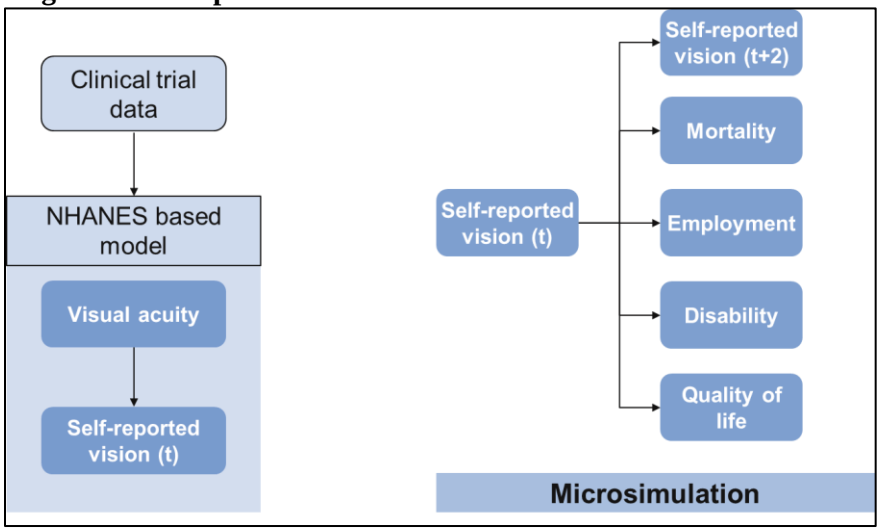
The Broader Economic Value of Treatment for DME

Appendix

1. Overview

We developed a microsimulation based on data from the Health and Retirement Study (HRS; a nationally representative longitudinal dataset of Americans aged 51 and older) that predicts outcomes such as life expectancy, QALY, employment, disability, and self-reported vision (SRV). Because clinical trial data in ophthalmology reports outcomes in terms of visual acuity (VA), we required a mapping from VA to SRV. We used the National Health and Nutrition Examination Study (NHANES; a nationally representative survey of Americans) which has data for both VA and SRV to generate a mapping between these outcomes. We used this mapping to estimate the SRV treatment effects for DRCR clinical trials. eeFigure 1 provides a conceptual framework of our modeling approach.

eFigure 1. Conceptual framework



2. Future Elderly Model

2.1. Summary of the Future Elderly Model

The Future Elderly Model (FEM) is a microsimulation model originally developed out of an effort to examine health and health care costs among the elderly Medicare population (age 65+). A description of the previous version of the model can be found in Goldman et al. (2004).[1] The original work was founded by the Centers for Medicare and Medicaid Services and carried out by a team of researchers composed of Dana P. Goldman, Paul G. Shekelle, Jayanta Bhattacharya, Michael Hurd, Geoffrey F. Joyce, Darius N. Lakdawalla, Dawn H. Matsui, Sydne J. Newberry, Constantijn W. A. Panis and Baoping Shang.

Since then, various extensions have been implemented to the original model. The most recent version now projects health outcomes for all Americans aged 51 and older and uses the HRS as a host dataset rather than the Medicare Current Beneficiary Survey (MCBS). The work has also been extended to include economic outcomes such as earnings, labor force participation and pensions. This work was funded by the National Institute on Aging through its support of the RAND Roybal Center for Health Policy Simulation (P30AG024968), the Department of Labor through contract J-9-P-2-0033, the National

Institutes of Aging through the R01 grant "Integrated Retirement Modeling" (R01AG030824) and the MacArthur Foundation Research Network on an Aging Society. A full technical appendix for that project is available here: https://healthpolicy.box.com/v/AD-FEM-Appendix.

2.2. Extending FEM to Incorporate Vision

2.2.1. Vision Measures

For this project we expanded the FEM to incorporate measures of vision from the HRS. Self-reported vision (SRV) is assessed each wave, and analogous questions are asked for near and distance vision. We focused on overall SRV because our implementation of the DME treatment effects relies on a mapping from visual acuity (VA) to SRV derived from the NHANES, which also uses overall SRV. eeTable 1 provides a summary of SRV questions for the HRS and NHANES and the final SRV categories used in the FEM.

eTable 1. Summary of Self-Reported Vision and Response Standardization

Dataset	Question	Response options	FEM: Final SRV categories (Original response %)			
			Excellent	Good	Fair	Poor
NHANES (1999-2008)	At the present time, would you say your eyesight, with glasses or contact lenses if you wear them is...	Excellent Good Fair Poor Very Poor	Excellent (24.3%)	Good (49.5%)	Fair (20.4%)	Poor (4.5%); Very Poor (1.3%)
HRS* (Waves 5-9)	Rate your eyesight while wearing glasses or corrective lenses as usual	Excellent Very Good Good Fair Poor	Excellent (9.3%); Very Good (25.5%)	Good (42.5%)	Fair (16.3%)	Poor (5.9%); Blind (0.5%)
HRS* (Waves 9-12)	Rate your eyesight while wearing glasses or corrective lenses as usual	Excellent Very Good Good Fair Poor	Excellent (8.3%); Very Good (25.3%)	Good (41.4%)	Fair (18.3%)	Poor (6.4%); Blind (0.3%)

*While not an explicit response option, <1% of the sample voluntarily told the interviewer that their SRV was blind.

