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ORIGINAL RESEARCH

Dry Age-Related Macular Degeneration: Distribution of Visual Acuity and Progression Risk in a Large Registry

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ABSTRACT

Introduction: Understanding the progression to geographic atrophy (GA) in late dry age-related macular degeneration (dAMD) can support development opportunities for dAMD treatments. We characterized dAMD by distribution of visual acuity (VA) categories and evaluated VA progression risk by disease stage.

Methods: This retrospective observational study used data from the American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight) to identify patients diagnosed with dAMD in ≥ 1 eye from January 2016 through December 2019 (index date) with ≥ 1 visit and ≥ 1 VA measurement recorded post-index date. Patients were followed until the date of last visit, last contribution for diagnosing provider, or diagnosis of neovascular AMD post-index. Models were utilized to describe the distribution of VA categories and progression to worsening VA.

Results: Data from 593,277 patients were analyzed. At baseline, 64.4% had mild disease, 29.4% intermediate, and 2.9%/3.3% had GA with/without subfoveal involvement. Most patients with mild (88.4%) and intermediate (79.7%) disease and GA without subfoveal involvement (57.1%) had baseline VA ≥ 20/63 in the study eye; 72.0% of patients with GA with subfoveal involvement had VA < 20/63. Modeled results showed lower VA with more progressive stage at baseline. Annual probability of stable dAMD based on baseline stage ranged from 82.1% (GA without) to 92.3% (GA with subfoveal involvement). Annual progression probability to GA without/with subfoveal involvement was 0.4% for mild and 5.5% for intermediate disease and from dry to neovascular AMD, 0.5% for mild and 8.0% for intermediate disease.

Conclusions: Results from this analysis of a large database of electronic health records complement those from randomized trials and show that patients with more advanced dAMD have lower VA at baseline and that VA progression is generally faster with each progressive stage. Together these findings highlight the disease burden and trajectory of dAMD as well as opportunities for addressing unmet needs.

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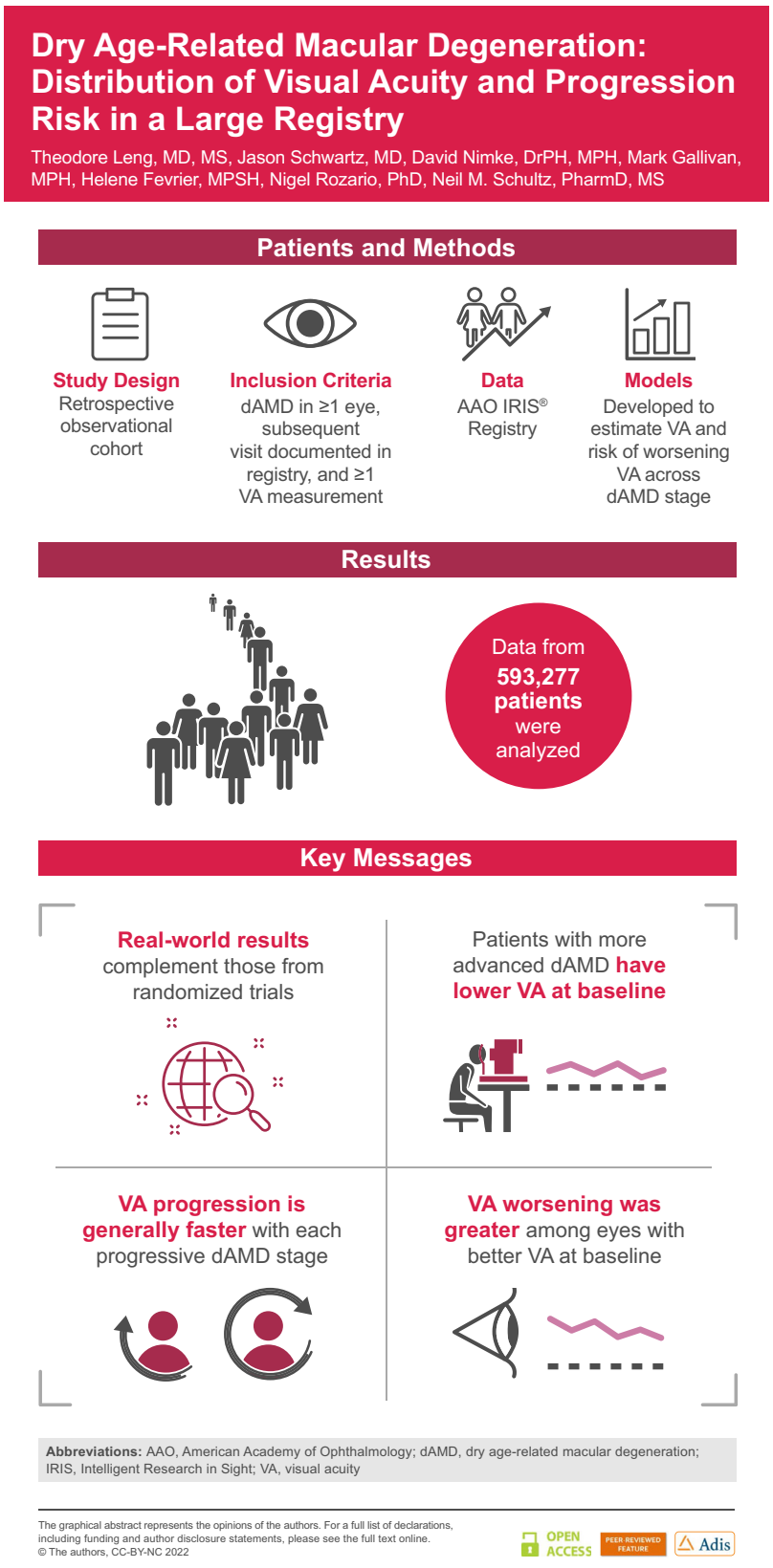
Graphical Abstract:



