A Cost-Benefit Analysis of VEGF-Inhibitor Therapy for Neovascular Age-Related Macular Degeneration in the United States

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• PURPOSE: To perform a societal cost-benefit analysis comparing intravitreal bevacizumab (Avastin), ranibizumab (Lucentis), and aflibercept (Eylea) monotherapies for treating neovascular age-related macular degeneration (NVAMD).
• DESIGN: Cost-benefit analysis.
• METHODS: Center for Value-Based Medicine using published clinical trial and Medicare data. Patient population: 168,400 estimated 2018 U.S. patients with new-onset NVAMD. Procedure(s): cost-benefit analysis using 2018 U.S. real dollars. Outcome measurements: 11-year direct ophthalmic medical costs expended for bevacizumab, ranibizumab, and aflibercept monotherapies were compared with ophthalmic and nonophthalmic direct medical, direct nonmedical, and indirect medical (productivity) costs saved by the therapies.
• RESULTS: Bevacizumab monotherapy had an individual, 11-year $14,772 treatment cost and net $357,680 societal return (11-year 2,421% return on investment [ROI]). Ranibizumab therapy cost $106,582 and returned $265,870 to society (249% ROI), whereas aflibercept treatment cost $61,811 and returned $310,611 to society (503% ROI). The 2018 NVAMD overall treatment cohort, 11-year net societal gain was $28.5 billion to patients and insurers, with $24.2 billion (84.9%) coming from bevacizumab therapy, $0.7 billion (2.5%) from ranibizumab therapy, and $3.6 billion (12.6%) from aflibercept therapy. Substituting bevacizumab for ranibizumab and aflibercept in the 2018 new-onset NVAMD patients would save an estimated $1.343 billion over 11 years. Vascular endothelial growth factor-inhibitor (VEGF-I) therapy in 2018 should contribute $12.2 billion to the Gross Domestic Product over 11 years. Late treatment would decrease this by 78% to $2.7 billion.
• CONCLUSIONS: Intravitreal NVAMD bevacizumab, ranibizumab and aflibercept monotherapies accrue considerable financial, ROIs to patients and insurers as they increase national wealth. (Am J Ophthalmol 2021;223:405–429. © 2020 Elsevier Inc. All rights reserved.)

ANALYSES OF INTRAVITREAL BEVACIZUMAB (AVASTIN, Genentech-Roche, South San Francisco, California), ranibizumab (Lucentis, Genentech-Roche, South San Francisco, California), and aflibercept (Eylea, Regeneron, Eastview, New York) monotherapies for treating neovascular, age-related macular degeneration (NVAMD) revealed that each drug resulted in a similar visual outcome and adverse systemic event profile over a 2-year period,[1–8] and likely, over an 11-year period.[1] All 3 vascular endothelial growth factor inhibitors (VEGF-Is) are cost-effective using societal and direct ophthalmic medical cost perspectives, average cost-utility ratios (CURs), although bevacizumab therapy was shown to be 621% more cost-effective than ranibizumab therapy and 306% more cost-effective than aflibercept therapy.[1]

It was decided to perform a societal cost-benefit analysis to estimate the national 2018 direct ophthalmic medical costs expended for bevacizumab, ranibizumab, and aflibercept NVAMD monotherapy, as well as the costs returned to society (patients and insurers) due to improved vision from NVAMD therapy. Both cost-benefit analysis and budget impact analysis are economic instruments estimating the financial consequences of new interventions. A cost benefit analysis, however, typically uses a longer time horizon (often a lifetime), analyzes the average population, uses a societal cost perspective, and uses discounting.[9] In contrast, a budget impact analysis assesses a budget-holder (payer)-specific population over 1-5 years and does not use discounting[9,10] In an era of emphasis on drug costs, cost-benefit information is important for all health care stakeholders.

METHODS

A SOCIETAL COST PERSPECTIVE, COST-BENEFIT ANALYSIS was performed for the use of ranibizumab, aflibercept, and

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See Accompanying Editorial/Article on page xxx.

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TABLE 1. Clinical and Cost-Benefit Parameters Used in the Monotherapy VEGF-I Analyses (Including Data from CATT,[6–8] VIEW,[4,5] MARINA[2] and ANCHOR[3] Clinical Trials)

- Entrance criteria[2–4,6]
  - Classic, minimally classic, or occult subfoveal choroidal neovascularization
  - Choroidal neovascular lesions <12 disc areas at baseline
  - Best corrected ETDRS baseline vision in the affected eye: 20/40-20/320
  - Age: 50 y or older
- Ophthalmic examinations. Visits: mean number of outpatient visits over the 11-y model. A visit cost was not accrued when an intravitreal VEGF-I was administered concomitantly.

Year	1	2	3	4	5	6-8	9-11	Total
Bevacizumab	11.8	11.1	8.0	7.2	6.5	4.0	4.0	68.6
Ranibizumab	11.8	11.1	8.0	7.2	6.5	4.0	4.0	68.6
Aflibercept	11.8	11.1	8.0	7.2	6.5	4.0	4.0	68.6

- Baseline vision: 20/63 in the bevacizumab and ranibizumab treatment and control cohorts,[6–8] 20/80 (adjusted in the analyses) in the VIEW cohorts using aflibercept.[4,5]
- Baseline age: 79 y, the mean age of enrollment in CATT[6]
- Number of estimated new cases of NVAMD in United States in 2018[12,13]: 168,400 (see Supplemental Table 1).
- Patients (combined n eligible for treatment = 151,055) treated with each drug (see Supplemental Tables 2 and 3)
  - Bevacizumab: 80.9% = 122,203 patients
  - Ranibizumab: 3.7% = 5,589 patients
  - Aflibercept: 15.4% = 23,263 patients
- Comparator drug usage for treatment of diabetic retinopathy and retinal vein occlusion[35–38]
- Analysis timeline: 11 y = the mean patient life expectancy.[1,12]
- Diagnostic studies
  - Fundus photographs and intravenous fluorescein angiographs were obtained at the baseline visit and at 13 months.
  - Optical coherence tomography was obtained at each patient visit.
- Visual outcomes. Intravitreal injections of ranibizumab and bevacizumab monthly demonstrated similar vision outcomes at 1 and 2 y.[5–7] Aflibercept vision outcomes in the cohort with 3 monthly injections followed by an injection every 2 months for 2 y revealed the mean visual acuity score was within 0.3 letters of monthly ranibizumab injections at approximately 24 months.[3,4]
- Intravitreal injections. The mean number of intravitreal injections for each drug cohort is shown below. CATT data were used for bevacizumab and ranibizumab for the first 5 y,[5–7] while VIEW 2-y data were used for aflibercept for the first 2 y.[3,4] After y 2, it was assumed that aflibercept injections were given 50% as often as the bevacizumab/ranibizumab injections. The numbers of bevacizumab and ranibizumab injections from y 6 to 11 were arbitrary and demonstrated a similar decrease in required injections as seen in 3-5 years. Administering aflibercept with the same frequency as bevacizumab and ranibizumab, as well as every 3 months after 2 y of therapy,[18] was analyzed in the sensitivity analysis.

Year	1	2	3	4	5	6-8	9-11	Total
Bevacizumab	11.8	11.1	4.8	4.5	4.0	3.0	2.0	51.2
Ranibizumab	11.8	11.1	4.8	4.5	4.0	3.0	2.0	51.2
Aflibercept	7.0	4.2	2.4	2.25	2.0	1.5	1.0	25.6

(Injections per y)

Approximately 11.8 (23% of first-eye injections) mean injections of bevacizumab and ranibizumab were given in second eyes converting to NVAMD in the 40% of baseline individuals in whom the first eye presented with NVAMD and the second eye had atrophic AMD. The corresponding number for aflibercept injections was 5.9, or 23% of first-eye injections. Atrophic fellow eyes converted to NVAMD each y during the 11 y, with markedly fewer injections given in eyes that converted later during the 11-y model.

- Injection-related adverse events. These were similar in the ranibizumab and aflibercept cohorts.[1] The total burden of adverse events was higher in the ranibizumab and bevacizumab cohorts as more intravitreal injections were given than in the aflibercept cohort.[1] This was accounted for in the present analyses. Adverse events included endophthalmitis, with an incidence of 1 per 1,756 intraocular injections,[5–7] ocular erythema for 2 day post-intravitreal injection, and ocular irritation for 1 day post-intravitreal injection.[1] Endophthalmitis therapies were taken from Rayess and associates.[20]The costs associated with the adverse events are included within the ophthalmic direct medical costs.[23–27]
- Systemic adverse events. These were similar for each drug[1–7] and not included, especially as the incidences versus age-matched control population are not well defined long-term.
- Mean patient life expectancy: assumed to be 11 y for the control, bevacizumab, ranibizumab, aflibercept, and study cohorts[12]
- Model time spans
  - 11 y = mean patient life expectancy[12]
  - 2 y = maximum time of double-blind randomization in the clinical trials[1–7]
- Treatment visual outcomes. These were equivalent for bevacizumab, ranibizumab and aflibercept monotherapy for NVAMD.[1–7]
- A combined-eye model[21] weighted the percentage of second-eye model cases, meaning the baseline fellow eye already has vision loss from NVAMD (60% for this analyis[7]) and the percent of first-eye model cases, meaning the baseline fellow eye does not have NVAMD and has good baseline vision (40% for this analyis[7]).
- Bilateral QALY gains and costs of treatment were integrated for fellow eyes with initial atrophic AMD at baseline that converted to NVAMD over the 11-y period of the study model. Because second-eye treatment was assumed to be given in 60% of treated patients at baseline, conversion to second-eye NVAMD involvement and treatment could thus only occur in the 40% of baseline patients with unilateral NVAMD at presentation.[7] For y 1 and 2, the conversion incidence of fellow eyes with atrophic AMD to NVAMD was calculated using data from Barbazetto and associates.[22] From y 3 forward, a 10% rate of conversion to per-y was assumed for the remaining fellow eyes that had atrophic AMD (Supplemental Table 4).
- Cost perspectives. Ophthalmic, and societal cost perspectives were used.[21,23–29]
- Expenditures
  - Ophthalmic direct medical cost basis: 2018 average, national, Medicare fee schedule.[23–25]
- Costs returned to society due to improved vision from VEGF-I therapy
  - Direct nonophthalmic medical costs (depression, injury, subacute nursing facility, unidentified Medicare costs, and nursing home costs) were taken from Javitt and associates.[26]
  - Direct nonmedical costs (caregiver costs, paid and nonpaid) were taken from Brown and associates[27] These included inside activities of daily living such as personal hygiene, house cleaning, preparing meals, preparing and taking medications, painting, making beds, etc. Outside activities of daily living encompassed lawn care, maintenance of gardens, and snow removal.
- Patient vision-related utilities were used.[1,21,38–40] The cost-utility ratios in the 11-y analysis using the ophthalmic cost perspective were: bevacizumab therapy = $11,033/QALY, ranibizumab therapy = $70,600/QALY, and aflibercept therapy = $44,801/QALY.[1]

AMD = age-related macular degeneration; ANCHOR[2] = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; CATT = Comparison of Age-Related Macular Degeneration Treatments Trials[5–7]; ETDRS = Early Treatment Diabetic Retinopathy Study; MARINA[2] = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; NVAMD = neovascular age-related macular degeneration; QALY = quality-adjusted life y; VEGF-I = vascular endothelial growth factor-inhibitor; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies.[3,4]

bevacizumab therapy for the treatment of NVAMD. Wills Eye Hospital Institutional Review Board approval was waived as no new patients were enrolled or identified as patient data users. The research adhered to the Declaration of Helsinki, and no state or federal regulations were violated.

