0.041 (0.199)	0.041 (0.199)
25-34	0.089 (0.285)	0.088 (0.283)
35-44	0.154 (0.361)	0.150 (0.357)
45-54	0.213 (0.409)	0.217 (0.413)
55-64	0.218 (0.413)	0.221 (0.415)
65-74	0.089 (0.284)	0.085 (0.278)
75-84	0.076 (0.265)	0.077 (0.266)
≥85	0.021 (0.145)	0.021 (0.145)
Region		
Northeast	0.145 (0.352)	0.145 (0.352)
Midwest	0.258 (0.438)	0.258 (0.438)
South	0.401 (0.490)	0.401 (0.490)
West	0.194 (0.395)	0.194 (0.395)
Unknown	0.002 (0.048)	0.002 (0.048)
Charlson Comorbidity Index	0.545 (1.155)	0.545 (1.155)
Characteristics Not Used in Matching		
Insurance plan sponsor		
Health plan	0.298 (0.457)	0.320 (0.467)
Employer	0.702 (0.457)	0.680 (0.467)
Plan type		
Comprehensive	0.124 (0.329)	0.125 (0.330)
EPO	0.007 (0.082)	0.005 (0.071)
HMO	0.193 (0.394)	0.200 (0.400)
POS	0.077 (0.268)	0.067 (0.250)
PPO	0.555 (0.497)	0.543 (0.498)
POS with capitation	0.006 (0.079)	0.011 (0.103)
CDHP	0.020 (0.141)	0.023 (0.149)
HDHP	0.002 (0.041)	0.005 (0.073)
Unknown	0.017 (0.128)	0.022 (0.147)
Cohort year		
2005	0.159 (0.366)	0.170 (0.376)
2006	0.154 (0.361)	0.170 (0.376)
2007	0.189 (0.391)	0.178 (0.382)
2008	0.240 (0.427)	0.242 (0.429)
2009	0.259 (0.438)	0.241 (0.428)

Abbreviations: CDHP, consumer-driven health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; RP, retinitis pigmentosa.

^aData are given as mean (SD). All values are proportions except where indicated otherwise. There were no statistically significant differences in mean values across groups using the Kruskal-Wallis equality of populations rank test ($P > .05$).

^bAge was exactly matched in 3-year bands but is further aggregated for parsimony.

ginal effects from these analyses are presented in **Figure 1**. Children (age <12 years) with RP incurred the highest differential in total health care costs (\$11 072; $P < .001$), followed by individuals aged 55 to 64 years (\$9909; $P < .001$), 45 to 54 years (\$6871; $P < .01$), and 85 years and older (\$6019; $P < .03$). The statistically significant impacts of RP in other age groups ranged from \$3663 for 13- to 17-year-olds ($P < .001$), to \$4641 ($P < .001$), to \$5027 ($P = .02$). For those aged 65 to 74 years, the difference was \$2750 ($P = .27$), and for the 75- to 85-year-olds, the difference was \$1862 ($P = .38$).

Table 2. Annual Health Services Utilization and Cost by Study Group^a

Variables	RP Group (n = 2990)			Non-RP Group (n = 2990)			Marginal Effect of RP, Mean (SE) ^b
	Mean	Median	SD	Mean	Median	SD	
Inpatient hospital admissions, No.	0.141	0.000	0.460	0.106	0.000	0.415	0.04 (0.01) ^c
Inpatient hospital days, No.	0.638	0.000	3.725	0.510	0.000	3.564	0.19 (0.08) ^d
Emergency department visits, No.	0.373	0.000	0.992	0.320	0.000	0.809	0.05 (0.02) ^d
Outpatient physician/clinic visits, No. ^c	7.806	6.000	6.672	5.279	4.000	5.352	2.74 (0.14) ^c
Prescriptions filled, No. ^a	19.296	12.000	22.544	17.704	10.000	22.118	2.18 (0.58) ^c
Total inpatient costs, \$	2539	0	15 425	1651	0	11 562	894 (316) ^c
Total outpatient costs, \$ ^c	10 589	3206	30 964	6791	1435	21 711	4855 (510) ^c
Total pharmacy costs, \$ ^c	1860	579	4378	1524	460	3054	452 (116) ^c
Total health care costs, \$ ^c	14 988	4973	37 949	9965	2778	26 736	7317 (869) ^c

Abbreviation: RP, retinitis pigmentosa.

