Characterizing the Healthcare Resource Utilization and Costs By Disease Severity Among Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

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Abstract

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Background: Geographic atrophy (GA) is an advanced form of dry age-related macular degeneration (AMD) that affects nearly one million people in the United States (US), and 5 million people worldwide, with no current treatments available to slow or prevent the progression of GA. The disease progression has been shown to be associated with a decline in vision-related quality of life and increased expenditures, particularly in bilateral GA. With considerable interpatient variability in the rate of GA progression due to lesion characteristics, there is no standardized GA severity scale that assesses disease severity and tracks disease progression. Previous research characterizing the burden of GA is scarce, and lacks stratification by lesion type.

Objective: To characterize the incidence and prevalence of GA, and examine incident cases of GA to determine the all-cause resource utilization and direct payer-related medical costs among patients diagnosed with GA in the US, overall and by disease severity.

Methods: A retrospective cohort analysis was conducted using IQVIA PharMetrics Plus administrative claims data from 2015-2018. Patients who were newly diagnosed with GA were identified between October 1, 2016 and June 30, 2017, and eligible patients were classified by disease severity (early or intermediate AMD, GA without subfoveal involvement, GA with subfoveal involvement) and laterality based on ICD-10 codes. Baseline characteristics were evaluated during the 1-year period prior to the index date. Follow up was 12 months (defined by continuous health plan enrollment), in which the outcomes, such as healthcare resource utilization (HCRU) and direct costs, were evaluated. Negative binomial regression models were used to estimate the number of outpatient, emergency department, and inpatient visits, and linear regression was used to estimate average inpatient hospitalizations. Generalized linear models with gamma distribution and a log-link function were used to analyze healthcare costs. Cost data were adjusted to 2019 dollars. All models adjusted for patient demographics and comorbidities. Cost models also adjusted for baseline HCRU and costs in the 12-months prior to index diagnosis.

Results: A total of 14,421 patients were included in the study: 20% had unilateral GA, of which 93.2% had early or intermediate AMD, 3.8% had GA without subfoveal involvement, and 2.9% had GA with subfoveal involvement. Eighty percent had bilateral GA, of which 96.7% had early or intermediate AMD, 1.7% had GA without subfoveal involvement, and 1.5% had GA with subfoveal involvement. The mean number of OP, ED, and IP visits per GA patient was 20.9, 3.7, and 1.4, respectively. The mean cost per GA patient was $2,829 and $11,533 for the patient and

payer, respectively. Patients with bilateral GA had, on average, higher unadjusted payer-related total healthcare costs and costs in each healthcare setting; however, significant associations did not persist after adjustment for baseline characteristics for costs and HCRU.

Conclusion: Results from this real-world claims analysis suggest that patients with more severe forms of GA neither consume significantly more healthcare resources nor accrue greater costs. This may be due to the fact that this study identified all-cause, rather than disease-specific or disease-related, resources and costs. Specific contributing factors to the burden of GA were not explored. As such, further research is warranted to identify the increase in overall disease burden in patients with more severe levels of GA due to having more comorbidities, such as falls and fractures.

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1. Introduction

Geographic Atrophy (GA) is a late stage manifestation of dry age-related macular degeneration (AMD) that affects nearly one million people in the United States (US) and five million people worldwide, and leads to significant visual function impairment and eventual blindness.[1] Characterized by the formation of drusen, or pigmentary changes at the macula, which is the part of the eye that provides sharp, central vision needed for seeing objects clearly, AMD is the most common cause of irreversible central vision loss in elderly patients in the US,[2] and consists of two major advanced forms that are mutually exclusive: dry, atrophic, or nonexudative AMD and wet, neovascular, or exudative AMD.[3] The nonexudative form is more prevalent, with nearly 85% of patients with AMD having the dry form,[1] and involves a slow progressive degeneration of the retina, while the exudative form is less frequent but is responsible for 90% of acute blindness due to choroidal neovascularization (CNV). Patients with CNV may develop atrophy after a few years, and similarly, patients with atrophy can also eventually develop CNV.

Though advanced stages of AMD consisting of GA and neovascular AMD can coexist due to common risk factors, GA occurs specifically through loss of the retinal pigment epithelium with associated loss of choriocapillaries, and scotomas, or blind spots, can develop.[3] Strong risk factors for GA include advanced age, history of smoking, and high levels of oxidative stress damaging the macula.[1] Patients with GA will experience ocular symptoms, in which a dark spot may appear in their central or peripheral vision, colors seem dull or washed out, their vision becomes less sharp or detailed, particularly in the dark.

GA can be categorized into three main levels of severity: early to intermediate GA, advanced atrophic dry AMD without subfoveal involvement, and advanced atrophic dry AMD with subfoveal involvement.[5] Patients with early or intermediate dry AMD may progress to GA without subfoveal involvement, which does not involve the center of the fovea, or GA with subfoveal involvement, which does involve the center of the fovea. While severe visual acuity loss occurs more slowly and less commonly in patients with GA and GA often spares the fovea until late in the source of the disease, GA involving the foveal center causes approximately 10% of all AMD-related visual loss. Patients with GA that does not involve the central fovea may

have relatively good distance visual acuity yet manifest a substantially decreased ability to perform near visual tasks, such as reading.[5]

Unlike exudative AMD, which can effectively be treated with anti-vascular endothelial growth factor drugs,[4] there are currently no approved treatments to prevent the onset and progression of GA.[1] Patients are given non-drug related treatments, such as nutritional supplements, vitamins, and advice on lifestyle modifications. Previous research has suggested that GA is associated with a significant decline in vision-related quality of life in patients, in areas such as driving, reading, recognizing faces, and watching television, and a greater risk for developing or experiencing cognitive dysfunction.[1,6-11] Disease progression has also been shown to be associated with increased annual Medicare expenditures.[12]

The current literature surrounding GA, specifically, is sparse; with many existing studies in late AMD lacking discrimination between neovascular and non-exudative AMD. Our aim is to expand the scope of previous studies to better understand the burden of GA in a nationally representative sample of Americans aged 50 years and older, as AMD is a leading cause of blindness in people age 50 and older.[1] We consider three severity levels of GA: early or intermediate AMD, GA without subfoveal involvement, and GA with subfoveal involvement. We aim to characterize the incidence and prevalence of GA, and examine incident cases of GA across the different severity levels, for which we will study their association with HCRU and cost, and assess whether the association is affected by laterality. We hypothesize that patients with more severe GA have significantly higher rates of healthcare resource utilization (HCRU), particularly in the emergency department or inpatient settings due to comorbidities, and total direct health care costs.

