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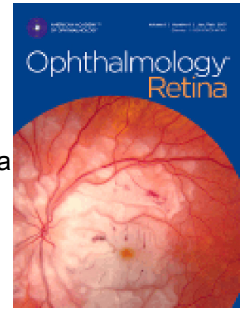
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Direct Ophthalmic Healthcare Resource Use among Geographic Atrophy Patients in a Large Cohort from the United Kingdom

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Running head [58/60 characters]: Health Care Resource Use among Geographic Atrophy Patients

Abbreviations/Acronyms:

AMD = age-related macular degeneration; **CNV** = choroidal neovascularization; **EMR** = electronic medical record; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FFA** = fundus fluorescein angiography; **GA** = geographic atrophy; **ICD** = International Classification of Diseases; **IOP** = intraocular pressure; **IQR** = interquartile range; **nAMD** = neovascular age-related macular degeneration; **NHS** = National Health Service; **OCT** = optical coherence tomography; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

Abstract (350/350 words)

Objective: To estimate the direct ophthalmic health care resource use in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Design: Retrospective analysis of anonymized data derived from electronic medical records acquired at 10 clinical sites in the United Kingdom.

Participants: Patients aged ≥ 50 years with ≥ 1 eye with a clinical record of GA or, for comparison, bilateral early/intermediate AMD. Four subgroups were identified: GA in both eyes (GA : GA); GA in 1 eye, choroidal neovascularization (CNV) in the fellow eye (GA : CNV); GA in 1 eye with early or intermediate AMD in the fellow eye (GA : E); and early/intermediate AMD in both eyes (E : E).

Methods: Electronic medical records were analyzed to derive the median number of visits over the first 2 years following diagnosis of GA or early/intermediate AMD. Clinical tests recorded at visits were used to calculate estimated costs (payer perspective) of monitoring. Analyses were restricted to patients with an initial diagnosis on or after January 1, 2011 to represent present day monitoring and costs associated with AMD.

Main Outcome Measures: Median number of visits and estimated monitoring costs per patient (in £) over the first 2 years among patients with ≥ 2 years of follow-up and in the individual subgroups. Intravitreal treatment costs in the GA : CNV group were excluded.

Results: For all 3 GA subgroups ($n = 1080$), the median number of visits over the first 2 years was 5 and monitoring costs were £460.80 per patient. The GA : CNV subgroup ($n = 355$) had the highest number of visits (median, 15), with a cost of £1581, compared with the GA : E subgroup ($n = 283$; median 4 visits; cost ~£369) and the GA : GA subgroup ($n = 442$; median 3 visits; cost ~£277). Ophthalmic tests were conducted most frequently in the GA : CNV subgroup. Visits and costs in the E : E subgroup ($n = 6079$) were lower.

Conclusions: Resource use in patients with GA varies considerably and is strongly influenced by the concomitant presence of CNV and lack of monitoring strategies for GA.

Geographic atrophy (GA) secondary to age-related macular degeneration (AMD) affects >5 million people worldwide and is associated with profound visual dysfunction and irreversible vision loss as the disease progresses.^{1,2} This currently untreatable disease interferes with everyday activities (such as reading and seeing in low-light conditions) and negatively impacts quality of life.^{2,3} Real-world information on the functional impact and ophthalmic resource use in GA is limited.^{4,5} We have shown through analysis of a multicenter UK electronic medical record (EMR) database that patients with bilateral GA (n = 1901) experience high degrees of visual impairment at levels that impede mobility and affect independence.⁶ In this study, 7% of patients were eligible for UK blindness registration based on visual acuity (VA) in the better-seeing eye at initial GA diagnosis, and 71% of patients had a VA that in the better-seeing eye would have rendered them ineligible to drive.⁶ A further reduction in VA over the subsequent 2 years in better eyes to <70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters resulted in an additional two-thirds of patients becoming ineligible to drive (UK driving standard: Snellen binocular 6/12; US Snellen binocular 20/40). Notably, one-sixth of the included population had a decline in VA to <20 ETDRS letters in the better-seeing eye, thus becoming eligible for blindness registration (UK blindness definition: Snellen 3/60; US Snellen 20/400).⁶ The rate of progression from GA to choroidal neovascularization (CNV) in either eye was ~7% per patient-year.⁶ These data reveal the inexorable progression of vision loss in GA, its strong association with CNV, and a lack of therapies for prevention of progression or amelioration of this condition. Thus, there is a high burden of disease and it will have an associated economic cost to patients, caregivers, and health care providers.

