Comparing healthcare resource use and costs for patients with Normal Tension Glaucoma across levels of severity: a nationally representative sample of commercially insured US adults age 40 and older

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Abstract

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Introduction: Normal tension glaucoma (NTG) is a subset of open-angle glaucoma (OAG), which is the most prevalent form of glaucoma globally. Projections into 2040 predict a 74% increase to 111.8 million people affected worldwide. Though global burden of disease is increasing, little has been done to understand the burden of disease for patients with NTG regarding their annual healthcare resource utilization (HCRU) or costs and how disease severity may impact this burden.

Objective: Our objective was to estimate the HCRU and costs for patients with NTG as well as their payers. We sought to understand if costs and HCRU depends on one's severity of disease and whether or not laterality of disease modifies the effect of this relationship.

Methods: Our study was a retrospective cohort study of 6,330 US patients, 40 years of age and older, within the IBM® MarketScan® Commercial and Medicare Supplemental databases. Patients were enrolled if they were 40 years or older and had two or more qualifying NTG diagnoses, with the first of the two qualifying diagnoses being the patients' index date. Baseline demographic and clinical characteristics were assessed for a 12-month pre-index period. The follow up period was 12-months post-index. Our analysis was carried out for two cohorts – those with unilateral disease and those with bilateral disease. The relationship between severity and HCRU was analyzed by fitting a generalized linear model with a Poisson distribution and log link for office visits. We relaxed the Poisson assumption and modeled prescription counts with a negative binomial model and log link to account for overdispersion. Costs were modeled with a generalized linear model with a gamma distribution and a log link. Cost data were adjusted to 2019 dollars.

Results: Patients with severe, bilateral disease, filled over two additional prescriptions annually (2.5, 95% CI [2.0, 3.1]) when compared to their mild counterparts and accounted for 111 (95% CI [83.5, 139.1]) extra days of supply of glaucoma medications. These patients face $121 (95% CI [87, 155]) more out-of-pocket (OOP), and payers an additional $348 (95% CI [$207, $488]), than their counterparts with a mild diagnosis on an annual basis.

Conclusion: Our results suggest that patient burden is higher for those with severe disease compared to those with mild NTG. The excess burden is not only attributed to additional HCRU, but also by a higher financial burden, which accompanies their higher resource use. Patients were

not alone in harboring burden as payers experienced a much larger financial burden from patients with severe disease compared to those with mild NTG. Most of the cost differences can be attributed to additional prescription use.

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1 Introduction

Normal tension glaucoma (NTG), sometimes referred to as low tension glaucoma, is an optic neuropathy characterized by structural damage to the optic nerve associated with visual field dysfunction.[1] NTG often presents with glaucomatous optic nerve head damage, progressive retinal nerve fiber layer thinning, characteristic visual field defects, open anterior chamber angles, and a maximum intra-ocular pressure (IOP) below 21 mmHg.[2] NTG is a type of open angle glaucoma (OAG). Despite having "normal" ranges of IOP (< 21 mmHg), the Collaborative Normal Tension Glaucoma Study Group demonstrated that a 30% reduction in IOP slowed disease progression for patients with NTG. Therefore, the treatment regimens are generally the same for NTG as OAG and are targeted toward reducing IOP, regardless of the patient's baseline.[3]

In 2013, the global prevalence of glaucoma was estimated to be 64.3 million, with projections into 2040 expecting a 74% increase to 111.8 million people affected worldwide.[4] Less is understood about the prevalence of NTG, though the Beaver Dam Eye study estimated that approximately one-third of OAG diagnoses could be classified as NTG while a Japanese study estimated that NTG accounts for 92% of that country's glaucoma cases.[5,6] Annual costs of glaucoma reported in one 2006 European study ranged from €455 to €969 from the early to late stage glaucoma, respectively.[7] The total attributable economic burden in the US has been estimated at $7.6 billion, which was estimated to be $2,841 per-patient in 2013 dollars.[8]

Though much is known about the general costs of glaucoma, less has been done to characterize healthcare resource use (HCRU) and the associated costs patients for with NTG. This study will address this gap by first characterizing HCRU and costs of patients with NTG, by severity and laterality; then by comparing the HCRU and costs of NTG patients compared to non-NTG OAG patients.

2 Methods

2.1 Study Design

Our study was a retrospective cohort study of 6,330 US patients who were 40 years or older at the end of their index year.

2.2 Data Source

We used administrative claims data from the IBM® MarketScan® Commercial and Medicare Supplemental databases. This dataset is a representation of nearly 40 million commercially insured US adults, or US adults qualifying for Medicare that have commercial supplemental insurance.

2.3 Sample Selection and Study Cohorts

We performed a retrospective cohort study with eight prevalent cohort groups. Groups were stratified by laterality (unilateral versus bilateral) disease, and within those categories, stratified by levels of severity – mild, moderate, severe, or indeterminate.

A patient's index date was the first of their two outpatient diagnoses in any position, with the second being with 365 days after the first, or one inpatient diagnosis, each for NTG. Included patients were required to be at least 40 years of age at index date and have at least 12 months of continuous enrollment pre- and post-index date. Excluded patients were those who had a glaucoma diagnosis other than OAG within 12 months prior to the patient's index date (Figure 1).

2.4 Study Period

The time period for possible enrollment spanned from October 1st, 2015, to December 31st, 2017. (Figure 2) To assess baseline characteristics and ensure the continuous enrollment criterion was met for each enrollee, data was collected from October 1st, 2014, to December 31st, 2018. HCRU and costs were estimated for a 12-month period following the index date.

2.5 Baseline Characteristics

2.5.1 Demographics

Demographic characteristics evaluated were age, gender, geographic region, and insurance. Age was defined as the age at the end of the index year. Laterality and severity were assigned as of the date of the index diagnosis.

2.5.2 Clinical

Diagnosis codes listed in medical claims were collected during the 12-month pre-index period and used to calculate the Charlson Comorbidity Index (CCI). The CCI was calculated per Quan et. al using ICD-9 and ICD-10 codes.[9] We used the17 common comorbidities and assigned weights specified in the Quan algorithm. CCI scores were categorized as 0, 1, 2, of 3+ comorbid conditions. Separately, other relevant comorbidities were assessed during the 12-month pre-index period, including non-exudative acute macular degeneration (AMD), exudative AMD, diabetic retinopathy, anxiety, and depression.

