Supplementary Online Content

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eMethods

1. Model Overview

We modeled a cohort of patients who are newly diagnosed with neovascular (also referred to as "wet") age-related macular degeneration (wAMD) over a five year time horizon. Treatment initiation is modeled as a one-time decision: patients initiate treatment in the first year and those who do not initiate cannot do so in subsequent model years. Patients receive treatment with anti-vascular endothelial growth factor (anti-VEGF). Anti-VEGF treatment frequency and impact on patient visual acuity (VA) varies according to model scenario, and is based on the published literature. Patients can discontinue treatment in each year, and treatment cannot be restarted once discontinued. Our model translates VA outcomes into quality of life weights, which are used to calculate the economic value of treatment.

2. Model Parameters

Table 1 presents baseline model parameters and sources. Our cohort size (N=168,820) was derived by applying the wAMD incidence rate to the total US population aged 50 years or older.[1,2] We assumed the cohort was 65 years old and incorporated mortality risk in the model using five year age-adjusted mortality rates from National Vital Statistics.[3] Risk is adjusted based on VA to account for increased mortality associated with poor VA outcomes.[4] To isolate the mortality risk associated with poor VA associated with AMD, we used the mortality risk adjustment parameter that was adjusted for age, sex, and confounders. We assumed a baseline VA for all patients of 55 ETDRS letters (Snellen equivalent: 20/80), which was the modal VA at diagnosis across seven community-based studies.[5] Annual VA outcomes vary by model scenario (see Table 4). We further assumed that patients who discontinue treatment have VA in subsequent years equal to the average of VA for treated and untreated patients. Baseline quality of life for perfect VA (i.e., 20/20) was assumed to be 0.853, which corresponds to our cohort age of 65. VA outcomes were mapped to quality of life weights according to Brown et al (2005).[6] Since each quality of life weight in Brown et al (2005) corresponds to a broad VA range (e.g., individuals with VA equal to 50-59.9 letters have the same quality of life), we linearized the quality of life weights to allow for small changes in VA to correspond to different quality of life weights. A summary of the mapping from VA to quality of life weights is provided in Table 2.

Treatment uptake was assumed to be 65%, which was based on a study 284,380 Medicare beneficiaries with wAMD which found that 60-72% of patients received anti-VEGF agents.[7] Patients who receive anti-VEGF treatment have injection visits and non-injection visits. The frequency of injection visits varies based on model scenario (see Table 4), and patients have 1.9 non-injection visits annually.[7–10] Patients receive optical coherence tomography (OCT) during all injection and non-injection visits and a fluorescein angiography (FA) during their first visit. Our annual treatment discontinuation rate was 50% (based on a study that found discontinuation after twelve (eighteen) months equal to 53.6% (61.7%)).[7]

The cost of treatment includes drug costs plus the cost of visits. Since we are interested in anti-VEGF therapies as a class, we assumed the cost of treatment equaled the weighted average of available anti-VEGF agents: ranibizumab, aflibercept, and bevacizumab. Weights were based on treatment utilization rates from a study of commercially insured and Medicare Advantage patients.[11] Costs were obtained using the CMS Physician Fee schedule.[12] Cost parameter components are presented in Table 3.

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eTable 1. Baseline Model Parameters

	Value	Source
Population parameters		
U.S. population, aged ≥50	112,546,395	U.S. Census[1]
wAMD incidence	0.0015	Rudnicka et al (2015)[2]
Baseline age	65 years	Assumption
Baseline visual acuity	55 letters	Ho et al (2017)[5]
Treatment parameters		
Treatment uptake	65%	Curtis et al (2012)[7]
Treatment discontinuation (annual)	50%	Curtis et al (2012)[7]
Number of non-injection visits (annual)	1.9	Curtis et al (2012)[7]
Proportion treated with bevacizumab	0.553	Parikh (2017)[11]
Proportion treated with aflibercept	0.277	Parikh (2017)[11]
Proportion treated with ranibizumab	0.170	Parikh (2017)[11]
Mortality Parameters		
Baseline probability of death, ages 65-69	0.015	Murphy et al (2017)[3]
Baseline probability of death, ages 70-74	0.022	Murphy et al (2017)[3]
Mortality adjustment factor: VA between 20/20 and 20/30	1.01	Thiagarajan et al (2005)[4]
Mortality adjustment factor: VA between 20/30 and 20/60	1.1	Thiagarajan et al (2005)[4]
Mortality adjustment factor: VA less than 20/60	1.17	Thiagarajan et al (2005)[4]
Cost Parameters		
Drug cost (per injection)	$896.38	Weighted average of bevacizumab, aflibercept, and ranibizumab
Injection visit cost	$225.36	Includes cost of office visit, OCT, and injection costs
Non-injection visit cost	$122.40	Includes cost of office visit and OCT

Notes: Cost of FA included in the first visit only. See Table 3 for components of the cost parameters.

