

## Appendix A: Base-Case Analysis: Optimal Age-Specific Screening Strategies

	Age 35 BRCA 1	Optimal Strategy with Budget Constraints					No Screening Strategy After Ten Years		Unlimited Budget Strategy After Ten Years	
		Lifetime QALYs	Ten-year Budget	Total QALYs Gain	First Ten Years QALYs Gain	ICER (\$/QALYs)	QALYs	ICER (\$/QALYs)	QALYs	ICER (\$/QALYs)
I	No Screening	37.611	\$0	NA	0	NA	37.611	NA	42.847	NA
II	1 US at age 35	37.641	\$279	0.0301	0.0301	Dominated	37.641	Dominated	42.904	Dominated
III	2 US at ages 35 and 40	42.189	\$508	4.5781	0.4349	1,167	38.711	461	43.249	1,266
IV	Biennial US between age 35-44	43.170	\$1,258	5.5596	0.6719	3,166	39.698	760	43.497	3,021
V	Annual US between age 35-44	43.535	\$2,232	5.9243	0.7599	11,078	40.128	2,264	43.612	8,475
VI	Annual MRI between age 35-44	43.613	\$16,451	6.0021	0.7654	Dominated	40.180	Dominated	43.613	Dominated
VII	Annual MRI+MAM between age 35-44	43.646	\$16,728	6.0350	0.7982	377,806	40.215	166,862	43.646	428,814

Note: The worst (i.e., no screening) and best (i.e., unlimited budget) strategies after the first ten years are the same for all ten-year strategies.

**Table A.1 Optimal Ten-year Strategies for 35 Year-old BRCA1+ Women**

	Age 45 BRCA 1	Optimal Strategy with Budget Constraints					No Screening Strategy After Ten Years		Unlimited Budget Strategy After Ten Years	
		Lifetime QALYs	Ten-year Budget	Total QALYs Gain	First Ten Years QALYs Gain	ICER (\$/QALYs)	QALYs	ICER (\$/QALYs)	QALYs	ICER (\$/QALYs)
I	No Screening	30.778	\$0	NA	0	NA	30.778	NA	33.573	NA
II	1 US at age 45	30.904	\$161	0.1262	0.1262	Dominated	30.904	Dominated	33.709	Dominated
III	2 US at ages 45 and 50	33.235	\$407	2.4571	0.5328	765	31.786	404	34.075	810
IV	2 MAM at ages 45 and 50	33.625	\$665	2.8466	0.5331	Dominated	31.831	Dominated	34.093	Dominated
V	Biennial US between age 45-54	34.257	\$916	3.4785	0.8781	1,474	32.674	574	34.429	1,439
VI	Biennial MAM between age 45-54	34.320	\$1,540	3.5418	0.8787	Dominated	32.693	Dominated	34.430	Dominated
VII	Annual US between age 45-54	34.532	\$1,618	3.7545	0.9960	5,949	33.025	1,999	34.576	4,768
VIII	Annual MAM between age 45-54	34.552	\$2,818	3.7741	1.0120	75,086	33.038	91,872	34.589	97,228
IX	Annual MRI between age 45-54	34.585	\$15,311	3.8070	1.0143	Dominated	33.083	Dominated	34.596	Dominated
X	Annual MRI+MAM between age 45-54	34.625	\$16,213	3.8466	1.0519	335,736	33.117	168,999	34.625	371,419

Note: The worst (i.e., no screening) and best (i.e., unlimited budget) strategies after the first ten years are the same for all ten-year strategies.

**Table A.2 Optimal Ten-year Strategies for 45 Year-old BRCA1+ Women**

	Age 65 BRCA 1	Optimal Strategy with Budget Constraints					No Screening Strategy After Ten Years		Unlimited Budget Strategy After Ten Years	
		Lifetime QALYs	Ten-year Budget	Total QALYs Gain	First Ten Years QALYs Gain	ICER (\$/QALYs)	QALYs	ICER (\$/QALYs)	QALYs	ICER (\$/QALYs)
I	No Screening	17.849	\$0	NA	0	NA	17.849	NA	18.150	NA
II	1 US at age 65	18.017	\$188	0.1676	0.1708	1,099	18.020	1,099	18.294	1,310
III	1 MAM at age 65	18.232	\$272	0.3825	0.1717	Dominated	18.062	Dominated	18.307	Dominated
IV	2 US at ages 65 and 70	18.388	\$388	0.5384	0.2760	1,907	18.202	1,100	18.417	1,632
V	2 MAM at ages 65 and 70	18.421	\$541	0.5715	0.2902	Dominated	18.253	Dominated	18.463	Dominated
VI	Biennial US between age 65-74	18.542	\$832	0.6927	0.3916	3,834	18.423	2,009	18.552	3,277
VII	Biennial MAM between age 65-74	18.559	\$1,182	0.7096	0.4086	Dominated	18.446	Dominated	18.559	Dominated
VIII	Annual US between age 65-74	18.600	\$1,479	0.7503	0.4493	11,234	18.510	7,480	18.600	13,593
IX	Annual MAM between age 65-74	18.610	\$2,150	0.7608	0.4597	64,385	18.523	50,479	18.610	64,385
X	Annual MRI between age 65-74	18.616	\$13,698	0.7671	0.4660	Dominated	18.530	Dominated	18.616	Dominated
XI	Annual MRI+MAM between age 65-74	18.625	\$15,226	0.7762	0.4751	848,538	18.542	696,093	18.625	846,729

Note: The worst (i.e., no screening) and best (i.e., unlimited budget) strategies after the first ten years are the same for all ten-year strategies.

**Table A.3 Optimal Ten-year Strategies for 65 Year-old BRCA1+ Women**

## Appendix B: Optimal Screening Strategies with Low US Specificity

	Age 35 BRCA 1	Optimal Strategy with Budget Constraints					No Screening Strategy After Ten Years	Unlimited Budget Strategy After Ten Years	
		Lifetime QALYs	Ten-year Budget	Total QALYs Gain	First Ten Years QALYs Gain	ICER (\$/QALYs)		QALYs	ICER (\$/QALYs)
I	No Screening	37.611	\$0	NA	0	NA	37.611	NA	42.837
II	1 MAM at age 35	37.633	\$327	0.0224	0.0224	Dominated	37.633	Dominated	42.895
III	1 US at age 35	41.010	\$438	3.3998	0.0234	Dominated	37.641	Dominated	42.900
IV	2 MAM at ages 35 and 40	41.557	\$682	3.9463	0.4157	1,641	38.581	703	43.201
V	2 US at ages 35 and 40	42.266	\$934	4.6551	0.4409	Dominated	38.711	Dominated	43.245
VI	Biennial MAM between age 35-44	43.129	\$1,654	5.5187	0.6213	4,729	39.561	993	43.440
VII	Biennial US between age 35-44	43.219	\$2,237	5.6081	0.6619	Dominated	39.698	Dominated	43.493
VIII	Annual MAM between age 35-44	43.510	\$3,119	5.8993	0.7311	13,347	40.054	2,973	43.576
IX	Annual US between age 35-44	43.543	\$4,294	5.9324	0.7642	35,500	40.128	15,838	43.608
X	Annual MRI between age 35-44	43.609	\$16,451	5.9983	0.7716	Dominated	40.180	Dominated	43.609
XI	Annual MRI+MAM between age 35-44	43.643	\$16,728	6.0319	0.8051	303,685	40.215	143,132	43.643
									362,475

Table B.1 Optimal Strategies for 35 Year-old BRCA1+ Women with Low US Specificity

	Age 45 BRCA 1	Optimal Strategy with Budget Constraints					No Screening Strategy After Ten Years	Unlimited Budget Strategy After Ten Years	
		Lifetime QALYs	Ten-year Budget	Total QALYs Gain	First Ten Years QALYs Gain	ICER (\$/QALYs)		QALYs	ICER (\$/QALYs)
I	No Screening	30.778	\$0	NA	0	NA	30.778	NA	33.569
II	1 MAM at age 45	30.900	\$306	0.1222	0.1222	Dominated	30.900	Dominated	33.702
III	1 US at age 45	32.788	\$446	2.0096	0.1258	Dominated	30.904	Dominated	33.705
IV	2 MAM at ages 45 and 50	33.625	\$665	2.8466	0.5264	1,263	31.831	631	34.088
V	Biennial MAM between age 45-54	34.291	\$1,540	3.5126	0.8537	2,675	32.693	1,015	34.425
VI	Annual MAM between age 45-54	34.548	\$2,818	3.7700	0.9811	10,033	33.038	3,705	34.573
VII	Annual MRI between age 45-54	34.585	\$15,311	3.8070	1.0255	Dominated	33.083	Dominated	34.592
VIII	Annual MRI+MAM between age 45-54	34.620	\$16,213	3.8424	1.0509	191,911	33.117	168,999	34.620
									284,610

Table B.2 Optimal Strategies for 45 Year-old BRCA1+ Women with Low US Specificity

	Age 65 BRCA 1	Optimal Strategy with Budget Constraints					No Screening Strategy After Ten Years	Unlimited Budget Strategy After Ten Years	
		Lifetime QALYs	Ten-year Budget	Total QALYs Gain	First Ten Years QALYs Gain	ICER (\$/QALYs)		QALYs	ICER (\$/QALYs)
I	No Screening	17.849	\$0	NA	0	NA	17.849	NA	18.148
II	1 MAM at age 65	18.020	\$272	0.1707	0.1707	Dominated	18.020	Dominated	18.286
III	2 MAM at ages 65 and 70	18.420	\$541	0.5705	0.3405	1,590	18.253	1,340	18.438
IV	Biennial MAM between ages 65-74	18.554	\$1,182	0.7043	0.4056	9,837	18.446	3,332	18.554
V	Annual MAM between age 65-74	18.603	\$2,150	0.7543	0.4556	19,386	18.523	12,511	18.603
VI	Annual MRI between age 65-74	18.610	\$13,698	0.7605	0.4618	Dominated	18.530	Dominated	18.610
VII	Annual MRI+MAM between age 65-74	18.619	\$15,226	0.7696	0.4708	854,943	18.542	696,093	18.619
									854,943

Table B.3 Optimal Strategies for 65 Year-old BRCA1+ Women with Low US Specificity

	Age 85 BRCA 1	Optimal Strategy with Budget Constraints					No Screening Strategy After Ten Years	Unlimited Budget Strategy After Ten Years	
		Lifetime QALYs	Ten-year Budget	Total QALYs Gain	First Ten Years QALYs Gain	ICER (\$/QALYs)		QALYs	ICER (\$/QALYs)
I	No Screening	6.503	\$0	NA	0	NA	6.503	NA	6.503
II	1 MAM at age 85	6.551	\$284	0.0485	0.0485	5,856	6.551	5,856	6.551
III	2 MAM at ages 85 and 90	6.556	\$426	0.0534	0.0534	28,761	6.556	28,761	6.556

Table B.4 Optimal Strategies for 85 Year-old BRCA1+ Women with Low US Specificity

## Appendix C: Results for BRCA2+ Carriers and Women with Family History

35 Year-old BRCA2+ Women				35 Year-old Women with Family History				
Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)	
No Screening	38.868	\$0	NA	Base-case Analysis	43.274	\$0	NA	
1 US at age 35	40.799	\$287	DOMINATED		44.197	\$287	311	
2 US at ages 35 and 40	42.460	\$493	137		44.533	\$451	485	
Biennial US between age 35-44	43.450	\$1,248	763		44.833	\$1,179	2,427	
Annual US between age 35-44	43.786	\$2,260	3,013		44.946	\$2,200	9,040	
Annual MRI between age 35-44	43.861	\$17,170	DOMINATED		44.973	\$17,484	DOMINATED	
Annual MRI+MAM between age 35-44	43.883	\$17,467	156,232		44.985	\$17,795	400,798	
35 Year-old BRCA2+ Women					35 Year-old Women with Family History			
No Screening	38.868	\$0	NA		43.274	\$0	NA	
1 MAM at age 35	38.890	\$337	DOMINATED		44.212	\$337	359	

35 Year-old BRCA2+ Women				35 Year-old Women with Family History			
Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	38.868	\$0	NA	Base-case Analysis	43.274	\$0	NA
1 MAM at age 35	38.890	\$337	DOMINATED		44.212	\$337	359
1 US at age 35	41.657	\$451	162		44.226	\$451	DOMINATED
2 MAM at ages 35 and 40	41.963	\$679	DOMINATED		44.556	\$646	901
2 US at ages 35 and 40	42.687	\$939	473		44.566	\$906	DOMINATED
Biennial MAM between age 35-44	43.448	\$1,670	960		44.832	\$1,619	3,524
Biennial US between age 35-44	43.539	\$2,281	DOMINATED		44.865	\$2,246	DOMINATED
Annual MAM between age 35-44	43.774	\$3,200	4,696		44.943	\$3,178	13,942
Annual US between age 35-44	43.796	\$4,440	56,123		44.950	\$4,461	208,130
Annual MRI between age 35-44	43.858	\$17,170	DOMINATED		44.967	\$17,484	DOMINATED
Annual MRI+MAM between age 35-44	43.880	\$17,467	155,173		44.979	\$17,795	454,451
35 Year-old BRCA2+ Women				35 Year-old Women with Family History			
No Screening	38.868	\$0	NA	43.274	\$0	NA	
1 MAM at age 35	38.890	\$337	DOMINATED	44.212	\$337	359	

Table C.1 Optimal Strategies for 35 Year-old Women with BRCA2+ and Family History

45 Year-old BRCA2+ Women				45 Year-old Women with Family History			
Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	31.091	\$0	NA	Base-case Analysis	34.137	\$0	NA
1 US at age 45	31.218	\$165	DOMINATED		34.534	\$165	DOMINATED
2 US at ages 45 and 50	33.214	\$385	181		35.013	\$337	385
2 MAM at ages 45 and 50	33.749	\$651	498		35.202	\$605	DOMINATED
Biennial US between age 45-54	34.033	\$890	616		35.425	\$805	1,135
Biennial MAM between age 45-54	34.385	\$1,546	DOMINATED		35.436	\$1,480	DOMINATED
Annual US between age 45-54	34.605	\$1,624	1,285		35.520	\$1,549	7,808
Annual MAM between age 45-54	34.630	\$2,894	51,818		35.534	\$2,864	98,933
Annual MRI between age 45-54	34.669	\$16,052	DOMINATED		35.549	\$16,430	DOMINATED
Annual MRI+MAM between age 45-54	34.697	\$17,023	210,955		35.560	\$17,459	546,028
45 Year-old BRCA2+ Women				45 Year-old Women with Family History			
No Screening	31.091	\$0	NA	34.137	\$0	NA	
1 MAM at age 45	31.214	\$315	DOMINATED	34.916	\$315	404	
1 US at age 45	32.992	\$459	242	34.921	\$459	DOMINATED	
2 MAM at ages 45 and 50	33.749	\$651	254	35.202	\$605	1,015	
Biennial MAM between age 45-54	34.379	\$1,546	1,419	35.436	\$1,480	3,732	
Annual MAM between age 45-54	34.626	\$2,894	5,462	35.528	\$2,864	15,165	
Annual MRI between age 45-54	34.659	\$16,052	DOMINATED	35.542	\$16,430	DOMINATED	
Annual MRI+MAM between age 45-54	34.693	\$17,023	210,936	35.554	\$17,459	547,873	
45 Year-old BRCA2+ Women				45 Year-old Women with Family History			
No Screening	31.091	\$0	NA	34.137	\$0	NA	
1 MAM at age 45	31.214	\$315	DOMINATED	34.916	\$315	404	

Table C.2 Optimal Strategies for 45 Year-old Women with BRCA2+ and Family History

55 Year-old BRCA2+ Women				55 Year-old Women with Family History			
	Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	23.880	\$0	NA	No Screening	25.725	\$0	NA
1 US at age 55	24.032	\$175	DOMINATED	1 US at age 55	25.878	\$175	DOMINATED
1 MAM at age 55	24.048	\$277	DOMINATED	1 MAM at age 55	26.236	\$277	DOMINATED
2 US at ages 55 and 60	25.247	\$409	192	2 US at ages 55 and 60	26.423	\$354	327
2 MAM at ages 55 and 60	25.499	\$601	DOMINATED	2 MAM at ages 55 and 60	26.461	\$545	DOMINATED
Biennial US between age 55-64	25.777	\$922	969	Biennial US between age 55-64	26.604	\$817	2,557
Biennial MAM between age 55-64	25.965	\$1,371	DOMINATED	Biennial MAM between age 55-64	26.625	\$1,279	DOMINATED
Annual US between age 55-64	26.096	\$1,638	2,242	Annual US between age 55-64	26.674	\$1,539	10,319
Annual MAM between age 55-64	26.124	\$2,505	31,014	Annual MAM between age 55-64	26.687	\$2,445	74,082
Annual MRI between age 55-64	26.145	\$14,787	DOMINATED	Annual MRI between age 55-64	26.700	\$15,209	DOMINATED
Annual MRI+MAM between age 55-64	26.164	\$16,435	349,593	Annual MRI+MAM between age 55-64	26.704	\$16,934	842,072