The cost-benefit analysis parameters were based upon Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) clinical trial data.[6–8] The decision was made to use CATT clinical trial data in reference case analysis because CATT: 1) enrolled 1 eye of patients with previously untreated NVAMD; 2) randomized treatment over 2 years with either ranibizumab or bevacizumab; 3) was large (n = 1,208 enrollees); 4) was multicentered (n = 44); 5) sponsored by the National Eye Institute; and 6) modeled after earlier ranibizumab trials.[2,3] CATT 2-year vision outcomes were similar to those in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study (n = 716 enrollees),[2] the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) (n = 423 enrollees),[3] and the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Studies (VIEW) (n = 2,457 enrollees),[4,5] VEGF-I clinical trials for treating NVAMD. Although CATT demonstrated the equivalence of ranibizumab and bevacizumab for treating NVAMD,[6–8] bevacizumab has not been approved by the U.S. Food and Drug Administration (FDA), whereas both ranibizumab and aflibercept have been FDA approved.[2–5]

The 11-year cost-benefit analysis model time horizon was the life expectancy of a 79-year-old baseline participant in CATT.[6–8,11] A 2-year time horizon model was also undertaken because 2 years is the maximum time that VEGF-I treatments for NVAMD have been studied in a double-blind, randomized fashion.[2–8]

In the 2018 cohort of estimated new NVAMD patients, the 11-year and 2-year direct ophthalmic medical (treatment) costs expended for bevacizumab, ranibizumab, and aflibercept monotherapy were compared, including the costs associated with the adverse events of treatment, with their respective financial returns on investment (ROIs). Multiple societal costs were accrued against the direct ophthalmic medical costs due to the improved vision resulting from VEGF-I therapy versus no treatment. The improved vision saved caregiver, depression, trauma, facility admission, wage loss, and other costs (Table 1).[1–8,11–41]

• **NUMBER OF NVAMD CASES:** Using data from the Eye Diseases Prevalence Research Group,[14] and from the U.S. Census Bureau, 168,400 new cases of NVAMD were estimated to occurred in the United States in 2018 (Supplemental Table 1). Among these new cases, 93.5% were in people aged 65 and older, whereas 6.5% occurred in people younger than age 65.[5]

• **DRUG ADMINISTRATION:** During the 11-year model, both bevacizumab- and ranibizumab-treated NVAMD eyes received a mean 51.2 intravitreal drug injections in the primary treated eye, whereas aflibercept-treated eyes received 25.6 injections, because aflibercept was often administered with half the bevacizumab and ranibizumab frequency.[1,3–7] Cases presenting with unilateral NVAMD and atrophic AMD in the fellow eye (40% of all cases) received extra injections when fellow eyes converted to NVAMD.

The number of fellow-eye, extra drug injections averaged out to an additional 23% of first-eye injections for all patients presenting with baseline NVAMD involvement of the first eye in each of the 3 drug cohorts over the 11-year model. The additional 23% equated with 11.8 second-eye injections for the average bevacizumab- or ranibizumab-treated patient, with half that number for the average aflibercept-treated patient. Patients who presented at baseline with involvement of the second eye were typically only treated in that eye in this model.

No matter the drug, each treatment cohort patient underwent 68.6 mean office visits over 11 years (Table 1), although an office visit charge was not accrued when an intravitreal injection was administered at the same visit. Bevacizumab and ranibizumab NVAMD treatment 2-year data were based upon the randomized MARINA, ANCHOR, and CATT data.[5–7] Data from the aflibercept VIEW trial,[3,4] with similar protocols to the earlier ranibizumab trials,[1,2] were used to model aflibercept treatment results for the first 24 months.

Part B Physician/Supplier National Data for 2018[23] for conventional Medicare patients revealed that 1,365,000 intravitreal aflibercept injections were given during the year, versus 660,166 ranibizumab injections and 14,351,978 bevacizumab injections. Because aflibercept only requires half the patient injections referent to bevacizumab and ranibizumab, it was estimated that 80.9% of NVAMD patients were treated with bevacizumab, whereas 3.7% were treated with ranibizumab, and 15.4% were treated with aflibercept (see calculations in Supplemental Table 2).

• **CONFOUNDING DISEASES:** The 3 VEGF-Is were also used to treat branch and central retinal vein occlusion, as well as nonproliferative and proliferative diabetic retinopathy.[34–37] Data from Willis and associates[35] for the treatment of diabetic maculopathy with VEGF-I from the Intelligent Research in Sight (IRIS) registry suggest the incidence of use of the 3 VEGF-I drugs was similar to the VEGF-I percentages used in the present analysis. Wu and associates[36] demonstrated the same for the treatment of branch retinal vein occlusion, which accounts for two-thirds of retinal venous occlusions.[37] The similar use of drugs for venous occlusion and diabetic retinopathy (Supplemental Table 3) gives us confidence that the present drug treatment distribution ratios for NVAMD are

TABLE 2. Distribution of the 2018 Estimated U.S. Cohort of 168,400 New NVAMD Patients

	A	B	C	D	E	F	G
Year	New Cases/Y A	Candidates (%) Eligible for Therapy B	Number of Candidates Eligible for Therapy = A × B	With 6.4% Annual Dropout = B × D	Number of Candidates Integrating Dropout = C × D	Bilateral NVAMD Cases F	Cases with Bilateral Involvement = E × F
1	168,400	89.7	151,055	89.7	151,055	60.0	90,633
2	168,400	89.7	151,055	84.0	141,387	69.1	97,699
3	168,400	89.7	151,055	78.6	132,339	74.6	98,725
4	168,400	89.7	151,055	73.6	123,869	77.1	95,503
5	168,400	89.7	151,055	68.8	115,941	79.4	92,057
6	168,400	89.7	151,055	64.4	109,521	81.5	88,445
7	168,400	89.7	151,055	60.3	101,576	83.3	84,613
8	168,400	89.7	151,055	56.5	95,075	85.0	80,814
9	168,400	89.7	151,055	52.8	88,990	86.5	76,976
10	168,400	89.7	151,055	49.5	83,295	87.8	73,133
11	168,400	89.7	151,055	46.3	77,764	89.0	69,388

NVAMD = neovascular age-related macular degeneration.

Note that Column F indicates what percentage of all cases are bilateral. As per CATT,[5] 60% of cases were bilateral at baseline, with the 40% of unilateral cases converting to bilateral cases, as shown over 11 y. The percentage of overall bilateral cases increased in y 1 and 2 as per Barbazetto and associates[22] and from y 3 through 11 per Supplemental Table 4.

reasonable and reflect the overall use of the drugs for treating all indicated diseases.

• **NUMBERS OF CANDIDATES ELIGIBLE FOR VEGF-I THERAPY:** To assess this aspect, the authors reviewed the cases of consecutive new patients with new NVAMD (within 1 year) referred to GCB for evaluation by general ophthalmologists, optometrists and other nonophthalmic physicians over a 10-year period from 2005 to 2014. Criteria for inclusion in the present analysis were the same as in the early ranibizumab clinical trials[1,2] and CATT.[5] They included an area of macular choroidal neovascularization in at least 1 eye ≤12 disc areas in size and best corrected vision ≥20/320. Among the new 175 new NVAMD patients, 157 (89.7%) met these criteria. Eighteen patients (10.3%) did not meet the criteria due to vision in the affected eye ≤20/400 or NVAMD with neovascularization >12 disc areas. These unidentified data were previously acquired with approval from the Wills Eye Hospital Institutional Review Board. The annual dropout rate used in the present analysis was the same as in the CATT study,[5–7] 6.4% per year, similar to that noted in clinical trials by other authors.[42]

To obtain aggregate (macroeconomic) treatment costs, the number of annual patients (168,400) was multiplied by the 89.7% candidate eligibility percentage x dropout rate (Tables 2-4) × direct medical ophthalmic treatment (drug, diagnostic, and physician) costs per individual (Table 5) to calculate 11-year and 2-year direct ophthalmic medical treatment expenditures.

Costs accruing against direct ophthalmic treatment expenditures typically occur when a second eye is treated. To calculate these macroeconomic costs, direct nonophthalmic medical costs (trauma, depression, facility fees, nursing home and so forth), direct nonmedical costs (caregiver, or activities of daily living, transportation and residence change) and indirect medical costs (wage loss and inability to volunteer) were multiplied per individual by 168,400 × candidate eligibility percentages × dropout rate × number of second-eye treatment cases (Table 6). When 1 eye is treated and the fellow eye still has good vision, systemic costs have been unable to be documented accruing against the direct ophthalmic medical costs.[27] In the instance of unilateral NVAMD treatment and good vision in the fellow eye, societal costs are accrued against the direct ophthalmic medical costs when the vision in the second eye deteriorates due to the development of NVAMD in that eye. This is because it was assumed the first eye had already been theoretically treated with a clinical result superior to the natural course of the untreated disease.

• **COSTS:** The direct ophthalmic medical costs were taken from the 2018 average national Medicare Fee Schedule (Tables 4-8).[23–25]

Eyes were assumed to be treated with 1 drug over the 11-year and 2-year models. The national average Part B and Part D conventional Medicare program costs were assumed to mirror those of other insurers. There are thousands of different health insurer programs in the United States, although the authors are confident that virtually all base their fee schedule in some manner upon the Medicare Fee Schedule.

While 1 eye was enrolled in the clinical trials studied,[4–8] the costs associated with treating fellow eyes were included

TABLE 3. Treatment Costs (2018 U.S. Dollars) Associated with an Annual U.S. NVAMD Cohort of 168,400 Patients, Including 89.7% Eligibility and 6.4% Dropout per Year

	Eligible Baseline Patients (151,055)	Bevacizumab (N = 80.9% = 122,203 Baseline Patients)[23]			Ranibizumab (N = 3.7%, or 5,589 Baseline Patients)[23]			Aflibercept (n = 15.4%, or 23,262 Baseline Patients)[23]			Total Costs 151, 055 Patients
Year	Number with 6.4% Annual Dropout	Bev. Treatment Cost/Patient.	Bev. Patients	Total Bev. tx Cost (000s)	Ran. Treatment Cost/patient	Ran.Patients	Total ran. tx Cost (000s)	Afl. Treatment Cost/Patient	Afl. Patients	Total Afl. tx Cost (000s)	Combined Drug tx Treatment Costs (000s)
1	151,055	1,765	122,203	215,688	23,466	5,989	131,152	14,819	23,262	344,727	691,567
2	141,387	2,064	114,382	236,085	22,190	5,231	116,083	9,739	21,774	212,053	564,221
3	132,339	1,597	107,062	170,978	10,546	4,897	51,639	6,267	20,380	127,723	350,340
4	123,869	1,564	100,210	156,729	9,783	4,583	44,837	5,871	19.076	111,994	313,560
5	115,941	1,491	93,796	139,850	8,680	4,290	37,236	5,282	17,855	94,310	271,396
6	109,521	1,352	88,602	119,791	6,767	4.052	27,422	4,250	16,866	71,681	218,894
7	101,576	1,269	82,175	104,280	6,498	3,758	24,422	4,061	15,643	63,525	192,227
8	95,075	1,148	76,916	88,299	6,166	3,518	21,691	3,814	14,642	55,843	165,832
9	88,990	958	71,993	68,969	4,347	3,293	14,313	2,790	14,704	38,235	121,518
10	83,295	856	67,386	57,682	4,096	3,082	12,624	2,596	12,827	33,300	103,606
11	77,764	719	62,911	45,233	3,788	2,877	10,899	2,350	11,976	28,143	84,275
Total cost				$1.403 billion			$492 million			$1.182 billion	$3.077 billion

Afl. = aflibercept; Bev. = bevacizumab; NVAMD = neovascular age-related macular degeneration; Ran. = ranibizumab; tx = treatment; VEGF-I = vascular endothelial growth factor-inhibitor.

The Total column figures, which represent the 2018 NVAMD treatment costs, are derived from adding the weighted averages of bevacizumab (80.9%), ranibizumab (3.7%), and aflibercept (15.4%) injection costs.