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eTable 2. Mapping Visual Acuity to Quality of Life (QoL)

VA	QoL associated with VA[6]	Final (age-adjusted) QoL weight
20/20 (both eyes)	1.00	0.853
20/20 (≤20/40 in other eye)	0.92	0.785
20/25	0.87	0.742
20/30	0.84	0.717
20/40	0.80	0.682
20/50	0.77	0.657
20/70	0.74	0.631
20/100	0.67	0.572
20/200	0.66	0.563
20/300	0.63	0.537
20/400	0.54	0.461
20/800	0.52	0.444

Notes: Quality of life (QoL) associated with perfect vision (0.853) is taken from Jia et al (2011)[13], and corresponds to the age-adjusted QoL for individuals 65-74.

eTable 3. Cost Parameter Components (2018 USD)

Cost	**Value**	**CPT Code**
Office visit (established patient)	$79.92	99214
Optical coherence tomography (OCT)	$42.48	92134
Fluorescein angiography (FA)	$172.44	99235
Injection, eye drug	$102.96	67028
Bevacizumab injection (10mg)	$77.17	J9035
Aflibercept injection (1mg)	$968.79	J2778
Ranibizumab injection (0.1mg)	$372.93	J0178

Notes: Cost components obtained from the CMS Physician Fee schedule and Medicare ASP drug pricing files.[12,14] Total aflibercept cost per injection (2mg dose) is $1937.58; total ranibizumab cost per injection (0.5mg dose) is $1864.65; although bevacizumab injection dose is 1.25 mg, we assumed the full 10mg cost of $77.17 in our model to be conservative.[15–17]

3. Model Scenarios and Outcomes

3.1. Current Treatment Scenarios

We estimated two model scenarios to determine the value of current therapies: 1) Less Frequent Injections and 2) More Frequent Injections. Results for these scenarios are presented relative to a baseline scenario ("No Treatment") in which patients do not receive treatment for wAMD. Less Frequent Injections assumes patients receive anti-VEGF treatment using a treat and extend regimen. Based on data from the literature, this results in an average of 8 anti-VEGF injections annually. More Frequent Injections assumes patients receive anti-VEGF

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treatments on a regular schedule, and receive 10.5 injections annually. Annual VA outcomes and anti-VEGF injection frequencies for these scenarios are presented in Table 4.

eTable 4. VA and Injection Parameters, by Model Scenario

Scenario	Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Baseline Scenario:							
No Treatment	VA Change	-10.1	-9.6	-11.8	-11.8	-16.1	HORIZON[8]
	# Injections	0	0	0	0	0	
Current Treatment Scenarios:							
Less Frequent Injections	VA Change	6.5	6.5	6.0	4.5	-0.5	Mrejen et al (2015)[10]
	# Injections	8.96	7.78	7.94	8.03	8.12	
More Frequent Injections	VA Change	13.2	16.1	15.4	14.6	14.0	Peden et al (2015)[9]
	# Injections	10.5	10.5	10.5	10.5	10.5	

Notes: The HORIZON VA and injection parameters correspond to the control group from that study. VA change is the change from baseline VA and is measured in ETDRS letters.

3.2. Treatment Innovation Scenarios

To explore the value of improved adherence, we considered several treatment innovation scenarios. Each treatment innovation scenario was run twice; once using the VA and injection parameters from Less Frequent Injections and once using the VA and injection parameters from More Frequent Injections. The "Improved Adherence" scenario modified two key model parameters: treatment uptake and discontinuation. We assumed 80% of patients initiated therapy; discontinuation rates were only 17% in year 1, and increased each year until they were 50% in year 5. We also considered two scenarios that isolated the effect of modifying the uptake and discontinuation parameters within the "Improved Adherence" scenario --- "Improved Uptake" and "Reduced Discontinuation," respectively.

In addition to the Improved Adherence scenario, which represents an incremental improvement over the current treatment scenarios, we considered a "Best Case" scenario that estimated an upper bound on potential value from current treatments. In the Best Case scenarios, we assumed 100% of wAMD patients initiate therapy, and discontinuation rates are 6% per year, which is the discontinuation rate observed in clinical trials.[8] Finally, to understand how much value could be gained from future therapies that provide better VA outcomes relative to current anti-VEGF therapies, we considered the "Hypothetical Cure" scenario, which assumed all wAMD patients receive a one-time treatment that results in permanent 20/40 vision. Table 5 presents the treatment uptake and discontinuation parameters for the current treatment scenarios and treatment innovation scenarios for comparison.

eTable 5. Treatment Uptake and Discontinuation Parameters, by Model Scenario

Scenario Name	Treatment Uptake	Discontinuation
Current Treatment Scenarios:		
Less Frequent Injections	65%[7]	50% (annual)[7]
More Frequent Injections	65%[7]	50% (annual)[7]
Treatment Innovation Scenarios:		
Improved Adherence	80%	17% (year 1); 26% (year 2); 31% (year 3); 39% (year 4); 50% (year 5)[10]
Improved Uptake	80%	50% (annual)[7]
Reduced Discontinuation	65%[7]	17% (year 1); 26% (year 2); 31% (year 3); 39% (year 4); 50% (year 5)[10]
Best Case	100%	6% (annual)[8]

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Notes: Model parameters for treatment innovation scenarios that do not have a corresponding source are based on assumption. We ran two sets of treatment innovation scenarios which correspond to the same VA outcomes and injection frequencies as the Less Frequent Injections and More Frequent Injections scenarios.