2.2.2. Vision Transition Model

The estimated model coefficients for the vison models (people under 65, people 65 and older who have had cataract surgery, and people 65 and older who have not had cataract surgery) are provided in eTable2, and the estimated coefficients on the SRV variables in the non-vision outcome models are in eTable3.

eTable 2. SRV Model Coefficients

	Under 65	Over 65, cataract surgery	Over 65, no cataract surgery
Good vision (lag)	0.3716 (0.2473)	0.4826* (0.2738)	0.8800*** (0.0566)
Fair vision (lag)	0.7862** (0.3137)	1.2250*** (0.2959)	1.6559*** (0.0776)

Poor vision (lag)	0.3995 (0.5553)	1.5740*** (0.3893)	2.3562*** (0.1464)
Good vision (lag) x age less than 65 (lag)	0.0096** (0.0043)		
Fair vision (lag) x age less than 65 (lag)	0.0138** (0.0055)		
Poor vision (lag) x age less than 65 (lag)	0.0336*** (0.0097)		
Age less than 65 (lag)	-0.011*** (0.0033)		
Good vision (lag) x age 65-74 (lag)		0.0002 (0.0341)	-0.007 (0.0097)
Fair vision (lag) x age 65-74 (lag)		-0.042 (0.0369)	0.0194 (0.0178)
Poor vision (lag) x age 65-74 (lag)		-0.025 (0.0481)	-0.001 (0.0036)
Good vision (lag) x age 75+ (lag)		-0.008 (0.0179)	0.0028 (0.0043)
Fair vision (lag) x age 75+ (lag)		0.0072 (0.0190)	0.0307 (0.0061)
Poor vision (lag) x age 75+ (lag)		0.0097 (0.0229)	0.0197*** (0.0056)
Age 65-74 (lag)		0.0139 (0.0293)	0.0178*** (0.0028)
Age 75+ (lag)		0.0243 (0.0153)	-0.043*** (0.0140)
Male indicator	-0.031** (0.0158)	0.0706 (0.0490)	0.1825*** (0.0206)
Race/ethnicity: Black	0.2775*** (0.0197)	0.3006*** (0.0782)	0.2366*** (0.0266)
Race/ethnicity: Hispanic	0.3955*** (0.0235)	0.3529*** (0.0949)	0.1354*** (0.0187)
Less than high school education	0.2029*** (0.0258)	0.1390** (0.0656)	-0.132*** (0.0155)
College education	-0.214*** (0.0175)	-0.117** (0.0533)	0.0039*** (0.0174)
Cancer (lag)	0.0291 (0.0304)	-0.113* (0.0596)	0.0388 (0.0228)
Diabetes (lag)	0.0766*** (0.0280)	-0.008 (0.0780)	0.0056* (0.0014)
Years since diabetes diagnosis (lag)	0.0084*** (0.0021)	0.0132*** (0.0046)	0.0898*** (0.0159)
Heart attack (lag)	0.1334*** (0.0255)	0.0864 (0.0539)	0.0560*** (0.0149)
Hypertension (lag)	0.0980*** (0.0170)	0.0063 (0.0515)	0.1636*** (0.0227)
Lung (lag)	0.2914*** (0.0321)	0.0661 (0.0750)	0.0869*** (0.0226)
Stroke (lag)	0.1420*** (0.0409)	0.2364*** (0.0799)	-0.063*** (0.0159)

Smoke (lag)	0.1836*** (0.0195)	-0.007 (0.0836)	0.0987*** (0.0245)
High cholesterol (lag)	-0.084*** (0.0189)	0.0213 (0.0506)	0.0053 (0.0145)
Cut1	-0.2351	0.6077	0.4711
Cut2	1.2417	1.8632	1.9256
Cut3	2.4614	2.6943	3.0254
N	22,222	2,326	28,212

Notes: Coefficients from an ordered probit model with SRV (1=Excellent; 2=Good; 3=Fair; 4=Poor) as the dependent variable using HRS waves 9-12. Standard errors in parenthesis. Excluded SRV category for covariates=Excellent. We considered models that included both one period and two period lags of SRV and found that the coefficients on the two period lag were statistically insignificant. Significance: ***p<0.01; **p<0.05; *p<0.1

eTable 3. Effect of SRV on Non-vision Outcomes

	Employed	Claim disability	Mortality	ADL status	IADL status	HUI3
Good vision (lag)	-0.085*** (0.0140)	0.2707*** (0.0312)	0.0961*** (0.0229)	0.1864*** (0.0156)	0.1731*** (0.0195)	-0.066*** (0.0145)
Fair vision (lag)	-0.245*** (0.0199)	0.4987*** (0.0372)	0.1983*** (0.0274)	0.4465*** (0.0190)	0.4302*** (0.0229)	-0.113*** (0.0210)
Poor vision (lag)	-0.641*** (0.0370)	0.7701*** (0.0517)	0.3575*** (0.0338)	0.7662*** (0.0259)	0.9019*** (0.0287)	-0.194*** (0.0337)
Estimation method	Probit	Probit	Probit	Ordered probit	Ordered probit	OLS

