Supplementary Online Content

Guzauskas GF, Garbett S, Zhou Z, et al. Cost-effectiveness of population-wide genomic screening for hereditary breast and ovarian cancer in the United States. *JAMA Netw Open.* 2020;3(10):e2022874. doi:10.1001/jamanetworkopen.2020.22874

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Additional Model Methods and Expanded Results

Decision Tree Parameters

The overall prevalence of pathogenic HBOC variant carriers (0.5%) was based on data from the Geisinger MyCode Community Health Initiative, a Geisinger system-wide DNA biobank with more than 190,000 patient-participants in Pennsylvania and New Jersey.[1, 2] We used test sensitivity (99%) and specificity (99%) to calculate the likelihood that tested individuals are correctly identified.[3] False positives were not considered other than our assumption that a confirmation test (with associated cost) would correct the screening error. The proportion of HBOC variants identified with family history testing was 17.4%, based on a prior cost-effectiveness analysis of HBOC population screening versus family history testing alone.[4] We then used a recent database analysis of 95,561 women who were tested for HBOC using a next generation sequencing panel to calculate the proportions of HBOC variants that were *BRCA1, BRCA2, ATM, CHEK2, MSH6, PALB2, RAD51C,* and *TP53*.[5]

Markov Model Transitions

A proportion of pre-cancer, known carriers who opted to undergo intensive screening entered the Markov model in starting state 1, in which they received mammography plus MRI according to age-based guidelines for high risk individuals.[6, 7] Pre-cancer (1) noncarriers, (2) known carriers who opted out of intensive screening, and (3) unknown

carriers entered the Markov model in starting state 2, in which they received mammography only according to age-based guidelines for average risk individuals.[8, 9] Known carriers could opt for prophylactic RRM or RRSO based on age-based cumulative uptake among BRCA1/2 positive women (Figure 2 in main text).[10] We modeled a 1-year health state for the year of the procedure, wherein we applied procedure costs and disutilities (Table 1 in main text). Women who underwent RRM or RRSO then transitioned to post-RRM or post-RRSO procedure health states with reduced risks of cancer incidence.[11] Individuals with one procedure could transition to another 1-year state for a second procedure using a weighted probability of RRM and RRSO, with weighted procedure costs and disutilities; these patients then transitioned to a post-2nd procedure health state where we assumed their breast cancer risk was zero, but the age-based, RRSO-adjusted probability of ovarian cancer remained.[11] We assumed the small number of individuals who receive RRM and/or RRSO and nonetheless go on to develop cancer transition to earlier stage cancers due to continued intensive screening.

All individuals were at risk for breast or ovarian cancer according to age-based cancer incidence among carriers and non-carriers (Figure 2 in main text).[12-14] We assumed women undergoing intensive mammography plus MRI would be diagnosed at an earlier stage, on average, than those undergoing standard mammography based on a study showing there were significantly fewer patients with positive lymph nodes at the time of cancer removal surgery in the MRI-screened group compared to the mammography-only screened group.[15] We assumed equivalent incidence of earlier versus later stage

breast or ovarian cancer, however we applied a mortality risk reduction to earlier stage breast cancer health states over the individual's remaining lifetime.[15] In both the earlier and later stage cancer states, we modeled first year-specific treatment costs and utility values. Patients who survived the first year of breast or ovarian cancer then transitioned to post-breast or post-ovarian cancer health states with long-term/continuing treatment costs and utility values.

We also derived age-based estimates of non-*BRCA* variant (*ATM*, *CHEK2*, *MSH6*, *PALB2*, *RAD51C*, *TP53*) cancer incidence from Lu et al., who conducted whole-exome sequencing and gene-phenotype associations on a sample of 11,416 patients with clinical features of breast cancer, ovarian cancer, or both from 1200 hospitals and clinics across the United States, plus 3988 controls who were referred for genetic testing for noncancer conditions.[13] Odds ratios from Lu et al. of breast and/or ovarian cancer risk were converted to relative risk estimates and applied to the cancer incidence data derived for the noncarrier population. Non-*BRCA* mutations were modeled in the Markov model as an HBOC variant prevalence-weighted pooled group. Annual age-based cancer incidence among noncarriers was derived from the Surveillance, Epidemiology, and End Results (SEER) Program.[14]