3.3. Model Outcomes

We estimated several outcomes for each model scenario: number treated, patient benefit, and total costs. Patient benefit is calculated as the total quality-adjusted life years (QALY) from VA gains multiplied by $150,000, which is assumed based on a range of values cited in the literature.[18,19] Total costs include drug cost and the cost of injection and non-injection visits. All future values are discounted at a rate of 3% per year. We also present social value estimates, which are calculated as the difference between patient benefit and total costs. All outcomes are presented for a single incident cohort as well as the population level. The population level results assume a new incident cohort enters the model each year.

4. Additional Results

4.1. Current Treatment Scenarios

eTable 6. Cumulative Patient Benefits, Costs, and Social Value

	Less Frequent Injections					More Frequent Injections				
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Single Incident Cohort										
Patient Benefits	1.1	1.8	2.3	2.5	2.6	1.6	2.9	3.8	4.5	5.0
Cost	1.1	1.5	1.7	1.8	1.9	1.3	1.9	2.1	2.3	2.3
Social Value	0.05	0.3	0.5	0.7	0.7	0.3	1.0	1.7	2.2	2.6
Population Level										
Patient Benefits	1.1	3.0	5.1	7.5	9.9	1.6	4.5	8.2	12.4	17.0
Cost	1.1	2.6	4.3	6.0	7.7	1.3	3.1	5.2	7.3	9.4
Social Value	0.05	0.4	0.9	1.5	2.2	0.3	1.4	3.0	5.2	7.6

Notes: All values are in billions of dollars (USD). Future values are discounted at a rate of 3%.

4.2. Treatment Innovation Scenarios

Since treatment innovation scenarios change the values for treatment uptake and discontinuation, the results are driven by the total number treated in each scenario. Table 7 presents the cumulative total number treated in each year for all model scenarios. The “best case” scenarios result in over 500,000 more patient-years of treatment relative to the current treatment scenarios.

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eTable 7. Cumulative Number of Patients Treated, Single Incident Cohort

	Year 1	Year 2	Year 3	Year 4	Year 5
Current Treatment Scenarios					
Less Frequent Injections	107,867	160,076	185,345	197,576	203,483
More Frequent Injections	107,867	160,076	185,345	197,576	203,483
Treatment Innovation Scenarios – (Less Frequent Injections and More Frequent Injections)					
Improved Adherence	132,760	240,827	319,069	371,805	403,130
Improved Uptake	132,760	197,017	228,117	243,170	250,441
Reduced Discontinuation	107,867	195,697	259,244	302,091	327,500
Best Case	165,950	319,289	460,975	591,894	712,733

Notes: Number treated are the same in both current treatment scenarios (Less Frequent Injections and More Frequent Injections) since the treatment uptake and discontinuation parameters are the same. Similarly, the number treated for treatment innovation scenarios that correspond to Less Frequent Injections and More Frequent Injections are the same since the treatment uptake and discontinuation parameters are the same.

Table 8 presents additional results for the treatment innovation scenarios that assume the same VA outcomes as the Less Frequent Injections scenario. Similarly, Table 9 presents treatment innovation results that assume the same VA outcomes as the More Frequent Injections scenario.

eTable 8. Treatment Innovation Results (Based on Less Frequent Injections VA), Single Incident Cohort

		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Less Frequent Injections (current treatment scenario)	Patient Benefits	1.1	1.8	2.3	2.5	2.6
	Cost	1.1	1.5	1.7	1.8	1.9
	Social Value	0.05	0.3	0.5	0.7	0.7
Improved Adherence	Patient Benefits	1.4	2.6	3.5	4.0	4.3
	Cost	1.3	2.3	2.9	3.3	3.6
	Social Value	0.06	0.3	0.5	0.7	0.7
Improved Uptake	Patient Benefits	1.4	2.3	2.8	3.1	3.2
	Cost	1.3	1.9	2.2	2.3	2.3
	Social Value	0.06	0.4	0.6	0.8	0.9
Reduced Discontinuation	Patient Benefits	1.1	2.1	2.8	3.3	3.5
	Cost	1.1	1.8	2.4	2.7	2.9
	Social Value	0.05	0.3	0.4	0.6	0.5
Best Case	Patient Benefits	1.8	3.4	4.8	6.0	6.6
	Cost	1.7	3.0	4.2	5.2	6.2
	Social Value	0.07	0.4	0.6	0.7	0.4

Notes: All values are in billions of dollars (USD). All scenarios use VA outcomes from the Less Frequent Injections current treatment scenario, and vary treatment uptake and discontinuation parameters according to Table 5.

