

THE COMPARATIVE EFFECTIVENESS AND COST-EFFECTIVENESS OF INTRAOCULAR ⁹⁰Sr BRACHYTHERAPY/ INTRAVITREAL VEGF INHIBITOR FOR NEOVASCULAR MACULAR DEGENERATION

Abstract

Purpose: To assess the comparative effectiveness and cost-effectiveness of a Phase 2 cohort of participants undergoing intraocular ⁹⁰Sr brachytherapy/vascular endothelial growth factor inhibitor therapy for neovascular, age-related macular degeneration.

Methods: A *Value-Based Medicine*[®] cost-utility analysis using 2008 US dollars was performed for second-eye, first-eye, and combined-eye models using third party insurer and governmental cost perspectives. Outcomes and costs were discounted at 3%/y.

Results: Treatment with the combined-eye model confers 0.981 QALY, a 15.8% improvement in quality-of-life over the 13-year cost-utility analysis, whereas the second-eye model confers a 22.4% improvement, and the first-eye model a 12.3% improvement.

The combined-eye model, governmental CUR is -\$7150/QALY and third party insurer CUR is \$10,973/QALY. The second-eye model, governmental cost perspective, cost-utility ratio (CUR) is -\$10,290/QALY and the third party insurer CUR is \$7728/QALY, whereas the first-eye model, societal CUR is -\$3678/QALY, and the third party insurer CUR is \$14,202/QALY.

Including caregiver costs, the governmental cost perspective, second-eye, first-eye, and combined-eye model CURs are, respectively, -\$89,259/QALY, -\$82,046/QALY, and -\$85,430/QALY. The combined-eye model accrues a net \$76,114 per capita Gross Domestic Product, a 16.2% annual return on investment, or an \$11.6 billion gain for the US economy over 13 years.

Conclusions: Preliminary data suggest intraocular ⁹⁰Sr brachytherapy/vascular endothelial growth factor inhibitor therapy for neovascular age-related macular degeneration confers considerable patient value and is cost-effective. Longer-term data from a larger treatment cohort will allow for a more robust model.

Increasing numbers of therapies have been proposed for the treatment of neovascular age-related macular degeneration (AMD), a disease which affects approximately 153,000 US citizens annually,¹⁻³ and typically results in blindness when untreated.⁴ Although some therapies have slowed the rate of visual loss from the disease,⁵⁻⁹ new treatment regimens with the vascular endothelial growth factor (VEGF)-A inhibitor ranibizumab have yielded visual improvement in the majority of treated eyes.¹⁰⁻¹² Early data on the VEGF inhibitor, bevacizumab, suggest it also improves vision in the majority of cases.¹³

Ranibizumab is a cost-effective therapy when used as in the MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD) clinical trial.¹² Nonetheless, researchers have worked to find equally or more effective therapies, especially combination therapies, which may be less costly.

Radiotherapy has also been undertaken for neovascular AMD treatment, both as external beam and transscleral brachytherapy, with varying results.¹⁴⁻¹⁶ Data on the treatment of neovascular AMD by brachytherapy via the vitreous cavity, however, are sparse.

Value-Based Medicine[®]

Value-Based Medicine[®] is an analysis methodology, which allows the practice of medicine based upon the *value* conferred

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by medical interventions.^{17,18} *Value* itself is measured by quantifying the improvement in length-of-life and/or quality-of-life, with the latter typically the case for ophthalmic interventions. Value refers to benefit, rather than in any way to cost.

This manuscript presents a value-based medicine, cost-utility analysis of Strontium-90 intraocular brachytherapy with intravitreal bevacizumab therapy for subfoveal neovascular AMD using Phase 2, NeoVista Study data.¹⁹ The analysis includes measures of: (1) conferred patient value using QALYs (quality-adjusted life-years) gained, (2) conferred value in the form of percent improvement in quality-of-life, and (3) cost-utility in terms of 2008 US dollars expended per QALY gained using for both the third party insurer and governmental cost perspectives.

Materials and Methods

NeoVista Study

This Phase 2 study was designed to assess the effectiveness of intraocular brachytherapy in conjunction with VEGF inhibitor therapy as a treatment for subfoveal choroidal neovascularization. One treatment naive eye of each participant with subfoveal choroidal neovascularization was treated and 34 consecutive participants completed treatment with follow-up of at least 12 months. Inclusion and exclusion criteria are shown in Table 1.

⁹⁰Sr Brachytherapy¹⁹

Radiation therapy was administered using the Epiretinal Brachytherapy System

(NeoVista, Fremont, CA), an intravitreal applicator containing a Strontium/Yttrium 90 (⁹⁰Sr/⁹⁰Yr) β-emitting isotope, referred to from hereon as ⁹⁰Sr brachytherapy.

The ⁹⁰Sr applicator was inserted through a pars plana incision and, after vitrectomy, was held for 3 to 5 minutes over the neovascular AMD lesion until a dose of 24 Gy was delivered to the lesion base.

Intravitreal Bevacizumab¹⁹

The ⁹⁰Sr brachytherapy was given in conjunction with two 1.25 mg intravitreal injections of bevacizumab. The first intravitreal injection was given within 1 week before the ⁹⁰Sr administration to the time of ⁹⁰Sr administration, and a second injection was routinely given 1 month later.

Additional doses of 1.25 mg of intravitreal bevacizumab were delivered as rescue therapy if an eye lost more than 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters of vision from baseline at 2 consecutive visits within 7 days, or if there was visual loss less than or equal to 10 letters in association with: (1) an increase of greater than 50 μm of central retinal thickness with optical coherence tomography, (2) new or increased subretinal blood, and/or (3) new neovascularization confirmed on fluorescein angiography.

One participant (3%) received 2 additional bevacizumab doses, 7 (21%) received 1 additional dose, and 26 (76%) required no further injections after the initial two. The average participant received a mean of 2.3 intravitreal bevacizumab injections over the 12-month period.

Table 1. Inclusion Criteria and Exclusion Criteria for the Neovascular AMD Cohort Treated With ⁹⁰Sr Brachytherapy/Intravitreal Bevacizumab Therapy¹⁹

Inclusion criteria	
Presence of classic, minimally classic or occult, subfoveal choroidal neovascularization	
Age: 50 y or older	
Vision in the affected eye ranging from 20/40 to 20/320 using the Early Treatment Diabetic Retinopathy Study vision chart	
Maximum permissible linear dimension of the choroidal neovascularization ≤ 5.4 mm	
Maximum size of choroidal neovascularization < 12 Macular Photocoagulation Study disc areas	
Exclusion criteria	
Previous treatment of choroidal neovascularization with:	
Laser photocoagulation	
Photodynamic therapy	
Intravitreal corticosteroids	
Anti-VEGF agents	
Transpupillary thermotherapy	
Chronic use of systemic corticosteroids	
Use of drugs with known macular toxicity	
Immunosuppressive therapy	
Anticoagulation	
Previous history of optic neuritis	
Presence of subretinal fibrosis	
Presence of diabetes mellitus	
Past head or neck radiation	

AMD indicates age-related macular degeneration; VEGF, vascular endothelial growth factor.