Although the economic burden of advanced AMD has been described in the literature, the majority of studies do not differentiate between GA and neovascular AMD (nAMD), which is characterized by the presence of CNV, or report data derived solely from patients with nAMD.⁷⁻¹¹ Two studies that included both types of advanced AMD reported that resource use costs were more than twice as high for nAMD compared with GA: a large US Medicare population (years 1999–2001),⁹ and a smaller study from Italy (based on data from 1998 and 1999).¹⁰ Because the last 2 decades have seen marked changes in the monitoring of patients with AMD as novel noninvasive

methods of retinal imaging have been introduced, the data acquired in the 1990s are of questionable relevance.

Therefore, the purpose of the present analysis was to estimate the per-patient current direct ophthalmic health care resource use associated with a diagnosis of GA in 1 or both eyes (i.e., clinic visits, estimated costs for monitoring and ophthalmic tests conducted, from a payer [National Health Service; NHS] perspective) to better understand resource consumption and address the economic burden associated with this condition.

Methods

Study Design

The study design has been fully described elsewhere.⁶ Briefly, data collected from 10 NHS clinical sites in the United Kingdom using Medisoft (MediSoft Limited, Leeds, UK),¹² an electronic medical information capture platform, were amalgamated to construct an anonymized, retrospective dataset that included patients seen between October 2000 and February 16, 2016. This EMR database contains mandated data fields that were defined prospectively, thus the data captured are similar to that captured by electronic case report forms used in clinical trials. Classified as a Service Evaluation study, in line with UK NHS National Research Ethics guidance, institutional review board/ethics committee approval was not required, and governance was provided by the NHS hospital service providers, known as Hospital trusts in the UK. The Caldicott Guardian at the Belfast Trust provided overall governance for the study, and a project oversight committee comprising 4 clinical retina specialists, data specialists (IQVIA), and representatives from the funder (Hoffmann-La Roche, Basel, Switzerland) ensured the scientific integrity of the study. The study had the approval of the Caldicott Guardian at each site to allow sharing of anonymized EMR data, and was conducted in accordance with the codes of conduct of the UK NHS regulations for the collection and use of patient-level data (as defined in the Data Protection Act of 1998).⁶

Analysis Populations

Selection criteria for the full cohort of patient data extracted from the UK EMR database has been described previously.⁶ Briefly, patients were aged ≥ 50 years, and patients in the GA subgroups had ≥ 1 eye with a clinical record of GA recorded at any visit and no evidence of CNV in that eye before the first record of GA. Patients in the bilateral early/intermediate subgroup had both eyes meeting the early/intermediate AMD definition at index date (the earliest dated record in the EMR) or fellow eye free from early/intermediate AMD at index date for the study eye. Analyses were restricted to patients with an initial diagnosis on or after January 1, 2011, with ≥ 2 years' follow-up since initial diagnosis. This cutoff date was used so that costs would reflect current practice, particularly that relating to the wider availability and use of spectral-domain optical coherence tomography (OCT).

A study eye and fellow eye were designated for each patient. In patients with bilateral GA (GA : GA) or bilateral early/intermediate AMD (E : E) the eye with the worse VA was designated as the study eye. If both eyes met inclusion criteria and had the same VA, the right eye was designated as the study eye. In patients with GA in only 1 eye at index date, the eye with GA was designated the study eye and the fellow eye was the eye with nAMD (designated as CNV in this study; i.e., GA : CNV) or early/intermediate AMD (GA : E). Important findings from prior analyses of this dataset, including mean change in VA over time, progression to CNV, progression to loss of ≥ 10 or ≥ 15 ETDRS letters, progression to blindness, and progression to loss of driving eligibility for the GA : GA subgroup, have been published previously.⁶

Outcomes

The main outcomes were the median number of visits over the first 2 years following diagnosis of GA in study eye, or following diagnosis of early/intermediate AMD in patients with bilateral early/intermediate AMD, and the clinical tests performed at visits. These were used to calculate the estimated NHS costs for monitoring over 2 years in the 4 patient populations, namely, GA : GA; GA : CNV; GA : E; and E : E.