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PLAIN LANGUAGE SUMMARY

Dry age-related macular degeneration (dAMD) is a disease that progressively worsens over time. As the disease progresses, patients start to lose their vision, leading to a substantial burden on their quality of life and finances due to the need for increased healthcare services. As of 2022, there are no medications available to reverse or stop worsening of dAMD. This study used real-world data from a large registry of electronic health records to increase the understanding of how patients progress through the stages of dAMD. By reviewing patient records, we were able to identify approximately 600,000 patients with confirmed dAMD. These patients were then followed over time, and we were able to confirm that patients with a lower ability to see at the beginning of our review period had more advanced dAMD. We also found that as patients' disease worsened, their vision also decreased. These findings highlight the need for new medication options to reverse or delay the worsening of dAMD and improve the quality of life for patients.

Keywords: Epidemiology; Geographic atrophy; Markov model; Visual acuity

Key Summary Points

Why carry out this study?

To simultaneously report on the dAMD population distribution by both VA and disease severity for all stages of dAMD, rather than just those patients who are diagnosed with geographic atrophy and progress to choroidal neovascularization.

To provide a window on a large dAMD patient population being actively managed by ophthalmologists in order to complement those results being reported within the smaller confines and controlled conditions of published randomized trials.

What did the study ask?

In dAMD, what is the prevalence of visual acuity (VA) impairment by dAMD stage and what is the risk of worsening VA by dAMD stage?

What has been learned from this study?

These data describe dAMD progression on VA over time and highlight the need and opportunity for treatments to slow progression and degradation of VA.

DIGITAL FEATURES

This article is published with digital features, which can be found at https://doi.org/10.6084/m9.figshare.21183265.

INTRODUCTION

Dry age-related macular degeneration (dAMD) is a chronic eye disease that can impair vision and progress to severe central vision loss [1]. Among the two types of AMD (dry and neovascular), dAMD constitutes the majority (80–90%) of cases and occurs when

photoreceptors are lost and drusen (yellow deposits) develop [1, 2]. The prevalence of AMD is estimated to increase by approximately 50% to 288 million people from the year 2020 to the year 2040 [3]. With the anticipated increase in AMD cases related to an aging population, there is an increasing and important unmet need for new dAMD therapies [4].

No treatments are approved as of 2022 to prevent disease progression in patients with dAMD [2]. Geographic atrophy (GA) poses a significant economic burden to the healthcare system and a humanistic burden to affected individuals [5, 6].

Although previous epidemiologic studies in dAMD have evaluated the deterioration of visual acuity (VA) and risk of dAMD progression among patients with dAMD, particularly progression from GA to neovascular AMD [7–13], this study assessed these outcomes in patients at all stages of dAMD receiving care in the ophthalmology setting.

This study aimed to describe the distribution of VA categories, disease characteristics, disease progression, and visual impairment progression in adults with dAMD, as well as the healthcare resources utilized by these patients using a large ophthalmology electronic health record (EHR) database.

METHODS

Study Design

This study was a retrospective, noncomparative, observational cohort study among patients with dAMD seen in ophthalmology offices (Fig. 1). This research was reviewed by the WCG Institutional Review Board. Research and analysis were conducted on anonymized data in accordance with the de-identification standard promulgated under 45 CFR § 164.514, and no research was conducted on human subjects. No patient authorization was required because solely de-identified data were analyzed.

Study data originated from the American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight). The IRIS Registry is a regulatory-grade, Centers for Medicare & Medicaid Services–approved Qualified Clinical Registry sourced from over 18,000 eligible clinicians at over 3000 EHR-based practices that contains over 70 million unique patients across 412 million encounters or patient visits since 2013. Patients were indexed upon first diagnosis of dAMD and followed longitudinally in the database until the first occurrence of the last visit date regardless of reason, the last contributing date for the diagnosing provider, or

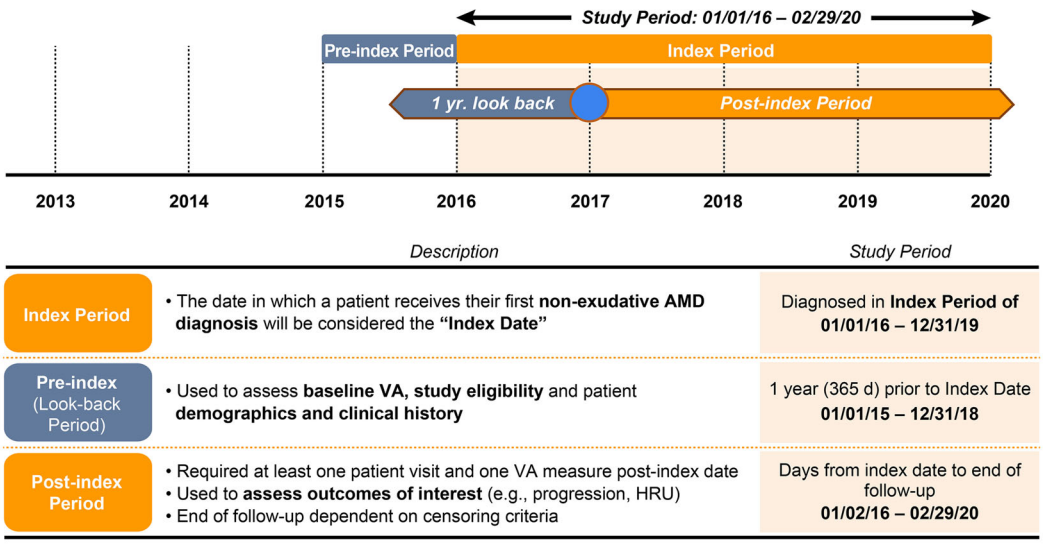

Fig. 1 Study design. *AMD* age-related macular degeneration, *HRU* healthcare resource utilization, *VA* visual acuity

the date of diagnosis of neovascular AMD post-index date.