2.6 Definition of Outcomes

Outcomes were characterized as OAG-related, NTG-related, or glaucoma-related. Resources defined as OAG-related were any visit to eye-related providers (i.e., ophthalmologists and optometrists), or visits associated with an ICD-10 OAG diagnosis code, OAG surgical/laser procedures or complications (Appendix). The OAG-related category was intended to be the broadest category our data could represent. Therefore, NTG-related outcomes were defined as a subset of OAG-related outcomes and represented only NTG-specific diagnoses, rather than the larger set of OAG diagnoses. The term 'glaucoma-related' was used for prescription metrics and indicated prescription drugs with any relevant glaucoma indication because the data did not allow us to attribute prescriptions to individual diagnoses.

2.6.1 Healthcare Resource Utilization

HCRU was defined as counts for OAG-related office visits, NTG-related office visits, days' supply for glaucoma-related prescriptions, and number of prescriptions filled for glaucoma-related prescriptions. We calculated all HCRU as 'per user', that is, those who used each element.

2.6.2 Costs

Costs were categorized as being patient and payer-related costs. Patient-related costs were those incurred by the patient and were defined as the sum of the patient's co-pay, co-insurance, and deductible costs. Payer-related costs were total payments made by the health plan to healthcare providers. Costs included four main elements: OAG-related office visits, NTG-related office

visits, glaucoma-related prescriptions, and total costs. Total costs were defined as NTG-related office visits and glaucoma-related prescriptions.

Since at least one visit was required to meet inclusion criteria, with the exception of glaucoma-related prescriptions, all costs were defined as 'per user'. Not all patients in the data set were predetermined to have been prescribed a glaucoma-related prescription, therefore glaucoma-related prescription use was calculated using both 'per user' and 'per patient' as the denominator. Costs were estimated as 2019 dollars.

2.7 Statistical Analysis

2.7.1 Study Characteristics

Descriptive statistics were calculated to assess differences in baseline characteristics among all study cohorts. Categorical variables were summarized using frequencies and percentages, continuous variables were summarized using means and standard deviations.

2.7.2 Healthcare Resource Utilization

To assess the relationship between disease severity of NTG and HCRU, both OAG and NTG-related office visits were analyzed using a generalized linear model with a Poisson distribution. To address the overdispersion found in prescription counts, we relaxed the Poisson assumption and modeled those counts with a negative binomial model. We estimated association using both unadjusted and adjusted models. Our adjusted models attempted to maximize the data available by using all relevant demographic variables therein. We believed that one's age, sex, and CCI would likely confound the relationship between severity and HCRU. Further, we wanted to account for any regional differences or differences by insurance type in our analysis. So, our model was adjusted in accordance to our assumptions:

$$log(\lambda) = \alpha + \beta_1 x_{severity} + \beta_2 x_{age} + \beta_3 x_{sex} + \beta_4 x_{region} + \beta_5 x_{insurance} + \beta_6 x_{CCI}$$

After the regression analysis, predicted probabilities were extracted while holding all other variables at their mean using the margins command and all counts used mild severity as the referent category. To assess whether laterality modified the association between severity and

HCRU, we included an interaction term between the two variables. Interactions for office visits were modeled as above with a Poisson distribution and estimated using the margins command. For glaucoma-related prescription counts, we used a negative binomial distribution and estimated our counts as incident rate ratios comparing patients with severe and moderate disease to the mild referent category and patient with bilateral disease to patients of the unilateral referent cohort.

$$log(\lambda) = \alpha + \beta_1 x_{severity} + \beta_2 x_{laterality} + \beta_3 x_{age} + \beta_4 x_{sex} + \beta_5 x_{region} + \beta_6 x_{insurance} + \beta_7 x_{CCI} + \beta_8 x_{laterality} * x_{severity}$$

Where $\beta_8 x_{laterality} * x_{severity}$ represents a shorthand version of four categorical severity levels and two categorical severity levels, with mild, unilateral patients as the referent.

2.7.3 Direct Healthcare Costs

To assess the relationship between disease severity and costs, we fit a generalized linear model using a gamma distribution and log link for each cost outcome (i.e, OAG-related office visits, NTG-related office visits, glaucoma-related prescriptions, and total costs). Similar to HCRU, all outcomes were evaluated using unadjusted and adjusted models with the adjustment variables being age, sex, insurance type, region, and CCI. After the regression analysis, predicted probabilities were extracted while holding all other variables at their mean using the margins command and all costs used mild severity as the referent category. To assess whether laterality modified the association between severity and costs, we included an interaction term between the two variables.

For all statistical comparisons, we used a two-sided alpha at a 5% significance level. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for constructing the analytic dataset and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct the statistical analyses.

The Truven MarketScan database is Health Insurance Portability and Accountability Act of 1966 (HIPAA) compliant and all data are de-identified. The current study did not require Institutional Review Board (IRB) review and approval, as the study protocol did not meet the federal

definition of "human subjects research," as determined by the University of Washington Human Subjects Division IRB.

3 Results

3.1 Patient Characteristics

Our data included patients 40 years and older, but most were > 60 years of age (*N* = 4,523) with a plurality of them in Preferred Provider Organizations (PPO) (*N* = 3,104) and living in the North Central or Southern Regions of the US (*N* = 3,891). Approximately 60% were female and the average (SD) CCI score ranged from 0.82 (1.4) to 0.94 (1.6) across cohorts (Table 1).

3.2 Healthcare Resource Utilization by Severity Level and Laterality

3.2.1 Office Visits

Patients with mild disease had fewer OAG and NTG-related office visits than their moderate or severe counterparts within laterality cohorts (Table 2). Patients with mild disease in the unilateral cohort on average (SD) had 4.36 (2.24) OAG-related visits and 3.65 (1.44) NTG-related visits. Patients with mild disease in the bilateral cohort had 4.10 (2.06) OAG-related and 3.51 (1.43) NTG-related visits on average.

Those with mild disease experienced an adjusted difference of 0.6 (95% CI [0.3, 0.9]) fewer OAG-related office visits and 0.4 (95% CI [0.1, 0.7]) fewer NTG-related office visit within the unilateral cohort. Our results were similar for the bilateral cohort, with and adjusted difference of 0.9 (95% CI [0.7, 1.1]) fewer OG-related visits and 0.6 (95% CI [0.4, 0.8]) fewer NTG-related office visits when comparing patients with mild disease to those with a severe diagnosis.

Patients with unilateral disease tended to experience a lower effect of severity on office visits when compared to their bilateral counterparts in both the moderate and severe categories; however, this association was not found to be statistically significant.

3.2.2 Glaucoma Prescriptions

Results also suggest that patients with mild NTG have significantly lower prescription counts than those diagnosed with severe NTG. On average (SD), patients with mild disease in the

unilateral cohort had 5.35 (3.66) glaucoma-related prescriptions filled and 253 (172) days of drug supply. Those in the bilateral cohort had similar averages for patients with mild disease. Patients with mild disease in the bilateral cohort had 5.93 (3.98) glaucoma-related prescriptions filled and 256.14 (158.50) days of drug supply (Table 2).