TABLE 4. 11-y and 2-y Ophthalmic Direct Medical Costs of VEGF-I Treatment per Individual Completing Therapy for NVAMD (2018 Average, National Medicare Fee Schedule,[23–25] All Costs in 2018 U.S. Nominal Dollars)

Drug Distribution (Baseline 151,055 Patients Treated per Annual Cohort of 168,400 NVAMD Patients)	Bevacizumab, 1.25 mg	Ranibizumab, 0.5 mg	Aflibercept, 2.0 mg	Weighted Cost per Patient
Eleven-y data per individual				
Physician and diagnostic costs[24]	$10,721	$10,721	$12,775	$11,016
Drug cost per injection[23]	$79[a]	$1,870[a]	$1,936[a]	$402
Drug ASP cost[7,23](11-y drug cost per initial treated eye)	$3,717	$87,727	$45,004	$12,292
Mean 11-y ophthalmic direct medical cost of drugs in second eyes [1,7,13,22,23]	$333	$7,860	$4,032	$1,101
Bilateral drug cost	$4,050	$95,587	$49,036	$14,364
Total cost per treated baseline eye treated over 11 -y[7,23–25]	$13,564	$97,574	$56,456	$22,371
Weighted, 11-y ophthalmic treatment cost of patients treated in 1 and 2 eyes in combined-eye model[7,13,22–25], (Additional cost to baseline eye treatment)	$14,772 (8.9%)	$106,582 (9.2%)	$61,811 (9.5%)	$24,419 (9.2%)
Percent total drug cost[23]/total direct ophthalmic treatment costs,[24,25] combined-eye model	$4,050/$14,772 = 27.4%	$95,587/$106,582 = 89.7%	$49,036/$61,811 = 79.3%	$14,365/$24,423 = 58.8%
Individual QALY gain	1.339	1.339	1.380	1.345
Ophthalmic cost perspective cost-utility ratio	($14,772/1.339 =) $11,033/QALY	($106,582/1.339 =) $79,600/QALY	($61,811/1.380 =) $44,801/QALY	($24,419/1.345 =) $18,151/QALY
Macroeconomic data – 11-year model				
Ophthalmic treatment costs if eligible patients as above[a] treated with each drug in proportion to reference case administration (see Table 3)[23]	$1.403 billion (80.9% = 122,203 baseline patients)	$0.492 billion (3.7% = 5,489 baseline patients)	$1.182 billion (15.4% = 23,362 baseline patients)	$3.077 billion (100% = 151,055 baseline patients)
Ophthalmic treatment costs if 100% of eligible NVAMD patients (151,055 + dropout) treated are treated with one of the 3 drugs[23]	$1.734 billion (n = 151,055 baseline patients)	$13.306 billion (n = 151,055 baseline patients)	$7.672 billion (n = 151,055 baseline patients)	NA
Savings if 2018 cohort of NVAMD patients have bevacizumab substituted for ranibizumab and aflibercept	NA	5,489 patients x cost per patient[b] ($88,030-$11,481) = $427.8 million	23,362 patients x cost per patient[b] ($50,812-$11,481) = $914.9 million)	Total savings = $1.342.7 million
Two-y data individual and macroeconomic data				
Two-y ophthalmic treatment cost of a patient treated in 1 and/or 2 eyes[13,22–25],	$5,690	$47,319	$26,377	$9,972
Ophthalmic treatment costs if 100% if eligible patients treated with one of the 3 drugs[23–25]	$0.59 billion (n = 151,055 baseline patients)	$6.68 billion (n = 151,055 baseline patients)	$3.62 billion (n = 151,055 baseline patients)	NA
Ophthalmic treatment costs if eligible patients treated with each drug as per reference case administration (Table 3)[23]	$0.45 billion (n = 122,203 baseline patients)	$0.25 billion (n = 5,489 baseline patients)	$0.56 billion (n = 23,262 baseline patients)	$1.25 billion (n = 151,055 baseline patients)

ASP = average sales price; NA = not applicable; HCPCS = Healthcare Common Procedure Coding System; NVAMD = neovascular age-related macular degeneration; VEGF-I = vascular endothelial growth factor inhibitor.

[a]Bevacizumab HCPCS (Health care Common Procedure Coding System) = J9035, $79 per dose; Ranibizumab HCPCS = J2778, $1,870 per dose; Aflibercept HCPCS = J0178, $1,936 per dose.[19]

[b]Note that the cost of treatment per average patient integrates the 6.4% annual dropout rate over 11 y.

TABLE 5. 11-y Societal Individual Patient Costs (2018 U.S. Real Dollars) Associated with VEGF-I Therapy

Costs	Bevacizumab	Ranibizumab	Aflibercept	Weighted Costs[b]
Medical Costs Expended				
Direct ophthalmic medical costs expended	+$14,772	+$106,582	+$61,811	+$24,419
Systemic healthcare costs due to VEGF-I therapy saving 1.0 year of life	+$24,800	+$24,800	+$24,800	+$24,800
Direct ophthalmic medical costs saved				
• Low vision services[27]	−$12,118	−$12,118	−$12,118	−$12,118
• Subtotal	−$12,118	−$12,118	−$12,118	−$12,118
Direct Nonophthalmic Medical Costs Saved				
• Injury costs[26]	−$1,607	−$1,607	−$1,607	−$1,607
• Depression costs[26]	−$4,108	−$4,108	−$4,108	−$4,108
• Subacute Nursing Facility costs[26]	−$6,263	−$6,263	−$6,263	−$6,263
• Yet unidentified Medicare costs[26a]	−$39,797	−$39,797	−$39,797	−$39,797
• Nursing home costs[26]	−$23,744	−$23,744	−$23,744	−$23,744
• Subtotal	−$75,519	−$75,519	−$75,519	−$75,519
• Subtotal, with systemic health care costs incurred	−$62,837	−$62,837	−$62,837	−$62,837
• by saving 1 year of life +				
• low vision costs saved				
Direct nonmedical (caregiver) costs saved				
• Inside activities of daily living[27]	−$138,051	−$138,051	−$138,051	−$138,051
• Outside activities of daily living[27]	−$18,038	−$18,038	−$18,038	−$18,038
• Transportation costs[27]	−$38,964	−$38,964	−$38,964	−$38,964
• Residence costs[27]	−$83,593	−$83,593	−$83,593	−$83,593
• Subtotal	−$276,646	−$276,646	−$276,646	−$276,646
Indirect medical (productivity) costs saved				
• Wage loss[28,29],	−$25,471	−$25,471	−$25,471	−$25,471
• Volunteer costs[27]	−$7,497	−$7,497	−$7,497	−$7,497
Subtotal	−$32,969	−$32,969	−$32,969	−$32,969
Total costs saved by therapy per individual	$372,452	$372,452	$372,452	$372,452
Total societal costs (direct ophthalmic and nonophthalmic Medical, direct nonmedical and indirect medical costs)	−$353,460	−$261,249	−$306,420	−$306,420
Individual patient costs				
Total direct ophthalmic medical costs	$14,772	$106,582	$61,811	$24,419
Total societal costs accruing against the direct ophthalmic medical costs	−$372,452	−$372,452	−$372,452	−$372,452
Aggregate societal costs per individual = 11-y net $ returned to society	−$357,680	−$265,870	−$310,611	−$348,033
11-y financial return-on-investment per individual completing VEGF-I treatment	($357,680/ $14,772) = 2,421%	($265,870/ $106,582) = 249%	($310,611/ $61,811) = 503%	($348,033/ $24/49) = 1,397%
11-y dollars gained by society for $1 spent on VEGF-I tx for each patient completing treatment	$24.21	$2.49	$5.03	$13.97
Annual financial ROI per individual completing 11-y VEGF-I treatment	34.1%	12.0%	17.7%	27.9%
11-y QALY gain[1]	1.339	1.339	1.380	1.345
11- y ophthalmic cost perspective cost-utility ratio	$11,033/ QALY	$79,600/ QALY	$44,801/ QALY	$18,151/ QALY
11-y societal cost perspective cost-utility ratio	−$267,124/ QALY	−$198,558/ QALY	−$225,102/ QALY	−$258,769/ QALY

NVAMD = neovascular age-related macular degeneration; pts = patients; QALY = quality-adjusted life-years; tx = treatment; VEGF-I = vascular endothelial growth factor inhibitor,.

Negative costs are accrued against direct ophthalmic medical costs.

[a]Examining a 5% Medicare database, Javitt and associates[22] noted increased trauma costs, increase depression costs and increased subacute nursing facility (SNF) costs in a cohort with decreased vision referent to those without decreased vision, as well as excess medical costs that could not be identified.

[b]Costs include treatment in fellow eyes that develop NVAMD over the 11-y model. Costs accruing against the direct ophthalmic medical costs are shown as negative costs.

TABLE 6. 11-Year Societal Macroeconomic Costs Accruing Against the Direct Ophthalmic Costs of VEGF-I Therapy for New 2018 NVAMD Patients Treated, Adjusted for 89.7% Eligibility and 6.4% Annual Dropout Rate (2018 U.S. Real Dollars) (Costs Accruing Against the Direct Ophthalmic Medical Costs are shown as Negative Costs.)

				Direct Non-Oph. Med. Costs (Trauma, Facility, Depression, etc.)[26] + Low Vision Costs[27]		Direct Non-Med. Costs (Caregiver Costs)[27]		Indirect Med. Costs (Wage Loss + Volunteering)[27–29]		Total
	A	B	C	D	E	F	G	H	I	J
Year of tx	Treatment Patients (151,055) with 6.4% Annual Dropout	Integrating Percent of 2nd-Eye Models	Patients, Adjusted for 2nd-Eye Model Cases	Direct Med.Costs Saved Per 11-Y Patient (Including low Vision)[a]	11-y Patient Costs Adjusted for 2nd-Eye Model (Millions)	Direct Non-Med. Costs Saved Per 11-y Patient	11-y Patient Costs Adjusted for 2nd-Eye Model (Millions)	Indirect med. Costs Saved Per 11-Yer Patient	11-y Patient Costs Adjusted for 2nd-Eye Model (Millions)	Total Costs Accruing Against VEGF-I tx (Millions)
	A	B	C = A x B	D	E = C x D	F	G = C x F	H	I = B x H	J = E+G+I
1	151,055	60.0%	90,633	−1,334	−121	−14,783	−1,340	−612	−55	−1,516
2	141,387	69.1%	97,699	−7,099	−694	−14,352	−1,402	−594	−58	−2,154
3	132,339	74.6%	98,725	−7,419	−732	−31,887	−3,148	−1,131	−112	−3,392
4	123,869	77.1%	95,503	−8,129	−776	−31,965	−5,053	−1,098	−105	−3,934
5	115,941	79.4%	92,057	−7,892	−727	−30,160	−2,776	−1,066	−98	−3,601
6	109,521	81.5%	88,445	−6,525	−577	−16,530	−1,462	−2,236	−198	−2,237
7	101,576	83.3%	84,613	−10,115	−856	−16,048	−1,358	−2,171	−184	−2,397
8	95,075	85.0%	80,814	−9,820	−794	−15,581	−1,259	−2,108	−170	−2,223
9	88,990	86.5%	76,976	−10,558	−813	−36,428	−2,804	−7,535	−580	−4,197
10	83,295	87.8%	73,133	−9,765	−714	−35,366	−2,586	−7,315	−535	−3,481
11	77,764	89.0%	69,388	+15,319[a]	+1,373	−34,366	−2,385	−7,102	−493	−1,858
	Total	NA	NA	−62,837	−5,430	−276,646	−23,573	−32,969	−2,588	−31,591

med. = medical; non-op. = non-ophthalmic; NVAMD = age-related macular degeneration; tx = treatment; VEGF-I = vascular endothelial growth factor inhibitor.

