

# Forecasting Age-Related Macular Degeneration Through the Year 2050

## *The Potential Impact of New Treatments*

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**Objective:** To forecast age-related macular degeneration (AMD) and its consequences in the United States through the year 2050 with different treatment scenarios.

**Methods:** We simulated cases of early AMD, choroidal neovascularization (CNV), geographic atrophy (GA), and AMD-attributable visual impairment and blindness with 5 universal treatment scenarios: (1) no treatment; (2) focal laser and photodynamic therapy (PDT) for CNV; (3) vitamin prophylaxis at early-AMD incidence with focal laser/PDT for CNV; (4) no vitamin prophylaxis followed by focal laser treatment for extra and juxtafoveal CNV and anti-vascular endothelial growth factor treatment; and (5) vitamin prophylaxis at early-AMD incidence followed by CNV treatment, as in scenario 4.

**Results:** Cases of early AMD increased from 9.1 million in 2010 to 17.8 million in 2050 across all scenarios. In non-vitamin-receiving scenarios, cases of CNV and GA increased from 1.7 million in 2010 to 3.8 million in 2050 (25% lower in vitamin-receiving scenarios). Cases of visual impairment and blindness increased from 620 000 in 2010 to 1.6 million in 2050 when given no treatment and were 2.4%, 22.0%, 16.9%, and 34.5% lower in scenarios 2, 3, 4, and 5, respectively.

**Conclusion:** Prevalence of AMD will increase substantially by 2050, but the use of new therapies can mitigate its effects.

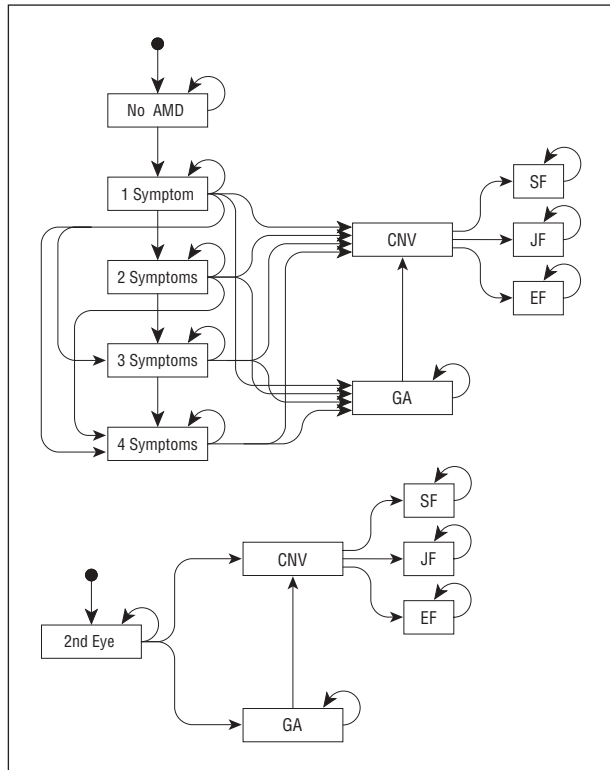
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**A**GE-RELATED MACULAR DEGENERATION (AMD) is a macular disorder characterized by drusen deposits, retinal pigment epithelium (RPE) abnormalities, geographic atrophy (GA) of the RPE and the choriocapillaris, and neovascular maculopathy.<sup>1</sup> In 2000, as many as 1.75 million Americans experienced advanced vision-threatening stages of AMD (choroidal neovascularization [CNV] and GA) and millions more had asymptomatic early disease.<sup>2</sup> In the United States, AMD is the estimated cause of 54.4% of visual impairment and 22.9% of blindness among white persons. Among Hispanic and black persons, the percentages are smaller but still significant.<sup>3</sup> The direct medical cost of AMD treatment was estimated at \$575 million in the United States in 2004 dollars, excluding nursing home costs, productivity losses, and home health care costs incurred by those with AMD,<sup>4</sup> a cost that is expected to increase with the increased use of new CNV treatments.

The prevalence of AMD and its resultant morbidity is likely to increase as the US population ages because the annual incidence of AMD increases with age from less than 1% for those younger than 60 years to greater than 5% for people aged 80 years and older.<sup>5</sup> By 2050, the number of people in the United States aged 65 years and older is expected to more than double from 2005 levels to 82.7 million.<sup>6</sup> By 2050, the number of Americans aged 80 years and older is forecast to grow to nearly the current number of people older than 65 years.