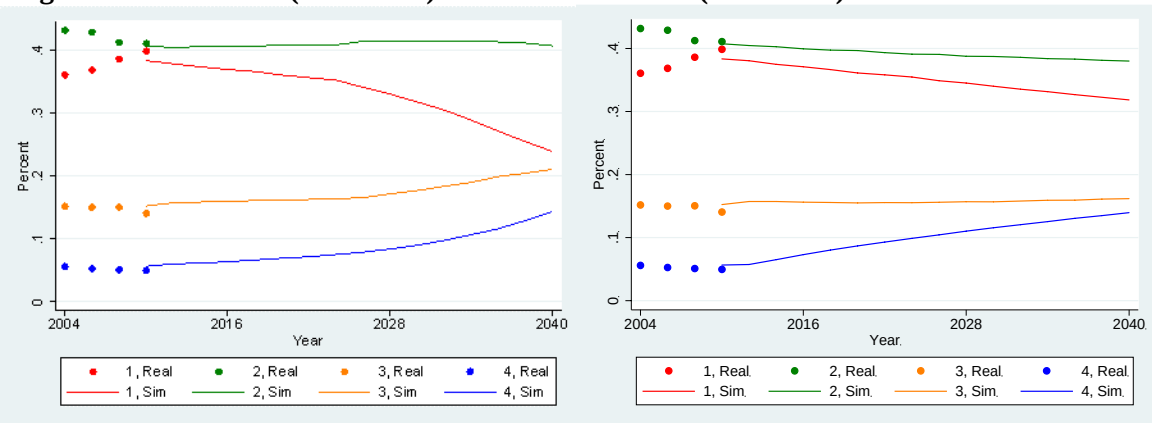
Notes: Each column presents coefficients on SRV (excluded category=Excellent) from a model with the dependent variable listed in the top row. All models except HUI3 include controls for age, gender, race/ethnicity, education. All models include controls for comorbidities.

2.2.3. Model Validation Results

eTable 4. Actual and Simulated SRV Distribution, 2014

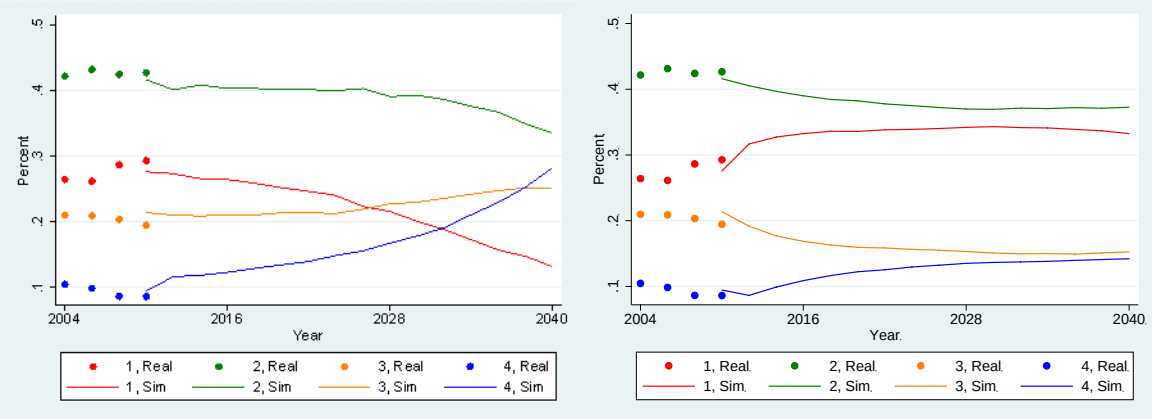
SRV Category	HRS (full sample)		Diabetes subpopulation	
	Actual	Simulated	Actual	Simulated
Excellent	0.3790	0.3737	0.2996	0.2653
Good	0.4058	0.4061	0.4141	0.4078
Fair	0.1631	0.1587	0.2025	0.2086
Poor	0.0521	0.0615	0.0838	0.1183

eFigure 2. Actual SRV (2004-2014) and Simulated SRV (2016-2040)



Notes: Left panel presents a cohort simulation. Right panel presents a population simulation, which allows new entrants in the model each cycle.

eFigure 3. Actual SRV (2004-2014) and Simulated SRV (2016-2040), Diabetes Subpopulation



Notes: Left panel presents a cohort simulation. Right panel presents a population simulation, which allows new entrants in the model each cycle.