Breast Screening Uptake

We based uptake of mammography and MRI on current guidelines.[6-9] Noncarriers and unknown carriers were assumed to undergo routine mammography according to

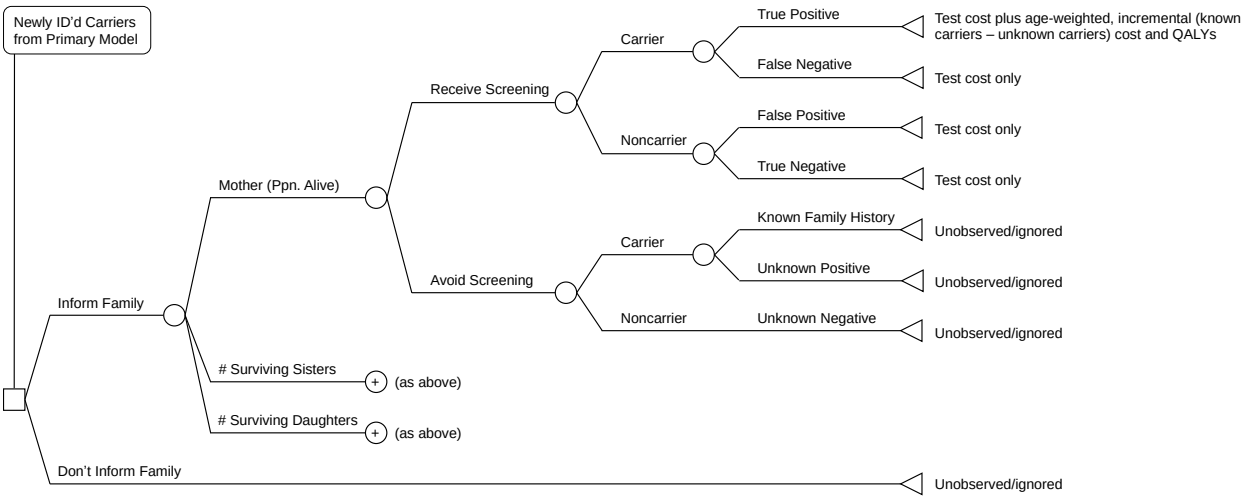
guidelines for average risk women; starting at age 40, we modeled that 50% chose to receive optional annual mammography, increasing to the recommended 100% from ages 45-54, then all women received recommended biannual mammography from age 55 until death. Known carriers were assumed to undergo routine mammography according to guidelines for increased risk women, which recommend annual mammography alternated with annual breast MRI every 6 months. We assumed 75% of women with known increased risk opted for intensive screening with MRI in addition to mammography. We further assumed the remainder of known increased risk women received mammography only at the recommended frequency.

Cascade Testing Module

We used a decision tree to organize key elements of cascade testing including (a) the probability a newly identified carrier will inform their family members, (b) the number of living first degree female relatives, (c) the probability that informed relatives will opt to undergo testing, (d) carrier/noncarrier status, and (e) testing and/or family history testing result. The probabilities for (a) and (c) were informed by a review of family communication of genetic results studies;[16, 17] based on our findings, we assumed that 70% of population screening identified carriers go on to inform their family members, and 20% of family members go on to receive cascade testing. Probability (b) was informed by the Panel Study of Income Dynamics (PSID), a longitudinal household survey[18]; from this we extracted the average number of surviving mothers, sisters, and

daughters by age per woman screened. Probabilities for (d) and (e) were equivalent to those used in the primary population screening model.