Study Cohort¹⁹

The clinical features of the cohort are summarized in Table 2. Six of 34 (18%) were younger than age 65 at the time of enrollment into the study; the mean age in this subgroup was 57 years.

Visual Results

The visual results at 1 year after treatment are shown in Table 3.¹⁹ The mean vision at the time of entrance into the study was 20/160 + 1 and at the end of 12 months was 20/100 + 2. This latter mean vision was used in a last observation carried forward fashion for the 13 years of the model, the average length-of-life for the study participants.²⁰ The baseline vision was worse in the study eye than in the contralateral eye in 22/34 (65%) of participants and was worse in the contralateral eye in 12 of the 34 (35%) participants. At 1 year, 41% of eyes gained ≥ 15 ETDRS letters, whereas 12% gained ≥ 30 ETDRS letters (6 lines) to 20/40 or better vision, and 72% of eyes gained >0 letters, meaning that they gained vision referent to their baseline.

Utilities

The time tradeoff utilities used in this manuscript were obtained with the unconditional approval of the Wills Eye Hospital Institutional Review Board from a cohort of over 1000 patients with ocular diseases with a methodology reported in multiple peer-reviewed papers.²¹⁻²⁹ The utilities, which correlate most highly with vision in the better seeing eye, are reproducible and validated across age, level of education, sex, ethnicity, level of income, and the presence of comorbidities.

Control Group

The NeoVista Phase 2 Study did not have a control arm. Thus, control group data were taken from the paper by Shah and Del Priore,⁴ in which the authors performed a meta-analysis on the control

groups from six Level 1 randomized clinical trials with follow-up ranging from 2 to 5 years. Shah and Del Priore⁴ demonstrated with an optimized, double-reciprocal (Lineweaver-Burke linear model) plot that the pattern of visual loss in subfoveal neovascular AMD eyes is uniform across this wide range of trials, with apparent differences arising primarily from the time of entry of patients into a trial, rather than other differences. Their model was very robust, with data from the 6 trials fitting along a single straight line with an $r^2 = 0.9521$.⁴ As the mean baseline vision in the NeoVista Study treatment group was poorer (20/160 + 1) than in the 6 trials, we used the Shah and Del Priore model⁴ to calculate the rate of visual loss in an untreated cohort starting with 20/160 + 1 vision. With this model, the course of progressive visual loss in the average untreated eye with subfoveal neovascular AMD deteriorates to a final level of 20/640 by approximately 9 years after initiation of the neovascular AMD.⁴

Adverse Events

A list of the adverse events believed to be related to treatment is shown in Table 4. Retinal tear, subretinal hemorrhage, subretinal fibrosis, epiretinal membrane, and cataract formation are all accounted for in the 1-year vision data. The utilities associated with the adverse events are derived from the Quality-of-Life Utility Database,³⁰ a time tradeoff utility analysis compendium of 45,000 patient utilities.²¹⁻²⁹ The total, weighted QALY loss associated with the adverse events is 0.00559.

Radiation Retinopathy

The radiation doses delivered to critical structures include: foveal retina, 24 Gy; temporal optic disc, 6.3 Gy; center of the optic disc, 2.4 Gy; and the lens, 0.56 Gy. No evidence of radiation retinopathy was observed in any eye in the study cohort.

Table 2. Clinical Features of the Neovascular AMD Cohort Treated With Intraocular ⁹⁰Sr Brachytherapy/Intravitreal Bevacizumab Therapy¹⁹

N = 34 patients
22 (65%) women and 12 (35%) men
Age range, 51 y to 91 y; mean age = 72 y; median age = 74 y
White: 27 (79%), Hispanic: 7 (21%)
Subfoveal choroidal neovascularization
Predominantly classic: 10 (29%)
Minimally classic: 7 (21%)
Occult: 15 (50%)
Initial vision range: 20/40 to 20/320
Mean initial vision: 20/160 + 1
First-eye model: 24/34 (65%)
Second-eye model: 12/34 (35%)
Initial mean foveal thickness: 302 μ m

Table 3. Mean Visual Acuities in 34 Eyes Treated With Intraocular ⁹⁰Sr Brachytherapy/Intravitreal Bevacizumab and Controls

Time (mo)	Treatment Group ¹⁹	Control Group ⁴
0	20/160 + 1	20/160 + 1
1	20/100 + 2	20/160
3	20/80 + 1	20/160 – 1
6	20/100 + 1	20/160 – 2
9	20/100 + 2	20/200
12	20/100 + 2	20/250 + 2
24	20/100 + 2	20/320 + 2
36	20/100 + 2	20/320 – 1
48	20/100 + 2	20/400 + 1
60	20/100 + 2	20/400 – 2
84	20/100 + 2	20/500
108 to 156	20/100 + 2 (LOCF)	20/640 (LOCF)

A LOCF (last observation carried forward) methodology was used from month 12 + through the end of the 13-year analysis period.

Previous studies have demonstrated the lowest dose of brachytherapy typically required to cause radiation retinopathy in a nondiabetic is 100 Gy.³¹ Because of this safety cushion and the exclusion of diabetic patients in the study, posterior segment damage from radiation retinopathy was not factored into the current analysis.

Total Value Conferred

As data are only available for 1 year, the analysis models out the value gain for the additional 12 years of the 13-year life expectancy using a last observation carried forward methodology. Possible scenarios for additional therapy and loss of clinical effectiveness are modeled in the sensitivity analysis.^{18,32} By the end of the 13-year life expectancy, the average treated participant accrues 9.026 QALYs. In the untreated control group the average patient accrues 7.330 QALYs over the same period.

