

**Forecasting Age-Related Macular Degeneration through 2050: The Potential Impact of
New Treatments**

Technical Appendix

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1 This technical report has been compiled to provide supporting documentation and
2 information for the manuscript “Forecasting Age-Related Macular Degeneration through 2050:
3 The Potential Impact of New Treatments”. The AMD model described below and a more
4 extensive technical report describing its functioning have been published elsewhere, and readers
5 of this report should also refer to those sources for additional detail and information on the
6 external validation of the model.^{1,2} This report contains abbreviated information providing:

- 7 • A brief technical overview of the model’s functioning
- 8 • A graphical representation of the model
- 9 • A discussion of how the use of the model for the forecasting paper differed from its use
10 in the past.

11 **1. Overview**

12 For this analysis we used the CDC-RTI Multiple Eye Disease Simulation model (CR-
13 MEDS), a stochastic, agent-based model to simulate the natural history and ophthalmologic care
14 of ocular disease. The CR-MEDS has also been used to assess the cost-effectiveness of vitamin
15 prophylaxis therapy for AMD,¹ to assess the impact and cost-effectiveness of office-based
16 assessment and treatment of primary open angle glaucoma in the United States,³ to assess the
17 cost-effectiveness of glaucoma interventions in the developing world,⁴ and to assess the relative
18 cost effectiveness of different screening intervals and modalities for diabetes patients with no or
19 mild diabetic retinopathy.⁵

20 The model creates a population of agents, each a representation of a person, and follows
21 them annually until death or age 100. Agents contain internal modules representing the
22 development of ocular disease in each eye, including age-related macular degeneration (AMD),
23 diabetic retinopathy (DR), primary open-angle glaucoma (POAG), nuclear cataract and
24 uncorrected refractive error (URE). Disease development may impact the agents’ visual acuity,
25 contrast sensitivity and visual field, which in turn impact agent utility, probability of long-term
26 care placement and expected productivity. Patients may interact with the healthcare system to
27 seek ophthalmologic screening and treatment, which impacts the incidence, progression or

28 outcomes of ocular disease. For this analysis, we used only the AMD and ophthalmologic care
29 modules and do not consider any outcomes other than the prevalence rates of disease and visual
30 impairment and blindness. However, the model also compiles the medical costs, quality adjusted
31 life years (QALYs), productivity, long-term care cost, medical care usage, disease prevalence,
32 and visual loss prevalence incurred by the population.

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34 **2. Model Type and Characteristics**

35 The MEDS model is as a stochastic, agent-based model (ABM) that simulates multiple
36 concurrent processes in a simulated population. ABMs simulate individual people and endow
37 them with the traits necessary to run the analysis. ABMs differ from traditional discrete event
38 simulations (including Markov models) in that they do not require the modeler to create a unique
39 state to represent each possible combination of variables or traits needed for the analysis. This
40 allows the simulation to more easily account for a large number of contingencies than a discrete
41 event simulation allowing the model to more easily capture a greater degree of complexity.
42 ABM techniques are generally employed for capturing interaction between members of a
43 population and their environment. The MEDS model does not require agent interaction, but
44 adherence to ABM methods and object-oriented programming practices allows the model to
45 effectively handle complex internal and external agent behavior.

46 In the case of the MEDS model, each agent encompasses separate internal discrete event
47 processes that:

- 48 • Assign baseline individual characteristics of gender, ethnicity, and prevalent
49 disease at model initiation, the presence of risk factors or co-morbidities and
50 determine patient mortality
- 51 • Simulate subsequent incidence and progression of eye-disease (in this case AMD)

- 52 • Simulate the use of routine eye-care services or if specified specific care
53 interventions
- 54 • Track the outcomes of the model such as whether the agent has AMD, and the
55 presence and extent of any impairment suffered by the patient

56

57 These modules interact to produce composite, person-level results. Person-level results
58 are then combined to produce estimates for the population. This design allows a person's vision
59 state to be modeled as a function of the vision state of both eyes and the vision state of each
60 individual eye to be modeled as a function of disease progression. Disease progression is then
61 determined in part by treatment (in the case of this application most interestingly vitamin therapy
62 or anti-VEGF therapy.

