

Economic Value of Anti-Vascular Endothelial Growth Factor Treatment for Patients With Wet Age-Related Macular Degeneration in the United States

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IMPORTANCE Anti-vascular endothelial growth factor (anti-VEGF) is a breakthrough treatment for wet age-related macular degeneration (wAMD), the most common cause of blindness in western countries. Anti-VEGF treatment prevents vision loss and has been shown to produce vision gains lasting as long as 5 years. Although this treatment is costly, the benefits associated with vision gains are large.

OBJECTIVE To estimate the economic value of benefits, costs for patients with wAMD, and societal value in the United States generated from vision improvement associated with anti-VEGF treatment.

DESIGN, SETTING, AND PARTICIPANTS This economic evaluation study used data from the published literature to simulate vision outcomes for a cohort of 168 820 patients with wAMD aged 65 years or older and to translate them into economic variables. Data were collected and analyzed from March 2018 to November 2018.

MAIN OUTCOMES AND MEASURES Main outcomes included patient benefits, costs, and societal value. Each outcome was estimated for a newly diagnosed cohort and the full population across 5 years, with a focus on year 3 as the primary outcome because data beyond that point may be less representative of the general population. Drug costs were the weighted mean across anti-VEGF therapies. Two current treatment scenarios were considered: less frequent injections (mean [SD], 8.2 [1.6] injections annually) and more frequent injections (mean [range], 10.5 [6.8-13.1] injections annually). The 2 treatment innovation scenarios, improved adherence and best case, had the same vision outcomes as the current treatment scenarios had but included more patients treated from higher initiation and lower discontinuation.

RESULTS The study population included 168 820 patients aged 65 years at the time of diagnosis with wAMD. The underlying clinical trials that were used to parameterize the model did not stratify visual acuity outcomes or treatment frequency by sex; therefore, the model parameters could not be stratified by sex. The current treatment scenario of less frequent injections generated \$1.1 billion for the full population in year 1 and \$5.1 billion in year 3, whereas the scenario of more frequent injections generated \$1.6 billion (year 1) and \$8.2 billion (year 3). Three-year benefits ranged from \$7.3 billion to \$11.4 billion in the improved adherence scenario and from \$9.7 billion to \$15.0 billion if 100% of the patients initiated anti-VEGF treatment and the discontinuation rates were 6% per year or equivalent to clinical trial discontinuation (best-case scenario). Societal value (patient benefits net of treatment cost) ranged from \$0.9 billion to \$3.0 billion across 3 years in the current treatment scenarios and from \$0.9 billion to \$4.3 billion in the treatment innovation scenarios.

CONCLUSIONS AND RELEVANCE This study's findings suggest that improved vision associated with anti-VEGF treatment may provide economic value to patients and society if the outcomes match published outcomes data used in these analyses; however, future innovations that increase treatment utilization may result in added economic benefit.

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Age-related macular degeneration (AMD) is an eye condition that affects approximately 11 million individuals in the United States.¹ It results in vision loss and could lead to blindness, which is associated with an economic burden of \$9 billion per year.² This eye condition is categorized as either dry or wet, with the latter manifesting with choroidal neovascularization. Treatments for patients diagnosed with dry AMD are limited to nutritional supplements and lifestyle changes that may slow the progression of the condition but do not provide vision improvement.³ In contrast, substantial innovation has occurred for wet AMD (wAMD), which accounts for approximately 10% of all AMD cases.^{1,4} The wAMD treatments (anti-vascular endothelial growth factor [anti-VEGF]) not only prevent further vision loss, but also produce vision improvement lasting as long as 5 years.^{5,6}

Although multiple anti-VEGF therapies exist, unmet need remains high owing to treatment underutilization, driven primarily by insufficient uptake and high discontinuation.⁷ Approximately 53% to 58% of Medicare patients discontinue treatment within the first year.^{7,8} Although cost is cited as a treatment barrier, a less expensive anti-VEGF treatment with similar efficacy and safety as one of the US Food and Drug Administration-approved therapies is available off-label.⁹ Other reasons for discontinuation include fear or discomfort associated with injections to the eye or lack of perceived need.¹⁰

Monthly anti-VEGF treatment has been standard in clinical trials and is associated with better vision improvement. However, regular treatment and monitoring requires substantial time commitment¹¹ and may contribute to poor compliance. This treatment burden has been recognized by ophthalmologists¹²; consequently, personalized treatment strategies attempt to balance the treatment burden against potentially reduced efficacy.

One strategy follows a treat-as-needed approach. Clinical trials have reported similar vision outcomes with monthly treatments during the first year; however, improvement in visual acuity was less likely to be maintained after 2 years.⁹ Moreover, even though patients are treated only as needed, they still receive a monthly examination. Alternatively, a treat-and-extend (TE) approach reduces treatments and visits. After 3 monthly injections, the interval between injections is extended up to 12 weeks based on patient response, and examinations are not needed between treatments.^{12,13} Most ophthalmologists (70%) primarily use the TE approach compared with 10% who use the as-needed approach, and 2% who treat monthly (the remaining 18% use a mixture of treatment strategies).¹⁴

Understanding the economic value associated with anti-VEGF therapies as a class may provide insight into the gains from current treatment and future innovations. Although some authors have focused on the cost of anti-VEGF treatment, their work does not consider the benefits of that spending.^{15,16} To quantify the economic value of anti-VEGF treatment in the United States, we estimated the value of vision improvements associated with this therapy across 5 years. We considered scenarios that reflected the trade-off between treatment burden and efficacy. To explore the potential value from

Key Points

Question How much economic value do anti-vascular endothelial growth factor (anti-VEGF) treatments generate for patients with wet age-related macular degeneration and society in the United States?