First-Eye and Second-Eye Models

The concept of first-eye and second-eye models was originated by researchers at the Center for Value-Based Medicine[®].³³⁻³⁷ It is clinically relevant as ocular quality-of-

life seems to correlate most highly with vision in the better-seeing eye.²¹⁻²⁹

The *first-eye model* assumes a patient who presents with visual loss in 1 eye, has a second eye with good vision.³³⁻³⁷ On the basis of actual ophthalmic patient preferences (utilities), the *first-eye model* presumes a patient does not accrue value from an intervention until the second eye is affected and vision is deteriorating; at this time, prior treatment in the first eye becomes critically important.³³⁻³⁷ Markov modeling is used to track the proportion of cases with baseline involvement in 1 eye, which become bilateral over time. Approximately 10% of unilateral neovascular AMD cases per year become bilateral.³⁸

The *second-eye model* presumes vision has already been lost in 1 eye from the untreated disease under study or some other ocular condition.^{12,18} In this instance, patient value accrues immediately after an intervention. In the NeoVista trial, 12 of 34 (35%) patients already had marked visual loss in the contralateral eye (second-eye model), whereas in 22 (65%) the first eye was involved and the other eye had no neovascular AMD (first-eye model).¹⁹

A *combined-eye model* weights the incidence of first-eye and second-eye models

Table 4. Adverse Events Associated With Intraocular ⁹⁰Sr Brachytherapy/Intravitreal Bevacizumab Therapy (n = 34)¹⁹

Adverse Event	Incidence (n)
Epiretinal membrane	2.9% (1/34)
Retinal tear	2.9% (1/34)
Subretinal hemorrhage	2.9% (1/34)
Subretinal fibrosis	5.8% (2/34)
Cataract	25% (6/24)*

*Twenty-four patients in the treatment cohort were phakic at the initiation of therapy.

to yield a model that, in all probability, most closely simulates the actual clinical situation.³³⁻³⁷

Costs

The third party insurer perspective assesses direct medical costs, including provider costs, facility costs, and drug costs. The governmental perspective encompasses all costs, including: (1) direct medical costs, (2) direct nonmedical costs (home caregiver cost is the major cost, travel cost to physician appointments, and so forth), and (3) indirect costs, such as disability costs and cost to the Gross Domestic Product (GDP), the sum of all goods and services (including salaries) produced in the country annually.

Third Party Insurer Perspective

Only year 2008, direct, incremental medical costs,¹⁸ or those associated with ⁹⁰Sr brachytherapy/bevacizumab therapy, are included. The national average, Medicare Fee Schedule cost basis, Medicare facility cost basis, and Medicare 2008 drug Average Sales Prices are listed in Table 5. The direct medical costs accrued are shown in Table 6.

Cost-Utility Analysis

The definition of cost-effective depends upon what a society is willing to pay for healthcare services.^{17,18,39} Interventions in the US costing less than \$50,000 per QALY gained are generally considered very cost-effective,^{40,41} whereas those costing less than \$100,000 per QALY gained are considered cost-effective.⁴² The World Health Organization has suggested that interventions costing less than 1 × per capita GDP (US \$46,600, 2008) for a DALY (disability-adjusted life-year, an entity similar to the QALY) are very cost-effective, whereas those costing less than 3 × per capita GDP (US \$139,800)/DALY are cost-effective.⁴³ The National Institute for Health and Clinical Excellence (NICE)⁴⁴ in the UK views interventions as cost-effective if they have a cost-utility ratio (CUR) less than £20,000/QALY (~US \$40,000/QALY), although exceptions can be made for select interventions costing up to £30,000/QALY (~US \$60,000/QALY).

Results

Value Gain

Unless otherwise stated, all value gains (QALYs gained and percent improvement in quality-of-life) and costs are discounted at a 3% annual rate.^{17,18,33}

Second-Eye Model

The total value conferred by ⁹⁰Sr brachytherapy/bevacizumab therapy over the 13-year period is 1.399 QALYs (Table 7). The diminution in value from the cumulative short-term adverse events is -0.00559 QALY, yielding a final value gain of 1.393 QALYs, or a 22.4% improvement in quality-of-life. Not discounting the value gain by 3% yearly yields a total gain of 1.689 QALYs, an improvement in quality-of-life of 23.0%.

First-Eye Model

With Markov modeling, 0.758 discounted QALY is accrued over 13 years. With a 10% annual incidence of conversion of the contralateral eye to neovascular AMD,³⁸ 74.6% of the unaffected fellow eyes will convert by the end of year 13. The overall improvement in quality-of-life with this model is 12.2%.

Combined-Eye Model

Integrating the 1.393 QALYs accrued by the 35% of NeoVista Study entrants who had baseline second-eye involvement and the 65% of entrants who had the first-eye model with baseline good vision in the second eye, the mean weighted QALY gain discounted at 3% annually is $[(0.35 \times 1.393) + (0.65 \times 0.764)] = 0.981$. This model results in a mean 15.8% improvement in quality-of-life.

Costs

Third Party Insurer Costs

The direct medical cost incurred with ⁹⁰Sr brachytherapy/bevacizumab treatment of neovascular AMD is \$8515 over the initial 1-year period, of which treating the adverse events of epiretinal membrane, retinal tear, and cataract account for \$266. Including the modeled costs (Table 6) for years 2 through 13, the total cost of therapy is \$11,227 or \$10,765 discounted at a 3% annual rate. If the baseline vitrectomy is performed in a hospital inpatient setting, rather than in an ambulatory surgical center, the total direct medical cost rises to \$13,697.

A breakdown of the costs is shown in Table 6. Physician costs account for 35.2%, drug costs for 1.2%, diagnostic testing/facility costs for 22.3%, radiation-related costs for 41.2%, and adverse events for 2.4%. Costs remain the same for the second-eye, first-eye, and combined-eye models.

Table 5. 2008 Year 1, Average, National, Medicare Physician Fee Schedule Costs*, Medicare Ambulatory Surgical Center Costs, Acute Hospital Costs, and Drug Costs Associated With the Treatment of Neovascular AMD Using Intraocular ⁹⁰Sr Brachytherapy and Intravitreal Bevacizumab

Description	CPT Code*	Cost*
Examination and diagnostic costs (100% of cases)		
Office consultation	99244	\$192
Ophthalmic examination	92012	\$70
Ophthalmic examination with treatment	92014	\$102
Eye examination with photographs	92250	\$55
Intravenous fluorescein angiography	92235	\$123
Optical coherence tomography	92135	\$43
Surgery (100% of cases)		
Intraocular injection of bevacizumab (average of 2.3 injections per eye)	67028	\$182
Bevacizumab, 1.25 mg intravitreal	J9035	\$57
Ranibizumab, 0.5 mg intravitreal (2008 Medicare Average Sales Price)	J2778	\$2028
Vitrectomy, pars plana approach	67036	\$788
Hospital inpatient fee, pars plana vitrectomy†	DRG# 36	\$3020
Ambulatory surgical center fee (pars plana vitrectomy)‡	66984	\$858
Anesthesia	67036	\$432
Postoperative corticosteroid/antibiotic NDC 68115-6957-05§		\$13
Radiation probe placement	0190T	\$200*
Radiation surgical pack¶	0190T	\$3500
Special treatment procedure (eg, total body irradiation, hemibody radiation, per oral endocavitary or intraoperative cone irradiation)	77470	\$359
Remote after loading high intensity brachytherapy; 1-4 source positions or catheters	77781	\$565
Adverse Event Costs		
Prophylaxis of retinal detachment (eg, retinal break, lattice degeneration) without drainage, one or more sessions; photocoagulation (laser or xenon arc) (2.9% of cases)	67145	\$428
Vitrectomy, mechanical, pars plana approach with removal of preretinal cellular membrane (2.9% of cases)	67041	\$1065
Anesthesia (2.9% of cases)	67041	\$270
Ambulatory surgical center fee, vitrectomy, mechanical, pars plana approach with removal of preretinal cellular membrane (eg, macular pucker) (2.9% of cases)‡	67041	\$1540
Postoperative corticosteroid/antibiotic NDC 68115-6957-05 (2.9% of cases)§		\$13
Cataract extraction (9% of cases)	66984	\$626
Anesthesia (9% of cases)	66984	\$270
Ambulatory Surgical Center fee (cataract surgery) (9% of cases)	66984	\$988
Postoperative corticosteroid/antibiotic NDC 68115-6957-05 (9% of cases)§		\$13

*CMS. Comparison of Practice Expense Relative Value Units under Different Methods. C: and Settings Settings Internet Files.IE5 TTA.zip, accessed 7-03-08.