eTable 5. Actual and simulated outcomes

Outcome	Actual HRS	Microsimulation Outcomes (Cohort)				
	2010	2010	2012	2014	2016	2018
Excellent SRV	0.3988	0.3835	0.3785	0.3737	0.3695	0.3662
Good SRV	0.4110	0.4074	0.4039	0.4061	0.4065	0.4066
Fair SRV	0.1407	0.1525	0.1573	0.1587	0.1603	0.1607
Poor SRV	0.0496	0.0566	0.0602	0.0615	0.0637	0.0664
Mortality	N/A	0.0540	0.0468	0.0501	0.0538	0.0577
Employment	0.3830	0.4408	0.4208	0.3839	0.3475	0.3097
ADL or IADL	0.2088	0.2300	0.2340	0.2453	0.2559	0.2672
HUI3	0.7627	0.7374	0.7324	0.7264	0.7198	0.7124

Notes: Results are from a cohort simulation.

eTable 6. Actual and simulated outcomes, diabetes subpopulation

Outcome	Actual HRS	Microsimulation Outcomes (Cohort)				
	2010	2010	2012	2014	2016	2018
Excellent SRV	0.2927	0.2758	0.2730	0.2653	0.2640	0.2586
Good SRV	0.4265	0.4159	0.4007	0.4078	0.4028	0.4026
Fair SRV	0.1946	0.2137	0.2101	0.2086	0.2104	0.2100
Poor SRV	0.0862	0.0946	0.1163	0.1183	0.1228	0.1288
Mortality	N/A	0.0813	0.0794	0.0834	0.0870	0.0922
Employment	0.2846	0.3135	0.2987	0.2676	0.2377	0.2063
ADL or IADL	0.3118	0.3542	0.3535	0.3692	0.3817	0.3921
HUI3	0.6167	0.6477	0.6448	0.6372	0.6293	0.6213

Notes: Results are from a cohort simulation.

3. Mapping VA to SRV

3.1. SRV Data Checks

We conducted several analyses to explore the suitability of SRV as a measure of vision. First, we used the HRS to check the correlation between overall SRV and near and distance vision (both self-reported) and the stability of the relationship across study waves (eeTable 7-eeTable 10). Second, we checked whether the relationship between VA and SRV was relatively stable over the years when NHANES collected vision data (eeTable 11). Finally, we used the NHIS to confirm that the SRV distribution has been relatively stable since 2008 (eeTable 12).

eTable 7. Correlation between Overall, Distance, and Near SRV

		Waves 5-12	Wave 5	Wave 6	Wave 7	Wave 8	Wave 9	Wave 10	Wave 11	Wave 12
Full sample	Distance SRV	0.687	0.717	0.713	0.691	0.697	0.668	0.659	0.672	0.682
	Near SRV	0.679	0.718	0.713	0.689	0.698	0.664	0.643	0.656	0.660
Diabetes, over age 50	Distance SRV	0.688	0.717	0.713	0.694	0.697	0.669	0.662	0.674	0.683
	Near SRV	0.681	0.718	0.714	0.690	0.700	0.665	0.647	0.658	0.661

eTable 8. Distribution of Distance and Overall SRV

		SRV (Overall)			
		Excellent	Good	Fair	Poor
Distance SRV	Excellent	67.03%	26.53%	5.58%	0.87%
	Good	12.43%	67.32%	17.34%	2.91%
	Fair	2.94%	17.95%	64.94%	14.17%
	Poor	1.08%	6.56%	19.05%	73.31%

Notes: Results generated using HRS waves 5-12 pooled. Sample was limited to people with diabetes over the age of 50. Excellent SRV combines the 'Excellent' and 'Very Good' responses in the HRS; Poor SRV combines the 'Poor' and 'Blind' responses in the HRS.

eTable 9. Distribution of Near and Overall SRV

		SRV (Overall)			
		Excellent	Good	Fair	Poor
Near SRV	Excellent	71.82%	23.42%	4.18%	0.57%
	Good	15.62%	67.09%	14.99%	2.3%
	Fair	5.93%	26.03%	57.12%	10.92%
	Poor	3.8%	12.08%	26.91%	57.2%

Notes: Results generated using HRS waves 5-12 pooled. Sample was limited to people with diabetes over the age of 50. Excellent SRV combines the 'Excellent' and 'Very Good' responses in the HRS; Poor SRV combines the 'Poor' and 'Blind' responses in the HRS.

eTable 10. Distribution of Near and Distance SRV

		Distance SRV			
		Excellent	Good	Fair	Poor
Near SRV	Excellent	83.04%	14.54%	1.97%	0.45%
	Good	21.03%	70.23%	7.12%	1.62%
	Fair	16.21%	37.62%	39.42%	6.75%
	Poor	12.1%	25.52%	18.16%	44.22%

Notes: Results generated using HRS waves 5-12 pooled. Sample was limited to people with diabetes over the age of 50. Excellent SRV combines the 'Excellent' and 'Very Good' responses in the HRS; Poor SRV combines the 'Poor' and 'Blind' responses in the HRS.