55 Year-old BRCA2+ Women				55 Year-old Women with Family History			
	Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	23.880	\$0	NA	No Screening	25.725	\$0	NA
1 MAM at age 55	24.048	\$277	DOMINATED	1 MAM at age 55	25.893	\$277	DOMINATED
2 MAM at ages 55 and 60	25.310	\$601	420	2 MAM at ages 55 and 60	26.461	\$545	740
Biennial MAM between age 55-64	25.961	\$1,371	1,184	Biennial MAM between age 55-64	26.619	\$1,279	4,630
Annual MAM between age 55-64	26.120	\$2,505	7,126	Annual MAM between age 55-64	26.680	\$2,445	19,251
Annual MRI between age 55-64	26.141	\$14,787	DOMINATED	Annual MRI between age 55-64	26.690	\$15,209	DOMINATED
Annual MRI+MAM between age 55-64	26.159	\$16,435	349,540	Annual MRI+MAM between age 55-64	26.697	\$16,934	846,846

Table C.3 Optimal Strategies for 55 Year-old Women with BRCA2+ and Family History

65 Year-old BRCA2+ Women				65 Year-old Women with Family History			
	Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	17.288	\$0	NA	No Screening	18.135	\$0	NA
1 US at age 65	17.456	\$193	DOMINATED	1 US at age 65	18.302	\$193	DOMINATED
1 MAM at age 65	17.471	\$280	DOMINATED	1 MAM at age 65	18.452	\$280	DOMINATED
2 US at ages 65 and 70	18.047	\$446	589	2 US at ages 65 and 70	18.550	\$372	895
2 MAM at ages 65 and 70	18.122	\$607	DOMINATED	2 MAM at ages 65 and 70	18.574	\$528	DOMINATED
Biennial US between age 65-74	18.323	\$939	1,780	Biennial US between age 65-74	18.653	\$814	4,294
Biennial MAM between age 65-74	18.348	\$1,292	DOMINATED	Biennial MAM between age 65-74	18.666	\$1,180	DOMINATED
Annual US between age 65-74	18.420	\$1,598	6,825	Annual US between age 65-74	18.691	\$1,489	17,757
Annual MAM between age 65-74	18.435	\$2,264	43,008	Annual MAM between age 65-74	18.699	\$2,196	91,526
Annual MRI between age 65-74	18.444	\$14,450	DOMINATED	Annual MRI between age 65-74	18.704	\$15,043	DOMINATED
Annual MRI+MAM between age 65-74	18.458	\$15,271	576,419	Annual MRI+MAM between age 65-74	18.711	\$15,945	1,190,374

65 Year-old BRCA2+ Women				65 Year-old Women with Family History			
	Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	17.288	\$0	NA	No Screening	18.135	\$0	NA
1 MAM at age 65	17.471	\$280	DOMINATED	1 MAM at age 65	18.452	\$280	DOMINATED
2 MAM at ages 65 and 70	18.122	\$607	728	2 MAM at ages 65 and 70	18.574	\$528	1,201
Biennial MAM between age 65-74	18.348	\$1,292	3,026	Biennial MAM between age 65-74	18.666	\$1,180	7,114
Annual MAM between age 65-74	18.435	\$2,264	11,180	Annual MAM between age 65-74	18.699	\$2,196	30,583
Annual MRI between age 65-74	18.444	\$14,450	DOMINATED	Annual MRI between age 65-74	18.704	\$15,043	DOMINATED
Annual MRI+MAM between age 65-74	18.458	\$15,271	576,419	Annual MRI+MAM between age 65-74	18.711	\$15,945	1,190,374

Table C.4 Optimal Strategies for 65 Year-old Women with BRCA2+ and Family History

## Appendix D: Sensitivity Analysis

In this section, we perform a series of univariate sensitivity analyses on the cost of screening technologies and biopsy, and the disutility associated with screening and biopsy, and discuss our findings.

75 Year-old BRCA2+ Women				75 Year-old Women with Family History			
	Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	11.581	\$0	NA	No Screening	11.660	\$0	NA
1 US at age 75	11.716	\$203	DOMINATED	1 US at age 75	11.789	\$203	1,567
1 MAM at age 75	11.726	\$281	1,940	1 MAM at age 75	11.801	\$281	DOMINATED
2 US at ages 75 and 80	11.774	\$380	2,077	2 US at ages 75 and 80	11.828	\$363	4,087
2 MAM at ages 75 and 80	11.785	\$513	DOMINATED	2 MAM at ages 75 and 80	11.837	\$494	DOMINATED
Biennial US between age 75-84	11.827	\$773	7,413	Biennial US between age 75-84	11.859	\$752	12,591
Annual US between age 75-84	11.833	\$1,357	93,114	Annual US between age 75-84	NOT OPTIMAL	NOT OPTIMAL	NOT OPTIMAL

75 Year-old BRCA2+ Women				75 Year-old Women with Family History			
	Screening Policy BRCA 2 Mutation	Expected QALYs	Expected Ten-year Cost	Screening Policy Family History	Expected QALYs	Expected Ten-year Cost	Updated ICER (\$/QALY)
No Screening	11.581	\$0	NA	No Screening	11.660	\$0	NA
1 MAM at age 75	11.726	\$281	1,940	1 MAM at age 75	11.801	\$281	1,981
2 MAM at ages 75 and 80	11.785	\$513	3,931	2 MAM at ages 75 and 80	11.837	\$494	5,949
Biennial MAM between age 75-84	11.824	\$1,059	13,834	Biennial MAM between age 75-84	11.855	\$1,042	31,423

**Table C.5 Optimal Strategies for 75 Year-old Women with BRCA2+ and Family History**

#### D.1. Sensitivity Analysis - Cost Function

We conduct sensitivity analysis on cost function by considering all possible combinations among low (minimum), medium (average), and high (maximum) cost scenarios separately (Table D.1), where medium (average) values are employed in the base case numerical study. A change in the cost of one of the technologies might result in a change in optimal screening strategies, comparing to the base study results. We name a change as “robust” if it occurs under all possible scenarios that are separately examined. The robust changes in optimal screening strategies, resulting from the use of alternative cost values for screening modalities or biopsy, are presented in Table D.2.

Imaging Technology/Cost	Minimum (Low)	Average (Medium)	Maximum (High)
Mammography (MAM)	\$94	\$116	\$161
MRI	\$1,075	\$1,395	\$2,016
Ultrasound (US)	\$94	\$94	\$94
MRI adjunct to MAM	\$1,169	\$1,511	\$2,177
Biopsy	\$1,379	\$1,693	\$2,363

**Table D.1 Cost Range of Screening Modalities and Biopsy**

Our study reveals two important findings regarding the impact of screening costs on optimal strategies: (1) the most critical cost factor, affecting both the optimality and cost-effectiveness of identified strategies, is the cost of mammography. Under high (maximum) cost scenario of mammography, “single MAM” loses its cost-effectiveness and/or optimality at all age groups (also making “single US” cost-effective) and “double MAM” becomes dominated for all “elderly” women. On the other hand, a decrease in the cost of mammography affects only “double MAM”, by making it cost-effective for all “elderly” women. (2) “Annual MRI+MAM” becomes cost-effective for 25-year-old high-risk women under all scenarios of low MRI cost. This result suggests that lowering the cost of MRI can make “Annual MRI+MAM” a cost-effective strategy for “young” high-risk women and that the cost of MRI plays a more critical role than cost of biopsy and mammography on cost-effectiveness of this strategy.

Revised Policy	MAM Low	MAM High	MRI Low
Annual MRI+MAM between age 25-34	-	-	ICER COST-EFFECTIVE
Biannual MAM between age 45-54	-	NOT OPTIMAL	-
1 MAM at age 55	-	DOMINATED	-
1 MAM at age 65	-	DOMINATED	-
1 US at age 75	-	ICER COST-EFFECTIVE	-
1 MAM at age 75	-	DOMINATED	-
2 MAM at ages 75 and 80	ICER COST-EFFECTIVE	-	-
1 MAM at age 85	-	NOT OPTIMAL	-
2 MAM at ages 85 and 90	-	DOMINATED	-

Table D.2 Robust Strategy Modifications due to Changes in Cost

## D.2. Sensitivity Analysis - Disutility Function

We utilize a disutility function, capturing the harms associated with a screening action, for elderly high-risk populations, for whom tolerance to aggressive screening is a significant concern and the benefits of screenings diminish due to increased comorbidities and complications (Braithwaite et al. 2016, Burnside et al. 2012, Moore et al. 2009). In our base case study, we consider a linear disutility function increasing with age both for screening technologies and biopsy for women over age 75. In this section, we investigate the impact of an alternative (i) structure (i.e., constant rather than linearly increasing) and (ii) initiation age (e.g., age 55 or 65). For “young” age groups, these changes in disutility function have no impact on their ten-year strategies. For “middle-aged” high-risk women, sensitivity analysis reveals that disutility initiation age affects cost-effectiveness or optimality of “annual MAM” screening only. Activating disutility at age 65 causes “annual MAM” strategy to be sub-optimal for women above 65 years old and activating it at age 55 makes “annual MAM” either sub-optimal or dominated (hence not cost-effective) for all “middle-aged” women. These results suggest that when affordable, “annual US”, instead of annual “MAM”, can be used for “middle-aged” high-risk individuals who have a significant intolerance to biopsy procedure or for whom biopsy has a significantly elevated complication risk. Finally, for “elderly” high-risk women, the structure of the disutility function has an impact on the cost-effectiveness of the strategies with the highest health benefits (namely, “annual US” for 75- and “biennial US” for 85-year old women). With a constant structure, “annual US” and “biennial US” both become cost-effective for 75-and 85-year old women, respectively.

## Appendix E: Proofs of Analytical Results

In this section, we provide the proofs of the analytical results we presented in the main text. We use the following notational conventions about the summation and product signs:  $\sum_{i=S}^M \dots = 0$  and  $\prod_{i=S}^M \dots = 1$  when  $M < S$ . We start with introducing additional notation that will be needed for the proofs (in addition to the ones defined in the main text):

- $\mu_t(i)$ : Proportion of women in health state  $i \in \{0,1,2\}$  in the targeted (sub-)population at time  $t \in \{1,2,\dots,10\}$ , which changes probabilistically over time as a function of disease prevalence, incidence and progression with respect to the natural history of breast cancer. Accordingly,  $\mu_1(i)$  corresponds to the initial health state distribution for  $i \in S_U$  and is equal to  $\sum_{a \in A} x_1(i, a)$ .
- $\hat{\mu}_t(i|\pi, \pi')$ : Proportion of women with so far undetected stage  $i \in \{1,2\}$  cancer at time  $t \in \{1,2,\dots,10\}$ , when strategy  $\pi$  or  $\pi'$  is implemented. That is,  $\hat{\mu}_t(i|\pi, \pi')$  corresponds to the fraction of stage  $i$  cancers that would not be detected by either one of the strategies  $\pi$  or  $\pi'$ , regardless of which one of them has been implemented by time  $t$ .

Next, we restate *Assumptions 1, 2, and 3* and present the resulting mathematical statements imposed by these assumptions.

**Assumption 1:** (*Detection is better than no detection*) For both *in situ* ( $i=1$ ) and *invasive* ( $i=2$ ) cancer states, detection at any time in the next ten-year period, i.e.,  $t \in \{1,2,\dots,10\}$ , yields higher expected QALYs than the scenario with no detection by the end of the next ten-year period (followed by a possible detection under any future strategy  $\phi$  implemented after ten years). Accordingly, the conditions (1.1) and (1.2), expressed below, hold for all  $t \in \{1,2,\dots,10\}$  under any future strategy  $\phi$ :

$$(1.1) \text{ Rew}(t, \phi|1) := R_t(1) - [r_t(1) + \sum_{j=t}^9 [\prod_{s=t}^j P_s(1|1)r_{j+1}(1)] + \prod_{j=t}^{10} P_j(1|1)E_\phi[s_{11}=1]] + \\ \sum_{s=1}^{10-t} [\prod_{j=t}^{s+2} P_j(1|1)P_{t+s-1}(2|1)[r_{s+t}(2) + \sum_{k=t+s}^9 [\prod_{j=s+t}^k P_j(2|2)r_{k+1}(2)] + \prod_{j=s+t}^{10} P_j(2|2)E_\phi[s_{11}=2]] + \\ \prod_{k=t}^9 P_k(1|1)P_{10}(2|1)E_\phi[s_{11}=2]] > 0$$

$$(1.2) \text{ Rew}(t, \phi|2) := R_t(2) - [r_t(2) + \sum_{j=t}^9 [\prod_{s=t}^j P_s(2|2)r_{j+1}(2)] + \prod_{j=t}^{10} P_j(2|2)E_\phi[s_{11}=2]] > 0$$

**Assumption 2:** (*Early detection is better than late detection*) For both *in situ* ( $i=1$ ) and *invasive* ( $i=2$ ) cancer states, detection at any time  $t \in \{1,2,\dots,9\}$  yields higher expected QALYs than detection at a later time point  $t+k$  in the ten-year period, where  $k \in \{1,2,\dots,10-t\}$ . Accordingly, the conditions (2.1) and (2.2) hold for all  $t \in \{1,2,\dots,9\}$  and  $k \in \{1,2,\dots,10-t\}$ :

$$(2.1) \text{ Rew}(t, k|1) =: R_t(1) - r_t(1) + \sum_{j=t}^{t+k-2} [\prod_{s=t}^j P_s(1|1)r_{j+1}(1)] + \prod_{j=t}^{t+k-1} P_j(1|1)R_{t+k}(1) + \\ \sum_{s=1}^{k-1} [\prod_{j=t}^{t+s-2} P_j(1|1)P_{t+s-1}(2|1)[r_{s+t}(2) + \sum_{m=t+s}^m [\prod_{j=s+t}^m P_j(2|2)r_{m+1}(2)] + \prod_{j=s+t}^{t+k-1} P_j(2|2)R_{t+k}(2)]] + \\ \prod_{j=t}^{t+k-2} P_j(1|1)P_{t+k-1}(2|1)R_{t+k}(2) > 0$$

$$(2.2) \text{ Rew}(t, k|2) =: R_t(2) - r_t(2) + \sum_{j=t}^{t+k-2} [\prod_{s=t}^j P_s(2|2)r_{j+1}(2)] + \prod_{j=t}^{t+k-1} P_j(2|2)R_{t+k}(2) > 0$$

**Assumption 3:** *Sensitivity of a screening modality  $a \in A_S$ , denoted by  $sens_t(a)$ , is greater than 50% at any time  $t \in \{1,2,\dots,10\}$ . That is,  $sens_t(\pi) \geq 0.50$  for all  $t \in \{1,2,\dots,10\}$  and for any screening strategy  $\pi$ .*

We use “ $\prec$ ” to denote the order between the strategies in terms of expected total QALYs. That is,  $\pi \prec \pi'$  means that strategy  $\pi'$  yields more expected QALYs than strategy  $\pi$ . We construct proofs by going backward in time and visiting each time point the compared strategies differ. For future reference, we name the time points, where the compared strategies (and hence, the clinical courses of women with breast cancer following these strategies) differ, as *critical time points*.

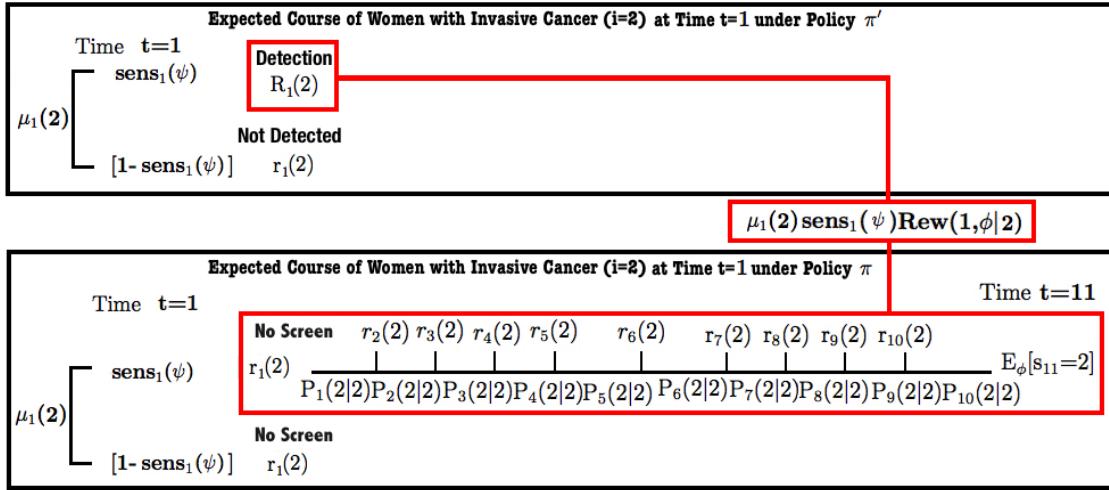
### E.1. Proof of Proposition 1

**Proposition 1:** *Between two strategies using the same screening modality with different frequencies, the strategy with higher screening frequency yields higher expected QALYs, regardless of the initial health state distribution and future strategy implemented.*

To prove *Proposition 1*, we fix the screening modality being used,  $\psi$ , and systematically compare the strategies utilizing this modality with different frequencies. In this context, the *critical time points*, where different strategies lead to different outcomes, are the times of extra screenings implemented by the more frequent strategy. At each *critical time point*, a portion of so far undetected cancers is detected with the extra screening of the more frequent ten-year strategy, denoted as strategy  $\pi'$ . These cancers either are detected later or remain undetected by the end of ten-year screening period when the less frequent ten-year strategy, denoted as strategy  $\pi$ , is implemented instead. Accordingly, to prove *Proposition 1*, we show that for all critical time points, the detections under the extra screenings of the more frequent strategy  $\pi'$  yield more expected QALYs than the QALYs obtained with the alternative clinical course and outcomes observed under the less frequent strategy  $\pi$  (in the ten-year period and afterwards). We complete this proof in four steps: *Propositions 1.1, 1.2, 1.3, and 1.4*.