^aHospital admissions, hospital days, and emergency department visits were specified as 2-part models (logit-negative binomial) with bootstrapped standard errors. Outpatient physician visits and prescription fills were negative binomial models. Inpatient costs were specified as a 2-part model (logit-generalized linear modeling with gamma/log) with bootstrapped standard errors, and all the other models were generalized linear modeling with gamma/log. All the models included the following covariates: Charlson Comorbidity Index score and indicator variables for 9 age groups, 4 regions, 8 plan types, and 4 cohort years, as well as dichotomous variables for male sex and employer plan sponsor.

^bMarginal effect estimates (from the following multivariate models) are taken at the mean of all other covariates.

^c $P < .01$, significant differences in mean values across groups using the Kruskal-Wallis equality of populations rank test.

^d $P < .05$, significant differences in mean values across groups using the Kruskal-Wallis equality of populations rank test.

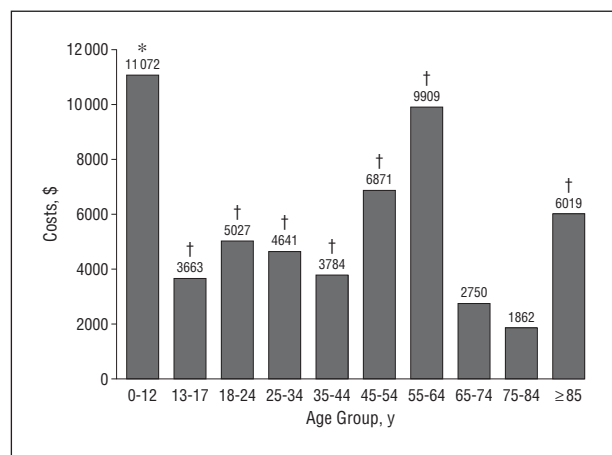


Figure 1. Annual total health care costs of retinitis pigmentosa by age. Presented are marginal effect estimates of retinitis pigmentosa from age group-specific generalized linear modeling with gamma/log models of total health care costs. * $P < .01$. † $P < .05$.

COMORBIDITIES

In an attempt to uncover underlying comorbidities associated with the observed higher health services utilization and cost of patients with RP, differences in the prevalence of Healthcare Cost and Utilization Project's Clinical Classification Software categories were examined. **Table 3** provides the clinical conditions in which statistically significant ($P < .001$) differences across the 2 groups emerged. Noteworthy was a higher prevalence of other ocular disorders ($P < .001$) (including cataract [$P < .001$], other eye disorders, blindness and vision defects, glaucoma [$P < .001$], and inflammation [$P < .001$] and infection of the eye [$P < .74$]), other sensory organ disorders, and headache, although mental health was not significantly worse in patients with RP ($P > .001$). Furthermore, an analysis of prescriptions filled by therapeutic class did not reveal statistically significant differences ($P > .05$) in the use of

Table 3. Prevalence of Comorbidities in the RP and Non-RP Groups

Comorbidity	Participants, %		P Value ^a
	RP Group	Non-RP Group	
HCUP clinical classification ^b			
Retinal detachment/defects/vascular occlusion/retinopathy	100.0	0.07	<.01
Cataract	20.7	6.7	<.01
Other nontraumatic joint disorders	18.7	15.1	.01
Other eye disorders	18.2	5.7	<.01
Blindness and vision defects	17.4	2.9	<.01
Other ear and sense organ disorders	11.5	5.8	<.001
Inflammation and infection of eye	11.2	4.1	<.01
Glaucoma	10.4	4.1	<.01
Other nervous system disorders	9.5	6.4	.03
Headache, including migraine	8.4	4.9	.02
Pharmacy therapeutic class use			
Antidepressants	18.3	17.5	.56
Opioids and analgesics	25.9	24.1	.23

Abbreviations: HCUP, Healthcare Cost and Utilization Project; RP, retinitis pigmentosa.

^aThe P values are from the Kruskal-Wallis equality of populations rank test of differences in mean values across groups.

^bOnly HCUP clinical classification comorbidities that differed significantly between groups are shown.

antidepressants or opioid/analgesics between groups, although the prevalence of both was slightly higher in magnitude for the RP cohort.