2. Methods

2.1 Data Source

The IQVIA PharMetrics Plus Electronic Medical Record database is a closed database of fully adjudicated pharmacy and medical claims data for more than 130 million unique enrollees across the US with commercial insurance, Medicare, and Medicaid. PharMetrics Plus was used to

provide de-identified patient-level data on patient demographics, comorbidities, healthcare resource utilization and costs.

2.2 Sample Selection and Study Cohorts

We performed a retrospective cohort study consisting of six newly diagnosed patient cohorts: (1) those with unilateral early or intermediate dry AMD, (2) those with unilateral GA without subfoveal involvement, (3) those with unilateral GA with subfoveal involvement (4) those with bilateral early or intermediate dry AMD, (5) those with bilateral GA without subfoveal involvement, and (6) those with bilateral GA with subfoveal involvement. As the ICD-10 codes for AMD involved both laterality and staging, cohorts were organized into three different severity levels within the unilateral and bilateral groups to ensure accurate documentation and characterization.

All patients were required to have at least 12 months of continuous enrollment data before and after the index date, and to be at least 50 years of age as of the index date. The first date of incident diagnosis of unilateral or bilateral GA was considered the index date, and patients were required to not have any evidence of GA diagnosis in the 12 months preceding the index date. Patients were excluded if they had nonexudative AMD with unspecified stage or eye, or prior history of GA.

2.3 Study Period

The study population was classified into six cohorts by disease severity between October 1, 2016 to June 30, 2017 (ie. the selection or enrollment period). Unilateral GA was defined as having one of the three severity levels in one eye only during the entirety of the follow up period, with the index date set as the date of first diagnosis of unilateral GA, provided that patients did not progress during the follow up period. Bilateral GA was defined as not only having GA in both eyes, but referring to the more severe eye, with the index date being the date of diagnosis of bilateral GA, if patients were diagnosed with having GA in both eyes on the same day, or the date at which the fellow eye developed GA, if at a later time. For instance, if a patient had early or intermediate AMD in the left eye but later developed GA without subfoveal involvement in the right eye, then the index date would be the date at which the patient developed GA without

subfoveal involvement, and the patient would be classified as having bilateral GA without subfoveal involvement, and thus, all outcomes would be calculated based on the individual having GA in both eyes. Similarly, if a patient were diagnosed with GA without subfoveal involvement in both eyes, the patient would also be classified as having bilateral GA without subfoveal involvement and outcomes would be measured identically, provided that neither eye progresses in the postindex period.

As shown in Figure 5.1, we defined the index period as the 9-month period in which patients were newly diagnosed with varying severity levels of unilateral or bilateral GA. Patients were required to have a 12-month preindex (baseline) period and were followed for 12 months.

Baseline characteristics

Baseline characteristics were assessed based on enrollment and claims information during the pre-index period, which for each patient is the standardized 12-month period prior to the index date (Table 6.1). The comorbidity index (e.g. Charlson Comorbidity Index (CCI)) and prevalence of specific comorbid ophthalmic conditions, such as exudative AMD, diabetic retinopathy, and glaucoma, and comorbid psychological conditions, such as depression and anxiety, were also collected.

2.4 Definition of Outcomes

The primary study outcomes included the total outpatient (OP), emergency department (ED), and inpatient (IP) HCRU (Table 6.2) and average IP length of stay (Table 6.3), all of which were reported from adjudicated medical and pharmacy claims. Direct health care costs were calculated as an overall total cost per patient in each cohort and for each cost element (i.e. OP, ED, IP visit), from the payer perspective, which included total payments made by the health plan to health care providers; and from the patient perspective, which included any copays, coinsurance, and deductibles. Costs shown in Table 6.4 were all-cause costs, and not disease-specific costs, and were adjusted for inflation using the 2019 medical care services of the Consumer Price Index.

2.5 Statistical Analyses

2.5.1 **Study Characteristics**

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

2.5.2 **Incidence and Prevalence of GA**

New incident cases of GA were identified within the index period by identifying newly diagnosed patients, and excluding individuals with a history of GA in the pre-index period, as shown in Figure 5.2. As shown in Figure 5.3, prevalent cases were simply calculated as the total number of patients with GA in the index period, regardless of whether they had been previously diagnosed.

2.5.3 **Healthcare Resource Utilization**

Multiple regression models were used to study the association between GA severity level and HCRU, using early-intermediate AMD as the reference group. A negative binomial regression model was used to estimate differences in number of OP, ED, and IP admissions in the one-year follow up period, as this model accounts for overdispersion in count data.[14] We fit the following unadjusted model to estimate incidence rate ratios (IRR), which characterize the relationship between disease severity and HCRU:

$$Log(\lambda) = \beta_0 + \beta_1 x_{GA\ without\ subfoveal\ involvement} + \beta_2 x_{GA\ with\ subfoveal\ involvement}$$

where λ is the incidence rate of OP, ED, IP admissions, and the exponentiated slope, β_1, gives the unadjusted IRR for those with GA without subfoveal involvement compared to those with early or intermediate AMD, and β_2 gives the unadjusted IRR for those with GA with subfoveal involvement compared to those with early or intermediate AMD.