eTable 11. SRV Distribution by VA and NHANES Survey Year

		SRV Category			
	NHANES sample	Excellent	Good	Fair	Poor
Better eye: VA 20/20-20/40	1999-2000	22.18%	48.5%	23.24%	6.08%
	2001-2002	24.23%	53.55%	17.68%	4.53%
	2003-2004	30.53%	47.86%	18.12%	3.49%
	2005-2006	28.41%	52.21%	16.29%	3.09%
	2007-2008	24.5%	51.43%	20.09%	3.98%
Better eye: VA worse than 20/40	1999-2000	11.11%	34.92%	30.69%	23.28%
	2001-2002	10.63%	43.48%	28.5%	17.39%
	2003-2004	13.73%	37.34%	32.62%	16.31%
	2005-2006	10.78%	39.22%	28.92%	21.08%
	2007-2008	10.43%	39.21%	32.01%	18.35%
Worse eye: VA 20/20-20/40	1999-2000	25.25%	49.36%	20.62%	4.78%
	2001-2002	27.16%	54.17%	15.75%	2.92%
	2003-2004	33.88%	47.49%	15.68%	2.96%
	2005-2006	31.11%	51.63%	15.02%	2.24%

	2007-2008	25.9%	53.96%	17.1%	3.04%
Worse eye: VA worse than 20/40	1999-2000	11.33%	41.95%	31.86%	14.87%
	2001-2002	12.52%	48.56%	26.06%	12.86%
	2003-2004	17.14%	44.76%	28.73%	9.37%
	2005-2006	15.81%	48.85%	23.8%	11.55%
	2007-2008	16.26%	41.23%	31.24%	11.27%

Notes: Results generated using NHANES 1999-2008 data; sample included all individuals who had non-missing vision data from the exam portion of the survey. The 'Poor' SRV category combines 'Poor' and 'Very Poor' responses form NHANES.

eTable 12. SRV Distribution by NHIS Survey Year

	SRV Category		
Year	Excellent/Good	Fair	Poor
2010	85.5	12.6	1.9
2011	88.0	10.5	1.5
2012	83.1	15.2	1.7
2013	81.7	16.2	2.2
2014	83.5	14.5	2.0
2015	83.5	14.5	2.1
2016	84.7	13.7	1.6
2017	83.8	14.6	1.7
2018	81.4	16.6	2.0
2019	85.5	13.1	1.4
2020	84.4	14.1	1.5

Notes: Results generated using NHIS 2010-2020; sample included all individuals who had non-missing response to the question "Do you have difficulty seeing, even when wearing glasses?" Responses were coded to match the approximate distribution in the SRV categories: Excellent/Good (combined) corresponded to "No difficulty"; Fair corresponded to "Some difficulty", and Poor corresponded to "A lot of difficulty" and "Cannot do at all".

3.2. SRV Model

eeTable 13 presents the VA distribution stratified by SRV for the NHANES 2005-06 and 2007-08 waves. Although our mapping uses the diabetes population aged 50 or older, the relationship between VA distribution is similar for the full NHANES sample and the population with diabetes. The correlation between SRV and VA in the worse eye is slightly stronger than SRV and VA in the better eye irrespective of which subgroup we consider. For the diabetes population aged 50 or older, the correlation between SRV and VA in the better (worse) eye is 0.240 (0.272).

eTable 13. VA distribution stratified by SRV

		Better eye		Worse eye	
		20/40 or better	<20/40	20/40 or better	<20/40
NHANES 2005-2008 [N=9,653]	Excellent	95.2%	4.9%	84.9%	14.9%
	Good	91.7%	8.4%	76.9%	23.0%
	Fair	84.2%	15.8%	62.3%	37.8%
	Poor	66%	34.1%	42.1%	57.9%
Diabetes population [N=1,085]	Excellent	95.7%	4.3%	78.1%	21.9%
	Good	90.1%	9.9%	70.0%	30.0%
	Fair	79%	21.0%	53.7%	46.3%
	Poor	60%	40.0%	34.5%	65.6%
	Excellent	96.0%	4.0%	78.2%	21.9%

Diabetes population age 50+ [N=882]	Good	90.3%	9.7%	68.5%	31.5%
	Fair	78.4%	21.6%	52.0%	48.1%
	Poor	56.4%	43.6%	32.1%	67.9%

Notes: Results derived using NHANES 2005-06 and 2007-08 waves pooled. The 'Poor' SRV category combines Poor and Very Poor responses in NHANES.

eTable 14. SRV Model: Estimated Coefficients for VA Variables

Visual acuity	Better eye	Worse eye
20/25	0.0274 (0.1057)	0.2081 (0.1309)
20/30	-0.041* (0.1490)	0.3851** (0.1563)
20/40	0.2618 (0.1967)	0.1491 (0.1740)
20/50	0.4866*** (0.1755)	0.6436*** (0.1694)
20/60	0.6151 (0.6089)	0.2215 (0.2515)
20/80	0.5611 (0.4291)	0.7101** (0.2837)
20/200	0.7117 (0.3770)	0.8574*** (0.2152)
<20/200	2.5085*** (0.7739)	0.9947*** (0.2702)