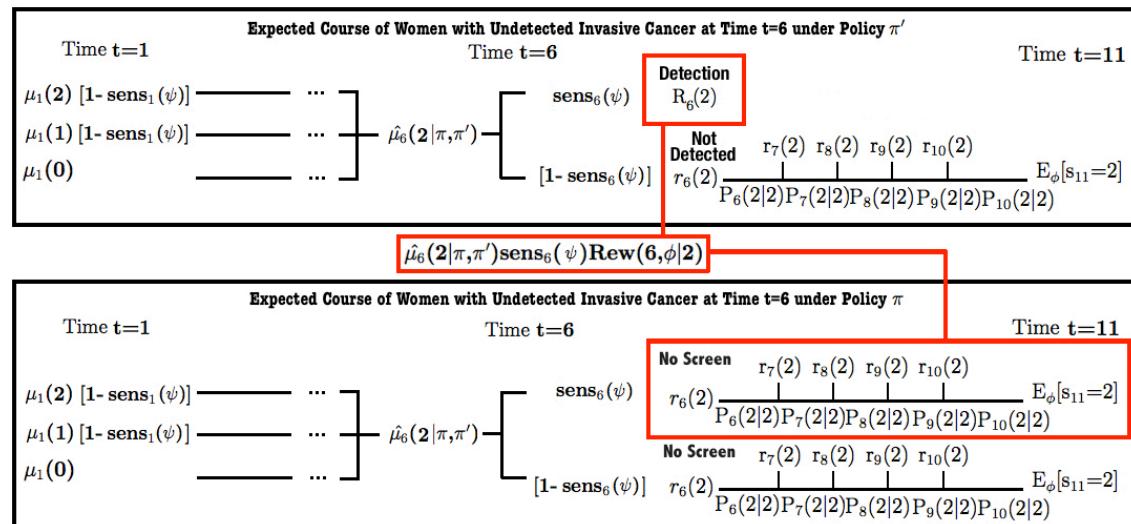
**E.1.1. Proposition 1.1: No Intervention Strategy  $\pi \prec$  Single-Screen Strategy  $\pi'$**  The only difference between “no intervention strategy”  $\pi$  and “single-screen strategy”  $\pi'$  is the clinical course of women whose cancers are detected at time  $t=1$  under strategy  $\pi'$ . These cancer patients leave the screening process and initiate their cancer treatments under strategy  $\pi'$ . However, if “no intervention strategy”  $\pi$  is implemented, these cancers remain undetected by the end of the ten-year interval. Accordingly, for a fixed future strategy  $\phi$ , implemented after ten years, the total expected QALYs difference between the strategies  $\pi'$  and  $\pi$  is equal to  $\mu_1(1)\text{sens}_1(\psi)\text{Rew}(1,\phi|1) + \mu_1(2)\text{sens}_1(\psi)\text{Rew}(1,\phi|2)$ . In this expression, the term  $\mu_1(i)\text{sens}_1(\psi)$  corresponds the proportion of cancers detected in stage  $i \in \{1,2\}$  at time  $t=1$  by strategy  $\pi'$ .  $\text{Rew}(1,\phi|i)$  is the total expected QALYs difference between strategies  $\pi'$  and  $\pi$  for a woman with stage  $i \in \{1,2\}$  cancer at time  $t=1$ . This difference in the expected QALYs arises from the difference in the course of women with breast cancer under strategies  $\pi'$  and  $\pi$ . Figure E.1 depicts the expected QALYs difference between the strategies  $\pi'$  and  $\pi$  for women with invasive cancer ( $i=2$ ) at time  $t=1$ . Since  $\mu_1(1) > 0$  and  $\mu_2(1) > 0$  for any initial health state distribution,  $\text{sens}_1(\psi) > 0$  and  $\text{Rew}(1,\phi|i) > 0$  for  $i \in \{1,2\}$  by *Assumption 1*, we conclude that “Single-Screen” strategy  $\pi'$  yields more total expected QALYs than “No Intervention” strategy  $\pi$  for any future strategy  $\phi$ .

**E.1.2. Proposition 1.2: Single-Screen strategy  $\pi \prec$  Double-Screen strategy  $\pi'$**  Under the single-screen and double-screen strategies  $\pi$  and  $\pi'$  the expected clinical course of healthy women and women with cancer does not differentiate until time  $t=6$ . At time  $t=6$ , an additional screening is conducted by strategy  $\pi'$ , detecting  $\hat{\mu}_6(i|\pi,\pi')\text{sens}_6(\psi)$  cancers in stage  $i \in \{1,2\}$ . These patients with detected breast cancer are assigned a one-time lump sum reward  $R_6(i)$ , corresponding to expected lifetime QALYs after stage  $i$  cancer treatment, and depart the screening process. Under single-screen strategy  $\pi$ , the cancers of these patients remain undetected by the end of the ten-year interval, and the patients continue to receive annual rewards



**Figure E.1** The Difference Between the Expected Courses of Women with Invasive Cancer under No Intervention Strategy  $\pi$  and Single-Screen Strategy  $\pi'$

associated with their health states. Given they survive, they receive further rewards after the ten-year period, depending on the implemented future strategy  $\phi$ .  $\text{Rew}(6,\phi|i)$  captures the total expected QALYs difference between these two clinical scenarios observed under the strategies  $\pi$  and  $\pi'$  for a woman with stage  $i \in \{1,2\}$  cancer at time  $t=6$ . Accordingly, for a fixed future strategy  $\phi$ , the total expected QALYs difference between the strategies  $\pi'$  and  $\pi$  is equal to  $\hat{\mu}_6(1|\pi,\pi')\text{sens}_6(\psi)\text{Rew}(6,\phi|1) + \hat{\mu}_6(2|\pi,\pi')\text{sens}_6(\psi)\text{Rew}(6,\phi|2)$  (Figure E.2). Since  $\hat{\mu}_6(1|\pi,\pi') > 0$  and  $\hat{\mu}_6(2|\pi,\pi') > 0$  for any initial health state distribution,  $\text{sens}_6(\psi) > 0$  and  $\text{Rew}(6,\phi|i) > 0$  for  $i \in \{1,2\}$  by *Assumption (1)*, we conclude that “Double-Screen” strategy  $\pi'$  yields more total QALYs than “Single-Screen strategy”  $\pi$  for any future strategy  $\phi$ .



**Figure E.2** The Difference Between the Expected Courses of Women with Invasive Cancer under Single-Screen strategy  $\pi$  and Double-Screen strategy  $\pi'$

**E.1.3. Proposition 1.3: Double-Screen strategy  $\pi \prec$  Biennial-Screen strategy  $\pi'$**  Biennial screening strategy  $\pi'$  has screenings at time  $t=1, 3, 5, 7$ , and  $9$  whereas double-screen strategy  $\pi$  recommends screenings at time  $t=1$  and  $6$ . We show the superiority of strategy  $\pi'$  step-by-step by visiting all critical points backward in time and stop at the time point  $t=3$ , where the strategies differ first. In order to reduce algebraic computations, we shift the screening at time  $t=5$  (under strategy  $\pi'$ ) to time  $t=6$  and only focus on time points  $t=3, 7$  and  $9$  (rather than time  $t=5$  and  $6$  as well).<sup>14</sup> Figure E.3 demonstrates the total QALYs differences at each critical time point  $t \in \{3, 7, 9\}$ .

We start the proof with the latest critical point  $t=9$ , where biennial strategy  $\pi'$  recommends an additional screening.  $\hat{\mu}_9(1|\pi,\pi')$  and  $\hat{\mu}_9(2|\pi,\pi')$  respectively corresponds to the proportions of women with undetected in situ ( $i=1$ ) and invasive ( $i=2$ ) cancers at time  $t=9$ , regardless of whether strategy  $\pi'$  or  $\pi$  has been implemented by this time point.  $[100*sens_9(\psi)]\%$  of these cancers are expected to be detected by the screening recommended by strategy  $\pi'$  at time  $t=9$ . Then, for a fixed future strategy  $\phi$ , the total expected QALYs difference of the strategies  $\pi'$  and  $\pi$  for so-far undetected cancer cases at time  $t=9$  is equal to  $[\hat{\mu}_9(1|\pi,\pi')sens_9(\psi)Rew(9,\phi|1)+ \hat{\mu}_9(2|\pi,\pi')sens_9(\psi)Rew(9,\phi|2)]$ . This term is positive for any initial health state distribution and future strategy  $\phi$  since  $Rew(9,\phi|i) > 0$  holds for  $i \in \{1,2\}$  by *Assumption 1*.

- Time  $t=9$ :  $\hat{\mu}_9(1|\pi,\pi')sens_9(\psi)Rew(9,\phi|1)+ \hat{\mu}_9(2|\pi,\pi')sens_9(\psi)Rew(9,\phi|2)$
- Time  $t=7$ :  $\hat{\mu}_7(1|\pi,\pi')sens_7(\psi)Rew(7,\phi|1)+ \hat{\mu}_7(2|\pi,\pi')sens_7(\psi)Rew(7,\phi|2)$
- Time  $t=3$ :  $\hat{\mu}_3(1|\pi,\pi')sens_3(\psi)[sens_6(\psi)Rew(3,3|1)+[1- sens_6(\psi)]Rew(3,\phi|1)]+ \hat{\mu}_3(2|\pi,\pi')sens_3(\psi)[sens_6(\psi)Rew(3,3|2)+[1- sens_6(\psi)]Rew(3,\phi|2)]$

**Figure E.3 The QALYs Differences between Biennial-Screen strategy  $\pi'$  and Double-Screen strategy  $\pi$  due to Screenings at time  $t=3, 7$ , and  $9$**

Now, we proceed to the preceding critical time point  $t=7$ , where biennial screening strategy  $\pi'$  recommends a screening.  $\hat{\mu}_7(i|\pi,\pi')$  corresponds to the proportions of women with so-far undetected stage  $i, i \in \{1,2\}$ , cancers at time  $t=7$ , regardless of whether strategy  $\pi'$  or  $\pi$  has been implemented by this time point. We will show that strategy  $\pi'$ , conducting a screening at time  $t=7$  and another one at time  $t=9$ , yields more total expected QALYs for these so-far undetected cancer cases. Among these cancer patients, we can discard the cancer cases that will be detected later at time  $t=9$ , since we have already shown the superiority of biennial strategy  $\pi'$  for them. Hence, to prove the superiority of  $\pi'$  for women with so-far undetected cancers at time  $t=7$ , it suffices to focus on cancer cases that are detected at time  $t=7$  by strategy  $\pi'$ . For a fixed future strategy  $\phi$ , the total expected QALYs difference between strategies  $\pi'$  and  $\pi$  for these cancer cases is equal to  $[\hat{\mu}_7(1|\pi,\pi')sens_7(\psi)Rew(7,\phi|1)+ \hat{\mu}_7(2|\pi,\pi')sens_7(\psi)Rew(7,\phi|2)]$ , which is positive for any initial health state distribution and future strategy  $\phi$ .

<sup>14</sup> This shift is justified because *Assumption 2* states that early detection yields higher QALYs in terms of time and hence, by shifting a screening to a later time, we cause strategy  $\pi'$  to lose some of its advantage on strategy  $\pi$ .

Finally, we proceed the first critical time point  $t=3$ . At time  $t=3$ , strategy  $\pi'$  recommends a screening, and detects a portion of so far undetected cancers. The expected course of cancers that are not detected at time  $t=3$  by the strategy  $\pi'$  is the same under both strategies  $\pi'$  or  $\pi$  by time  $t=7$ , where the strategies differ again. We can discard these cases, as we have already shown the superiority of  $\pi'$  at time  $t=7$  and afterwards, and can turn our attention to the cancers that are detected under strategy  $\pi'$  at time  $t=3$ . Under double-screen strategy  $\pi$ , these cancers remain undetected at time  $t=3$ , as no screening is conducted, a fraction of them are expected to be detected later at time  $t=6$  and given they survive, the rest remains undetected at least by the end of ten-year period with their future clinical course depending on the future strategy  $\phi$ . By taking all these possible scenarios into account, the total expected QALYs difference between strategies  $\pi'$  and  $\pi$  for these cancer cases can be expressed by  $\hat{\mu}_3(1|\pi,\pi')\text{sens}_3(\psi)[\text{sens}_6(\psi)\text{Rew}(3,3|1)+[1-\text{sens}_6(\psi)]\text{Rew}(3,\phi|1)]+\hat{\mu}_3(2|\pi,\pi')\text{sens}_3(\psi)[\text{sens}_6(\psi)\text{Rew}(3,3|2)+[1-\text{sens}_6(\psi)]\text{Rew}(3,\phi|2)]$ . The term  $\text{Rew}(3,3|i)$  captures the expected QALYs difference between detecting a stage  $i$  cancer at time  $t=3$  or later at time  $t=6$  ( $3+3$ ). The term  $\text{Rew}(3,\phi|i)$  captures the expected QALYs difference between detecting a stage  $i$  cancer at time  $t=3$  and not detecting it by time  $t=10$ , with possible detection after the ten-year period under the future strategy  $\phi$ . By *Assumptions (1)* and *(2)*, the terms  $\text{Rew}(3,3|i)$  and  $\text{Rew}(3,\phi|i)$  are both positive for both cancer states  $i=1,2$ . As a result, the overall term  $\hat{\mu}_3(1|\pi,\pi')\text{sens}_3(\psi)[\text{sens}_6(\psi)\text{Rew}(3,3|1)+[1-\text{sens}_6(\psi)]\text{Rew}(3,\phi|1)]+\hat{\mu}_3(2|\pi,\pi')\text{sens}_3(\psi)[\text{sens}_6(\psi)\text{Rew}(3,3|2)+[1-\text{sens}_6(\psi)]\text{Rew}(3,\phi|2)]$  is positive for any health state distribution  $\mu$  and future strategy  $\phi$ .

Combining the results for the critical time points  $t=3, 7$  and  $9$ , we conclude that biennial screening strategy  $\pi'$  yields more expected QALYs than double-screen strategy  $\pi$  over the entire ten-year period under any health state distribution  $\mu$  and future strategy  $\phi$ .

**E.1.4. Proposition 1.4: Biennial-Screen strategy  $\pi \prec$  Annual-Screen strategy  $\pi'$**  The biennial and annual strategies  $\pi$  and  $\pi'$  differ at times  $t=2, 4, 6, 8$  and  $10$ , where only the annual-screen strategy recommends screenings. Again, we construct our proof iteratively by analyzing these critical time points backward in time and show that the annual-screen strategy  $\pi'$  yields higher QALYs at each critical time point  $t \in \{2, 4, 6, 8, 10\}$  for any health state distribution  $\mu$  and future strategy  $\phi$ . Figure E.4 demonstrates the total QALYs differences between the strategies  $\pi'$  and  $\pi$  for so-far undetected cancer cases at each critical time point.

Time  $t=2$  is the first time point the strategies  $\pi$  and  $\pi'$  differ in the ten-year screening period. At time  $t=2$ , a screening is performed under annual strategy  $\pi'$  and detects a portion of so-far undetected cancer cases. These cancers remain undetected at time  $t=2$  if biennial strategy  $\pi$  is implemented instead but they might be detected later by one of the screenings performed by strategy  $\pi$  at times  $t=3, 5, 7, 9$  or after the first ten-year period by future strategy  $\phi$ . The total expected QALYs between the strategies  $\pi$  and  $\pi'$  for so-far undetected cancers at time  $t=2$  is computed by taking all of these scenarios into account (Figure E.4). The component  $\text{Rew}(2,k|i)$  captures the expected QALYs between detecting a stage  $i$  cancer at time  $t=2$  or later at time  $t+k$ . The term  $\text{Rew}(2,\phi|i)$  captures the expected QALYs between detecting a stage  $i$  cancer at time  $t=2$  or not detecting it by time  $t=10$ , with possible detection later with the future strategy  $\phi$ . These terms (i.e.,  $\text{Rew}(2,k|i)$  for  $i=1, 2$  and  $k=1, 3, 5, 7$ , and  $\text{Rew}(2,\phi|i)$  for  $i=1, 2$  and any future strategy  $\phi$ )

- Time  $t=10$ :  $\hat{\mu}_{10}(1|\pi,\pi')\text{sens}_{10}(\psi)\text{Rew}(10,\phi|1) + \hat{\mu}_{10}(2|\pi,\pi')(2)\text{sens}_{10}(\psi)\text{Rew}(10,\phi|2)$
- Time  $t=8$ :  $\hat{\mu}_8(1|\pi,\pi')\text{sens}_8(\psi)[\text{sens}_9(\psi)\text{Rew}(8,1|1) + [1-\text{sens}_9(\psi)]\text{Rew}(8,\phi|1)] + \hat{\mu}_8(2|\pi,\pi')\text{sens}_8(\psi)[\text{sens}_9(\psi)\text{Rew}(8,1|2) + [1-\text{sens}_9(\psi)]\text{Rew}(8,\phi|2)]$
- Time  $t=6$ :  $\sum_{i=1,2}\hat{\mu}_6(i|\pi,\pi')\text{sens}_6(\psi)[\text{sens}_7(\psi)\text{Rew}(6,1|i) + [1-\text{sens}_7(\psi)]\text{sens}_9(\psi)\text{Rew}(6,3|i) + [1-\text{sens}_7(\psi)][1-\text{sens}_9(\psi)]\text{Rew}(6,\phi|i)]$
- Time  $t=4$ :  $\sum_{i=1,2}\hat{\mu}_4(i|\pi,\pi')\text{sens}_4(\psi)[\text{sens}_5(\psi)\text{Rew}(4,1|i) + [1-\text{sens}_5(\psi)]\text{sens}_7(\psi)\text{Rew}(4,3|i) + [1-\text{sens}_5(\psi)][1-\text{sens}_7(\psi)]\text{sens}_9(\psi)\text{Rew}(4,5|i) + [1-\text{sens}_5(\psi)][1-\text{sens}_7(\psi)][1-\text{sens}_9(\psi)]\text{Rew}(4,\phi|i)]$
- Time  $t=2$ :  $\sum_{i=1,2}\hat{\mu}_2(i|\pi,\pi')\text{sens}_2(\psi)[\text{sens}_3(\psi)\text{Rew}(2,1|i) + [1-\text{sens}_3(\psi)]\text{sens}_5(\psi)\text{Rew}(2,3|i) + [1-\text{sens}_3(\psi)][1-\text{sens}_5(\psi)]\text{sens}_7(\psi)\text{Rew}(2,5|i) + [1-\text{sens}_3(\psi)][1-\text{sens}_5(\psi)][1-\text{sens}_7(\psi)][1-\text{sens}_9(\psi)]\text{Rew}(2,\phi|i)]$

**Figure E.4** The QALYs Differences between Annual-Screen strategy  $\pi'$  and Biennial-Screen strategy  $\pi$  due to Screenings at time  $t=2, 4, 6, 8$ , and  $10$

are positive by *Assumptions (1)* and *(2)*, and  $\hat{\mu}_2(i|\pi,\pi') \geq 0$  for  $i \in \{1,2\}$  for any health state distribution  $\mu$ . Accordingly, the whole term capturing the total QALYs difference between  $\pi$  and  $\pi'$  at time  $t=2$  is positive. This result shows the superiority of annual strategy  $\pi'$  over biennial strategy  $\pi$  for the cancers detected under strategy  $\pi'$  at time  $t=2$ .