Statistical Analysis

Number of visits and approximate yearly average cost per patient (in £) was evaluated among those with a minimum of 2 years of follow-up in each of the diagnostic subgroups. A patient was considered to have had 1 visit for a given date if their study eye had ≥ 1 record on that date in any of the following: VA, diagnosis/clinical findings, OCT, or any type of record in the EMR system, including fundus fluorescein angiography (FFA).

Visits related to the study eye were categorized as either a standard monitoring visit at a NHS cost of £92.15 (relating to Healthcare Resource Group service code 130: Ophthalmology; national average unit cost, years 2014–2015) or a retinal tomography visit at a cost of £114.53 (relating to Healthcare Resource Group cost code BZ88A; national average unit cost, years 2014–2015).¹³ Standard monitoring visits included measurements of VA, intraocular pressure (IOP), and/or a record of a diagnosis/clinical findings on a given date. For the purposes of this analysis, visits were classified as retinal tomography visits if either an OCT or FFA finding was recorded on a given date regardless of whether the patient had a record of VA, IOP, or diagnosis/clinical findings. In the UK health care system, NHS costing for visits allows only 1 investigation to drive the tariff, so a visit with both OCT and FFA tests would be billed only as OCT even though the true costs are greater.¹⁴

Results

Patients

The initial dataset from the 10 clinical sites consisted of 83,425 unique patients, of whom 32,655 met the inclusion criteria for the bilateral early/intermediate AMD subgroup, and 4769 met the clinical inclusion criteria for the GA subgroups. Restricting records to those with an index initial diagnosis of GA on or after 2011 and with >2 years of follow-up resulted in 1080 patients with GA available for analysis. Of the GA subgroups, classification by GA status in the 2 eyes of an individual resulted in available data for 442 patients in the GA : GA subgroup, 355 in the GA : CNV subgroup, and 283 in the GA : early/intermediate AMD subgroup (Table 1). A validation exercise on the accuracy of the clinical diagnoses and the effectiveness of the case definition algorithm in

correctly classifying the status of both the study and fellow eyes of each patient has been previously published.⁶

Patients in the GA : GA and GA : CNV subgroup were approximately the same mean (standard deviation [SD]) age (80 [6] and 81 [5] years, respectively), while patients in the GA : early/intermediate subgroup were slightly younger, with a mean (SD) age of 78 (7) years. Females accounted for more than half of the population within each subgroup. Median (interquartile range [IQR]) VA in study eyes at baseline was lower in patients in the GA : GA and GA : early/intermediate AMD subgroups (47 [20–65] and 45 [20–70] ETDRS letters, respectively; US Snellen ~20/125), than in the GA : CNV subgroup (60 [35–73] ETDRS letters; US Snellen ~20/63). Median (IQR) follow-up time was 3 (2–3) years in the GA : GA and GA : early/intermediate groups, and 3 (2–4) years in the GA : CNV subgroup (Table 1).

Direct Ophthalmology-Related Visits and Costs

In the 1080 patients with GA in ≥ 1 eye, the median (IQR) number of visits in the first 2 years of follow up was 5 (2.0–11), with an associated median (IQR) direct cost of £460.80 (£206.70–1068.30). The median (IQR) number of visits was highest in the GA : CNV subgroup (15 [5–21]) and lowest in the GA : GA subgroup (3 [2–5]). Patients in the GA : early/intermediate AMD subgroup had a median (IQR) of 4 (2–6) visits over 2 years (Fig 1).

The estimated median (IQR) monitoring costs over 2 years across GA subgroups were highest for patients in the GA : CNV subgroup (£1581.00 [£483.10–2211.60]). The estimated median (IQR) monitoring costs for patients in the GA : GA subgroup were £276.50 (£184.30–505.50) and for Patients in the GA : early/intermediate AMD subgroup were £368.60 (£184.30–552.90; Fig 1).

We also estimated the costs of monitoring in 6079 patients with bilateral early/intermediate AMD who had at least 2 years of follow up. In this group of patients the median (IQR) number of visits over the first 2 years was 2.0 (0.0–4.0), with an associated median (IQR) direct cost of £184.30 (£0.0 – 391.0) (Fig 1). These costs were lower than those for any of the GA subgroups.