An additional censoring date was included for the VA change endpoint to isolate the impact of dAMD on VA. Specifically, patients were censored at the first date of intraocular surgery (meaning glaucoma surgery, corneal transplant, retinal detachment surgery, other vitrectomy surgery, and cataract surgery) for the eye to account for procedures that may improve VA.

Study Endpoints

The primary endpoint was the distribution of specific VA categories among patients with dAMD. Five AMD severity stages were defined on the basis of International Classification of Diseases (ICD) diagnosis coding: mild dAMD (H35.3111, H35.3121, H35.3131, H35.3191), intermediate dAMD (H35.3112, H35.3122, H35.3132, H35.3192), GA without subfoveal involvement (H35.3193, H35.3113, H35.3123, H35.3133), GA with subfoveal involvement (H35.3194, H35.3114, H35.3124, H35.3134), and neovascular AMD (362.51, H35.32, H35.3210, H35.3220, H35.3230, H35.3290, H35.3221, H35.3231, H35.3291, H35.3212, H35.3222, H35.3232, H35.3292, H35.3213, H35.3223, H35.3233, H35.3293). Secondary endpoints included (1) best documented visual acuity (BDVA) as a continuous and categorical outcome and (2) ophthalmology-related healthcare resource utilization (HRU). Five categories of BDVA were defined: VA category 1, vision $\geq$ 20/63; VA category 2, vision $<$ 20/63 and $\geq$ 20/160; VA category 3, vision $<$ 20/160 and $\geq$ 20/400; VA category 4, vision $<$ 20/400 and $\geq$ 20/1000; VA category 5, vision $<$ 20/1000. BDVA was sourced from a practice's EHR data using a previously described methodology [14]. Pinhole VA measurements were not considered.

Study Population

All patients diagnosed with dAMD within the IRIS Registry from 2016 through 2019 were included who met the following criteria:

- ICD-9 or ICD-10 diagnosis code, indicating dAMD with known stage in at least one eye between January 1, 2016, and December 31, 2019 (index date)
- Subsequent visit(s) following the index date in the database for any reason
- At least one VA measurement recorded after the index date

Patients meeting any of the following criteria were excluded from the study:

- Did not have a baseline VA value within 365 days on or prior to the index date
- Had a history of, or actively had, advanced glaucoma, branch retinal artery or vein occlusion, central retinal artery or vein occlusion, choroidal neovascularization, corneal transplant, diabetic macular edema, inherited retinal disease (e.g., Stargardt disease), intraocular surgery, macular holes, or pathologic myopia within 365 days of the index date
- Were missing age or sex data
- Were aged $<$ 50 or $>$ 90 years at index date

For patients with dAMD in both eyes, the worse-seeing eye was selected as the study eye.

Variables

Other variables included demographic information, US census region, treating provider characteristics, comorbidities, all-cause visits by specialist (i.e., retina specialist, general ophthalmologist, non-retina specialist, optometrist, unknown), and all-cause imaging visits (i.e., fluorescein angiography [FA], optical coherence tomography [OCT], fundus autofluorescence [FAF]).

The treating provider was documented as a retina specialist if the participant saw a retina specialist during the study period. If no appointment with a retina specialist was documented, then the provider specialty with the highest number of encounters was defined as the patient's treating provider. Non-retina specialists included those treating cornea/external disease, glaucoma, neuro-ophthalmology, ocular oncology, oculofacial plastics/reconstruction, uveitis, or vision rehabilitation. The type

of provider was sourced from the specialty listed in the Centers for Medicare & Medicaid Services National Plan and Provider Enumeration System (NPPES) National Provider Identifier (NPI) Registry [15].

Statistical Methods

The study was descriptive; therefore, no statistical comparisons across groups were performed. Outcomes are presented as counts and percentages for categorical variables and as mean, standard deviation, median, quartile, and range for continuous variables.

Linear regression models were developed to describe VA at index date by dAMD stage. Mixed-effects linear models were used to describe VA change over time by index dAMD stage; the effects of age and sex on VA change over time were also evaluated. A mixed-effects model was used to address the non-independence of multivariate data, inherent intra-patient correlation between VA measurements, unequal number (i.e., unbalanced) of follow-up time between patients, and heterogeneous variability over time. Covariates in this model included VA, time since the patient's first VA measurement, dAMD stage at the index date, and age. Random intercepts were computed for each patient with fixed effects for the variables described below. Both linear models were further adjusted for age (as a continuous variable) at baseline and sex.

Multistate Markov models were developed to understand progression through worsening VA categories. The first date when an eye progressed into a new, and worse, VA category was used as the change date. A patient was assumed to stay in this state until another observation showed the patient progressed into a worse BDVA category. In this study, VA was characterized into five increasingly severe stages of disease progression as previously defined. Eyes could continue in the same VA category or progress to the next worse VA category. For example, eyes in VA category 1 could stay in VA category 1 or progress to VA category 2 but could not progress to VA categories 3, 4, or 5. The worst-seeing vision category, vision worse than 20/1000, was considered an absorbing state meaning that patients who reached that health state (i.e., VA category 5, vision $< 20/1000$) were unable to leave or move to another health state. Four VA progression Markov models were created to compare VA progression rates between each prevalent dAMD stage.