We also need to show the superiority of strategy  $\pi'$  for the cancer cases that are not detected by the additional screening of strategy  $\pi'$  at time  $t=2$ . These undetected cancers might be detected at times  $t=3, 5, 7, 9$ , which is a clinical scenario that doesn't impact the QALYs difference between the strategies  $\pi$  and  $\pi'$  as both recommend screenings at these points. Alternatively, if they survive, they join the proportion of women with so-far undetected cancers at time  $t=4, 6, 8, 10$ . As a result, we need to show the superiority of strategy  $\pi'$  at times  $t \in \{4, 6, 8, 10\}$  to demonstrate the superiority of strategy  $\pi'$  at time  $t=2$  over the entire targeted population. Thus, we follow a backward-style proof because the complete result for any critical time point, where the strategies differ, relies on the results shown for the critical time points that will come later.

The proofs for the time points  $t \in \{4, 6, 8, 10\}$  follow the same structure as of the proof for the time point  $t=2$  presented above. That is, the objective is to show that the total expected QALYs differences between strategies  $\pi'$  and  $\pi$  at each one of these critical time points are positive, and the results follow from the fact that the terms  $\text{Rew}(t,k|i)$  and  $\text{Rew}(t,\phi|i)$  are positive by *Assumptions (1)* and *(2)*, and  $\hat{\mu}_t(i|\pi,\pi') \geq 0$ . Accordingly, the overall terms (Figure E.4), each capturing the total expected QALYs difference at one of the critical time points, are positive. Combined, these results show that annual-screening strategy  $\pi'$  yields higher total expected QALYs than biennial screening strategy  $\pi$  over the entire ten-year screening period for any future strategy  $\phi$  and any health state distribution  $\mu$ .

## E.2. Proof of Proposition 2

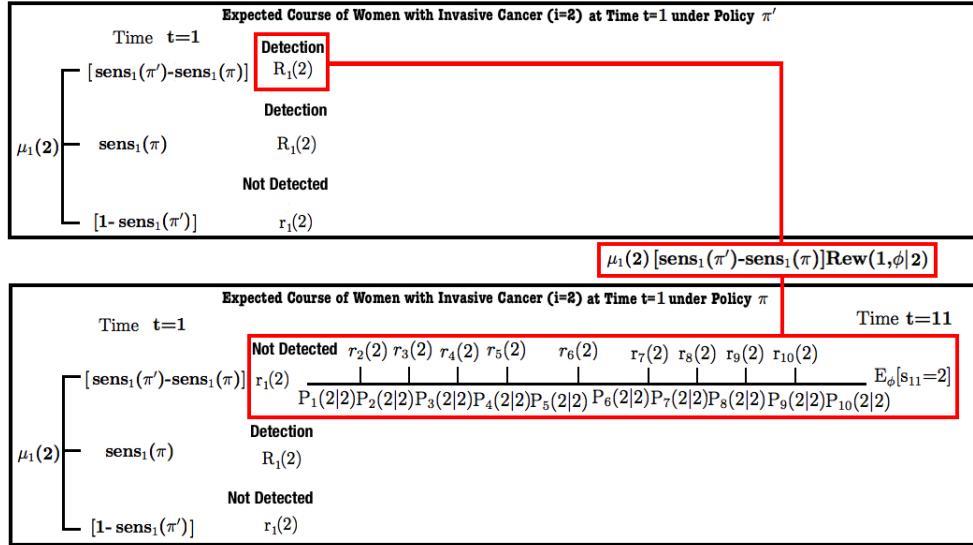
**Proposition 2:** *Between two strategies using different screening modalities with the same frequency, the strategy utilizing a more sensitive modality yields higher expected QALYs, regardless of the initial health state distribution and future strategy implemented.*

To prove *Proposition 2*, we compare the strategies that utilize different modalities with different sensitivity rates under the same fixed screening schedule. The critical time points, where the difference in compared strategies causes a difference in the clinical course of women with cancers, correspond to the time points where screenings are conducted. For any two strategies that are compared, the expected result of screenings with different modalities can be categorized into three groups: (i) so far undetected cancer cases that remain undetected under both strategies, (ii) so far undetected cancer cases that are detected under both strategies and (iii) so far undetected cancer cases that are detected under the strategy using the more sensitive modality but remains undetected at that time point under the other strategy. Since the implementation of one strategy instead of the other affects the clinical course of the women in group (iii) only, it suffices to focus on these patients to prove *Proposition 2*.

We evaluate the four practical schedule cases (i.e., 1, 2, 5 and 10 screenings in the ten-year interval) separately and complete the proof in four steps: *Propositions 2.1, 2.2, 2.3, and 2.4*. For each fixed screening schedule, we begin with the latest critical time point, where a screening is recommended, and then visit all critical points step-by-step backward in time because the proof at any critical time point relies on the proof of a later point in time. We use  $\text{sens}_t(\pi)$  and  $\text{sens}_t(\pi')$  to respectively denote the sensitivity of the modality used at time  $t \in \{1, \dots, 10\}$  by strategies  $\pi'$  and  $\pi$ , where strategy  $\pi'$  always uses a more sensitive modality (i.e  $\text{sens}_t(\pi') > \text{sens}_t(\pi) \forall t \in \{1, \dots, 10\}$ ).

**E.2.1. Proposition 2.1: Single Screening Strategy (Frequency=1)** Under single screening strategy, a screening is performed at the beginning (i.e., at time  $t=1$ ) and no other intervention is taken during the ten-year interval. Due to utilizing a more sensitive technology, strategy  $\pi'$  is expected to detect  $\mu_1(i)[\text{sens}_1(\pi') - \text{sens}_1(\pi)]$  more stage  $i$  cancers at time  $t=1$ . These cancers remain undetected under strategy  $\pi$  by the end of the ten-year period and might be detected later by the future strategy  $\phi$ . Since the clinical course of cancer cases (Figure E.5) constitute the only difference between the impacts of strategies  $\pi'$  and  $\pi$ , the total expected QALYs difference between these two policies is equal to  $\mu_1(1)[\text{sens}_1(\pi') - \text{sens}_1(\pi)]\text{Rew}(1,\phi|1) + \mu_1(2)[\text{sens}_1(\pi') - \text{sens}_1(\pi)]\text{Rew}(1,\phi|2)$  for a future strategy  $\phi$ . The term  $\text{Rew}(1,\phi|i) > 0$  for  $i \in \{1, 2\}$  under any future strategy  $\phi$  by *Assumption (1)*,  $\mu_1(1) > 0$  and  $\mu_1(2) > 0$  for any health state distribution  $\mu$ , and  $\text{sens}_1(\pi') > \text{sens}_1(\pi)$  as the strategy  $\pi'$  uses a more sensitive modality. Hence, the overall term, capturing the total QALYs difference of strategies  $\pi'$  and  $\pi$ , is positive, which shows the superiority of strategy  $\pi'$  that utilizes a more sensitive modality than strategy  $\pi$ .

**E.2.2. Proposition 2.2: Double Screening Strategy (Frequency=2)** Double screening strategies  $\pi'$  and  $\pi$  conduct two screenings in the ten-year interval, one at time  $t=1$  and the other at time  $t=6$ . We analyze the critical time point  $t=6$  first and then  $t=1$ . Regardless of whether strategy  $\pi'$  or  $\pi$  has been implemented by time  $t=6$ , there are women with so-far undetected cancers at time  $t=6$ . Among these women, strategy



**Figure E.5 The Difference Between the Expected Courses of Women with Invasive Cancer under Strategies  $\pi$  and  $\pi'$**

$\pi'$  is expected to detect  $\hat{\mu}_6(i|\pi,\pi')[\text{sens}_6(\pi')-\text{sens}_6(\pi)]$  more stage  $i$  cancers at time  $t=6$  due to utilizing a more sensitive modality. These cancers remain undetected under strategy  $\pi$  by the end of ten-year period and might be detected later by the future strategy  $\phi$ . Then, the total expected QALYs difference between strategies  $\pi'$  and  $\pi$  for these so-far undetected cancer cases at time  $t=6$  is equal to  $\sum_{i=1,2} \hat{\mu}_6(i|\pi,\pi')[\text{sens}_6(\pi')-\text{sens}_6(\pi)]\text{Rew}(6,\phi|i)$  for a future strategy  $\phi$ . This term is positive since  $\text{Rew}(6,\phi|i) > 0$  for  $i \in \{1,2\}$  under any future strategy  $\phi$  by *Assumption (1)*,  $\text{sens}_6(\pi') > \text{sens}_6(\pi)$ , and  $\hat{\mu}_6(i|\pi,\pi') > 0$  for  $i \in \{1,2\}$  with any health state distribution  $\mu$ . As a result, strategy  $\pi'$ , the strategy with more sensitive modality, yields more expected QALYs for women with so far undetected cancers at time  $t=6$ .

At time  $t=1$ , both strategies schedule a screening. Due to its more sensitive modality, strategy  $\pi'$  is expected to detect  $\mu_1(i)[\text{sens}_1(\pi')-\text{sens}_1(\pi)]$  more stage  $i$  cancers at time  $t=1$ . These cancers remain undetected at time  $t=1$  under strategy  $\pi$  but might be detected later either at time  $t=6$ , or after the ten-year period by the future strategy  $\phi$ . Taking all these possible scenarios into account, the total expected QALYs difference between strategies  $\pi'$  and  $\pi$  at time  $t=1$  is equal to  $\sum_{i=1,2} \mu_1(i)[\text{sens}_1(\pi')-\text{sens}_1(\pi)][\text{sens}_6(\pi)\text{Rew}(1,5|i)+[1-\text{sens}_6(\pi)]\text{Rew}(1,\phi|i)]$ . Given that  $\text{Rew}(1,5|i)^{15} > 0$  for  $i \in \{1,2\}$  by *Assumption (2)*,  $\text{Rew}(1,\phi|i)^{16} > 0$  for  $i \in \{1,2\}$  under any future strategy  $\phi$  by *Assumption (1)*,  $\text{sens}_1(\pi') > \text{sens}_1(\pi)$  and  $\mu_1(i) > 0$  for  $i \in \{1,2\}$  with any health state distribution  $\mu$ , the overall term for the total QALYs difference is positive, indicating that strategy  $\pi'$  yields more expected QALYs at time  $t=1$ . Combining the results for both critical time points  $t=1$  and  $t=6$ , we conclude that for any future strategy  $\phi$  and health state distribution  $\mu$ , strategy  $\pi'$ , the strategy with a more sensitive modality, yields higher expected QALYs when two screenings are scheduled in the ten-year screening interval.

<sup>15</sup>  $\text{Rew}(1,5|i)$  is the QALYs difference between detecting a stage  $i$  cancer at time  $t=1$  or later at time  $t=6$  (1+5).

<sup>16</sup>  $\text{Rew}(1,\phi|i)$  is the QALYs difference between the detection of a stage  $i$  cancer at time  $t=1$  and no detection by the end of the ten-year period.

**E.2.3. Proposition 2.3: Biennial Screening Strategy (Frequency=5)** Biennial screening strategies  $\pi'$  and  $\pi$  both schedule five screenings at times  $t=1, 3, 5, 7$  and  $9$ . Since strategy  $\pi'$  uses a more sensitive modality at each  $t \in \{1, 3, 5, 7, 9\}$ , it is expected to detect  $\hat{\mu}_t(i|\pi, \pi')[\text{sens}_t(\pi') - \text{sens}_t(\pi)]$  more stage  $i$  cancers among the women with so-far undetected cancers. If strategy  $\pi$  is implemented, these cancer cases, which are detected at time  $t$  only by strategy  $\pi'$ , remain undetected at this time point but might be detected later by either a subsequent screening of strategy  $\pi$  or future strategy  $\phi$ . The expected QALYs difference between strategies  $\pi'$  and  $\pi$  at  $t \in \{1, 3, 5, 7, 9\}$  is calculated by probabilistically taking all of these clinical scenarios into account (Figure E.6). At each critical time point, the expected QALYs difference is positive as  $\text{Rew}(t, \phi|i) > 0$  by *Assumption 1*,  $\text{Rew}(t, k|i) > 0$  by *Assumption 2*,  $\text{sens}_t(\pi') - \text{sens}_t(\pi) > 0$  due to the higher sensitivity of strategy  $\pi'$  modality, and  $\hat{\mu}_t(i|\pi, \pi') > 0$  as  $\mu$  is a probability distribution. Accordingly, the summation of the results for  $t \in \{1, 3, 5, 7, 9\}$ , each corresponding to the expected QALYs difference at one of critical time points, is positive, which shows that strategy  $\pi'$ , the strategy using a more sensitive modality, yields more total expected QALYs over the entire ten-year screening interval.

- Time  $t=9$ :  $\sum_{i=1,2} \hat{\mu}_9(i|\pi, \pi')[\text{sens}_9(\pi') - \text{sens}_9(\pi)] \text{Rew}(9, \phi|i)$
- Time  $t=7$ :  $\sum_{i=1,2} \hat{\mu}_7(i|\pi, \pi')[\text{sens}_7(\pi') - \text{sens}_7(\pi)][\text{sens}_9(\pi) \text{Rew}(7, 2|i) + [1 - \text{sens}_9(\pi)] \text{Rew}(7, \phi|i)]$
- Time  $t=5$ :  $\sum_{i=1,2} \hat{\mu}_5(i|\pi, \pi')[\text{sens}_5(\pi') - \text{sens}_5(\pi)][\text{sens}_7(\pi) \text{Rew}(5, 2|i) + [1 - \text{sens}_7(\pi)] \text{sens}_9(\pi) \text{Rew}(5, 4|i) + [1 - \text{sens}_7(\pi)][1 - \text{sens}_9(\pi)] \text{Rew}(5, \phi|i)]$
- Time  $t=3$ :  $\sum_{i=1,2} \hat{\mu}_3(i|\pi, \pi')[\text{sens}_3(\pi') - \text{sens}_3(\pi)][\text{sens}_5(\pi) \text{Rew}(3, 2|i) + [1 - \text{sens}_5(\pi)] \text{sens}_7(\pi) \text{Rew}(3, 4|i) + [1 - \text{sens}_5(\pi)][1 - \text{sens}_7(\pi)] \text{sens}_9(\pi) \text{Rew}(3, 6|i) + [1 - \text{sens}_5(\pi)][1 - \text{sens}_7(\pi)][1 - \text{sens}_9(\pi)] \text{Rew}(3, \phi|i)]$
- Time  $t=1$ :  $\sum_{i=1,2} \mu_1(i)[\text{sens}_1(\pi') - \text{sens}_1(\pi)][\text{sens}_3(\pi) \text{Rew}(1, 2|i) + [1 - \text{sens}_3(\pi)] \text{sens}_5(\pi) \text{Rew}(1, 4|i) + [1 - \text{sens}_3(\pi)][1 - \text{sens}_5(\pi)] \text{sens}_7(\pi) \text{Rew}(1, 6|i) + [1 - \text{sens}_3(\pi)][1 - \text{sens}_5(\pi)][1 - \text{sens}_7(\pi)] \text{sens}_9(\pi) \text{Rew}(1, 8|i) + [1 - \text{sens}_3(\pi)][1 - \text{sens}_5(\pi)][1 - \text{sens}_7(\pi)][1 - \text{sens}_9(\pi)] \text{Rew}(1, \phi|i)]$

**Figure E.6 The QALYs Differences between Biennial-Screen Strategies  $\pi'$  and  $\pi$  due to Screenings at time  $t=1, 3, 5, 7$ , and  $9$**

**E.2.4. Proposition 2.4: Annual Screening Strategy (Frequency=10)** Annual screening strategies  $\pi'$  and  $\pi$  both schedule yearly screenings all time points  $t=1, 2, \dots, 10$  within ten-year period. Due to employing a more sensitive modality, strategy  $\pi'$  is expected to detect  $\hat{\mu}_t(i|\pi, \pi')[\text{sens}_t(\pi') - \text{sens}_t(\pi)]$  more stage  $i$  cancers at each  $t \in \{1, 2, \dots, 10\}$  from the population with so-far undetected cancers. If strategy  $\pi$  is implemented, these cancer cases remain undetected at this time point but might be detected later by either a subsequent screening of strategy  $\pi$  or future strategy  $\phi$ . The difference in the clinical course of these cancer cases leads to the expected QALYs difference between strategies  $\pi'$  and  $\pi$  at each time  $t \in \{1, 2, \dots, 10\}$ , which is

calculated by probabilistically taking all of the clinical scenarios into account (Figure E.7). At each time point  $t \in \{1, 2, \dots, 10\}$ , the expected QALYs difference is positive since  $\text{Rew}(t, \phi|i)^{17} > 0$  by *Assumption (1)*,  $\text{Rew}(t, k|i)^{18} > 0$  by *Assumption (2)*,  $\text{sens}_t(\pi') - \text{sens}_t(\pi) > 0$  due to the higher sensitivity of strategy  $\pi'$  modality, and  $\hat{\mu}_t(i|\pi, \pi') > 0$  as  $\mu$  is a probability distribution. Accordingly, the total QALYs difference, the summation of the results for  $t \in \{1, 2, \dots, 10\}$ , is positive, which indicates that the strategy using a more sensitive modality (i.e., strategy  $\pi'$ ) yields more total expected QALYs under annual screening schedule.