[a]Note that the extra $24,800 per patient in non-ophthalmic medical cost accrued by VEGF-I treated patients during the 1.0 y of life saved from VEGF-inhibitor therapy is included in the 11th-y data in column D. Had untreated NVAMD patients died at 10.0 y. after baseline, these costs would not have been accrued.

with atrophic age-related macular degeneration (AMD) that converted to NVAMD during the 11-year and 2-year model timelines. Direct nonophthalmic medical costs[26] were adjusted to 2018 U.S. real dollars using the Consumer Price Index (CPI) for All Urban Consumers, Medical care,[43] and direct nonmedical costs (caregiver costs)[27] were adjusted to 2018 real dollars with the medical CPI for All Urban Consumers, All items.[43] Indirect medical (productivity costs were calculated using Bureau of Labor Statistics data[28] and information from the U.S. Census Bureau, Household Economic Studies,[29] both adjusted to 2018 real dollars with the CPI for All Urban Consumers, All items.[43] Among all direct nonmedical (caregiver) costs received over time against the direct ophthalmic medical costs, 27% were accrued for salary-paid caregivers and 73% for unpaid family and friend caregivers, both costed at the same mean mid-2018 U.S. hourly wage of $27.07, unless patients specified a different cost basis. These caregiver costs were typically lumped together, except for the calculation of the contribution of societal costs to the Gross Domestic Product (GDP), in which paid caregiver salaries lost due to visual improvement from VEGF-I therapy due to better vision were assumed to decrease the GDP. The authors assumed that freed-up unpaid caregivers could obtain gainful use in the 2018 environment with the unused rate close to zero after taking into account the 3%-4% of people changing jobs at any one time.[1,44] Our analysis used an ophthalmic direct medical cost perspective to calculate ophthalmic treatment expenditures and a societal cost perspective (including direct nonophthalmic medical costs expended during the 1.0-year life expectancy gain due to the improved vision from VEGF-I treatment) to assess the costs accrued against ophthalmic direct medical expenditures.

Out-of-pocket expenses for co-pays and deductibles vary widely among the thousands of U.S. insurance plans. Thus, we based them upon the expenses the average person pays for their Medicare B drugs weighted with the 8.5% of Medicare enrollees who do not have supplemental insurance (American Association of Retired Persons. The Medicare Beneficiary Population. Fact Sheet, AARP Public Policy Institute. Available at: https://assets.aarp.org/rgcenter/health/fs149_medicare.pdf. Accessed June 4, 2019). Out-of-pocket expenses for insured patients were thus assumed to consist of 4.6% of VEGF-I treatment expenses. The uninsured, with 100% out-of-pocket expenses, were considered in a separate individual category than insured patients when the distribution of societal costs accrued against the direct ophthalmic medical costs was calculated (Table 9).

• **COST-BENEFIT ANALYSIS:** The present Value-Based Medicine cost benefit methodology[38–40] used patient vision outcomes, national average Medicare fee schedule payments, a 3% discount rate/year for clinical outcomes (quality-adjusted life years [QALY] and costs), and the inclusion of systemic medical cost expenditures made necessary by the year of life gain associated with better vision from VEGF-I therapy.

A combined-eye model cost basis was used.[1,14–16] This included a weighted average of first-eye and second-eye models. CATT data[6] showed that 60% of baseline cases were second-eye model cases in which first-eye vision was already decreased and the NVAMD was undergoing VEGF-I treatment in the better-seeing second eye. Forty-percent of CATT participants at baseline had the first-eye model, with the first eye undergoing VEGF-I NVAMD treatment and second eye with good vision and no NVAMD at baseline. With first-eye model cases, unaffected fellow eyes could convert from AMD to NVAMD over the 11-year and 2-year models (Supplemental Table 4).

• **MORTALITY:** Christ and associates[45] calculated the risk of premature death associated with vision loss in the better-seeing eye and made further calculations for analysis of patients with vision as poor as 20/630. Using these data, the difference in mortality was calculated based upon the vision in each year in treated and untreated NVAMD patients. No VEGF-I treatment from baseline resulted in a loss of 1.0 year of life from 11 years to 10 years. Conversely, 11-year VEGF-inhibitor treatment prevented the loss of 1.0 year of life from the 11-year life expectancy in an age-matched general population.[11] Treatment over 2 years resulted in 1 month of life saved.

RESULTS

UNLESS OTHERWISE NOTED, THE RESULTS ARE REPORTED for the combined-eye model using weighted treatment costs in baseline treated primary eyes for all enrolled participants in addition to fellow eyes with atrophic AMD that converted to NVAMD over the 11-year and 2-year models in cases presenting with unilateral NVAMD. Model assumptions are shown in Table 1.

Medicare drug distribution data were used from 2018[23] to estimate NVAMD, VEGF-inhibitor use. For 2018, among all eligible new cases of NVAMD (151,055) treated, 80.9% (122,203 patients) were assumed to receive bevacizumab, 3.7% (5,489 patients) ranibizumab, and 15.4% (23,262 patients) aflibercept (Supplemental Table 2).

• **LATERALITY:** At baseline, 60% of patients had the second-eye model in which the first eye had already lost vision from NVAMD. The second eye was therefore treated. Forty-percent had the first-eye model with which the first eye with NVAMD was treated, and the fellow eye had good vision and no NVAMD. By the end of year 2, or the beginning of year 3, among the 40% of baseline participants with the first-eye model (14.6%/40% =),

36.5% of atrophic second eyes had converted to NVAMD (Supplemental Section 4, Table 4), and 74.6% of all patients had bilateral NVAMD. By year 11, (29%/40% =) 72.5% of the 40% of unilateral NAVMD cases at baseline became bilateral, resulting in an 89% incidence of bilateral NVAMD among all (first-eye model and second-eye model) patients.[1,13,22]

• **PATIENT VALUE GAIN:** The 11-year patient value gains, or benefits, for bevacizumab, ranibizumab, and aflibercept for the treatment of NVAMD were similar,[1–8] differing only because the aflibercept cohort had less adverse event QALY loss due to fewer intravitreal injections.[1] We calculated that the 1.339 QALY (value) gain in the bevacizumab and ranibizumab treatment cohorts correlated with a 26.1% quality-of-life gain, whereas the 1.380 aflibercept QALY gain correlated with a 26.9% quality-of-life gain.[1] Two-year value gains were 0.141 QALY for bevacizumab and ranibizumab, correlating with a 10.4% quality-of-life gain, and 0.164 QALY for aflibercept, correlating with a 12.1% quality-of-life gain.

• **DRUG AND OTHER TREATMENT COSTS PER PATIENT:** The estimated 11-year ophthalmic direct medical (treatment) costs of 2018 VEGF-inhibitor therapy, according to the national average Medicare Fee Schedule, are shown in Table 4.[23–25] Costs included Medicare deductibles and payment from Medicare and Medicare coinsurance. The 11-year, combined-eye model treatment cost was $14,722 for bevacizumab therapy. The respective treatment costs for ranibizumab and aflibercept therapy were $106,582 and $61,811. The average overall treatment cost per patient integrating and weighting the 3 treatment cohorts was $24,423. The bilateral $4,050 drug cost for each bevacizumab-treated individual treated for 11 years accounted for ($4,050/$14,722 =) 27.4% of ophthalmic direct medical treatment costs. The $95,587 ranibizumab drug cost comprised ($95,587/$106,582 =) 89.7% of each ranibizumab patient treatment cost, and the $49,036 aflibercept drug cost accounted for ($49,036/$61,811 =) 79.3% of each aflibercept patient treatment cost. The mean 11-year weighted drug cost for the average patient across all 3 drug cohorts was ($14,365/$42,423 =) 58.8%.

• **SAVING FROM SWITCHING TO BEVACIZUMAB:** With the current distribution of drugs, changing ranibizumab and aflibercept to bevacizumab for the 2018 168,400-person cohort of new NVAMD patients in the United States would theoretically save $1.343 billion in 2018 U.S. real dollars over 11 years. Although per capita switching from ranibizumab to bevacizumab saves more than switching from aflibercept to bevacizumab, many more cases in 2018 were treated with aflibercept than ranibizumab (Table 4). Thus, the overall 11-year saving from switching ranibizumab to bevacizumab would be $428 million, while the amount saved from switching from aflibercept to bevacizumab would be $915 million.

• **SOCIETAL COSTS PER PATIENT ACCRUING AGAINST DRUG AND OTHER TREATMENT COSTS:** With the exception of systemic medical costs incurred due to living 1 year longer with VEFG-I NVAMD therapy, the remainder of societal costs accrue against the ophthalmic direct medical costs of therapy because they are made unnecessary by the better vision associated with VEGF-I therapy versus no therapy. Table 5 shows the societal costs for an individual. These 11-year costs totaled −$372,452 per individual undergoing 11 years of VEGF-I therapy. Table 6 shows the derivation of the 11-year, macroeconomic societal costs accruing against the direct medical costs expended for treatment.

Integrated with the direct non-ophthalmic medical treatment costs were a −$12,118 ophthalmic direct medical cost obviated for low vision services and devices,[27] a −$75,519 non-ophthalmic medical cost obviated by better vision, decreasing depression, trauma, facility admissions and other conditions and a +$24,800 cost expended due to extra systemic health care costs incurred in the extra year of life made possible by VEGF-I therapy.[51] Together they totaled −$62,837.

The 11-year direct nonmedical (caregiver) costs (Tables 5, 6) accruing against the treatment costs of VEGF-inhibitor therapy were −$276,646 for each drug.[27] A total of 27% of caregiver costs accrued were for paid services obviated and 73% for unpaid services made unnecessary, the latter typically for care given by families and friends.[27]

The indirect medical costs (Tables 5, 6), wage loss (productivity) cost, and loss of volunteering cost were also the same for each drug at −$32,969. With better vision from VEGF-I therapy, more people could work and volunteer. The wage costs were calculated using an age-matched use rate of 8.1% for people over 75 years of age.[28] Those with severe difficulty seeing earned a median $2,564 monthly (98% that of a nondisabled person) but were only 47% as likely to be employed as people without disabilities.[29]

With the 2-year model (Table 8), the mean weighted, direct ophthalmic medical cost of VEGF-I therapy per individual completing the 2-year course was $9,971, whereas the societal costs accruing against direct ophthalmic medical costs totaled −$41,211.

• **RETURN-ON-INVESTMENT:** The overall, 11-year, societal ROI per NVAMD individual for the weighted direct ophthalmic medical costs of all VEGF-I therapy was 1,397%, which converted to a 27.9% annual compounded ROI for the direct medical costs expended (Table 5). The 11-year ROI and annual ROI for the associated treatment costs with each drug were 2,421%/34.1% for bevacizumab,

249%/12.0% for ranibizumab, and 503%/17.7% for aflibercept. Corresponding 2-year model values per NVAMD individual (Table 8) for the 2-year ROI/annual ROI were: 213%/103% for the weighted average of the 3 drugs, 624%/269% for bevacizumab, −12.9%/−6.7% for ranibizumab, and 56%/25% for aflibercept.

• **MACROECONOMIC COSTS:** The national 11-year, societal costs associated with VEGF-I therapy are shown in Tables 3, 6 and 7. The total Medicare Fee Schedule (including co-pays and 20% co-insurance), direct ophthalmic medical cost expenditure for VEGF-I therapy for patients was $3.077 billion, while the cost for VEGF-I drugs was $1.809 billion (Table 7). The costs accruing against the direct ophthalmic medical costs due to better vision in VEGF-I-treated eyes totaled −$31.6 billion. Subtracting the $3.077 billion direct ophthalmic medical costs from the negative costs accrued against them resulted in a total societal cost of −$28.5 billion. The weighted 11-year ROI for therapy with the 3 drugs was 925%, whereas bevacizumab therapy had an 11-year ROI of 1,729%, aflibercept therapy returned 314%, and ranibizumab therapy returned 139%. These were less than the ROIs of individual patients who completed the 11-year therapy due to the yearly dropout rate and subsequent decreasing negative societal costs accruing against the direct ophthalmic medical costs in later years when they should have been the highest due to greater vision disparities between the treated and untreated cohorts.