63 For each individual agent, AMD incidence, progression through disease states, and the
64 visual consequences of disease are determined by probabilities collected from data and published
65 studies (outlined in the manuscript tables 2 and 3 and in the previously published sources), and
66 random chance. For example, in any given year without vitamin treatment a patient in the
67 earliest stage of AMD (stages outlined below) has a 0.888 probability of remaining in that state
68 and a 0.112 probability of transitioning to another state. Computationally, the model generates a
69 random number between 0 and 1 and compares this random value to transition parameter.
70 Agents with a value of 0.888 or lower remain in the mild state while agents with greater values
71 transition to other states.

72 Because of the stochastic nature of the model, each individual agent follows a separate
73 trajectory. To generate results, the model runs a series of simulated samples containing 10,000
74 agents each and calculates population estimates for each outcome of interest for each sample. In

75 order to achieve stable estimates we run 2,000 sets of samples (20 million simulated agents) for
76 each model scenario. Model results represent the average sample outcome value across these
77 2,000 simulated samples. CR-MEDS was programmed in java using AnyLogic Version 5.2 (XJ
78 Technologies Company, LTD, <http://www.xjtech.com>). The model is run on RTI's 128-node
79 Linux-based computer cluster.

80 **3. AMD Module**

81 The AMD module simulates the incidence, progression, and visual consequences of AMD.
82 The model logic divides AMD into early and vision threatening AMD states (Figure 1). Early
83 AMD states are simulated at the agent level and characterized based on presence or absence of
84 drusen and/or RPE abnormalities in one or both eyes. Early AMD is classified into no disease
85 and then four mutually exclusive states based on the Age-related Eye Disease Study (AREDS)
86 simplified severity scale.⁶

87 State zero is no disease

- 88 • In State 1, patients have either large drusen (defined as greater than 125 μm) in one
89 eye or RPE abnormalities in one eye, with no other symptoms.
- 90 • In State 2, patients either have large drusen in both eyes, with no RPE abnormalities;
91 or no large drusen, with RPE abnormalities in both eyes; or large drusen in one eye,
92 with RPE abnormalities in one eye.
- 93 • In State 3, patients have large drusen in both eyes, with RPE abnormalities in one
94 eye; or large drusen in one eye, with RPE abnormalities in both eyes.
- 95 • In State 4, patients have large drusen in both eyes, with RPE abnormalities in both
96 eyes.

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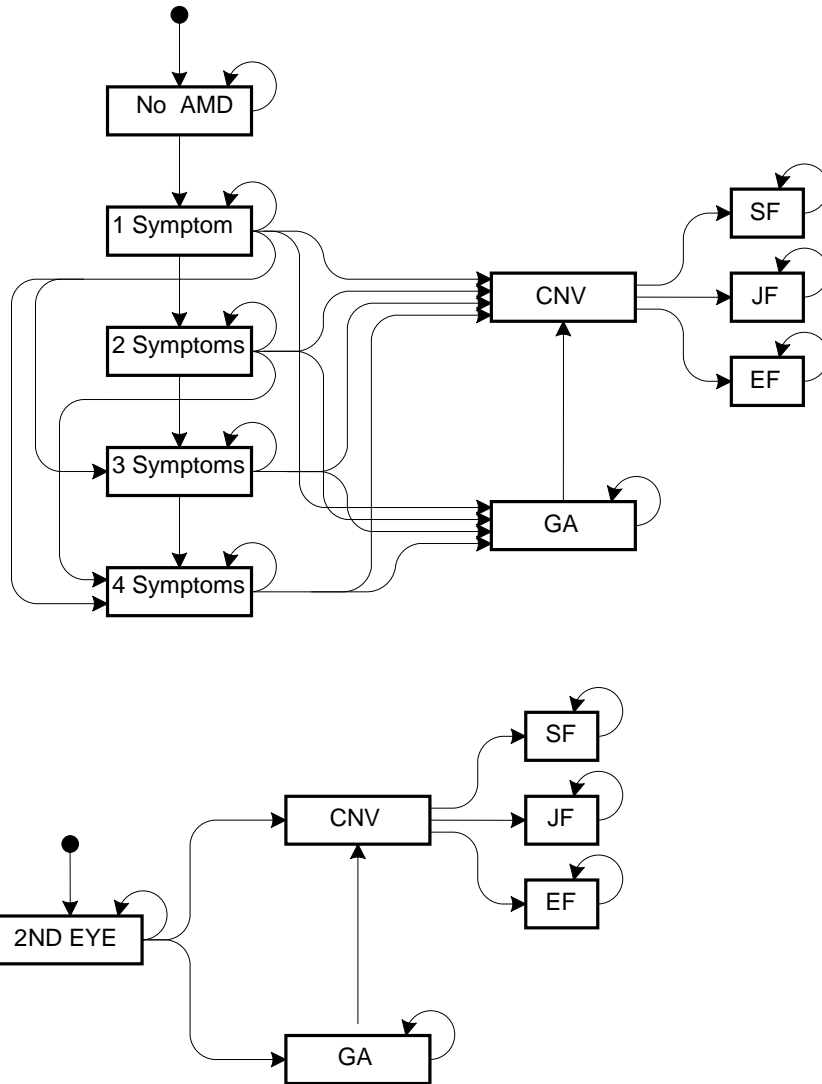
98 Patients in any early state have an annual probability of transitioning to any other state or
99 to one of two advanced vision threatening states geographic atrophy (GA) or choroidal
100 neovascularization (CNV) (Table 1).