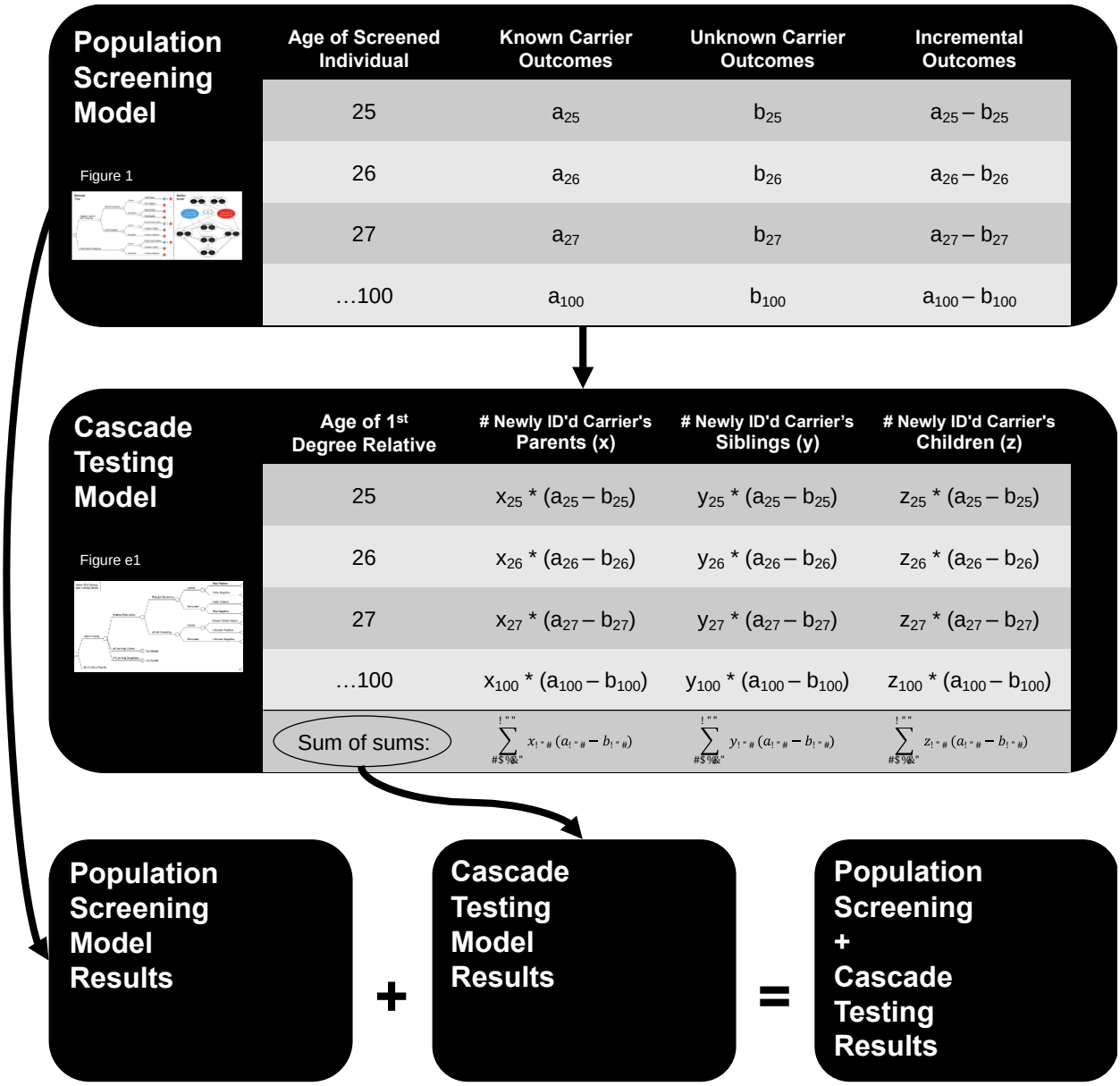
eFigure 1. Cascade Testing Module Decision Tree



The cascade testing module utilized age-based results from the primary screening model, combined with publicly available data on the number of first-degree female relatives of each identified carrier,[18] to calculate the incremental cost and benefits and their impact on the overall model ICER. We estimated age-based incremental outcomes from ages 20 to 100, and estimated a weighted (by number and ages of mother, sisters, and daughters) sum of incremental cost and QALYs over all newly identified family members. These weighted incremental estimates were then "fed back" into the primary population screening model, such that the incremental outcomes from the cascade model are tied to the age of the patient entering the primary model. The process of using the primary model to inform cascade testing incremental outcomes, and then

adding back to the primary model for the cascade screening scenario, is depicted below.