Patients with mild disease in the unilateral cohort had 0.9 (95% CI [0.5, 1.3]) fewer adjusted prescription fills and 41 (95% CI [4, 77]) fewer adjusted days of drug supply than patients with severe disease. In the bilateral cohort, patients with mild disease filled 2.5 (95% CI [2.0, 3.1]) fewer prescriptions with 111.3 (95% CI [83.5, 139.1]) less days of drug supply compared to their counterparts with severe disease.

Results were also generally significant, though with a more modest effect size in almost all cases, when comparing patients with moderate disease to those with mild, than when comparing patients with severe disease to those with mild. For those with indeterminate severity, only prescription fills, both adjusted and unadjusted, in the unilateral cohort, was found to be significant with 0.5 (95% CI [0.0, 1.0]) additional prescription fills on average. No significant differences in HCRU were found for the bilateral cohort for any outcome when comparing patients with and indeterminate disease status to those with diagnosed with mild disease.

Laterality was an effect modifier for glaucoma-related prescription fills for patients with moderate (IRR 1.12, 95% CI [1.02, 1.23) and severe (IRR 0.82, 95% CI [0.73, 0.93]) disease (Table 5). The effect of severe disease on prescription fills were attenuated to a rate of 82% (95% CI [7, 27]) for patients with unilateral disease compared to those with bilateral disease. The same was true for days of prescription supply (81%, 95% CI [6, 30]).

3.3 Direct Healthcare Costs by Severity Level and Laterality

Patient-related and payer-related costs were significantly greater for patients with severe disease compared to the those with a mild form of NTG for most cost components (Tables 3 and 4).

3.3.1 Payer Related Costs

3.3.1.1 Office Visits

In the unilateral cohort, the average (SD) annual costs for payers were $202 ($399) and $157 ($229) for OAG and NTG-related office visits. This pattern was consistent in the bilateral cohort as well. Patients with mild disease in the bilateral cohort cost payers $178 ($501) and $131.91 ($430) annually for OAG and NTG-related visits, respectively.

Only payers for patients in the bilateral cohort had significantly higher annual costs for visits. In the unilateral cohort, compared to patients with mild disease, payers of patients diagnosed moderate or severe disease had no significant cost differences, adjusted or unadjusted, for visit outcomes. For the bilateral cohort, payers of patients with severe disease had an additional $86 (95% CI [28, 143]) of adjusted costs for OAG-related visits and $64 (95% CI [16, 113]) for NTG-related visits, annually. Notably, NTG-related costs are included in OAG-related costs and as such they should not be considered additive.

3.3.1.2 Glaucoma Prescriptions

Patients associated with both the unilateral and bilateral cohorts had significantly higher annual payer-related costs for prescriptions. Approximately 98% of patients in the unilateral and 97% in the bilateral cohort had at least one prescription filled. For those in the unilateral category, patients with moderate and severe disease had an additional $145 (95% CI [51, 238]) and $194 (95% CI [47, 340]) of annual adjusted payer-related prescription costs. Of those in the bilateral cohort that had at least one prescription filled, severe and moderate disease diagnoses were associated with $265 (95% CI [140, 390]) and $88 (95% CI [31, 146]) higher payer-related costs, respectively.

3.3.1.3 Total Costs

For those in the unilateral group, total payer-related costs were $145 (95% CI [56, 234]) and $196 (95% CI [51, 341]) higher for patients with moderate and severe disease, respectively. In the bilateral group, compared to patients with mild NTG, adjusted total payer-related healthcare costs were $125 (95% CI [68, 181]) and $348 (95% CI [$207, $488]) higher for those with moderate and severe NTG, respectively.

We did not find laterality to be a significant effect modifier for any cost component as it relates to the impact of disease severity on payer-related costs (Table 5).

3.3.2 Patient Related Costs

Patient-related costs tended to follow a similar trend as payer-related costs; however, patient-related costs were uniformly lower than those attributed to payers.

3.3.2.1 Office Visits

In the unilateral cohort, the average (SD) annual costs for patients with mild disease were $108 ($134) and $91 ($110) for OAG and NTG-related office visits, respectively. Those with mild disease in the bilateral cohort had similar averages.

Patient-related costs were only significantly higher, amongst both cohorts, for patients with severe compared to those with mild disease. For the unilateral cohort, patients with severe disease had higher out-of-pocket (OOP) costs for OAG-related visits ($58, 95% CI [27, 143]) and NTG-related visits ($42; 95% CI [16, 68]) annually. Similarly, those in the bilateral group had higher annual OOP costs for OAG-related visits ($24; 95% CI [5, 43]) and NTG-related visits ($32; 95% CI [16, 49]) for patients with severe compared to those with mild disease.

3.3.2.2 Glaucoma Prescriptions

A diagnosis of mild, unilateral severity was associated with an average (SD) OOP prescription spending of $119 ($168) and $131 ($185) in the unilateral and bilateral cohort, respectively, given that they had at least one prescription claim. In the unilateral group, only patients with severe disease had significantly higher annual prescription OOP spending ($40; 95% CI [7, 72]) compared to the referent. A moderate or severe diagnosis in the bilateral cohort was associated with additional $36 (95% CI [20, 52]) and $87 (95% CI [57, 117]) of OOP costs annually, respectively, when compared to patients with mild disease.

3.3.2.3 Total Costs

Total OOP costs for patients with mild disease, on average (SD), was $188 ($208) and $192 ($217) for the unilateral and bilateral cohorts, respectively. In the unilateral group, only patients with severe NTG had a significantly higher OOP cost compared to those with mild NTG ($80;

CI 95% [40, 120]). In the bilateral group, total OOP costs were significantly higher for both the patients with moderate ($52; 95% CI [35, 69]) and severe ($121; 95% CI [87, 155]) disease. Laterality was only found to be an effect modifier for total OOP costs for patients with moderate severity.

4 Discussion

4.1 Results Summary

We evaluated the cost and HCRU of patients with NTG over levels of disease severity, stratified into two cohorts, bilateral and unilateral disease. Patients with more severe diagnoses in both cohorts consistently experienced a greater burden of HCRU and costs. Payer costs followed a similar trend with an even greater effect size in most cases.