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eTable 9. Treatment Innovation Results (Based on More Frequent Injections VA), Single Incident Cohort

		Year 1	Year 2	Year 3	Year 4	Year 5
More Frequent Injections (current treatment scenario)	Patient Benefits	1.6	2.9	3.8	4.5	5.0
	Cost	1.3	1.9	2.1	2.3	2.3
	Social Value	0.3	1.4	3.0	5.2	7.6
Improved Adherence	Patient Benefits	2.0	4.0	5.6	6.8	7.6
	Cost	1.6	2.8	3.6	4.2	4.5
	Social Value	0.4	1.2	1.9	2.6	3.1
Improved Uptake	Patient Benefits	2.0	3.6	4.7	5.5	6.1
	Cost	1.6	2.3	2.6	2.8	2.9
	Social Value	0.4	1.3	2.1	2.7	3.2
Reduced Discontinuation	Patient Benefits	1.6	3.3	4.5	5.5	6.2
	Cost	1.3	2.3	3.0	3.4	3.7
	Social Value	0.3	1.0	1.6	2.1	2.5
Best Case	Patient Benefits	2.5	5.2	7.6	9.8	11.7
	Cost	2.0	3.7	5.3	6.7	7.9
	Social Value	0.5	1.5	2.3	3.1	3.8

Notes: All values are in billions of dollars (USD). All scenarios use VA outcomes from the More Frequent Injections current treatment scenario, and vary treatment uptake and discontinuation parameters according to Table 5.

5. Sensitivity Analyses

We ran several sensitivity analyses for key model parameters for all current treatment scenarios. Our first sensitivity varied the drug utilization weights (summarized in Table 10), which impact the total cost of injections. Parikh et al (2017) reports annual utilization rates from 2006-2015, and we limited our potential parameter sources to the 2011-2015 results in their paper, since aflibercept was not available before 2011.[11] Drug shares in the baseline model were based on 2015 (the most recent reported year) drug utilization rates. Our "High bevacizumab share" sensitivity used the utilization rates from 2012, which had the highest share of bevacizumab use. Since our baseline drug utilization shares also corresponded to the lowest bevacizumab share in that study, we used drug utilization rates from Erie et al (2016) for the "Low bevacizumab share" sensitivity.[20] Finally, the "Very low bevacizumab share" sensitivity assumed the share of bevacizumab was equal to the total FDA-approved drug share (i.e., the sum of aflibercept and ranibizumab) from the "High bevacizumab share" sensitivity, and remaining drug share was split equally across aflibercept and ranibizumab.

eTable 10. Drug Utilization Shares

	Very Low Bevacizumab Share	Low Bevacizumab Share	Baseline Bevacizumab Share	High Bevacizumab Share
Bevacizumab	27.7	49.1	55.3	72.3
Aflibercept	36.2	29.2	27.7	7.45
Ranibizumab	36.2	21.7	17.0	20.2
Total drug cost	$1397.78	$1008.29	$896.38	$577.20

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Notes: Low, Baseline, and High Bevacizumab Share utilization are based on the literature. Very Low Bevacizumab Share assumed the share of Bevacizumab is equal to the sum of aflibercept and ranibizumab from the High Bevacizumab Share sensitivity. The remaining share (72.3%) was split equally across aflibercept and ranibizumab.

Results for the drug utilization weights sensitivity for both current treatment scenarios are presented in Table 11. Patient benefits are not impacted by the changing drug shares since VA outcomes are the same irrespective of drug type in our model. The differential between the bevacizumab and ranibizumab point estimates for the VA delta from the CATT trials range from 1 letter in year 1 to 2 letters in year 5.[21] Therefore, even if we allowed differential VA outcomes by drug type in our model, we expect the impact of drug share to be relatively small. Since bevacizumab is the least expensive anti-VEGF therapy, the cost of treatment decreases as the share of bevacizumab increases. Consequently, the High Bevacizumab Share generates the most social value across all sensitivities. Social value switches from positive to negative if the bevacizumab drug share gets too low (27.7% in the Very Low sensitivity), however, social value remains positive over both three- and five-year time horizons for the Low Bevacizumab Share sensitivity.