A Markov model was also developed to describe the probability of conversion among dAMD stages and neovascular AMD. AMD progression was simplified into the following five increasingly severe stages of disease: mild dAMD, intermediate dAMD, GA without subfoveal involvement, GA with subfoveal involvement, and neovascular AMD. In the model, eyes with mild dAMD could continue in the same dAMD stage or progress to the intermediate dAMD stage. Eyes with intermediate dAMD and those with GA without or with subfoveal involvement could continue in the same dAMD stage or progress to any worse stage. For example, an eye in the mild dAMD stage must transition to the intermediate dAMD stage before progressing to neovascular AMD. However, an eye with intermediate dAMD or GA without subfoveal involvement at index can progress directly to neovascular AMD. Neovascular AMD was considered an absorbing state meaning that patients who reached this health state (i.e., neovascular AMD) were unable to leave or move to another health state.

Healthcare resource utilization was reported by counts and annualized rates of visits by visit type and dAMD stage.

RESULTS

Disposition of Study Cohort

A total of 3,588,207 patients were diagnosed with dAMD in at least one eye from January 1, 2016, through December 31, 2019 (Fig. 2). Median patient follow-up time was 2.03 years. After selection criteria were applied, the final study population consisted of 593,277 patients; approximately 50% of patient attrition occurred after excluding eyes without at least one VA measurement recorded after the dAMD index date. Most patients had mild dAMD at baseline, with approximately 6% of patients having GA

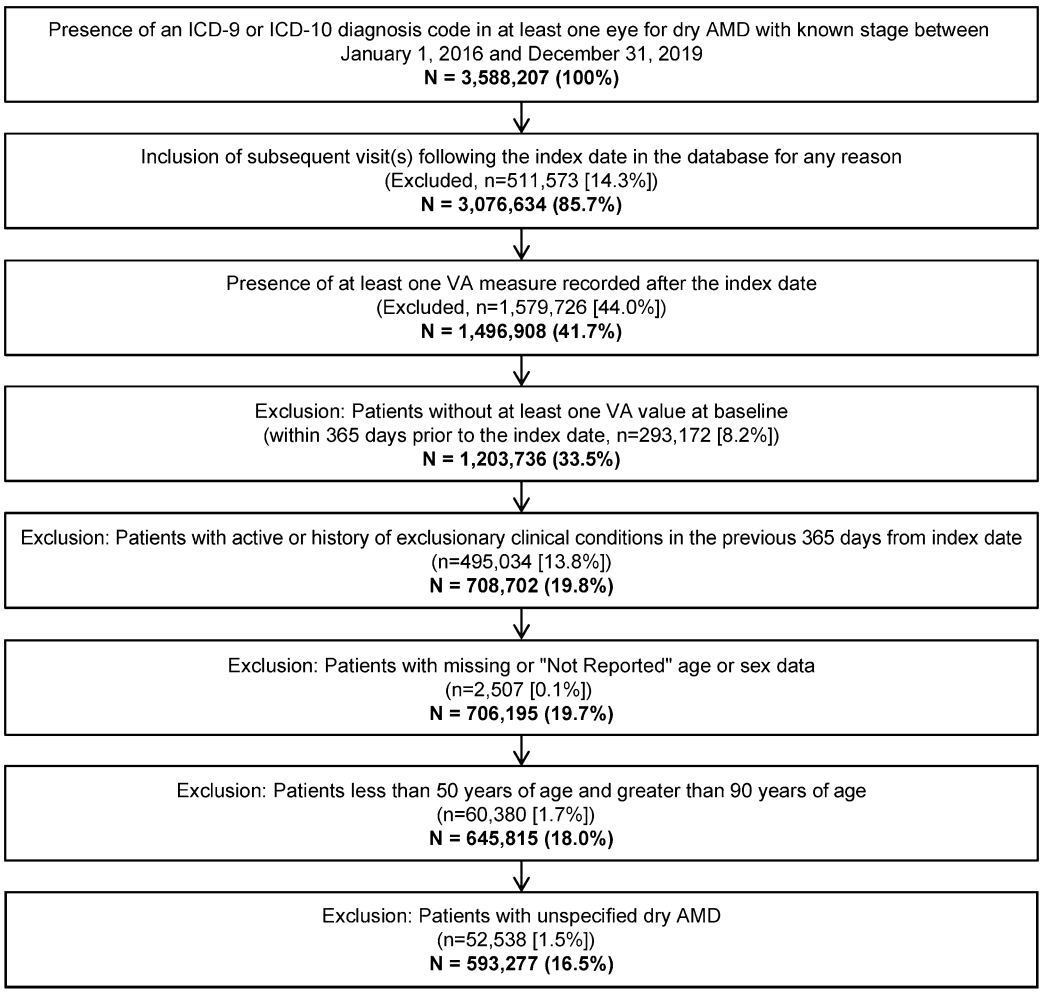

Fig. 2 Patient flow diagram. *AMD* age-related macular degeneration, *ICD* International Classification of Diseases, *VA* visual acuity

without or with subfoveal involvement (Table 1). Additionally, most patients (86.6%) had bilateral disease.