Patients with severe disease were only estimated to experience an increase in any office visit by approximately 0.9 visits annually, at most. This may not be considered clinically significant; however, for patients with visual impairments, any increase in office visits could create an additional burden, both economically and psychologically, for both patients and their caregivers. The most notable increases in HCRU were tied to glaucoma-related prescription use. We found that patients with severe, bilateral disease, filled over two additional prescriptions annually when compared to their mild counterparts and accounted for 111 extra days of supply of glaucoma medications.

Patient-related healthcare costs were significantly higher for all components when comparing those with severe disease to patients with mild NTG. The largest estimate demonstrated that total OOP costs was $121 greater annually for patients with severe, bilateral disease, compared to those with mild disease in the same cohort. Payers of these patients face an additional $348 annually. Alone, annual additional costs of $121 for patients and $348 for payers are meaningful. These costs are magnified by the fact that the US is expected to have 3 million people with POAG by 2020, and one Japanese study estimated that 92% of these cases were attributed to NTG.[6,11]

Though no cost or utilization studies have been published for patients with NTG, results from other studies examining broader classifications of glaucoma, including glaucoma suspect, ocular hypertension, and all open angle glaucoma, largely coincide with our findings. One such study by Traverso et al. agreed with our findings – describing patients with more severe disease as having greater total costs, with medication expenditure accounting for approximately half of that cost.[7] Another study by Lee et al. described a similar trend in resource utilization for patients with glaucoma.[10] Patients in this study with more severe glaucoma had higher counts for office visits and medication use compared to patients with a less severe diagnosis. Both studies mentioned used chart reviews to acquire their data as well as broad classifications of glaucoma.

Much work has been done to understand the HCRU and costs attributed to patients with glaucoma; however, less is known about patients with NTG, specifically. Our research is the first to estimate annual HCRU and costs for those patients.

4.2 Strengths and Limitations

Our data set does not include vision insurance plans and therefore is likely to miss many routine services for patients that anticipate the need for these services, year-to-year. Further, our data only represents Medicare supplemental and those otherwise commercially insured. So, our elderly population is not representative of a true Medicare population nor does it reflect patients enrolled in Medicaid. All of these limitations are likely to bias our estimates towards the null. Further, these estimates are likely understating the true burden of disease, and do not account for indirect costs incurred by patients, or direct and indirect costs realized by caregivers.

Another limitation may be the miscoding of ophthalmic prescription medications. Glaucoma medications are frequently packaged within bottles or droppers. Often our data represented a fill of a particular drop as a one-day supply. Therefore, reporting the days' supply for glaucoma medications potentially biases our estimate towards the null as well. For this reason, we reported both days' supply and drug fills in our resource utilization estimates.

A major strength of this study relies on a more exacting 7-digit medical code introduced the ICD-10 updates, which allowed us to stratify our patients not only by severity but also by disease

laterality. Disease laterality became an important factor in understanding potential interactions in our data and provide a more comprehensive characterization and comparison of our patient population.

4.3 Conclusion

Our results suggest that patient burden is higher for those with severe and moderate disease compared to those with mild NTG. The excess burden is not only attributed to additional HCRU, but also by a higher financial burden, which accompanies their higher resource use. Patients were not alone in harboring burden as payers experienced a much larger financial burden from patients with severe and moderate disease compared to those with mild NTG. Most of the cost differences can be attributed to additional prescription burden.

As noted above, these estimates are likely understating the true burden of disease, and do not account for indirect costs incurred by patients, or direct and indirect costs realized by caregivers. As such, our estimates should serve as a minimum estimate for HCRU and costs of US patients 40 years and older diagnosed with normal tension glaucoma.