eTable 11. Sensitivity Analysis: Drug Utilization Shares

	Less Frequent Injections				More Frequent Injections			
	Bevacizumab Drug Share				Bevacizumab Drug Share			
	Very Low	Low	Baseline	High	Very Low	Low	Baseline	High
	One-year horizon (single incident cohort=full population)							
Patient Benefit	1.1	1.1	1.1	1.1	1.6	1.6	1.6	1.6
Cost	1.6	1.2	1.1	0.8	1.8	1.4	1.3	0.92
Social Value	-0.4	-0.06	0.05	0.3	-0.2	0.2	0.3	0.7
	Three-year horizon (single incident cohort)							
Patient Benefit	2.3	2.3	2.3	2.3	3.8	3.8	3.8	3.8
Cost	2.5	1.9	1.7	1.3	3.1	2.4	2.1	1.6
Social Value	-0.2	0.4	0.5	1.0	0.7	1.5	1.7	2.3
	Three-year horizon (full population)							
Patient Benefit	5.1	5.1	5.1	5.1	8.2	8.2	8.2	8.2
Cost	6.1	4.7	4.3	3.1	7.4	5.7	5.2	3.7
Social Value	-1.0	0.5	0.9	2.0	0.8	2.5	3.0	4.4
	Five-year horizon (single incident cohort)							
Patient Benefit	2.6	2.6	2.6	2.6	5.0	5.0	5.0	5.0
Cost	2.7	2.1	1.9	1.4	3.4	2.6	2.3	1.7
Social Value	-0.1	0.5	0.7	1.2	1.7	2.4	2.6	3.3
	Five-year horizon(full population)							
Patient Benefit	9.9	9.9	9.9	9.9	17.0	17.0	17.0	17.0
Cost	11.0	8.5	7.7	5.6	13.5	10.3	9.4	6.8
Social Value	-1.1	1.4	2.2	4.3	3.6	6.7	7.6	10.2

Notes: All values are in billions of dollars (USD). Parameter ranges are shown in Table 10.

Our second sensitivity varied the assumed value of a QALY for both current treatment scenarios. For a one-year time horizon, anti-VEGF treatments generate negative social value (regardless of scenario) if we assume the value of a QALY is less than or equal to $100K. Social value is also negative in the longer-run (three and five years) for QALY values less than or equal to $100K under Less Frequent Injections. In contrast, under More Frequent Injections, over three- and five-year horizons, social value is positive for a QALY value of $100K, but negative for a QALY value of $50K.

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eTable 12. Sensitivity Analysis: Value of a QALY

	Less Frequent Injections			More Frequent Injections		
	QALY Value			QALY Value		
	$50K	$100K	$300K	$50K	$100K	$300K
	One-year horizon (single incident cohort = full population)					
Patient Benefit	0.4	0.8	2.3	0.5	1.1	3.3
Cost	1.1	1.1	1.1	1.3	1.3	1.3
Social Value	-0.7	-0.3	1.2	-0.7	-0.2	2.0
	Three-year horizon (single incident cohort)					
Patient Benefit	0.8	1.5	4.5	1.3	2.5	7.6
Cost	1.7	1.7	1.7	2.1	2.1	2.1
Social Value	-1.0	-0.2	2.8	-0.9	0.4	5.5
	Three-year horizon (full population)					
Patient Benefit	1.7	3.4	10.3	2.7	5.5	16.4
Cost	4.3	4.3	4.3	5.2	5.2	5.2
Social Value	-2.6	-0.8	6.0	-2.4	0.3	11.2
	Five-year horizon (single incident cohort)					
Patient Benefit	0.9	1.7	5.2	1.7	3.3	9.9
Cost	1.9	1.9	1.9	2.3	2.3	2.3
Social Value	-1.0	-0.2	3.3	-0.7	1.0	7.6
	Five-year horizon (full population)					
Patient Benefit	3.3	6.6	19.8	5.7	11.4	34.1
Cost	7.7	7.7	7.7	9.4	9.4	9.4
Social Value	-4.4	-1.1	12.1	-3.7	2.0	24.7

Notes: All values are in billions of dollars (USD). Baseline value of a QALY was $150K.

Our final sensitivity analysis varied the two VA parameters in our model: baseline VA and the VA deltas for each year. The baseline VA sensitivity values were derived using data from the UK EMR study, which had mean baseline VA that ranged from 52.8 to 63.2 letters across thirteen sites.[22] We constructed 95% confidence intervals for baseline VA at each site reported in the study, and selected the maximum and minimum values across all sites. Our final parameter values were 47 letters for the lower bound sensitivity ("Low Baseline VA") and 66 letters for the upper bound sensitivity ("High Baseline VA"). We used the reported mean plus or minus one standard error results from Peden et al (2015) to derive the bounds for VA change used in our sensitivities.[9] The difference from mean VA was applied to both More Frequent Injections and Less Frequent Injections scenarios so that the VA gains were comparable across both scenarios. Table 13 summarizes the VA delta parameters for all sensitivities.

eTable 13. VA Delta Sensitivity Parameters

	Less Frequent Injections			More Frequent Injections		
	Low deltas	Main deltas	High deltas	Low deltas	Main deltas	High deltas
Year 1	4.8	6.5	8.2	11.5	13.2	14.9
Year 2	4.7	6.5	8.4	14.3	16.1	18.0
Year 3	4.1	6.0	8.0	13.5	15.4	17.4
Year 4	2.7	4.5	6.4	12.8	14.6	16.5
Year 5	-2.7	-0.5	1.6	11.8	14.0	16.1

Notes: Parameter values are rounded to the nearest tenth decimal place. VA deltas are measured in ETDRS letters.