Newly discovered prophylactic and treatment therapies for AMD offer substantial improvements over past therapies and could potentially offset some degree of future AMD morbidity. While thermal laser photocoagulation has been used to treat extrafoveal and juxtafoveal CNV since the 1980s,<sup>7,8</sup> before 2000 no therapies existed for the prevention or treatment of subfoveal CNV, the most common vision-threatening form of the disease (treatments are still unavailable for GA). In 2001, the Age-Related Eye Disease Study (AREDS)

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**Figure 1.** Visual representation of a natural history model of age-related macular degeneration (AMD). No AMD indicates no drusen or retinal pigment epithelium (RPE) abnormalities in either eye; 1 symptom, either large drusen (defined as greater than 125  $\mu\text{m}$ ) in one eye or RPE abnormalities in one eye; 2 symptoms, large drusen in both eyes with no RPE abnormalities, RPE abnormalities in both eyes with no large drusen, or large drusen in one eye with RPE abnormalities in one eye; 3 symptoms, large drusen in both eyes with RPE abnormalities in one eye or large drusen in one eye with RPE abnormalities in both eyes; 4 symptoms, large drusen and RPE abnormalities in both eyes; CNV, choroidal neovascularization; EF, extrafoveal; GA, geographic atrophy; JF, juxtafoveal; SF, subfoveal; 2nd eye, first eye has transitioned to CNV or GA and second eye has the risk of transitioning seen with 4 symptoms. Modified from *Ophthalmology*.<sup>11</sup>

reported a 25% reduction in the risk of progression to advanced AMD (GA or any form of CNV) in patients with early AMD who took antioxidant vitamin supplements plus zinc.<sup>9</sup> Also in 2001, the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy Study reported that treatment with photodynamic therapy (PDT) using verteporfin could stem the rate of visual loss in patients with subfoveal CNV,<sup>10</sup> the first effective treatment identified for subfoveal CNV. Subsequent research has established the cost-effectiveness of both antioxidant vitamin prophylaxis and PDT.<sup>11,12</sup> More recently in 2006, clinical trials demonstrated that ocular injections of anti-vascular endothelial growth factor (anti-VEGF) such as ranibizumab or bevacizumab can improve vision and/or prevent additional vision loss for up to 2 years in patients with subfoveal CNV with far greater efficacy than that achieved with PDT.<sup>13-15</sup>

If widely adopted, new AMD treatments could alter the future burden of the disease by delaying the onset of advanced AMD and by diminishing the visual impact of CNV. In this paper, we use a simulation model to forecast the epidemiology of AMD in a variety of treatment scenarios for the years 2010 through 2050.

We modified a previously published agent-based simulation model of AMD and its outcomes to forecast future rates of AMD and its visual sequelae. Agent-based simulations differ from traditional simulation and Markov models in that they do not require an abstraction of the disease to a population level—the processes are resolved at the level of the individual. This allows agents to exhibit more flexible and complex internal and external behavior, which facilitates the simulation of more complex models. In this section we focus on the key components of the model and any modifications made to the previous models to create forecasts. Diagrams and additional explanation of the model are published elsewhere<sup>11,16</sup> and in an online technical appendix ([www.rti.org/AMDForecasts.pdf](http://www.rti.org/AMDForecasts.pdf)).

Our model is based on the AREDS simplified scale, which defines early AMD as drusen greater than 125  $\mu\text{m}$  or RPE abnormalities in one or both eyes and advanced AMD as any evidence of CNV or GA (**Figure 1**).<sup>17</sup> We defined CNV as extrafoveal, juxtafoveal, or subfoveal CNV without regard to its occult or classic status. Geographic atrophy was defined as an area of partial or complete depigmentation of the RPE involving the center of the macula.<sup>17,18</sup> To create forecasts, we first used our simulation model to estimate the prevalence rate of each disease state.<sup>11,16</sup> We then calculated cases of each condition in 2010, 2020, 2030, 2040, and 2050 by multiplying sex-, race/ethnicity-, and age-specific prevalence rates from the model by sex-, race/ethnicity-, and age-specific US Census Bureau population forecasts for each year.<sup>6</sup>

To estimate AMD prevalence rates, our model simulated a population of individuals beginning at 50 years of age until death or 100 years of age and output the prevalence rates of each disease state for each age-, sex-, and race/ethnicity-specific group. We multiplied the simulated prevalence rates by the Census population forecasts<sup>6</sup> to estimate the number of people in each disease state in each year. We varied life expectancy and incidence of early AMD by age, sex, and race/ethnicity (**Table 1**). We used AMD incidence data from the Beaver Dam Eye Study<sup>5</sup> and the Blue Mountains Eye Study<sup>21</sup> for white persons; from the Multi-ethnic Study of Atherosclerosis<sup>19</sup> for African American persons; and from the Los Angeles Latino Eye Study for Hispanic persons.<sup>20</sup>