• **ROI TO INSURERS AND PATIENTS:** The payer expenditures and financial ROIs for 2018 NVAMD-treated patients are shown in Table 9. The costs did not include expenditures for the purchase of health care insurance except in the special case of insured patient costs below.

Among the NVAMD-treated patients, 93.5% were 65 years or older and therefore Medicare eligible, as are select people with disabilities and those with end-stage renal disease. A total of 6.5% of NVAMD patients were younger than age 65.

Medicare typically pays 80% of its approved cost for a medical intervention, whereas a secondary insurance or patient pays the remaining 20%. In the present analysis, original Medicare paid 52.9% of all expenditures or $1.63 billion. In return, Medicare received $1.36 billion, reducing the $1.63 billion direct ophthalmic medical expenditure by 83% to $0.27 billion due to health care costs saved from better vision, primarily from non-ophthalmic direct medical costs (depression, trauma, facility fees, and so forth) obviated. Had not the 11-year, $24,800 systemic healthcare expenditure incurred by living an extra year of life due to better vision with VEGF-I therapy versus no therapy been integrated,[52] Medicare would have had a $1.9 billion, 11-year profit gain above its direct ophthalmic medical costs expended for the treatment of NVAMD.

The greatest financial beneficiaries of NVAMD therapy were insured patients. The dollars returned to insured patient are demonstrated in Table 9. Patient costs, however, are less clear. Therefore, it was arbitrarily decided to use as the expense basis for this group the 2% percent of the health care dollar insurance premium and out-of-pocket costs that typically cover eye care services.[46] For people aged 65 or older, 98.7% are covered by some form of health insurance, the number dropping to 90.7% for those under age 65.[47] Assuming that insured patients had expenses consisting of 2% of health care insurance premiums and out-of-pocket costs,[46] the cost basis over 11 years for the VEGF-I insured patient population herein was $110 million.

This investment yielded a $27.5 billion, 11-year financial accrual above direct ophthalmic treatment costs, a 25,027% societal ROI (Table 9).

• **GROSS DOMESTIC PRODUCT:** The GDP is the monetary value of all finished goods and services a country produces, typically within 1 year.[52] It is an indicator of a country's overall economic activity and reflects the wealth of a nation. The U.S. GDP consists of 1) personal consumption and expenditures (69%); 2) government consumption expenditure and gross investment (17%); 3) private domestic investment (16%); and 4) net exports minus imports (−3%). The last is calculated by subtracting the monetary value of imports from exports.[52]

The 11-year contribution to the GDP in 2018 dollars from VEGF-I therapy for the 1-year cohort of new NVAMD patients was $12.2 billion (Table 10). This equated to $3.95 added to the GDP for each dollar expended upon VEGF-I therapy. Late treatment with baseline vision of 20/160 to 20/320, decreased this contribution by 78% to $2.7 billion. With the 2-year model, each dollar spent on direct ophthalmic medical costs contributed $1.59 to the GDP.

• **SENSITIVITY ANALYSIS:** Sensitivity analysis results are shown in Table 11 and Supplemental Table 5.

• **LATE TREATMENT VERSUS REFERENCE CASES:** It has been shown with MARINA data[53] that earlier treatment (baseline vision of 20/40-20/80) of NVAMD with ranibizumab therapy resulted in a mean 24-month vision of $20/40^{-1}$ versus late treatment (baseline vision of 20/160 to 20/320), which resulted in a mean 24-month vision of $20/160^{+2}$. Mean CATT vision outcome data were close to early treatment MARINA cohort data, with long-term vision of 20/63 in both CATT and the early treatment MARINA study.[8,53]

Nonetheless, late treatment vision outcomes conferred considerably less patient value gain (12% QALY gain)

TABLE 7. 11-Y Societal Macroeconomic Costs (Millions) Associated With VEGF-I Therapy for a 2018 Cohort of 168,400 Patients Estimated to Develop NVAMD (89.7% Eligibility for Treatment and 6.4% Annual Dropout Are Integrated for Costs Expended and Eligibility, Dropout and Combined-Eye Model Are Integrated for Costs Saved) (Costs Expended Include Treatment in Fellow Eyes That Develop NVAMD Over the 11-Y Model. Costs Accruing Against the Direct Ophthalmic Medical Costs Are Shown As Negative Costs.)

Costs (Millions) (Baseline Candidates)	Bevacizumab (n = 122,203)[23]	Ranibizumab (n = 5,589)[23]	Aflibercept (n = 23,262)[23]	Total Costs (n = 151,055)
Ophthalmic direct medical treatment costs expended				
• Total: drug + physician + diagnostic	$1,403	$492	$1,182	$3,077
• Drug	$384	$441	$937	$1,809
• Physician/diagnostic	$1,019	$51	$245	$1,268
Ophthalmic direct medical costs saved = low vision costs				
• Low vision[27]	−$874	−$40	−$274	−$1,080
Nonophthalmic direct medical costs saved				
• Trauma, depression, facility, etc., including direct non-oph. medical costs accrued by 1.0 y of life saved by VEGF-Is[26]	−$3,518	−$161	−$626	−$4,349
Direct nonmedical (caregiver) costs saved				
• ADLs, transportation, residence[27]	−$19,071	−$872	−$5,988	−$23,573
Indirect medical costs saved				
• Wage loss and volunteer costs saved[27–29]	−$2,094	−$96	−$657	−$2,588
Macroeconomic costs				
• Macroeconomic 11-y ophthalmic costs expended, (89.7% eligible patients, 6.4% annual dropout)	$1.40 billion (n = 122,203 = 80.9%)	$0.49 billion (n = 5,589 = 3.7%)	$1.18 billion (n = 23,262 = 15.4%)	$3.08 billion (n = 151,055 = 100%)
• Macroeconomic societal costs accrued against direct ophthalmic medical costs	−$25.5 billion (n = 122,203 baseline patients)	−$1.17 billion (n = 5,589 baseline patients)	−$4.9 billion (n = 23,262 baseline patients)	−$31.6 billion (n = 151,055 baseline patients)
• Macroeconomic societal costs = 11-y cost returned to society above direct ophthalmic costs	−$24.2 billion (84.9%)	−$0.7 billion (2.4%)	−$3.6 billion (12.6%)	−$28.5 billion (100%)
• Macroeconomic 11-y societal financial ROI	($24.2B/1.403B) = 1,729%	($0.7B/$0.49B) = 139%	($3.6B/$1.18B) = 314%	($28.5B/$3.08B) = 925%
• Macroeconomic annual societal financial ROI	30.2%	8.2%	13.8%	23.6%
• Macroeconomic 11-y $ gained by society for $1 spent on VEGF-I treatment for each patient enrolled	$17.29	$1.39	$3.14	$9.25

ADLs = activities of daily living; diag. = diagnostic testing; NVAMD = neovascular age-related macular degeneration; oph. = ophthalmic; phy. = physician; ROI = return-on-investment; VEGF-I = vascular endothelial growth factor inhibitor.

Negative costs are accrued against the direct ophthalmic medical costs and comprise the costs returned to society due to VEGF-I therapy.

TABLE 8. Nationwide 2-Year Societal Costs (2018 Millions of U.S. Real Dollars) and Cost-Effectiveness Outcomes Associated with VEGF-I Therapy for a 2018 Cohort of 168,400 U.S. Patients Estimated to Develop NVAMD (89.7% Eligibility for Treatment and 6.4% Annual Dropout are Integrated for Costs Expended and Eligibility, Dropout and 2nd-Eye Model Costs are Integrated for Costs Saved) (Costs Include Treatment in Fellow Eyes that Develop NVAMD Over the 2-y Model. Costs Accruing against the Direct Ophthalmic Medical Costs are shown as Negative Costs.)

	Bevacizumab	Ranibizumab	Aflibercept	Weighted Value
Individual costs				
Two-y direct ophthalmic medical costs expended	$5,690	$47,319	$26,377	$9,971
Two-y QALY gain	0.141 QALY	0.141 QALY	0.157 QALY	0.143 QALY
Percent QALY gain	10.4%	10.4%	12.1%	10.6%
Two-y ophthalmic cost perspective cost-utility ratio	$40,371/QALY	$335,726/QALY	$168,006/QALY	$67,995/QALY
Individual costs induced by therapy				
Systemic medical costs added by 1 month of life saved	+$1,407	+$1,407	+$1,407	+$1,407
Individual costs saved by therapy				
Costs				
Direct ophthalmic medical costs saved				
• Low vision services saved[27]	−$827	−$827	−$827	−$827
Direct nonophthalmic Medical Costs Saved				
• Injury costs[26]	−$867	−$867	−$867	−$867
• Depression costs[26]	−$1,281	−$1,281	−$1,281	−$1,281
• Subacute Nursing Facility costs[26]	−$1,941	−$1,941	−$1,941	−$1,941
• Yet unidentified Medicare costs[26]	−$5,899	−$5,899	−$5,899	−$5,899
• Nursing home costs[26]	−$1,451	−$1,451	−$1,451	−$1,451
• Subtotal	−$11,440	−$11,440	−$11,440	−$11,440
Direct nonmedical costs saved				
• Inside activities of daily living[27]	−$13,533	−$13,533	−$13,533	−$13,533
• Outside activities of daily living[27]	−$874	−$874	−$874	−$874
• Transportation costs[27]	−$6,155	−$6,155	−$6,155	−$6,155
• Residence costs[27]	−$8,573	−$8,573	−$8,573	−$8,573
• Subtotal	−$29,135	−$29,135	−$29,135	−$29,135
Indirect medical costs saved				
• Wage loss[28,29],	$0	−$0	$0	−$0
• Volunteer costs[27]	−$1,206	−$1,206	−$1,206	−$1,206
• Sub−Total	−$1,206	−$1,206	−$1,206	−$1,206
Total Costs Saved (Nonophthalmic Direct Medical, Direct Nonmedical and Indirect Medical	−$41,211	−$41,211	−$41,211	−$41,211
Individual costs				
Total costs saved by therapy per individual	−$41,211	−$41,211	−$41,211	−$41,211
Ophthalmic costs expended per Individual	$5,690	$47,319	$26,377	$9,971
Total societal costs per individual	−$35,521	$6,108	−$14,834	−$21,240
Individual, 2-y ROI for the direct ophthalmic medical costs expended	624%	−12.9%	56%	213%
Individual annual ROI for the direct ophthalmic medical costs expended	269%	−6.7%	25%	103%
Ophthalmic cost perspective cost-utility ratio[1]	$40,355/QALY ($5,690/0.141)	$335,596/QALY ($47,319/0.141)	$168,006/QALY ($26,377/0.157)	$67,978/QALY ($9,972/0.143)
Societal cost perspective cost-utility ratio	−$251,922/QALY (−$35,521/0.141)	$43,419/QALY ($6,108/0.141)	−$94,484/QALY (−$14,835/0.157)	−$148,532/QALY (−$21,240/0.143)
Macroeconomic costs				
Ophthalmic costs expended, macroeconomic	$452 million (n = 122,203)	$247 million (n = 5,989)	$577 million (n = 23,262)	$1,256 million (n = 151,055)

Continued on next page

TABLE 8. Nationwide 2-Year Societal Costs (2018 Millions of U.S. Real Dollars) and Cost-Effectiveness Outcomes Associated with VEGF-I Therapy for a 2018 Cohort of 168,400 U.S. Patients Estimated to Develop NVAMD (89.7% Eligibility for Treatment and 6.4% Annual Dropout are Integrated for Costs Expended and Eligibility, Dropout and 2nd-Eye Model Costs are Integrated for Costs Saved) (Costs Include Treatment in Fellow Eyes that Develop NVAMD Over the 2-y Model. Costs Accruing against the Direct Ophthalmic Medical Costs are shown as Negative Costs.) (*Continued*)

	Bevacizumab	Ranibizumab	Aflibercept	Weighted Value
Societal costs accrued against direct ophthalmic medical costs	−$2,969 million	−$136 million	−$565 million	−$3.67 billion
Aggregate (with direct ophthalmic) societal costs, macroeconomic	−$2.52 billion (n = 122,203 at baseline)	+$111 million (n = 5,589 at baseline)	+$12 million (n = 23,262 at baseline)	−$2.414 billion (n = 151,055, at baseline)
Macroeconomic, 2-y ROI for the direct ophthalmic medical costs expended	557%	−45%	−2.1%	192%
Macroeconomic annual ROI for the direct ophthalmic medical costs expended	256%	−26%	−1%	71%

NVAMD = neovascular age-related macular degeneration; QALY = quality-adjusted life-years; ROI = return-on-investment; VEGF-I = vascular endothelial growth factor inhibitor.