Notes: Regression coefficients from an ordered probit model where the dependent variable is the four SRV categories (1=Excellent; 2=Good; 3=Fair; 4=Poor) and the sample was restricted to people with diabetes over the age of 50. Model includes controls for sex, race/ethnicity, age, and time since diabetes diagnosis. 20/20 is the omitted VA category. A positive coefficient implies that a person is more likely to have worse SRV relative to someone with 20/20 vision. This model was used to generate predictions for the starting vision distributions (see Table 1 in the main paper). Significance: ***p<0.01; **p<0.05; *p<0.1

eTable 15. SRV Model: Estimated Coefficients for Demographic Variables

Variable	Coefficient (standard error)
Female	0.0415 (0.0764)
Hispanic	0.0970 (0.1188)
Black	0.1166 (0.1024)
Age 55-59	0.1006 (0.1297)
Age 60-64	-0.066 (0.1297)
Age 65-69	-0.154 (0.1302)
Age 70-74	-0.408 (0.1431)
Age 75+	-0.174 (0.1344)

Years since diabetes diagnosis	-0.004 (0.0033)

Notes: Regression coefficients from an ordered probit model where the dependent variable is the four SRV categories (1=Excellent; 2=Good; 3=Fair; 4=Poor) and the sample was restricted to people with diabetes over the age of 50. Model also includes controls for VA in better and worse eye. A positive coefficient implies that a person is more likely to have worse SRV. Significance: ***p<0.01; **p<0.05; *p<0.1

We adjusted the estimated cut points for the model to ensure the predicted SRV distribution matched that of the microsimulation data (i.e., HRS) rather than NHANES. The results presented in eeTable 16 imply that matching the HRS distribution requires two modifications to the original model: 1) shifting some people from the good to the excellent and fair SRV categories and 2) shifting some people from the poor to fair SRV category.

eTable 16. Estimated and modified SRV category model cut points

	Original model cut points (NHANES distribution)	Final cut points (Match HRS distribution)
Cutpoint 1	-0.6074	-0.2845
Cutpoint 2	0.9098	0.9142
Cutpoint 3	2.0932	1.8613

4. Untreated Scenario Implementation

First, we use the baseline data from Protocol T to classify each person's DME severity according to area and degree of retinal thickening.[2] Next, to derive their counterfactual (untreated) VA in year 2, we subtract the mean vision loss for the relevant severity category. Finally, we use the counterfactual VA data and Protocol T demographics to predict SRV using the model described in Section 3. eeTable 17 provides a summary of the mean VA for the Protocol T and counterfactual, and eeTable 18 shows how the data and counterfactual translate to the VA categories used in our mapping.

eTable 17. Protocol T and Untreated Counterfactual Mean VA (Letters)

		Mean VA (letters)		
DME severity	N (%)	Baseline Protocol T	2-year (VEGF) Protocol T	2-year Untreated Counterfactual
1	54 (8.7)	68.1	79.4	62.5
2	41 (6.7)	69.6	79.2	59.6
3	32 (5.2)	68.5	80.6	58.2
4	58 (9.4)	68.2	77.8	57.6
5 (worst)	431 (70.0)	63.5	75.7	50.9
Full sample	616	64.9	76.7	53.5

eTable 18. Protocol T and Untreated Counterfactual VA Distribution

	Baseline Protocol T	2-year (VEGF) Protocol T	2-year Untreated Counterfactual
20/20	0.0	43.7	0.0
20/25	12.4	21.1	0.0
20/30	27.3	14.3	1.0
20/40	20.5	6.9	6.0
20/50	11.5	5.0	22.2

20/60	9.6	2.8	25.3
20/80	5.8	1.6	14.3
20/200	10.8	2.8	22.2
<20/200	2.3	1.8	8.9

5. Cohort estimate input parameters

eeTable 19 presents baseline inputs used to generate cohort level estimates and their sources. Our cohort size (N=1,108,500) was derived by applying the DME incidence rate to the total US population with diabetes aged 45 or older. We then scaled up the individual level results from the microsimulation model based on the 2020 Vestrum treatment mix to derive the benefit of current treatment for DME in the U.S.

