Supplemental Materials

Supplemental Tables

eTable 1. Cumulative risk of colon cancer by age and gene

Age at Cumulative Risk Estimate	Cumulative Risk	Range for Sensitivity Analysis	Reference
MLH1			[1,2]
30 years	6.45%	5.805%-7.095%	
40 years	19.9%	17.91%-21.89%	
50 years	33.45%	30.11%-36.80%	
60 years	45.60%	50.16%-41.04%	
70 years	56.70%	51.03%-62.37%	
MSH2			[1,2]
30 years	1.21%	1.09%-1.33%	
40 years	5.77%	5.19%-6.35%	
50 years	16.50%	14.85%-18.15%	
60 years	30.05%	27.05%-33.06%	
70 years	46.68%	42.01%-51.35%	
MSH6			[1,3]
40 years	1.04%	0.93%-1.14%	
50 years	2.67%	2.40%-2.94%	
60 years	6.88%	6.19%-7.57%	
70 years	15.35%	13.82%-16.89%	
PMS2			[1,4,5]
40 years	0.49%	0.44%-0.54%	
50 years	1.37%	1.23%-1.50%	
60 years	4.27%	3.84%-4.70%	
70 years	8.74%	7.87%-9.61%	

eTable 2. Cancer stage at diagnosis at varying colonoscopy surveillance intervals

Surveillance Interval	Stage I	Stage II	Stage III	Stage IV	Reference
No Surveillance	40%	36%	19%	5%	[6]
1 Year	53%	29%	17%	1%	[7,8]
2 Years	53%	29%	17%	1%	[7,8]
3 Years	47%	42%	9%	2%	[7,8]
≥ 4 Years	47%	42%	9%	2%	[7,8]

eTable 3. Modeled outcomes under current management guidelines

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost
MLH1	Q1Y, Start age: 25 (Current Guidelines)	29.506	46.477	17.04%	2.43%	$40,783.80
MSH2	Q1Y, Start age: 25 (Current Guidelines)	29.699	46.734	13.27%	1.57%	$29,298.71
MSH6	Q1Y, Start age: 25 (Current Guidelines)	29.835	46.916	4.38%	0.43%	$25,999.77
PMS2	Q1Y, Start age: 25 (Current Guidelines)	29.853	46.938	2.05%	0.22%	$25,094.03

QALYs: quality-adjusted life-years, CRC: colorectal cancer

eTable 4. Modeled outcomes with no intervention

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost
MLH1	Natural History	27.730	43.562	57.46%	15.54%	$105,496.21
MSH2	Natural History	28.933	45.329	47.65%	10.21%	$51,932.14
MSH6	Natural History	29.814	46.644	18.66%	3.06%	$12,920.36
PMS2	Natural History	29.902	46.768	9.20%	1.66%	$7,073.75

QALYs: quality-adjusted life-years, CRC: colorectal cancer

eTable 5. Outcomes of All Strategies by gene

eTable 5a. MLH1 Model Outcomes

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
MLH1	Q5Y, Start age: 40 (Family History Guidelines)	27.867	43.557	52.80%	13.95%	$102,074.89	Dominated
MLH1	Q5Y, Start age: 35	27.939	43.239	52.15%	13.49%	$99,038.00	Dominated
MLH1	Q5Y, Start age: 30	28.034	43.132	51.49%	12.98%	$95,114.62	Dominated
MLH1	Q4Y, Start age: 40	28.040	44.557	45.74%	12.26%	$94,716.12	Dominated
MLH1	Q5Y, Start age: 25	28.157	44.249	50.85%	12.44%	$88,995.03	Dominated
MLH1	Q4Y, Start age: 35	28.191	45.191	44.03%	11.35%	$88,292.80	Dominated
MLH1	Q1Y, Start age: 40	28.342	45.732	30.58%	8.85%	$84,600.56	Dominated
MLH1	Q3Y, Start age: 40	28.291	45.428	34.42%	9.68%	$84,387.14	Dominated
MLH1	Q2Y, Start age: 40	28.320	45.824	33.14%	9.31%	$83,594.89	Dominated
MLH1	Q4Y, Start age: 30	28.385	45.151	42.32%	10.35%	$79,934.64	Dominated
MLH1	Q1Y, Start age: 35	28.630	45.838	26.18%	6.95%	$74,287.70	Dominated
MLH1	Q3Y, Start age: 35	28.558	45.241	30.75%	8.05%	$73,022.45	Dominated
MLH1	Q2Y, Start age: 35	28.596	45.560	29.24%	7.56%	$72,757.00	Dominated
MLH1	Q4Y, Start age: 25	28.637	45.152	40.59%	9.24%	$68,679.24	Dominated
MLH1	Q1Y, Start age: 30	29.003	45.850	21.75%	4.87%	$60,638.67	Dominated

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
MLH1	Q3Y, Start age: 30	28.896	45.716	27.07%	6.28%	$58,993.77	Dominated
MLH1	Q2Y, Start age: 30	28.956	46.068	25.31%	5.64%	$57,888.51	Dominated
MLH1	Q1Y, Start age: 25 (Current Guidelines)	29.506	46.447	17.04%	2.48%	$40,783.80	$44,790.96
MLH1	Q3Y, Start age: 25	29.347	46.138	23.19%	4.26%	$38,982.50	Dominated
MLH1	Q2Y, Start age: 25	29.433	46.291	21.16%	3.45%	$37514.06	--

QALYs: quality-adjusted life-years, CRC: colorectal cancer

eTable 5b. MSH2 Model Outcomes

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
MSH2	Q5Y, Start age: 40 (Family History Guidelines)	29.032	45.900	42.36%	8.53%	$51,362.57	Dominated
MSH2	Q5Y, Start age: 35	29.052	45.779	42.11%	8.35%	$50,569.52	Dominated
MSH2	Q5Y, Start age: 30	29.078	45.539	41.79%	8.27%	$49,769.34	Dominated

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
MSH2	Q5Y, Start age: 25	29.093	45.687	41.63%	8.05%	$48,531.17	Dominated
MSH2	Q4Y, Start age: 40	29.192	45.853	34.30%	6.79%	$44,485.53	Dominated
MSH2	Q4Y, Start age: 35	29.248	45.842	33.58%	6.41%	$42,151.82	Dominated
MSH2	Q4Y, Start age: 30	29.292	46.138	33.58%	6.41%	$40,520.20	Dominated
MSH2	Q4Y, Start age: 25	29.329	46.050	32.67%	5.91%	$38,928.68	Dominated
MSH2	Q1Y, Start age: 40	29.467	46.192	17.12%	3.34%	$35,386.00	Dominated
MSH2	Q3Y, Start age: 40	29.423	46.311	21.46%	4.16%	$35,000.25	Dominated
MSH2	Q2Y, Start age: 40	29.448	46.237	20.01%	3.80%	$34265.87	Dominated
MSH2	Q1Y, Start age: 30	29.627	46.442	14.22%	2.08%	$33,265.61	Dominated
MSH2	Q1Y, Start age: 35	29.571	46.315	15.23%	2.53%	$33,103.20	Dominated
MSH2	Q1Y, Start age: 25	29.699	46.734	13.27%	1.61%	$32,261.21	$2,009,850.42
MSH2	Q2Y, Start age: 35	29.554	46.462	18.34%	3.06%	$30,841.79	Dominated
MSH2	Q3Y, Start age: 35	29.530	46.186	19.89%	3.46%	$30,477.17	Dominated
MSH2	Q2Y, Start age: 30	29.620	46.547	17.42%	2.63%	$28,819.34	Dominated
MSH2	Q3Y, Start age: 30	29.593	46.443	19.01%	3.06%	$28,570.21	Dominated
MSH2	Q2Y, Start age: 25	29.696	46.643	16.57%	2.20%	$26,231.66	$29,298.71
MSH2	Q3Y, Start age: 25	29.668	46.568	18.21%	2.66%	$25,323.40	--

QALYs: quality-adjusted life-years, CRC: colorectal cancer

eTable 5c. MSH6 Model Outcomes

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
MSH6	Q1Y, Start age: 25	29.835	46.916	4.38%	0.44%	$25,999.77	Dominated
MSH6	Q1Y, Start age: 30	29.843	46.871	4.64%	0.56%	$23,532.68	Dominated
MSH6	Q1Y, Start age: 35	29.852	46.899	4.90%	0.68%	$20,505.33	Dominated
MSH6	Q5Y, Start age: 30	29.778	46.675	15.79%	2.38%	$19,017.17	Dominated
MSH6	Q5Y, Start age: 25	29.771	46.678	15.74%	2.35%	$18,812.71	Dominated
MSH6	Q5Y, Start age: 35	29.784	46.690	15.85%	2.41%	$18,343.68	Dominated
MSH6	Q5Y, Start age: 40	29.785	46.684	15.95%	2.46%	$18,164.77	Dominated
MSH6	Q1Y, Start age: 40	29.863	46.869	5.17%	0.78%	$17,869.17	Dominated
MSH6	Q2Y, Start age: 25	29.886	46.896	5.54%	0.60%	$17,443.38	Dominated
MSH6	Q4Y, Start age: 25	29.825	46.764	11.77%	1.67%	$16,997.13	Dominated
MSH6	Q2Y, Start age: 30	29.884	46.877	5.78%	0.71%	$16,686.72	Dominated
MSH6	Q4Y, Start age: 30	29.829	46.746	11.90%	1.73%	$16,655.23	Dominated
MSH6	Q4Y, Start age: 35	29.830	46.730	12.02%	1.79%	$16,309.91	Dominated
MSH6	Q4Y, Start age: 40	29.827	46.772	12.18%	1.86%	$16,296.75	Dominated
MSH6	Q2Y, Start age: 35	29.881	46.818	6.02%	0.82%	$15,926.33	Dominated
MSH6	Q3Y, Start age: 30	29.892	46.840	6.36%	0.82%	$14,871.72	Dominated
MSH6	Q3Y, Start age: 25	29.895	46.842	6.13%	0.72%	$14,813.35	$246,980.73

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
MSH6	Q2Y, Start age: 40	29.882	46.810	6.27%	0.92%	$14,736.66	Dominated
MSH6	Q3Y, Start age: 40	29.885	46.823	6.83%	1.02%	$14,272.85	Dominated
MSH6	Q3Y, Start age: 35	29.892	46.837	6.56%	0.92%	$14,072.41	--