- Time  $t=2, 3, \dots, 9, 10$ : 
$$\sum_{i=1,2} \hat{\mu}_t(i|\pi, \pi') [\text{sens}_t(\pi') - \text{sens}_t(\pi)] \left[ \sum_{s=t+1}^{10} \left[ \prod_{k=t+1}^{s-1} [1 - \text{sens}_k(\pi)] \text{sens}_s(\pi) \text{Rew}(t, s-t|i) \right] + \prod_{k=t+1}^{10} [1 - \text{sens}_k(\pi)] \text{Rew}(t, \phi|i) \right]$$
- Time  $t=1$ : 
$$\sum_{i=1,2} \mu_1(i) [\text{sens}_1(\pi') - \text{sens}_1(\pi)] \left[ \sum_{s=2}^{10} \left[ \prod_{k=2}^{s-1} [1 - \text{sens}_k(\pi)] \text{sens}_s(\pi) \text{Rew}(1, s-1|i) \right] + \prod_{k=2}^{10} [1 - \text{sens}_k(\pi)] \text{Rew}(1, \phi|i) \right]$$

**Figure E.7 The QALYs Differences between Annual-Screen Strategies  $\pi'$  and  $\pi$  due to Screenings at time  $t=1$ , 2, 3, ... and 10**

### E.3. Proof of Corollary 1

**Corollary 1:** *Among affordable ten-year screening strategies using only one of two different modalities, either the one with the highest frequency or the one with the most sensitive modality is the optimal policy over the entire planning horizon for the given budget level. This result holds for any initial health state distribution and any future strategy that is implemented after the ten-year period.*

The proof of *Corollary 1* immediately follows from *Propositions 1* and *2*. We show that *Corollary 1* holds by “proof by contradiction”. Assume that *Corollary 1* is not true. Then there is an optimal ten-year screening strategy that achieves the highest expected QALYs, let’s say strategy  $\delta$ , without utilizing neither (i) the highest screening frequency nor (ii) the most sensitive modality that is affordable. Alternative (i) cannot be true since *Proposition 1* states that the strategy using the same modality with strategy  $\delta$  and having higher frequency yields more expected QALYs than strategy  $\delta$ . Similarly, alternative (ii) cannot be true either since *Proposition 2* states that the strategy having the same frequency with strategy  $\delta$  and utilizing a more sensitive modality yields more expected QALYs than strategy  $\delta$ . As a result, a strategy cannot be optimal without utilizing either (i) the highest frequency or (ii) the most sensitive modality options.

<sup>17</sup>  $\text{Rew}(t, \phi|i)$  captures the expected QALYs difference resulting from the detection of a stage  $i$  cancer at time  $t$  and no detection by the end of the ten-year interval.

<sup>18</sup>  $\text{Rew}(t, k|i)$  captures the expected QALYs difference resulting from the detection of a stage  $i$  cancer at time  $t$ , by strategy  $\pi'$ , or later at time  $t+k$  by strategy  $\pi$ .

#### E.4. Proof Lemma 1

For a fixed given future strategy  $\phi$ , *Lemma 1* establishes the conditions under which single screening strategy  $\pi$  is outperformed by “double” screening strategy  $\pi'$ , which utilizes a less sensitive modality than strategy  $\pi$ . After proving *Lemma 1*, we generalize this result to all future strategies by proving *Theorem 1 (A)*.

**Lemma 1:** Consider two ten-year screening strategies: single (i.e., every 10-year) screening strategy,  $\pi$ , and double (i.e., every 5-year) screening strategy,  $\pi'$ , which utilizes a less sensitive modality (i.e.,  $sens_t(\pi') < sens_t(\pi) \forall t = 1, 2, \dots, 10$ ). Then, under a fixed future strategy  $\phi$ , strategy  $\pi'$  yields higher QALYs than strategy  $\pi$ , if the following condition (E.1) holds for both cancer states  $i=1$  and  $i=2$ :

$$\frac{\mu_1(0)}{1 - \mu_1(0)} > \frac{1}{Pr(s_6=i|s_1=0)} \frac{sens_1(\pi) - sens_1(\pi')}{sens_6(\pi')} \frac{[sens_6(\pi')Rew(1,5|i) + [1 - sens_6(\pi')]Rew(1,\phi|i)]}{Rew(6,\phi|i)} \quad (\text{E.1})$$

**Proof (Lemma 1):** Let either double-screen strategy  $\pi'$  or single-screen strategy  $\pi$  be implemented in the ten-year screening interval and a fixed future strategy  $\phi$  be implemented afterwards. Both strategies  $\pi'$  and  $\pi$  conduct a screening at time  $t=1$ , and strategy  $\pi'$  conducts an additional screening at time  $t=6$ . Due to utilizing a more sensitive screening modality, strategy  $\pi$  is expected to detect  $\mu_1(i)[sens_1(\pi)-sens_1(\pi')]$  more cancers in health state  $i \in \{1,2\}$  at time  $t=1$ . These cancer cases are not detected at time  $t=1$  if strategy  $\pi'$  is implemented. Yet, given these patients survive, these cases might be detected later by strategy  $\pi'$  at time  $t=6$  or after the ten-year period by future strategy  $\phi$ . Figure E.8 depicts the expected clinical course of these cancer cases under strategies  $\pi'$  and  $\pi$ , based on which the total expected QALYs surplus of strategy  $\pi$  over strategy  $\pi'$  at time  $t=1$  is calculated. The total expected QALYs surplus of strategy  $\pi$ , due to utilizing a more sensitive modality at time  $t=1$ , is equal to  $\sum_{i=1,2} \mu_1(i)[sens_1(\pi)-sens_1(\pi')][sens_6(\pi')Rew(1,5|i) + [1 - sens_6(\pi')]Rew(1,\phi|i)]$ .

At time  $t=6$ , strategy  $\pi'$  conducts an additional screening and is expected to detect  $\hat{\mu}_6(i|\pi,\pi')sens_6(\pi')$  stage  $i$  cancers, which would remain undetected regardless whether strategy  $\pi'$  or  $\pi$  has been implemented by time  $t=6$ . Since single-screen strategy  $\pi$  does not conduct a screening at time  $t=6$ , these cancers remain undetected by the end of the ten-year interval. Figure E.9 depicts the expected clinical course of these cancer cases under strategies  $\pi'$  and  $\pi$ . The total expected QALYs surplus of strategy  $\pi'$ , due to utilizing an additional screening at time  $t=6$ , is equal to  $\sum_{i=1,2} \hat{\mu}_6(i|\pi,\pi')sens_6(\pi')Rew(6,\phi|i)$ .

Accordingly, double-screen strategy  $\pi'$  generates a QALYs surplus at time  $t=6$ , due to utilizing an additional screening, and single-screen strategy  $\pi$  generates a QALYs surplus at time  $t=1$ , due to utilizing a more sensitive modality. Now, we will show that if the inequality (E.1) holds, then the QALYs surplus of double-screen strategy  $\pi'$  is higher and hence, strategy  $\pi'$  yields more expected QALYs. Assume that the inequality (E.1) holds for cancer states  $i=1,2$ . Then  $\frac{\hat{\mu}_6(i|\pi,\pi')}{\mu_1(i)} > \frac{\mu_1(0)Pr(s_6=i|s_1=0)}{\mu_1(i)}$  holds for cancer states  $i=1,2$ . This implies that  $\frac{\hat{\mu}_6(i|\pi,\pi')}{\mu_1(i)} > \frac{sens_1(\pi)-sens_1(\pi')}{sens_6(\pi')}$  holds for  $i=1,2$ . Accordingly, under the fixed future strategy  $\phi$ ,  $\frac{\hat{\mu}_6(i|\pi,\pi')}{\mu_1(i)} \frac{sens_6(\pi')}{sens_1(\pi)-sens_1(\pi')} \frac{Rew(6,\phi|i)}{[sens_6(\pi')Rew(1,5|i) + [1 - sens_6(\pi')]Rew(1,\phi|i)]} > 1$  holds for each cancer state  $i=1$  and  $i=2$ . This leads to  $\sum_{i=1,2} \hat{\mu}_6(i|\pi,\pi')sens_6(\pi')Rew(6,\phi|i) > \sum_{i=1,2} \mu_1(i)[sens_1(\pi)-sens_1(\pi')][sens_6(\pi')Rew(1,5|i) + [1 - sens_6(\pi')]Rew(1,\phi|i)]$ , which shows the superiority of double-screen strategy  $\pi'$  and concludes the proof.

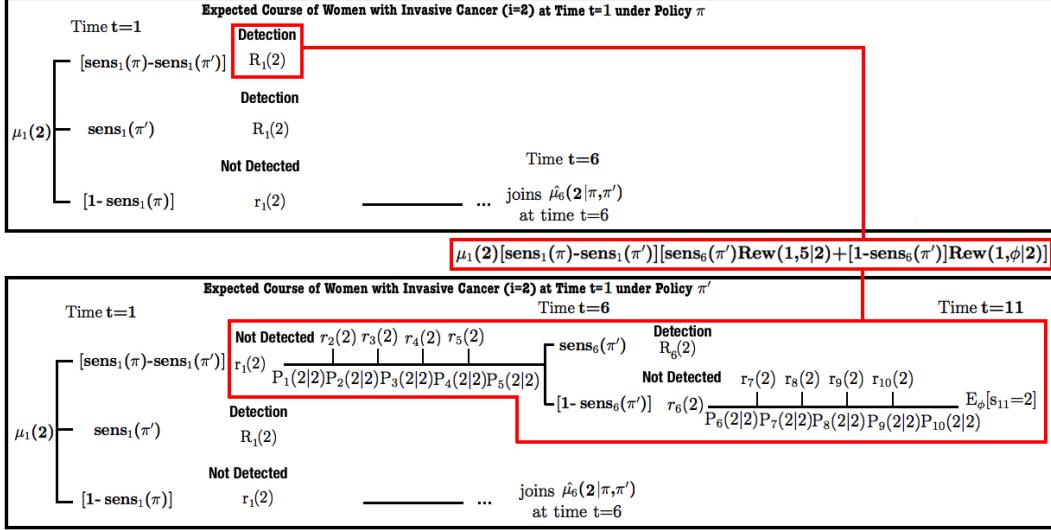


Figure E.8 The Clinical Course of Women with Invasive Cancer at time  $t=1$  under Strategies  $\pi$  and  $\pi'$

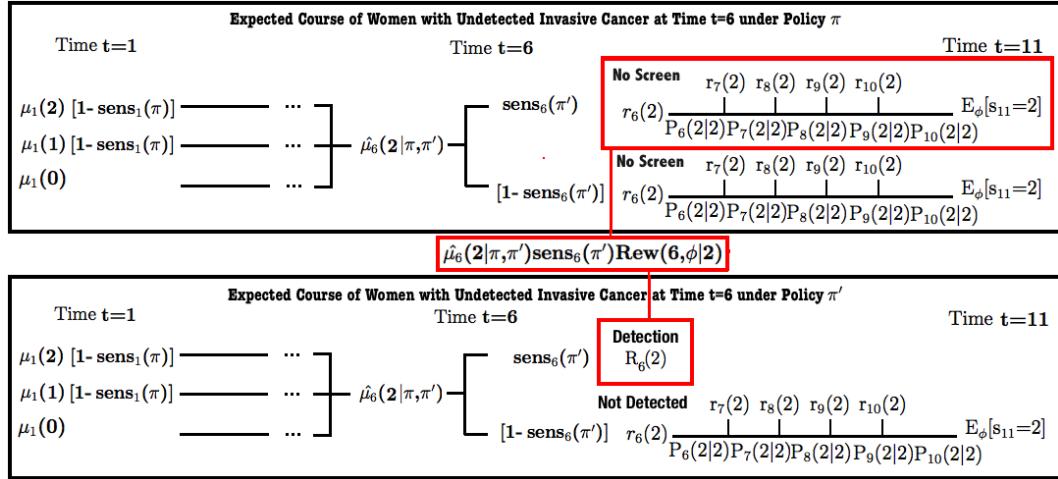


Figure E.9 The Clinical Course of Women with Invasive Cancer at time  $t=6$  under Strategies  $\pi$  and  $\pi'$

## E.5. Proof for Theorem 1 A

**Theorem 1 A:** Consider two ten-year screening strategies: single (i.e., every 10-year) screening strategy,  $\pi$ , and double (i.e., every 5-year) screening strategy,  $\pi'$ , which utilizes a less sensitive modality (i.e.,  $sens_t(\pi') < sens_t(\pi) \forall t = 1, 2, \dots, 10$ ). Then, under any future strategy, policy  $\pi'$  yields higher QALYs than policy  $\pi$ , if the following condition holds:

$$\frac{\mu_1(0)}{1 - \mu_1(0)} > \frac{1}{Pr(s_6=i|s_1=0)} \frac{sens_1(\pi) - sens_1(\pi')}{sens_6(\pi')} \frac{sens_6(\pi')Rew(1,5|i) + [1 - sens_6(\pi')]Rew(1|i)_{UB}}{Rew(6|i)_{LB}} \quad \text{for } i=1,2 \quad (\text{E.2})$$

**Proof (Theorem 1 A):** When the inequality (E.2) holds the inequality (E.1) holds for any future strategy  $\phi$  since by definition,  $Rew(1|i)_{UB} > Rew(1, \phi|i)$  and  $Rew(6|i)_{LB} > Rew(6, \phi|i)$  for both in situ ( $i=1$ ) and invasive ( $i=2$ ) cancer states. Then, the result follows immediately from Lemma 1.

### E.6. Proof for Theorem 1 B

**Theorem 1 B:** Consider two ten-year screening strategies: double screening strategy,  $\pi$ , and biennial (i.e., every 2-year) screening screening strategy,  $\pi'$ , which utilizes a less sensitive modality (i.e.,  $sens_t(\pi') < sens_t(\pi) \forall t = 1, 2, \dots, 10$ ). Then, under a fixed future strategy  $\phi$ , policy  $\pi'$  yields higher QALYs than policy  $\pi$ , if the following conditions hold:

$$\frac{\mu_1(0)}{\frac{1}{\prod_{t=1}^5 P_t(0|0)} - \mu_1(0)} > \frac{1}{Pr(s_7=i|s_6=0) + Pr(s_9=i|s_6=0)} \frac{sens_6(\pi)}{\min\{sens_7(\pi'), sens_9(\pi')\}} \frac{X(i)}{Rew(9, \phi|i)} \quad \text{for } i=1, 2 \quad (\text{E.3})$$

$$\frac{\mu_1(0)}{1-\mu_1(0)} > \frac{1}{Pr(s_3=i|s_1=0) + Pr(s_5=i|s_1=0)} \frac{sens_1(\pi) - sens_1(\pi')}{\min\{sens_3(\pi'), sens_5(\pi')\}} \frac{Y(i)}{Z(i)} \quad \text{for } i=1, 2 \quad (\text{E.4}) \text{ where,}$$

$$\begin{aligned} X(i) &= sens_7(\pi)Rew(6,1|i) + [1-sens_7(\pi)]sens_9(\pi)Rew(6,3|i) + [1-sens_7(\pi)][1-sens_9(\pi)]Rew(6,\phi|i), \\ Y(i) &= sens_3(\pi')Rew(1,2|i) + [1-sens_3(\pi')]sens_5(\pi')Rew(1,4|i) + [1-sens_3(\pi')][1-sens_5(\pi')]sens_7(\pi')Rew(1,6|i) + [1- \\ &\quad sens_3(\pi')][1-sens_5(\pi')][1-sens_7(\pi')]sens_9(\pi')Rew(1,8|i) + [1-sens_3(\pi')][1-sens_5(\pi')][1-sens_7(\pi')][1-sens_9(\pi')]Rew(1,\phi|i), \\ \text{and } Z(i) &= sens_6(\pi)\min\{Rew(3,3|i), Rew(5,1|i)\} + [1 - sens_6(\pi)]\min\{Rew(3,\phi|i), Rew(5,\phi|i)\}. \end{aligned}$$

**Proof (Theorem 1 B):** Let either biennial-screen strategy  $\pi'$  or double-screen strategy  $\pi$  be implemented in the ten-year screening interval and a fixed future strategy  $\phi$  be implemented afterwards. Biennial-screen strategy  $\pi'$  conducts five screenings at time  $t= 1, 3, 5, 7$  and  $9$ . Double-screen strategy  $\pi$  utilizes a more sensitive modality and conducts two screenings at times  $t= 1$  and  $6$ . Accordingly, strategy  $\pi$  generates more QALYs at times  $t= 1, 6$ , whereas strategy  $\pi'$  yields QALYs surplus at times  $t= 3, 5, 7$  and  $9$ . We will show that the additional QALYs obtained under strategy  $\pi'$  offsets the additional benefits of strategy  $\pi$  when the inequalities (E.3) and (E.4) hold.