†DRG Relative Weights. From the Internet @ <http://www.cms.hhs.gov/AcuteInpatientPPS/FFD/itemdetail.asp?filterType=none&filterByDID=99&sortByDID=2&sortOrder=ascending&itemID=CMS022597&intNumPerPage=10>, accessed 7-01-08.

‡From the Medicare Fee Schedule (†available at www.cms.hhs.gov/PhysicianFeeSched, accessed 6-8-08).

§Topical antibiotic/corticosteroid: dexamethasone/neomycin sulfate/polymyxin b sulfate; NDC 68115-6957-05, Dispense Xpress, Average Wholesale Price = \$12.99 (from Engle K (ed), RED BOOK 2008 Edition, Montvale, NJ, Thomson Healthcare, 2008, p.558).

||Estimate from American Academy of Ophthalmology Reimbursement Committee members.

¶Estimate from NeoVista, Inc.

AMD indicates age-related macular degeneration; ASC, ambulatory surgical center; CPT, current procedural terminology; DRG, disease-related group; NDC, National Drug Code.

Governmental Costs

to \$8928, resulting in a gain of \$20,030 from therapy.⁴⁵

Direct Nonmedical Costs

Paid nonfamily caregivers account for 27.7% of the overall caregiver expense, resulting in an annual payment of \$5548 per patient. Therapy theoretically frees up the 72.3% of the non-paid cohort of caregivers so they can also undertake gainful employment, accruing \$14,482 annually to the GDP in the form of newly created wages that otherwise would not be possible. Bureau of Labor and Statistics data show that, among people under age 65 years without disabilities, the US employment rate is 78.2%.⁴⁶ Assuming that

Caregiver Cost

Caregiver costs for AMD patients have been assiduously measured by Schmier and colleagues,⁴⁵ who found the yearly cost per ophthalmic patient with $\leq 20/250$ vision or worse is \$28,958.⁴⁵ When the vision is improved to 20/80-20/150, as is the case for ⁹⁰Sr brachytherapy/ bevacizumab therapy, the caregiver cost is reduced

Table 6. Direct Medical Costs Associated With the Treatment of Neovascular Macular Degeneration With Intraocular ⁹⁰Sr Brachytherapy and Intravitreal Bevacizumab

Timeline	Medical Costs	All Costs	MD Costs	Drug Costs	Diagnostic Tests/Facility Fees	Radiation
Initial visit-Day 0	Office consultation	192	192	0	0	0
	IVFA	123	0	0	123	0
	Fundus photographs	55	0	0	55	0
	OCT	43	0	0	43	0
	Bevacizumab	57	0	57	0	0
	Bevacizumab injection fee	182	182	0	0	0
Day 1	Antibiotic*	13	0	13	0	0
	Vitrectomy	788	788	0	0	0
	Sr90 application	200	(200)	0	0	200
	Radiation pack	3500	0	0	0	3500
	Radiation therapist(s)	924	(924)	0	0	924
	Anesthesia	432	432	0	0	0
	Ambulatory surgical center	858	0	0	858	0
	Bevacizumab injection fee	182	182	0	0	0
	Bevacizumab	57	0	57	0	0
Month 1	OCT	43	0	0	43	0
Month 2	OCT	43	0	0	43	0
Month 3	OCT	43	0	0	43	0
Month 6	Bevacizumab injection fee (26% of cases)	149	47 + 102	0	0	0
	Bevacizumab (26% of cases)	15	0	15	0	0
	OCT	43	0	0	43	0
	IVFA + photographs (26% of cases)	46	0	0	46	0
	Ophthalmic examination (26% of cases treated)	78	78	0	0	0
Month 9	Ophthalmic examination	70	70	0	0	0
	OCT	43	0	0	43	0
Month 12	Ophthalmic examination	70	70	0	0	0
	OCT	43	0	0	43	0
Adverse events†	AE costs	266	127	3	136	0
Year 1	Total costs	8515	2270	145	1476	4624
Year 1	% of costs	100%	27%	2%	17%	54%
Month 18	Ophthalmic examination	70	70	0	0	0
	OCT	43	0	0	43	0
Month 24	Ophthalmic examination	70	70	0	0	0
	OCT	43	0	0	43	0
Yrs 1,2	Total	\$8741	\$2410	\$145	\$1562	\$4624
Yrs 1,2	Percent of costs	100%	27.6%	1.7%	17.9%	52.9%
Yrs 1,2	Year 2 costs, discounted (3%)	\$219	\$136	0	\$83	0
Yrs 1,2	Years 1 and 2, discounted (3%)	\$8734	\$2406	\$145	\$2559	\$4624
Yrs 1,2	Percent of costs	100%	27.5%	1.7%	17.9%	52.9%
Yrs 3-13 annually	Ophthalmic examination	70	70	0	0	0
	OCT	43	0	0	43	0
Yrs 1-13 Total costs	Total costs, nondiscounted	\$11,227	\$3950	\$145	\$2508	\$4624
Yrs 1-13 annually	Total costs, discounted 3%	\$10,765	\$3664	\$145	\$2331	\$4624
	% of total cost	100%	35.2%	1.3%	22.3%	41.2%

Costs in parentheses () are not included in All Costs, so as not to include them twice. They are to demonstrate the area(s) to which the costs could be accrued.

*Topical antibiotic/corticosteroid: dexamethasone/neomycin sulfate/polymyxin b sulfate; NDC 68115-6957-05, Dispense Xpress, Average Wholesale Price = \$12.99 (from Engle K (ed), RED BOOK 2008 Edition, Montvale, NJ, Thomson Healthcare, 2008, p.558) is assumed to be used for both the initial bevacizumab injection and vitrectomy surgery for irradiation.

†Adverse events are presumed to occur during the first year after treatment.