Findings In this economic evaluation study, visual acuity improvement associated with anti-VEGF treatments generated \$5.1 billion to \$8.2 billion in patient benefits and \$0.9 billion to \$3.0 billion in societal value (patient benefits net of treatment costs) across 3 years. Treatment innovations associated with improved adherence generated an additional \$7.3 billion to \$15.0 billion in patient benefits and \$0.9 million to \$4.3 billion in societal value compared with current treatment scenarios.

Meaning This study's findings suggest that improved visual acuity associated with anti-VEGF treatment may provide economic value, and future innovations may result in added economic benefit.

future innovations that improve treatment compliance, we modeled scenarios that increased the number of treated patients relative to current estimates. Finally, we quantified the potential economic benefit from a best-case, idealized scenario to represent the unmet need that could be addressed by future treatment advances.

Methods

The data were collected and analyzed from March 2018 to November 2018. In this economic evaluation study, we simulated visual acuity (VA) for a cohort of patients with wAMD aged 65 years across 5 years, and translated VA into quality-adjusted life-years (QALYs).¹⁷ Our cohort of 168 820 adults was derived by applying the wAMD incidence rate to the total population of the United States aged 50 years or older.^{18,19} We assumed the cohort was 65 years old and incorporated mortality risk using 5-year age-adjusted mortality rates from the National Vital Statistics.²⁰ Mortality was adjusted to account for increased mortality associated with poor VA (adjusted for age, sex, and other confounders).²¹ Baseline VA was 55 letters (modal VA at diagnosis across 7 community-based studies²²). Treatment was initiated in year 1, and we allowed for discontinuation each year. Patients underwent fluorescein angiography at their first visit and optical coherence tomography at noninjection visits. During injection visits, patients received anti-VEGF treatment and optical coherence tomography. Model variables were drawn from the published literature and are described in the eMethods, eTable 1, eTable 2, eTable 3, eTable 4, and eTable 5 in the [Supplement](#), along with a full description of model assumptions. The institutional review board at the University of Southern California approved the study and deemed it exempt from review because it does not involve human subjects.

Model Scenarios

Current Treatment Scenarios

All scenarios were compared with a baseline no-treatment scenario, which assumed that all patients in the cohort were

Table 1. Model Scenarios

Scenario (Source)	Description	Year 1		Year 2		Year 3		Year 4		Year 5	
		VA Change ^a	Injections, No.	VA Change ^a	Injections, No.	VA Change ^a	Injections, No.	VA Change ^a	Injections, No.	VA Change ^a	Injections, No.
Baseline scenario											
No treatment ^b (HORIZON ²⁵)	Patients do not receive anti-VEGF therapy	-10.1	0	-9.6	0	-11.8	0	-11.8	0	-16.1	0
Current treatment scenarios											
Less frequent injections (Mrejen et al, ²³ 2015)	Patients receive anti-VEGF therapy following a TE regimen	6.5	8.96	6.5	7.78	6.0	7.94	4.5	8.03	-0.5	8.12
More frequent injections (Peden et al, ⁵ 2015)	Patients receive anti-VEGF therapy (10.5 injections annually)	13.2	10.5	16.1	10.5	15.4	10.5	14.6	10.5	14.0	10.5

Abbreviations: TE, treat and extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

^a Visual acuity change is the change from baseline VA and is measured in Early Treatment Diabetic Retinopathy Study letter score.

^b The HORIZON VA and injection parameters correspond to the control group.

untreated. To estimate the value of current therapy, we considered 2 scenarios that reflected the treatment strategies used by ophthalmologists. The first scenario (less frequent injections) is based on the study by Mrejen et al²³ and assumes that patients receive a mean (SD) of approximately 8.2 (1.6) anti-VEGF injections per year under a TE regimen.

The second scenario (more frequent injections) is based on the study by Peden et al⁵ and assumes that patients receive a mean (range) of 10.5 (6.8-13.1) injections annually. This scenario approximates the label indication for ranibizumab, which recommends monthly injections.²⁴ Table 1 provides VA changes and injection frequencies for both scenarios.

Treatment Innovation Scenarios

To explore the value of improved adherence, we considered several treatment innovation scenarios. For each current treatment scenario, we estimated innovation scenarios that assumed VA outcomes and injection frequencies were the same but with modified treatment uptake and discontinuation.

The improved adherence scenario assumed that 80% of patients initiated therapy vs 65% in current treatment scenarios.⁷ In addition, discontinuation rates were only 17% in year 1 and increased annually, reaching 50% in year 5.²³ We also considered a best-case scenario that estimated an upper bound on the potential value from current treatments. In these scenarios, 100% of patients with wAMD initiated therapy, and discontinuation rates were 6% annually, which was the rate observed in clinical trials.²⁵ Finally, to understand the potential value gains from future therapies with better VA outcomes compared with current anti-VEGF treatments, we considered the hypothetical cure scenario, which assumed that all patients with wAMD received a 1-time treatment resulting in permanent 20/40 visual acuity.