For the VA parameter sensitivities, we ran all nine combinations of baseline VA and VA deltas. Patient benefits for the VA sensitivities are presented in Figure 1 for both current treatment scenarios for a single incident cohort. In the Less Frequent Injections scenario, patient benefit is negative for all time horizons for patients with low baseline VA, irrespective of their VA deltas. However, patient benefit is positive for patients with low baseline VA in the More Frequent Injections scenario for all VA delta levels. For both scenarios, changing the VA deltas has

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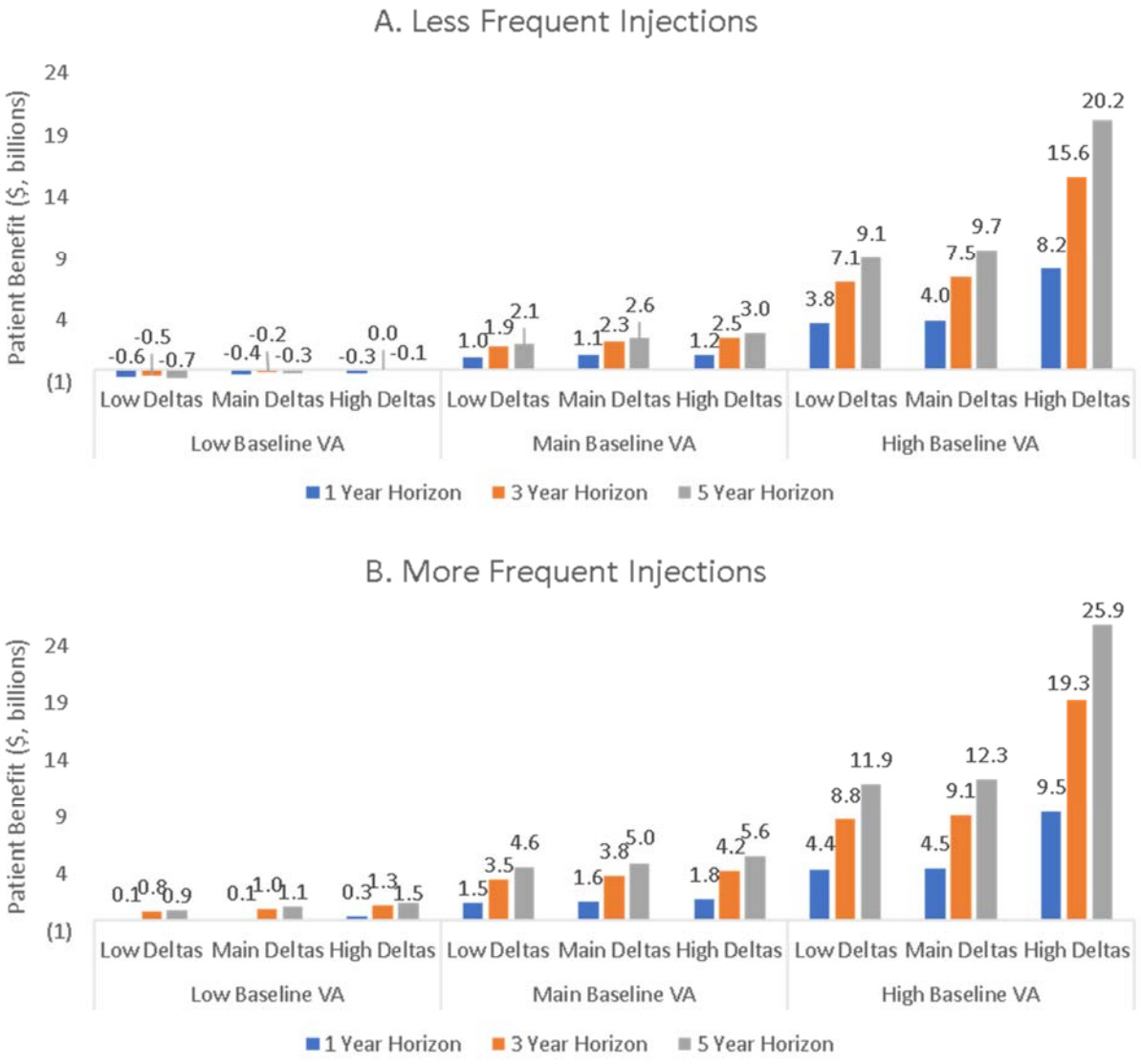
less impact on patient benefit compared with changing baseline VA. This result suggests the value generated from anti-VEGF treatment will be higher if patients initiate therapy as soon as possible, rather than waiting for their VA to decline.

eFigure 1. Sensitivity Analysis: VA Parameters, Single Incident Cohort



Notes: Low, Main, and High Baseline VA parameters are 47, 55, and 66 ETDRS letters, respectively. VA delta parameters are presented in Table 13.