Negative costs are costs returned to society for the direct ophthalmic medical costs expended. Negative cost-utility ratios indicate that there is a net return of dollars to society (predominantly patients and insurers) because of the intervention. The lower the cost-utility ratio, the greater the dollars returned to society per QALY gained.

than mean CATT vision data (26.1% QALY gain).[1] Cost analysis revealed that, instead of the $28.5 billion cost returned to society with VEGF-I treatment in the present reference case, the resultant return to society with late treatment was $9.6 billion, an $18.9 billion (66.3%) decrease versus the reference case (Table 11). Thus, late treatment of NVAMD versus earlier treatment is undesirable from both the financial and patient value gain (QALY) perspectives.

• **DECREASED AFLIBERCEPT INJECTIONS:** Aflibercept therapy was also examined, given that the FDA in August 2018 changed aflibercept labeling to "Although not as effective as the recommended every 8 week dosing regimen, the FDA approved giving aflibercept injections every three months after one year of effective therapy."[41] Thus a scenario was modeled where aflibercept was given with one-third the frequency of bevacizumab and ranibizumab after year 2 when the randomized clinical trial ended (Table 11).[1] With the QALY gain associated with aflibercept therapy increasing from 1.382 to 1.386 due to 3 fewer injections over 11 years, the combined-eye therapeutic cost of aflibercept deceased from $61,811 to $51,129, and the 11-year ophthalmic cost perspective cost-utility ratio of aflibercept improved by 17.7% from $44,801/QALY to $36,890/QALY. This resulted in a $209 million direct medical cost saving annually from the overall, annual, direct ophthalmic medical expenditure of $1.182 billion (Table 7) for aflibercept therapy for NVAMD.

• **INCREASED AFLIBERCEPT INJECTIONS:** If aflibercept injections were given with the same frequency as bevacizumab and ranibizumab injections after 24 months, the 11-year QALY gain decreases from 1.380 to 1.364 due to more adverse events associated with more intravitreal injections. The total aflibercept direct ophthalmic medical cost rises to $85,335 from $61,881, yielding a cost-utility ratio of $63,730, and direct ophthalmic medical cost increase of $450 million above the $1.182 billion (Table 7) to $1.632 for the annual expenditure for aflibercept treatment of NVAMD. This situation may theoretically be applicable if the similar real-world, 1-year number of injections and vision outcomes for bevacizumab, ranibizumab, and aflibercept therapy reported by Ciulla and associates[54] held up on a long-term basis.

• **TREAT-AND-EXTEND:** Treat-and-extend (T/E) therapy is used for NVAMD VEGF-I therapy in approximately two-thirds of patients in the United States, despite the fact that clinical trial data comparing T/E regimens to monthly injections over the first 2 years are scarce.[55–57] One-year results from a meta-analysis were non-inferior to the present reference case results with monthly injections.[6,56] Second-year data in a meta-analysis, however, were underpowered.[56] Nonetheless, the Canadian Treat-and-Extend Analysis Trial with Ranibizumab in Patients with Neovascular Age-Related Macular Disease (CANTREAT) in January, 2020, reported 24-month non-inferiority at 24 months for T/E therapy with ranibizumab versus monthly therapy.[58] A comparison of the costs associated with our reference case and the T/E methodology is shown in Supplemental Table 6.

The respective 11-year, T/E direct ophthalmic costs for bevacizumab, ranibizumab, and aflibercept therapy (vs. the reference case costs in parentheses) were $11,792 ($14,772), $98,853($106,582) and $56,744 ($61,811).

TABLE 9. Expenditures and Distributions (in Negative Numbers) Associated With a 2018, 168,400 Patient Cohort Developing NVAMD, Assuming a Medicare Fee Schedule Reimbursement (Billions of U.S. 2018 $) [23–29,38–41,47] (89.7% Eligibility for Treatment and 6.4% Annual Dropout Are Integrated for Direct Medical Costs Expended, and Eligibility. Dropout and the Combined-Eye Model Are Integrated For Costs Saved) (Costs Expended Include Treatment in Fellow Eyes that Develop NVAMD Over the 11-Y Model.) (Costs Accruing Against the Direct Ophthalmic Medical Costs are shown as Negative Costs.

	Payer	Payer	Payer	Payer	Payer	Payer	Payer	Payer	Payer
Costs[45]	Total	Original Medicare	Medicare Advantage	Medicaid	Employer-Sponsored Insurance	Medigap	Military Insurance	Uninsured Patients	Patients
Direct ophthalmic costs	$3.08	$1.63	$0.81	$0.15	$0.19	$0.14	$0.12	$0.04	$0.11[a]
of treatment cost[23–25]	100%	52.9%	26.3%	4.9%	6.2%	4.5%	3.9%	1.3%	NA
Drug component of direct	$1.77	$0.95	$0.45	$0.09	$0.11	$0.08	$0.07	$0.02	NA
oph. tx[23]	100%	52.9%	26.3%	4.9%	6.2%	4.5%	3.9%	1.3%	NA
Physician/diagnostic dir.	$1.31	$0.68	$0.36	$0.06	$0.08	$0.06	$0.05	$0.02	NA
oph. tx[24]	100%	52.9%	$26.3%	4.9%	6.2%	4.5%	3.9%	1.3%	NA
Low vision costs[27]	−$1.08 (100%)	−$0.06 (6.0%)	−$0.04 (3.50%)	−$0.06 (6.0%)	$0.000 (0.0%)	−$0.01 (1.0%)	−$0.01 (0.7%)	−$0.01 (1.3%)	−$0.88 (81.1%)
Non-ophthalmic direct medical costs[26]	−$2.26 (100%)	−$1.13 (50.2%)	−$0.57 (25.1%)	−$0.10 (4.6%)	−$0.13 (5.9%)	−$0.10 (4.5%)	−$0.09 (3.8%)	−$0.03 (1.4%)	−$0.10 (4.6%)
Nursing home[26]	−$2.08 (100%)	−$0.17 (8.0%)	−$0.10 (5.0%)	−$0.94 (−45.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	−$0.03 (1.3%)	−$0.85 (40.7%)
Direct nonmedical (caregiver)[27]	−$23.57 (100%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	−$0.31 (1.3%)	−$23.26 (98.7%)
Employment[27–29]	−$2.01 (100%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	−$0.03 (1.3%)	−$1.98 (98.7%)
Volunteer[27]	−$0.58 (100%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	$0.000 (0.0%)	−$0.01 (1.3%)	−$0.57 (98.7%)
Negative costs accruing against direct ophthalmic medical costs	−$31.58 (100%)	−$1.36 (4.3%)	−$0.91 (2.2%)	−$1.10 (3.5%)	−$0.13 (0.4%)	−$0.11 (0.3%)	−$0.10 (0.3%)	−$0.42 (1.3%)	−$27.64 (87.5%)
Societal costs[21–27,45] = direct ophthalmic + negative costs	−$28.50 (100%)	+$0.27 (−0.9%)	−$0.10 (0.4%)	−$0.95 (3.3%)	+$0.6 (−0.2%)	+$0.03 (−0.1%)	+$0.02 (−0.1%)	−$0.38 (1.3%)	−$27.54 (96.5%)
11−y financial ROI for the NVAMD therapy costs expended	925%	−17%	12%	633%	−32%	−21%	−17%	950%	25,027%
Annual compounded interest rate (ROI) to achieve the total revenue return for NVAMD therapy	23.6%	−1.6%	1.1%	19.9%	−3.5%	−2.0%	−1.0%	23.7%	65.3%

Dir. oph. tx = direct ophthalmic treatment, NVAMD = neovascular age-related macular degeneration, ROIs = returns-on-investment, VEGFI = vascular endothelial growth factor inhibitor, NA = not applicable.

Note that some of the numbers are approximate since there is overlap among the different insurances. For example, some have multiple insurances, and it is difficult to know which they primarily used. Medicare, however, was considered the primary insurance when people were enrolled in Medicare Part B. The Medicare costs in this table are the 80% of the total Medicare-approved costs that Medicare pay (not including the supplemental 20% of the Medicare-approved costs paid by secondary insurers or patients).

[a]Note that this number for patients includes health insurance premiums + out-of-pocket costs over 11 y proportional to the number of patients treated each y (Table 6, Column A). The insurance payments accrued as patient expenses include 2% of the premium[46,48–50] and out-of-pocket costs that are proportional to the 2% of the healthcare dollar devoted to eye care services, whether paid by an employer or a patient.[46] This arbitrarily chosen 2% patient cost was not included within the direct ophthalmic costs, the drug costs, or the physician/diagnostic costs in the other columns, but merely as a guide to give some idea of the 11-y ROI for insured patient costs.

TABLE 10. 11-y Addition to the Gross Domestic Product (in 2018 Millions of US Real Dollars) from VEGF-I Treatment of the Annual Cohort of 168,400 People Estimated to Develop NVAMD in 2018 (89.7% Eligibility for Treatment, 6.4% Annual Dropout are Integrated for Costs Expended and Eligibility, Dropout and 2nd-Eye Model are Integrated for Costs Saved) (Costs Expended Include Treatment in Fellow Eyes that Develop NVAMD Over the 11-y Model.)

Costs (Baseline Candidates)	Bevacizumab (n = 122,203)[23]	Ranibizumab (n = 5,989)[23]	Aflibercept (n = 23.263)[23]	Total cost (n = 151,055)
Ophthalmic direct medical treatment costs expended				
Total: drug + phy. + diag.[23–25]	$1,403	$492	$1,182	$3,077
Nonophthalmic direct medical costs saved, including non-ophthalmic direct medical costs accrued during 1.0 year of life saved				
Trauma, depression, subacute nursing facility, nursing home and so forth costs[26]	−$3,588	−$135	−$626	−$4,349
Direct nonmedical (caregiver) costs saved				
ADLs, transportation, residence[27] (27% of paid caregivers whose jobs become unnecessary with better patient vision)	− $5,251	− $197	− $917	− $6,365
ADLs, transportation, residence[27] (73% of unpaid caregivers freed up with better patient vision)	$14,197	$533	$2478	$17,208
Indirect medical costs saved				
Wage loss prevented[,27–29]	$2,094	$96	$657	$2,588
Total				
11-y contribution of VEGF-I therapy to the Gross Domestic Product	$8,895	$773	$2,490	$12,159
11-y contribution to the GDP for each dollar expended upon VEGF-I therapy	$6.34	$1.57	$2.11	$3.95
2-y contribution of VEGF-I therapy to the Gross Domestic Product	$1,555	$58	$271	$1,885
2-y contribution to the GDP for each dollar expended upon VEGF-I therapy	$3.37	$0.28	$0.52	$1.59

ADLs = activities of daily living; diag. = diagnostic studies; diag. = diagnostic testing; NVAMD = neovascular age-related macular degeneration; phy. = physician; VEGF-I = vascular endothelial growth factor-inhibitor.

Note that negative costs are costs accruing against the gross domestic product.

Their respective ophthalmic cost perspectives, cost-utility ratios (vs. reference case values in parentheses) were $8,793/QALY ($11,033/QALY), $73,716/QALY ($79,600/QALY), and $41,059/QALY ($44,801/QALY) (Table 11) ranging from 7.6% improved cost effectiveness for ranibizumab therapy to 20.3% greater cost effectiveness with bevacizumab therapy. The overall cost returned to society above the $2.67 direct ophthalmic treatment cost was −$28.9 billion, $405 million (1.4%) greater than the −$28.5 billion returned to society with the reference case analysis over 11 years.