101 Vision threatening states are simulated at the eye, as opposed to the patient level. The
102 first agent transition to vision threatening disease is considered to take place in the first eye.
103 The patient's second eye is then assumed to have the same probability of transitioning to

104 advanced disease as if it were in State 4. Eyes with GA can also develop CNV, whereas eyes
105 that developed CNV remain there until a patient's death.^{7,8} Based on its proximity to the
106 fovea, CNV was classified as extrafoveal, juxtafoveal, or subfoveal, with treatment options
107 and the annual probability of visual loss depending on the type and the simulated scenario.
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Figure 1. Visual Representation of AMD Model. The upper image represents the non-vision threatening or early stages of disease, and the transition of the first eye to vision threatening states. The lower image represents the second eye following the progression of the first eye to a vision threatening state. (Images modified from Rein, Saaddine, and Wittenborn, Et Al 2007)¹



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118 No AMD = no drusen or retinal pigment epithelium (RPE) abnormalities in either eye; 1 Symptom = either large
119 drusen (defined as greater than 125 μm) in one eye or RPE abnormalities in one eye; 2 Symptoms = large drusen in
120 both eyes, with no RPE abnormalities, or RPE abnormalities in both eyes with no large drusen; or large drusen in

121 one eye, with RPE abnormalities in one eye; 3 Symptoms = large drusen in both eyes with RPE abnormalities in one
122 eye or large drusen in one eye with RPE abnormalities in both eyes; 4 Symptoms = large drusen in and RPE
123 abnormalities in both eyes; CNV = choroidal neovascularization; SF = subfoveal; JF = juxtafoveal; EF =
124 extrafoveal; GA = geographic atrophy; 2nd Eye = first eye has transitioned to CNV or GA and second eye has the
125 risk of transitioning seen with 4 symptoms.

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128 Loss of visual function occurred in each eye individually only from CNV or GA in
129 increments of 0.3 or 0.6 log units of visual acuity. Patients with CNV without treatment or
130 patients who received focal laser or PDT with verteporfin treatments lost acuity based on the
131 values observed in untreated and treated eyes of participants enrolled in clinical trials for
132 laser therapy and PDT (Table 3).⁹⁻¹² Individuals who progressed to GA also lost acuity based
133 on published values.¹³ Visual impairment and blindness were defined based on the visual
134 health of the agent's better-seeing eye. Agents with acuity of 20/40 or worse were defined as
135 visually impaired and those with an acuity of 20/200 or worse were defined as blind.

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137 Table 1. Annual AMD Progression Rates of Leading Eye Through AMD Categories (Reprinted
 138 from Rein, Saaddine, and Wittenborn, et al 2007 technical report)²

		To						
		0	1	2	3	4	GA	CNV
From	0	AD ^a	AD ^a	0	0	0	0	0
	1	AD ^a	0.888	0.036	0.012	0.004	0.001	0.005
	2	0	0.038	0.851	0.057	0.026	0.002	0.017
	3	0	0.014	0.043	0.824	0.078	0.012	0.030
	4	0	0.002	0.012	0.034	0.881	0.039	0.037
	5-GA	0	0	0	0	0	0.971	0.029
	6-CNV	0	0	0	0	0	0	1.00

139 ^aAge-dependent (AD) incidence probabilities derived from population-based study data as reported in the literature.