eTable 19. Cohort Estimates: Input Parameters

	Value	Source
Population parameters		
U.S. population with diabetes, aged ≥ 45	29,100,000	CDC (2020) [3]
DME incidence	0.038	Varma et al (2014) [4]
Mean age at baseline	62.78	DRCR Protocol T [5]
Share with Excellent SRV at baseline	0.2460	DRCR Protocol T [5]; VA to SRV mapping
Share with Good SRV at baseline	0.3954	DRCR Protocol T [5]; VA to SRV mapping
Share with Fair SRV at baseline	0.2285	DRCR Protocol T [5]; VA to SRV mapping
Share with Poor SRV at baseline	0.1300	DRCR Protocol T [5]; VA to SRV mapping
Treatment weights		
Untreated	0.28	Vestrum 2020 analysis
Treated with anti-VEGFs	0.68	Vestrum 2020 analysis
Treated with laser monotherapy	0.03	Vestrum 2020 analysis
Treated with steroid monotherapy	0.01	Vestrum 2020 analysis
Annual treatment cost		
Untreated	$478.65	Includes cost of office visits
Anti-VEGF treatment (real world frequency)	Year 1: 4,369.4 Year 2+: 3277.1	Includes cost of office visit, eye injection, and weighted average of drug cost
Anti-VEGF treatment (Protocol T frequency)	Year 1: $10,923.60 Year 2: 6,554.10 Year 3+: $1,092.40	Includes cost of office visit, eye injection, and weighted average of drug cost
Laser treatment	Year 1: $2075.40 Year 2+: 478.65	Includes cost of office visits, laser therapy
Steroid treatment*	Year 1: $1304.10 Year 2-3:$978.40	Includes cost of office visit, eye injection, and weighted average of drug cost

Notes: See eTable 20 and eTable 21 for drug weights, treatment frequencies, and components of cost parameters used to derive annual treatment costs. *Steroid treatment cost follows a 3 year cycle for the duration of the 20 year time horizon.

eTable 20. Treatment Frequency and Drug Weights

Treatment Type	Drug weights	Treatment frequency scenario	
		Real world treatment frequency	Protocol T treatment frequency
Anti-VEGF	Bevacizumab: 45% Aflibercept: 36% Ranibizumab: 19%	Year 1: 4 injections Year 2+: 3 injections	Year 1: 10 injections Year 2: 6 injections Year 3+: 1 injection
Laser	N/A	Year 1: 3 treatments Year 2+: 4 office visits (no treatments)	
Steroid	Dexamethasone implant: 64% Triamcinolone acetonide: 33% Fluocinolone implant: 3%	Dexamethasone intravitreal implant: 0.75 injections per year Triamcinolone acetonide: 3 injections (year 1); 1 injection (years 2+) Fluocinolone intravitreal implant: 0.33 injections per year	
Untreated	N/A	4 office visits per year	

Notes: Drug weights and real world treatment frequency derived from authors' analysis of Vestrum 2020 data. Protocol T treatment frequency based on mean injection data from DRCR Protocol T.[5]

eTable 21. Cost Parameter Components (2022 USD)

Description	**CPT Code**	**Cost**
Office visit	99214	$119.66
Laser treatment	67210	$532.24
Injection cost (eye drug)	67028	$107.72
Bevacizumab (1.25mg)	J9035	$67.86
Aflibercept (2mg)	J9400	$1,841.50
Ranibizumab (0.3mg)	J2778	$921.60
Triamcinolone Acetonide (1mg)	J3304	$17.63
Dexamethasone intravitreal implant (0.7mg)	J7312	$1400.00
Fluocinolone intravitreal implant	See note	$7500.00

Note: Costs are from the 2022 Physician Fee Schedule[6]. Fluocinolone intravitreal implant was not priced by CMS at the time of our model development; cost reflects the wholesale acquisition cost.

6. Sensitivity analyses

eTable 22. Simulated lifetime outcomes for a hypothetical 51-year old, treatment durability = 6 years

		Untreated	Anti-VEGF	Laser	Steroid
Vision outcomes	Years with Excellent or Good SRV	15.5	17.1	16.5	16.5
	Years with Fair or Poor SRV	12.5	11.8	11.9	12.0
Direct effects	Life expectancy (years)	28.0	28.8	28.5	28.5
	Quality-adjusted life years	16.3	17.3	16.8	16.8
	QALY ($)	1,680,698	1,774,349	1,728,763	1,734,005
Indirect effects	Disability free life years	15.7	16.8	16.2	16.3
	Years claiming disability	2.9	2.5	2.7	2.7
	Disability benefits ($)	14,392	12,433	13,738	13,295
	Years working	8.1	8.5	8.3	8.3
	Earnings ($)	161,613	188,096	176,133	176,111

Notes: The value of a QALY is assumed to be $150,000. Future dollar values are discounted at a rate of 3% per year. Disability benefits reflect government disability payments to an individual, which implies anti-VEGF, laser, or steroid treatment results in savings to the government.

eTable 23. Simulated lifetime outcomes for a hypothetical 51-year old, treatment durability = 12 years

		Untreated	Anti-VEGF	Laser	Steroid
Vision outcomes	Years with Excellent or Good SRV	15.5	17.5	17.0	16.9
	Years with Fair or Poor SRV	12.5	11.4	11.5	11.6
Direct effects	Life expectancy (years)	28.0	28.9	28.5	28.5
	Quality-adjusted life years	16.3	17.4	16.9	17.0
	QALY ($)	1,680,698	1,786,537	1,740,987	1,746,398
Indirect effects	Disability free life years	15.7	16.9	16.3	16.4
	Years claiming disability	2.9	2.5	2.7	2.6
	Disability benefits ($)	14,392	12,191	13,474	13,032
	Years working	8.1	8.6	8.4	8.4
	Earnings ($)	161,613	189,731	177,774	177,784