If the inequality (E.3) holds for both cancer states  $i=1, 2$ , then  $\frac{\mu_1(0) \prod_{t=1}^5 P_t(0|0)}{1-\mu_1(0) \prod_{t=1}^5 P_t(0|0)} [Pr(s_7=i|s_6=0) + Pr(s_9=i|s_6=0)] > \frac{sens_6(\pi)}{\min\{sens_7(\pi'), sens_9(\pi')\}} \frac{X(i)}{Rew(9, \phi|i)}$ . This result is equivalent to  $\mu_6(0)[Pr(s_7=i|s_6=0) + Pr(s_9=i|s_6=0)] \min\{sens_7(\pi'), sens_9(\pi')\} Rew(9, \phi|i) > [1-\mu_6(0)] sens_6(\pi) X(i)$ ,  $i \in \{1, 2\}$ . Using the definition of  $X(i)$  and summing up both sides of the inequality over  $i=1, 2$ , we derive the inequality  $\sum_{i=1,2} \hat{\mu}_7(i|\pi, \pi') sens_7(\pi') Rew(7, \phi|i) + \hat{\mu}_9(i|\pi, \pi') sens_9(\pi') Rew(9, \phi|i) > \sum_{i=1,2} \hat{\mu}_6(i|\pi, \pi') sens_6(\pi) [sens_7(\pi) Rew(6,1|i) + [1-sens_7(\pi)]sens_9(\pi)Rew(6,3|i) + [1-sens_7(\pi)][1-sens_9(\pi)]Rew(6,\phi|i)]$ .<sup>19</sup> This shows that the total expected QALYs surplus obtained under strategy  $\pi'$  due to the screenings at time points  $t=7$ , and  $9$  is higher than the QALYs surplus obtained under strategy  $\pi$  due to the screening conducted at time point  $t=6$ .

If the inequality (E.4) holds for both cancer states  $i=1, 2$ , then the inequality  $\mu_1(0) [Pr(s_3=i|s_1=0) + Pr(s_5=i|s_1=0)] \min\{sens_3(\pi'), sens_5(\pi')\} Z(i) > [1-\mu_1(0)] [sens_1(\pi) - sens_1(\pi')] Y(i)$  is satisfied. This implies that  $\sum_{i=1,2} \hat{\mu}_3(i|\pi, \pi') sens_3(\pi') [sens_6(\pi)Rew(3,3|i) + [1-sens_6(\pi)]Rew(5,1|i)] > [1-\mu_1(0)] [sens_1(\pi) - sens_1(\pi')] Y(i)$ .

<sup>19</sup> The inequality (E.3) leads to this result since following inequalities hold both for  $i=1$  and  $i=2$ :

- $\hat{\mu}_7(i|\pi, \pi') sens_7(\pi') Rew(7, \phi|i) + \hat{\mu}_9(i|\pi, \pi') sens_9(\pi') Rew(9, \phi|i) > \mu_6(0)[Pr(s_7=i|s_6=0) + Pr(s_9=i|s_6=0)] \min\{sens_7(\pi'), sens_9(\pi')\} Rew(9, \phi|i)$ ,
- $[1-\mu_6(0)] > \mu_6(i)$ ,
- $X(i) = sens_7(\pi)Rew(6,1|i) + [1-sens_7(\pi)]sens_9(\pi)Rew(6,3|i) + [1-sens_7(\pi)][1-sens_9(\pi)]Rew(6,\phi|i)$ .

$\text{sens}_6(\pi)]\text{Rew}(3,\phi|i)] + \hat{\mu}_5(i|\pi,\pi')\text{sens}_5(\pi')[\text{sens}_6(\pi)\text{Rew}(5,1|i) + [1-\text{sens}_6(\pi)]\text{Rew}(5,\phi|i)] > \sum_{i=1,2} \mu_1(i)[\text{sens}_1(\pi)-\text{sens}_1(\pi')]$   
 $Y(i)$  holds for both cancer states  $i=1,2$ .<sup>20</sup> The summation of both sides of the inequality over  $i=1,2$  shows that the total expected QALYs surplus obtained under strategy  $\pi'$  due to the screenings at time points  $t=3$ , and 5 is higher than the QALYs surplus obtained under strategy  $\pi$  due to the screening conducted at time point  $t=1$ .

As shown, the inequality (E.3) implies that the screenings of strategy  $\pi'$  at time points  $t=7$ , and 9 yields more additional QALYs than the screening conducted at time point  $t=6$  by strategy  $\pi$ . Similarly, the inequality (E.4) implies that the screenings of strategy  $\pi'$  at time points  $t=3$ , and 5 yields more additional QALYs than the QALYs surplus of screening strategy  $\pi$ , due to its more sensitive screening at time point  $t=1$ . Combined, these results show that when the inequalities (E.3) and (E.4) both hold for cancer states  $i=1, 2$ , biennial screening strategy  $\pi'$  is expected to generate more QALYs surplus with its screenings at  $t=1, 3, 5, 7$  and 9 than double screening strategy  $\pi$  under a fixed future strategy  $\phi$ . This concludes the proof.

## Appendix F: Intermediate Rewards and Disutility Function

We use  $r_t(s, a)$  to denote the intermediate expected QALYs accrued between time  $t$  and  $t+1$  when a woman's current health state is  $s \in S_U$  and the screening action is  $a \in A$ . It consists of two main components: the reward function, denoted by  $\hat{r}_t(s, a)$ , and the disutility function, denoted by  $u_t(s, a)$ .

We employ the “half-cycle correction method”, described by Sonnenberg and Beck (1993), to calculate the first component of intermediate rewards. Accordingly, we assign the full decision interval length to the intermediate reward of each woman if she remains alive and the half decision interval length in the case of death. The underlying assumption is that if death occurs, it happens, on average, in the middle of the decision interval. Then, the general form of the reward function corresponding to health state  $s \in S_U$  and action  $a \in A$  at time  $t \in T_A$  is the following:

$$\hat{r}_t(s, a) = CP_t^a(\text{Alive}|s) + \frac{C}{2}P_t^a(\text{Dead}|s) \quad (\text{F.1})$$

$C$  is a constant that denotes the length of time interval between consecutive decision epochs,  $P_t^a(\text{Dead}|s)$  denotes the probability of death and  $P_t^a(\text{Alive}|s)$  denotes the probability of survival given the health state is  $s \in S_U$  and action is equal to  $a \in A$  at time  $t \in T_A$ . In our study,  $C=1$  since decisions are made every year,  $P_t^a(\text{Dead}|s) = P_t^1(5|s)$ , i.e., probability of death under natural history of disease progression, and  $P_t^a(\text{Alive}|s) = 1 - P_t^a(\text{Dead}|s) \forall s \in S_U, a \in A$  and  $t \in T_A$ .

We account for quality of life reductions due to the harms associated with diagnostic actions (i.e., screening and biopsy) by subtracting a certain amount from  $\hat{r}_t(s, a)$ . This reduction is captured by disutility function  $u_t(s, a)$ . In our study, we activate this disutility function starting from a certain age, where the harm associated with diagnostic actions is not negligible and hence, cannot be ignored. We employ an indicator function

<sup>20</sup> The inequality (E.4) leads to this result since the following inequalities hold both for  $i=1$  and  $i=2$ :

- $\hat{\mu}_3(i|\pi,\pi')\text{sens}_3(\pi')[\text{sens}_6(\pi)\text{Rew}(3,3|i) + [1-\text{sens}_6(\pi)]\text{Rew}(3,\phi|i)] + \hat{\mu}_5(i|\pi,\pi')\text{sens}_5(\pi')[\text{sens}_6(\pi)\text{Rew}(5,1|i) + [1-\text{sens}_6(\pi)]\text{Rew}(5,\phi|i)] > \mu_1(0) [\Pr(s_3=i|s_1=0) + \Pr(s_5=i|s_1=0)] \min\{\text{sens}_3(\pi'), \text{sens}_5(\pi')\} Z(i)$
- $[1-\mu_1(0)] > \mu_1(i)$ .

$1_{\{t \geq DIT\}}$ , which is equal to 1 if time  $t$  is no less than the disutility initiation time  $DIT$  and 0 otherwise. Accordingly, the general form of the intermediate reward corresponding to health state  $s \in S_U$  and action  $a \in A$  at time  $t \in T_A$  is the following:

$$r_t(s, a) = \hat{r}_t(s, a) - 1_{\{t \geq DIT\}} u_t(s, a) \quad (\text{F.2})$$

In our base case analysis, we choose “ $DIT$ ” in a way that it corresponds to age 75 and conduct sensitivity analysis to measure its impact on optimal strategies (e.g. changing initiation age to age 65 or 55). This concludes the general description of intermediate rewards. We now proceed with the detailed description of disutility function. Similar to intermediate rewards, disutility function consists of two main components: Disutility associated with screening, denoted by  $u_t^{scr}(s, a)$ , and disutility associated with (follow-up) biopsy, denoted by  $u_t^{bio}(s)$ . The general form of the disutility function, corresponding to harms associated with action  $a \in A$  for health state  $s \in S_U$  at time  $t \in T_A$ , is the following:

$$u_t(s, a) = u_t^{scr}(s, a) + q_t^{bio}(s, a) u_t^{bio}(s) \quad (\text{F.3})$$

where the probability of performing a biopsy  $q_t^{bio}(s, a) = 1 - spec_t(a)$  when  $s=0$  (healthy) and  $q_t^{bio}(s, a) = sens_t(a)$  when  $s=1, 2$  (undetected -asymptomatic- cancer states) for all  $a \in A_{SCR}=\{2,3,4,5\}$ . There is no disutility when the chosen action is “No Screening” (i.e.,  $u_t(s,a) = 0$  when  $a=1$ ).

The literature reports that false positive screening has higher disutility than a true positive one ([Earle et al. 2000](#)) and disutility (both associated with screening and biopsy) increases as women get older ([Walter and Schonberg \(2014\)](#) and the references therein). Accordingly, we penalize false positive screening results higher than true positive ones and use a linear function both for screening and biopsy disutility functions (accounting for increasing disutility with age) in our base case (numerical) study. There are three parameters, allowing us to adjust for these features of the disutility function: (i) false-positive penalty constant  $\alpha_{FPP}$ , accounting the ratio of disutility of a false positive screening to the one of a true positive screening, (ii) screening linearity factor  $\alpha_{SLF}$ , setting the ratio of screening disutility at age 100 when compared to the one at age 40 and (iii) biopsy linearity factor  $\alpha_{BLF}$ , setting the ratio of biopsy disutility at age 100 when compared to the one at age 40.

We continue discussing the disutility function, by analyzing the mathematical expression of its components in detail. We start with providing the relation between time  $t$ , the current age of patient  $a_t$  and screening initial age  $a_1$ :

$$t = a_t - a_1 + 1 \quad \forall \quad t \in \{1, 2, \dots, T - a_1 + 1\} \quad (\text{F.4})$$

We use this relationship below when we define the components of disutility function. Terminal age  $T$  is set to age 100 in our study.

### F.1. Disutility Associated with Screening $u_t^{scr}(s, a)$

The disutility of negative screening is set to 0.5 days at age 40 (and at younger ages) for any single modality (Mandelblatt et al. 1992) and 1 day when two modalities (i.e., MRI adjunct to mammography) is utilized together. We designate  $n(a)$  to denote the number of modalities employed by screening action  $a \in A$ , which is equal to 0 when  $a=1$ , 1 when  $a \in \{2,3,4\}$  and 2 when  $a=5$ . Then general form of the disutility associated with screening is the following:

$$u_t^{scr}(s, a) = \begin{cases} \frac{0.5}{365} * n(a) & \text{when } a_t \in \{25, 26, \dots, 40\}, a \in A \text{ and } s \in S_U \\ [\frac{0.5}{365} + \beta_S(a_t - 40)] * n(a) & \text{when } a_t \in \{41, \dots, 99\}, a \in A \text{ and } s \in S_U \\ \alpha_{SLF} * \frac{0.5}{365} * n(a) & \text{when } a_t = 100, a \in A \text{ and } s \in S_U \end{cases}$$

Screening disutility linearity slope  $\beta_S = \frac{0.5}{365} \frac{\alpha_{SLF}-1}{100-40}$ . Screening linearity factor  $\alpha_{SLF}=1$  and  $=2$  when a constant or an increasing disutility function is employed, respectively. Accordingly,  $\beta_S$  disappears when harm associated with screening is assumed to remain constant with age (i.e., when  $\alpha_{SLF}$  is set to 1).

### F.2. Disutility Associated with Biopsy $u_t^{bio}(s)$

The disutility of true positive screening at age 40 (and at younger ages) is set equal to two weeks (Gram et al. 1990, Velanovich 1995).

$$u_t^{bio}(s) = \begin{cases} \frac{2}{52} & \text{when } a_t \in \{25, 26, \dots, 40\} \text{ and } s \in \{1, 2\} \\ \frac{2}{52} + \beta_B(a_t - 40) & \text{when } a_t \in \{41, 42, \dots, 99\} \text{ and } s \in \{1, 2\} \\ \alpha_{BLF} * \frac{2}{52} & \text{when } a_t = 100 \text{ and } s \in \{1, 2\} \\ \alpha_{FPP} * u_t^{bio}(s+1) & \text{when } a_t \in \{25, 26, \dots, 99\} \text{ and } s = 0 \end{cases}$$

Biopsy disutility linearity slope  $\beta_B = \frac{2}{52} \frac{\alpha_{BLF}-1}{100-40}$ . Biopsy linearity factor  $\alpha_{BLF}=1$  and  $=2$  when a constant or an increasing disutility function is employed, respectively. Accordingly,  $\beta_B$  disappears when harm associated with biopsy is assumed to remain constant with age (i.e., when  $\alpha_{BLF}$  is set to 1). False-positive penalty constant  $\alpha_{FPP}$  is set to 2.

## Appendix G: The Impact of the Regularity Constraints

To assess the impact of regularity constraints, enforcing structured screening strategies, we solve the MILP formulation excluding the regularity constraints. In particular, we solve the MILP formulation without the regularity constraints at the budget levels that correspond the optimal ten-year strategies presented in the main text. This allows us to compare the QALYs for the optimal ten-year strategies with and without the regularity constraints. We present the results for each age category below. As expected, the computational time for solving the MILP formulation increases when the regularity constraints are removed. After the regularity constraints are removed, the increases in lifetime QALYs are always less than 1.5% with only one exception, where the optimal strategy “1 US at age 35” yields QALYs 3.66% worse than its irregular counterpart. These results indicate that for any optimal irregular lifetime strategy, there exists a regular policy with a comparable performance that is more practical for implementation.