Statistical Analysis

Model Outcomes

Microsoft Excel was used for the study analyses. We estimated the following outcomes for each scenario: number

treated, patient benefits, and total costs. Patient benefits equal the total QALYs from VA improvements multiplied by \$150 000 (assumed based on the literature),^{26,27} Total costs include drug and clinical treatment costs.^{28,29} We assumed a per-injection drug cost of \$896, which represents the weighted average of ranibizumab (\$1865), aflibercept (\$1938), and bevacizumab (\$77). Weights were based on a study of commercially insured and Medicare Advantage patients.³⁰ Treatment cost included the costs of injection visits (\$225) and noninjection visits (\$122). Future dollar values were discounted at 3% per year. Societal value estimates were calculated as the difference between patient benefits and total costs. All outcomes are presented for a single incident (ie, newly diagnosed) cohort and at the population level, which assumed that new incident cohorts entered the model annually.

Sensitivity Analysis

We ran sensitivity analyses for key parameters for all scenarios. Our first sensitivity analysis varied drug utilization weights, which altered the total cost. We also conducted a sensitivity analysis on the assumed value for QALYs. Because patient benefits are derived from VA improvements, we performed sensitivity analyses that varied VA-related parameters, as follows: (1) baseline VA; (2) annual VA changes; and (3) simultaneously varied baseline VA and annual changes. Finally, we considered alternative scenarios that used injection frequency data from the study by Peden et al⁵ and VA outcome data from the study by Mrejen et al²³ and vice versa as well as scenarios with subgroup data (subgroups are classified by neovascular subtype). Parameters used in sensitivity analyses are provided in eTable 10, eTable 13, and eTable 15 in the Supplement.

Results

Benefits for a Single Patient

The study population included 168 820 patients aged 65 years or older and diagnosed with wAMD. The underlying clinical trials

that were used to parameterize the model did not stratify visual acuity outcomes or treatment frequency by sex; therefore, the model parameters could not be stratified by sex. To provide a sense of the magnitude of dollar benefits generated from VA improvements, we presented the benefits for a single patient who received the anti-VEGF treatment for the full 5-years. Visual acuity improvements from the less frequent injections scenario translated into \$10 918 in benefits after 1 year, which increased to \$32 158 at 3 years and \$49 558 at 5 years. The more frequent injections scenario generated \$15 525, \$50 839, and \$84 873 in benefits at 1, 3, and 5 years, respectively. The hypothetical cure scenario measured unmet need as follows: increasing VA to 20/40 permanently generated \$29 215 in benefits at 1 year, \$63 506 at 3 years, and \$98 308 at 5 years.

Current Treatment Scenarios

The studies used for VA outcomes experienced attrition over time and therefore may be less representative of the general population, particularly after year 3. Rather than truncate our model horizon, we provided results for the time frame for which we had data (5 years) in eTable 6, eTable 7, eTable 8, and eTable 9 in the [Supplement](#) and focused on year 3 results because estimates in later years may be less generalizable.

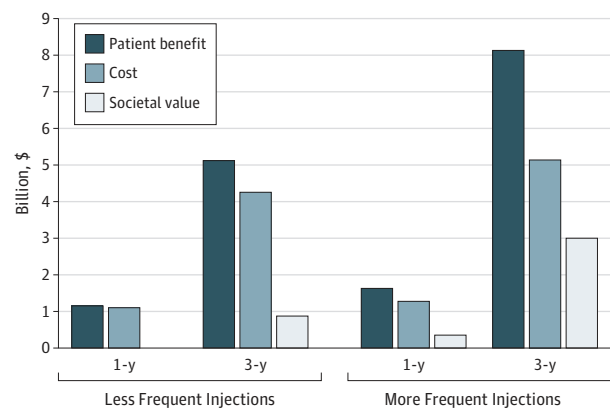
Figure 1 shows cumulative patient benefits, total costs, and societal value for current treatment scenarios for the full population. Year 1 results for the full population include only 1 cohort and therefore are identical to 1-year single incident cohort results (eTable 6 in the [Supplement](#)). Compared with the no-treatment scenario, the less frequent injections scenario generated \$1.1 billion in patient benefits in year 1 vs \$1.6 billion generated by the more frequent injections scenario. At 3 years, patient benefits from the less frequent injections scenario increased to \$5.1 billion, and patient benefits from the more frequent injections scenario increased to \$8.2 billion.

In the single incident cohort, the total costs incurred were \$1.7 billion across 3 years for the less frequent injections scenario and \$2.2 billion for the more frequent injections scenario, reflecting the higher number of injections. At the population level, 3-year total costs were \$4.3 billion for the less frequent injections scenario and \$5.2 billion for the more frequent injections scenario. Societal value (patient benefits net of treatment cost) ranged from \$0.9 billion to \$3.0 billion across 3 years in the current treatment scenarios (eTable 8 and eTable 9 in the [Supplement](#)). Across 3 years, societal value for less frequent injections was \$0.9 billion for the full population. In comparison, the more frequent injections scenario generated \$2.1 billion additional societal value across 3 years. Therefore, even though the more frequent injections scenario incurred additional costs, the additional patient benefits were substantially higher than those of the less frequent injections scenario, resulting in higher societal value.