For all scenarios, we used starting prevalence rates of early and advanced disease based on 2004 data<sup>2,19,20</sup> and estimated the subsequent prevalence rates for those older than 50 years of early AMD, CNV, GA, AMD-related visual impairment, and AMD-related blindness by age group, sex, and race/ethnicity. Age groups were divided into 5-year increments starting at 50 years (eg, 50-54 years, 55-59 years). We used current life expectancy estimates in forecasts for all future years.

We modeled the progression of early AMD to CNV and GA based on the presence or absence of large drusen and/or RPE abnormalities in one or both eyes from AREDS data.<sup>11,17</sup> We modeled visual acuity losses in increments of 0.3 or 0.6 logarithmic units.

We generated forecasts for 5 universal treatment scenarios: (1) no treatment; (2) focal laser for extrafoveal and juxtafoveal CNV or PDT for subfoveal CNV; (3) vitamin prophylaxis at early-AMD incidence with CNV treatment, as specified in scenario 2; (4) no vitamin prophylaxis followed by focal laser treatment for extrafoveal and juxtafoveal CNV and anti-VEGF treatments for subfoveal CNV; and (5) vitamin prophylaxis at early AMD incidence followed by CNV treatment, as specified in scenario 4 (**Table 2**). In the vitamin prophylaxis scenarios, we assume individuals are treated with the AREDS-recommended antioxidant vitamins plus zinc regimen on incidence of AMD.<sup>9</sup>

**Table 1. AMD Epidemiology and Population Inputs**

Input	Value	Source
Population older than 40 y by year, No. in thousands		
Black		US Census Bureau, 2000 <sup>6</sup>
2010	10 138	
2050	20 673	
White		
2010	82 488	
2050	114 447	
Hispanic		
2010	8336	
2050	26 910	
Prevalence of AMD at 49 y of age		
Black	0.004	Klein et al, 2006 <sup>19</sup>
White	0.030	Friedman et al, 2004 <sup>2</sup>
Hispanic	0.062	Varma et al, 2004 <sup>20</sup>
Annual incidence of early AMD by age in y		
Black		Klein et al, 2006 <sup>19</sup>
55-64	0.002	
>65	0.004	
75-84	0.004	
White		Klein et al, 2002, <sup>5</sup> and Mitchell et al <sup>21</sup>
50-59	0.005	
60-69	0.014	
70-79	0.030	
>80	0.038	
Hispanic		Varma et al, 2004 <sup>20</sup>
50-59	0.002	
60-69	0.003	
70-79	0.007	
>80	0.012	

Abbreviation: AMD, age-related macular degeneration.

**Table 2. Use of Treatments in Each Simulated Scenario**

Scenario	Vitamins	Laser Therapy and PDT <sup>a</sup>	Anti-VEGF Treatment
1	No	No	No
2	No	Yes	No
3	Yes	Yes	No
4	No	Laser only <sup>b</sup>	Yes
5	Yes	Laser only <sup>b</sup>	Yes

Abbreviations: CNV, choroidal neovascularization; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

<sup>a</sup>Laser therapy was for extrafoveal and juxtafoveal CNV; PDT for subfoveal CNV.

<sup>b</sup>Focal laser was used to treat extrafoveal and juxtafoveal CNV; anti-VEGF treatment was used in place of PDT to treat subfoveal CNV.

Patients who received vitamins experienced a 25% reduction in their annual probability of forward progression to a more advanced stage of disease.<sup>9</sup> Patients with CNV without treatment or patients who received focal laser or PDT with verteporfin treatments lost acuity based on the values observed in untreated and treated eyes of participants enrolled in clinical trials for laser therapy and PDT (**Table 3**).<sup>22-25</sup> Individuals who progressed to GA also lost acuity based on published values.<sup>9</sup> Patients with subfoveal CNV who received anti-VEGF treatment experienced a one-time probability of improving vision and a subsequently reduced probability of losing vision for a period of 2 years regardless of whether vision initially improved.<sup>10</sup> We assumed only a 2-year efficacy period to avoid projecting the ef-