Ocular-Related Tests

The types of monitoring tests recorded for the 4 subgroups over the first 2 years are shown in Figure 2. Visual acuity was the most common test in all subgroups and was most frequently conducted in patients in the GA : CNV subgroup, with a median (IQR) of 14 (5–19) times over the 2-year period. Visual acuity was recorded a median (IQR) of 3 (2–5) times over the 2-year period in patients in both the GA : GA and GA : early/intermediate AMD subgroups, and 3 (2–4) times in the E : E subgroup. Optical coherence tomography was the next most frequently conducted test in the GA : CNV subgroup, and was performed a median (IQR) of 5 (0–12) times over 2 years. Optical coherence tomography and FFA were recorded at a very low frequency across the other subgroups.

Discussion

Because direct ophthalmic health care resource utilization data among patients with GA in clinical practice are limited, we sought to address this knowledge gap by using a large EMR database to calculate direct ophthalmology-related costs in a large cohort of patients who were attenders in 10 clinical sites in the United Kingdom. We calculated that the median (IQR) cost of monitoring patients with GA only in 1 or both eyes was £460.80 (£206.7–1068.3) over 2 years of follow-up following diagnosis. We observed, however, that there was no consistent pattern of care in patients diagnosed with GA only in 1 or both eyes. Our data showed that the number of visits and associated costs among patients with GA with CNV in their fellow eye (GA : CNV) was ~4–5 times higher than those in the GA : GA and GA : E categories. We also calculated the direct monitoring costs associated with a diagnosis of early/intermediate AMD in both eyes, and observed these to be lower than for patients with GA, with a median of only 2 associated visits over the first 2 years following diagnosis.

The economic burden associated with GA in the published literature is scarce, possibly because of inconsistencies with respect to GA diagnosis due to the use of differing grading systems and imaging modalities resulting in variation in terminology,¹⁵ or because GA was only recently granted a diagnosis code (9B75.02) by the World Health Organization.¹⁶ Also, the lack of any

approved therapies for GA has likely resulted in the absence of incentive within the research community to explore costs relating to GA only. Only 2 studies have estimated costs of GA, and in both of these the aim was to quantify resource utilization across a broad spectrum of both early and late AMD, with GA being included opportunistically. In 1 of these studies, which was conducted in Italy between 1998 and 1999, resource utilization and direct medical costs were evaluated in 476 patients aged ≥ 50 years with diagnoses of any AMD, and with follow-up for 1 year. The majority of the patients included in the study had CNV ($n = 285$; 59.9% of the study population), and a smaller proportion ($n = 113$; 23.7%) had early AMD, defined as those with drusen. Those with GA were the smallest group in the study, and accounted for fewer than one-fifth ($n = 78$; 16.4%) of the entire sample.¹⁰ The mean cost per patient per year was highest in patients with CNV and lowest in those diagnosed with GA, while services directly paid for by patients were highest for patients with GA and lowest for those with CNV.¹⁰ On comparing the GA subgroup in the Italian study (95% of whom had bilateral disease) with ours, we observed that the mean cost calculated over 1 year (excluding hospitalization costs and private expenditure, which were not captured by our analysis) was similar to that of our study after accounting for the longer duration of follow-up. Thus, despite the passage of over 2 decades since the Italian study, the costs remain similar, indicating minimal change in clinical monitoring practice in the GA-only group. By contrast, the monitoring costs for the GA : CNV group were much higher in our study compared with the Italian study and almost certainly relate to the availability of anti-vascular endothelial growth factor (VEGF) treatments for nAMD, which necessitate more frequent monitoring. These patients were seen more often and their eyes with GA monitored because of their fellow eye diagnosis of CNV, the treatment of which would drive visits for follow-up monitoring. The lower health care resource use reported for managing GA compared with CNV most likely reflects the lack of an effective drug treatment for GA and a lack of recognition that GA may be a precursor to CNV. In fact, because the number of patients with glaucoma in the GA : GA and GA : E groups were higher than in the GA : CNV group, it is possible that monitoring of these former groups was occurring mainly for non-AMD-related pathology. In addition, some of the patients in all the groups and in all the centers may have had cataract or other ocular surgery, or

ocular complications, during follow-up that were not captured in our analyses, which would have increased the number of visits and investigations for those patients.