AE indicates adverse events; discounted 3%, costs and outcomes discounted at a 3% annual rate; IVFA, intravenous fluorescein angiography; MD, physician; OCT, optical coherence tomography; Yrs, years.

78.2%⁴⁷ of both unpaid caregivers and released paid caregivers now enter or stay, respectively, within the paid workforce, the resultant net gain to the GDP is (\$11,325-\$1210) \$10,115 annually.⁴⁵ Assuming this gain in employment occurs at the end of year 1, the discounted gain over the remaining 12 years results in a

Table 7. Quality-Adjusted Life-Years (QALYs) Gained With Intraocular ⁹⁰Sr Brachytherapy/ Intravitreal Bevacizumab Therapy Over the 13-year, Reference Case, Average Life Expectancy

	QALY Gain
Undiscounted	
Treated cohort	9.026
Untreated cohort	7.331
Value (QALY) gain with treatment	1.695
Minus adverse events	0.006
QALY gain with adverse events	1.689
Percent gain in QOL	23.0%
Discounted (3% annually)	
Treated cohort	7.605
Untreated cohort	6.210
Value (QALY) gain with treatment	1.399
Minus adverse events	0.006
QALY gain with adverse events	1.393
Percent gain in QOL	22.4%

QALY indicates quality-adjusted life-year; QOL, quality-of-life.

negative cost of -\$109,704 for the second-eye model, -\$59,240 for the first-eye model, and -\$76,793 for the combined-eye model.

Indirect Costs

Disability Cost

Social Security disability benefits are available for people who are legally blind, with the average payment approximately \$900/month.⁴⁷ With 18% of the cohort herein under age 65, 14.1% (18% × 78.2%) are candidates for Social Security disability payments to replace lost wages; these disability payments per capita average approximately \$10,800 annually. The annual disability payment obviated by treatment, which prevents blindness is therefore (\$10,800 × 14.1%) \$1520. This lasts for 8 years, as the average age of the patient receiving the disability costs is 57 years. The total discounted (3%) cost over the 8 years for the second-eye model is \$10,990. The weighted cost for the first-eye model is \$5,935 and for the combined-eye model is \$7693.

Unemployment Cost

Among people with mild difficulty seeing (vision of 20/50-20/160), 44.1% are employed, while their average earnings are 72% those of a nondisabled person. Among those with severe difficulty seeing (vision of 20/200 or worse), 30.6% are employed, with the average employee earning 64% of the average wage earned by a person without a disability.⁴⁶ Thus, the average person with mild visual loss earns 41% as much as a person without a disability and the average person with severe visual loss earns 35% as much.⁴⁶

The employment rate for a person 21 to 63 years is 78.2%, whereas that of

the ≥65-year-old group is 14%.⁴⁶⁻⁴⁸ A weighted average therefore discloses that 25.6% of the overall treatment cohort herein could therefore be expected to be employed if they had no visual disability.

Assuming the average annual 2008 US wage estimate of \$40,524,⁴⁹ the average person with mild visual loss earns an annual salary of \$16,615, whereas the average person with severe visual loss earns \$14,183.⁴⁶ If the 12% of the participants who achieve 20/40 vision with treatment are considered employed at a normal salary versus a mild visual loss salary, and assuming that 25.6% of participants in the cohort herein are employed, the increased contribution to the GDP made possible by treatment is (12% × 25.6% × \$23,909) = \$741. An additional \$547 is added to wages, and to the GDP, when the participants who have untreated severe visual loss are converted to the mild visual loss group by therapy. Thus, the total sum per capita due to increased and improved patient salaries is (\$741 + \$547) = \$1288 annually (Table 8). Over a 13-year period, the discounted, wage loss averted by therapy is \$14,409. The corresponding cost for the first-eye model is \$7781 and for the combined-eye model is \$10,086.

Integrating the discounted third party insurer cost, the direct nonmedical costs, and the indirect costs using the combined model yields a net gain of \$83,807. This indicates that, despite the medical cost of \$10,765, the treatment of each person with ⁹⁰Sr brachytherapy/bevacizumab therapy can theoretically generate \$83,807, of which \$76,114 (excluding disability payments) contributes to the GDP, the overall wealth of the US. Over the 13 year time of analysis, the direct medical costs invested yield a 16.2% annual return on investment accrual to the GDP.

Table 8. Increased Patient Salaries Made Possible by Intraocular ⁹⁰Sr/Intravitreal Bevacizumab Therapy for Neovascular AMD

	Employed at Normal Salary (Va > 20/40)	Employed at Mild Va Loss (Va 20/50 to 20/160)	Employed at Severe Va Loss (Va < 20/200)
Wages	\$40,524	\$16,615	\$14,183
No treatment	0%	0%	25.6%*
⁹⁰ Sr/bevacizumab treatment	3.1% (12% × 25.6%)	22.5% (88% × 25.6%)	0%
Marginal gain above \$14,183	\$23,909	\$2431	NA
Marginal gain/y (weighted)	+ \$741	+ \$547	NA

*Assuming the 25.6% of cohort who are employed would receive the minimum wage, average annual salary of \$14,183 if they had no treatment.^{47,49}
 AMD indicates age-related macular degeneration; NA, not applicable.

Cost-Utility

CURs associated with therapy are shown in Table 9. Unless otherwise indicated, they are discounted at a 3% annual rate.

Second-Eye Model

Third Party Insurer Costs

The discounted CUR of therapy is (\$10,765/1.393) = \$7728/QALY and undiscounted CUR is \$11,227/1.689 = \$6646/QALY.

Governmental Costs

The CUR without caregiver costs for the second-eye model is (-\$14,634/1.393) = -\$10,505/QALY. When caregiver cost gain is added to that saved by increased patient employment and decreased disability payments, the CUR is [(-\$14,634 - 109,704)/1.393] = -\$89,259/QALY.

First-Eye model

Third Party Insurer Costs

The CUR of treatment is (\$10,765/0.758) = \$14,202/QALY.

Governmental Costs

The CUR for the second-eye model is (-\$2951/0.758) = -\$3893/QALY. The addition of caregiver costs yields a CUR of [(-\$62,191)/0.758] = -\$82,046/QALY.

Combined-Eye Model

Third Party Insurer Costs

The CUR of therapy is (\$10,765/0.981) = \$10,973/QALY.

Governmental Costs

The CUR for the combined-eye model is (-\$7014/0.981) = -\$7150/QALY. The addition of caregiver costs results in a combined CUR of [(-83,807)/0.981] = -\$85,430/QALY.

Sensitivity Analyses

Unless otherwise specified, the outcomes and costs in this section are discounted at a 3% annual rate for a second-eye model to allow comparability with other analyses in the literature.^{3,9,12} A third party insurer (direct medical) cost perspective is used unless otherwise specified.