eFigure 2. Calculation of Cascade Testing Outcomes



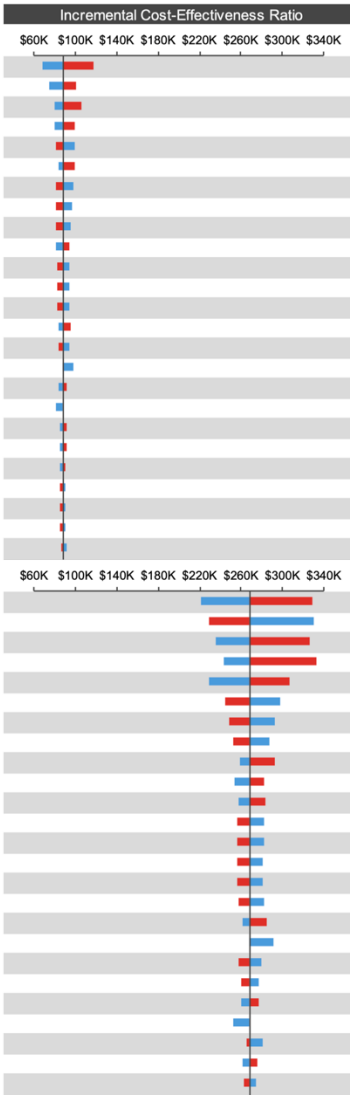
eTable. Expanded Model Results

	Incremental Results						
Screened Age	Earlier Stage Cases/100K	Later Stage Cases/100K	Total Cancer Cases/100K	Cost/ Woman Screened	QALYs/ Woman Screened	Life Years/ Woman Screened	ICER
20	125	-215	-90	$245	0.0027	0.0022	$90,600
21	126	-215	-89	$245	0.0028	0.0023	$89,100
22	127	-215	-88	$245	0.0028	0.0023	$87,600
23	128	-215	-87	$245	0.0028	0.0023	$86,200
24	128	-215	-86	$245	0.0029	0.0024	$84,900
25	131	-216	-86	$246	0.0029	0.0024	$83,800
26	132	-216	-83	$247	0.0029	0.0024	$84,200
27	134	-215	-81	$248	0.0029	0.0024	$84,700
28	135	-214	-79	$249	0.0029	0.0024	$85,400
29	137	-214	-77	$251	0.0029	0.0024	$86,500
30	**138**	**-214**	**-75**	**$252**	**0.0029**	**0.0024**	**$87,700**
31	140	-212	-72	$252	0.0028	0.0023	$90,700
32	143	-211	-68	$253	0.0027	0.0022	$94,400
33	145	-209	-64	$253	0.0026	0.0021	$99,200
34	147	-207	-60	$254	0.0024	0.0020	$105,300
35	150	-206	-56	$255	0.0023	0.0019	$112,500
36	152	-204	-52	$255	0.0022	0.0019	$118,100
37	154	-203	-49	$255	0.0020	0.0018	$125,200
38	155	-201	-46	$256	0.0019	0.0017	$134,300
39	157	-199	-42	$256	0.0017	0.0016	$146,900
40	157	-194	-37	$257	0.0016	0.0014	$164,100
41	157	-192	-35	$258	0.0015	0.0014	$175,800
42	158	-190	-32	$258	0.0014	0.0013	$190,400
43	158	-188	-30	$258	0.0012	0.0012	$209,200
44	159	-185	-27	$259	0.0011	0.0011	$234,500
45	**159**	**-183**	**-24**	**$261**	**0.0010**	**0.0010**	**$268,200**
46	159	-181	-22	$261	0.0009	0.0009	$291,300
47	159	-179	-20	$262	0.0008	0.0009	$320,800
48	159	-177	-18	$262	0.0007	0.0008	$359,800
49	159	-175	-16	$263	0.0006	0.0008	$415,100
50	159	-173	-14	$265	0.0005	0.0007	$482,100
51	157	-171	-13	$265	0.0005	0.0007	$512,600
52	156	-168	-13	$264	0.0005	0.0006	$549,200
53	154	-166	-12	$264	0.0004	0.0006	$593,900
54	153	-164	-11	$264	0.0004	0.0006	$649,700
55	148	-157	-9	$263	0.0003	0.0005	$831,500
56	146	-155	-8	$262	0.0003	0.0005	$889,700
57	144	-152	-8	$261	0.0003	0.0005	$961,100
58	143	-150	-7	$260	0.0002	0.0004	$1,051,100