We also compared the results of our study with that of an analysis of US Medicare claims data from 1999–2001, which used the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification diagnosis codes to classify patients. We assumed that the group classified as dry AMD in the US study had GA because there was a subclassification of drusen only. The annual rate of ophthalmic resource utilization and cost per patient in the GA group was similar to that of ours.⁹ The mean annual cost in the “wet AMD” group in the US Medicare claims had been calculated for visits, diagnostic procedures, therapeutic interventions, and physician consultations. In our study, costs arising from therapeutic interventions were not included in the costing model. Therefore, on comparing the costs in the US Medicare study for the subgroup labeled “wet and dry,” with therapeutic interventions excluded, with those in our study, we observed a >2-fold increase in the median costs in our GA : CNV group, albeit over the first 2 years. Again, the increase in costs reflects the increased need for monitoring of patients managed with anti-VEGF therapies.⁹ Future research could make use of the ICD 11th Revision coding on GA to facilitate a better understanding of resource use around this form of AMD.

We also considered the potential impact of our EMR database studies on both policy and guidance that is widely available in the literature.^{17,18} That GA is often a precursor to CNV, with a progression rate of 4.8% per patient year in patients with bilateral GA,⁶ suggests that vigilance should be employed in terms of both advice and follow up for patients who present with unilateral or bilateral GA. While repeated review at short intervals is unlikely to be beneficial as the exudative manifestations of CNV can appear suddenly and dramatically, information should be provided on the risk estimates and the symptoms that would alert the patient to the onset of CNV. Additionally, the data on progression rates will prove useful for future health economic analysis on the value of devices that can be used for home monitoring to detect onset of CNV. Our findings also add emphasis to existing guidance on giving advice to patients with GA or early/intermediate AMD. Our data support the issue of strong public health messages on lifestyle modification and smoking

cessation, which are more likely to be heeded if the true risks of sight loss associated with both GA and CNV are made explicit.

The present study has several strengths. Firstly, the data represent the largest cohort of patients with GA managed in a routine clinical setting with a minimum follow-up for 2 years. Secondly, the disease definitions (i.e., GA, CNV, and early/intermediate AMD) were validated and found to be accurate in a large random selection of patients in this dataset with high positive and negative predictive values for progression to CNV.⁶ Thirdly, data on VA, IOP, and OCT are recorded in dropdown fields and captured in the EMR system with high fidelity.

This work has a number of limitations. Firstly, key among the limitations is that the EMR database does not record information regarding secondary health care outcomes, including hospital admissions, social/vision aids, or tests conducted by community optometrists, thus limiting the ability to conduct full health care resource use analyses. Secondly, underreporting of tests is likely to have occurred and may have been driven by the way clinical tariffs are set, with the most expensive test driving the tariff, so that if multiple tests were undertaken on a single visit, not all may have been captured.¹⁴ Thirdly, we observed evidence of variation in clinical practice both within and between study centers as shown by the wide ranges in visit frequency, particularly in the GA : GA and GA : early/intermediate AMD subgroups. These variations in clinical practice are not surprising because there are no approved treatments for GA, and follow-up of GA is unlikely, particularly for services with capacity issues. To date, the only intervention that has some benefit in the early non-neovascular stages of AMD is the Age-Related Eye Disease Study (AREDS) formulation (a nutritional supplement containing vitamin C, vitamin E, beta-carotene, zinc and copper; later modified to exclude beta-carotene and include lutein and zeaxanthin on the basis of the AREDS2 study)^{19,20}, but even this was not shown to retard the progression to GA.¹⁹ Finally, a further limitation of our study is its focus on direct resource utilization within the chosen clinical sites in a single country. However, we believe that clinical practice in the monitoring of early AMD and GA is similar across most developed economies. Neither direct treatment costs (e.g., anti-VEGF injection or antioxidant vitamins and minerals [as used in the AREDS^{19,20}]) nor indirect costs (e.g., vision-related

hospital admissions, caregiver costs, lost income, vision aids) were included in this analysis. Finally, we did not employ a micro-costing approach in each of the centers but relied instead on the use of published NHS costs for visits and procedures, which may underestimate the true costs of monitoring incurred by the centers.

In conclusion, direct ophthalmic health care resource use costs estimated using a large clinical dataset revealed a modest cost over a 2-year period in patients with GA in 1 or both eyes. However, the prevalence of GA in the United Kingdom was estimated in 2012 at 276,000 and was projected to rise over the next decade.²¹ Based on the prevalence of GA in 2012, the cost of monitoring-only eye care services over a 2-year period is likely to be of the order of £127 million. With promising therapies being tested in the prevention of progression from early AMD to GA and even from early GA to more advanced GA, the potential cost of managing this condition is likely to escalate dramatically in the future. Our clinic-based data provide information for health care providers interested in the burden of illness due to GA, particularly with respect to planning and organization of resource allocation. However, there is a remaining need for additional research on the indirect costs of GA, including those related to caregiving, transportation, and lost income. We recommend ICD 11th Revision coding for GA to be used uniformly across the nations for better understanding of resource utilization in managing these patients.