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Figure 1. Attrition Diagram

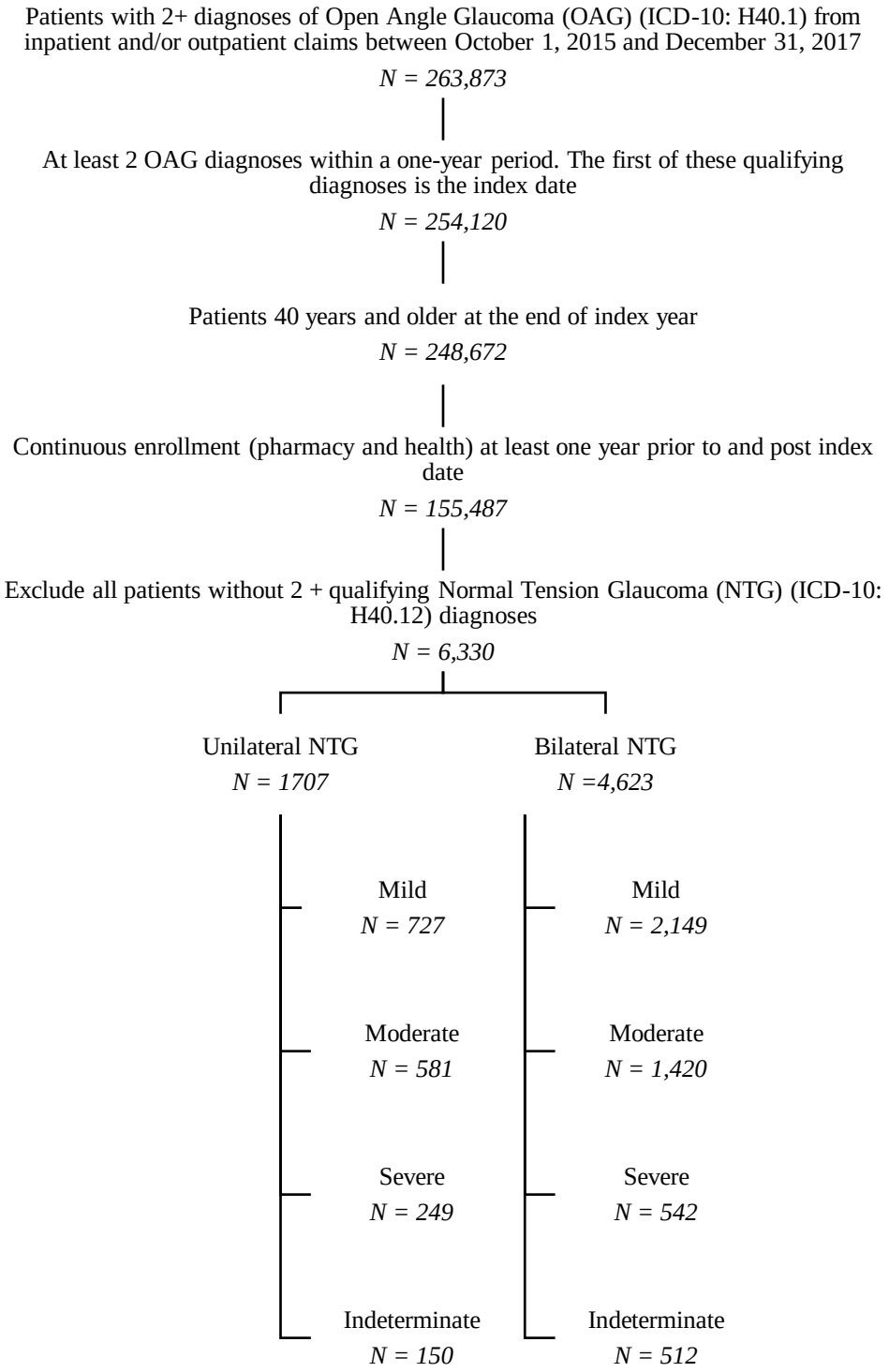

Figure 2. Study Timeline

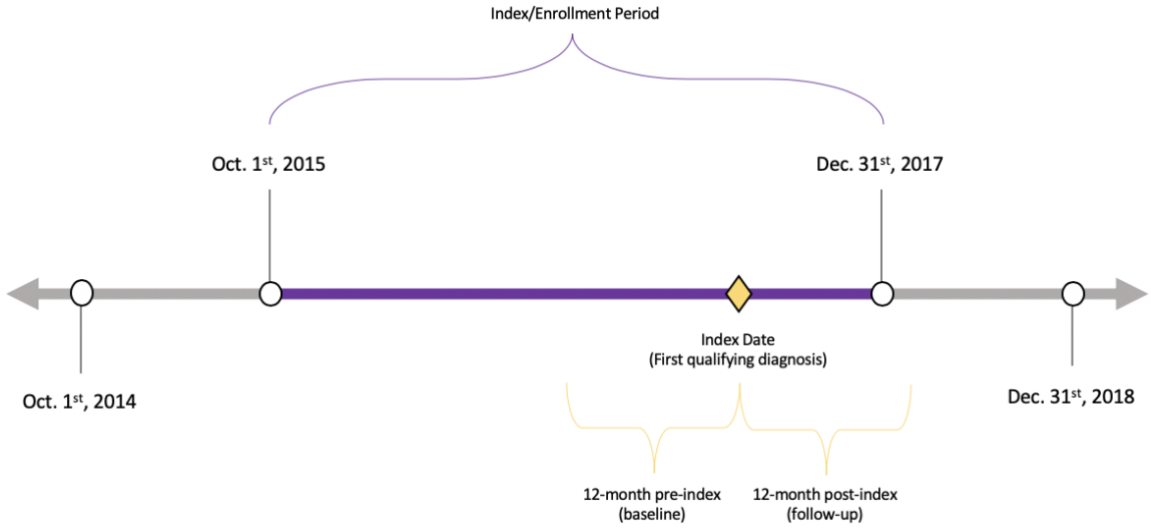

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Table 1. Clinical and Demographic Characteristics of Patients with NTG Stratified by Disease Laterality and Severity

	Unilateral				Bilateral			
	Mild (n = 727)	Moderate (n = 581)	Severe (n = 249)	Indeterminate (n = 150)	Mild (n = 2149)	Moderate (n =1420)	Severe (n = 542)	Indeterminate (n = 512)
Demographic Characteristics								
Age Group, *n (%)*								
40 - 44 y	13 (1.8)	10 (1.7)	4 (1.6)	3 (2.0)	52 (2.4)	20 (1.4)	9 (1.7)	9 (1.8)
45 - 49 y	32 (4.4)	23 (4.0)	7 (2.8)	6 (4.0)	118 (5.5)	49 (3.5)	14 (2.6)	27 (5.3)
50 - 54 y	50 (6.9)	48 (8.3)	17 (6.8)	15 (10.0)	188 (8.7)	85 (6.0)	36 (6.6)	49 (9.6)
55 - 59 y	112 (15.4)	74 (12.7)	37 (14.9)	26 (17.3)	348 (16.2)	192 (13.5)	58 (10.7)	76 (14.8)
60 - 64 y	159 (21.8)	112 (19.3)	42 (16.9)	29 (19.3)	473 (22.0)	265 (18.7)	87 (16.1)	98 (19.1)
65 - 69 y	80 (11.0)	47 (8.1)	20 (8.0)	13 (8.7)	231 (10.7)	135 (9.5)	55 (16.1)	59 (11.5)
70 -74 y	94 (12.9)	62 (10.7)	22 (8.8)	18 (12.0)	218 (10.1)	157 (11.1)	57 (10.1)	60 (11.7)
≥ 75 y	187 (25.7)	205 (35.3)	100 (40.2)	40 (26.7)	521 (24.2)	517 (36.4)	226 (41.7)	134 (26.2)
Age Years, *mean (SD)*	66.7. (11.9)	68.3 (12.3)	69.6 (12.9)	66.5 (12.2)	65.6 (11.9)	69.1 (12.3)	70.9 (13.2)	66.5 (12.2)
Gender								
Male, *n (%)*	280 (38.5)	258 (44.4)	102 (40.9)	61 (40.7)	870 (40.9)	585 (41.2)	229 (42.3)	221 (43.2)
Geographic Region, *n (%)*								
Northeast	172 (23.7)	139 (23.9)	55 (22.1)	37 (24.7)	505 (23.5)	377 (26.5)	139 (25.6)	112 (21.9)
North Central	215 (30.0)	176 (30.3)	91 (36.5)	30 (20.0)	600 (27.9)	364 (25.6)	161 (29.7)	97 (18.9)
South	220 (30.3)	178 (30.6)	71 (28.5)	55 (36.7)	773 (36.0)	487 (34.3)	170 (31.4)	203 (39.6)
West	119 (16.4)	88 (15.1)	32 (12.9)	28 (18.7)	269 (12.5)	191 (13.5)	72 (13.3)	100 (19.5)