	Incremental Results						
Screened Age	Earlier Stage Cases/100K	Later Stage Cases/100K	Total Cancer Cases/100K	Cost/ Woman Screened	QALYs/ Woman Screened	Life Years/ Woman Screened	ICER
59	141	-148	-7	$259	0.0002	0.0004	$1,169,200
60	136	-141	-5	$257	0.0002	0.0004	$1,666,100
61	133	-138	-5	$256	0.0001	0.0004	$1,773,100
62	130	-136	-5	$255	0.0001	0.0003	$1,897,200
63	128	-133	-5	$254	0.0001	0.0003	$2,043,600
64	125	-130	-5	$253	0.0001	0.0003	$2,219,700
65	119	-123	-4	$250	0.0001	0.0003	$4,424,400
66	116	-120	-4	$249	0.0000	0.0003	$5,360,300
67	113	-116	-3	$248	0.0000	0.0003	$6,856,400
68	110	-113	-3	$246	0.0000	0.0002	$9,655,100
69	106	-110	-3	$245	0.0000	0.0002	$16,930,700
70	100	-102	-2	$243	-0.0001	0.0002	-$4,391,900
71	96	-98	-2	$242	-0.0001	0.0002	-$3,910,000
72	92	-94	-2	$241	-0.0001	0.0002	-$3,522,000
73	88	-90	-2	$239	-0.0001	0.0002	-$3,200,900
74	84	-85	-2	$238	-0.0001	0.0002	-$2,929,200
75	83	-84	-1	$239	-0.0001	0.0001	-$2,448,000
76	78	-79	-1	$237	-0.0001	0.0001	-$2,309,600
77	73	-75	-1	$236	-0.0001	0.0001	-$2,185,700
78	68	-70	-1	$235	-0.0001	0.0001	-$2,073,400
79	63	-64	-1	$234	-0.0001	0.0001	-$1,970,500
80	57	-58	-1	$231	-0.0002	0.0001	-$1,492,500
81	54	-55	-1	$230	-0.0002	0.0001	-$1,448,000
82	51	-52	-1	$228	-0.0002	0.0001	-$1,406,500
83	48	-49	-1	$227	-0.0002	0.0001	-$1,367,500
84	45	-46	-1	$225	-0.0002	0.0001	-$1,330,200
85	43	-44	-1	$224	-0.0002	0.0001	-$1,314,100
86	40	-41	-1	$223	-0.0002	0.0001	-$1,283,200
87	37	-37	-1	$221	-0.0002	0.0001	-$1,253,800
88	33	-34	-1	$220	-0.0002	0.0001	-$1,225,300
89	30	-30	-1	$219	-0.0002	0.0001	-$1,196,600
90	24	-25	0	$216	-0.0002	0.0000	-$1,037,300
91	23	-23	0	$214	-0.0002	0.0000	-$1,025,400
92	22	-22	0	$213	-0.0002	0.0000	-$1,014,100
93	21	-21	0	$212	-0.0002	0.0000	-$1,003,100
94	20	-20	0	$211	-0.0002	0.0000	-$991,800
95	15	-15	0	$208	-0.0002	0.0000	-$940,100
96	14	-14	0	$206	-0.0002	0.0000	-$930,000
97	12	-13	0	$205	-0.0002	0.0000	-$919,700
98	10	-10	0	$202	-0.0002	0.0000	-$908,500
99	7	-8	0	$199	-0.0002	0.0000	-$894,900

In one-way sensitivity analysis, one parameter at a time is varied to its low and high value while keeping all other parameters constant. Parameters with the greatest impact on results have the largest bars in the “tornado” diagram and are located on top.

