

Supplementary Online Content

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eAppendix. Additional Funding and Acknowledgements for Carriers

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

eTable 1. Age-Specific Odds Ratios for Breast Cancer Used in Base Case Analysis and Sensitivity Analyses. Lower and upper bounds were estimated by adding and subtracting one standard error from the base case.

Age	<i>ATM</i>			<i>CHEK2</i>			<i>PALB2</i>		
	Lower	Base	Upper	Lower	Base	Upper	Lower	Base	Upper
35	2.29	3.01	3.97	2.44	3.15	4.06	2.15	3.22	4.84
40	2.16	2.72	3.43	2.40	2.98	3.69	2.36	3.31	4.65
45	2.04	2.46	2.97	2.36	2.82	3.36	2.57	3.40	4.49
50	1.91	2.23	2.59	2.31	2.66	3.07	2.78	3.49	4.38
55	1.78	2.01	2.28	2.25	2.52	2.83	2.96	3.59	4.35
60	1.63	1.82	2.04	2.15	2.38	2.64	3.06	3.69	4.44
65	1.46	1.64	1.86	2.02	2.25	2.51	3.07	3.79	4.67
70	1.28	1.49	1.73	1.87	2.13	2.43	3.02	3.89	5.02

Odds ratios were provided from the CARRIERS consortium and estimated using logistic regression adjusted for study, first degree family history of breast cancer, race/ethnicity, age, and an interaction of age and pathogenic variant.

eTable 2. Specificity of Screening With Mammography Alone, MRI Alone, and Mammography Combined With MRI Stratified by Age Group and Screening Round. Data provided from the Breast Cancer Surveillance Consortium. Specificity was calculated based on 7,424 MRI and 5,671 mammography screening examinations performed for high-risk screening in women without a personal history of breast cancer at BCSC facilities from 2005 through 2020.

	Initial Screen			Rescreen		
	<i>MMG</i>	<i>MRI</i>	<i>MMG+MRI</i>	<i>MMG</i>	<i>MRI</i>	<i>MMG+MRI</i>
Age <50	59%	79%	68%	82%	92%	87%
Age ≥50	70%	85%	77%	88%	95%	92%

eTable 3. Incremental Screening Harms per Life Year Gained for Screening Strategies With Varying Start Age of Magnetic Resonance Imaging. Incremental ratios are calculated for each strategy relative to the next least screening intensive strategy.

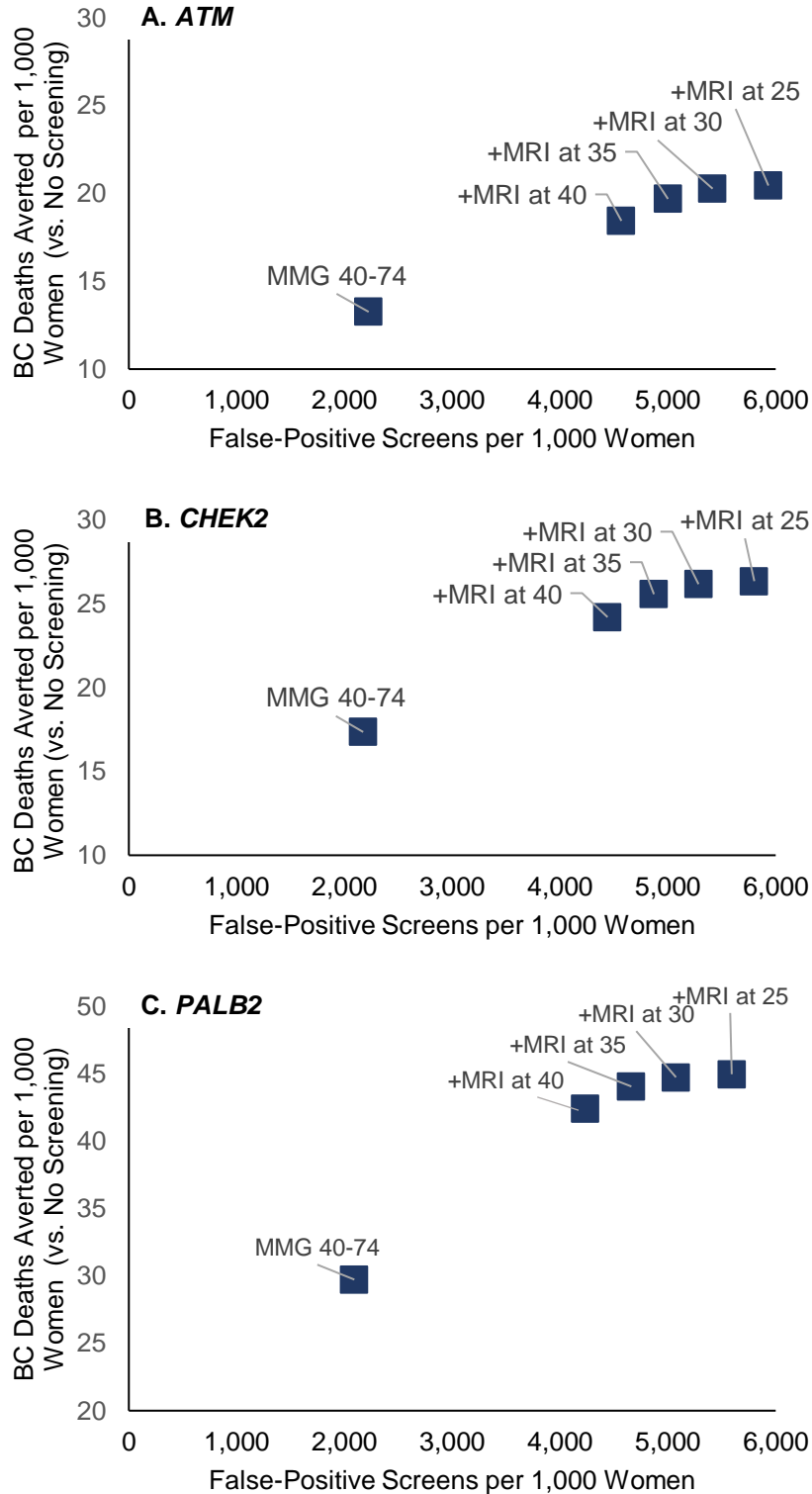
	False-Positive Screens per LYG Model Average (Range)			Benign Biopsies per LYG Model Average (Range)		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	7.7 (7.0-8.5)	5.9 (5.3-6.6)	3.4 (3.7-3.1)	1.0 (0.9-1.1)	0.8 (0.7-0.9)	0.5 (0.4-0.5)
+MRI at 40	18.1 (17.7-18.6)	13.8 (13.5-14.2)	7.2 (6.7-7.6)	7.0 (6.8-7.1)	5.3 (5.2-5.5)	2.8 (2.6-3.0)
+MRI at 35	15.3 (14.9-15.6 ^a)	12.2 (12.0-12.4 ^a)	7.0 (6.4-7.6) ^a	5.9 (5.8-6.0 ^a)	4.7 (4.6-4.8 ^a)	2.7 (2.5-3.0 ^a)
+MRI at 30	15.2 (14.9-15.5 ^b)	14.4 (14.0-14.7)	12.8 (11.6-14.0)	5.9 (5.8-6.0 ^b)	5.5 (5.4-5.7)	4.9 (4.5-5.4)
+MRI at 25	57.9 (43.5-72.3)	54.3 (41.2-67.3)	47.0 (32.6-61.3)	22.2 (16.7-27.7)	20.8 (15.8-25.7)	18.0 (12.5-23.4)