QALYs: quality-adjusted life-years, CRC: colorectal cancer

eTable 5d. PMS2 Model Outcomes

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
PMS2	Q1Y, Start age: 25	29.853	46.938	2.05%	0.23%	$25,094.03	Dominated
PMS2	Q1Y, Start age: 30	29.875	46.931	2.18%	0.29%	$22,016.02	Dominated
PMS2	Q1Y, Start age: 35	29.894	46.934	2.33%	0.35%	$18,555.61	Dominated
PMS2	Q2Y, Start age: 25	29.910	46.927	2.61%	0.31%	$16,213.19	Dominated
PMS2	Q1Y, Start age: 40	29.915	46.906	2.45%	0.39%	$15,488.07	Dominated
PMS2	Q2Y, Start age: 30	29.922	46.925	2.73%	0.37%	$14,875.89	Dominated
PMS2	Q5Y, Start age: 30	29.873	46.829	7.71%	1.29%	$14,495.62	Dominated
PMS2	Q5Y, Start age: 25	29.863	46.804	7.68%	1.27%	$14,449.22	Dominated
PMS2	Q4Y, Start age: 25	29.890	46.853	5.66%	0.89%	$13,856.57	Dominated
PMS2	Q2Y, Start age: 35	29.927	46.924	2.86%	0.43%	$13,704.22	Dominated
PMS2	Q5Y, Start age: 35	29.883	46.806	7.73%	1.30%	$13,657.54	Dominated
PMS2	Q3Y, Start age: 25	29.926	46.919	2.86%	0.38%	$13,359.57	Dominated
PMS2	Q5Y, Start age: 40	29.887	46.817	7.80%	1.32%	$13,349.79	Dominated
PMS2	Q4Y, Start age: 30	29.902	46.852	5.73%	0.92%	$13,186.89	Dominated
PMS2	Q3Y, Start age: 30	29.933	46.919	3.01%	0.43%	$12,866.76	Dominated
PMS2	Q4Y, Start age: 35	29.909	46.849	5.79%	0.95%	$12,578.88	Dominated
PMS2	Q4Y, Start age: 40	29.912	46.858	5.88%	0.99%	$12,328.57	Dominated

Gene	Strategy	QALYs	Life-Years	CRC Incidence	CRC Death	Cost	ICER
PMS2	Q2Y, Start age: 40	29.938	46.891	2.98%	0.47%	$12,108.99	Dominated
PMS2	Q3Y, Start age: 35	29.940	46.908	3.13%	0.48%	$11,672.08	Dominated
PMS2	Q3Y, Start age: 40	29.941	46.890	3.25%	0.52%	$11,491.14	--

QALYs: quality-adjusted life-years, CRC: colorectal cancer

eTable 6. One-way Sensitivity Analysis (OWSA) Results by Gene

eTable 6a. MLH1 One-Way Sensitivity Analysis (OWSA) Results

Costs						
Parameter	**High Value**	**Low Value**	**High Optimal Strategy**	**High ICER**	**Low Optimal Strategy**	**Low ICER**
Colonoscopy without biopsy	$1,174.97	$783.31	Q1Y, Start age: 25	$70,504.08	Q1Y, Start age: 25	$19,077.83
Colonoscopy with biopsy	$1,443.60	$962.40	Q1Y, Start age: 25	$44,814.32	Q1Y, Start age: 25	$44,767.59
Colectomy	$36,807.60	$24,538.40	Q1Y, Start age: 25	$44,988.61	Q1Y, Start age: 25	$44,988.61
Stage I CRC continued care	$4,017.54	$2,678.36	Q1Y, Start age: 25	$43,598.08	Q1Y, Start age: 25	$45,983.83
Stage II CRC continued care	$3,780.44	$2,520.30	Q1Y, Start age: 25	$43,559.03	Q1Y, Start age: 25	$46,022.88
Stage III CRC continued care	$5,296.57	$3,531.05	Q1Y, Start age: 25	$44,473.44	Q1Y, Start age: 25	$45,108.47
Stage IV CRC continued care	$16,041.20	$10,694.14	Q1Y, Start age: 25	$44,789.06	Q1Y, Start age: 25	$44,792.86
Stage I CRC initial care	$54,491.17	$36,327.45	Q1Y, Start age: 25	$43,849.38	Q1Y, Start age: 25	$45,732.53
Stage II CRC initial care	$73,135.19	$48,756.79	Q1Y, Start age: 25	$43,102.21	Q1Y, Start age: 25	$46,479.7
Stage III CRC initial care	$88,769.66	$59,179.78	Q1Y, Start age: 25	$44,148.92	Q1Y, Start age: 25	$45,432.99
Stage IV CRC initial care	$115,554.01	$77,036.01	Q1Y, Start age: 25	$44,624.74	Q1Y, Start age: 25	$44,957.17
Colonoscopy complications	$4,777.42	$3,184.94	Q1Y, Start age: 25	$45,006.18	Q1Y, Start age: 25	$44,745.73
Parameter	**High Value**	**Low Value**	**High Optimal**	**High ICER**	**Low Optimal**	**Low ICER**

			Strategy		**Strategy**	
Stage I CRC end-of-life care	$84,050.93	$44,666.80	Q1Y, Start age: 25	$44,212.74	Q1Y, Start age: 25	$45,369.17
Stage II CRC end-of-life care	$83,716.93	$44,488.50	Q1Y, Start age: 25	$40,678.13	Q1Y, Start age: 25	$48,903.78
Stage III CRC end-of-life care	$83,307.61	$46,928.72	Q1Y, Start age: 25	$40,440.49	Q1Y, Start age: 25	$49,141.43
Stage IV CRC end-of-life care	$116,399.88	$61,857.64	Q1Y, Start age: 25	$42,840.14	Q1Y, Start age: 25	$46,741.78
Quality of Life Utilities						
Stage I CRC initial care	0.9152	0.8448	Q1Y, Start age: 25	$45,520.8	Q1Y, Start age: 25	$44,042.48
Stage II CRC initial care	0.8528	0.7872	Q1Y, Start age: 25	$45,992.02	Q1Y, Start age: 25	$43,575.53
Stage III CRC initial care	0.7904	0.7296	Q1Y, Start age: 25	$45,084.96	Q1Y, Start age: 25	$44,394.92
Stage IV CRC initial care	0.312	0.288	Q1Y, Start age: 25	$44,793.82	Q1Y, Start age: 25	$44,780.03
Stage I CRC continued care	0.988	0.912	Q1Y, Start age: 25	$51,899.8	Q1Y, Start age: 25	$38,200.89
Stage II CRC continued care	0.988	0.912	Q1Y, Start age: 25	$53,946.3	Q1Y, Start age: 25	$36,840.04
Stage III CRC continued care	0.7904	0.7296	Q1Y, Start age: 25	$46,509.29	Q1Y, Start age: 25	$43,192.19
Stage IV CRC continued care	0.312	0.288	Q1Y, Start age: 25	$44,794.96	Q1Y, Start age: 25	$44,780.96
Stage I CRC end-of-life care	0.312	0.288	Q1Y, Start age: 25	$45,120.8	Q1Y, Start age: 25	$44,442.48

Stage II CRC end-of-life care	0.312	0.288	Q1Y, Start age: 25	$45,202.02	Q1Y, Start age: 25	$44,375.53
Stage III CRC end-of-life care	0.312	0.288	Q1Y, Start age: 25	$44,884.96	Q1Y, Start age: 25	$44,574.92
Stage IV CRC end-of-life care	0.312	0.288	Q1Y, Start age: 25	$44,793.82	Q1Y, Start age: 25	$44,780.03
Colonoscopy (disutility)	0.00572	0.00528	Q1Y, Start age: 25	$47,676.68	Q1Y, Start age: 25	$42,309.65
Colonoscopy complications (disutility)	0.039936	0.036864	Q1Y, Start age: 25	$44,792.38	Q1Y, Start age: 25	$44,786.86
Probabilities						
Parameter	**High Value**	**Low Value**	**High Optimal Strategy**	**High ICER**	**Low Optimal Strategy**	**Low ICER**
Lifetime CRC risk[a]			Q1Y, Start age: 25	$27,302.15	Q1Y, Start age: 25	$70,110.89
Adenoma Risk[b]			Q1Y, Start age: 25	$39,978.66	Q1Y, Start age: 25	$47,095.8
Advanced Adenoma Risk[b]			Q1Y, Start age: 25	$42,073.32	Q1Y, Start age: 25	$45,646.24
Q1Y colonoscopy interval CRC rate	0.22575	0.20425	Q1Y, Start age: 25	$84,066.92	Q1Y, Start age: 25	$26,353.94
Q2 colonoscopy interval CRC rate	0.2877	0.2603	Q1Y, Start age: 25	$22,279.12	Q2Y, Start age: 25	$107,673.35
Q3Y colonoscopy interval CRC rate	0.3192	0.2888	Q1Y, Start age: 25	$44,790.96	Q1Y, Start age: 25	$44,790.96
Q4Y colonoscopy interval CRC rate	0.63	0.57	Q1Y, Start age: 25	$44,790.96	Q1Y, Start age: 25	$44,790.96
Q5Y colonoscopy	0.87045	0.78755	Q1Y, Start	$44,790.96	Q1Y, Start	$44,790.96

interval CRC rate			age: 25		age: 25	
Colectomy death <60	0.000315	0.000285	Q1Y, Start age: 25	$44,342.76	Q1Y, Start age: 25	$45,244.77
Colectomy death 60-70	0.00084	0.00076	Q1Y, Start age: 25	$44,640.73	Q1Y, Start age: 25	$44,941.81
Colectomy death 70-80	0.00063	0.00057	Q1Y, Start age: 25	$44,779.55	Q1Y, Start age: 25	$44,802.37
Stage 1 CRC death[d]						
Stage 2 CRC death	0.01995	0.01805	Q1Y, Start age: 25	$43,374.92	Q1Y, Start age: 25	$46,282.62
Stage 3 CRC death	0.07245	0.06555	Q1Y, Start age: 25	$44,014.07	Q1Y, Start age: 25	$45,620.74
Stage 4 CRC death	0.96705	0.87495	Q1Y, Start age: 25	$44,782.34	Q1Y, Start age: 25	$44,800.45
Colonoscopy complications	0.000088	0.000072	Q1Y, Start age: 25	$44,790.96	Q1Y, Start age: 25	$44,790.96

ICER: incremental cost-effectiveness ratio, CRC: colorectal cancer.
[a]Lifetime CRC risk OWSA values can be found in eTable1
[b]Adenoma and advanced adenoma risk OWSA values can be found in References 9,10
[c]Stage 1 CRC death OWSA is represented in the colectomy death rows because Stage 1 CRC death was assumed to be from only colectomy death

eTable 6b. MSH2 One-Way Sensitivity Analysis (OWSA) Results

Costs						
Parameter	**High Value**	**Low Value**	**High Optimal Strategy**	**High ICER**	**Low Optimal Strategy**	**Low ICER**
Colonoscopy without biopsy	$1,174.97	$783.31	Q2Y, Start age: 25	$50,222.59	Q2Y, Start age: 25	$8,374.83
Colonoscopy with biopsy	$1,443.60	$962.40	Q2Y, Start age: 25	$29,313.9	Q2Y, Start age: 25	$29,283.52
Colectomy	$36,807.60	$24,538.40	Q2Y, Start age: 25	$29,298.71	Q2Y, Start age: 25	$29,298.71
Stage I CRC continued care	$4,017.54	$2,678.36	Q2Y, Start age: 25	$29,838.45	Q2Y, Start age: 25	$28,758.98