We also fit a model adjusting for potential confounders including demographic characteristics, (age, sex, geographic region, insurance type, CCI) and both ophthalmic and psychologic comorbidities, separately for unilateral and bilateral patients.

$$Log(\lambda) = \beta_0 + \beta_1 x_{GA\ without\ subfoveal\ involvement} + \beta_2 x_{GA\ with\ subfoveal\ involvement} + \beta_3 x_{age} + \beta_4 x_{gender} + \beta_5 x_{region} + \beta_6 x_{insurance} + \beta_7 x_{CCI}$$

An ordinary least squares (OLS) model was used to study the association between GA severity level and inpatient length of stay (LOS):

$$E(LOS) = \beta_0 + \beta_1 x_{GA\ without\ subfoveal\ involvement} + \beta_2 x_{GA\ with\ subfoveal\ involvement} + \beta_3 x_{age} + \beta_4 x_{gender} + \beta_5 x_{region} + \beta_6 x_{insurance} + \beta_7 x_{CCI} + \beta_8 x_{laterality}$$

Furthermore, a negative binomial regression model was used to assess whether the association between HCRU and severity of GA is affected by laterality, as shown below:

$$Log(\lambda) = \beta_0 + \beta_1 x_{GA\ without\ subfoveal\ involvement} + \beta_2 x_{GA\ with\ subfoveal\ involvement} + \beta_3 x_{age} + \beta_4 x_{gender} + \beta_5 x_{region} + \beta_6 x_{insurance} + \beta_7 x_{CCI} + \beta_8 x_{laterality} + \beta_9 x_{GA\ without\ subfoveal\ involvement} x_{laterality} + \beta_{10} x_{GA\ with\ subfoveal\ involvement} x_{laterality}$$

2.5.4 Direct healthcare costs

To study the association between GA severity level and costs, we used a one-part generalized linear model (GLM) with gamma distribution and log-link function. GLM models with gamma distribution are considered to be the most suitable option for the cost data analysis due to the advantage of analyzing both the mean and variance functions on the original dollar scale and addressing the frequently right-skewed distribution of cost data.[15-18] The incremental costs between cohorts were obtained by applying the method of recycled predictions to the GLM model.[19]

Finally, similar to the negative binomial regression model shown above which tests for an interaction, we also fit a multivariate GLM to assess whether the association between cost and severity of GA affected by laterality. This model is similar to the previous GLM assessing the association between either HCRU or cost and laterality, with the interaction term between severity and laterality, as shown below:

$$Log(\lambda) = \beta_0 + \beta_1 x_{GA\ without\ subfoveal\ involvement} + \beta_2 x_{GA\ with\ subfoveal\ involvement} + \beta_3 x_{age} + \beta_4 x_{gender} + \beta_5 x_{region} + \beta_6 x_{insurance} + \beta_7 x_{CCI} + \beta_8 x_{laterality} + \beta_9 x_{GA\ without\ subfoveal\ involvement} x_{laterality} + \beta_{10} x_{GA\ with\ subfoveal\ involvement} x_{lateralityA\ involvement}$$

For all statistical comparisons, a two-sided 5% significance level was used. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for constructing the analytic dataset and STATA 15 software (StataCorp LP Lakeway, TX, US) was used for the statistical analyses.

All data were de-identified to protect patient privacy in compliance with the Health Insurance Portability and Accountability Act of 1966 (HIPAA). 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 Study Characteristics

A total of 14,421 patients with GA were included in the study. The mean age was 67.2 years, and 58% were female. Early or intermediate AMD was the most common clinical form of GA, regardless of laterality (96% of all patients). The impact of comorbidity was greater in individuals with more severe GA. with disease progression. Demographic and clinical characteristics are shown in Table 6.1.

In terms of the prevalence of comorbid conditions, patients with unilateral GA had higher rates of nonexudative AMD, compared to patients with bilateral GA, though the rates increased across severity levels.

3.2 Prevalence and Incidence of GA

The prevalence of GA was 2.22 cases per 10,000 individuals, and there were 2.21 new incident cases per 10,000 individuals.

3.2 Healthcare Resource Utilization, by Severity Level and Laterality

The mean number of OP, ED, and IP visits for patients in the one-year follow-up period is shown in Table 6.2, across severity and laterality. The unadjusted number of visits in each care setting was higher in patients with bilateral GA, compared to those with unilateral GA. Results of the adjusted HCRU from the negative binomial model, which computes inter-cohort differences as IRR, however, suggest that having bilateral GA without subfoveal involvement was associated with an 11% decrease in outpatient visits compared to those with bilateral early or intermediate AMD (adjusted IRR 0.89, 95% confidence interval (CI) (0.79, 1.00), p = 0.045). No other significant associations or differences were observed between the different GA severity levels and HCRU.

After adjusting for all possible confounders, the mean number of OP visits was estimated to be 0.216 visits lower for patients with bilateral GA without subfoveal involvement, compared to patients with unilateral GA without subfoveal involvement (-0.216, 95% CI (-0.400, -0.032), p=0.021).

The differences in inpatient mean LOS for patients with more severe forms of GA were not significant, compared to early or intermediate AMD, regardless of laterality.

3.3 Direct Healthcare Costs, by Severity Level and Laterality

The mean unadjusted and adjusted direct healthcare costs are shown in Table 6.3, by increasing severity and laterality. The mean total costs during the follow-up period per GA patient were $2,829 and $11,533 for the patient and payer, respectively. The unadjusted payer-related mean costs are higher in patients with bilateral GA with subfoveal involvement, compared to bilateral early or intermediate AMD in all care settings, though this trend is not apparent in patients with unilateral GA.

After adjusting for baseline characteristics and comorbidities, the mean payer-related costs were not significantly higher in patients with more severe forms of bilateral GA. The adjusted patient-related outpatient costs, payer-related inpatient and total healthcare costs were, however,

significantly lower in the more severe unilateral GA with subfoveal involvement group, compared to the unilateral early or intermediate AMD group (-$162, 95% CI (-$317, -$7), p-0.041; -$11,018, 95% CI (-$16,669, -$5,367), p=0.01; -$3,760, 95% CI (-$7,112, -$408), p=0.028, respectively).

After adjusting for all possible confounders, the interaction between disease severity and laterality was significant with respect to patient-related ED costs comparing those with subfoveal involvement vs. early or intermediate AMD in the bilateral GA group vs. the unilateral GA group (-$2.394, 95% CI (-4.701, -0.086), p=0.042), and payer-related IP costs comparing those with subfoveal involvement vs. early or intermediate AMD in the bilateral GA group vs. the unilateral GA group ($2.022, 95% CI (0.040, 4.004), p=0.046).

4. Discussion

4.1 Results Summary

We evaluated the relationship between increasingly severe forms of GA and disease burden in a US population that is primarily commercially insured. The findings of this study suggest that patients with incident cases of GA still have an unmet need as evidenced by the high level of utilization and costs in these patients who are generally older and more frail. However, we observed no significant association between increasing severity levels of GA and HCRU and costs. With respect to laterality, our study found that patients with bilateral GA without subfoveal involvement had fewer OP visits than those with unilateral GA without subfoveal involvement, and patient-related ED costs and payer-related IP costs were different in those with bilateral vs. unilateral GA with subfoveal involvement. Overall, this finding was inconsistent with our hypothesis.