Patient Demographic and Clinical Characteristics

The study cohort was predominantly female (63%) and resided in the Southeast region of the USA (Table 1). Mean patient age ranged from 75.7 years for patients with mild dAMD to 79.9 years for patients with GA with subfoveal involvement. Medicare was the predominant payer (70.1%); retina specialists were the most common treating provider (39.4%). In general, more advanced dAMD had a higher percentage of patients who were older, female, Caucasian, insured by Medicare, and who saw a retina specialist as their treating provider.

At baseline, the proportion of patients with mild dAMD was 64.4% and the proportion with GA with subfoveal involvement was 3.3% (Table 1). BDVA was $\geq$ 20/63 in 88.4% of patients with mild dAMD and 28% of patients with GA with subfoveal involvement. Conversely, only 3.6% of patients with mild dAMD had BDVA $<$ 20/160 compared with 50% of patients with GA with subfoveal involvement.

The most prevalent comorbid conditions at baseline were cataracts (58.0%), followed by diabetes (19.5%; diabetic retinopathy, 3.4%) and cardiovascular conditions (4.7%) (Table 1).

Table 1 Baseline characteristics of all unique patients by dAMD disease stage

Baseline characteristic	dAMD stage							
	Mild		Intermediate		GA without subfoveal involvement		GA with subfoveal involvement	
	n	%	*n*	%	*n*	%	*n*	%
Patients	381,829	64.4	174,719	29.4	17,423	2.9	19,306	3.3
Female sex	238,343	62.4	109,598	62.7	11,035	63.3	12,144	62.9
Age, years,[a] mean, SD	75.7	8.4	77	8.3	79.1	8	79.9	7.7
Age category								
50–55 years	5742	1.5	1906	1.1	128	0.7	109	0.6
56–61 years	16,895	4.4	5878	3.4	438	2.5	355	1.8
62–67 years	42,733	11.2	16,448	9.4	1111	6.4	1009	5.2
68–73 years	81,105	21.2	32,717	18.7	2386	13.7	2384	12.4
74–79 years	97,318	25.5	43,172	24.7	3895	22.4	4072	21.1
80–85 years	87,127	22.8	44,253	25.3	5007	28.7	5959	30.9
86–90 years	50,909	13.3	30,345	17.4	4458	25.6	5418	28.1
Race								
White or Caucasian	309,983	81.2	143,276	82.0	14,553	83.5	16,356	84.7
Black or African American	9146	2.4	3023	1.7	245	1.4	257	1.3
Asian	9094	2.4	2918	1.7	220	1.3	239	1.2
Other	2477	0.7	1110	0.6	122	0.7	128	0.7
Unknown	51,129	13.4	24,392	14.0	2283	13.1	2326	12.1
US census region								
Midwest	97,227	25.5	40,904	23.4	3780	21.7	4826	25
North	64,659	16.9	33,995	19.5	3104	17.8	3385	17.5
South	137,766	36.1	60,769	34.8	6426	36.9	6754	35
West	79,974	20.9	37,981	21.7	4033	23.2	4229	21.9
Payer type								
Medicare	262,106	68.6	126,427	72.4	12,775	73.3	14,439	74.8
Medicaid	6077	1.6	2498	1.4	238	1.4	277	1.4
Military, government	6554	1.7	2922	1.7	322	1.9	341	1.8
Commercial	87,205	22.8	34,339	19.7	3366	19.3	3284	17.0
Treating provider								
Retina specialist	103,365	27.1	106,085	60.7	10,695	61.4	13,681	70.9
Ophthalmologist	107,493	28.2	30,157	17.3	3026	17.4	2663	13.8

Table 1 continued

Baseline characteristic	dAMD stage							
	Mild		Intermediate		GA without subfoveal involvement		GA with subfoveal involvement	
	n	%	*n*	%	*n*	%	*n*	%
Non-retina specialist	105,665	27.7	25,568	14.6	2352	13.5	2003	10.4
Optometrist	63,549	16.6	12,201	7.0	1284	7.4	881	4.6
Unknown	1757	0.5	708	0.4	66	0.4	78	0.4
VA at index, study eye								
Snellen categorization, no. %								
Vision $\geq$ 20/63	337,602	88.4	139,166	79.7	9942	57.1	5399	28
Vision $<$ 20/63 and $\geq$ 20/160	30,139	7.9	23,099	13.2	3038	17.4	4263	22.1
Vision $<$ 20/160 and $\geq$ 20/400	10,345	2.7	9053	5.2	2457	14.1	5558	28.8
Vision $<$ 20/400 and $\geq$ 20/1000	155	$<$ 0.01	164	0.1	58	0.3	210	1.1
Vision $<$ 20/1000	3588	0.9	3237	1.9	1928	11.1	3876	20.1
Comorbid conditions, no. %								
Glaucoma disorders[b]	12,191	3.2	6601	3.8	543	3.1	722	3.7
Diabetes mellitus	77,580	20.3	31,680	18.1	3054	17.5	3434	17.8
Diabetic retinopathy	11,785	3.1	6961	4.0	599	3.4	691	3.6
Cataracts	236,039	61.8	92,835	53.1	7432	42.7	7609	39.4
Unspecified retinal neovascular	438	0.1	609	0.4	61	0.4	92	0.5
Depression	6	$<$ 0.1	4	$<$ 0.1	0	–	0	–
Cardiovascular	15,747	4	9939	6	1152	6.6	1230	6.4
None of above	106,125	27.8	60,203	34.5	7449	42.8	8642	44.8

dAMD dry age-related macular degeneration, *GA* geographic atrophy, *IQR* interquartile range, *SD* standard deviation, *VA* visual acuity

[a]Data presented as mean and standard deviation

[b]Includes open-angle, angle-closure, and secondary glaucoma (glaucoma secondary to eye trauma, eye inflammation, other eye disorders, and drugs, and other glaucoma) and ocular hypertension

Open-angle glaucoma was the most common form of glaucoma (2.6%) followed by secondary glaucoma (0.2%) and angle-closure glaucoma (0.1%).