Stage II CRC continued care	$3,780.44	$2,520.30	Q2Y, Start age: 25	$27,527.91	Q2Y, Start age: 25	$31,069.52
Stage III CRC continued care	$5,296.57	$3,531.05	Q2Y, Start age: 25	$28,994.93	Q2Y, Start age: 25	$29,602.5
Stage IV CRC continued care	$16,041.20	$10,694.14	Q2Y, Start age: 25	$29,295.14	Q2Y, Start age: 25	$29,302.28
Stage I CRC initial care	$54,491.17	$36,327.45	Q2Y, Start age: 25	$29,921.85	Q2Y, Start age: 25	$28,675.57
Stage II CRC initial care	$73,135.19	$48,756.79	Q2Y, Start age: 25	$26,324.6	Q2Y, Start age: 25	$32,272.82
Stage III CRC initial care	$88,769.66	$59,179.78	Q2Y, Start age: 25	$28,604.13	Q2Y, Start age: 25	$29,993.3
Stage IV CRC initial care	$115,554.01	$77,036.01	Q2Y, Start age: 25	$28,983.25	Q2Y, Start age: 25	$29,614.17
Colonoscopy complications	$4,777.42	$3,184.94	Q2Y, Start age: 25	$29,384.23	Q2Y, Start age: 25	$29,213.2
Stage I CRC end-of-life care	$84,050.93	$44,666.80	Q2Y, Start age: 25	$29,622.02	Q2Y, Start age: 25	$28,975.4
Stage II CRC end-of-life care	$83,716.93	$44,488.50	Q2Y, Start age: 25	$25,023.33	Q2Y, Start age: 25	$33,574.1
Stage III CRC end-of-life care	$83,307.61	$46,928.72	Q2Y, Start age: 25	$25,909.92	Q2Y, Start age: 25	$32,687.51
Stage IV CRC end-of-life care	$116,399.88	$61,857.64	Q2Y, Start age: 25	$26,419.2	Q2Y, Start age: 25	$32,178.22
Quality of Life Utilities						
Parameter	**High Value**	**Low Value**	**High Optimal Strategy**	**High ICER**	**Low Optimal Strategy**	**Low ICER**
Stage I CRC initial care	0.9152	0.8448	Q2Y, Start age: 25	$29,068.65	Q2Y, Start age: 25	$29,530.87

Stage II CRC initial care	0.8528	0.7872	Q2Y, Start age: 25	$30,077.56	Q2Y, Start age: 25	$28,537.17
Stage III CRC initial care	0.7904	0.7296	Q2Y, Start age: 25	$29,433.96	Q2Y, Start age: 25	$29,164.57
Stage IV CRC initial care	0.312	0.288	Q2Y, Start age: 25	$29,317.6	Q2Y, Start age: 25	$29,280.43
Stage I CRC continued care	0.988	0.912	Q2Y, Start age: 25	$26,292.96	Q2Y, Start age: 25	$32,583.09
Stage II CRC continued care	0.988	0.912	Q2Y, Start age: 25	$42,409.56	Q2Y, Start age: 25	$19,723.92
Stage III CRC continued care	0.7904	0.7296	Q2Y, Start age: 25	$30,357.57	Q2Y, Start age: 25	$28,271.09
Stage IV CRC continued care	0.312	0.288	Q2Y, Start age: 25	$29,300.54	Q2Y, Start age: 25	$29,297.48
Stage I CRC end-of-life care	0.312	0.288	Q2Y, Start age: 25	$28,935.38	Q2Y, Start age: 25	$29,644.34
Stage II CRC end-of-life care	0.312	0.288	Q2Y, Start age: 25	$29,819.62	Q2Y, Start age: 25	$28,941.48
Stage III CRC end-of-life care	0.312	0.288	Q2Y, Start age: 25	$29,429.43	Q2Y, Start age: 25	$29,078.12
Stage IV CRC end-of-life care	0.312	0.288	Q2Y, Start age: 25	$29,330.17	Q2Y, Start age: 25	$29,134.03
Colonoscopy (disutility)	0.00572	0.00528	Q2Y, Start age: 25	$31,186.16	Q2Y, Start age: 25	$27,507.1
Colonoscopy complications (disutility)	0.039936	0.036864	Q2Y, Start age: 25	$29,309.64	Q2Y, Start age: 25	$29,288.38
Probabilities						

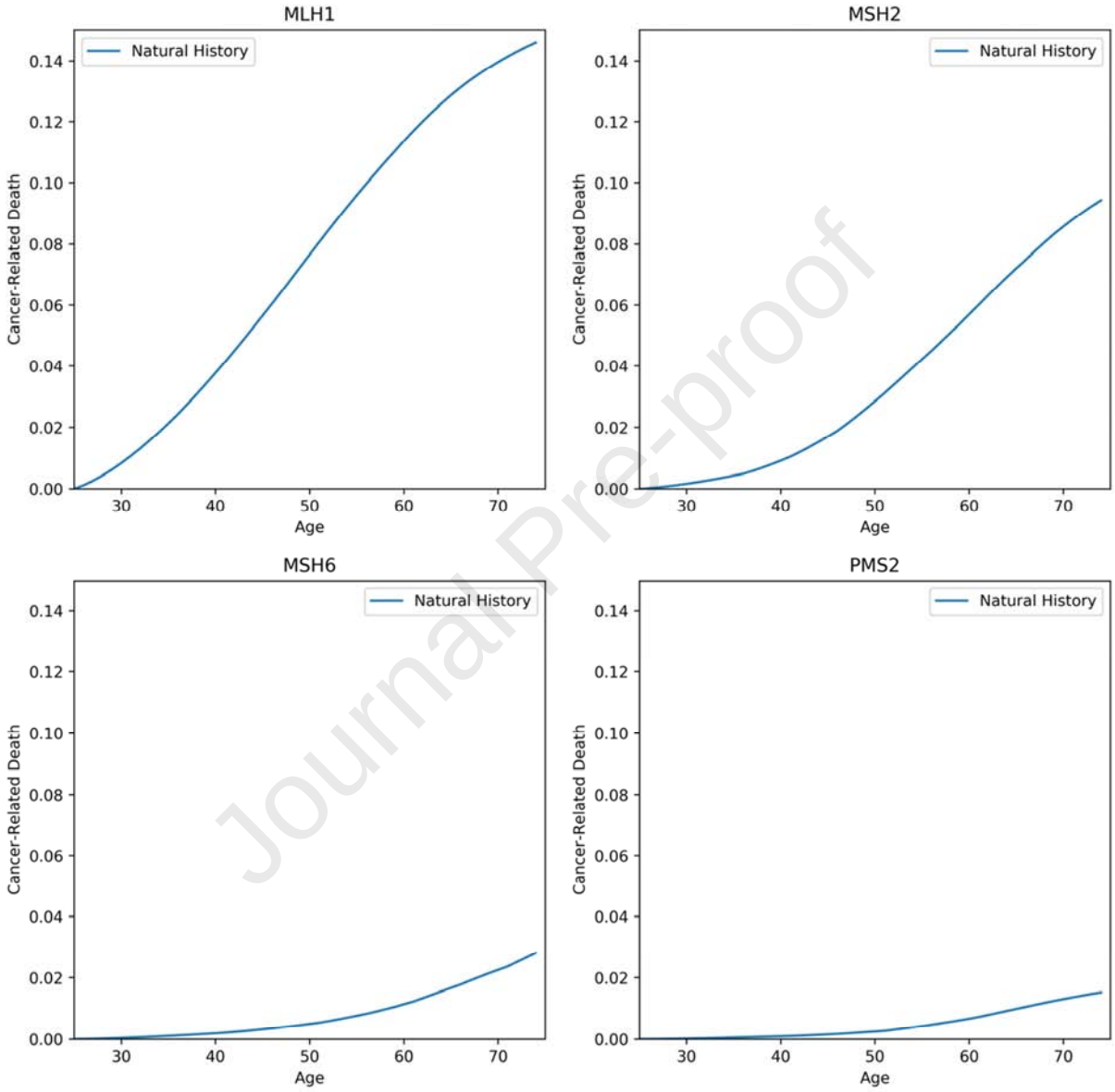
Parameter	High Value	Low Value	High Optimal Strategy	High ICER	Low Optimal Strategy	Low ICER
Lifetime CRC risk[a]			Q2Y, Start age: 25	$15,980.47	Q2Y, Start age: 25	$48,099.65
Adenoma Risk			Q2Y, Start age: 25	$23,219.43	Q2Y, Start age: 25	$37,425.45
Advanced Adenoma Risk			Q2Y, Start age: 25	$27,080.59	Q2Y, Start age: 25	$32,174.71
Q1Y colonoscopy interval CRC rate	0.22575	0.20425	Q2Y, Start age: 25	$29,298.71	Q2Y, Start age: 25	$29,298.71
Q2 colonoscopy interval CRC rate	0.2877	0.2603	Q3Y, Start age: 25	$132,535.46	Q2Y, Start age: 25	$2,332.85
Q3Y colonoscopy interval CRC rate	0.3192	0.2888	Q2Y, Start age: 25	--	Q3Y, Start age: 25	$115,467.61
Q4Y colonoscopy interval CRC rate	0.63	0.57	Q2Y, Start age: 25	$29,298.71	Q2Y, Start age: 25	$29,298.71
Q5Y colonoscopy interval CRC rate	0.87045	0.78755	Q2Y, Start age: 25	$29,298.71	Q2Y, Start age: 25	$29,298.71
Colectomy death <60	0.000315	0.000285	Q2Y, Start age: 25	$29,483.24	Q2Y, Start age: 25	$29,115.16
Colectomy death 60-70	0.00084	0.00076	Q2Y, Start age: 25	$29,421.84	Q2Y, Start age: 25	$29,176.02
Colectomy death 70-80	0.00063	0.00057	Q2Y, Start age: 25	$29,315.33	Q2Y, Start age: 25	$29,282.09
Stage 1 CRC death[b]						
Stage 2 CRC death	0.01995	0.01805	Q2Y, Start age: 25	$27,504.34	Q2Y, Start age: 25	$31,215.48
Stage 3 CRC death	0.07245	0.06555	Q2Y, Start age: 25	$28,673.57	Q2Y, Start age: 25	$29,963.79