Treatment Innovation Scenarios

Figure 2 shows patient benefits for the treatment innovation scenarios, which reflect the potential value of innovation compared with the corresponding current treatment scenario. The improved adherence scenario generated \$3.5 billion to

Figure 1. Patient Benefits, Costs, and Societal Value Associated With Anti-Vascular Endothelial Growth Factor (VEGF) Treatment Compared With No Treatment



The figure shows the benefits and costs for current treatment scenarios for the full population. Societal value is calculated as patient benefits net of treatment costs. Population benefits and costs assume that new incident cohorts enter the model each year. Future values are discounted at a rate of 3%.

\$5.6 billion in patient benefits (single incident cohort) and \$7.3 billion to \$11.4 billion (full population) across 3 years. Results for scenarios that only include individual effects (eg, only modify adherence or only modify discontinuation) are provided in eTable 8 and eTable 9 in the [Supplement](#).

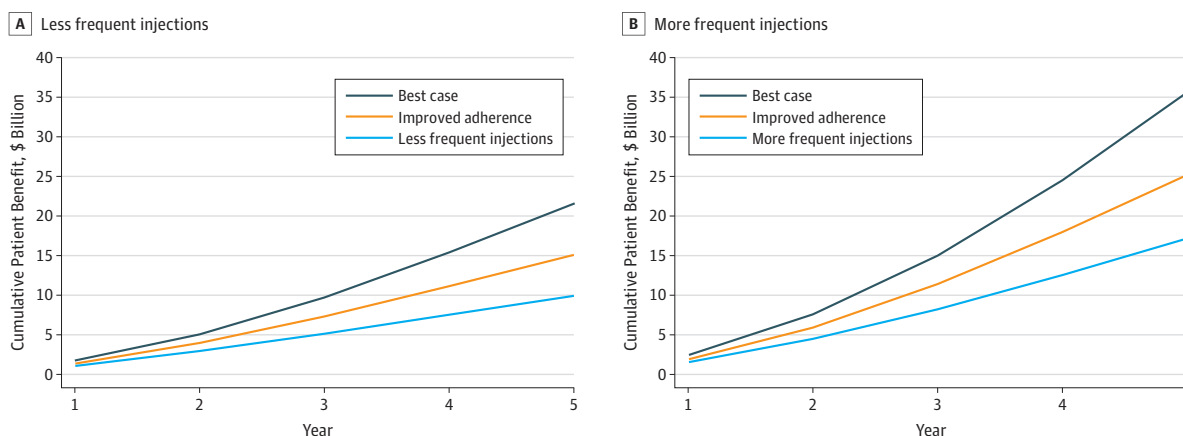
The best-case less frequent injections scenario generated \$9.7 billion in patient benefits for the full population across 3 years, which corresponds to an approximately 42% increase in patient benefits compared with that of the improved adherence scenario (\$7.3 billion) and an 89% increase compared with that of the less frequent injections scenario (\$5.1 billion). Similarly, the best-case more frequent injections scenario generated \$15.0 billion in patient benefits for the full population across 3 years, or almost double that of the more frequent injections scenario (\$8.2 billion). We compared the patient benefits for both current treatment scenarios along with their corresponding best-case scenarios with the hypothetical cure scenario in [Table 2](#). For the full population, hypothetical cure would generate \$6.8 billion in patient benefits at year 1 and \$23.7 billion at year 3.

Sensitivity Analyses

Full results for sensitivity analyses are provided in eTable 11, eTable 12, eTable 14, eTable 16, eFigure 1, and eFigure 2 in the [Supplement](#). Patient benefits from the more frequent injections scenario were positive under all parameter values tested. Less frequent injections also generated positive patient benefits under all values except for low baseline VA sensitivities.

Drug utilization shares altered societal value through drug costs. For the full population, if we reduced the share of bevacizumab from 55% to 28%, the societal value across 3 years was -\$964 million to \$783 million. Conversely, if we increased the bevacizumab share to 72%, the 3-year societal value for the full population increased from \$2.0 billion to \$4.4 billion.

Figure 2. Value of Treatment Innovation Compared With No Treatment



The current treatment scenarios, less and more frequent injections, assume that 65% of the patients initiate anti-vascular endothelial growth factor (VEGF) treatment and 50% discontinue it each year. Improved adherence assumes

80% uptake and 17% discontinuation in year 1 (50% by year 5). The best-case scenario assumes 100% uptake and 6% discontinuation annually. Future values are discounted at 3%.

Table 2. Patient Benefits From Treatment Innovation Relative to No Treatment^a

Patient Benefit	Less Frequent Injections	More Frequent Injections	Best-Case Less Frequent Injections	Best-Case More Frequent Injections	Hypothetical Cure
For single incident cohort, billion \$					
Year 1	1.1	1.6	1.8	2.5	4.8
Year 3	2.3	3.8	4.8	7.6	10.1
Year 5	2.6	5.0	6.6	11.7	14.9
For entire population, billion \$					
Year 1	1.1	1.6	1.8	2.5	6.8
Year 3	5.1	8.2	9.7	15.0	23.7
Year 5	9.9	17.0	21.5	35.3	47.7

^a Less and more frequent injection scenarios assume 65% uptake and 50% discontinuation (annually). Best case assumes 100% uptake and 6% discontinuation annually. Visual acuity in best case less (more) frequent injections is equivalent to that in less (more) frequent injections. Hypothetical cure assumes that patients receive 1-time treatment resulting in 20/40 visual acuity. Future values are discounted at 3%.