Regardless of laterality and severity, patients who are diagnosed with GA are seen almost exclusively in the outpatient setting, due to the fact that there is no current treatment for GA. As such, we observed no significant change in number of outpatient or office visits in these patients, or costs associated with being treated in the outpatient setting, as expected since no treatment can be given in the outpatient setting to slow or prevent the progression of any severity level of GA.

As such, the number of outpatient visits then would be expected, and have been shown, to be relatively stable and consistent across severity and laterality. However, where we expected to see a change was in the utilization and costs within the emergency department or inpatient setting, as patients with more severe levels of GA in one or both eyes are, on average, at least 70 years old and have more comorbidities.

In addition, we expected the rates of nonexudative AMD to be higher in patients with bilateral GA, compared to unilateral GA, since patients with bilateral GA are older and would have had the underlying disease longer. Many patients with GA are known to concurrently have nonexudative AMD, which can be treated pharmacologically. The results were contrary to what we expected, despite ensuring that patients with unilateral GA who progressed to bilateral GA during the follow-up period were excluded. Despite the higher rates of nonexudative AMD in unilateral patients, however, the average total healthcare costs remain higher in patients with bilateral GA.

4.2 References to Previous Research

Though very few studies exist in the literature that examine or describe the burden of nonexudative AMD, specifically, our findings were inconsistent with the few existing studies published, of which one retrospective cohort study using a multicenter electronic medical record database suggested that high levels of visual impairment are associated with losses in mobility and independence in patients with bilateral GA.[1] Patients with milder levels of impairment at the time of GA diagnosis have been shown to still have a high risk of vision loss over time. This study did not compare patients with unilateral vs bilateral GA and looked at disease-specific burden, whereas we assessed total disease burden and as a result, we did not find a consistent trend in increased utilization of resources in patients with bilateral GA. This published study paves way, however, for future work to consider the association between high levels of visual impairment with losses in mobility and independence, which can encompass other comorbidities that are debilitating, such as falls and fractures. Additionally, another retrospective study using Medicare claims data which examined the costs of disease progression among individuals with AMD over time.[21] In this context, disease progression referred to patients who developed either dry or wet AMD from previously never having AMD. Patients with dry AMD had average annual Medicare

ophthalmic expenditures at least three times more than those without AMD, and those with wet AMD had costs at least five-fold more than that of those with the dry form. This study differs in that patients with dry AMD were compared to those without AMD, and dry AMD was not further stratified by severity levels.

The current literature suggests that given that among older adults with AMD, increased visual impairment was significantly associated with an increased incidence of falls and other injuries, and numerous studies have suggested that AMD is associated with impaired postural stability, mobility and gait, and a greater physiological fall risk profile.[20] However, only a limited number of studies have explored the relationship between AMD an falls, and none have identified the visual risk factors for falls and injuries specifically in the AMD population.[20]

In our study, we expected an increase in overall disease burden with increased disease severity, as patients may have progressively more ED visits or hospitalizations with disease progression due to an increased risk of other comorbidities, such as falls and fracture; however, this was not apparent in the data. As such, further research is warranted to assess specific drivers of HCRU and costs, particularly the incidence of falls and fractures during the follow-up period.

4.3 Strengths and Limitations

Strengths of this study include the use of real-world data to identify patients with differing severity and laterality levels of GA. The PharMetrics Plus claims data provides visibility into the full 7-digit ICD-coding, which allows for clear distinction between patients who are unilaterally vs. bilaterally affected.

The results of this study should be interpreted cautiously due to several limitations. This study used claims data from a primarily commercial insurance database. The mean age of patients in our dataset was 70 years. As such, our dataset may not entirely capture those patients with more severe forms of GA. With a lack of Medicare and Medicaid representation in the database, the conclusions drawn from this study may not be generalizable beyond the study sample. This discrepancy may be because of the process by which inpatient stays and costs were estimated. The method used to identify costs attributed to hospitalized patients was not standardized and