Mixed-Effects VA Progression Model

The yearly loss of VA letters ranged from − 1.19 letters for mild dAMD to − 3.93 letters for GA without subfoveal involvement (Table 2). A 1-year increase in age was associated with a small decrease in ETDRS letter score for all four models. No consistent directional trend was observed for the sex estimate.

Table 2 Adjusted annual loss in VA by dAMD disease stage: mixed-effects linear regression VA progression models

dAMD disease stage	Estimate	Standard error	*T* statistic
Mild			
BDVA	70.50	0.62	113.97
Time from index (1-year increase)	− 1.19	0.04	− 32.99
Intermediate			
BDVA	72.73	0.79	91.56
Time from index (1-year increase)	− 2.50	0.04	− 70.38
GA without subfoveal involvement			
BDVA	72.12	2.75	26.18
Time from index (1-year increase)	− 3.93	0.10	− 39.92
GA with subfoveal involvement			
BDVA	67.14	2.35	28.62
Time from index (1-year increase)	− 2.50	0.09	− 28.01

BDVA best documented visual acuity, *dAMD* dry age-related macular degeneration, *EHR* electronic health record, *GA* geographic atrophy, *VA* visual acuity

Snellen VA chart measurements sourced from a practice's EHR data were converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letters to determine the BDVA measurement using a previously described methodology [14]

Markov Models for VA and Stage Progression

Model results showed greater VA progression among eyes in the better-seeing VA categories (VA 1 and 2) with each increasing index dAMD stage at baseline (Table 3). Notably, the 1-year probability of transition from VA category 4 to 5 was at least 90% for all index dAMD stages.

Age-related macular degeneration progression modeling results (Table 4) reported the highest 1-year probability of transition between mild and intermediate dAMD (11.9%), followed by GA without subfoveal involvement to GA with subfoveal involvement (11.0%). The annual probability of progression to neovascular AMD was lowest among eyes with mild dAMD at baseline (0.5%), increasing to approximately 7–8% among eyes with intermediate to GA with subfoveal involvement at baseline.

Healthcare Resource Utilization

On average, patients with dAMD visited a provider 3.2 times per year with similar frequencies of visits to retina specialists, general ophthalmologists, and non-retina specialists. There was a noticeable increase in the number of retina specialist visits once a patient had intermediate disease that increased for patients with GA without and with subfoveal involvement.

On average, patients with dAMD had 1.9 imaging visits annually. Optical coherence tomography visits accounted for most imaging visits, with 1.4 visits annually. Across dAMD stages, the annualized number of imaging visits increased the most from mild to intermediate dAMD. Healthcare resource utilization related to imaging visits (FA, FAF, OCT) increased from mild to intermediate dAMD and remained steady thereafter.

Table 3 Adjusted annual probability of VA progression by dAMD stage at index date[a]

VA at start of study	VA progression probability matrix for 1 year, % (95% CI)				
	VA 1	VA 2	VA 3	VA 4	VA 5
Mild					
VA 1	95.0 (94.9, 95.0)	4.4 (4.4, 4.5)	0.6 (0.5, 0.6)	< 0.1 (< 0.1, < 0.1)	< 0.1 (< 0.1, < 0.1)
VA 2	–	77.7 (77.2, 78.1)	20.1 (19.7, 20.5)	0.6 (0.5, 0.6)	1.7 (1.7, 1.8)
VA 3	–	–	80.9 (80.3, 81.5)	2.6 (2.5, 2.8)	16.4 (15.9, 17.0)
VA 4	–	–	–	0.1 (0.1, 0.2)	99.9 (99.8, 99.9)
VA 5	–	–	–	–	–
Intermediate					
VA 1	91.0 (90.8, 91.1)	7.9 (7.7, 8.0)	1.1 (1.1, 1.1)	< 0.1 (< 0.1, < 0.1)	< 0.1 (< 0.1, < 0.1)
VA 2	–	75.8 (75.4, 76.3)	21.7 (21.3, 22.2)	0.7 (0.7, 0.8)	1.7 (1.7, 1.8)
VA 3	–	–	81.3 (80.6, 81.9)	3.3 (3.1, 3.5)	15.4 (14.9, 16.1)
VA 4	–	–	–	0.5 (0.4, 0.6)	99.5 (99.4, 99.6)
VA 5	–	–	–	–	–
GA without subfoveal involvement					
VA 1	83.1 (82.4, 83.8)	13.8 (13.3, 14.4)	2.8 (2.6, 2.9)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
VA 2	–	67.3 (66.0, 68.6)	28.6 (27.4, 29.8)	1.5 (13.4, 16.2)	2.6 (2.4, 2.8)
VA 3	–	–	77.7 (76.3, 79.0)	5.3 (4.8, 5.8)	17.1 (16.0, 18.3)
VA 4	–	–	–	2.0 (1.5, 2.8)	98.0 (97.2, 98.5)
VA 5	–	–	–	–	–
GA with subfoveal involvement					
VA 1	74.2 (73.0, 75.3)	20.3 (19.5, 21.2)	5.2 (4.9, 5.5)	0.2 (0.2, 0.2)	0.2 (0.1, 0.2)
VA 2	–	62.1 (60.7, 63.4)	34.1 (32.9, 35.3)	2.0 (1.8, 2.1)	1.9 (1.8, 2.0)
VA 3	–	–	81.7 (80.9, 82.5)	6.9 (6.5, 7.3)	11.4 (10.8, 12.0)
VA 4	–	–	–	10.0 (8.7, 11.4)	90.0 (88.6, 91.3)
VA 5	–	–	–	–	–