Alternative scenarios that combined VA and injection parameters from the studies by Peden et al⁵ and Mrejen et al²³ provided insight into how societal value changed if the relationship between VA and injection frequency were reversed. The scenario with relatively low VA (Mrejen et al²³) and relatively high injection frequency (Peden et al⁵) resulted in negative societal value estimates. Conversely, a scenario with relatively high VA (Peden et al⁵) and relatively low injection frequency (Mrejen et al²³) generated almost \$1 billion more in societal value across 3 years compared with more frequent injections because the same patient benefit is obtained at lower cost. Similarly, subgroup analyses show a range of societal values, suggesting that more injections will generate higher value only if patients experience better VA outcomes than with fewer injections.

Discussion

We estimated patient benefits, total costs, and societal value generated from anti-VEGF treatment for wAMD across several scenarios. We found that the current treatment scenarios generated substantial value, which increased with injection frequency. However, because both treatment uptake and dis-

continuation rates could be improved, there is a high degree of unmet need. If all patients with wAMD received anti-VEGF therapy and discontinuation was equivalent to the clinical trial rates, the treatment could generate \$95 million to \$648 million in additional societal value across 3 years. Because we assumed no additional cost associated with innovation, these estimates represent an upper bound.

Although we considered the value of anti-VEGF therapies as a class, our results are most directly comparable to prior studies^{31,32} that compared anti-VEGF treatment with the best supportive care or usual care. The estimated incremental cost-effectiveness ratios (ICER) from these studies were highly variable (\$11 412-\$308 400), reflecting differences in underlying model assumptions and data.^{31,32} Nevertheless, our implied 3-year ICERs (\$114 716 for less frequent injections, \$83 557 for more frequent injections) fall within the range from prior studies. Although recent studies¹⁵ have questioned the cost of anti-VEGF therapies, a comparison of our implied ICERs with those from recent analyses of newly approved therapies in other disease areas indicates that anti-VEGF therapies provide larger returns on investment. For example, the lower-bound ICER estimate for targeted immune modulator treatments for rheumatoid arthritis is \$168 660; similarly, estimates across new oncology therapies range from \$146 210 to \$291 454.³³⁻³⁶

One-year estimates for less frequent injections and more frequent injections were similar, which is consistent with recent studies that show noninferiority of the TE approach compared with monthly injections.³⁷ Optimal treatment frequency has received considerable attention, and although TE is a predominant approach among ophthalmologists in the United States, there is limited head-to-head evidence comparing treatment frequencies, particularly for times beyond 1 to 2 years.^{38,39} However, if more frequent injections on average result in better VA outcomes as modeled in our scenarios, the potential value of more frequent injections would be apparent over a longer time; the more frequent injections scenario provided an additional \$3.0 billion in patient benefits across 3 years compared with that provided by less frequent injections. The more frequent injections scenario still provided more value than did the less frequent injections scenario even after adjusting for the added cost of more injections, generating \$2.1 billion more in societal value. The discrepancy between the long-term estimates favoring more injections and short-term clinical studies highlights the need for additional long-term data comparing treatment frequencies.

Both best-case scenarios show that innovations resulting in higher treatment rates may generate additional patient benefits. Although such innovations would not influence patients whose VA does not respond to current anti-VEGF treatments or whose vision has stabilized, they would benefit patients who report modifiable reasons for discontinuation, such as cost or missing visits.^{10,40,41} Although hypothetical cure would represent a meaningful advance in treatment, the relative value of maximizing treatment adherence under current treatment scenarios should not be understated. The best-case more frequent injections scenario generates 3-year patient benefit equal to 63% of that of the hypothetical cure scenario. This suggests that incremental innovations that increase patient adherence even without providing VA improvements beyond current anti-VEGF therapies are an important step toward maximizing value.

Although we have shown that anti-VEGF therapies as a class may provide substantial economic benefits, policy makers often focus on treatment cost. Medicare Part B made \$3.0 billion in payments for aflibercept and ranibizumab combined in 2015, and individually these drugs accounted for the highest and fifth-highest Part B drug spending, respectively.⁴² Consequently, policy makers have indicated that Medicare could reduce its spending on wAMD if more patients switched to bevacizumab, which has been shown to be more cost-effective compared with ranibizumab and aflibercept.^{15,43,44} The sensitivity analysis that varied drug share parameters found that increasing the share of bevacizumab from 55% to 72% may reduce total costs for the full population across 3 years by \$1.8 billion to \$2.2 billion.