140 **4. Differences in The Forecasting Application Of This Model From Previous Applications**

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142 The model presented in our forecasting application was run differently from the previously
143 application of the model of AMD in the following ways.

- 144 • As outlined in the text, this version of the model contained parameters governing the use
145 of anti-vascular endothelial growth factor (anti-VEGF) therapies. In scenarios in which
146 anti-VEGF therapies were used, agents who developed subfoveal CNV were treated with
147 anti-VEGF injections and experienced a one-time probability of improving vision and a
148 subsequent reduced probability of losing vision for a period of 2 years regardless of
149 whether vision initially improved.¹⁴ Our baseline model assumed only a 2-year efficacy
150 period of anti-VEGFs after which individuals are assumed to experience rates of visual
151 loss associated with PDT.¹²
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- 153 • We updated the model to use AMD incidence rates stratified by ethnicity, age, and
154 gender. The previous model stratified only by age and gender. Further, we ran the model
155 separately by ethnicity to develop our population forecasts. Prevalence rates shown in
156 the manuscript represent the overall population prevalence after weighting for ethnicity.
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- 158 • Also as outlined in the manuscript, we generated forecasts by multiplying model
159 generated age-specific prevalence rates by the U.S. Census population forecasts, shown
160 in Table 2.

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164 Table 2. Forecast US Population, in thousands

WHITE	2005	2010	2015	2020	2025	2030	2035	2040	2045
50 to 54 years.....	16,429	18,119	17,861	15,756	14,645	14,926	16,037	16,617	17,065
55 to 59 years.....	14,334	16,041	17,703	17,470	15,431	14,378	14,681	15,793	16,379
60 to 64 years.....	11,022	13,824	15,482	17,112	16,923	15,001	14,020	14,339	15,449
65 to 69 years.....	8,621	10,393	13,059	14,664	16,247	16,112	14,343	13,435	13,801
70 to 74 years.....	7,270	7,724	9,360	11,816	13,322	14,828	14,766	13,207	12,415
75 to 79 years.....	6,563	6,237	6,685	8,162	10,389	11,794	13,217	13,250	11,931
80 to 84 years.....	4,972	4,976	4,797	5,219	6,449	8,298	9,517	10,765	10,882
85 to 89 years.....	2,746	3,131	3,208	3,160	3,508	4,408	5,761	6,709	7,693
90 to 94 years.....	1,257	1,453	1,714	1,816	1,842	2,102	2,705	3,616	4,303
95 +	464	590	735	923	1066	1162	1,364	1,784	2,462
total	73,678	82,488	90,604	96,098	99,822	103,009	106,411	109,515	112,380

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BLACK	2005	2010	2015	2020	2025	2030	2035	2040	2045
50 to 54 years.....	2,270	2,676	2,792	2,653	2,661	2,787	3,009	3,322	3,438
55 to 59 years.....	1,749	2,194	2,589	2,705	2,577	2,593	2,732	2,953	3,267
60 to 64 years.....	1,274	1,676	2,112	2,502	2,627	2,518	2,548	2,685	2,912
65 to 69 years.....	1,042	1,230	1,632	2,057	2,446	2,581	2,489	2,527	2,685
70 to 74 years.....	780	872	1,038	1,385	1,758	2,105	2,240	2,174	2,217
75 to 79 years.....	621	648	732	879	1,184	1,520	1,839	1,975	1,933
80 to 84 years.....	383	428	454	522	635	869	1,127	1,377	1,492
85 to 89 years.....	202	230	263	284	332	412	573	752	929
90 to 94 years.....	105	118	138	162	178	213	269	382	508
95 +	55	66	79	97	119	139	170	217	308
total	8,481	10,138	11,829	13,246	14,517	15,737	16,996	18,364	19,689

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HISPANIC	2005	2010	2015	2020	2025	2030	2035	2040	2045
50 to 54 years.....	1,778	2,270	2,714	2,862	3,017	3,330	3,643	3,997	4,669
55 to 59 years.....	1,352	1,759	2,231	2,667	2,814	2,976	3,288	3,600	3,953
60 to 64 years.....	989	1,330	1,716	2,175	2,600	2,753	2,918	3,228	3,538
65 to 69 years.....	770	963	1,284	1,654	2,095	2,508	2,660	2,827	3,134
70 to 74 years.....	599	716	889	1,183	1,526	1,936	2,322	2,469	2,633
75 to 79 years.....	470	544	648	806	1,076	1,391	1,771	2,130	2,274
80 to 84 years.....	308	387	449	538	672	902	1,171	1,496	1,807
85 to 89 years.....	155	220	279	325	393	496	672	878	1,130
90 to 94 years.....	78	98	142	182	215	264	338	464	614
95 +	34	49	66	94	128	161	204	267	371
total	6,533	8,336	10,418	12,486	14,536	16,717	18,987	21,356	24,123