Stage 4 CRC death	0.96705	0.87495	Q2Y, Start age: 25	$29,286.49	Q2Y, Start age: 25	$29,312.16
Colonoscopy complications	0.000088	0.000072	Q2Y, Start age: 25	$29,298.71	Q2Y, Start age: 25	$29,298.71

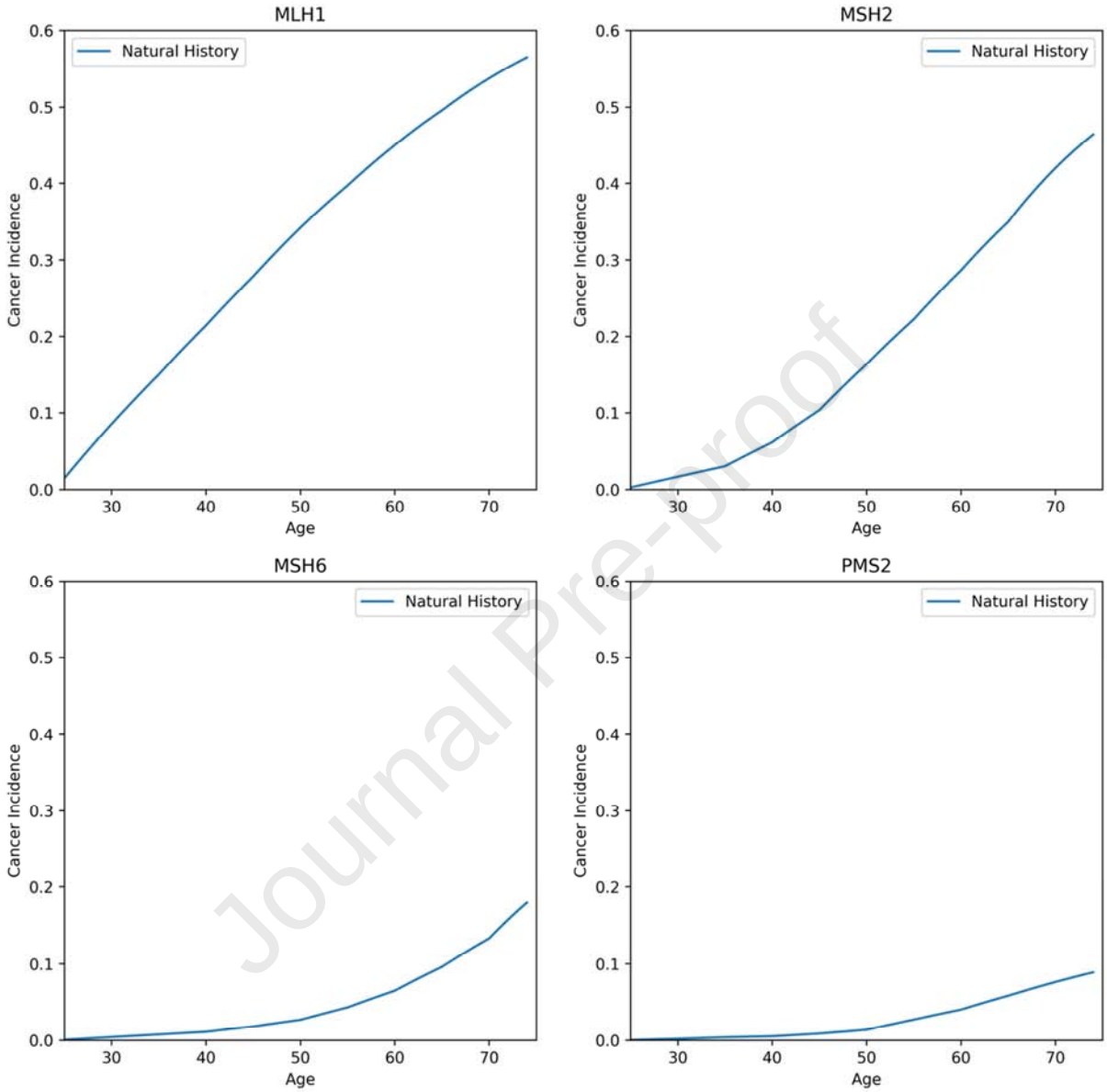
ICER: incremental cost-effectiveness ratio, CRC: colorectal cancer.
[a]Lifetime CRC risk OWSA values can be found in eTable1
[b]Adenoma and advanced adenoma risk OWSA values can be found in References 9,10
[c]Stage 1 CRC death OWSA is represented in the colectomy death rows because Stage 1 CRC death was assumed to be from only colectomy death

Supplemental Figures

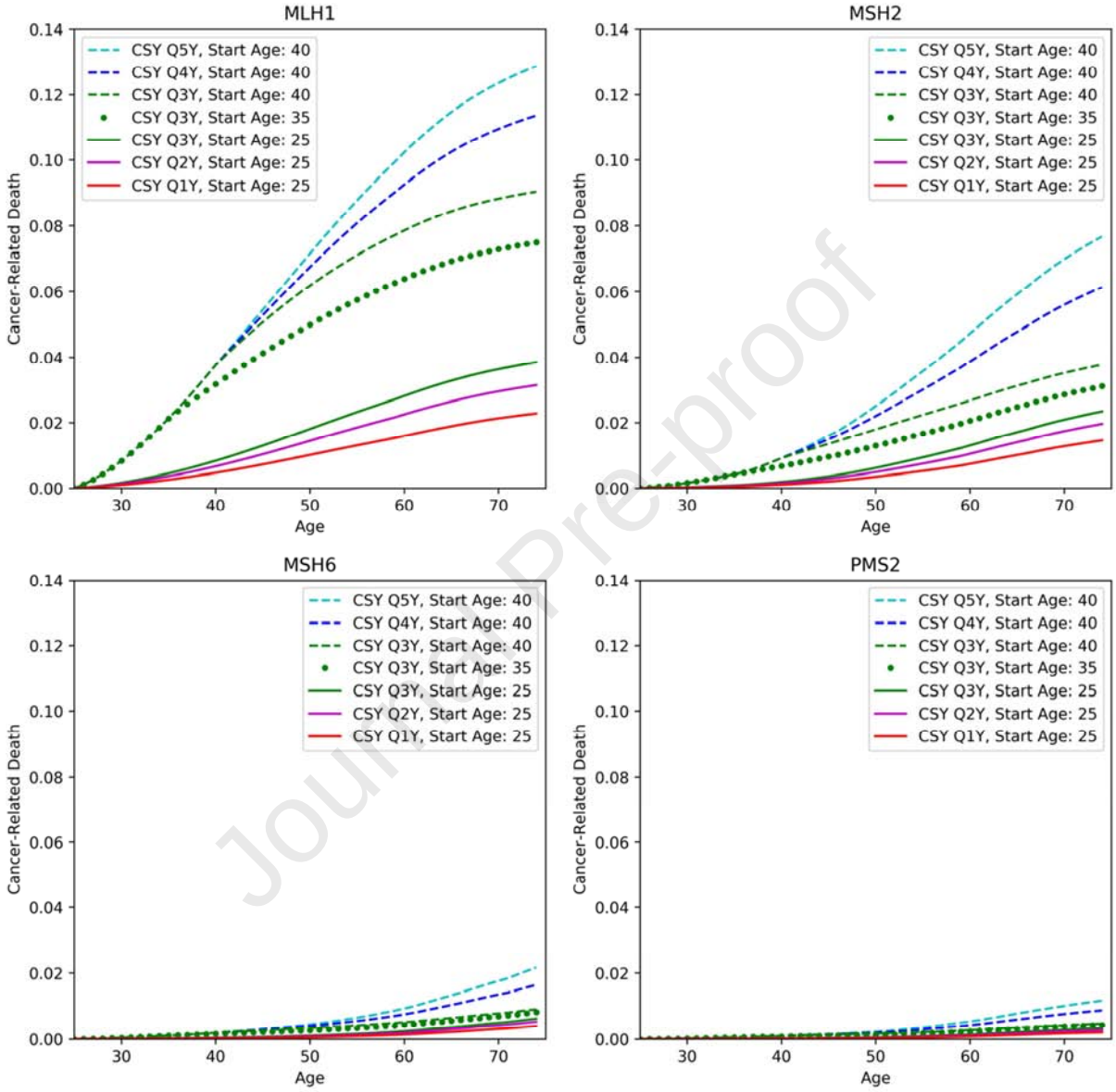
eFigure 1. Modelled Natural History Cancer Death by Gene



eFigure 2. Modelled Natural History Cancer Incidence by Gene



eFigure 3. Colon Cancer Death for Strategies on the Efficiency Frontier, by Gene and Age.

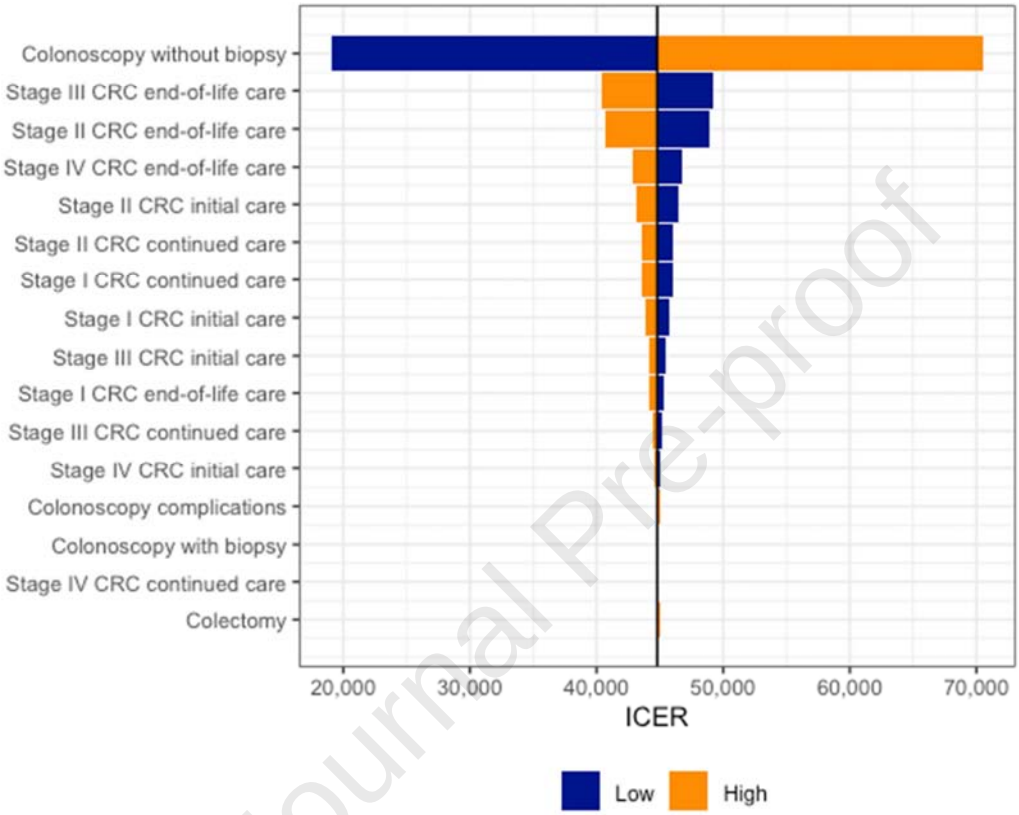


Strategies are represented as CSY (Colonoscopy) interval (years), starting age.