Table 9. Cost-Utility Ratios Associated With Intraocular ⁹⁰Sr Brachytherapy/Intravitreal Bevacizumab Therapy (Modeled Over 13-year Life Expectancy)

Second-eye model	
Third party insurer costs \$/QALY (3% discount)	\$7728
Societal costs \$/QALY (3% discount)*	-\$10,505
First-eye model	
Third party insurer costs \$/QALY (3% discount)	\$ 14,202
Societal costs \$/QALY (3% discount)*	-\$3893
Combined model	
Third party insurer costs \$/QALY (3% discount)	\$ 10,973
Societal costs \$/QALY (3% discount)*	-\$7150

*Caregiver costs are not included.
 \$/QALY indicates dollars expended per quality-adjusted life-year.

Value Gain

If the value gain is increased by 50%, the QALY gain is 2.090, a 33.7% improvement in quality-of-life associated with a CUR of \$5150/QALY. If the value gain is decreased by 50%, the QALY gain is 0.697, a quality-of-life gain of 11.2%. The CUR associated with a 50% decrease in value gain is \$15,451/QALY.

Costs, Direct Medical

If these costs are increased by 50%, the QALY gain (1.393) and improvement in quality-of-life (22.4%) remain unchanged. The cost is \$16,148 and the resultant CUR is \$11,588/QALY. If the direct medical costs are decreased by 50% to \$5383, resultant CUR is \$3863/QALY. If the baseline vitrectomy is performed in a hospital setting, rather than an ambulatory surgical center, the discounted CUR is $(\$13,697/1.393) = \$9833/\text{QALY}$. For a CUR of \$100,000/QALY using an ambulatory surgical center for the baseline vitrectomy, the direct medical cost needs to be increased by \$128,535, or 1194%.

Costs, Governmental

With the governmental cost-perspective, if the medical costs are increased by 50%, the resultant CUR is $(\$1514/1.393) = \$1087/\text{QALY}$, whereas if the governmental cost perspective medical costs are decreased by 50%, the CUR is $(-\$9252/1.393) = -\$6641/\text{QALY}$. For a CUR of \$100,000, the direct medical costs would need to be increased by \$142,869, or 1327%.

Substitution of Ranibizumab for Bevacizumab

Third Party Insurer Costs

The discounted CUR of therapy is $(\$15,219/1.393) = \$10,926/\text{QALY}$.

Governmental Costs

The CUR without caregiver costs for the second-eye model is $(\$585/1.393) = \$420/\text{QALY}$. When caregiver cost gain is added to that saved by increased patient employment and decreased disability payments, the CUR is $[(\$585-109,704)/1.393] = -\$78,333/\text{QALY}$.

Frequency of Drug Administration

Two Hundred Percent Increase in Bevacizumab/Ranibizumab Injections

If bevacizumab is given with a 200% higher frequency, 6.8 doses over 1 year, the overall

cost is \$12,075 and the CUR is $\$12,075/1.393 \text{ QALYs} = \$8,666/\text{QALY}$. If ranibizumab is substituted for bevacizumab, the CUR is $(\$24,168/1.393 \text{ QALYs}) = \$17,349$. The combined model CUR with bevacizumab is $\$12,075/0.981 = \$12,313/\text{QALY}$ and the first-eye model CUR is $(\$12,075/0.758 \text{ QALY}) = \$15,921/\text{QALY}$.

Bevacizumab 5 × /y for Years 2 to 13

The PRONTO Study demonstrated that ranibizumab intravitreal injections 5 × /y for 2 years were effective in maintaining vision return in eyes with neovascular AMD.^{50,51} If bevacizumab injections are given 5 × yearly from years 2 through 13, for a total of 62.3 doses, the total cost is \$28,274. In this instance, the third party insurer cost perspective, second-eye model CUR is $(\$28,274/1.393 \text{ QALYs}) = \$20,291/\text{QALY}$. The first-eye model CUR is $(\$28,274/0.758 \text{ QALY}) = \$37,281/\text{QALY}$ and the combined model CUR is $(\$28,274/0.981 \text{ QALY}) = \$28,831/\text{QALY}$. The governmental, second-eye model CUR with caregiver costs is $(-\$81,430/1.393 \text{ QALY}) = -\$58,457/\text{QALY}$.

If ranibizumab is substituted for bevacizumab, the third party insurer cost perspective, second-eye model CUR is $(\$147,046/1.383 \text{ QALY}) = \$105,561/\text{QALY}$. The analogous governmental cost perspective model CUR with caregiver costs included is $(\$37,342/1.393) = \$26,802/\text{QALY}$.

Discount Rate

If the discount rate is 0%, the cost is \$11,227 and the CUR is $(\$11,277/1.689) = \$6646/\text{QALY}$. If the discount rate is increased to 5% annually, the 13-year QALY gain is 1.281 and costs are \$10,518. The resultant \$/QALY is $(\$10,518/1.231) = \$8544/\text{QALY}$.

Adverse Events

Excluding Adverse Events

If the adverse events, are not included, the \$/QALY discounted at a 3% is $(\$10,449/1.399) \text{ QALYs} = \$7505/\text{QALY}$.

Assuming 100% of Phakic Patients Develop Cataract After Vitrectomy

In this instance, when 24 phakic (10 of the cohort are already pseudophakic) eyes are assumed to require cataract surgery during year 1, the additional discounted (3%

per annum) cost is \$1167 and the QALY loss from adverse events is increased from 0.00559 to 0.00855, an additional QALY loss of 0.00296 QALY. The second eye, CUR in this instance is ($\$11,932/1.390 =$) \$8584/QALY.

A summary of the sensitivity analysis results is shown in Table 10.

Discussion

Value

The study herein demonstrates that combination therapy with intravitreal ^{90}Sr radiation and bevacizumab confers a 22.4% value (quality-of-life) gain on a daily basis for the average person losing vision in the better eye due to subfoveal neovascular AMD. Laser therapy has been shown to confer a 4.4% quality-of-life gain,⁵² pegapantib therapy a 5.9% gain,⁵² photodynamic therapy⁹ an 8.1% gain, and ranibizumab a 15.8% gain.⁵² Nonetheless, it should be noted that a different control cohort was used for comparison with the brachytherapy-treated study participants herein than for the value-based analyses of the other aforementioned interventions. Had the same control cohort been used for the comparator interventions, the value gain for each would have been greater than stated above.

A comparison of the value conferred by ^{90}Sr brachytherapy/bevacizumab therapy with other ophthalmic and non-ophthalmic interventions is shown in Tables 11. ^{90}Sr brachytherapy/bevacizumab therapy confers value in the same range as ranibizumab in the MARINA trial,¹² although different control groups preclude an exact comparison.