Given that 20.7% of patients with RP had cataracts, triple the rate in the comparison group, an age-specific analysis was conducted. **Figure 2** shows the cumulative proportion of individuals in both cohorts with cataracts. Although no control group member had cataracts before age 45 years, the youngest patient in the RP group was 14 years old. Moreover, the density of cumulative cataract prevalence increased rapidly between ages 14 and

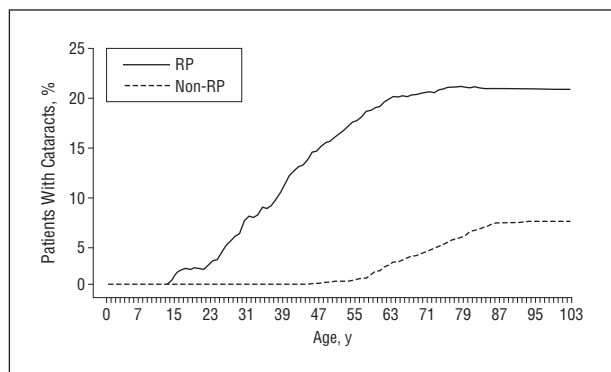


Figure 2. Cumulative percentage of patients with cataracts by age in the retinitis pigmentosa (RP) and non-RP groups.

64 years in the RP cohort, yet the incline in the control group did not commence until their late 50s. Although not necessarily causal evidence, these curves suggest that patients with RP experience a much earlier onset and far greater likelihood of cataracts.

COMMENT

To our knowledge, this study is the first to estimate the health services utilization and costs associated with RP, a rare disease with a long duration of visual disability relative to other common retinal disorders. Compared with individuals without the disorder, patients with RP had significantly more inpatient, outpatient, and emergency department services and prescription drug use. This greater use of health care translated into significantly higher expenditures. Annual total health care costs for an average patient with RP were \$7317 higher than those for an average individual without RP but who was otherwise comparable on age, sex, geographic region, Charlson Comorbidity Index, and insurance plan characteristics. This finding is similar to a recently reported estimate of the costs of blindness in a managed care population.⁴⁸ In that study, total mean charges were \$20 677 per blind patient and \$13 321 per nonblind patient per year, a difference of \$7356.

In the present analysis, the marginal effect of RP on total health care costs varied by age, with children younger than 12 years and adults aged 55 to 64 years having the highest incremental costs. In younger patients diagnosed as having RP and associated congenital comorbidities (eg, hearing impairment), additional expenditures would be expected owing to primary and specialty care required to manage the presenting chronic conditions. The older age group likely had more vision loss progression but did not yet have access to Medicare coverage, under which reimbursement rates may be substantially lower.

A large proportion of the differential in total health care costs were outpatient. With an average of 2.74 more visits annually, higher outpatient service use was likely related to the management of RP (ie, retinal diagnostics, low-vision device services, and VI rehabilitation) and other comorbidities that occurred more frequently in these patients. As an example of these added outpatient costs, cataracts were 3 times more prevalent in the RP cohort and were present at much younger ages. Individuals with RP

also typically have multiple vision deficits, including loss of visual acuity, narrowing of the visual field, and difficulty with light and dark adaptation. These sequelae all require extensive testing, ongoing and incrementally increasing low-vision rehabilitation treatment, and long-term psychological counseling.^{4,20} These patients also develop other ocular problems, have a higher frequency of hearing impairment because of associated Usher syndrome,³ and more frequently experience headaches, nervous system disorders, and depression.²⁸

Data used in this study provided a comprehensive picture of reimbursed health care services, offering a real-world estimate of costs that accrue to payers. The sample of almost 3000 patients with RP is, to our knowledge, the largest ever assembled, allowing for robust analyses that controlled for many observed characteristics stratified by age. In addition, because the 2 cohorts were constructed to differ only on the presence of RP, the likelihood that differences in health services utilization and cost could be attributed to RP was maximized. With a cross-sectional observational study, however, one cannot infer a causal effect of RP since other unobserved confounders may have persisted in the analysis.

Only health care costs captured by insurance claims were examined in the present study. The full cost of care for the patient with RP, however, should also include expenses for caregivers, rehabilitation, home assistance, and institutional care. Most people with VI rely on caregivers, who provide an estimated mean of 152 hours of assistance per visually impaired person per year.⁴⁹ Long-term care and nursing home costs, which can account for a substantial portion of the burden of illness from VI,⁵⁰ also were not assessed. Furthermore, costs for low-vision rehabilitation, guide dogs, and many other services specific to patients with VI are often not covered by managed care plans and, therefore, could not be factored into the estimate.^{51,52} A societal perspective would also include probable productivity losses due to reduced labor force participation and increased absenteeism and disability. In the aggregate, the magnitude of these economic consequences would likely be substantial given RP's early onset and longer duration of VI during employable years.

In summary, the health services utilization and cost of RP are substantial. Annual total health care costs were estimated to be \$7317 higher for patients with RP. Interventions that can treat RP progression and improve visual and functional outcomes have the potential to reduce health care costs and enhance quality of life. As new treatments are developed, economic analyses will be needed to help payers assess the comparative benefits of each therapy. This study provides foundational data that can be used in those efforts.

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