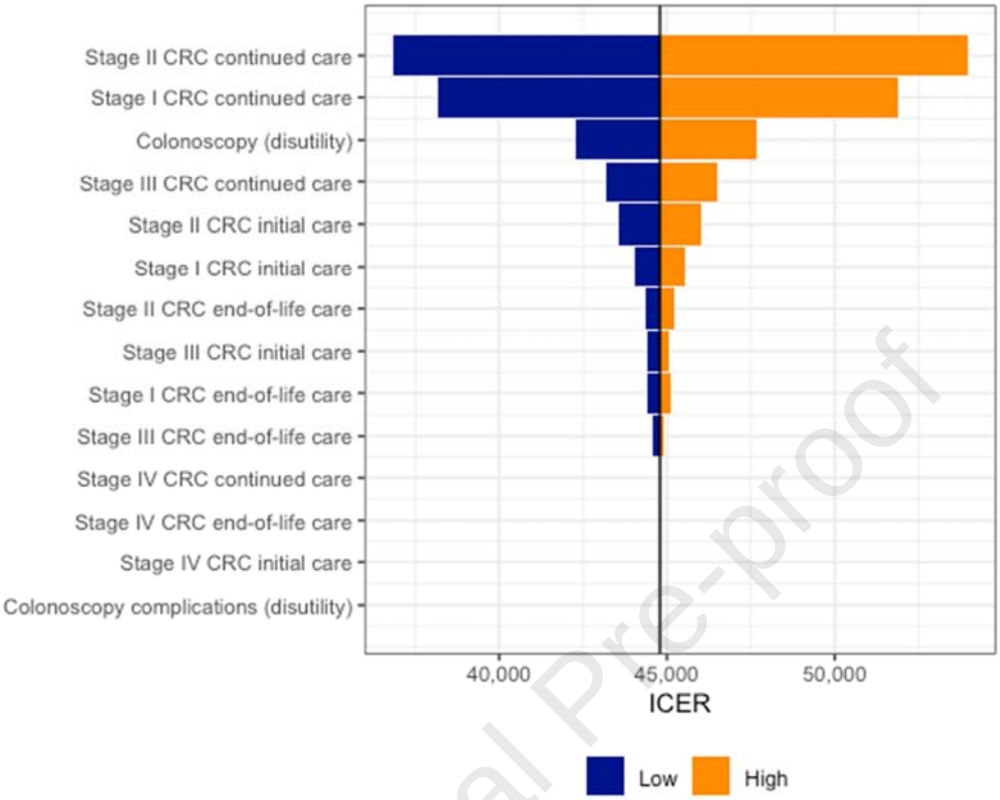
eFigure 4. One-Way Sensitivity Analysis (OSWA) Results by Gene*

eFigure 4a. MLH1 OWSA Results

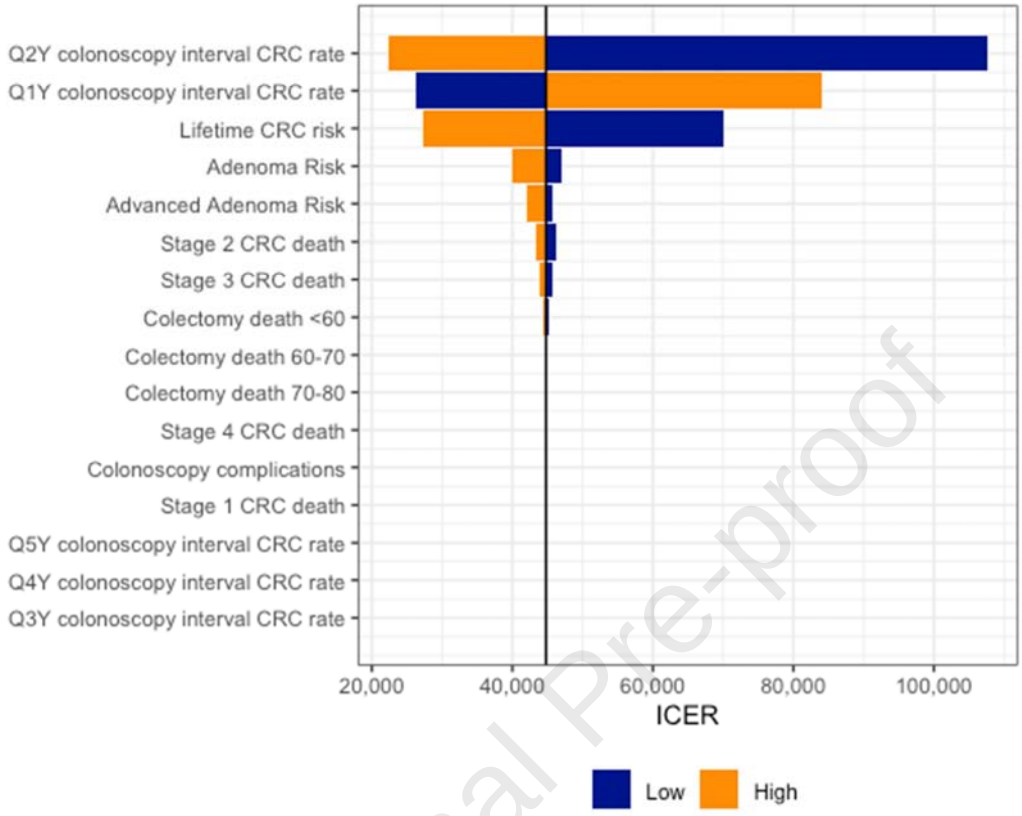
eFigure 4ai. MLH1 Q1Y, Start Age 25 Costs OWSA Results