Adverse Events

The frequency of radiation therapy and 2.3 injections of bevacizumab in the NeoVista study¹⁹ is considerably less than the 22 injections of intravitreal ranibizumab administered in the MARINA trial over 2 years.¹² The QALY loss due to adverse events in the current study was 0.00559, whereas that associated with adverse events in the MARINA Trial,¹² was 0.027 QALY. The value loss due to adverse events in the gold standard MARINA trial was $4.83 \times$, or 383% greater than that in the current study.

Costs

Third Party Insurer Cost Perspective
The cost of ^{90}Sr brachytherapy/bevacizumab is 20.4% that of treatment as given in the MARINA Trial¹² for neovascular

AMD, although it rises to 30.0% if ranibizumab is substituted for bevacizumab. Conversely, the cost of intravitreal ranibizumab therapy¹² is 383% greater than that of ^{90}Sr brachytherapy/bevacizumab therapy.

Governmental Cost Perspective

In the current analysis, the governmental cost-perspective with caregiver costs yielded a large negative CUR, indicating the intervention of ^{90}Sr brachytherapy/bevacizumab creates greater financial resources than it consumes. Over the 13-year life expectancy of the average combined-eye model case, the intervention consumes \$10,765 in direct medical costs, whereas it creates assets of \$94,572, for a net gain of \$76,114 in GDP and \$7693 in disability payments averted. The great increase in employment comes from the facts that the treatment saves vision, thereby allowing neovascular AMD patients to be gainfully employed at the same time it frees up unpaid caregivers to do the same. This phenomenon, which occurs with ranibizumab therapy for neovascular AMD,¹² as well as other highly effective ophthalmic interventions, has received little notice to date.

Cost-Utility

With a third party insurer cost-utility of \$7726/QALY for the second-eye model and \$10,973/QALY for combined-eye model, the cost-utility associated with ^{90}Sr brachytherapy/bevacizumab therapy falls within the range of what is considered quite cost-effective by NICE,⁴⁴ World Health Organization,⁴³ and US⁴⁰⁻⁴² cost-effectiveness criteria. The current model is robust as sensitivity analyses demonstrate excellent cost-effectiveness across a wide range of input variables (Table 10 and 12).

Potential Weaknesses

As with all analyses, there are inherent weaknesses in the present study. The most obvious potential weakness herein is the fact that the cost-utility analysis is based upon a treatment cohort of 34 eyes with only 1-year follow-up. Of note, however, is the fact that the value gain observed in the first year of the MARINA Trial was almost identical to that observed during the second year.¹⁰

The absence of therapeutic data beyond 1 year for ^{90}Sr brachytherapy/bevacizumab therapy is a drawback as the treatment group vision could deteriorate with time. On the other hand, the 5-year, mean 20/500 vision of untreated neovascular AMD eyes in the Macular

Table 10. Sensitivity Analyses Demonstrating Value Gain and Cost-Utility for Intraocular ⁹⁰Sr Brachytherapy/Intravitreal Bevacizumab Therapy Over a 13-Year Period

Altered Parameter	Value Gain (QALYs/%)	Cost	Cost-Utility Ratio
Eye Models			
Third party insurer cost perspective			
Second-eye model	1.393 QALYs/22.4%	\$10,765	\$7728
First-eye model	0.758 QALY/12.2%	\$10,765	\$14,202
Combined-eye model	0.981 QALY/15.8%	\$10,765	\$10,973
Governmental cost perspective without caregiver costs			
Second-eye model	1.393 QALYs/22.4%	-\$14,634	-\$10,505
First-eye model	0.758 QALY/12.2%	-\$2951	-\$3893
Combined-eye model	0.981 QALY/15.8%	-\$7014	-\$7150
Governmental cost perspective with caregiver costs			
Second-eye model	1.393 QALYs/22.4%	-\$124,338	-\$89,259
First-eye model	0.758 QALY/12.2%	-\$62,191	-\$82,046
Combined-eye model	0.981 QALY/15.8%	-\$83,807	-\$85,430
Value gain			
50% increase, second-eye model	2.090 QALYs/33.7%	\$10,765	\$5150
50% decrease, second-eye model	0.697 QALY/11.2%	\$10,765	\$15,451
50% decrease, combined-eye model	0.490 QALY/7.9%	\$10,765	\$21,954
\$100,000/QALY	0.1077 QALY/1.7%	\$10,765	\$100,000
Costs			
Third party insurer cost perspective			
50% increase	1.393 QALYs/22.4%	\$16,148	\$11,588
50% decrease	1.393 QALYs/22.4%	\$5383	\$3863
Baseline vitrectomy in hospital	1.393 QALY/22.4%	\$13,697	\$9833
Cost for \$100,000/QALY	1.393 QALYs/22.4%	\$139,300	\$100,000
Governmental cost perspective, no caregiver costs			
50% increase	1.393 QALYs/22.4%	\$1514	\$1807
50% decrease	1.393 QALYs/22.4%	-\$9252	-\$6641
Cost (direct medical) for \$100,000/QALY	1.393 QALYs/22.4%	\$153,634	\$100,000
Substitution of ranibizumab for bevacizumab			
Third party insurer cost perspective			
Second-eye model	1.393 QALYs/22.4%	\$15,219	\$10,926
Governmental cost perspective, no caregiver costs			
Second-eye model	1.393 QALYs/22.4%	\$585	\$420
Governmental cost perspective, with caregiver costs			
Second-eye model	1.393 QALYs/22.4%	-\$109,119	-\$78,333
Treatment frequency—injections increased by 200%			
Third party insurer cost perspective			
Second-eye model, bevacizumab	1.393 QALYs/22.4%	\$12,075	\$8666
Second-eye model, ranibizumab	1.393 QALYs/22.4%	\$24,168	\$17,349
First-eye model, bevacizumab	0.758 QALYs/12.2%	\$12,075	\$15,921
Combined, bevacizumab	0.981 QALYs/15.8%	\$12,075	\$12,313
Treatment frequency, 5 injections/y, years 2-13			
Third party insurer cost perspective			
Second-eye model, bevacizumab	1.393 QALYs/22.5%	\$28,274	\$20,291
Second-eye model, ranibizumab	1.393 QALYs/22.5%	\$147,046	\$105,561
First-eye model, bevacizumab	0.758 QALYs/1.2%	\$28,274	\$37,281
Combined, bevacizumab	0.981 QALYs/15.9%	\$28,274	\$28,831
Governmental cost perspective			
Second-eye model, bevacizumab without caregiver costs	1.393 QALYs/22.4%	\$3175	\$2279
Second-eye model, ranibizumab with caregiver costs	1.393 QALYs/22.4%	\$37,342	\$26,802
Bevacizumab monthly × 24	1.393 QALYs/22.4%	\$33,125	\$23,780
Discount rate			
0% discount rate	1.689 QALYs/23.0%	\$11,227	\$6646
3% discount rate	1.393 QALYs/22.4%	\$10,765	\$7726
5% discount rate	1.231 QALYs/21.9%	\$10,518	\$8544
Adverse events excluded			
Excluding all adverse events	1.399 QALYs/22.4%	\$10,499	\$7505
Cataract surgery in all phakic eyes			
Second eye model, third party insurer cost perspective			
Second eye model, governmental cost perspective, no caregiver costs	1.390 QALYs/22.4%	-\$2702	-\$1943
Second eye model governmental cost perspective, with caregiver costs	1.390 QALYs/22.4%	-\$112,406	-\$80,868

Note that, within a grouping with negative costs (eg, Governmental cost perspective with caregiver costs below), the most cost-effective cost-utility ratio is that which is the most negative number. Unless otherwise indicated, a second-eye model, third party insurer cost perspective, and a 3% annual discount rate are applied to the sensitivity analyses. Unless otherwise indicated, a second eye model is used and all costs and outcomes (QALYs) are discounted at a 3% annual rate. QALYs indicates quality-adjusted life-years; %, percent improvement in quality-of-life.