Author Contributions

Concept and design: U.C., C.C.B., M.M., A.V., A.M., R.A.C.

Acquisition, analysis, or interpretation of data: U.C., C.C.B., P.S., M.M., R.S.K., S.M., L.D., N.D., C.B., A.V., A.M.

Drafting of the manuscript: U.C., A.V., A.M., R.A.C.

Critical revision of the manuscript for important intellectual content: U.C., C.C.B., P.S., M.M., R.S.K., S.M., L.D., N.D., C.B., C.J.B., J.W., A.V., A.M., R.A.C.

Statistical analysis: A.V.

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References

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2:e106–e16.
2. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology*. 1997;104:1677–1691.
3. Kimel M, Leidy NK, Tschosik E, et al. Functional Reading Independence (FRI) Index: a new patient-reported outcome measure for patients with geographic atrophy. *Invest Ophthalmol Vis Sci*. 2016;57:6298–6304.
4. Joachim N, Mitchell P, Kifley A, Rochtchina E, Hong T, Wang JJ. Incidence and progression of geographic atrophy: observations from a population-based cohort. *Ophthalmology*. 2013;120:2042–2050.
5. Klein R, Meuer SM, Knudtson MD, Klein BE. The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2008;146:692–699.
6. Chakravarthy U, Bailey CC, Johnston RL, et al. Characterizing disease burden and progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:842–849.
7. Bonastre J, Le Pen C, Soubrane G, Quentel G. The burden of age-related macular degeneration: results of a cohort study in two French referral centres. *Pharmacoeconomics*. 2003;21:181–190.
8. Cruess AF, Zlateva G, Xu X, et al. Economic burden of bilateral neovascular age-related macular degeneration: multi-country observational study. *Pharmacoeconomics*. 2008;26:57–73.
9. Halpern MT, Schmier JK, Covert D, Venkataraman K. Resource utilization and costs of age-related macular degeneration. *Health Care Financ Rev*. 2006;27:37–47.

10. Garattini L, Castelnovo E, Lanzetta P, Viscarra C, Ricci E, Parazzini F; CARMA Study Group. Direct medical costs of age-related macular degeneration in Italian hospital ophthalmology departments. A multicenter, prospective 1-year study. *Eur J Health Econ*. 2004;5:22–27.
11. Ke KM. The direct, indirect and intangible costs of visual impairment caused by neovascular age-related macular degeneration. *Eur J Health Econ*. 2010;11:525–531.
12. Medisoft Limited. Medisoft Ophthalmology. Available at: <http://www.medisoft.co.uk/medisoft-ophthalmology>. Accessed February 3, 2018.
13. UK Government. Reference cost collection: national schedule of reference costs - year 2014-15 NHS trusts and NHS foundation trusts. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/480791/2014-15_National_Schedules.xlsx. Accessed February 4, 2018.
14. NHS England. 2016/17 National Tariff Payment System. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/509697/2016-17_National_Tariff_Payment_System.pdf. Accessed November 28, 2018.
15. Sadda SR, Chakravarthy U, Birch DG, Staurengi G, Henry EC, Brittain C. Clinical endpoints for the study of geographic atrophy secondary to age-related macular degeneration. *Retina*. 2016;36:1806–1822.
16. World Health Organization. International Classification of Diseases for Mortality and Morbidity Statistics, 11th Revision (ICD-11). Available at: <http://www.who.int/classifications/icd/en/>. Accessed August 29, 2018.
17. National Institute for Health and Care Excellence (2018). Age-related macular degeneration. NICE Guideline NG82. Available at: <https://www.nice.org.uk/guidance/ng82/chapter/Recommendations#monitoring-amd> [accessed 23 January 2019].

18. The Royal College of Ophthalmologists. RCOphth Clinical Guidelines. Available at: <https://www.rcophth.ac.uk/standards-publications-research/clinical-guidelines> [Accessed 23 January 2019].
19. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* 2001;119:1417–1436.
20. Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA.* 2013;309:2005-15.
21. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol.* 2012;96:752–756.