eFigure 4aii. MLH1 Q1Y, Start Age 25 Utilities OWSA Results

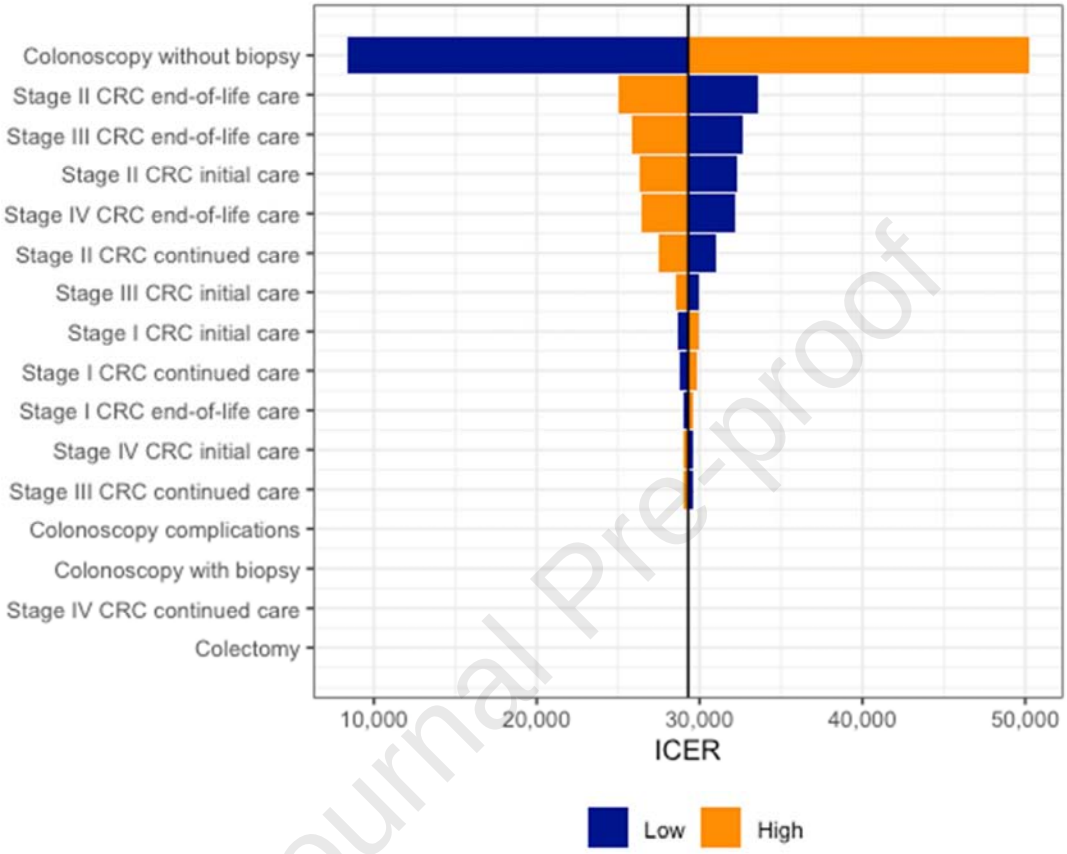


eFigure 4aiii. MLH1 Q1Y, Start Age 25 Probabilities OWSA Results

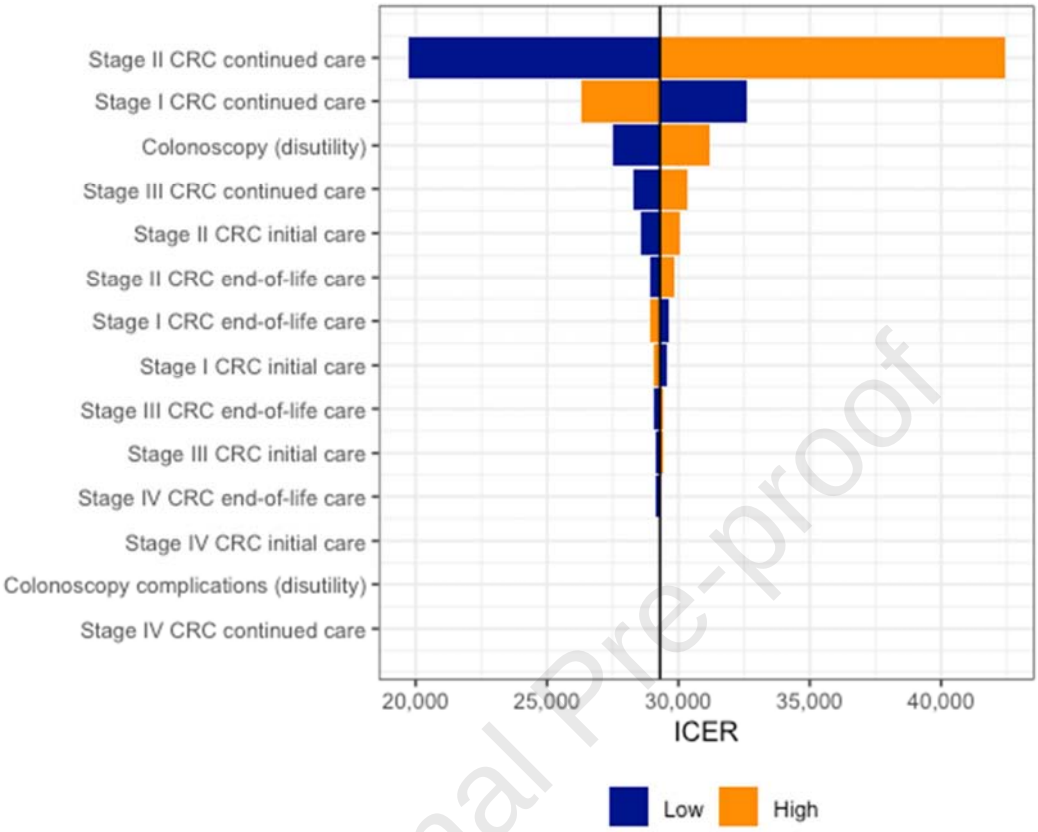


eFigure 4b. MSH2 OWSA Results

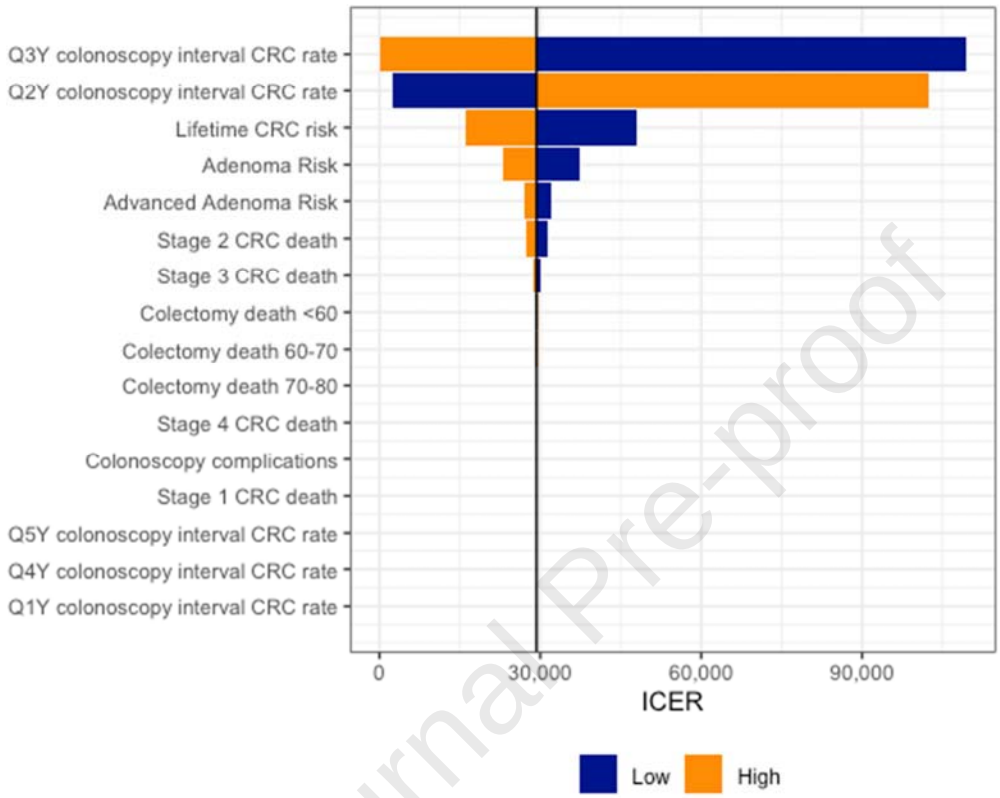
eFigure 4bi. MSH2 Q2Y, Start Age 25 Costs OWSA Results



eFigure 4bii. MSH2 Q2Y, Start Age 25 Utilities OWSA Results

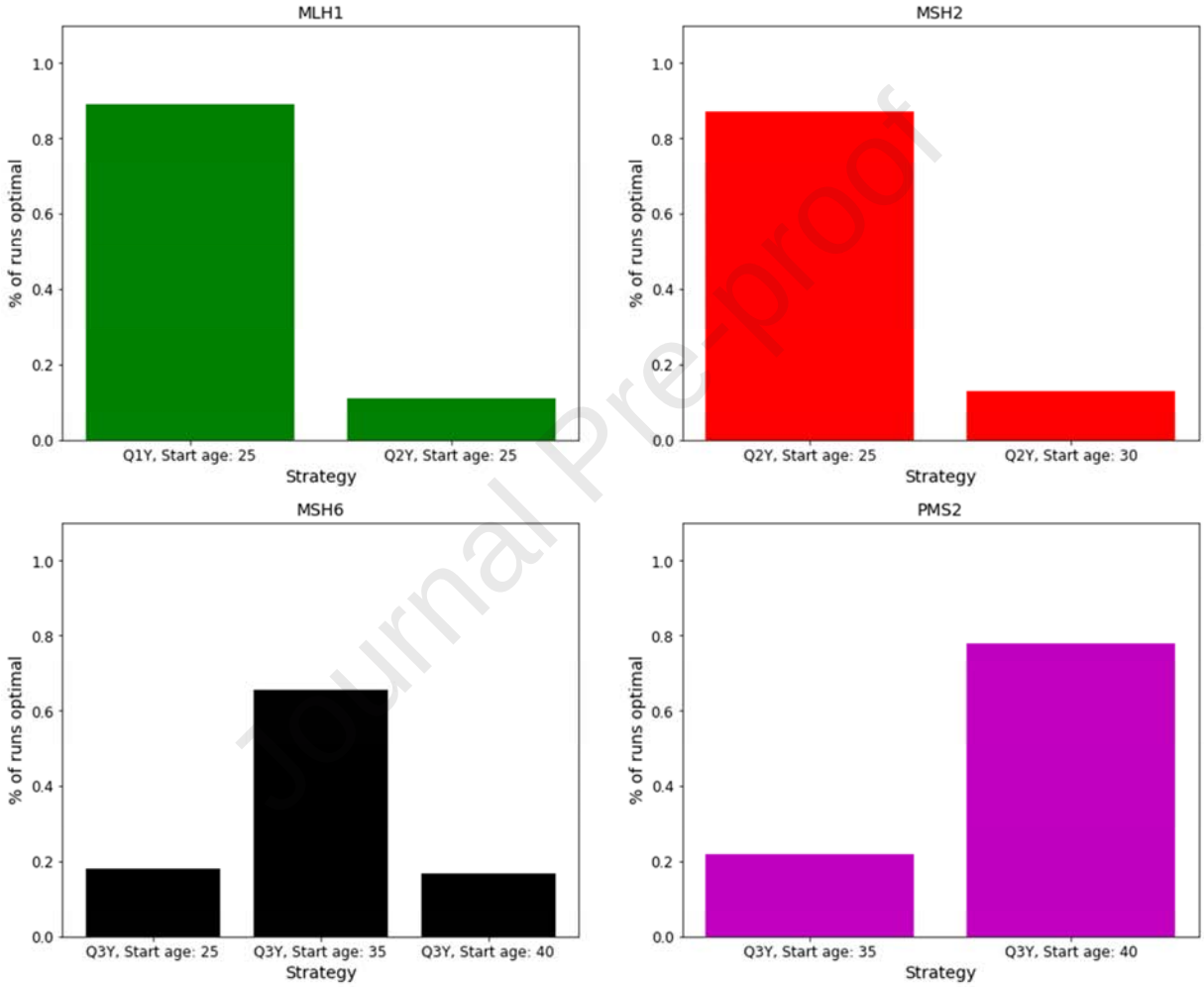


eFigure 4biii. MSH2 Q2Y, Start Age 25 Probabilities OWSA Results



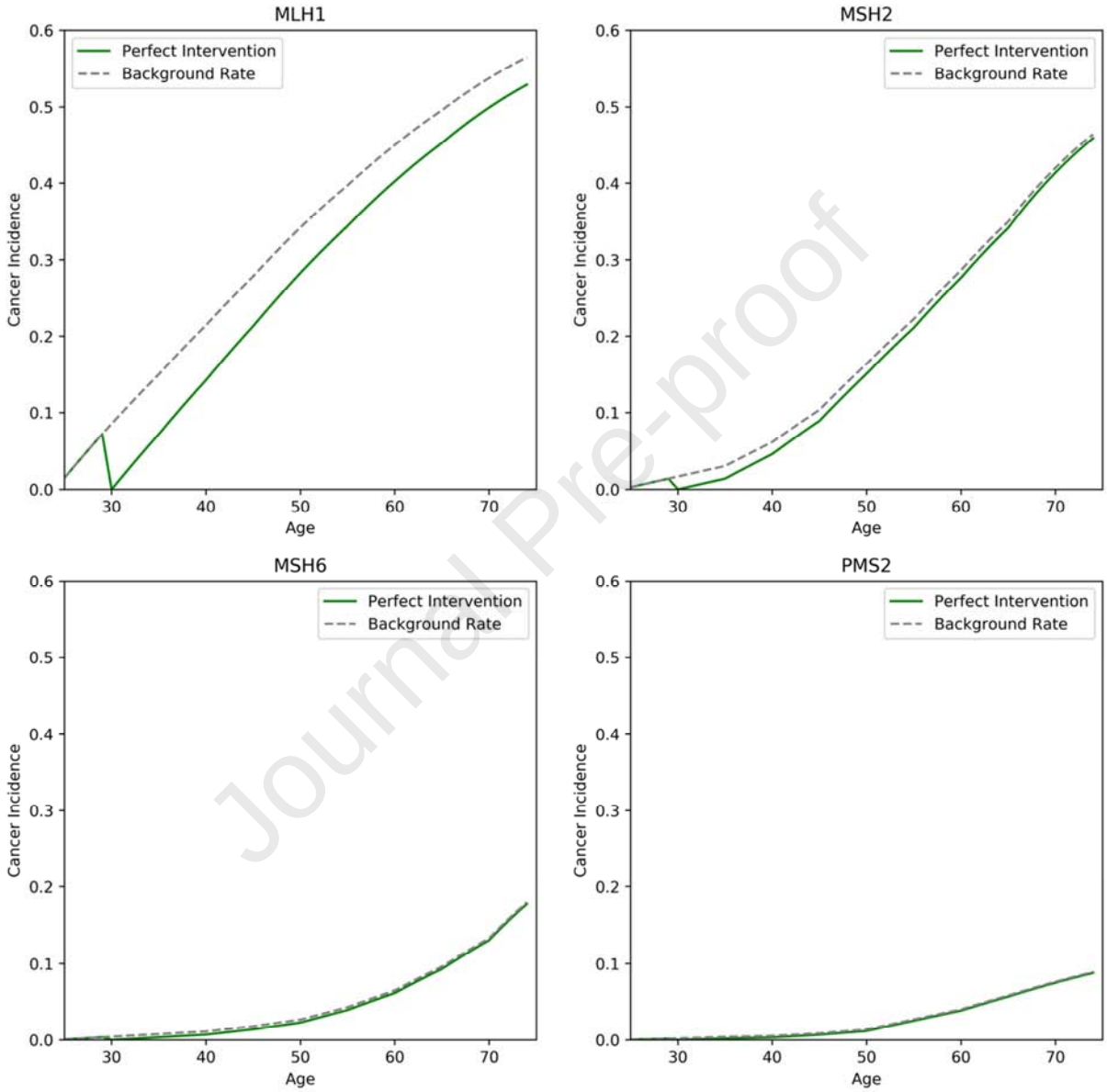
*MSH6 and PMS2 was excluded because strategy remained the lowest cost-effective strategy in every run resulting in a blank ICER
**Lifetime CRC risk could not be represented in the table vary based on age and gene in the model

eFigure 5. Probabilistic Sensitivity Analysis (PSA) Results by Gene.