Although our main scenarios are based on published real world data for VA outcomes and injection frequency, they might not represent all patient outcomes. In particular, some patients might receive injections monthly yet have relatively poor VA gains relative to if they did not receive treatment. Conversely, other patients may respond well to treatment even at low injection frequencies. Since most published studies only present average

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outcomes, our main results reflect these averages rather than the full range of the relationship between injections and VA.

To address this issue, we conducted two sensitivity analyses. The first estimates two alternative scenarios that use a mixture of the underlying study data. The study data used for Less Frequent Injections had lower injection frequency as well as lower VA gains compared with More Frequent Injections. This sensitivity considered how results would be impacted under two alternative scenarios: 1) lower injection frequency (Mrejen) with higher VA gains (Peden) and 2) higher injection frequency (Peden) with lower VA gains (Mrejen). The value of these scenarios is known a priori (but the exact magnitude is not). Conceptually, the social value of treatment will be higher than either current treatment scenario if patients can achieve relatively high VA gains with fewer injections. Conversely, the social value of treatment will be lower than either current treatment scenario if patients who receive more injections also experience relatively worse VA outcomes. This sensitivity therefore provides reasonable bounds for social value based on both underlying study populations.

Table 14 provides results for this sensitivity. Column 2 corresponds to Less Frequent Injections, which uses data from Mrejen. Column 1 uses the same VA outcomes but assumes injection frequency from Peden, and therefore will have the same patient benefit as Less Frequent Injection but higher cost. Consequently, social value is lower for column 1 compared with Less Frequent Injections. Similarly, column 3 corresponds to More Frequent Injections, which uses data from Peden. Column 4 uses the same VA outcomes but assumes injection frequency from Mrejen, and therefore will have the same patient benefit as More Frequent Injections but at lower cost. Consequently, social value is higher for column 4 compared with More Frequent Injections.

eTable 14. Sensitivity Analysis: Alternative Scenarios With Varied VA and Injection Frequency

			(1)	(2)	(3)	(4)
VA outcomes			Lower (Mrejen)	Lower (Mrejen)	Higher (Peden)	Higher (Peden)
Injection frequency			More frequent (Peden)	Less frequent (Mrejen)	More frequent (Peden)	Less frequent (Mrejen)
Social value ($, billions)	1-year	Current treatment	-0.13	0.05	0.35	0.53
		Improved adherence	-0.16	0.06	0.43	0.65
		"Best case" scenario	-0.20	0.07	0.54	0.82
	3-year, full population	Current treatment	-0.02	0.87	3.02	3.91
		Improved adherence	-0.53	0.93	3.52	4.99
		"Best case" scenario	-0.97	1.08	4.29	6.34
	5-year, full population	Current treatment	0.48	2.18	7.64	9.33
		Improved adherence	-0.97	2.20	8.94	12.1
		"Best case" scenario	-2.91	2.09	10.8	15.8

Notes: All values are in USD (billions). Column 2 corresponds to Less Frequent Injections and column 3 corresponds to More Frequent Injections.

One key finding from this sensitivity is that anti-VEGF treatments would not provide social value if on average patients receive injections on a nearly monthly basis but experience relatively low VA outcomes. Innovation that improves adherence in this case would result in even worse (i.e., more negative) social value since more patients are treated, which results in higher costs, but their VA outcomes are relatively low, and benefits do not offset added costs.

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The second finding from this sensitivity is the gains from innovation for anti-VEGF treatment could be even higher if on average patients experience relatively high VA outcomes and required less frequent injections. For More Frequent Injections (column 3), 3-year social value is 42% higher under the Best Case scenario compared with current treatment. If patients could experience the same VA outcomes but with approximately 2 fewer injections per year (column 4), social value would be 62% higher under Best Case scenario compared with current treatment.

Our second sensitivity uses subgroup data from Peden and Mrejen to explores how value is affected by variation in injection frequency and VA outcomes. Mrejen provides VA outcomes and injection frequency for four subgroups. Peden provides VA outcomes (but not injection frequency) for three subgroups. These data are provided for reference in Table 15. Rather than refer to subgroups as 1, 2, etc., we have given each subgroup a scenario label (column 2) that corresponds to the relative VA outcomes for each publication.

eTable 15. VA Outcomes and Injection Frequency by Subgroup

		VA Change (ETDRS Letters)			Injections		
Subgroup	Subgroup scenario label	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Mrejen subgroups:							
Type 1	Low	6.55	6.2	7.6	9.4	8.2	8.6
Type 2	High	11.8	8.35	7.5	8.3	6.0	7.8
Type 3	Very Low	2.9	5.05	2.85	8.7	8.0	7.5
Type 4	Medium	10.25	8.2	8.55	8.8	7.3	7.4
Peden subgroups:							
20/40 or better	Low	3.5	3.8	3.3			
20/50 to 20/100	Medium	9.2	10.0	9.5			
20/200 or worse	High	19.9	25.7	25.0			

Notes: Peden did not publish injection frequency data by subgroup.