CI confidence interval, *dAMD* dry age-related macular degeneration, *GA* geographic atrophy, *VA* visual acuity

[a]Covariates set to their mean value. Parentheses indicate the normal 95% CI from the assumed multivariate normal distribution

The model assumes a constant risk over time. VA classifications defined as follows: VA 1, ≥ 20/63; VA 2, < 20/63 and ≥ 20/160; VA 3, < 20/160 and ≥ 20/400; VA 4, < 20/400 and ≥ 20/1000; and VA 5, < 20/1000

DISCUSSION

The need for dAMD treatments is expected to grow as the population demographics shift as a result of changes in longevity [4]. We used the largest known ophthalmology data source in the USA to characterize both VA and dAMD disease stage in patients being managed by an

Table 4 Adjusted annual probability of AMD progression by AMD disease stage[a]

Stage at index date	Disease stage at end of study, % (95% CI)				
	Mild	Intermediate	GA without subfoveal involvement	GA with subfoveal involvement	Neovascular AMD
Mild	87.2 (87.1, 87.3)	11.9 (11.8, 12.0)	0.2 (< 0.1, < 0.1)	0.2 (0.2, 0.2)	0.5 (0.5, 0.5)
Intermediate	–	86.5 (86.4, 86.6)	2.9 (2.8, 2.9)	2.6 (2.6, 2.7)	8.0 (7.9, 8.1)
GA without subfoveal involvement	–	–	82.1 (81.6, 82.6)	11.0 (10.6, 11.4)	6.9 (6.6, 7.2)
GA with subfoveal involvement	–	–	–	92.3 (92.0, 92.6)	7.7 (7.4, 8.0)

AMD age-related macular degeneration, *CI* confidence interval, *dAMD* dry AMD, *GA* geographic atrophy
The model assumes a constant risk over time
[a]Covariates set to their mean value. Parentheses indicate the normal 95% CI from the assumed multivariate normal distribution

ophthalmologist. Unlike previously reported studies that evaluated smaller sample sizes and generally examined dAMD progression from GA to choroidal neovascularization [7–13], our evaluation included more than 593,000 eyes regardless of dAMD disease stage. In contrast, Sunness et al. evaluated 40 eyes with GA. In that study, GA was associated with a significant decline in VA with 31% of all study eyes demonstrating a three-line VA loss from baseline at 2 years, with the highest rate of VA loss noted for eyes with vision > 20/50 at baseline [12]. Keenan et al. analyzed VA progression using data from the Age-Related Eye Diseases Studies (AREDS) that included 517 eyes from 411 participants with GA at baseline. VA progression was evaluated using a mixed-model regression analysis with multiple parameters, including GA central involvement, GA lesion size, and GA lesion configuration. The overall loss in VA observed was 2.3 letters per year (95% CI − 2.6 to − 2.0; $P < 0.0001$) [8]. Last, results from a population-based study estimating the 9-year incidence and progression of AMD in Black patients conducted as part of the Barbados Eye Studies found that among 692 patients identified with early AMD in either eye at baseline, progression from early to late AMD was 1.7% (95% CI 0.7–2.8%) and progression to GA was 0.7% (95% CI 0.01–1.4%) [9]. Higher rates of progression were reported among 197 patients identified with early AMD in both eyes at baseline.

Our findings add to and build on progression data obtained from previous studies and are potentially more reflective of what clinicians are encountering in everyday practice. Specifically, we found that among the study population, vision was ≥ 20/63 in most affected eyes and over 80% of patients had bilateral dAMD; the risk of VA progression generally increased with increasing dAMD severity; and progression to GA and neovascular AMD occurred considerably faster in patients with intermediate dAMD. Results from mixed-effects models, adjusted by age and sex, showed 1-year changes in BDVA ranging from − 1.2 for mild dAMD to − 3.9 letters for GA without subfoveal involvement. Ophthalmologic-related visits were consistent across dAMD stages, at about three visits annually. Retina specialist visits and imaging studies were increased for patients with intermediate dAMD to GA with subfoveal involvement compared with mild dAMD.

These results do highlight differences between our progression data, which reflect

diagnosis and progression in clinical practice, and that reported for the 5-year AREDS study, a randomized controlled trial. Additionally, we identified dAMD categories through use of physician ICD-9/10 coding practices, whereas the AREDS study defined AMD categories using drusen size and area and pigment abnormalities [16, 17].

Interestingly, we found that a large proportion of the more than 3.5 million patients (n = 511,573) initially diagnosed with dAMD did not have a subsequent visit to an IRIS Registry contributing provider. One possible explanation for patients not returning for further care is the lack of approved treatments for dAMD, potentially highlighting an unmet treatment need in this population.

To our knowledge, this is the first study to report Markov model-derived VA and AMD transition probabilities among patients stratified by dAMD stage. These model results showed, on average, the annual probability of progression from VA $\geq$ 20/63 to VA $<$ 20/400 was almost tenfold greater among GA with subfoveal involvement study eyes compared with mild dAMD study eyes (37.7% vs 4%).