**Table 3. Effects of AMD Prevention and Treatment Interventions Used in the Model**

Variable	Parameter Value	Source
Relative risk of AMD progression with vitamins	0.75	AREDS Research Group, 2001 <sup>9</sup>
Extrafoveal		
Lose 0.3 log units of acuity from extrafoveal	0.040	Macular Photocoagulation Study Group, 1991 <sup>22</sup>
Lose 0.6 log units of acuity from extrafoveal	0.178	Macular Photocoagulation Study Group, 1991 <sup>22</sup>
Lose 0.3 log units of acuity from extrafoveal with laser therapy	0.035	Rein et al, 2007, <sup>16</sup> and Macular Photocoagulation Study Group, 1991 <sup>22</sup>
Lose 0.6 log units of acuity from extrafoveal with laser therapy	0.136	Rein et al, 2007, <sup>16</sup> and Macular Photocoagulation Study Group, 1991 <sup>22</sup>
Juxtafoveal		
Lose 0.3 log units of acuity from juxtafoveal	0.052	Macular Photocoagulation Study Group, 1994 <sup>23</sup>
Lose 0.6 log units of acuity from juxtafoveal	0.186	Macular Photocoagulation Study Group, 1994 <sup>23</sup>
Lose 0.3 log units of acuity from juxtafoveal with laser therapy	0.050	Rein et al, 2007, <sup>16</sup> and Macular Photocoagulation Study Group, 1991 <sup>22</sup>
Lose 0.6 log units of acuity from juxtafoveal with laser therapy	0.157	Rein et al, 2007, <sup>16</sup> and Macular Photocoagulation Study Group, 1991 <sup>22</sup>
Subfoveal		
Lose 0.3 log units of acuity from subfoveal with no care	0.423	Verteporfin in Photodynamic Therapy Study Group, 2001 <sup>24</sup>
Lose 0.6 log units of acuity from subfoveal with no care	0.275	Verteporfin in Photodynamic Therapy Study Group, 2001 <sup>24</sup>
Annual probability of losing 3 lines of visual acuity with PDT	0.206	Verteporfin in Photodynamic Therapy Study Group, 2001 <sup>24</sup>
Annual probability of losing 6 lines of visual acuity with PDT	0.134	Verteporfin in Photodynamic Therapy Study Group, 2001 <sup>24</sup>
Annual probability of losing 3 lines of visual acuity with anti-VEGF therapy	0.066	Takeda et al, 2007 <sup>15</sup>
Annual probability of losing 6 lines of visual acuity with anti-VEGF therapy	0	Takeda et al, 2007 <sup>15</sup>
Annual probability of gaining 3 lines of visual acuity with anti-VEGF therapy	0.266	Takeda et al, 2007 <sup>15</sup>

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; log, logarithmic; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

fects of these medications beyond the period demonstrated in clinical trials. After 2 years, we assumed individuals continued to receive anti-VEGF therapies, but that they experience rates of visual loss associated with undergoing PDT.<sup>24</sup> We assumed the alternative anti-VEGF therapies of ranibizumab and bevacizumab injections were equally efficacious.

### SENSITIVITY ANALYSIS

We evaluated how sensitive our results were to changes in the major model parameters by altering the values of AMD inci-

**Table 4. Average Model Estimated Population Prevalence Rates of Each AMD State From 2010 to 2050 Given 5 Different Treatment Assumptions for All Patients Aged 50 Years and Older**

Scenario <sup>b</sup>	Percentage in Each Stage <sup>a</sup>					
	AMD	CNV	GA	Visual Impairment	Blindness	Total Impairment
1	12.01	1.37	0.58	0.42	0.31	0.73
2	12.01	1.37	0.58	0.47	0.25	0.72
3	11.70	1.06	0.43	0.36	0.20	0.57
4	12.01	1.37	0.58	0.42	0.19	0.61
5	11.70	1.06	0.43	0.32	0.15	0.48

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; GA, geographic atrophy; VEGF, vascular endothelial growth factor.

<sup>a</sup>Note that CNV and GA are not mutually exclusive of visual impairment, blindness, and total impairment; visual impairment, blindness, and total impairment refer to that attributable to AMD only.

<sup>b</sup>Scenario 1 indicates no treatment (baseline); scenario 2, focal laser or PDT for CNV; scenario 3, universal vitamin prophylaxis at early AMD incidence with focal laser or PDT for CNV treatment; scenario 4, no vitamin prophylaxis followed by focal laser treatment for extrafoveal and juxtafoveal CNV and anti-VEGF treatments for subfoveal CNV for 2 years followed by PDT; and scenario 5, universal vitamin prophylaxis followed by focal laser and anti-VEGF treatments for subfoveal CNV for 2 years followed by PDT.

dence, the magnitude of the effects of vitamin prophylaxis and anti-VEGF treatments, and the duration of anti-VEGF therapies. We examined the effect of a 25% decrease and a 25% increase on AMD incidence rates, of 25% reductions on the efficacy of vitamin and anti-VEGF therapies, and the effect of extending the efficacy of anti-VEGF therapies for 5 years as opposed to the 2 years assumed in our baseline model. We also calculated the effect of using the US Census lower and upper series population estimates in place of the middle series used in our baseline estimate.