Type of Insurance, *n (%)*								
Basic	192 (26.4)	160 (27.5)	82 (32.9)	27 (18.0)	472 (22.0)	366 (25.8)	162 (29.9)	123 (24.1)
PPO/EPO	351 (48.3)	273 (47.0)	120 (48.2)	75 (50.0)	1113 (51.8)	732 (51.5)	268 (49.5)	246 (48.0)
Other	184 (25.4)	148 (25.5)	47 (18.8)	48 (32.0)	564 (26.2)	332 (22.6)	112 (20.6)	143 (28.0)
Clinical Characteristics								
Prevalence of Comorbid Conditions, *n (%)*								
Non-exudative AMD	43 (5.9)	50 (8.6)	19 (7.6)	13 (8.7)	168 (7.8)	111 (7.8)	62 (11.4)	38 (7.4)
Exudative AMD	12 (1.7)	7 (1.2)	7 (2.8)	7 (4.7)	20 (0.9)	23 (1.6)	11 (2.0)	8 (1.6)
Diabetic Retinopathy	6 (0.8)	8 (1.4)	2 (0.8)	3 (2.0)	40 (1.9)	23 (1.6)	14 (2.6)	16 (3.1)
Anxiety	47 (6.5)	32 (5.5)	10 (4.0)	10 (6.7)	141 (6.6)	104 (7.3)	26 (4.8)	26 (5.1)
Depression	40 (5.5)	35 (6.0)	11 (4.4)	10 (6.7)	146 (6.8)	95 (6.7)	29 (5.4)	33 (6.4)
CCI Score, *n (%)*								
0	456 (62.7)	376 (64.7)	160 (64.3)	87 (58.0)	1323 (61.6)	867 (61.1)	317 (58.5)	303 (59.2)
1	120 (16.5)	85 (14.6)	29 (11.6)	30 (20.0)	347 (16.1)	209 (14.7)	82 (15.1)	85 (16.6)
2	84 (11.6)	61 (10.5)	30 (12.0)	18 (12.0)	281 (13.1)	183 (12.9)	84 (15.5)	77 (15.0)
3+	67 (9.2)	59 (10.2)	30 (12.0)	15 (10.0)	198 (9.2)	161 (11.3)	59 (10.9)	47 (9.2)
CCI Score, *mean (SD)*	0.85 (1.6)	0.80 (1.5)	0.9 (1.6)	0.85 (1.4)	0.82 (1.4)	0.89 (1.5)	0.94 (1.6)	0.84 (1.3)

Insurance categories were collapsed for succinctness. Preferred/Exclusive Preferred Organizations = PPOs and EPOs were collapsed together; Basic = Basic/Major Medical and Comprehensive; Other = CDHP, HDHP, POS, and HMO.

Table 2. Healthcare Resource Utilization Counts Stratified by Disease Laterality

Outcome	Unilateral				Marginal Counts					
					Moderate		Severe		Indeterminate	
	Mild (n = 727)	Moderate (n = 581)	Severe (n = 249)	Indeter-minate (n = 150)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)
OAG related OP visits‡, *n*										
# of visits, *mean (SD)*	4.36 (2.24)	4.51 (2.39)	4.94 (2.73)	4.46 (2.92)	0.15 (-0.08, 0.38)	0.16 (-0.07, 0.39)	**0.57*** (0.26, 0.89)**	**0.60*** (0.28, 0.91)**	0.10 (-0.26, 0.48)	0.07 (-0.30, 0.45)
NTG related OP visits as a subset of OAG OP visits, *n*										
# of visits, *mean (SD)*	3.65 (1.44)	(1.	4.05 (1.82)	3.70 (1.90)	0.20 (-0.01, 0.42)	0.20 (-0.01, 0.41)	**0.40** (0.12, 0.69)**	**0.43** (0.14, 0.72)**	0.06 (-0.28, 0.40)	0.06 (-0.28, 0.41)
Glaucoma related prescriptions, *n*†										
# patients with >=1, *n (%)*	707 (97.2)	568 (97.8)	243 (97.8)	147 (98.0)						
# unique fills, *mean (SD)*	5.35 (3.66)	6.62 (4.69)	6.33 (4.14)	5.85 (3.84)	**1.27*** (0.80, 1.75)**	**1.19*** (0.72, 1.67)**	**0.98** (0.35, 1.6)**	**0.92** (0.30, 1.53)**	0.50 (-0.25, 1.25)	0.51 (-0.22, 1.28)
# days' supply, *mean (SD)*	253.95 (171.99)	283.20 (201.78)	295.43 (213.47)	256.17 (161.12)	**29.25* (3.01, 55.49)**	26.16 (-0.18, 52.50)	**41.47* (5.20, 77.75)**	**40.65* (4.35, 76.94)**	2.22 (-38.56, 42.99)	2.16 (-39.07, 43.40)

	Bilateral				Marginal Counts					
					Moderate		Severe		Indeterminate	
	Mild (n = 2149)	Moderate (n = 1420)	Severe (n = 542)	Indetermi nate (n = 512)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)
OAG related OP visits, *n*										
# of visits, *mean (SD)*	4.10 (2.06)	4.43 (2.35)	5.03 (2.95)	4.29 (2.36)	**0.33*** (0.19, 0.47)**	**0.29*** (0.15, 0.44)**	**0.93*** (0.72, 1.14)**	**0.87*** (0.66, 1.08)**	0.19 (-0.01, 0.39)	0.18 (-0.02, 0.38)
NTG related OP visits as a subset of OAG OP visits, *n*										
	3.51	3.76	4.15	3.62	**0.25***	**0.24***	**0.63***	**0.61***	0.10	0.10

# of visits, *mean (SD)*	(1.43)	(1.60)	(2.10)	(1.62)	**(0.12, 0.38)**	**(0.11, 0.37)**	**(0.45, 0.82)**	**(0.42, 0.81)**	(-0.08, 0.29)	(-0.08, 0.29)
Glaucoma related prescriptions, *n*†										
# patients with >=1, *n (%)*	2096 (97.5)	1390 (97.9)	530 (97.8)	487 (95.1)						
# unique fills, *mean (SD)*	5.93 (3.98)	6.62 (4.73)	8.75 (6.18)	6.10 (4.36)	**0.69*** (0.37, 1.00)**	**0.55*** (0.24, 0.87)**	**2.82*** (2.28, 3.35)**	**2.54*** (2.01, 3.07)**	0.16 (-0.28, 0.62)	0.16 (-0.30, 0.62)
# days' supply, *mean (SD)*	256.14 (158.50)	293.10 (187.82)	380.87 (270.11)	279.44 (186.38)	**36.96*** (21.05, 52.87)**	**29.39*** (13.38, 45.39)**	**124.73*** (96.58, 152.87)**	**111.28*** (83.47, 139.09)**	23.30 (-0.29, 46.89)	18.23 (-5.50, 41.95)

*p < 0.05, **p < 0.01, ***p < 0.001

Normal tension glaucoma, NTG, is a subset of an open angle glaucoma diagnosis

Glaucoma related prescriptions were defined as any prescription with an indication for glaucoma

‡All visit-related metrics were estimated using generalized linear models with a Poisson distribution and a margins command to return counts, using "Mild" as the reference category

† Prescription metrics were estimated using a negative binomial model with margins to return counts, using "Mild" as the reference category

Adjusted models controlled for age, sex, geographical region, insurance type, and CCI