Figure Legends

Figure 1. Direct ophthalmology-related costs (in £; bars with interquartile range [IQR] shown as error bars) and median number of visits (in circles) for patients with geographic atrophy (GA) in the study eye and GA, choroidal neovascularization (CNV), or early/intermediate age-related macular degeneration (AMD) in the fellow eye, and for patients with bilateral early/intermediate AMD. Costs applied per visit were £92.15 (relating to Healthcare Resource Group service code 130: Ophthalmology; average unit cost, years 2014–2015) for a standard monitoring visit, and £114.53 (relating to Healthcare Resource Group cost code BZ88A; average unit cost, years 2014–2015) for a retinal tomography visit. The estimated median cost (represented by columns, value shown top left of column) does not include treatment costs (e.g., anti-vascular endothelial growth factor agent plus injection). Error bars represent IQR. The median number of visits over the first 2 years among patients is shown to the right of each solid column. Patients were identified in the electronic medical record system from 10 clinical sites in the United Kingdom. Analyses were restricted to patients with the year of the index date being on or after January 1, 2011 and who underwent at least 2 years of follow up.

Figure 2. Tests conducted over the first 2 years among patients with geographic atrophy (GA) in the study eye and GA, choroidal neovascularization (CNV), or early/intermediate age-related macular degeneration (AMD) in the fellow eye, and among patients with bilateral early/intermediate AMD. Patients were identified in the electronic medical record system from 10 clinical sites in the United Kingdom. Analyses were restricted to patients with the year of the index date being on or after January 1, 2011 and who underwent at least 2 years of follow up.

Box plot shows the median (middle line in each box with corresponding value noted), first and third quartile (bottom and top of each box, respectively), and the minimum and maximum number of times each test was performed over a 2-year period (lower and upper error bars, respectively). FFA

= fundus fluorescein angiography; IOP = intraocular pressure; IQR = interquartile range; OCT = optical coherence tomography; VA = visual acuity.

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Table 1. Baseline Demographics of Patients Diagnosed on or after January 1, 2011 with ≥ 2 Years of Follow-up and Included in This Analysis

Status	Study Eye : Fellow Eye		
	GA : GA (n = 442)	GA : CNV (n = 355)	GA : E (n = 283)
Age (yrs), mean (SD)	80 (6)	81 (5)	78 (7)
Female, n (%)	267 (60.4)	235 (66.2)	153 (54.1)
Follow-up time (yrs), median (IQR) ^a	3 (2–3)	3 (2–4)	3 (2–3)
Study eye VA at baseline (ETDRS letters), median (IQR) ^a	47 (20–65)	60 (35–73)	45 (20–70)
Fellow eye VA at baseline (ETDRS letters), median (IQR)	70 (55–75)	47 (25–64)	75 (70–76)
Intraocular pressure (n = 644) (mmHg), mean (SD) ^a	17 (4)	16 (4)	17 (5)
Glaucoma, n (%) ^a	32 (7.2)	8 (2.3)	18 (6.4)
Phakic, n (%) ^a	355 (80.3)	303 (85.4)	223 (78.8)
Pseudophakic, n (%) ^a	87 (19.7)	52 (14.7)	60 (21.2)
Eligible for blindness registration, n (%)			
UK definition ^b	25 (5.7)	5 (1.4)	2 (0.7)
US definition ^c	48 (10.9)	26 (7.3)	7 (2.5)
Ineligible to drive, n (%) ^d	265 (60.0)	223 (62.8)	98 (34.6)

AMD = age-related macular degeneration; CNV = choroidal neovascularization; E = early/intermediate AMD; ETDRS = Early Treatment Diabetic Retinopathy Study; GA = geographic atrophy; IQR = interquartile range; SD = standard deviation; VA = visual acuity.