• **REDUCED TREATMENT VISION AFTER 24 MONTHS:** When vision decreased from 20/63 to a mean 20/80 from year 3 to 11, the aggregate societal costs decreased to −$24.5 billion from −$28.5 billion in the reference case, a $4.0 (14.0%) decrease in dollars returned to society. If vision decreased to a mean 20/200 from year 3 to 11, the aggregate societal costs decreased to −$4.25 billion, a $24.25 billion (85.1%) decrease from the reference case.

• **SECOND-EYE TREATMENT:** Average vision results were used as the basis for the reference case calculations. Nonetheless, CATT results showed that 20% of ranibizumab- and bevacizumab-treated eyes were legally blind at 5 years, with vision ≤20/200.[8] If one assumes no correlation between VEGF-I-treated first-eye and VEGF-I-treated second-eye vision outcomes, therapy of the second eye in a patient already treated for NVAMD in the first eye decreases the long-term incidence of legal blindness from 20% to 4% (20% × 20%), a 16% decrease. Baseline involvement of 1 eye with NVAMD is the case for 40% of participants enrolled at baseline into CATT and assumed to be the case in the present cost-benefit model.[6]

For an annual cohort of 151,055 NVAMD patients treated in 2018, treating 1 eye and not those unilateral NVAMD cases with atrophic fellow eyes that convert from atrophic AMD to NVAMD over 11 years, results in an overall direct ophthalmic medical cost saving of $0.282 billion (Supplemental Table 5). Nonetheless, treating the second eyes of unilateral cases of NVAMD that

TABLE 11. Sensitivity Analysis (All Costs in 2018 U.S. Real Dollars) (Negative Costs Accrue Against the Direct Ophthalmic Medical Costs)

Reference Case: Societal Cost Perspective			
Combined-Eye Model	Bevacizumab	Ranibizumab	Aflibercept
Ophthalmic costs per individual	$14,772	$106,582	$61,811
Societal costs per individual	−$357,680	−$265,870	−$310,611
QALY gain/percent gain	1.339/26.1%	1.339/26.1%	1.380/26.9%
$/QALY, ophthalmic cost perspective	$11,033/QALY	$79,600/QALY	$44,801/QALY
$/QALY, societal cost perspective	−$267,124/QALY	−$198,558/QALY	−$225,102/QALY
Total direct ophthalmic costs			
Total = $3.077 billion	$1.403 billion	$0.492 billion	$1.182 billion
Costs accruing against direct ophthalmic medical costs			
Total = −$31.6 billion	−$25.6 billion	−$1.17 billion	−$4.6 billion
Aggregate societal costs = dollars returned to society			
Total = −$28.5 billion	−$24.2 billion	−$.68 billion	−$3.7 billion
Late Treatment[53] Versus Reference Case Treatment			
Combined-Eye Model	Bevacizumab	Ranibizumab	Aflibercept
Ophthalmic costs per individual	$14,772	$106,582	$61,811
Societal costs per individual	−$119,400	−$27,636	−$72,363
QALY gain/percent QALY gain	0.587 (11.7%)	0.587 (11.7%)	0.622 (12.5%)
$/QALY, ophthalmic cost perspective	$25,152/QALY	$181,481/QALY	$99,296/QALY
$/QALY, societal cost perspective	−$203,408/QALY	−$47,080/QALY	−$116,340/QALY
Total direct ophthalmic costs			
Total = 3.077 billion	$1.403 billion	$0.492 billion	$1.182 billion
Costs accruing against direct ophthalmic medical costs			
Total = −$12.7 billion	−$10.27 billion	−$0.47 billion	−$1.96 billion
Aggregate societal costs = dollars returned to society			
Total = −$9.623	−$8.87 billion	+0.022 billion	−$0.77 billion
Decreasing the Frequency of Aflibercept Injections After 24 Months to One Third the Number of Ranibizumab and Bevacizumab Injections[41]			
Combined-Eye Model	Bevacizumab	Ranibizumab	Aflibercept
Cost	$14,772	$106,582	$51,129
QALY gain	1.339	1.339	1.386
$/QALY	$11,033	$79,600	$36,890
Societal costs (direct medical, direct non-medical and indirect medical)			
Total = −$29.21 billion	−$24.2 billion	−$0.68 billion	−$4.141 billion
Increasing the Frequency of Aflibercept Injections After 24 Months to the Same Number As the Number of Ranibizumab and Bevacizumab Injections			
Combined-Eye Model	Bevacizumab	Ranibizumab	Aflibercept
Cost	$14,772	$106,582	$85,335
QALY gain	1.339	1.339	1.364
$/QALY	$11,033	$79,600	$62,562
Societal costs (direct medical, direct non-medical and indirect medical)			
Total = −$27.85 billion	−$24.2 billion	−$0.68 billion	−$2.97 billion
Treatment Cohort Vision Decreasing to 20/80 After 24 Months and Remaining So Thru 11 Years – Societal Cost Perspective			
Combined-Eye Model	Bevacizumab	Ranibizumab	Aflibercept
Ophthalmic cost per individual	$14,772	$106,582	$61,811
Societal cost per individual	−$336,630	−$241,819	−$286,590
QALY gain	1.212 (23.8%)	1.212 (23.8%)	1.247 (24.4%)
$/QALY, ophthalmic cost perspective	$12,188/QALY	$87,939/QALY	$49,568/QALY

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TABLE 11. Sensitivity Analysis (All Costs in 2018 U.S. Real Dollars) (Negative Costs Accrue Against the Direct Ophthalmic Medical Costs) (*Continued*)

Treatment Cohort Vision Decreasing to 20/80 After 24 Months and Remaining So Thru 11 Years – Societal Cost Perspective			
Combined-Eye Model	Bevacizumab	Ranibizumab	Aflibercept
$/QALY, societal cost perspective	−$277,748/QALY	−$199,521/QALY	$229,834/QALY
Total direct ophthalmic costs Total = $3.077 billion	$1.403 billion	$0.492 billion	$1.182 billion
Costs accruing against direct ophthalmic medical costs Total = −$27.537 billion	−$4.974 billion	−$19.975 billion	−$2.588 billion
Aggregate societal cost (direct medical, direct non-medical and indirect medical) Total = −$24.46 billion	−$3.571 billion	−$19.482 billion	−$1.406 billion
Treatment Cohort Vision Decreasing to 20/200 After 24 months and Remaining So Thru 11 Years – Societal Cost Perspective			
Combined-Eye Model	Bevacizumab	Ranibizumab	Aflibercept
Ophthalmic costs per individual	$14,772	$106,582	$61,811
Societal costs per individual	−$93,536	−$1,725	−$46,496
QALY gain	0.610 (12.0%)	0.610 (12.0%)	0.617 (12.7%)
$/QALY, ophthalmic cost perspective	$24,212/QALY	$174,694/QALY	$95,815/QALY
$/QALY, societal cost perspective	−$153,338/QALY	−$2,828/QALY	−$75,358/QALY
Total direct ophthalmic costs	$1.403 billion	$0.492 billion	$1.182 billion
Costs accruing against direct ophthalmic medical costs Total = −$7.331 billion	−$5.931 billion	−$0.271 billion	−$1.129 billion
Aggregate societal costs (direct medical, direct non-medical and indirect medical) including 89.7% eligibility for treatment and 6.4% annual dropout) Total = −$4.25 billion	−$4.528 billion	+$0.222 million	+$0.053 billion
Treating Second Eyes Converting to NVAMD After the First Eye Has Already Been Treated for NVAMD: Ophthalmic Cost Perspective			
Combined−Eye Model	Bevacizumab	Ranibizumab	Aflibercept
Cost	$1,207	$9,009	$5526
QALY gain	0.102	0.102	0.105
$/QALY	$11,813	$88,174	$51,540
Treating Second Eyes Converting to NVAMD After the First Eye Has Already Been Treated for NVAMD: Societal Cost Perspective			
Treating 2nd Eye after the 1st Eye	Bevacizumab	Ranibizumab	Aflibercept
Cost	−$17,640	−$9,838	−$13,581
QALY gain	0.102	0.102	0.105
$/QALY	−$172,645	−96,284	−$132,918
Dropout Rate at 17.25% per Year[54]			
Combined-eye model, total direct ophthalmic costs	Bevacizumab (80.9% of patients)	Ranibizumab (3.7% of patients)	Aflibercept (15.4% of patients)
$2.230 billion	$0.961 billion	$0.376 billion	$0.893 billion
Total costs accruing against direct ophthalmic costs	Bevacizumab (80.9% of patients)	Ranibizumab (3.7% of patients)	Aflibercept (15.4% of patients)
−$18.007 billion	−$14.567 billion	−0.666 billion	−$2.773 billion
Total societal costs (costs returned to society)	Bevacizumab societal costs	Ranibizumab societal costs	Aflibercept societal costs
−$15.777 billion	−$13.606 billion	−0.29 billion	−$1.88 billion
Cost-utility ratio, ophthalmic cost perspective, for patients treated 11 y	$11,033/QALY	$79,600/QALY	$44,801/QALY

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TABLE 11. Sensitivity Analysis (All Costs in 2018 U.S. Real Dollars) (Negative Costs Accrue Against the Direct Ophthalmic Medical Costs) (*Continued*)

Dropout Rate at 17.25% per Year[54]			
Cost-utility ratio, societal cost perspective, for patients treated 11 y	−$267,124/QALY	−$198,558/QALY	- $225,102/QALY
Treatment Costs With Varying Rates of Different Drug Usage – Patients Treated With Each Drug (Direct Ophthalmic Treatment Cost)			
Year	Bevacizumab cost	Raanibizumab cost	Aflibercept cost
Year 2014 Total cost = $2.596 billion	89.0% ($1.544 billion)	3.7% ($492 million)	7.3% ($560 million)
Year 2017 Total cost = $2.947 billion	82.5% ($1.431 billion)	3.1% ($412 million)	14.4% ($1.104 billion)
Year 2018 (Total cost = $3.077 billion)	80.9% ($1.403 billion)	3.7% ($492 million)	15.4% ($1.181 billion)
Costs Based Upon VEGF-I Therapy for NVAMD Based Upon the Work of Suner and Associates[33] Administering VEGF-I Injections at Fixed Intervals 10× Annually for 10 Years (Aflibercept Administered 5× Annually)			
Combined-Eye Model	Bevacizumab (80.9% of Patients = 122,203)	Ranibizumab (3.7% of Patients = 5,589)	Aflibercept (15.4% of Patients = 23,262)
11-y direct ophthalmic medical cost per individual	$24,213	$200,455	$101,909
11-y costs accruing against the direct ophthalmic medical costs per individual	−$372,452	−$372,452	−$372,452
Societal cost per individual	−$348,239	−$211,840	−$296,112
QALY gain	1.248	1.248	1.335
$/QALY, ophthalmic cost perspective	$19,401/QALY	$160,612/QALY	$76,340/QALY
$/QALY, societal cost perspective	−$279,038/QALY	−$169,744/QALY	−$221,807/QALY
Macroeconomic direct ophthalmic medical costs (Total = $3.618 billion)	$1.37 billion	$0.93 billion	$1.32 billion
Costs accruing against direct ophthalmic medical costs (Total = −$31.6 billion)	−$25.5 billion	−$1.17 billion	−$4.9 billion
Aggregate societal costs (Total = −$28.0 billion)	−$24.1 billion	−$0.24 billion	−$3.58 billion

NVAMD = neovascular age-related macular degeneration; QALY = quality-adjusted life-years; VEGF-I = vascular endothelial growth factor inhibitor; Ophthalmic cost perspective $/QALY (cost-utility ratio) = direct medical costs/QALY gain, societal cost perspective $/QALY = total societal costs, including direct medical costs/QALY gain

Negative costs are those accruing against the direct ophthalmic medical costs. In the case of negative cost-utility ratios, the cost aspect indicates the amount returned to society per QALY gained.

convert from atrophic to NVAMD accrues a net $0.452 billion in costs saved., Thus, for each dollar expended treating second eyes, society receives a net $1.60 (11-year 160% gain) above that direct ophthalmic medical cost. Having better vision in both eyes also improves depth perception, reduces patient anxiety, and decreases accidents,[59] features not broken out and defined individually due to lack of quality-of-life correlates.