Note that all inpatient values were 0 and therefore inpatient claims were excluded from the reported analysis

All patients were considered users given the selection criteria and therefore the number of patients in the outpatient claims analysis reflects 100% of our population

Table 3. Healthcare Costs for Patient with Unilateral Disease

Outcome	Unilateral Disease				Marginal Costs					
					Moderate		Severe		Indeterminate	
	Mild (n = 727)	Moderate (n = 581)	Severe (n = 249)	Indeterminate (n = 150)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)
OAG related OP visits, *mean (SD)*										
Per User										
Patient Related Costs	$108.01 ($134.29)	$116.95 ($157.11)	$152.77 ($206.38)	$108.44 ($134.29)	8.30 (-8.64, 25.23)	11.39 (-4.86, 27.65)	**47.70** (19.19, 76.20)**	**58.21*** (26.51, 89.90)**	-0.82 (-26.85, 25.22)	-1.78 (-25.36, 21.81)
Payer Related Costs	$202.16 ($399.31)	$226.16 ($439.19)	$206.81 ($330.98)	$254.32 ($526.89)	19.12 (-27.68, 65.93)	19.95 (-132.80, 172.71)	7.17 (-53.13, 67.46)	29.16 (-110.15, 168.48)	51.45 (-35.00, 137.89)	16.70 (-50.33, 83.73)
NTG related OP visits as a subset of all OAG OP visits, *mean (SD)*										
Per User										
Patient Related Costs‡	$91.18 ($109.93)	$96.29 ($123.64)	$123.58 ($181.74)	$92.91 ($155.15)	5.01 (-9.35, 19.38)	7.72 (-6.24, 21.68)	**33.98** (10.57, 57.40)**	**42.32** (16.22, 68.42)**	1.07 (-21.62, 23.76)	0.13 (-20.67, 20.92)
Payer Related Costs‡	$157.32 ($338.73)	$171.18 ($328.58)	$162.70 ($261.92)	$177.86 ($249.05)	15.16 (-22.19, 52.51)	22.18 (-21.11, 65.46)	7.01 (-41.38, 55.41)	23.37 (-39.03, 85.77)	20.94 (-42.25, 84.12)	15.73 (-49.99, 81.45)
Glaucoma related prescriptions, *mean (SD)*										
Per User										
Patient Related Costs	$118.87 ($168.26)	$133.56 ($161.38)	$155.06 ($192.68)	$90.07 ($122.14)	15.78 (-5.66, 37.22)	12.02 (-9.04, 33.07)	**38.96* (6.52, 71.40)**	**39.32* (6.88, 71.75)**	**-30.55* (-57.01, -4.09)**	**-28.83* (-55.48, -2.18)**
Payer Related Costs	$275.60 ($504.96)	$411.73 ($879.54)	$450.78 ($770.14)	$246.52 ($548.61)	**146.81** (56.96, 236.66)**	**144.54** (51.29, 237.79)**	**189.49** (53.13, 325.85)**	**193.65** (47.08, 340.22)**	-30.79 (-134.51, 72.92)	-29.07 (-133.35, 75.21)
Per Patient										
Patient Related Costs	$96.63 ($158.62)	$110.80 (155.32)	$130.15 ($185.46)	$70.86 ($114.39)	14.17 (-3.31, 31.65)	12.85 (-4.38, 30.07)	**33.52* (6.55, 60.49)**	**35.07* (7.92, 62.21)**	**-25.77* (-46.18, -5.36)**	**-23.79* (-44.21, -3.36)**
Payer Related Costs	$224.05 ($467.75)	$341.57 ($815.81)	$378.37 ($724.54)	$193.93 ($496.59)	**117.53** (46.20, 188.86)**	**117.79** (43.85, 191.73)**	**154.32** (44.13, 264.52)**	**159.00** (40.99, 277.03)**	-30.12 (-107.76, 47.52)	-26.63 (-104.99, 51.73)

Total Costs, *mean (SD)* **Per User**										
Patient Related Costs	$187.81 ($207.54)	$207.09 (204.64)	$253.73 ($275.61)	$163.77 ($196.04)	19.11 (-4.73, 42.94)	23.11 (-0.02, 46.25)	**67.94*** (30.14, 105.75)**	**80.10*** (40.22, 119.99)**	-24.83 (-57.38, 7.71)	-20.06 (-51.16, 11.03)
Payer Related Costs	$381.37 ($585.75)	$512.75 ($892.09)	$541.07 ($789.40)	$371.80 ($580.57)	**132.97** (51.59, 214.35)**	**145.24** (56.39, 234.09)**	**160.18** (42.50, 277.85)**	**196.13** (51.64, 340.62)**	-9.49 (-116.52, 97.54)	-15.34 (-121.11, 90)

*p < 0.05, **p < 0.01, ***p < 0.001
Payer costs were identified by the net payment variable
Patient costs were identified by the total of one's copay, coinsurance, and deductible
'Per User' Refers to all patients that used the resource of concern whereas 'Per Patient' refers to all patients whether or not they were counted as utilizers. Notably, all patients were users of office visits by design and therefore the distinction is only relevant for prescription claims.
Bold values indicate a p-value < 0.05
Estimates were generated as margins using generalized linear models with a gamma distribution
Models were adjusted for age, sex, CCI score, region, and insurance plan type unless otherwise noted
‡ Adjusted for age, sex, and CCI