The study demonstrates the importance of economic valuation of therapies for ocular diseases. Outside ophthalmology, a growing body of literature eschews cost-effectiveness and focuses on valuing the clinical benefits derived from innovative therapies in monetary terms. This literature spans various disease areas and has shown that new therapies for treating HIV infection, hepatitis C, and several cancer types have generated hundreds of billions of dollars in economic benefits.⁴⁵⁻⁴⁸ As the

pressure to contain health care costs increases, it will be important for ophthalmology as a specialty to generate the data necessary to demonstrate the value of the services provided. The present study suggests that for wAMD, anti-VEGF treatment has generated billions in benefits to patients. However, unmet need remains, suggesting that novel therapies with better efficacy, more durable benefits, or mechanisms that reduce discontinuation may lead to substantial benefits.

Limitations

This study has several limitations related to simplifying assumptions and data availability. Because the underlying data for each treatment scenario correspond to different publications with varied patient populations, there may be concern that the association between injection frequency and VA outcomes in our scenarios may not generalize to the broader US population. This limitation highlights the need for more comprehensive and nationally representative patient data. As a result of this limitation, we note that comparisons across more and less frequent injection scenarios only hold in the real world to the extent that more injections tend to be associated with better VA outcomes. If the reverse were true (more injections associated with lower VA), anti-VEGF therapy for wAMD would not generate positive societal value (see alternative and subgroup data scenarios in eTable 14 in the [Supplement](#)).

Second, because we modeled cohort outcomes, we did not capture individual-level VA variation. For example, patients with lower baseline VA tend to have a better response to treatment. However, because we are unaware of VA and injection frequency data stratified by baseline VA spanning at least 5 years, we were unable to incorporate this aspect of heterogeneity into the model. The implications of this limitation were explored in the sensitivity analyses in eTable 16 and eFigure 2 in the [Supplement](#).

Third, the decision to receive anti-VEGF therapy was static; patients could initiate treatment only in year 1 and could not restart treatment after discontinuation. Consequently, the estimates understate benefits because dynamic uptake would increase the number of patients treated. A related issue is our assumption of fixed drug utilization rates. The implication of the assumption could go in either direction: if patients switch to more or less expensive therapies over time, treatment cost may be underestimated or overestimated. These limitations highlight the need for additional data related to treatment dynamics.

Fourth, our patient benefit estimates reflect only the economic value from improved VA and do not incorporate indirect costs. Examples include use of vision aids, higher incidence of depression, falls, functional limitations, and caregiver burden (approximately 82% of patients with wAMD receive caregiver support).⁴⁹⁻⁵² Excluding indirect costs from the present analysis underestimates patient benefits and societal value from anti-VEGF treatment.

Conclusions

This study suggests that improved VA associated with anti-VEGF treatment provides economic value to patients and

society, and if the association between VA and injection frequency is positive, this value increases with the number of injections. However, a substantially higher value may be realized if adherence improved. This finding suggests

that even incremental treatment innovations that lead to improved adherence, such as drug delivery or longer-lasting therapy (lower injection frequency), may provide additional patient benefits.

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Author Contributions: Drs Mulligan and Seabury had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: Mulligan, Seabury, Dugel, Blim, Goldman.

Drafting of the manuscript: Mulligan, Seabury, Dugel.

Critical revision of the manuscript for important intellectual content: All authors.

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Supervision: Seabury, Dugel, Goldman.

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REFERENCES

1. Prevent blindness. Living with AMD. <https://www.preventblindness.org/living-amd>. Accessed December 17, 2018.
2. Wittenborn J, Rein D. Cost of Vision Problems: The Economic Burden of Vision Loss and Eye Disorders in the United States. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&cad=rja&uact=8&ved=2ahUKEwiO5fXz5I_IahXwFjQHrDPBIIQQJfACegQIARAC&url=https%3A%2F%2Fwww.preventblindness.org%2Fsites%2Fdefault%2Ffiles%2Fnational%2Fdocuments%2FEconomic%2520Burden%2520of%2520Vision%2520Final%2520Report_130611.pdf&usg=AOvVaw3vKugHeQIHLWwf75C3225. Published 2013. Accessed October 10, 2019.
3. Duffy M. New research: two potential treatments for dry macular degeneration and geographic atrophy. VisionAware website. <https://www.visionaware.org/blog/visionaware-blog/new-research-two-potential-treatments-for-dry-macular-degeneration-and-geographic-atrophy/12>. Published October 2017. Accessed February 1, 2019.
4. National Eye Institute. Age-related macular degeneration (AMD) data and statistics. <https://nei.nih.gov/learn-about-eye-health/resources-for-health-educators/eye-health-data-and-statistics/age-related-macular-degeneration-amd-data-and-statistics>. Accessed April 13, 2018.
5. Peden MC, Suñer IJ, Hammer ME, Grizzard WS. Long-term outcomes in eyes receiving fixed-interval dosing of anti-vascular endothelial growth factor agents for wet age-related macular degeneration. *Ophthalmology*. 2015;122(4):803-808. doi:10.1016/j.ophtha.2014.11.018
6. Qin VL, Young J, Silva FQ, Conti FF, Singh RP. Outcomes of patients with exudative age-related macular degeneration treated with anti-vascular endothelial growth factor therapy for three or more years: a review of current outcomes. *Retina*. 2018; 38(8):1500-1508. doi:10.1097/IAE.0000000000001753
7. Curtis LH, Hammill BG, Qualls LG, et al. Treatment patterns for neovascular age-related macular degeneration: analysis of 284 380 Medicare beneficiaries. *Am J Ophthalmol*. 2012;153(6):1116-24.e1. doi:10.1016/j.ajo.2011.11.032
8. Lad EM, Hammill BG, Qualls LG, Wang F, Cousins SW, Curtis LH. Anti-VEGF treatment patterns for neovascular age-related macular degeneration among Medicare beneficiaries. *Am J Ophthalmol*. 2014;158(3):537-543. doi:10.1016/j.ajo.2014.05.014
9. Maguire MG, Martin DF, Ying GS, et al; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(8):1751-1761. doi:10.1016/j.ophtha.2016.03.045
10. Varano M, Eter N, Winyard S, Wittrup-Jensen KU, Navarro R, Heraghty J. Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey. *Clin Ophthalmol*. 2015; 9:2243-2250. doi:10.2147/OPTH.S92548
11. Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-molar study. *Am J Ophthalmol*. 2015;160(4):725-31.e1. doi:10.1016/j.ajo.2015.06.023
12. Roach L. Treat-and-extend strategy: is there a consensus? EyeNet Magazine. <https://www.aao.org/eyenet/article/treat-extend-strategy-is-there-consensus>. Published January 2016. Accessed August 2018.