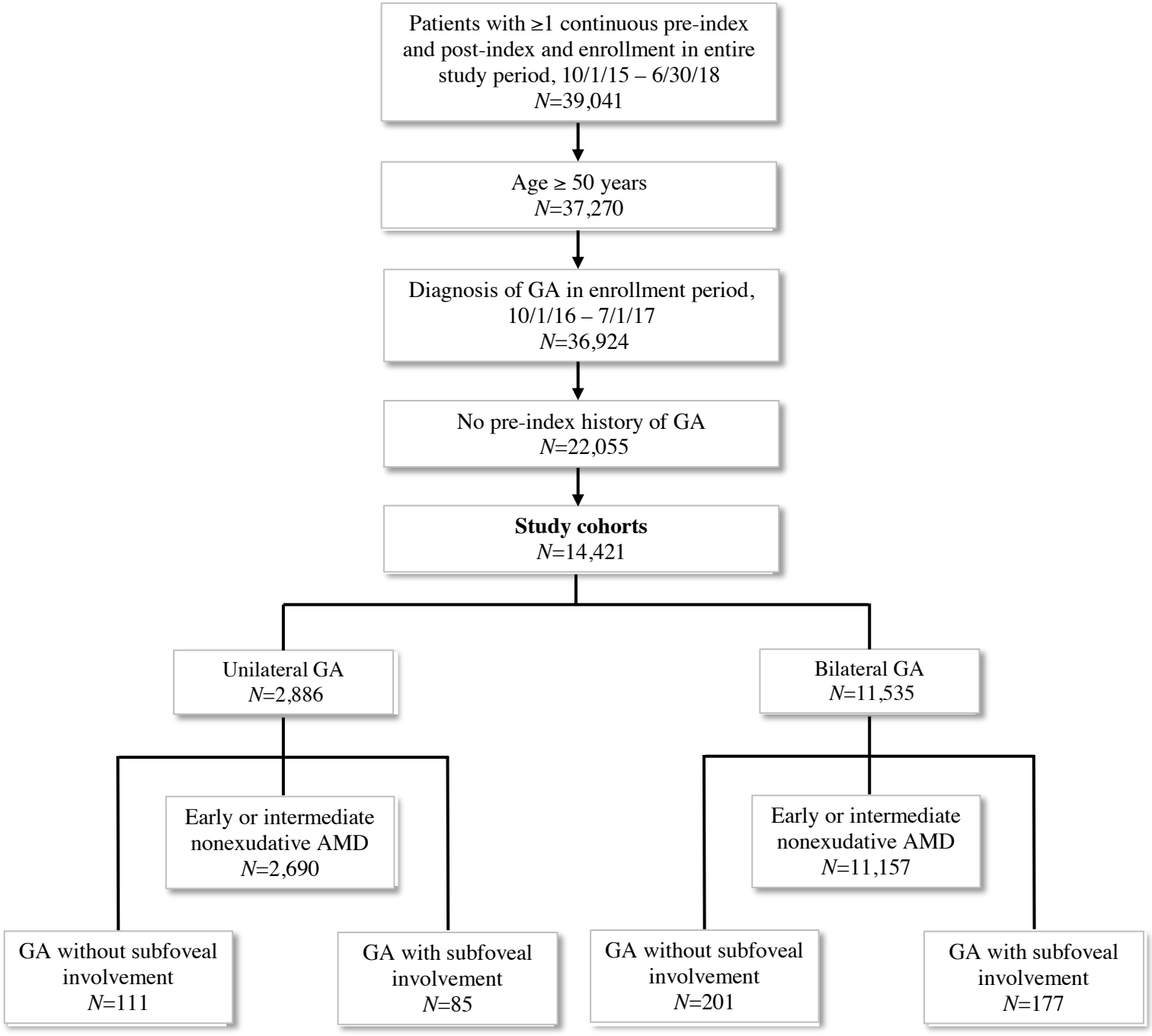
clear in the IQVIA data, where inpatient claims were defined as those with a confinement number. If a patient were hospitalized following an ED visit, the ED visit would be bundled in and not appropriately separated, and the number of ED visits and associated ED costs may be underrepresented. Sample size was also a major limitation, as it may be hard to characterize the rate of visits in the different care settings and associated costs when only a very small portion of the study population (less than 20 individuals) had ED visits and hospitalizations. Furthermore, in both patients with unilateral and bilateral GA, 13,847 patients (96%) were classified as having early-intermediate AMD, while 574 patients (4%) had more severe forms of GA. Finally, the 12-month follow up period may not be long enough to observe changes in costs and outcomes with a slow progressing disease such as GA.

4.4 Future Work

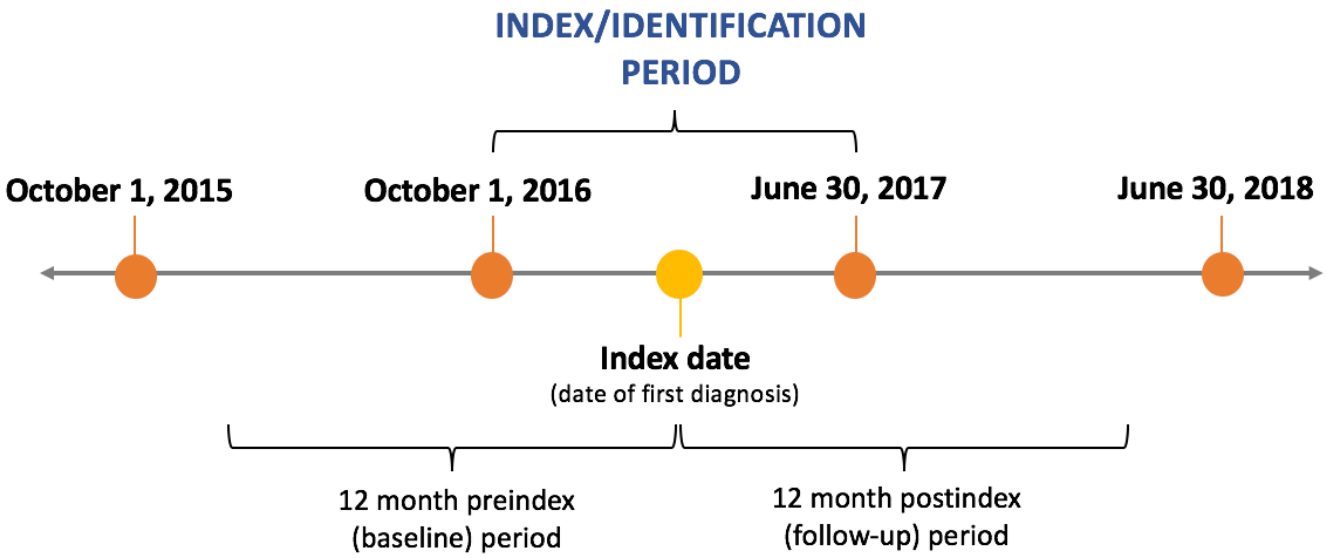
We plan to conduct secondary analyses to study the association between GA severity level and the frequency of falls and fractures. We plan on using multivariable logistic regression models to estimate the odds ratio of falls and fractures between cohorts, using early or intermediate AMD as the referent category. Also, to better capture the frequency of OP, ED, and IP visits, and account for very few patients going to the ED or being hospitalized, we will dichotomize the patient-level outcomes from counts into binary indicators of whether or not at least one visit took place. We plan on using logistic regression to assess the association between these dichotomized HCRU outcomes and disease severity. Finally, in this study, only patients with unilateral or bilateral GA whose severity level did not change over the follow-up period were included. Future analyses will consider including GA severity level as a time-varying exposure.