## MODEL VALIDATION

We validated our model by comparing the overall prevalence rates of early and advanced AMD in those older than 50 years estimated by our model using our focal laser and PDT treatment scenario (scenario 2, the closest treatment match to past practice) with the mean value and range of published estimates and to the results from an National Eye Institute–sponsored meta-analysis for advanced AMD only (we could not compare our estimates of early AMD with the National Eye Institute results because of differences between their definition of early AMD and ours).<sup>26-30</sup>

## RESULTS

Our model produced valid replications of prevalence rates observed in previously published studies. Our model's prevalence rates from the validation scenario (scenario 2) were 12.01% for early AMD compared with a mean of 14.7% (range, 9.9% to 19.5%) from published studies, and 1.95% for advanced AMD compared with a mean of 2.6% for advanced AMD (range, 1.1% to 3.9%) from published studies, and 2.1% from the National Eye Institute meta-analysis estimate.

We forecasted that the combined prevalence rate (**Table 4**) of AMD-attributable visual impairment and blindness in people aged 50 years and older could be decreased from 0.73% when forecasting the outcomes that would occur without treatment to 0.48% when assuming fully compliant use of antioxidant vitamin prophylaxis, anti-VEGF treatment for subfoveal CNV, and focal laser therapy for extrafoveal and juxtafoveal CNV (scenario 5).

Prevalence rates of early and advanced AMD did not vary between the 3 scenarios in which vitamins were not

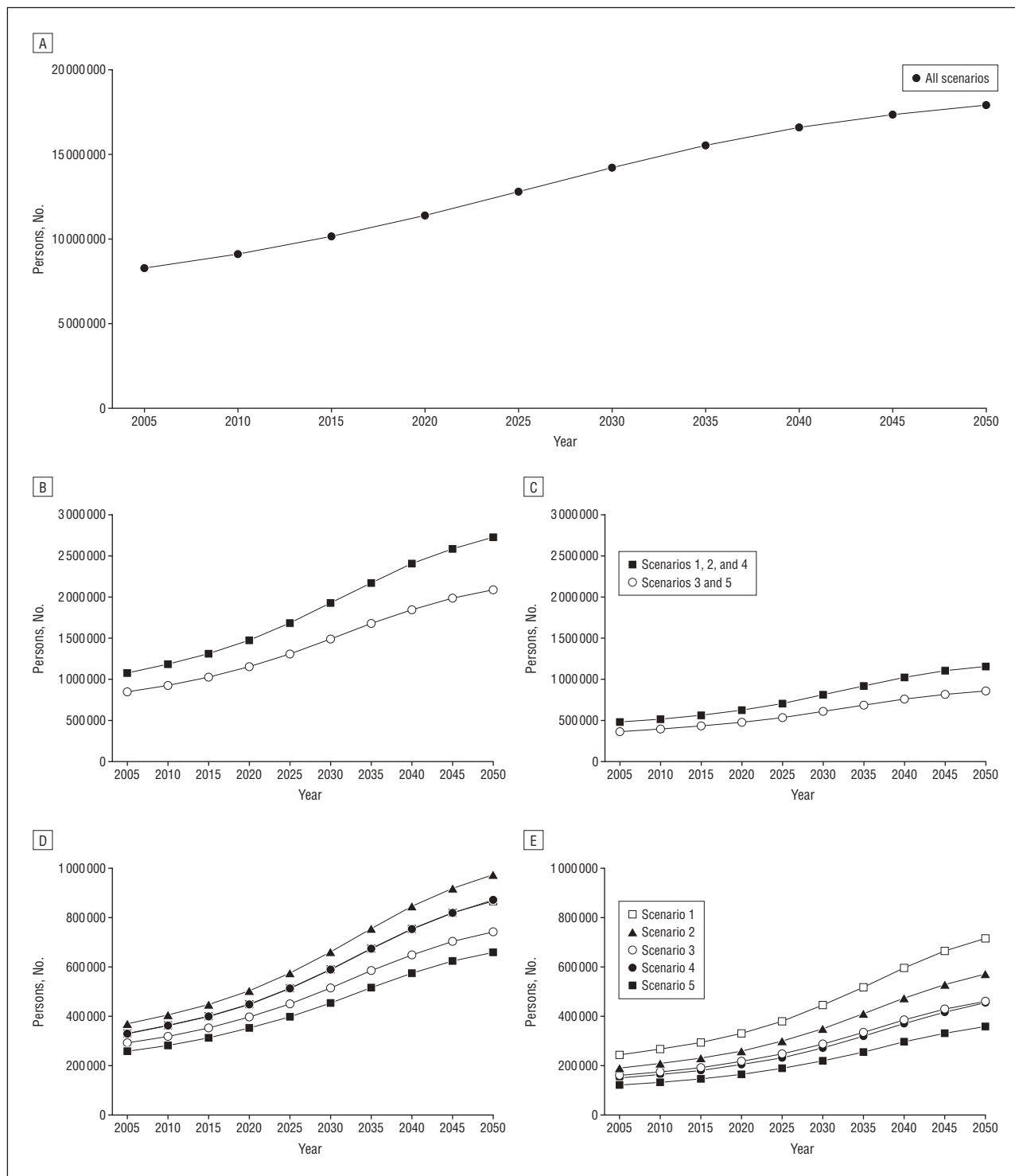
used (1, 2, and 4) because the medical treatments used only affect visual loss and not disease progression. Prevalence rates of early and advanced AMD were slightly lower in the 2 scenarios in which vitamins were used (3 and 5) because patients who remained in early AMD due to vitamin prophylaxis experienced a greater number of years in which to possibly transition backward to no AMD symptoms as a result of their lower probability of progression to advanced AMD.<sup>16,17</sup>