Ten-Year Strategy with Regularity	Ten-Year Budget per Individual	Lifetime QALYs with Regularity	Lifetime QALYs without Regularity	QALYs Reduction due to Regularity
No Screening	\$0	45.754	45.754	NA
1 US at age 25	\$277	45.756	45.852	0.21%
2 US at ages 25 and 30	\$577	51.626	51.790	0.32%
Biennial US between age 25-34	\$1,430	52.707	52.942	0.44%
Annual US between age 25-34	\$2,793	53.089	53.130	0.08%
Annual MRI between age 25-34	\$16,841	53.197	53.212	0.03%
Annual MRI+MAM between age 25-34	\$17,135	53.208	53.212	0.01%

**Table G.1 The Impact of the Regularity on the Lifetime QALYs of 25 Year-old Women with BRCA1+**

Ten-Year Strategy with Regularity	Ten-Year Budget per Individual	Lifetime QALYs with Regularity	Lifetime QALYs without Regularity	QALYs Reduction due to Regularity
No Screening	\$0	37.611	37.611	NA
1 US at age 35	\$279	37.641	39.073	3.66%
2 US at ages 35 and 40	\$508	42.189	42.439	0.59%
Biennial US between age 35-44	\$1,258	43.170	43.358	0.43%
Annual US between age 35-44	\$2,232	43.535	43.544	0.02%
Annual MRI between age 35-44	\$16,451	43.613	43.643	0.07%
Annual MRI+MAM between age 35-44	\$16,728	43.646	43.660	0.03%

**Table G.2 The Impact of the Regularity on the Lifetime QALYs of 35 Year-old Women with BRCA1+**

Ten-Year Strategy with Regularity	Ten-Year Budget per Individual	Lifetime QALYs with Regularity	Lifetime QALYs without Regularity	QALYs Reduction due to Regularity
No Screening	\$0	30.778	30.778	NA
1 US at age 45	\$161	30.904	31.062	0.51%
2 US at ages 45 and 50	\$407	33.235	33.617	1.14%
2 MAM at ages 45 and 50	\$665	33.625	34.125	1.47%
Biennial US between age 45-54	\$916	34.257	34.339	0.24%
Biennial MAM between age 45-54	\$1,540	34.320	34.527	0.60%
Annual US between age 45-54	\$1,618	34.532	34.546	0.04%
Annual MAM between age 45-54	\$2,818	34.552	34.559	0.02%
Annual MRI between age 45-54	\$15,311	34.585	34.623	0.11%
Annual MRI+MAM between age 45-54	\$16,213	34.625	34.627	0.01%

**Table G.3 The Impact of the Regularity on the Lifetime QALYs of 45 Year-old Women with BRCA1+**

Ten-Year Strategy with Regularity	Ten-Year Budget per Individual	Lifetime QALYs with Regularity	Lifetime QALYs without Regularity	QALYs Reduction due to Regularity
No Screening	\$0	24.460	24.460	NA
1 US at age 55	\$170	24.613	24.934	1.29%
1 MAM at age 55	\$269	25.346	25.568	0.87%
2 US at ages 55 and 60	\$399	25.651	25.848	0.76%
2 MAM at ages 55 and 60	\$586	25.832	26.039	0.79%
Biennial US between age 55-64	\$886	26.136	26.172	0.14%
Biennial MAM between age 55-64	\$1,321	26.176	26.267	0.35%
Annual US between age 55-64	\$1,572	26.281	26.299	0.07%
Annual MAM between age 55-64	\$2,414	26.304	26.322	0.07%
Annual MRI between age 55-64	\$14,328	26.323	26.336	0.05%
Annual MRI+MAM between age 55-64	\$15,928	26.337	26.340	0.01%

**Table G.4 The Impact of the Regularity on the Lifetime QALYs of 55 Year-old Women with BRCA1+**

Ten-Year Strategy with Regularity	Ten-Year Budget per Individual	Lifetime QALYs with Regularity	Lifetime QALYs without Regularity	QALYs Reduction due to Regularity
No Screening	\$0	17.849	17.849	NA
1 US at age 65	\$188	18.017	18.175	0.87%
1 MAM at age 65	\$272	18.232	18.281	0.27%
2 US at ages 65 and 70	\$388	18.388	18.410	0.12%
2 MAM at ages 65 and 70	\$541	18.421	18.446	0.14%
Biennial US between age 65-74	\$832	18.542	18.546	0.02%
Biennial MAM between age 65-74	\$1,182	18.559	18.578	0.10%
Annual US between age 65-74	\$1,479	18.600	18.601	0.01%
Annual MAM between age 65-74	\$2,150	18.610	18.611	0.01%
Annual MRI between age 65-74	\$13,698	18.616	18.619	0.01%
Annual MRI+MAM between age 65-74	\$15,226	18.625	18.627	0.01%

**Table G.5 The Impact of the Regularity on the Lifetime QALYs of 65 Year-old Women with BRCA1+**

Ten-Year Strategy with Regularity	Ten-Year Budget per Individual	Lifetime QALYs with Regularity	Lifetime QALYs without Regularity	QALYs Reduction due to Regularity
No Screening	\$0	11.643	11.643	NA
1 US at age 75	\$197	11.743	11.758	0.14%
1 MAM at age 75	\$272	11.785	11.790	0.04%
2 US at ages 75 and 80	\$357	11.817	11.820	0.02%
2 MAM at ages 75 and 80	\$486	11.827	11.829	0.01%
Biennial US between age 75-84	\$734	11.852	11.854	0.01%
Annual US between age 75-84	\$1,308	11.852	11.859	0.05%

**Table G.6 The Impact of the Regularity on the Lifetime QALYs of 75 Year-old Women with BRCA1+**

Ten-Year Strategy with Regularity	Ten-Year Budget per Individual	Lifetime QALYs with Regularity	Lifetime QALYs without Regularity	QALYs Reduction due to Regularity
No Screening	\$0	6.503	6.503	NA
1 US at age 85	\$211	6.548	6.549	0.01%
1 MAM at age 85	\$284	6.551	6.552	0.01%
2 US at ages 85 and 90	\$316	6.555	6.555	0.01%
2 MAM at ages 85 and 90	\$426	6.556	6.559	0.05%
Biennial US between age 85-94	\$594	6.557	6.561	0.06%

**Table G.7 The Impact of the Regularity on the Lifetime QALYs of 85 Year-old Women with BRCA1+**

## Appendix H: Model and Parameter Validation: Disease Incidence and Mortality

To validate the disease incidence and progression model and its parameters, we solve the optimization problem under “no intervention (i.e., no screening and treatment)” scenario, for all high-risk sub-populations (BRCA1, BRCA 2, and Family History) and different ages (e.g., age 25, 35, 45). This model corresponds to the natural history of disease and is done by enforcing “no action” constraints on the optimization model, which reduces it into a simulation model. This analysis verifies that the incidence and mortality rates generated by our model are within the values reported by the clinical literature and further, are in agreement with the other models, such as BOADICEA(for BRCA mutations) and BRCAT. For instance, the incidence rates reported by the literature range from 40% to 87% for BRCA1 and from 27% to 84% for BRCA2 ([Kuchenbaecker et al. 2017](#)), and the BRCAT model estimates around 20% lifetime risk for women with family history.

<b>Population Level Simulations</b>	<b>BRCA 1</b>			<b>BRCA 2</b>			<b>Family History</b>		
	<b>Health State by Age 100</b>	<b>Age 25</b>	<b>Age 35</b>	<b>Age 45</b>	<b>Age 25</b>	<b>Age 35</b>	<b>Age 45</b>	<b>Age 25</b>	<b>Age 35</b>
Alive - Healthy	1.15%	1.26%	1.48%	1.15%	1.21%	1.35%	1.94%	1.96%	2.01%
Alive - in Situ BC	0.10%	0.11%	0.12%	0.11%	0.12%	0.13%	0.14%	0.14%	0.15%
Alive - Invasive BC	0.05%	0.06%	0.06%	0.07%	0.07%	0.07%	0.06%	0.06%	0.06%
Dead due to in Situ BC	8.83%	8.95%	9.10%	10.75%	10.94%	11.29%	6.04%	6.07%	6.09%
Dead due to Invasive BC	42.04%	38.20%	30.31%	38.20%	36.22%	31.45%	14.71%	14.55%	13.59%
Dead - No BC	47.83%	51.43%	58.92%	49.71%	51.44%	55.71%	77.11%	77.22%	78.10%
<b>Statistics at Age 100</b>									
Cumulative BC Incidence	51.02%	47.32%	39.59%	49.13%	47.35%	42.94%	20.95%	20.82%	19.89%
BC Mortality Rate	50.87%	47.15%	39.41%	48.95%	47.16%	42.74%	20.75%	20.62%	19.68%

**Table H.1 Breast Cancer Incidence and Mortality under No Intervention for High-risk Populations**

## Appendix I: The Impact of Inflation on Screening Cost-Effectiveness

Using the typical 3% annual increase in screening-related costs per year, we perform an additional study to assess the impact of inflation rate on our numerical results. In our numerical study, we consider three different future scenarios (namely, constrained future budget, no/zero future budget, and unlimited future budget after ten years) to study the cost-effectiveness of the identified optimal ten-year screening strategies

and assess the robustness of our findings under different future scenarios. Accordingly, we evaluate the impact of inflation on the cost-effectiveness of the optimal ten-year screening strategies under each one of these future budget scenarios separately. For each of these three scenarios, we observe that the incorporation of a standard annual inflation rate does not change our qualitative findings and conclusions regarding the cost-effectiveness of the optimal ten-year strategies. Here, we briefly discuss our findings and conclusions for each future budget scenario:

**Constrained Future Budget:** As expected, except for the single-screening strategies that perform a screening at the beginning of the ten year interval, an inflation rate causes an increase in the total costs, where the increase is more for the strategies that conduct frequent screenings. Yet, this change in costs associated with screening does not affect the cost-effectiveness findings of our study. This is mainly due to two factors. First, the cost-effectiveness intervals, defined as the cost range a cost-effective strategy continues to remain cost-effective, are large enough to absorb the effect of a reasonable inflation. Second, in our numerical study, in line with our concentration on the first ten-year policies, we focus specifically on the QALYs attributable to the first ten-year strategies, rather than total lifetime QALYs, when we assess the cost-effectiveness of the identified optimal ten-year strategies. Accordingly, the QALYs attributable to the first ten-year strategies remain mostly immune to the increased screening and biopsy costs after ten years. The details of this analysis are presented in the main text.

**No Future Budget:** Under no future budget scenario, the impact of inflation remains limited to the screening and follow-up biopsy costs associated with the screenings performed only within the first ten-year period. As expected, the cost of each ten-year year strategy, except for the single-screening strategies, increases but the cost-effectiveness findings remain robust to this change.

**Unlimited Future Budget:** When the budgetary constraints corresponding to the future ten-year periods are removed from the MILP formulation, the optimization model chooses the same lifetime strategy for the future following each first ten-year strategy. As expected, without any financial considerations after the initial ten-year period, the chosen strategy corresponds to the most clinically effective strategy for the future, maximizing the QALYs, and is already highly costly without inflation. The introduction of an inflation rate further significantly increases the costs yet this increase is the same for all first-ten year strategies after ten years since the same future lifetime strategy is chosen and implemented for each afterwards. As a result, even though the effect of inflation is highly significant over the lifetime costs, our findings regarding the cost-effectiveness of the first ten-year strategy remain unchanged also under an unlimited future budget scenario. In other words, despite the non-negligible impact of inflation on lifetime costs, the cost-effectiveness results of first ten-year strategy are robust mainly because the same clinically most effective future strategy is implemented after each first ten-year strategy, which keeps the impact of inflation more or less the same for each first ten-year screening policy.

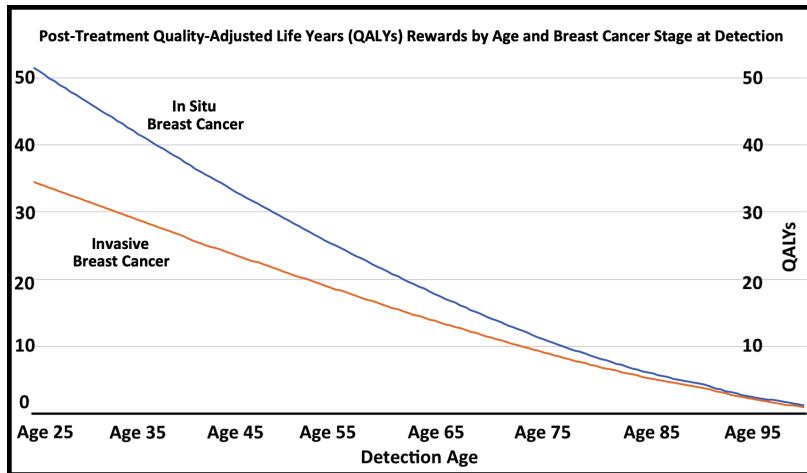
Finally, we note that the impact of an inflation rate could be significant and change the cost-effectiveness outcomes if the lifetime strategies (e.g., 75 year-long screening strategies for 25-year old high-risk women), rather than initial ten-year policies, are studied. In such a case, frequent screenings (e.g., annual mammography for 45-year old women until age 75) that are cost-effective without inflation could become highly expensive and lose their cost-effectiveness depending on the inflation rate.

## Appendix J: The Assumptions of the Structural Analysis: A Numerical Analysis

In the main text, we state that the assumptions presented in *Section 4* are in line with the evidence in the medical literature and are satisfied for young and middle-aged high-risk women in our data, for whom the harms associated with screening are negligible compared to its potential health benefits. The theoretical results discussed in *Section 4* rely on these three assumptions. Here, we briefly demonstrate and discuss how each assumption is supported by our numerical results and clinical data.

**Assumption 1:** In particular, *Assumption 1: “Detection is better than no detection”* always holds as the empirical evidence from the published literature shows that treatment benefits achieved through early detection of breast cancer in high-risk women is always positive. This is further verified by our numerical analysis based on the estimated parameters, where the lump-sum post-treatment QALYs rewards obtained following a screen-detected cancer are always higher than the total rewards obtained under alternative scenarios.

**Assumption 2:** Similar to *Assumption 1*, *Assumption 2: “Early detection is better than late detection”* is also well-established for high-risk women (e.g., BRCA1/2 carriers) in the medical literature. This assumption is also further validated by our post-detection QALY estimation data, where women detected with breast cancer at an earlier age or stage achieve higher (quality-adjusted) survival (Figure J.1).



**Figure J.1 Post-Treatment QALYs by Breast Cancer Detection Age and Stage**

**Assumption 3:** Finally, *Assumption 3*, stating that the sensitivities of the considered imaging technologies are always greater than 0.5, is also validated by real data. This can be seen from Table 5 in the manuscript, where the estimated sensitivity rates of all four modalities considered in our study are above 50% for any age between 25 and 100.

## Appendix K: Budget Estimations for the Screening Programs

The allocated budgets correspond to the total surveillance cost per person in a screening horizon of interest (e.g., ten years), which includes the cost of screenings and when performed, diagnostic follow-up biopsies. A rough estimate on the total surveillance budget can be quickly calculated as follows:

$$B = N_{ALL} * n_{SCREEN} * \text{cost}_{SCREEN} + [ N_{BC} * \text{sens} + (N_{ALL} - N_{BC}) * (1-\text{spec}) ] * n_{SCREEN} * \text{cost}_{BIOPSY}$$

**B:** Budget required over the specified screening interval.

**N<sub>ALL</sub>:** Size of the targeted screening population.

**n<sub>SCREEN</sub>:** Number of screens to be performed during the screening interval

**cost<sub>SCREEN</sub>:** Cost of performing a screening per person.

**N<sub>BC</sub>:** Estimated number of individuals with breast cancer in the targeted population

**sens:** Sensitivity of the imaging technology used for screenings.

**spec:** Specificity of the imaging technology used for screenings.

**cost<sub>BIOPSY</sub>:** Cost of performing a diagnostic biopsy procedure per person.

This formula estimates the total surveillance budget based on the total cost of screenings for the targeted population and the total cost of follow-up diagnostic tests, considering both true-positives and false-positives.

## Appendix L: Strategies under Imperfect Adherence for BRCA1 Mutation Carriers

Here, we present the results under imperfect adherence for BRCA1 mutation carriers and report ICER values for each age group based on adherence function, intolerance parameter (k) and screening strategy.