More than 80% of our study population had bilateral AMD, which is consistent with results from previous studies reporting that more than 80% of patients with AMD have bilateral involvement [18, 19]. In this study, both the patient's studied eye and their non-studied eye had baseline vision $\geq$ 20/63 (83% and 96%, respectively); however, mean baseline VA decreased with each successive dAMD stage. Among patients with GA with and without subfoveal involvement, most patients had VA scores of $\geq$ 20/160; however, more than 20% of eyes with GA studied had $<$ 20/400 vision. In patients with GA, the proportion of non-studied eyes with VA $<$ 20/400 was 1.7%. In a published study from the UK that included patients with bilateral GA, approximately 7% had VA $<$ 20/400 in the better-seeing eye at baseline [7]. However, in that study only patients with bilateral GA were included, potentially indicating greater disease severity.

Although our model allows for patients to progress directly from mild to severe disease, clinically, patients with disease progression will progress from mild to intermediate to neovascular AMD. However, this progression may not be captured if a patient is diagnosed with mild disease, does not visit a clinician during the progression phase, and is diagnosed with neovascular AMD during their next visit. Therefore, the EHR would not include a diagnosis of intermediate dAMD. Patients who progress from mild dAMD to neovascular AMD may also have been misdiagnosed with mild disease when, in actuality, they had intermediate dAMD. Again, the EHR would not include such an intermediate dAMD diagnosis.

Both our descriptive and modeling results demonstrated a faster and more prominent vision decline with each progressive dAMD stage, particularly among those with better baseline VA scores. Among patients with GA in at least one eye and an observation 1-year post-index date, VA dropped in the eye with GA by approximately five letters annually. Results from mixed-effects linear models, adjusting for age and sex, showed an average yearly drop between 2.5 and 3.9 letters among patients with GA. In addition, results from a Markov model showed the annual probability of progression from a $\geq$ 20/63 to $<$ 20/1000 Snellen category was almost fivefold greater among study eyes with GA with subfoveal involvement compared with mild dAMD. These results suggest that a rapid vision decline is associated with the most progressive disease stages when the central fovea becomes affected with GA.

Our estimates on rates of AMD progression are similar to other published estimates, although differences exist. Among a prevalent GA cohort with a mean follow-up of at least 2 years, 13.8% demonstrated subsequent neovascular AMD [20]. We found that at a mean follow-up of 1.8 years (following adjustment for censoring criteria), 8% of prevalent eyes with GA developed subsequent neovascular AMD. In another study, the rate of progression in patients with bilateral mild/intermediate dAMD to GA was 2.0 per 100 person-years and to neovascular AMD was 3.2 per 100 person-years [21]. We found rates of progression of 1.7 per 100 person-years for GA and 2.5 per 100 person-years for neovascular AMD.

Strengths and Limitations

The strength of this study is powered by the heterogeneous patient cohort from approximately 75% of ophthalmic encounters in the USA, largely representative of national ophthalmology care and to a lesser extent, optometric care. Other strengths are the size and scale of the data source, the longitudinal records of reliable and critical outcomes seen in clinical practice, codified clinical activity, and the recorded VA measurement and dAMD staging from ophthalmology specialists.

However, identification and follow-up were limited to eye specialist care, thus disease progression and care received outside of this setting were not captured. Additionally, lesion size/imaging data were not available through IRIS, and as our analysis was based on the worst-seeing eye, our ability to evaluate bilateral disease progression was limited. We balanced the cut points used in our VA definitions, which were similar to those used in select clinical trials, with samples sizes needed for modeling and therefore lost some granularity in data, primarily for the better VA categories.

The IRIS Registry also lacks full academic medical center coverage which may result in the current study observing patients with less severe dAMD compared to a population-based study. It may also appear that ophthalmology clinicians do not holistically capture the comorbidity profile. While this should be considered in the interpretation of this study and future studies, one could argue that these numbers align with common clinical practice. Additionally, we relied on diagnostic coding for disease progression; given that progression rates were based on physician ICD-9/10 coding practices, there could be inaccuracies in coding that influenced our results. Finally, information on vision loss due to comorbidities such as cataracts and the use of AREDS supplements is not included in the registry.

A limitation of the progression analyses is the Markov property, a limitation of all Markov models, which states that the probability distribution of moving from one state to another depends only upon the present state and not on the sequence of events that preceded it. Furthermore, it is assumed that the risk of transition is constant over time.

CONCLUSIONS

This is the first known study to report the distribution of the dAMD population by both VA and disease severity for all stages of dAMD. Index VA was progressively worse with more severe dAMD, and progression was generally faster with each progressive dAMD stage. Disease progression to GA and neovascular AMD occurred considerably faster once a patient reached intermediate dAMD. The progression rates to neovascular AMD, and the availability of anti-VEGF injection therapy for this condition, indicate the importance of close monitoring of the dAMD population, particularly once patients reach the intermediate stage. The annual rate of ophthalmologic-related visits was consistent across dAMD stages, at about three visits annually, with increases noted for those with intermediate dAMD to GA with subfoveal involvement compared to mild dAMD. By understanding how dAMD progresses over time and the resources required by patients with dAMD, prospects could emerge to impact the burden of dAMD and advance opportunities to resolve unmet needs.

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Compliance with Ethics Guidelines. This research was reviewed by the WCG Institutional Review Board. Research and analysis were conducted on anonymized data in accordance with the de-identification standard promulgated under 45 CFR § 164.514, and no research was conducted on human subjects. No patient authorization was required because solely de-identified data were analyzed.

Data Availability. Researchers may request access to anonymized participant level data, trial level data, and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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