We compared value for all subgroup combinations across the two publications. Since Peden did not publish injection data by subgroup, we use the mean value (10.5 injections) for all subgroups. The 3-year value for each subgroup is presented in Table 16. As expected, social value is increasing in VA outcomes. The Mrejen subgroups provide variation in both VA outcomes and injection frequency. Even though mean injections were highest for the "Very Low" and "Low" subgroups, the social value for these groups is also relatively low since their VA outcomes were not as high compared with the other Mrejen subgroups. This result suggests that treatment efficacy is the primary driver of social value, and more frequent injections will result in relatively more social value only to the extent that they are coupled with better VA outcomes

eTable 16. Sensitivity Analysis: Subgroup Results

	3-Year Cumulative Social Value	
	Single Incident Cohort	Full Population
Baseline Results		
Less Frequent Injections (Mrejen)	0.5	0.9
More Frequent Injections (Peden)	1.7	3.0
Mrejen Subgroups:		
Very Low	-0.01	-0.3
Low	0.50	2.4
Medium	1.0	4.4
High	1.3	5.4
Peden Subgroups:		
Low	-0.4	-1.6
Medium	0.7	3.0
High	3.6	16.3

Notes: All values are in USD (billions). Social value is equal to patient benefit net cost. Subgroup names and their corresponding data are presented in Table 15.

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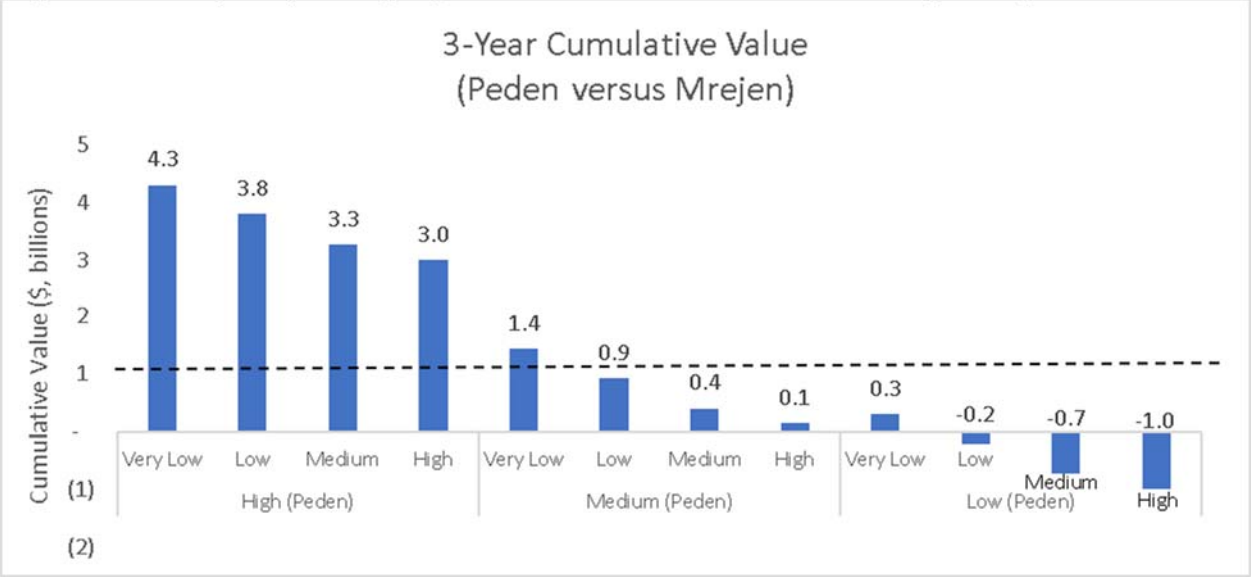
Figure 2 shows the difference in value for all twelve study subgroup combinations, and Table 17 shows the difference in patient benefit and total cost. We used mean injections for the Peden scenarios; results are similar if we use minimum or maximum injections. In particular, the relative magnitude of the bars moving from the left to right side of the figure will be the same, but the absolute magnitude will be different. In the baseline model scenarios, More Frequent Injections provided an additional $1.1 billion in social value compared with Less Frequent Injections. This sensitivity confirms that More Frequent Injections will provide value above and beyond Less Frequent Injections if VA outcomes are increasing in injection frequency. However, if better VA outcomes are attained with fewer injections (e.g., Low Peden vs. Medium/High Mrejen), then social value will be higher with fewer injections. While this sensitivity shows a range of results for different VA and injection parameters, we note that they are comparing subgroup data across studies and should be interpreted with caution since patient characteristics are different across studies and subgroups.

eFigure 2. Sensitivity Analysis: Subgroup Results (Difference Between Peden and Mrejen), Single Incident Cohort



Notes: Subgroup labels and corresponding data are provided in Table 15. Black dotted line (approximately. $1.1 billion) shows difference between Peden and Mrejen in the baseline scenario (More Frequent Injections and Less Frequent Injections).

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