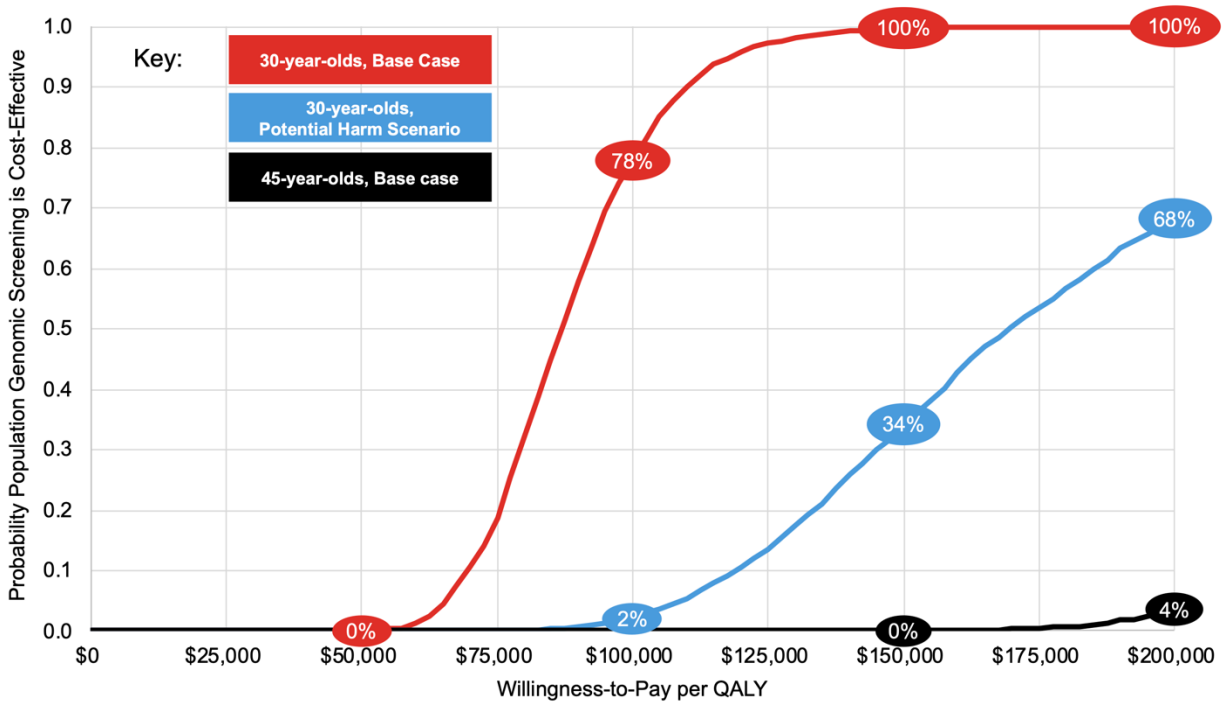
eFigure 3. Results of One-Way Sensitivity Analysis