For visual outcomes, PDT and laser therapy alone (scenario 2) relative to no treatment delayed the onset of blindness in patients with existing visual impairment but only reduced the total rate of any impairment by a small amount. In contrast, vitamins and anti-VEGF therapies reduced both the proportion of patients who developed blindness and the total proportion of patients who experienced any impairment. Reductions in the total proportion of patients who experienced any impairment in the better-seeing eye were lower in scenarios that used vitamins (3 and 5) than in the scenario that used anti-VEGF therapy alone (4).

Because none of our treatments prevented incident disease, we projected a nearly identical number of early AMD cases across treatment scenarios, a total of approximately 9.1 million cases in 2010 increasing to approximately 17.8 million in 2050 for scenarios 1, 2, and 4 (**Figure 2**). These numbers were slightly lower in the vitamin-use scenarios (3 and 5, by a degree that is difficult to see in the figure). The number of forecasted cases for advanced AMD varied by the use of vitamins, with approximately 25% more cases of advanced AMD in scenarios in which vitamins were not used (1, 2, and 4) than in scenarios in which vitamins were used (3 and 5).

In 2010, we forecast 620 000 cumulative cases of visual impairment and blindness for scenario 1, 605 000 for scenario 2, 485 000 for scenario 3, 515 000 for scenario 4, and 410 000 for scenario 5. In 2050, we forecast these numbers to grow to 1.57 million, 1.54 million, 1.20 million, 1.32 million, and 1.00 million for scenarios 1 through 5, respectively.

In 2050, assuming no treatment (scenario 1), decreasing and increasing the incidence of AMD by 25% resulted



**Figure 2.** Number of Americans with pre-vision-threatening age-related macular degeneration (AMD) (A), choroidal neovascularization (CNV) (B), geographic atrophy (GA) (C), AMD-related visual impairment (D), and blindness (E), with 5 alternative treatment scenarios from 2010 to 2050. Scenario 1 indicates no treatment (baseline); scenario 2, focal laser or photodynamic therapy (PDT) for CNV; scenario 3, universal vitamin prophylaxis at early AMD incidence with focal laser or PDT for CNV treatment; scenario 4, no vitamin prophylaxis followed by focal laser treatment for extrafoveal and juxtafoveal CNV and anti-vascular endothelial growth factor (anti-VEGF) treatments for subfoveal CNV for 2 years followed by PDT; scenario 5, universal vitamin prophylaxis followed by focal laser and anti-VEGF treatments for subfoveal CNV for 2 years followed by PDT.

in forecasts of 14.5 million to 20.8 million cases of early AMD, 3.2 million to 4.5 million cases of advanced AMD, and 1.3 million to 1.8 million cases of combined visual impairment and blindness. In 2050, assuming the maximum benefit of treatment, (scenario 5) decreasing and in-

creasing the incidence of AMD by 25% resulted in forecasts of 860 000 to 1.15 million cases of combined visual impairment and blindness. Based on scenario 1, using the highest or lowest Census projections results in a 2050 prevalence of AMD from 15.4 million to 20.5 million (17.8

million baseline) and visual impairment and blindness from 1.3 million to 1.8 million (1.57 million baseline). Results for the other scenarios showed similar sensitivity to changes in census estimates.