• **DROPOUT RATE:** McGrath and Lee[60] noted a 17.25% dropout rate per year over 2 years in a real-world setting of NVAMD patients treated with ranibizumab. Extrapolating this rate of dropout to 11 years, reduced direct ophthalmic medical costs from $3.077 billion to $2.230 billion and aggregate societal costs returned to patients and insurers from −$28.5 billion to −$15.8 billion (Table 11), a $12.7 billion (44.6%) decrease from the reference case with 6.4% annual dropout. The number of patients remaining in the study at 11 years with 151,055 baseline patients and a 17.25% annual dropout rate was 22,741, a decrease of 132,314 patients (84.9%) from baseline. In the reference case with 151,055 patients at baseline, a 6.4% annual dropout rate resulted in 77,764 patients remaining at 11 years, a decrease of 73,291 (48.5%) from baseline.

• **USING SUNER DATA:** Suner and associates[33] administered 10 VEGF-I injections annually for 10 years to NVAMD patients and achieved a mean 10-year vision of 20/63, essentially the long-term vision modeled in the present reference case. Modeling 10 injections of bevacizumab and ranibizumab annually and 5 injections of aflibercept annually at fixed intervals over 11 years, there was a $541 million increase (17.6%) in 11-year direct ophthalmic costs associated with VEGF-I therapy from $3.077 billion to $3.618 billion. The net gain to society associated with this method of therapy was calculated to be $28.0 billion over 11 years versus $28.5 billion in the reference case.

DISCUSSION

THE PRESENT COST-BENEFIT ANALYSES DEMONSTRATED A positive ROI for the treatment of NVAMD using VEGF-inhibitors. The 11-year net financial ROI on VEGF-I treatment costs expended for an individual undergoing 11 years of therapy ranged from 2,421% for bevacizumab to 503% for aflibercept, to 249% for ranibizumab, converting respectively to annual compounded ROIs of 34.1%, 17.7%, and 12.0%. The weighted 11-year, average ROI of the 3 VEGF-I agents for treating NVAMD in the United States was 1,397% (Table 5). Integrating the annual 6.4% dropout rate from treatment, the 11-year weighted, macroeconomic ROI for all treated patients was 925%, with a 1,729% ROI for bevacizumab therapy, 314% for aflibercept therapy and 139% for ranibizumab therapy (Table 7). This resulted in an 11-year return of $31.6 billion to patients and payers, or ($31.6 billion - $3.1 billion =) $28.5 billion above the direct ophthalmic medical costs expended. Two-year model macroeconomic ROIs with dropout were considerably less, with a weighted average of 192%, with 557% for bevacizumab, −45% for ranibizumab and −2.1% for aflibercept. These data are relevant because aflibercept ranked first, ranibizumab ranked seventh, and bevacizumab ranked ninth in 2018 Medicare Part B drug expenditures.[23]

• **ROI FOR DIFFERENT ORGANIZATIONS AND PATIENTS:** Conventional Medicare paid $1.63 billion, or 52.9% of all costs for 2018 NVAMD VEGF-inhibitor therapy. A total of $1.36 billion, however, was accrued against these ophthalmic direct medical costs. Thus, Medicare actually spent ($1.63 billion − $1.36 billion =) $270 million over 11 years, 19.9% of what it would have paid if the negative costs of health care savings were not accrued. Medicaid paid $0.15 billion in direct ophthalmic medical costs but accrued a cost saving of $1.1 billion, indicating an 11-year profit of $0.95 billion, a 633% ROI on direct ophthalmic medical costs expended. Most health care savings for Medicaid came from decreased nursing home costs made possible by better vision associated with VEGF-I therapy. Had it not been for the increased systemic health care expenditure required by the year of life gained from VEGF-I therapy in the 11-year model, a situation analogous to the increased systemic costs associated with smoking cessation due to a longer life expectancy,[61] all insurers would have made an overall profit.

The highest overall ROI, however, went to insured patients, the primary recipients of the societal costs saved. The 2% ophthalmology-related component of health insurance premiums plus out-of-pocket cost used as the theoretical insured patient, direct medical cost for 11-year NVAMD therapy costs were $110 million. The net financial ROI in profit above the VEGF-I treatment costs, or total societal cost, returned to patients and their families was −$27.64 billion or 87.5% of the total ROI and −$27.54 billion or 96.5% of the profit gained from NVAMD therapy. The 11-year negative cost of −$31.6 billion accrued against the positive $3.08 billion direct medical cost of all VEGF-I therapy over 11 years. After subtracting the $3.08 billion in direct ophthalmic medical costs, the resultant societal cost of −$28.5 billion yielded an insured patient 25,027% 11-year ROI, equating to an 65.3% annual ROI on the direct ophthalmic medical cost of VEGF-I therapy.

• **GDP:** The GDP contribution suggests NVAMD therapy increases the overall wealth of the nation, even though the non-ophthalmic, direct medical costs (depression, trauma, facility admissions, and so forth) obviated by better vision decrease the GDP. The GDP contribution ($12.2 billion) from the 2018 VEGF-I treated NVAMD cohort over 11 years is a small part (0.06%) of the estimated 2018 U.S. GDP of more than $20.5 trillion.[62] Nonetheless, the 2018 original Medicare-allowed Part B drug charges paid for aflibercept, ranibizumab, and bevacizumab of $4.570 billion for all ophthalmic diseases made up 15.5% of the total 2018 Medicare-allowed Part B drug-allowed charges of $29.482 billion.[23] The authors' estimates herein suggest the cost of VEGF-I for NVAMD therapy constitutes ($3.077/$29.482 =) 10.4% of the Medicare Part B drug budget.

It is reasonable that a healthier, less dependent population contributes to greater resource generation from gainful uses and enables people such as unpaid caregivers to be freed to pursue gainful employment. William Nordhaus,[63] the Nobel Prize-winning economist, suggested that 50% of the U.S. wealth created in the 20th century came from advances in health and health care. Our analysis supports this supposition. Nordhaus showed the economic productivity associated with health care spending exceeds that of many other economic expenditures.

• **EARLY TREATMENT:** Late treatment with a mean vision outcome of $20/160^{+2}$, instead of a reference case treatment with a mean vision outcome of 20/63, resulted in a $18.9 billion (66.3%) loss in costs accruing against VEGF-I NVAMD therapy. It also diminished the contribution to the GDP. Reference case bevacizumab and ranibizumab treatments were 253% more cost effective than late treatment, whereas aflibercept treatment was 244% more cost effective than late treatment.[1] The favorability of early treatment versus late treatment has been previously addressed, although not in such detailed financial terms.[53,64] The data herein demonstrate earlier treatment is critical to maximize the financial value gain from NVAMD therapy, as well as patient well-being.[64]

• **POSSIBLE LIMITATIONS:** We did not include health insurance premium costs in addition to direct medical costs because of the "double counting" of expenditures. Total

insurance premiums also cover much more than ophthalmologic interventions, which only accounts for approximately 2% of all health care expenditures.[46] Ascribing all health insurance expenditures to ophthalmic interventions there would be vast overpayment of premiums for just ophthalmologic interventions.

Our societal costs saved by therapy were calculated from the costs associated with a cohort of NVAMD patients with different levels of vision loss.[27] However, we do not know how systemic comorbidity costs that might have influenced caregiver costs from age 79 (baseline age) through the 11-year model end age of 89 years.

Real-world outcomes could differ from the information used for the clinical course of therapy coming from clinical trials. Nonetheless, data from the real-world study of Suner and associates[33] demonstrated that NVAMD patients who received a mean of 10 VEGF-I injections per year over 10 years, had the same 10-year mean vision outcome as in the CATT study at 5 years.[8] These authors demonstrated that the 20/63 vision outcome with treatment at 24 months can be present at 10 years as well.[2,3,7,8,32,65]

The absence of 11-year randomized data is a drawback, although it is doubtful that an 11-year trial will be performed due to cost and new interventions coming about. We believe the Lineweaver-Burke meta-analysis of Shah and DelPriore[19] data that were used, however, provides an excellent long-term model for the vision associated with untreated NVAMD. Additionally, although non-randomized data after 24 months are not available, longer-term available data suggest treated outcomes.[8,30–33,65] Because longer-term economic analyses are preferable to shorter-term analyses,[66] many economic analyses use assumptions to make meaningful models when long-term randomized data are not available. The present 2-year data used here are from randomized trials,[2–5,7] but the economic analysis demonstrates considerably less favorable financial ROI outcomes, as well as less favorable patient benefits (QALY gains) and cost-effectiveness ratios, referent to the 11-year model.[1]

The decision not to use T/E data may be considered a weakness due to popularity of the therapeutic methodology, although T/E therapy was modeled in a sensitivity analysis (Supplemental Table 6). Nonetheless, in their meta-analysis, Okada and associates[56] noted a remarkable scarcity of clinical data past 12 months comparing T/E therapy with monthly treatment. Only recently have more convincing data been published for the 2-year noninferiority of T/E therapy versus monthly therapy for 24 months.[58] Furthermore, 1 study[55] using a 5-year T/E methodology reported more injections at 5 years than in CATT[8] at 5 years due to higher numbers of injections in years 3-5. The present direct ophthalmic medical costs of $2.67 billion associated with what were consider representative data for the T/E methodology[55–57] are 13.2% less than the $3.08 billion costs in the reference case analysis, which was modeled on clinical trial data.

Due to the rapidly changing usage patterns, new drugs and new indications for VEGF-I therapy, further analyses of this type with Medicare sample drug usage patterns from different areas of the country would elucidate continuing and changing VEGF-I expenditures.

There are important issues not emphasized in the data presented. For example, the fact that bevacizumab for treating NVAMD has not been approved by the U.S. FDA theoretically exposes the physician to greater medicolegal liability. Lacking the FDA imprimatur also potentially creates patient concerns and decreased quality-of-life issues. There are also situations in which NVAMD may not respond to one drug but will respond to another VEGF-I.[67] For these reasons, the authors believe physicians and patients should be allowed a degree of autonomy in regard to NVAMD therapy.

CONCLUSIONS

IN SUMMARY, INTRAVITREAL BEVACIZUMAB, RANIBIZUmab, and aflibercept therapy for a modeled 2018 cohort of new NVAMD patients delivered a considerable financial ROI to society, with bevacizumab returning the greatest financial value. The drug treatments have an 11-year, individual, financial ROI for the ophthalmic direct medical costs of therapy expended ranging from 249% for intravitreal ranibizumab to 2,421% for bevacizumab. Use of these drugs for treating NVAMD in 2018 was estimated to deliver a net $28.5 billion return to society over an 11-year period, with 87.5% of returned assets going to patients. Late NVAMD treatment (baseline vision of 20/160-20/320) would decrease the societal return by 66.3% to $9.6 billion. VEGF-I treatment for NVAMD in 2018 was estimated to contribute $12.2 billion to the GDP over 11 years. Treatment of NVAMD with VEGF-Is contributes a substantial financial return to primarily patients and secondarily to insurers as it increases national wealth.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

GARY C. BROWN: CONCEPTUALIZATION, METHODOLOGY, Formal analysis, Resources, Writing - original draft, Writing - review & editing. **Melissa M. Brown:** Conceptualization, Methodology, Formal analysis, Resources, Writing - original draft, Writing - review & editing. **Sara B. Rapuano:** Writing - original draft, Writing - review & editing, Methodology, Validation, Resources. **David Boyer:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Validation.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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