5. List of Figures

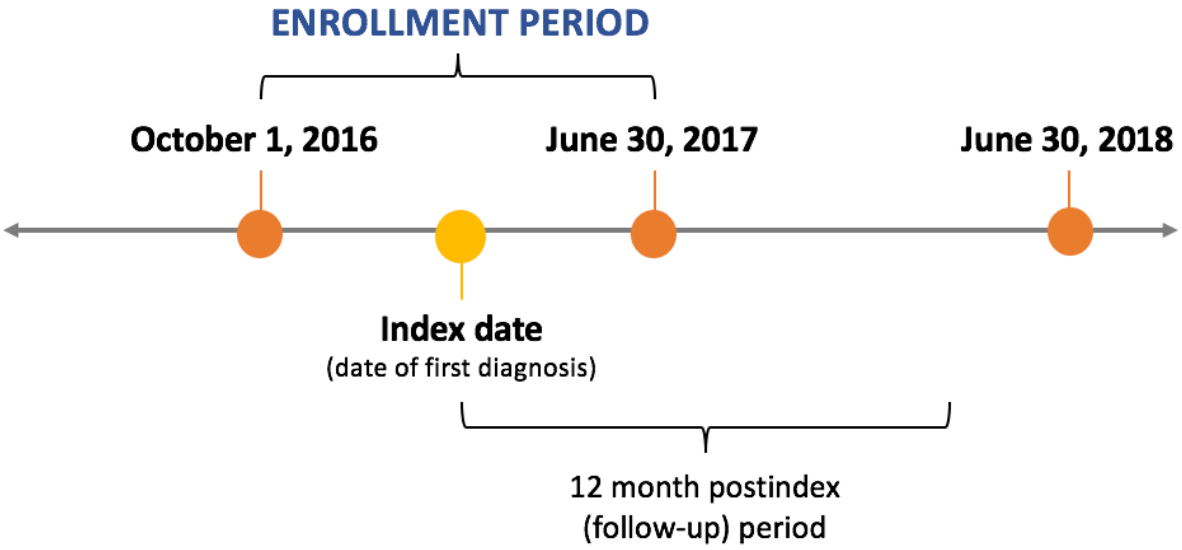
5.1 Study Cohort Criteria



5.2 Study Timeline for Incidence Analysis and Definition of Study Period



5.3 Study Timeline for Prevalence Estimate



6. List of Tables

6.1 Demographic and Clinical Characteristics Among Patients with GA, by Severity at Baseline

Characteristic	UNILATERAL			BILATERAL		
	Early/int AMD (n=2,690)	**GA w/o subfoveal** (n=111)	**GA w/ subfoveal** (n=85)	**Early/int AMD** (n=11,157)	**GA w/o subfoveal** (n=201)	**GA w/ subfoveal** (n=177)
Demographic						
Age, *mean (SD)*	65.4 (9.6)	69.5 (10.5)	72.8 (10.5)	67.4 (9.6)	71.2 (11.0)	74.3 (10.8)
Female, *n (%)*	1427 (53.1)	60 (54.1)	41 (48.2)	6575 (58.9)	140 (69.7)	118 (66.7)
Geographic region, *n (%)*						
Northeast	804 (29.9)	31 (27.9)	22 (25.9)	3300 (29.6)	83 (41.3)	53 (29.9)
Midwest	736 (27.4)	38 (34.2)	31 (36.5)	2610 (25.4)	40 (19.9)	35 (19.8)
South	708 (26.3)	34 (30.6)	19 (22.4)	2877 (25.8)	48 (23.9)	32 (18.1)
West	442 (16.4)	8 (7.2)	13 (15.3)	2370 (21.2)	30 (14.9)	57 (32.2)
Type of insurance, *n (%)*						
Commercial*	2027 (75.4)	86 (77.5)	61 (71.8)	8732 (78.3)	136 (67.7)	100 (56.5)
Medicaid	16 (0.6)	2 (1.8)	2 (2.4)	98 (0.9)	5 (2.5)	2 (1.1)
Medicare Advantage	293 (10.9)	12 (10.8)	13 (15.3)	1748 (15.7)	46 (22.9)	63 (35.6)
Medicare Supplemental	122 (4.5)	11 (9.9)	9 (10.6)	357 (3.2)	10 (5.0)	11 (6.2)
Prevalence of comorbid conditions, *n (%)*						
Wet AMD	632 (23.5)	44 (39.6)	56 (65.9)	345 (3.1)	27 (13.4)	41 (23.2)
Diabetic retinopathy	95 (3.5)	5 (4.5)	4 (4.7)	530 (4.8)	18 (9.0)	6 (3.4)
Glaucoma	573 (21.3)	18 (16.2)	16 (18.8)	2687 (24.1)	51 (25.4)	41 (23.2)
Anxiety	488 (18.1)	18 (16.2)	13 (15.3)	1993 (17.9)	41 (20.4)	40 (22.6)
Depression	397 (14.8)	15 (13.5)	11 (12.9)	1744 (15.6)	37 (18.4)	37 (20.9)
CCI Score, *n (%)*						
0	1368 (50.9)	39 (35.1)	32 (37.7)	5033 (45.1)	76 (37.8)	57 (32.2)
1	553 (20.6)	25 (22.5)	18 (21.2)	2432 (21.8)	44 (21.9)	37 (20.9)
2	334 (12.4)	23 (20.7)	9 (10.6)	1413 (12.7)	22 (11.0)	27 (15.3)
3+	435 (16.2)	24 (21.6)	26 (30.6)	2279 (20.4)	59 (29.4)	56 (31.6)
CCI Score, *mean (SD)*	1.16 (1.74)	1.55 (1.74)	1.75 (2.04)	1.38 (1.90)	1.75 (2.11)	2.07 (2.37)

Note: SD, Standard deviation; CCI, Charlson Comorbidity Index
*Follows US Census regions: Northeast = New England, Mid-Atlantic states; Midwest = East North Central, West North Central states; South = South Atlantic, East South Central, West South Central states; West = Mountain, Pacific states
**Includes self-insured patients

6.2 Total Healthcare Resource Utilization

Outcome	UNILATERAL			Incident rate ratios (IRR)*			
				GA w/o subfoveal		GA w/ subfoveal	
	Early/int AMD (n=2,690)	GA w/o subfoveal (n=111)	GA w/ subfoveal (n=85)	Unadjusted (95% CI)	Adjusted (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)
OP visits, *n*	48,632	2,227	1,554	1.014 (0.844, 1.217)	0.928 (0.786, 1.095)	1.014 (0.844, 1.217)	0.928 (0.786, 1.095)
# of patients, *n (%)*	2,348	99	74				
# of visits, *mean (SD)*	20.71 (18.66)	22.49 (20.06)	21.00 (16.50)				
ED visits, *n*	1,141	69	45	0.776 (0.497, 1.210)	0.652 (0.420, 1.011)	0.776 (0.497, 1.210)	0.652 (0.420, 1.011)
# of patients, *n (%)*	295	18	15				
# of visits, *mean (SD)*	3.87 (4.38)	3.83 (3.24)	3.00 (3.42)				
IP admissions, *n*	336	26	15	0.844 (0.490, 1.455)	0.677 (0.396, 1.157)	0.844 (0.490, 1.455)	0.677 (0.396, 1.157)
# of patients, *n (%)*	208	17	11				
# of admissions, *mean (SD)*	1.62 (1.52)	1.53 (1.18)	1.36 (0.67)				
Length of stay, *mean (SD)*	7.02 (13.89)	9.47 (12.89)	7.55 (11.34)				