13. Freund KB, Korobelnik J-F, Devenyi R, et al. Treat-and-extend regimens with anti-VEGF agents in retinal diseases: a literature review and consensus recommendations. *Retina*. 2015;35(8):1489-1506. doi:10.1097/IAE.0000000000000627
14. Stone T. *ASRS 2017 Preferences and Trends Membership Survey*. Chicago, IL: American Society of Retina Specialists; 2017.
15. Hutton D, Newman-Casey PA, Tavag M, Zacks D, Stein J. Switching to less expensive blindness drug could save Medicare Part B \$18 billion over a ten-year period. *Health Aff (Millwood)*. 2014;33(6):931-939. doi:10.1377/hlthaff.2013.0832
16. Patel S. Medicare spending on anti-vascular endothelial growth factor medications. *Ophthalmol Retina*. 2018;2(8):785-791. doi:10.1016/j.oret.2017.12.006
17. Brown GC, Brown MM, Sharma S, et al. The burden of age-related macular degeneration: a value-based medicine analysis. *Trans Am Ophthalmol Soc*. 2005;103:173-184. doi:10.1016/S0008-4182(05)80070-5
18. United States Census Bureau. National population totals, 2017. <https://www.census.gov/data/tables/2017/demo/age-and-sex/2017-age-sex-composition.html>. Accessed October 11, 2019.
19. Rudnicka AR, Kapetanakis VV, Jarrar Z, et al. Incidence of late-stage age-related macular degeneration in American Whites: systematic review and meta-analysis. *Am J Ophthalmol*. 2015;160(1):85-93.e3. doi:10.1016/j.ajo.2015.04.003
20. Murphy SL, Xu J, Kochanek KD, Curtin SC, Arias E. Deaths: Final Data for 2015. *Natl Vital Stat Rep*. 2017;66(6):1-75.
21. Thiagarajan M, Evans JR, Smeeth L, Wormald RP, Fletcher AE. Cause-specific visual impairment and mortality: results from a population-based study of older people in the United Kingdom. *Arch Ophthalmol*. 2005;123(10):1397-1403. doi:10.1001/archophth.123.10.1397
22. Ho AC, Albini TA, Brown DM, Boyer DS, Regillo CD, Heier JS. The potential importance of detection of neovascular age-related macular degeneration when visual acuity is relatively good. *JAMA Ophthalmol*. 2017;135(3):268-273. doi:10.1001/jamaophthol.2016.5314
23. Mrejen S, Jung JJ, Chen C, et al. Long-term visual outcomes for a treat and extend anti-vascular endothelial growth factor regimen in eyes with neovascular age-related macular degeneration. *J Clin Med*. 2015;4(7):1380-1402. doi:10.3390/jcm4071380
24. Genentech. Lucentis (ranibizumab injection). [Package insert]. 2006.
25. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology*. 2012;119(6):1175-1183. doi:10.1016/j.ophtha.2011.12.016
26. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making*. 2000;20(3):332-342. doi:10.1177/0272989X0002000310
27. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-797. doi:10.1056/NEJMp1405158
28. 2018 ASP drug pricing files. Centers for Medicare & Medicaid Services website. <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html>. Accessed April 2018.
29. 2018 Physician fee schedule. Centers for Medicare & Medicaid Services website. <https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx>. Accessed April 2018.
30. Parikh R, Ross JS, Sangaralingham LR, Adelman RA, Shah ND, Barkmeier AJ. Trends of anti-vascular endothelial growth factor use in ophthalmology among privately insured and Medicare Advantage patients. *Ophthalmology*. 2017;124(3):352-358. doi:10.1016/j.ophtha.2016.10.036
31. Mitchell P, Anemans L, White R, Gallagher M, Thomas S. Cost effectiveness of treatments for wet age-related macular degeneration. *Pharmacoeconomics*. 2011;29(2):107-131. doi:10.2165/11585520-000000000-00000
32. Elshout M, Webers CAB, van der Reis MI, Schouten JSAG. A systematic review on the quality, validity and usefulness of current cost-effectiveness studies for treatments of neovascular age-related macular degeneration. *Acta Ophthalmol*. 2018;96(8):770-778. doi:10.1111/aos.13824
33. Institute for Clinical and Economic Review. Targeted immune modulators for rheumatoid arthritis: effectiveness and value. Published January 2017. https://icer-review.org/wp-content/uploads/2016/08/NECEPAC_RA_Draft_Report_012017.pdf. Accessed October 4, 2019.