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170 **References**

171

- 172 **1.** Rein DB, Saaddine JB, Wittenborn JS, et al. Cost-effectiveness of vitamin therapy for age-
173 related macular degeneration. *Ophthalmology*. Jul 2007;114(7):1319-1326.
- 174 **2.** Rein DB, Saaddine JB, Wittenborn JS, et al. Technical appendix: cost-effectiveness of
175 vitamin therapy for age-related macular degeneration. *Ophthalmology*. Jul
176 2007;114(7):e13-20.
- 177 **3.** Rein DB WJ, Lee PP, Wirth KE, Sorensen SW, Hoerger TJ, Saaddine JB. The Cost-
178 Effectiveness of Routine Office-Based Identification and Subsequent Medical Treatment
179 of Primary Open-Angle Glaucoma. *Ophthalmology*. In press.
- 180 **4.** Wittenborn JW, DB R. Simulating Visual Outcomes in the Developing World: The
181 Epidemiologic Burden of Glaucoma and the Cost-effectiveness of Interventions to
182 Reduce Glaucomatic Visual Loss in the Barbados and Ghana. Working Paper.
- 183 **5.** Rein DB, Wittenborn JW, Allaire BA, S L, Klein R, Saaddine J. The cost-effectiveness of
184 telemedicine monitoring of diabetic retinopathy among patients with type 2 diabetes.
185 Working Paper.
- 186 **6.** Ferris FL, Davis MD, Clemons TE, et al. A simplified severity scale for age-related
187 macular degeneration: AREDS Report No. 18. *Arch Ophthalmol*. Nov
188 2005;123(11):1570-1574.
- 189 **7.** van Leeuwen R, Klaver CCW, Vingerling JR, Hofman A, de Jong P. The risk and natural
190 course of Age-Related Maculopathy. Follow-up at 6 1/2 years in the Rotterdam Study.
191 *Archives of Ophthalmology*. 2003;121:519-526.

- 192 **8.** Sunness JS, Gonsalez-Baron J, Bressler NM, Hawkins B, Applegate CA. The
193 development of choroidal neovascularization in eyes with the geographic form of Age-
194 related Macular Degeneration. *Ophthalmology*. 1999;106:910-919.
- 195 **9.** Macular Photocoagulation Study G. Argon laser photocoagulation for neovascular
196 maculopathy. Five year results from randomized clinical trials. *Archives of*
197 *Ophthalmology*. 1991;109:1109-1114.
- 198 **10.** Macular Photocoagulation Study G. Laser photocoagulation for juxtafoveal choroidal
199 neovascularization. Five year results from randomized clinical trials. *Archives of*
200 *Ophthalmology*. 1994;112:500-509.
- 201 **11.** Chung PY, Schuman JS, Netland PA, Lloyd-Muhammad RA, Jacobs DS. Five-year
202 Results of a Randomized, Prospective, Clinical Trial of Diode vs Argon Laser
203 Trabeculoplasty for Open-Angle Glaucoma. *American Journal of Ophthalmology*.
204 1998;126:185-190.
- 205 **12.** Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal
206 choroidal neovascularization in Age-Related Macular Degeneration: Two-year results of
207 a randomized clinical trial including lesions with occult with no classic choroidal
208 neovascularization - Verteporfin in Photodynamic Therapy report 2. *American Journal of*
209 *Ophthalmology*. 2001;131:541-560.
- 210 **13.** Age-Related Eye Disease Study Research G. A randomized, placebo-controlled clinical
211 trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-
212 related macular degeneration and vision loss. AREDS report no. 8. *Archives of*
213 *Ophthalmology*. 2001;119:1417-1436.

214 **14.** Moshfeghi AA, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin)
215 therapy for neovascular age-related macular degeneration: twenty-four-week results of an
216 uncontrolled open-label clinical study. *Ophthalmology*. Nov 2006;113(11):2002 e2001-
217 2012.
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