Outcome	BILATERAL			Incident rate ratios (IRR)*			
				GA w/o subfoveal		GA w/ subfoveal	
	Early/int AMD (n=11,157)	GA w/o subfoveal (n=201)	GA w/ subfoveal (n=177)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
OP visits, *n*	198,930	2,992	3,061	0.953 (0.838, 1.083)	**0.888 (0.791, 0.997)**	1.016 (0.892, 1.157)	0.974 (0.865, 1.096)
# of patients, *n (%)*	1,359	149	143				
# of visits, *mean (SD)*	21.08 (19.00)	20.08 (17.94)	21.41 (19.30)				
ED visits, *n*	4,894	97	122	1.171 (0.872, 1.573)	1.158 (0.878, 1.527)	1.027 (0.796, 1.324)	0.916 (0.720, 1.165)
# of patients, *n (%)*	1,359	23	33				
# of visits, *mean (SD)*	3.60 (3.38)	4.22 (3.27)	3.70 (2.42)				
OP visits, *n*	1,595	37	41	0.873 (0.627, 1.218)	0.861[b] (0.621, 1.194)	1.325 (0.963, 1.822)	1.165[b] (0.852, 1.593)
# of patients, *n (%)*	979	26	19				
# of admissions, *mean (SD)*	1.63 (1.33)	1.42 (0.90)	2.16 (2.57)				
Length of stay, *mean (SD)*	7.21 (12.94)	6.85 (8.77)	13.21 (27.36)				

Note: OP, Outpatient; ED, Emergency department; IP, Inpatient; SD, Standard deviation; 95% CI, 95% confidence interval. Bold denotes P < .05.
*Estimated using negative binomial regression model, using "Early/int AMD" as the reference category, controlling for age, sex, geographical region, insurance type, CCI, and ocular/psychological comorbidities.
[b]Not adjusted for insurance and gender.

6.3 Regression-adjusted differences in length of stay during 12-month follow-up period between patients with differing severity levels of GA

Variables	Coefficient[a]	95% CI	p-value
Unilateral GA			
GA without subfoveal involvement	0.0274	-0.0174, 0.0722	0.23
GA with subfoveal involvement	0.0001	-0.0520, 0.0521	0.998
Bilateral GA			
GA without subfoveal involvement	0.0287	-0.0093, 0.0667	0.139
GA with subfoveal involvement	-0.0127	-0.0510, 0.0257	0.518

"Early/int AMD" is reference category.
[a]Estimated using ordinary least squares model. Bold denotes P < .05. Adjustments made for age, sex, geographical region, insurance type, CCI, and ocular/psychological comorbidities.

6.4 Total Direct Healthcare Costs

Outcome	UNILATERAL						
	Early/int AMD (n=2,690)	GA w/o subfoveal (n=111)	GA w/ subfoveal (n=85)	GA w/o subfoveal		GA w/ subfoveal	
				Adjusted Difference (95% CI)		Adjusted Difference (95% CI)	
Outpatient visits, *mean (SD)*							
Patient related*	657 (1,045)	575 (766)	447 (820)	-34	(-210, 141)	**-162**	**(-317, -7)**
Payer-related†	2,055 (3,532)	1,882 (2,379)	1,574 (1,725)	-50	(-751, 650)	-555	(-1175, 72)
ED visits, *mean (SD)*							
Patient related	165 (486)	36 (82)	355 (1,344)	-113[a]	(-298, 72)	4,782[a]	(-6278, 15842)
Payer-related	339 (593)	171 (221)	178 (197)	-120	(-298, 58)	-114	(-324, 96)
Inpatient admissions, *mean (SD)*							
Patient related	471 (1,145)	368 (591)	831 (1,966)	-70[a]	(-546, 405)	305[a]	(-855, 1466)
Payer-related	12,164 (38,005)	9,459 (14,911)	2,082 (4,052)	4,153[a]	(-14,768, 23,075)	**-11,018[a]**	**(-16,669, -5367)**
Total healthcare cost, *mean (SD)*							
Patient related	2,965 (8,192)	1,958 (2,903)	2,025 (5,032)	-771	(-1,721, 179)	-899	(-1938, 139)
Payer-related	11,410 (27,152)	11,410 (18,239)	8,207 (11,639)	1077	(-3,358, 5512)	**-3,760**	**(-7112, -408)**

Outcome	BILATERAL						
	Early/int AMD (n=11,157)	GA w/o subfoveal (n=201)	GA w/ subfoveal (n=177)	GA w/o subfoveal		GA w/ subfoveal	
				Adjusted Difference (95% CI)		Adjusted Difference (95% CI)	
Outpatient visits, *mean (SD)*							
Patient related*	591 (937)	434 (520)	516 (915)	-68.8	(-193, 55)	15	(-33, 163)
Payer-related†	1,871 (3,768)	1,839 (3,183)	2,554 (11,534)	-61	(-543, 421)	381	(-230, 992)
ED visits, *mean (SD)*							
Patient related	96 (396)	53 (95)	77 (218)	99[a]	(-220, 418)	20[a]	(-143, 184)
Payer-related	309 (536)	288 (409)	421 (672)	-34	(-232, 163)	81	(-159, 320)
Inpatient admissions, *mean (SD)*							
Patient related	419 (849)	421 (708)	793 (1,230)	33[b]	(-539, 605)	318[b]	(-781, 1,416)
Payer-related	9,180 (19,221)	12,830 (24,139)	17,926 (32,649)	-328	(-8,752, 8,096)	1,920	(-10,324, 14,165)
Total healthcare cost, *mean (SD)*							
Patient related	2,801 (8,842)	2,371 (5,100)	3,950 (13,533)	-107	(-1,251, 1,037)	549	(-947, 2,045)
Payer-related	11,527 (27,208)	13,672 (29,182)	13,086 (28,269)	758	(-2,786, 4,301)	-344	(-3,820, 3,133)

*Patient-related costs includes patient copay, coinsurance, deductible.