34. Institute for Clinical and Economic Review. Treatment options for advanced non-small cell lung cancer: effectiveness, value and value-based price benchmarks. Updated October 2016. https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Evidence_Report_Plus_Supplement_101716.pdf. Accessed October 4, 2019.
35. Institute for Clinical and Economic Review. Treatment options for relapsed or refractory multiple myeloma: effectiveness, value, and value-based price benchmarks. Published May 2016. https://icer-review.org/wp-content/uploads/2016/05/MWCEPAC_MM_Evidence_Report_050516-002.pdf. Accessed October 4, 2019.
36. Institute for Clinical and Economic Review. Poly ADP-ribose polymerase (PARP) inhibitors for ovarian cancer: effectiveness and value. Published August 2017. https://icer-review.org/wp-content/uploads/2017/02/MWCEPAC_OVARIAN_EVIDENCE_REPORT_08302017.pdf. Accessed October 4, 2019.
37. Silva R, Berta A, Larsen M, McFadden W, Feller C, Monés J; TREND Study Group. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. *Ophthalmology*. 2018;125(1):57-65. doi:10.1016/j.ophtha.2017.07.014
38. Okada M, Kandasamy R, Chong EW, McGuinness M, Guymer RH. The treat-and-extend injection regimen versus alternate dosing strategies in age-related macular degeneration: a systematic review and meta-analysis. *Am J Ophthalmol*. 2018;192:184-197. doi:10.1016/j.ajo.2018.05.026
39. Rezaei K. American Society of Retina Specialists: Global Trends in Retina. 2015. https://www.asrs.org/content/documents/2015_global_trends_in_retina_survey_-_for_website.pdf. Accessed August 1, 2018.
40. Rasmussen A, Bloch SB, Fuchs J, et al. A 4-year longitudinal study of 555 patients treated with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(12):2630-2636. doi:10.1016/j.ophtha.2013.05.018
41. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol*. 2015;99(2):220-226. doi:10.1136/bjophthalmol-2014-305327
42. Medicare Payment Advisory Commission. Report to the Congress: Medicare and the Health Care Delivery System. http://www.medpac.gov/docs/default-source/reports/jun17_ch2.pdf?sfvrsn=0 Washington. Accessed August 2018.
43. Ginsburg P, Williams G. Treatment-specific payment approaches: the case of macular degeneration. Health Affairs website. <https://www.healthaffairs.org/doi/10.1377/hblog20171117.667415/full/>. Published November 27, 2017. Accessed October 4, 2019.
44. van Asten F, Michels CTJ, Hoyng CB, et al. The cost-effectiveness of bevacizumab, ranibizumab and aflibercept for the treatment of age-related macular degeneration—A cost-effectiveness analysis from a societal perspective. *PLoS One*. 2018;13(5):e0197670. doi:10.1371/journal.pone.0197670
45. Van Nuys K, Brookmeyer R, Chou JW, Dreyfus D, Dieterich D, Goldman DP. Broad hepatitis C treatment scenarios return substantial health gains, but capacity is a concern. *Health Aff (Millwood)*. 2015;34(10):1666-1674. doi:10.1377/hlthaff.2014.1193
46. Romley JA, Juday T, Solomon MD, Seekins D, Brookmeyer R, Goldman DP. Early HIV treatment led to life expectancy gains valued at \$80 billion for people infected in 1996-2009. *Health Aff (Millwood)*. 2014;33(3):370-377. doi:10.1377/hlthaff.2013.0623
47. Jena AB, Blumenthal DM, Stevens W, Chou JW, Ton TGN, Goldman DP. Value of improved lipid control in patients at high risk for adverse cardiac events. *Am J Manag Care*. 2016;22(6):e199-e207.
48. Yin W, Penrod JR, Maclean R, Lakdawalla DN, Philipson T. Value of survival gains in chronic myeloid leukemia. *Am J Manag Care*. 2012;18(11)(suppl):S257-S264.
49. Casten RJ, Rovner BW. Update on depression and age-related macular degeneration. *Curr Opin Ophthalmol*. 2013;24(3):239-243. doi:10.1097/ICU.0b013e32835f8e55
50. Soubrane G, Cruess A, Lotery A, et al. Burden and health care resource utilization in neovascular age-related macular degeneration: findings of a multicountry study. *Arch Ophthalmol*. 2007;125(9):1249-1254. doi:10.1001/archophth.125.9.1249
51. Berger S, Porell F. The association between low vision and function. *J Aging Health*. 2008;20(5):504-525. doi:10.1177/0898264308317534
52. Schmier JK, Halpern MT, Covert D, Delgado J, Sharma S. Impact of visual impairment on use of caregiving by individuals with age-related macular degeneration. *Retina*. 2006;26(9):1056-1062. doi:10.1097/O1.iae.0000254890.48272.5a