Incremental Cost-Effectiveness Ratio	Parameter	Low Input	High Input	Low Result	High Result	Spread
	Population: 30-Year-Old Women					
	Breast Cancer 5-Year Survival	-20%	+20%	$68,291	$117,098	$48,806
	Screening Assay Cost	$160	$240	$74,438	$100,866	$26,428
	Breast Cancer HR Post-Oophorectomy: BRCA2	0.16	0.82	$79,879	$106,015	$26,136
	Breast Cancer HR Post-Oophorectomy: BRCA1	0.41	0.96	$79,998	$99,216	$19,218
	BRCA2 Oophorectomy Annual Uptake	-50%	+50%	$99,879	$80,808	$19,071
	Ovarian Cancer HR Post-Oophorectomy: BRCA1	0.12	0.82	$83,332	$99,657	$16,325
	BRCA1 Oophorectomy Annual Uptake	-50%	+50%	$97,705	$81,649	$16,056
	Proportion of Carriers: BRCA2	0.232	0.348	$96,186	$80,563	$15,623
	BRCA2 Mastectomy Annual Uptake	-50%	+50%	$95,302	$81,659	$13,643
	Annual Intense Screening (MRI) Cost	$1,122	$1,683	$81,519	$93,785	$12,266
	BRCA1 Mastectomy Annual Uptake	-50%	+50%	$94,345	$82,126	$12,219
	HBOC Carrier Prevalence (Overall)	0.452%	0.538%	$94,014	$82,318	$11,696
	Proportion of Carriers: BRCA1	0.221	0.332	$93,929	$82,250	$11,679
	Breast Cancer HR Post-Oophorectomy: Non-BRCA	0.16	0.82	$84,192	$95,711	$11,518
	BRCA2 Breast Cancer Annual Incidence	-20%	+20%	$93,476	$83,091	$10,385
	Utility: Well	0.950	1.000	$97,388	$87,652	$9,737
	Utility: Post Breast Cancer	0.770	0.851	$83,958	$91,686	$7,729
	Mammography+MRI Uptake, Increased Risk, 30-74	0.800	1.000	$80,696	$87,652	$6,955
	Proportion of Known Carriers Who Get MRI	0.600	0.900	$84,401	$90,867	$6,466
	Breast Cancer Mortality Relative Reduction: Early Stage	0.900	1.000	$85,025	$91,227	$6,202
	Proportion ID'd Mutations with FH Testing	0.139	0.209	$84,842	$90,709	$5,867
	BRCA1 Breast Cancer Annual Incidence	-20%	+20%	$90,651	$85,263	$5,388
	Breast Cancer Odds Ratio: PALB2	2.24	17.65	$90,249	$84,892	$5,357
	General Population Breast Cancer Annual Incidence	-20%	+20%	$90,142	$85,553	$4,589
	Screening Test Sensitivity	0.950	1.000	$91,405	$86,917	$4,488
	Population: 45-Year-Old Women					
	Breast Cancer 5-Year Survival	-20%	+20%	$221,245	$329,244	$107,999
	BRCA2 Oophorectomy Annual Uptake	-50%	+50%	$329,820	$228,412	$101,408
	Breast Cancer Mortality Relative Reduction: Early Stage	0.900	1.000	$235,115	$326,329	$91,214
	Breast Cancer HR Post-Oophorectomy: BRCA2	0.16	0.82	$242,693	$333,326	$90,633
	Screening Assay Cost	$160	$240	$229,033	$307,290	$78,257
	Proportion of Carriers: BRCA2	0.232	0.348	$297,360	$244,649	$52,711
	BRCA1 Oophorectomy Annual Uptake	-50%	+50%	$291,885	$248,740	$43,145
	HBOC Carrier Prevalence (Overall)	0.452%	0.538%	$286,997	$252,369	$34,629
	Ovarian Cancer HR Post-Oophorectomy: BRCA1	0.12	0.82	$259,153	$292,391	$33,238
	Annual Intense Screening (MRI) Cost	$1,122	$1,683	$253,667	$282,656	$28,988
	Breast Cancer HR Post-Oophorectomy: BRCA1	0.41	0.96	$257,221	$283,770	$26,549
	Proportion of Carriers: BRCA1	0.221	0.332	$281,943	$255,961	$25,982
	Cascade Screening: Proportion. Carriers	0.400	0.600	$281,510	$256,195	$25,315
	Cascade Screening: Proportion. Tell Family	0.560	0.840	$281,441	$256,257	$25,184
	Cascade Screening: Proportion. Family Tested	0.160	0.240	$281,441	$256,257	$25,184
	BRCA2 Breast Cancer Annual Incidence	-20%	+20%	$282,360	$257,215	$25,145
	Breast Cancer HR Post-Oophorectomy: Non-BRCA	0.16	0.82	$260,972	$284,644	$23,671
	Utility: Well	0.950	1.000	$291,409	$268,162	$23,247
	BRCA2 Mastectomy Annual Uptake	-50%	+50%	$279,792	$257,541	$22,251
	BRCA1 Mastectomy Annual Uptake	-50%	+50%	$277,446	$259,541	$17,905
	Proportion ID'd Mutations with FH Testing	0.139	0.209	$260,171	$276,830	$16,659
	Mammography+MRI Uptake, Increased Risk, 30-74	0.800	1.000	$252,315	$268,162	$15,847
	Screening Test Sensitivity	0.950	1.000	$281,387	$265,576	$15,811
	Utility: Post Breast Cancer	0.770	0.851	$261,536	$275,132	$13,596
	BRCA1 Breast Cancer Annual Incidence	-20%	+20%	$274,661	$262,817	$11,844

Probabilistic sensitivity analysis results are presented as cost-effectiveness acceptability curves, which show the Bayesian probability that the results are cost-effective at increasing willingness-to-pay per QALY thresholds (supplementary Figure e4). For 30-year-olds, population screening had a 0%, 78%, and 100% probability of being cost-effective versus family history testing alone at the $50,000, $100,000, and $150,000 per QALY thresholds, respectively. When we added potential harm to noncarriers who avoid recommended mammography, the probability of population screening being cost-effective fell to 0%, 2%, 34% at the $50,000, $100,000, and $150,000 per QALY thresholds, respectively. Population screening was not cost-effective for 45-year-olds in any probabilistic simulations with a willingness-to-pay per QALY threshold below $150,000.

eFigure 4. Results of Probabilistic Sensitivity Analysis



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