Reducing the effectiveness of vitamin prophylaxis by 25% resulted in an increase in the prevalence rates of CNV, GA, visual impairment, and blindness to, respectively, 1.12%, 0.46%, 0.39%, and 0.21% in scenario 3, and to 1.12%, 0.46%, 0.34%, and 0.16% in scenario 5. Reducing the effect of anti-VEGF therapy by 25% had no effect on the prevalence rates of CNV and GA and resulted in a modest increase in the prevalence rates of visual impairment and blindness to 0.43% and 0.20% in scenario 4 and 0.34% and 0.16% in scenario 5. The primary effect of increasing the duration of efficacy of anti-VEGF therapies from 2 to 5 years was to prevent patients from progressing from visual impairment to blindness. In scenario 5, this resulted in a reduction in the prevalence of blindness from 0.15% to 0.13%, while the additive prevalence of cumulative visual impairment and blindness remained the same as when assuming an efficacy period of 2 years.

## COMMENT

Our model predicts large increases in both cases of early and advanced AMD and the visual impairment and blindness attributable to it over the next 40 years regardless of the treatment steps taken, with virtually all of these increases attributable to the aging of the US population. However, existing medical therapies have the potential to reduce the visual impairment and blindness attributable to AMD by as much as 35%, translating to 565 000 fewer cases of visual impairment and blindness in 2050.

We found that a 23% reduction in cases of visual impairment and blindness could be achieved using only vitamin prophylaxis in conjunction with focal laser and PDT therapies for patients who develop CNV, a reduction of 375 000 cases of visual impairment and blindness in 2050. Conversely, scenario 4, which simulated the outcomes expected with no vitamin therapy followed by universal use of anti-VEGF therapies, reduced cases of visual impairment and blindness a smaller amount, 16%, compared with no treatment. This comparative effect of anti-VEGF therapies is substantial considering that in this model, anti-VEGFs were used only to treat subfoveal CNV after that condition had led to initial visual loss in at least 1 eye. In contrast, vitamins were used on an untargeted basis by all patients with early AMD.

With a low annual cost of approximately \$100 per patient per year, vitamin therapy is a cost-effective<sup>11</sup> prophylactic therapy for individuals with early AMD that can substantially reduce impairment resulting from AMD.<sup>4</sup> Recent evidence indicates that though antioxidant use in the United States is improving, opportunities exist to increase their use. Only 61% of patients indicated for antioxidants surveyed from the patient pool of a tertiary ophthalmic center reported using antioxidant supplements of the correct dosage.<sup>31</sup> Information from the Beaver Dam Eye Study also suggests that at least some US patients currently use antioxidant therapy but that more patients would likely benefit from their use.<sup>32</sup> Evidence from Canada and Australia indicates

that vitamin use is well below universal levels, and patients who use supplements rarely take the correct dose. For example, although 68% of patients with early AMD who visited a retinal specialty practice in Edmonton, Canada, took some form of AREDS-recommended antioxidant supplement, no patients were taking the correct dosage of all 4 recommended vitamins.<sup>33</sup> Among patients with early AMD attending an academic ophthalmology center at the University of Adelaide, 38% had used some form of antioxidant supplements, but only 1% used the correct dosage.<sup>34</sup> Several efforts have been made to package the correct dosage of AREDS vitamin supplement at an affordable price.<sup>35</sup> Additional efforts to expand the use of these supplements may be a cost-effective use of health care resources.

Anti-VEGF therapies also show great promise for mitigating the effects of advanced AMD. However, their current use is mired in controversy. Bevacizumab and ranibizumab are similar chemical compounds,<sup>36</sup> but bevacizumab costs approximately \$40 per dose compared with approximately \$2000 per dose for ranibizumab. The relative efficacy of bevacizumab compared with ranibizumab is unknown, but cost-effectiveness research from the United Kingdom indicates that ranibizumab would have to be more than twice as effective in preventing vision loss to justify its use over bevacizumab at current prices.<sup>37</sup> Interested parties have moved to restrict the sale of bevacizumab to compounding pharmacies for ocular use, citing safety concerns as their motivation.<sup>38</sup>

Not surprisingly, our sensitivity analysis indicated that lower rates of efficacy for both vitamin prophylaxis and anti-VEGF therapies would result in greater numbers of visually impaired and blind patients. Our sensitivity analyses also indicated that assumed increases or decreases in the incidence of AMD of 25% translated into less than 25% increases or decreases in threatened vision and vision loss stages of AMD. This was because the greatest amount of incidence in our model occurred at older ages in patients who were likely to die of natural causes prior to developing complications of AMD. Our estimates were also sensitive to possible error in the Census population projections, and our results varied by as much as 17% in either direction when using the low and high Census estimates of future population.