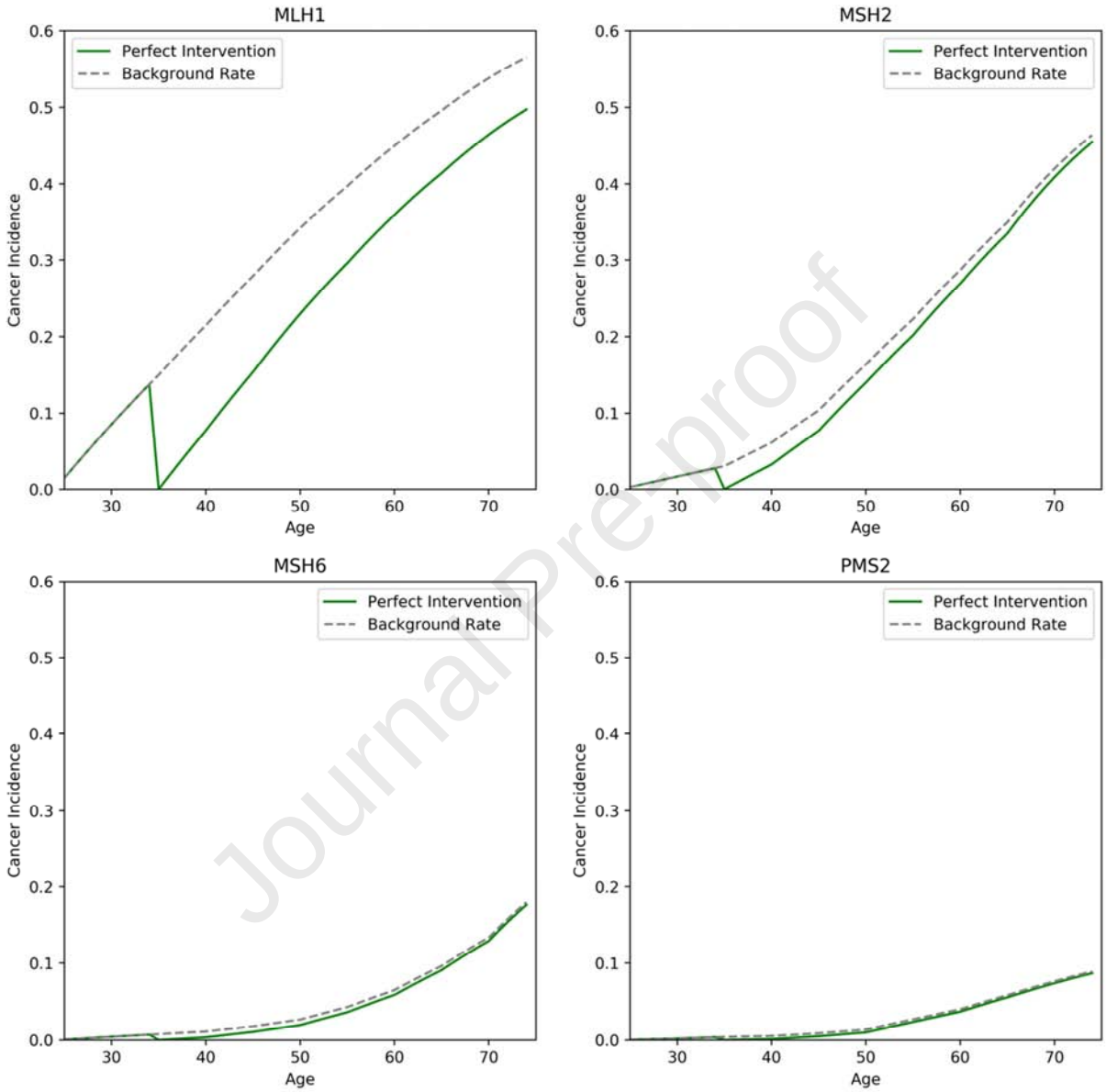


Results of 10,000 iterations of the PSA, which shows the percentage of trials in which the base case was the dominant strategy.

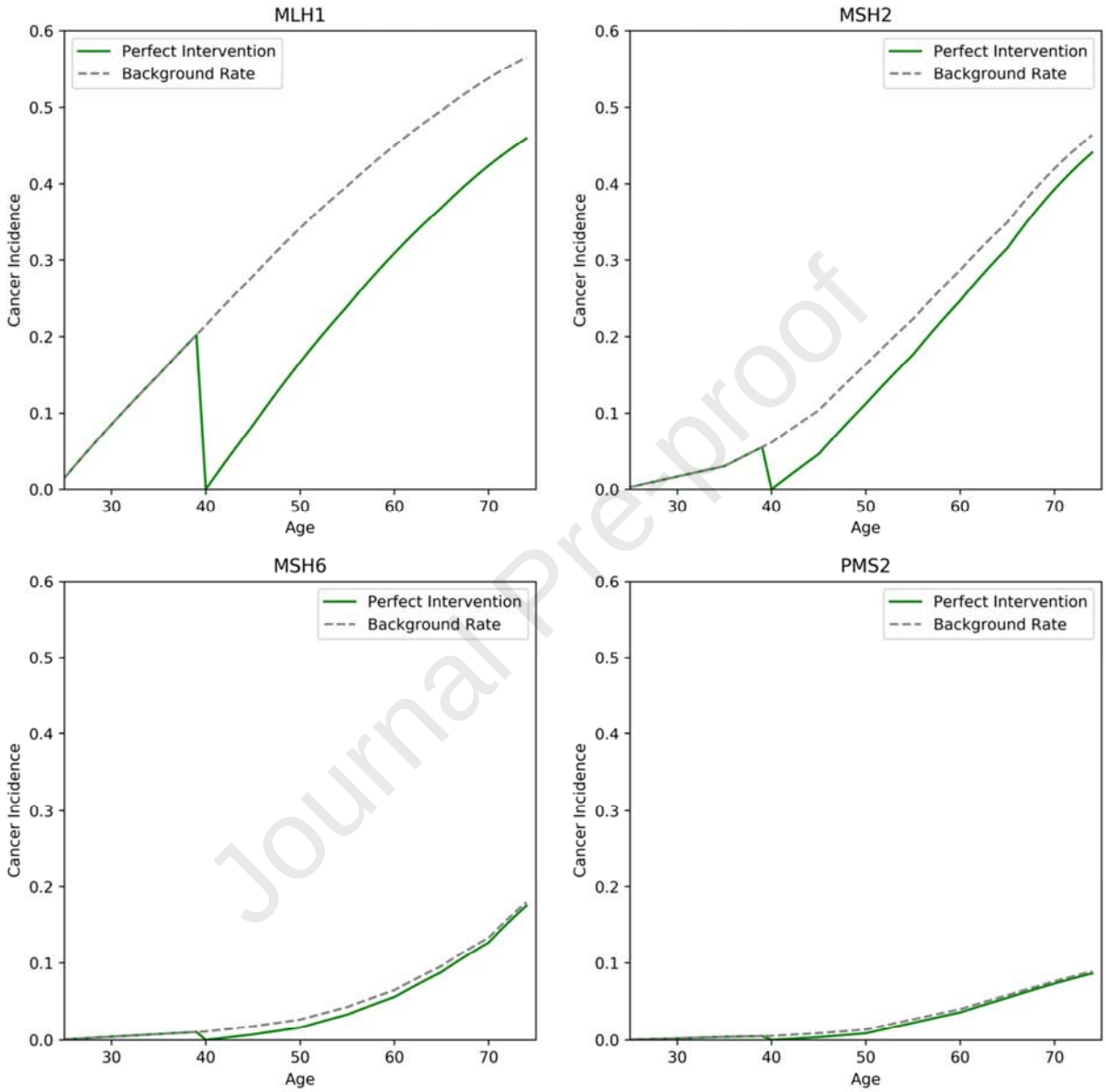
eFigure 6a. Natural History CRC Incidence Compared to Perfect Intervention at age 30