†Payer-related costs includes payer-paid costs.

"Early/int AMD" is reference category. Bold denotes P < .05. Adjustments made for age, sex, geographical region, insurance type, CCI, and comorbidities. Costs shown in 2019 US dollars.

[a]Not adjusted for insurance.

[b]Not adjusted for insurance, gender, geographical region.

6.5 Effect of Laterality on Association Between HCRU and Costs

Outcome - HCRU	Estimate (visits)	p-value	95% CI
OP Visits			
GAw/oSF*Laterality	**-0.216**	0.021	(-0.400, -0.032)
GAw/SF*Laterality	-0.018	0.86	(-0.221, 0.185)
ED Visits			
GAw/oSF*Laterality	-0.074	0.779	(-0.591, 0.443)
GAw/SF*Laterality	0.448	0.147	(-0.157, 1.054)
Inpatient admissions			
GAw/oSF*Laterality	0.199	0.376	(-0.241, 0.638)
GAw/SF*Laterality	0.306	0.194	(-0.156, 0.768)
Outcome - Costs	**Estimate ($)**	**p-value**	**95% CI**
OP Visits			
Patient-related costs			
GAw/oSF*Laterality	-0.095	0.62	(-0.470, 0.280)
GAw/SF*Laterality	0.224	0.285	(-0.187, 0.635)
Payer-related costs			
GAw/oSF*Laterality	-0.007	0.975	(-0.433, 0.419)
GAw/SF*Laterality	0.324	0.178	(-0.147, 0.795)
ED Visits			
Patient-related costs			
GAw/oSF*Laterality	1.556	0.179	(-0.716, 3.827)
GAw/SF*Laterality	**-2.394**	0.042	(-4.701, -0.086)
Payer-related costs			
GAw/oSF*Laterality	0.315	0.562	(-0.748, 1.377)
GAw/SF*Laterality	0.337	0.539	(-0.739, 1.413)
IP Admissions			
Patient-related costs			
GAw/oSF*Laterality	0.843	0.697	(-3.404, 5.089)
GAw/SF*Laterality	0.036	0.989	(-5.006, 5.077)
Payer-related costs			
GAw/oSF*Laterality	0.27	0.75	(-1.389, 1.928)
GAw/SF*Laterality	**2.022**	0.046	(0.040, 4.004)

Early/int AMD" is reference category. Bold denotes P < .05. Adjustments made for age, sex, geographical region, insurance type, CCI, and comorbidities

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8. Appendix

Appendix 1: ICD-10 Codes for Select Conditions and Comorbidities

Condition	ICD-10 Code(s)
Nonexudative AMD	H3531
Nonexudative AMD, right eye	H35311
Nonexudative AMD, right eye, early dry stage	H353111
Nonexudative AMD, right eye, intermediate dry stage	H353112
Nonexudative AMD, right eye, advanced atrophic without subfoveal involvement	H353113
Nonexudative AMD, right eye, advanced atrophic with subfoveal involvement	H353114
Nonexudative AMD, left eye	H35312
Nonexudative AMD, left eye, early dry stage	H353121
Nonexudative AMD, left eye, intermediate dry stage	H353122
Nonexudative AMD, left eye, advanced atrophic without subfoveal involvement	H353123
Nonexudative AMD, left eye, advanced atrophic with subfoveal involvement	H353124
Nonexudative AMD, bilateral eyes	H35313
Nonexudative AMD, bilateral eyes, early dry stage	H353131
Nonexudative AMD, bilateral eyes, intermediate dry stage	H353132
Nonexudative AMD, bilateral eyes, advanced atrophic without subfoveal involvement	H353133
Nonexudative AMD, bilateral eyes, advanced atrophic with subfoveal involvement	H353134
Nonexudative AMD, unspecified eye	H35319
Nonexudative AMD, unspecified eye, early dry stage	H353191
Nonexudative AMD, unspecified eye, intermediate dry stage	H353192
Nonexudative AMD, unspecified eye, advanced atrophic without subfoveal involvement	H353193
Nonexudative AMD, unspecified eye, advanced atrophic with subfoveal involvement	H353194
Exudative AMD	H3532
Diabetic Retinopathy	E10.3, E11.35
Glaucoma	H40
Major Depressive Disorder	F33
Anxiety Disorders	F41

Appendix 2: Variables used in the analysis

Variable	Description	Notes
	Descriptive Variables	
pat_id	Person identifiers	
der_sex	Gender	M=Male; F=Female; U=Unknown
der_yob	Age	Year of birth
pat_region	Region	E=Northeast; S=South; MW=Midwest; W=West; O=Unknown
pay_type	Insurance type	C=Commercial; K=State Children's Health Insurance Program (SCHIP); M=Medicaid; R=Medicare Risk (presently known as Medicare Advantage); S=Self-Insured; T=Medicare Cost (Medicare Supplemental); U=Unknown/Missing; X=RX Only; "-"=No Enrollment
dx_cd; diag_vers_type_id; diag_admit	Medical conditions (primary)	ICD diagnosis code (without decimal); 1=ICD-9; 2=ICD-10
diag1	Medical comorbidity: Exudative AMD	Each record may include up to 12 diagnosis codes (and the admitting diagnosis for inpatient claims)
diag2	Medical comorbidity: Diabetic retinopathy	
diag3	Medical comorbidity: Glaucoma	
diag4	Medical comorbidity: Anxiety	
diag5	Medical comorbidity: Depression	
	Outcome (Resource Use) Variables	
pos (22); from_dt; to_dt	Hospital outpatient visits, number of	22=Outpatient Hospital
pos (23); from_dt; to_dt	Hospital emergency room visits, number of	23=Emergency Room-Hospital
pos (21); from_dt; to_dt	Hospital inpatient stays, number of + total length	21=Inpatient Hospital
	Outcome (Direct Costs) Variables	
pos (22); paid; allowed; deductible; copay; coinsamt; cobamt	Cost of outpatient visits	22=Outpatient Hospital
pos (23); paid; allowed; deductible; copay; coinsamt; cobamt	Cost of ED visits	23=Emergency Room-Hospital
pos (21); paid; allowed; deductible; copay; coinsamt; cobamt	Cost of inpatient visits	21=Inpatient Hospital