Our study had several limitations. First, like all projections our model attempts to use contemporary data to predict outcomes occurring in the distant future. Error embedded in our current data or in the Census population projections could lead to substantial differences in our results compared with those that actually occur in the future. Our model does not account for any future changes in treatment technologies that could dramatically alter forecasts of AMD and its consequences. Further, because of a lack of trend data indicating otherwise, we assume that the age-specific incidence of AMD and disease progression of AMD will remain constant into the future. Changes in personal behavior such as reductions in smoking rates and greater intake of dietary antioxidants may contribute to lower future rates of AMD incidence and progression. Although we have tried to mitigate the effect of uncertain data using sensitivity analyses, like all forecasts these should be treated as estimates that contain a good deal of embedded uncertainty.

Second, little is known about the efficacy of anti-VEGF therapy after the 24 months observed in clinical trials, and the ability of anti-VEGF therapies to treat forms of CNV other than subfoveal CNV is undemonstrated. To be conservative and stay within the bounds of what has been demonstrated in clinical trials, our baseline estimates assumed that anti-VEGF therapies were only efficacious for 2 years and that thereafter patients would only realize the efficacy associated with PDT. Our sensitivity analyses, in which we assume anti-VEGF therapies would be efficacious for up to 5 years, indicate that the potential benefits of these treatments may be larger than we have demonstrated. Further, the relative efficacy of bevacizumab vs ranibizumab is currently unknown, although clinical trials are under way to examine their relative performance.<sup>39</sup> In this study, we assumed equivalence between the 2 therapies, given a lack of evidence to the contrary.

Third, for each of our scenarios, we assumed full diagnosis and compliance with clinical recommendations for the use of antioxidant vitamins and anti-VEGF treatments. Actual patients are likely to use these therapies at substantially lower rates than assumed in our forecasts. Considerable investment of time and resources would be required to achieve full compliance.

Fourth, our forecasts of future cases of each stage of AMD use US Census Bureau population estimates first developed in the early 1990s, and mortality databased on current trends. Any inaccuracies contained in the Census estimates are reflected in our AMD forecasts.

Finally, we assume patient compliance with each treatment scenario for their entire lives. In our analysis some patients are assumed to have contracted AMD and begun treatment in the past; obviously this could not be the case, as all modeled AMD treatments except focal laser treatment have been developed within the past 10 years. Thus, forecasts in the near future should be interpreted as what could have been and not what will be under each treatment scenario. However, the error introduced by this assumption is limited, because most patients with AMD do not reach an advanced stage until they are older.

We found that the number of cases of early and advanced AMD and AMD-attributable visual impairment and blindness will increase substantially between 2010 and 2050 regardless of the treatment steps taken. However, expanding the use of antioxidant vitamins in patients with early AMD and using anti-VEGF therapy to treat subfoveal CNV can reduce the levels of future AMD-attributable visual impairment and blindness by as much as 35%. Public prevention efforts should focus on expanding the use of antioxidant vitamins in people with early AMD and ensuring that these patients use the correct dosage. Expanded use of anti-VEGF therapies is also highly likely to reduce morbidity from CNV, although its cost-effectiveness remains uncertain. Additional efforts should be made to make these treatments widely available to patients with CNV at a price that is fair to both the payer and the producer.

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#### From the Archives of the Archives

**N**uel describes 16 cases of sympathetic amblyopia. In all except one, in which there had been a burn, a perforating injury had taken place, after which, often years later, amblyopia developed with partial atrophy of the nerve. The disturbance came on at a time when the injured eye was free from irritation, and even after an early enucleation had been done. The latter was of no avail when once the affection had appeared. The ophthalmoscopic picture consists in a woolliness of the disc and capillary hyperemia. Finally there is temporal atrophy; pure atrophy was never observed. The prognosis, as compared with other sympathetic affections, is favorable. Treatment with gray ointment and rest is of value, but the effect of enucleation of the injured eye is doubtful. The origin of the affection is doubtful.

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