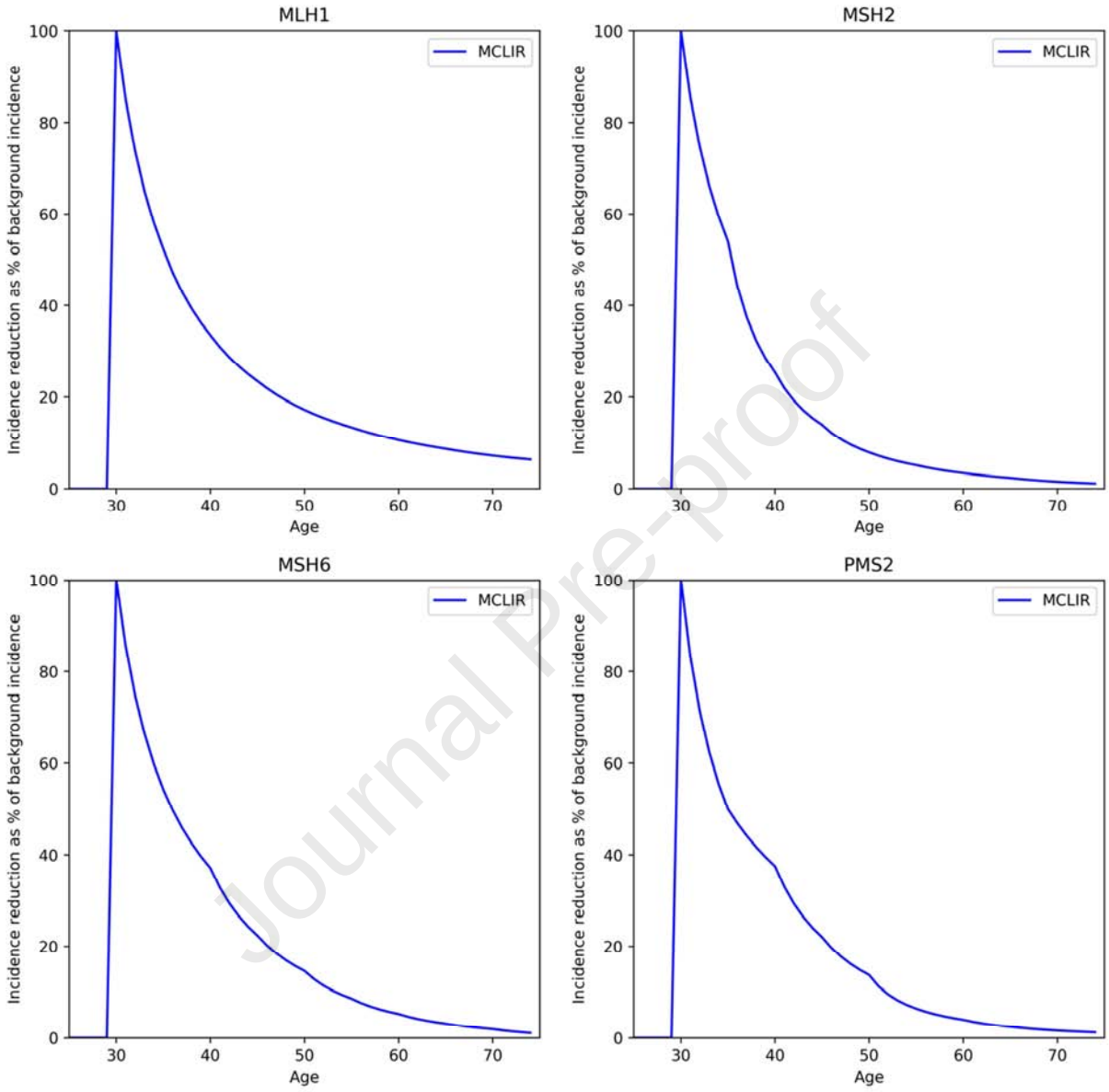
eFigure 6b. Natural History CRC Incidence Compared to Perfect Intervention at age 35



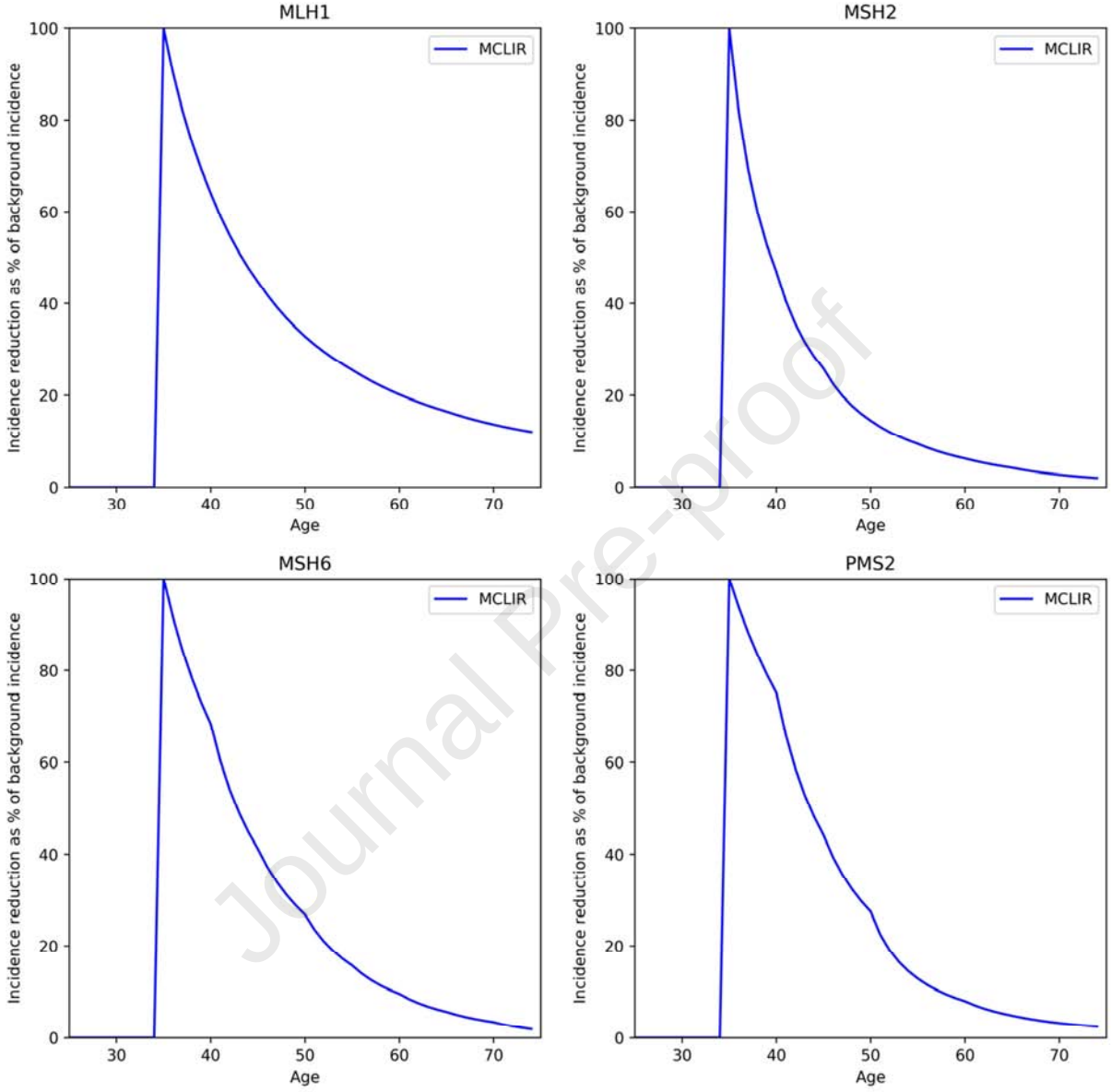
eFigure 6c. Natural History CRC Incidence Compared to Perfect Intervention at age 40



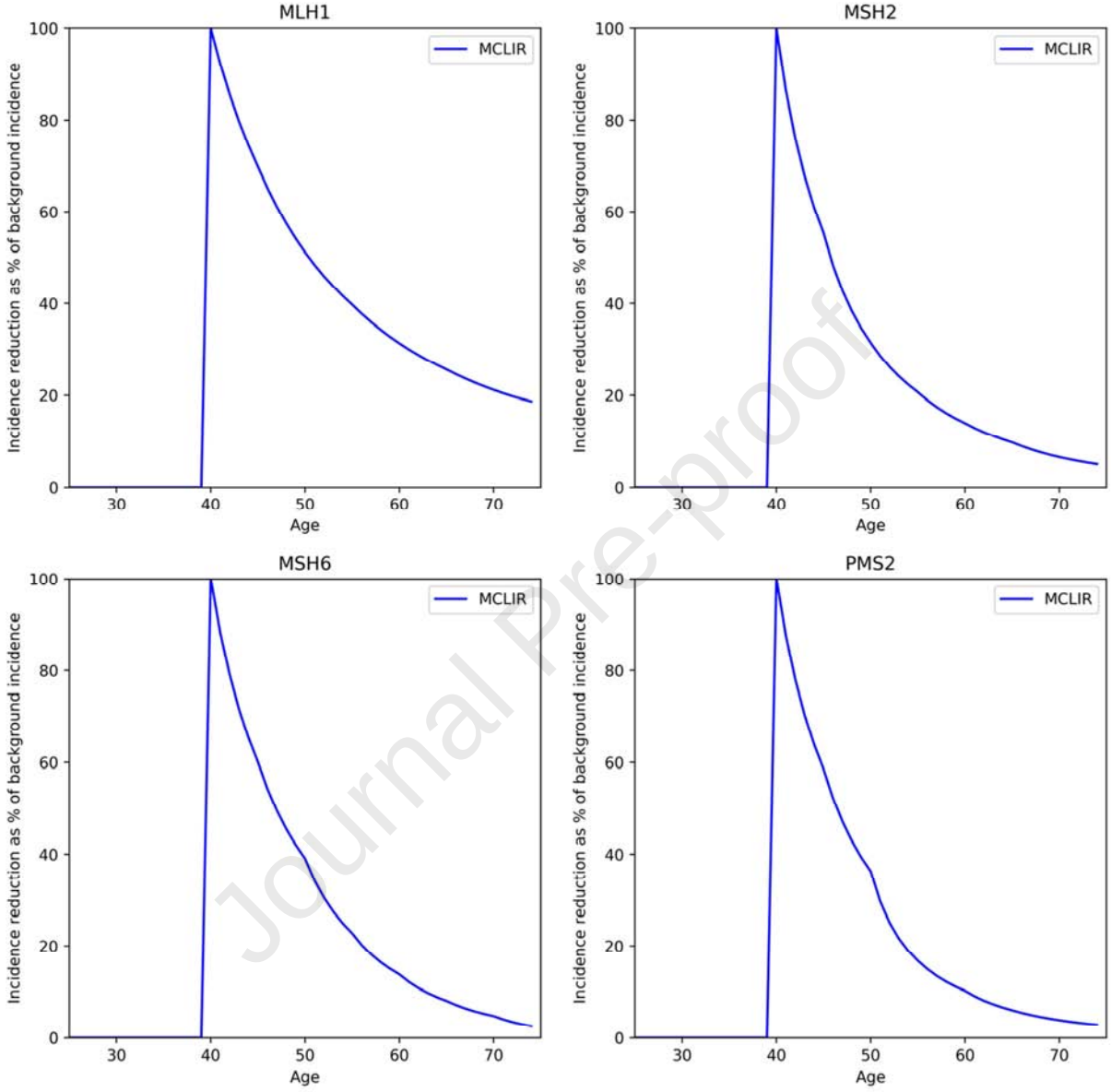
eFigure 7a. Maximum Clinical Incidence Reduction (MCLIR): Age 30



eFigure 7b. Maximum Clinical Incidence Reduction (MCLIR): Age 35



eFigure 7c. Maximum Clinical Incidence Reduction (MCLIR): Age 40



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