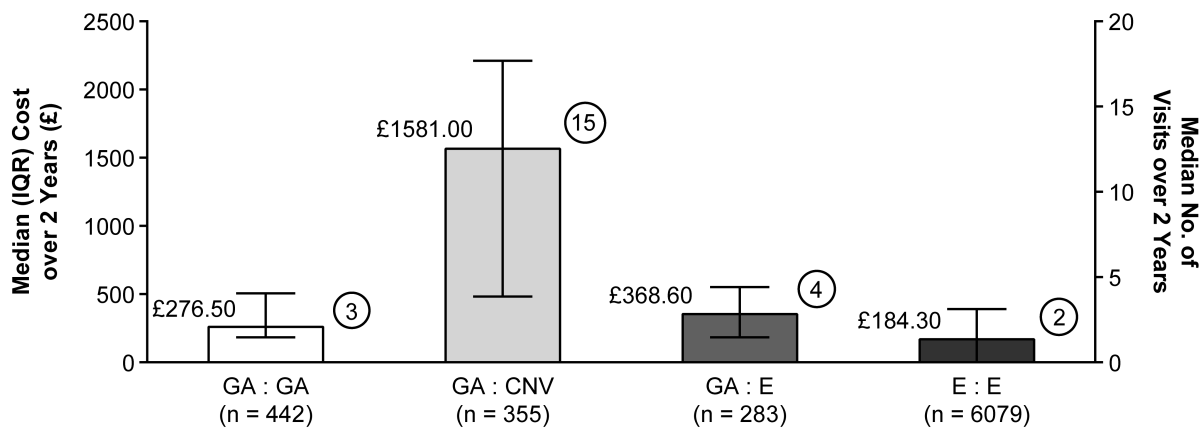
Patients had GA in the study eye and GA (GA : GA), CNV (GA : CNV), or early or intermediate AMD (GA : E) in the fellow eye and were identified in the electronic medical record system from 10 clinical sites in the United Kingdom.

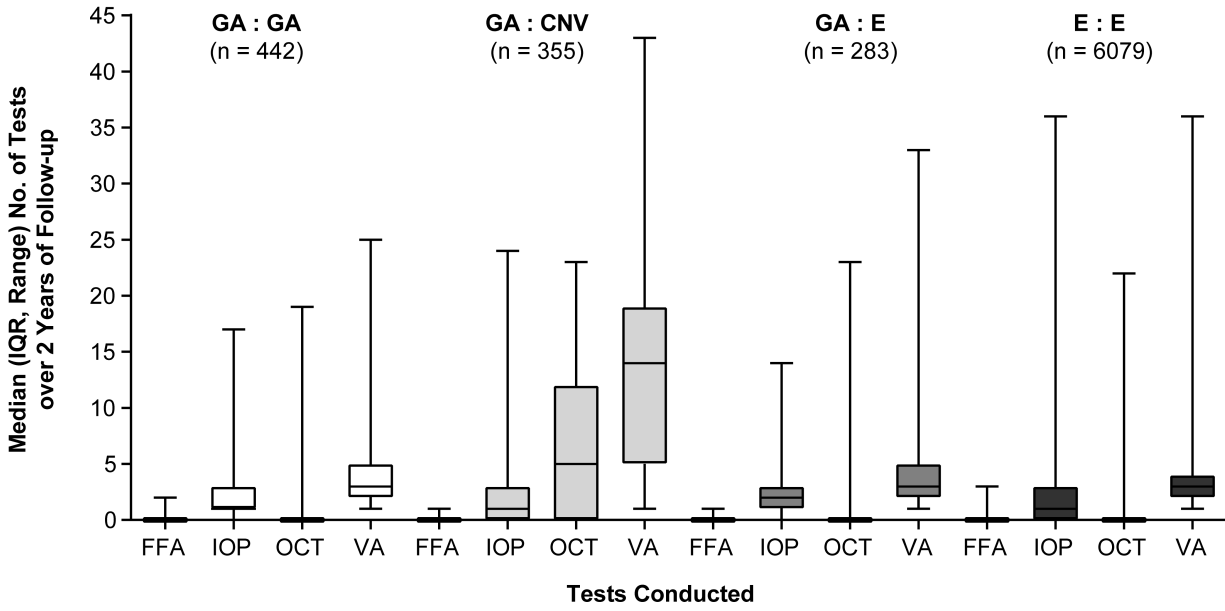
^aReported variables are based on the predefined study eye diagnosed with GA except for the measures relating to blindness/UK driving standard definitions.

^bUK blindness definition: VA <20 letters or Snellen 3/60 (US Snellen 20/400) in the better-seeing eye.

^cUS blindness definition: Snellen 20/200.

^dUK and US driving standard (VA >70 letters or Snellen 6/12 [US Snellen 20/40]) in the better-seeing ey





1 **Précis [35/35 words]**

2

3 Direct ophthalmic healthcare resource use associated with geographic atrophy over the first 2 years
4 was £460 per patient. Costs were £1581 if choroidal neovascularization was present in the fellow eye,
5 reflecting more frequent, structured follow-up.

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