	Age 25 BRCA 1		Perfect Adherence		Adherence Function = Logistic Sigmoid					Adherence Function = Rational Linear Decay				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 25	\$277	0.0026	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	2 US at ages 25 and 30	\$577	0.1078	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357
IV	Biennial US between age 25-34	\$1,430	0.1939	9,903	9,992	10,089	10,196	10,314	10,443	10,076	10,256	10,443	10,636	10,838
V	Annual US between age 25-34	\$2,793	0.2281	39,869	45,562	54,692	71,528	112,441	353,041	51,899	74,486	132,397	Dominated	Not Optimal
VI	Annual MRI between age 25-34	\$16,841	0.2561	Dominated	501,010	501,010	501,010	501,010	501,010	501,010	501,010	501,010	507,505	645,475
VII	Annual MRI+MAM between age 25-34	\$17,135	0.2673	366,239	534,053	1,229,056	Not Optimal	Not Optimal	Not Optimal	764,666	12,135,316	Not Optimal	Not Optimal	Not Optimal

	Age 25 BRCA 1		Perfect Adherence		Adherence Function = Exponential Decay					Adherence Function = Hyperbolic Tangent				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 25	\$277	0.0026	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	2 US at ages 25 and 30	\$577	0.1078	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357	5,357
IV	Biennial US between age 25-34	\$1,430	0.1939	9,903	10,083	10,284	10,510	10,765	13,149	10,089	10,314	10,586	10,922	11,343
V	Annual US between age 25-34	\$2,793	0.2281	39,869	53,200	87,953	404,918	Not Optimal	107,690	54,692	112,441	Not Optimal	Not Optimal	Not Optimal
VI	Annual MRI between age 25-34	\$16,841	0.2561	Dominated	501,010	501,010	782,832	501,010	501,010	501,010	501,010	650,659	2,930,025	Not Optimal
VII	Annual MRI+MAM between age 25-34	\$17,135	0.2673	366,239	926,012	Not Optimal	Not Optimal	Not Optimal	1,229,056	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal

Table L.1 Results under Imperfect Adherence for 25 Year-old Women with BRCA1+

	Age 35 BRCA 1		Perfect Adherence		Adherence Function = Logistic Sigmoid					Adherence Function = Rational Linear Decay				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 35	\$279	0.0301	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	2 US at ages 35 and 40	\$508	0.4349	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167
IV	Biennial US between age 35-44	\$1,258	0.6719	3,166	3,224	3,289	3,361	3,443	3,535	3,280	3,402	3,535	3,678	3,833
V	Annual US between age 35-44	\$2,232	0.7599	11,078	13,390	17,793	29,305	133,325	Not Optimal	16,342	32,004	2,580,513	Not Optimal	Not Optimal
VI	Annual MRI between age 35-44	\$16,451	0.7654	Dominated	2,580,938	2,580,938	2,580,938	2,580,938	Not Optimal	2,580,938	2,580,938	2,580,938	Not Optimal	Not Optimal
VII	Annual MRI+MAM between age 35-44	\$16,728	0.7982	377,806	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal
Age 35 BRCA 1		Perfect Adherence		Adherence Function = Exponential Decay					Adherence Function = Hyperbolic Tangent					
Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 35	\$279	0.0301	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	2 US at ages 35 and 40	\$508	0.4349	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167	1,167
IV	Biennial US between age 35-44	\$1,258	0.6719	3,166	3,284	3,422	3,583	3,776	6,306	3,289	3,443	3,640	3,900	4,256
V	Annual US between age 35-44	\$2,232	0.7599	11,078	17,005	48,705	Not Optimal	Not Optimal	104,441	17,793	133,325	Not Optimal	Not Optimal	Not Optimal
VI	Annual MRI between age 35-44	\$16,451	0.7654	Dominated	2,580,938	2,580,938	Not Optimal	Not Optimal	2,580,938	2,580,938	2,580,938	Not Optimal	Not Optimal	Not Optimal
VII	Annual MRI+MAM between age 35-44	\$16,728	0.7982	377,806	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal

Table L.2 Results under Imperfect Adherence for 35 Year-old Women with BRCA1+

	Age 45 BRCA 1		Perfect Adherence		Adherence Function = Logistic Sigmoid					Adherence Function = Rational Linear Decay				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 35	\$161	0.1262	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	2 US at ages 35 and 40	\$407	0.5328	765	765	765	765	765	765	765	765	765	765	765
IV	2 MAM at ages 45 and 50	\$665	0.5331	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
V	Biennial US between age 35-44	\$916	0.8781	1,474	1,491	1,510	1,531	1,554	1,581	1,507	1,543	1,581	1,620	1,663
VI	Biennial MAM between age 45-54	\$1,540	0.8787	Dominated	Dominated	Dominated	Dominated	Dominated	1,086,707	Dominated	Dominated	Dominated	1,086,707	1,086,707
VII	Annual US between age 35-44	\$1,618	0.9960	5,949	7,143	9,377	14,978	53,731	Not Optimal	8,647	16,243	Dominated	Not Optimal	Not Optimal
VIII	Annual MAM between age 45-54	\$2,818	1.0120	75,086	75,086	75,086	75,086	75,086	Not Optimal	75,086	75,086	92,226	Not Optimal	Not Optimal
IX	Annual MRI between age 35-44	\$15,311	1.0143	Dominated	5,443,342	5,443,342	5,443,342	5,443,342	Not Optimal	5,443,342	5,443,342	5,443,342	Not Optimal	Not Optimal
X	Annual MRI+MAM between age 35-44	\$16,213	1.0519	335,736	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal
Age 45 BRCA 1		Perfect Adherence		Adherence Function = Exponential Decay					Adherence Function = Hyperbolic Tangent					
Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 35	\$161	0.1262	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	2 US at ages 35 and 40	\$407	0.5328	765	765	765	765	765	765	765	765	765	765	765
IV	2 MAM at ages 45 and 50	\$665	0.5331	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
V	Biennial US between age 35-44	\$916	0.8781	1,474	1,509	1,548	1,594	1,647	2,223	1,510	1,554	1,610	1,681	1,773
VI	Biennial MAM between age 45-54	\$1,540	0.8787	Dominated	Dominated	Dominated	1,086,707	1,086,707	Dominated	Dominated	Dominated	1,086,707	1,086,707	1,086,707
VII	Annual US between age 35-44	\$1,618	0.9960	5,949	8,981	23,703	Not Optimal	Not Optimal	44,712	9,377	53,731	Not Optimal	Not Optimal	Not Optimal
VIII	Annual MAM between age 45-54	\$2,818	1.0120	75,086	75,086	75,086	Not Optimal	Not Optimal	75,086	75,086	75,086	Not Optimal	Not Optimal	Not Optimal
IX	Annual MRI between age 35-44	\$15,311	1.0143	Dominated	5,443,342	5,443,342	Not Optimal	Not Optimal	5,443,342	5,443,342	5,443,342	Not Optimal	Not Optimal	Not Optimal
X	Annual MRI+MAM between age 35-44	\$16,213	1.0519	335,736	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal

Table L.3 Results under Imperfect Adherence for 45 Year-old Women with BRCA1+

	Age 55 BRCA 1		Perfect Adherence		Adherence Function = Logistic Sigmoid					Adherence Function = Rational Linear Decay				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 55	\$170	0.1529	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	1 MAM at age 55	\$269	0.1530	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
IV	2 US at ages 55 and 60	\$399	0.3815	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046
V	2 MAM at ages 55 and 60	\$586	0.3988	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
VI	Biennial US between age 55-64	\$886	0.5884	2,354	2,392	2,434	2,482	2,536	2,597	2,429	2,509	2,596	2,691	2,793
VII	Biennial MAM between age 55-64	\$1,321	0.6016	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	33,117
VIII	Annual US between age 55-64	\$1,572	0.6683	8,598	10,302	Dominated	Dominated	Not Optimal	Not Optimal	Dominated	Dominated	Not Optimal	Not Optimal	Not Optimal
IX	Annual MAM between age 55-64	\$2,414	0.7414	11,495	11,495	12,269	14,245	17,447	23,475	11,884	14,541	18,518	25,121	42,372
X	Annual MRI between age 55-64	\$14,328	0.7427	Dominated	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200
XI	Annual MRI+MAM between age 55-64	\$15,928	0.7466	2,588,932	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal
Age 55 BRCA 1		Perfect Adherence		Adherence Function = Exponential Decay					Adherence Function = Hyperbolic Tangent					
Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 55	\$170	0.1529	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	1 MAM at age 55	\$269	0.1530	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
IV	2 US at ages 55 and 60	\$399	0.3815	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046
V	2 MAM at ages 55 and 60	\$586	0.3988	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
VI	Biennial US between age 55-64	\$886	0.5884	2,354	2,432	2,522	2,628	2,756	4,433	2,434	2,536	2,666	2,837	3,072
VII	Biennial MAM between age 55-64	\$1,321	0.6016	Dominated	Dominated	Dominated	Dominated	33,117	Dominated	Dominated	Dominated	33,117	33,117	33,117
VIII	Annual US between age 55-64	\$1,572	0.6683	8,598	Dominated	Dominated	Not Optimal	Not Optimal	Dominated	13,466	70,633	Not Optimal	Not Optimal	Not Optimal
IX	Annual MAM between age 55-64	\$2,414	0.7414	11,495	12,066	15,742	23,959	58,604	17,155	12,269	17,447	43,614	Not Optimal	Not Optimal
X	Annual MRI between age 55-64	\$14,328	0.7427	Dominated	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200	9,068,200
XI	Annual MRI+MAM between age 55-64	\$15,928	0.7466	2,588,932	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal

Table L.4 Results under Imperfect Adherence for 55 Year-old Women with BRCA1+

	Age 65 BRCA 1		Perfect Adherence		Adherence Function = Logistic Sigmoid					Adherence Function = Rational Linear Decay				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 65	\$188	0.1708	1,099	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	1 MAM at age 65	\$272	0.1717	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
IV	2 US at ages 65 and 70	\$388	0.2760	1,907	1,407	1,407	1,407	1,407	1,407	1,407	1,407	1,407	1,407	1,407
V	2 MAM at ages 65 and 70	\$541	0.2902	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
VI	Biennial US between age 65-74	\$832	0.3916	3,834	3,927	4,032	4,152	4,290	4,452	4,018	4,222	4,451	4,710	5,005
VII	Biennial MAM between age 65-74	\$1,182	0.4086	Dominated	Dominated	Dominated	20,703	20,703	20,703	Dominated	20,703	20,703	20,703	20,703
VIII	Annual US between age 65-74	\$1,479	0.4493	11,234	13,215	16,708	37,620	Not Optimal	Not Optimal	15,595	53,320	Not Optimal	Not Optimal	Not Optimal
IX	Annual MAM between age 65-74	\$2,150	0.4597	64,385	64,385	64,385	59,790	215,597	64,385	64,385	71,382	427,473	Not Optimal	Not Optimal
X	Annual MRI between age 65-74	\$13,698	0.4660	Dominated	1,830,104	1,830,104	1,830,104	1,830,104	1,830,104	1,830,104	1,830,104	1,830,104	1,830,104	1,830,104
XI	Annual MRI+MAM between age 65-74	\$15,226	0.4751	848,538	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal
Age 65 BRCA 1		Perfect Adherence		Adherence Function = Exponential Decay					Adherence Function = Hyperbolic Tangent					
Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 65	\$188	0.1708	1,099	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
III	1 MAM at age 65	\$272	0.1717	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
IV	2 US at ages 65 and 70	\$388	0.2760	1,907	1,407	1,407	1,407	1,407	1,407	1,407	1,407	1,407	1,407	1,407
V	2 MAM at ages 65 and 70	\$541	0.2902	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
VI	Biennial US between age 65-74	\$832	0.3916	3,834	4,025	4,254	4,538	4,896	13,222	4,032	4,290	4,641	5,138	5,894
VII	Biennial MAM between age 65-74	\$1,182	0.4086	Dominated	Dominated	20,703	20,703	20,703	Dominated	20,703	20,703	20,703	20,703	20,703
VIII	Annual US between age 65-74	\$1,479	0.4493	11,234	16,108	Not Optimal	Not Optimal	Not Optimal	16,708	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal
IX	Annual MAM between age 65-74	\$2,150	0.4597	64,385	64,385	103,498	Not Optimal	Not Optimal	338,817	64,385	594,145	Not Optimal	Not Optimal	Not Optimal
X	Annual MRI between age 65-74	\$13,698	0.4660	Dominated	1,830,104	1,830,104	Not Optimal	Not Optimal	1,830,104	1,830,104	1,830,104	Not Optimal	Not Optimal	Not Optimal
XI	Annual MRI+MAM between age 65-74	\$15,226	0.4751	848,538	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal

Table L.5 Results under Imperfect Adherence for 65 Year-old Women with BRCA1+

	Age 75 BRCA 1		Perfect Adherence		Adherence Function = Logistic Sigmoid					Adherence Function = Rational Linear Decay				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 75	\$197	0.0921	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137
III	1 MAM at age 75	\$272	0.1007	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
IV	2 US at ages 75 and 80	\$357	0.1322	4,001	4,023	4,045	4,069	4,094	4,120	4,044	4,089	4,134	4,181	4,230
V	2 MAM at ages 75 and 80	\$486	0.1422	Dominated	Dominated	Dominated	Dominated	12,884	12,884	Dominated	12,884	12,884	12,884	12,884
VI	Biennial US between age 75-84	\$734	0.1669	10,887	11,397	12,007	12,746	14,200	16,471	11,922	13,399	16,463	21,939	34,518
VII	Annual US between age 75-84	\$1,308	0.1672	1,649,468	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal
Age 75 BRCA 1		Perfect Adherence		Adherence Function = Exponential Decay					Adherence Function = Hyperbolic Tangent					
Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 75	\$197	0.0921	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137	2,137
III	1 MAM at age 75	\$272	0.1007	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
IV	2 US at ages 75 and 80	\$357	0.1322	4,001	4,045	4,091	4,141	4,194	4,250	4,045	4,094	4,148	4,207	4,272
V	2 MAM at ages 75 and 80	\$486	0.1422	Dominated	Dominated	12,884	12,884	12,884	12,884	Dominated	12,884	12,884	12,884	12,884
VI	Biennial US between age 75-84	\$734	0.1669	10,887	11,963	13,769	17,987	28,530	Not Optimal	12,007	14,200	20,170	46,096	Not Optimal
VII	Annual US between age 75-84	\$1,308	0.1672	1,649,468	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal

**Table L.6 Results under Imperfect Adherence for 75 Year-old Women with BRCA1+**

	Age 85 BRCA 1		Perfect Adherence		Adherence Function = Logistic Sigmoid					Adherence Function = Rational Linear Decay				
	Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 85	\$211	0.0450	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678
III	1 MAM at age 85	\$284	0.0485	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
IV	2 US at ages 85 and 90	\$316	0.0519	15,247	15,608	16,002	16,434	16,911	17,438	15,978	16,800	17,731	18,794	20,020
V	2 MAM at ages 85 and 90	\$426	0.0534	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250
VI	Biennial US between age 85-94	\$594	0.0546	145,448	486,534	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal
Age 85 BRCA 1		Perfect Adherence		Adherence Function = Exponential Decay					Adherence Function = Hyperbolic Tangent					
Ten-Year Screening Strategy	Ten-year Budget	First Ten Years QALYs	ICER (\$/QALYs)	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	k = 0.01	k = 0.02	k = 0.03	k = 0.04	k = 0.05	
I	No Screening	\$0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II	1 US at age 85	\$211	0.0450	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678	4,678
III	1 MAM at age 85	\$284	0.0485	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	21,174
IV	2 US at ages 85 and 90	\$316	0.0519	15,247	15,990	16,854	17,872	19,090	20,570	16,002	16,911	18,024	19,418	21,389
V	2 MAM at ages 85 and 90	\$426	0.0534	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250	73,250
VI	Biennial US between age 85-94	\$594	0.0546	145,448	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal	Not Optimal

**Table L.7 Results under Imperfect Adherence for 85 Year-old Women with BRCA1+**

## Appendix M: Population-Level Simulation Analysis under Screening Interventions

Here, we present the population-level simulation results under various screening interventions corresponding to all age groups and high-risk populations considered in our study.













## Appendix N: Incorporating Patient Adherence into the Optimization Model

This appendix discusses the potential adjustments required to integrate patient adherence into the optimization framework. In particular, below, we outline the necessary modifications and considerations for incorporating adherence into the mixed integer linear programming formulation, providing a foundation for future research.

- **Defining an Adherence Function:** We define  $A_t(a, n)$ , an adherence function that depends on the screening action  $a \in A$ , capturing the modality used for screening at time  $t \in T_A$ , and screening frequency  $n$ , capturing the frequency of screening within the corresponding screening interval of length  $L$  (e.g.,  $L = 10$  years). In the adjusted formulation,  $A_t(a, n)$  is used to scale (down) the benefits or costs associated with screening recommendations, ensuring that outcomes are adjusted for adherence behavior.
- **Adjusting Disease Detection Rates and Disease Dynamics:** The natural history of breast cancer (i.e., disease incidence and progression) is independent of adherence to screening recommendations and hence, remains unchanged in the model. However, disease detection rates, specifically transitions from undetected cancer states ( $s = 1$  and  $s = 2$ ) to treatment states ( $s = 3$  and  $s = 4$ ), must be adjusted to account for adherence.

In the original formulation,  $x_t(s, a)$  denotes the proportion of women in health state  $s \in S$ , taking the screening action  $a \in A$  at time  $t \in T_A$ . Accordingly, if adherence is to be accounted for directly in the formulation, the corresponding variables in *Constraints (3)* and *(4)* should be replaced with  $x_t(s, a)A_t(a, n)$  to accurately reflect the proportion of women in health state  $s \in S$ , who adhere to taking the screening action  $a \in A$  at time  $t \in T_A$ . On the other hand,  $x_t(s, a)(1 - A_t(a, n))$  would represent women who do not take the screening action  $a \in A$  at time  $t \in T_A$  despite the recommendation, and their disease dynamics would follow the natural history of breast cancer.

- **Modifying Other Constraints and the Objective Function:** All other constraints involving  $x_t(s, a)$  must be updated to include adherence in a similar fashion. For example, in *Constraints (5)* (i.e., in budgetary constraints),  $x_t(s, a)$  should be replaced with  $x_t(s, a)A_t(a, n)$  as only women who adhere to the screening recommendations would impact the screening-associated costs. Similarly, the original objective function must be adjusted to reflect the effect of adherence and should incorporate adherence-adjusted terms.
- **Parameterizing the Adherence Function:** The adherence function  $A_t(a, n)$  represents a critical component of the new model and must be parameterized carefully. It should account for *(i)* population-specific factors, such as differences across age groups or different high-risk populations, *(ii)* frequency-specific factors, as more frequent screenings may lead to lower adherence, and *(iii)* modality-specific factors, such as variations in adherence levels across different screening technologies due to differences in cost, convenience, discomfort, or patient preferences.
- **Limitations and Future Directions:** While theoretically feasible, incorporating adherence into the optimization model presents significant challenges and currently, would not be practical mainly due to significant data limitations. That is, while adherence integration might enhance theoretical robustness,

the lack of reliable input data undermines its practical utility. Unfortunately, reliable empirical data on adherence levels across different modalities and frequencies is unavailable, especially for high-risk women. Without such data across different age groups and high-risk populations, any results derived from the model would be speculative and unlikely to provide actionable insights for decision-makers. However, once sufficient empirical data on adherence becomes available, future studies could build upon this framework to explore how adherence variability impacts screening outcomes and cost-effectiveness and investigate strategies to improve adherence and assess their effects within the optimization model.