Table 11. Value Conferred by Ophthalmic and Nonophthalmic Interventions

Intervention	Value Gain (%)
Statins (HMG-CoA reductase inhibitors) for hyperlipidemia*	3.9
Laser, subfoveal neovascular AMD ⁵²	4.4
Pegaptanib therapy for subfoveal neovascular AMD ⁵²	5.9
Photodynamic therapy for classic, subfoveal neovascular AMD ^{9,52}	8.1
β-blockers for systemic arterial hypertension*	6.3-9.1
Cataract surgery, second eye ⁵³	12.7
⁹⁰ Sr intravitreal brachytherapy/intravitreal bevacizumab for subfoveal, neovascular AMD (current study)	15.8†
Ranibizumab, intravitreal, subfoveal neovascular AMD, minimally classic occult choroidal neovascularization ¹²	15.8†
Ranibizumab, intravitreal, subfoveal neovascular AMD, minimally classic and occult choroidal neovascularization*	17.0
Cataract surgery, first eye ⁵⁴	20.8
Antidepressants (SSRIs)*	20 to 24
Proton pump inhibitors, acute erosive esophagitis*	13.3 to 26.2

For ocular interventions, a second eye model was used other than for cataract surgery in the Second eye.
 *Data from the Center for Value-Based Medicine, Pharmaceutical Value Index internal files.
 †Different control groups do not allow a direct comparison.
 AMD indicates age-related macular degeneration; SSRI, selective serotonin reuptake inhibitor.

Photocoagulation Study,⁵ as well as the data from Shah and Del Priore,⁴ suggest the disparity between the treatment and sham groups will likely continue to increase. Even if the value of ⁹⁰Sr brachytherapy/bevacizumab therapy is decreased by 50%, the intervention still remains very cost-effective with the third party insurer second-eye model at \$15,451/QALY (Table 10) and in the third party insurer, combined-eye model at \$21,954/QALY. For a CUR of \$100,000, the third party insurer,

second-eye model, conferred value would need to be reduced by 92%, whereas for the third party insurer, combined-eye model to have a CUR of \$100,000/QALY, the conferred value would need to be reduced by 89%.

Aberrations in costs, utilities, the frequency of drug administration and the possibility that a ⁹⁰Sr brachytherapy/bevacizumab therapy trial population may differ from the population in a clinic setting are all possible causes of weakness in the study.

Table 12. Comparison of the Cost-Utility of Intraocular ⁹⁰Sr Brachytherapy/Intravitreal Bevacizumab Therapy for Subfoveal Neovascular AMD With Other Medical Interventions (Adjusted to 2008 US Dollars)

Intervention	\$/QALY Gained
Laser therapy for threshold retinopathy of prematurity ⁵⁵	848
Cataract surgery, initial eye ⁵⁴	2444
Use of β-blockers for the treatment of systemic arterial hypertension*	7201
⁹⁰ Sr intravitreal brachytherapy/intravitreal bevacizumab for subfoveal, neovascular AMD, (current study)	10,973
Use of proton pump inhibitor instead of histamine-2 receptor inhibitors for heartburn ⁵⁶	11,183
Computer tomography (CT) for equivocal neurologic symptoms ⁵⁷	24,672
Photodynamic therapy with verteporfin for classic, subfoveal, neovascular AMD ⁵²	31,634
Radiation therapy after conservative surgery for early-stage breast cancer ⁵⁸	36,336
Growth hormone replacement (children, aged 3-18 y) ⁵⁹	44,536
Chemoprophylaxis after occupational HIV exposure ⁶⁰	48,124
Silicone oil for vitrectomy-naive eye with retinal detachment and proliferative vitreoretinopathy ³⁸	48,947
Ranibizumab, intravitreal, for occult, minimally classic subfoveal choroidal neovascularization ¹²	51,958
Treating mildly symptomatic Herpes zoster 70-year old ⁶¹	58,835
Use of mitoxantrone for the treatment of progressive relapsing multiple sclerosis ⁶²	60,711
Pegaptanib therapy for subfoveal neovascular AMD ⁵²	67,178
Statins (HMG-CoA reductase inhibitors) for the treatment of hyperlipidemia*	69,773
Treating mildly symptomatic Herpes zoster 40-year old ⁶¹	128,945
Magnetic resonance imaging for equivocal neurologic symptoms ⁵⁶	135,385
Bisphosphonates for the treatment of osteoporosis*	152,519
Use of interferon-β 1-b for the treatment of progressive relapsing multiple sclerosis ⁶²	288,547

Adapted from Ref. 12.

*Pharmaceutical Value Index from the Center for Value-Based Medicine. For ocular interventions, a second-eye model was used other than for cataract surgery in the first eye.

AMD indicates age-related macular degeneration; \$/QALY gained, dollars expended per quality-adjusted life-year gained; HIV, human immunodeficiency virus; ROP, retinopathy of prematurity.

Nevertheless, such anomalies are likely captured in the sensitivity analyses.

Despite potential weaknesses, the clinician should realize the value-based medicine, cost-utility analysis herein builds upon evidence-based data gathered in a well-performed Phase 2 study,¹⁹ integrating all drug benefits, all adverse events, and patient-based quality-of-life parameters often overlooked in clinical trials. Value-based analyses therefore, compared with evidence-based data alone, more accurately predict which therapies provide the greatest patient benefit in this era of rapid change in neovascular macular degeneration treatment.^{9,12,51}

Summary

In summary, Phase 2 study data suggest that ⁹⁰Sr brachytherapy/bevacizumab therapy likely provides considerable patient value, and is a cost-effective treatment across the first-eye, second-eye, and combined-eye models, as well as the third party insurer and governmental cost perspectives. Assuming Phase 3 data are similar to those of the Phase 2 cohort in the analysis herein, the intervention could save considerable resources and sizably contribute to the GDP of the United States.

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