Table 4. Healthcare Costs for Patients with Bilateral Disease

Outcome	Bilateral Disease				Marginal Costs					
					Moderate		Severe		Indeterminate	
	Mild (n = 2149)	Moderate (n = 1420)	Severe (n = 542)	Indeterminate (n = 512)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)
OAG related OP visits, *mean (SD)*										
Per User										
Patient Related Costs‡	$112.28 ($164.23)	$117.26 ($170.73)	$133.64 ($176.15)	$117.22 ($185.03)	4.51 (-6.78, 15.81)	5.39 (-6.51, 17.29)	**22.43* (4.50, 40.37)**	**24.01* (4.86, 43.16)**	5.55 (-10.92, 22.02)	6.69 (-10.83, 24.22)
Payer Related Costs‡	$177.86 ($501.01)	$206.81 ($461.30)	$278.87 ($599.39)	$208.83 ($372.50)	30.00 (-2.19, 62.19)	29.51 (-2.40, 61.43)	**84.39** (27.49, 141.28)**	**85.54** (28.40, 142.69)**	26.98 (-20.07, 74.04)	25.70 (-20.72, 72.12)
NTG related OP visits as a subset of all OAG OP visits, *mean (SD)*										
Per User										
Patient Related Costs•	$90.97 ($114.70)	$95.27 ($132.17)	$107.03 ($144.84)	$90.12 ($133.60)	4.87 (-4.10, 13.85)	**13.84** (4.48, 23.20)**	**17.67* (3.64, 31.71)**	**32.30*** (15.54, 49.07)**	-0.86 (-13.28, 11.56)	1.13 (-10.53, 12.79)
Payer Related Costs†	$131.91 ($429.69)	$143.81 ($310.65)	$191.41 ($422.60)	$151.60 ($261.99)	13.99 (-12.71, 40.68)	14.38 (-11.32, 40.08)	**64.39** (15.71, 113.07)**	**65.88** (18.40, 113.36)**	21.08 (-19.51, 61.67)	21.51 (-17.63, 60.65)
Glaucoma related prescriptions, *mean (SD)*										
Per User										
Patient Related Costs	$131.07 ($185.07)	$161.23 ($210.63)	$202.98 ($246.14)	$130.28 ($157.51)	**32.30*** (16.41, 48.18)**	**36.37*** (20.42, 52.32)**	**77.36*** (49.53, 105.19)**	**87.19*** (57.25, 117.13)**	-1.43 (-22.13, 19.27)	0.72 (-19.74, 21.19)
Payer Related Costs	$349.08 ($605.61)	$421.55 ($680.88)	$561.72 ($992.88)	$279.21 ($570.01)	**78.83** (25.77, 131.89)**	**88.45** (30.96, 145.95)**	**229.11** (131.75, 326.47)**	**265.29*** (140.42, 390.17)**	-30.51 (-44.71, 105.72)	15.81 (-57.79, 89.41)
Per Patient										
Patient Related Costs	$100.57 ($171.46)	$135.00 (201.71)	$174.52 ($238.86)	$96.19 ($146.94)	**34.29*** (21.27, 47.31)**	**37.47*** (24.34, 50.80)**	**73.81*** (49.57, 98.06)**	**83.42*** (56.34, 110.49)**	-4.52 (-19.35, 10.31)	-3.22 (-17.85, 11.40)
Payer Related Costs	$267.86 ($550.60)	$352.97 ($642.15)	$428.96 ($940.98)	$279.21 ($570.01)	**85.65*** (43.08, 128.23)**	**92.46*** (46.09, 138.82)**	**215.33*** (132.10, 298.55)**	**237.72*** (132.72, 342.96)**	11.57 (-41.08, 64.23)	2.58 (-49.44, 54.61)
Total Costs, *mean (SD)*										
Per User										

Patient Related Costs†	$197.54 ($216.95)	$230.28 ($255.34)	$253.73 ($275.61)	$163.77 ($196.04)	**39.07*** (22.48, 55.65)**	**52.39*** (35.48, 69.29)**	**91.41*** (62.76, 120.06)**	**120.87*** (86.60, 155.15)**	-5.46 (-26.20, 15.29)	0.45 (-19.50, 20.41)
Payer Related Costs†	$399.77 ($707.41)	$496.78 ($754.52)	$674.36 ($1065.68)	$430.81 ($643.62)	**99.67*** (47.95, 151.39)**	**145.24*** (56.39, 234.09)**	**279.67*** (180.69, 378.64)**	**347.53*** (207.17, 487.89)**	32.60 (-36.05, 101.26)	30.39 (-37.63, 98.38)

*p < 0.05, **p < 0.01, ***p < 0.001
Payer costs were identified by the net payment variable
Patient costs were identified by the total of one's copay, coinsurance, and deductible
'Per User' Refers to all patients that used the resource of concern whereas 'Per Patient' refers to all patients whether or not they were counted as utilizers. Notably, all patients were users of office visits by design and therefore the distinction is only relevant for prescription claims.
Bold values indicate a p-value < 0.05
Estimates were generated as margins using generalized linear models with a gamma distribution
Models were adjusted for age, sex, CCI score, region, and insurance plan type unless otherwise noted
† Adjusted for age, sex, CCI score, and insurance plan type
‡ Adjusted for sex, CCI, and region
⋆ Adjusted for age, sex, and CCI

Table 5. Effect of Laterality on Association Between HCRU and Costs

HCRU†		Estimates (95% CI) Moderate	Severe	Indeterminate
OAG related OP visits		-0.27	-0.07	-0.07
		(-0.4, 0.15)	(-0.64, 0.11)	(-0.48, 0.37)
NTG related OP visits as a subset of all eye related OP,		-0.04	-0.2	-0.02
		(-0.28, 0.21)	(-0.54, 0.14)	(-0.40, 0.38)
Glaucoma related prescriptions‡				
	Drug Fills	1.12*	0.82**	1.07
		(1.02, 1.23)	(0.73, 0.93)	(0.92, 1.24)
	Days' Supply	0.98	0.81**	0.93
		(0.88, 1.10)	(0.70, 0.94)	(0.78, 1.12)

COSTS		Estimates (95% CI) Moderate	Severe	Indeterminate
OAG related OP visits				
	Patient Related	0.98	0.86	1.08
		(0.82, 1.18)	(0.67, 1.10)	(0.81, 1.44)
	Payer Related	1.08	1.44	0.92
		(0.81, 1.45)	(0.96, 2.10)	(0.58, 1.44)
NTG related OP visits as a subset of all eye related OP				
	Patient Related	0.95	1.09	0.95
		(0.82, 1.11)	(0.89, 1.35)	(0.74, 1.21)
Total Healthcare Costs				
	Patient Related	0.87*	0.87	0.89
		(0.76, 0.99)	(0.73, 1.04)	(0.72, 1.09)
	Payer Related	1.04	0.78	0.86
		(0.84, 1.29)	(0.59, 1.05)	(0.62, 1.21)

*p < 0.05, **p < 0.01, ***p < 0.001
†Estimated as margins unless otherwise noted
‡Estimated as Incident Rate Ratios
Models not represented here could not converge and therefore were not presented; Payer Related NTG related OP visits and Glaucoma Related Prescription Models

7 Appendix.

Procedure Codes and Their Description for OAG-related Procedures

Procedure Code	Procedure Description
'66170' '66172'	Trabeculectomy
66180' '66185' ‘L8612’, '66183' '0192T'	Aqueous shunt or Express shunt
65855'	Laser Trabeculoplasty
'65820'	Trabectome
0191T', ‘0253T', ‘0191T + 0376T’	iStent
'66710' '66711'	Ciliary body destruction/ECP
0176T' '0177T' '66174' '66175' ‘65850’	Canaloplasty or GATT or KDB
‘0449T’ ‘0450T’	Xen
‘0474T’	Cypass

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