Notes: The value of a QALY is assumed to be $150,000. Future dollar values are discounted at a rate of 3% per year. Disability benefits reflect government disability payments to an individual, which implies anti-VEGF, laser, or steroid treatment results in savings to the government.

eTable 24. Simulated lifetime outcomes for a hypothetical 51-year old, treatment durability = 2 years

		Untreated	Anti-VEGF	Laser	Steroid
Vision outcomes	Years with Excellent or Good SRV	15.5	16.9	16.3	16.3
	Years with Fair or Poor SRV	12.5	12.0	12.1	12.2
Direct effects	Life expectancy (years)	28.0	28.8	28.4	28.4
	Quality-adjusted life years	16.3	17.2	16.7	16.8
	QALY ($)	1,680,698	1,765,729	1,720,011	1,725,457
Indirect effects	Disability free life years	15.7	16.7	16.1	16.2
	Years claiming disability	2.9	2.5	2.7	2.7
	Disability benefits ($)	14,392	12,570	13,862	13,429
	Years working	8.1	8.5	8.3	8.3
	Earnings ($)	161,613	187,499	175,558	175,517

Notes: The value of a QALY is assumed to be $150,000. Future dollar values are discounted at a rate of 3% per year. Disability benefits reflect government disability payments to an individual, which implies anti-VEGF, laser, or steroid treatment results in savings to the government.

eTable 25. Cohort Sensitivity Analysis: Treatment Durability Assumptions

		Net Value (USD, billions)	
Durability assumption	Time horizon	Treatment frequency assumption	
		"Real world" 4 injections in year 1 3 in year 2+	"Protocol T" 10 injections in year 1 6 in year 2 1 in year 3+
Permanent	2 years	1.0	-5.8
	5 years	10.0	6.9
	10 years	25.3	26.4
	20 years	47.8	52.8
12 years	2 years	1.0	-5.8
	5 years	9.5	6.4
	10 years	21.6	22.7
	20 years	34.2	39.1
6 years	2 years	1.0	-5.8
	5 years	9.0	5.9
	10 years	18.6	19.6
	20 years	28.1	33.1
2 years	2 years	1.0	-5.8
	5 years	8.5	5.3
	10 years	14.2	15.2
	20 years	16.5	21.5

Notes: Net value calculated as total benefit minus total cost. Results assume value of a QALY equal to $150K.

eTable 26. Cohort Sensitivity Analysis: Value of a QALY

	Real world treatment frequency			Protocol T treatment frequency		
	QALY Value			QALY Value		
	$50K	$100K	$300K	$50K	$100K	$300K
Two-year horizon						
Direct benefit	1.5	3.0	9.1	1.5	3.0	9.1
Indirect benefit	1.05	1.05	1.05	1.05	1.05	1.05
Total cost	4.6	4.6	4.6	11.4	11.4	11.4
Net value	-2.1	-0.6	5.6	-8.9	-7.4	-1.3
Five-year horizon						
Direct benefit	5.5	11.0	32.0	5.5	11.0	32.0
Indirect benefit	2.87	2.87	2.87	2.87	2.87	2.87
Total cost	9.3	9.3	9.3	12.5	12.5	12.5
Net value	-0.9	4.6	25.6	-4.1	1.4	22.4
Twenty-year horizon						
Direct benefit	21.0	42.0	126.1	21.0	42.0	126.1
Indirect benefit	4.76	4.76	4.76	4.76	4.76	4.76
Total cost	20.0	20.0	20.0	15.0	15.0	15.0
Net value	5.8	26.8	110.9	10.8	31.8	115.9

Notes: All values are in USD (billions). Results assume permanent treatment durability.

eTable 27. Cohort Sensitivity Analysis: Annual Weighted Drug Cost of Anti-VEGFs

	Real world treatment frequency			Protocol T treatment frequency		
	Annual cost of anti-VEGF drugs			Annual cost of anti-VEGF drugs		
	$432.49 (-50%)	$864.98 (Main)	$1,297.47 (+50%)	$432.49 (-50%)	$864.98 (Main)	$1,297.47 (+50%)
Two-year horizon						
Total benefit	5.6	5.6	5.6	5.6	5.6	5.6
Total cost	2.6	4.6	6.7	6.7	11.4	16.2
Net value	3.0	1.0	-1.1	-1.1	-5.8	-10.6
Five-year horizon						
Total benefit	19.4	19.4	19.4	19.4	19.4	19.4
Total cost	5.1	9.3	13.5	7.0	12.5	18.0
Net value	14.3	10.1	5.9	12.4	6.9	1.4
Twenty-year horizon						
Total benefit	67.8	67.8	67.8	67.8	67.8	67.8
Total cost	10.9	20.0	29.0	7.9	15.0	22.1
Net value	56.9	47.8	38.8	59.9	52.8	45.7

Notes: All values are in USD (billions). Results assume permanent treatment durability and value of a QALY equal to $150K.

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