MMG, mammography; MRI, magnetic resonance imaging; LYG, life years gained

^aStarting MRI at 40 is less efficient than MRI at 35; incremental ratios for MRI at 35 are calculated relative to Mammography at 40 (without MRI)

^bStarting MRI at 35 or 40 is less efficient than MRI at 30; incremental ratios for MRI at 30 are calculated relative to Mammography at 40 (without MRI)

eFigure 1. False-Positive Exams and Breast Cancer (BC) Deaths Averted for Screening Strategies for Women With Pathogenic Variants in *ATM* (panel A), *CHEK2* (panel B), and *PALB2* (panel C). Results are shown as model averages of cumulative lifetime outcomes per 1000 women screened across Model E and Model W-H. MMG=Mammography; MRI=Magnetic resonance imaging. In all strategies, MMG is performed annually from ages 40-74; MRI start age varies by strategy.



eTable 4. Sensitivity Analysis of Screening Outcomes Assuming Higher Breast Cancer Risk. Age-specific risk estimates from CARRIERS were increased by one standard error (see eTable 1). Results are shown as model averages (ranges) of cumulative lifetime outcomes per 1,000 women screened across Model E and Model W-H.

	<i>Breast Cancer Mortality Reduction (%)</i>			<i>Life Years Gained</i>			<i>Deaths Averted</i>		
	<i>Model Average (Range)</i>			<i>Model Average (Range)</i>			<i>Model Average (Range)</i>		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	37.7 (36.9-38.5)	38.0 (37.4-38.5)	37.6 (35.1-40.2)	339 (303-375)	418 (377-459)	765 (692-837)	15.5 (10.3-20.6)	19.4 (13.3-25.5)	36.4 (27.6-45.2)
+MRI at 40	52.7 (51.8-53.5)	53.1 (52.7-53.5)	53.8 (51.9-55.8)	490 (448-531)	604 (560-649)	1131 (1079-1183)	21.6 (14.4-28.7)	27.1 (18.7-35.4)	51.8 (40.8-62.8)
+MRI at 35	57.0 (57.3-56.7)	56.8 (56.3-57.3)	56.2 (55.1-57.4)	557 (524-592)	678 (641-714)	1224 (1197-1251)	23.0 (16.0-30.4)	28.8 (20.3-37.3)	53.9 (43.3-64.6)
+MRI at 30	59.0 (58.0-60.0)	58.6 (57.6-59.6)	57.3 (56.6-58.0)	593 (565-622)	717 (683-750)	1271 (1257-1285)	23.9 (16.7-31.1)	29.6 (21.1-38.2)	54.9 (44.5-65.4)
+MRI at 25	59.7 (58.4-60.9)	59.1 (57.9-60.3)	57.7 (57.1-58.2)	606 (579-633)	729 (698-760)	1287 (1279-1296)	24.2 (17.0-31.3)	29.9 (21.4-38.3)	55.2 (44.9-65.6)

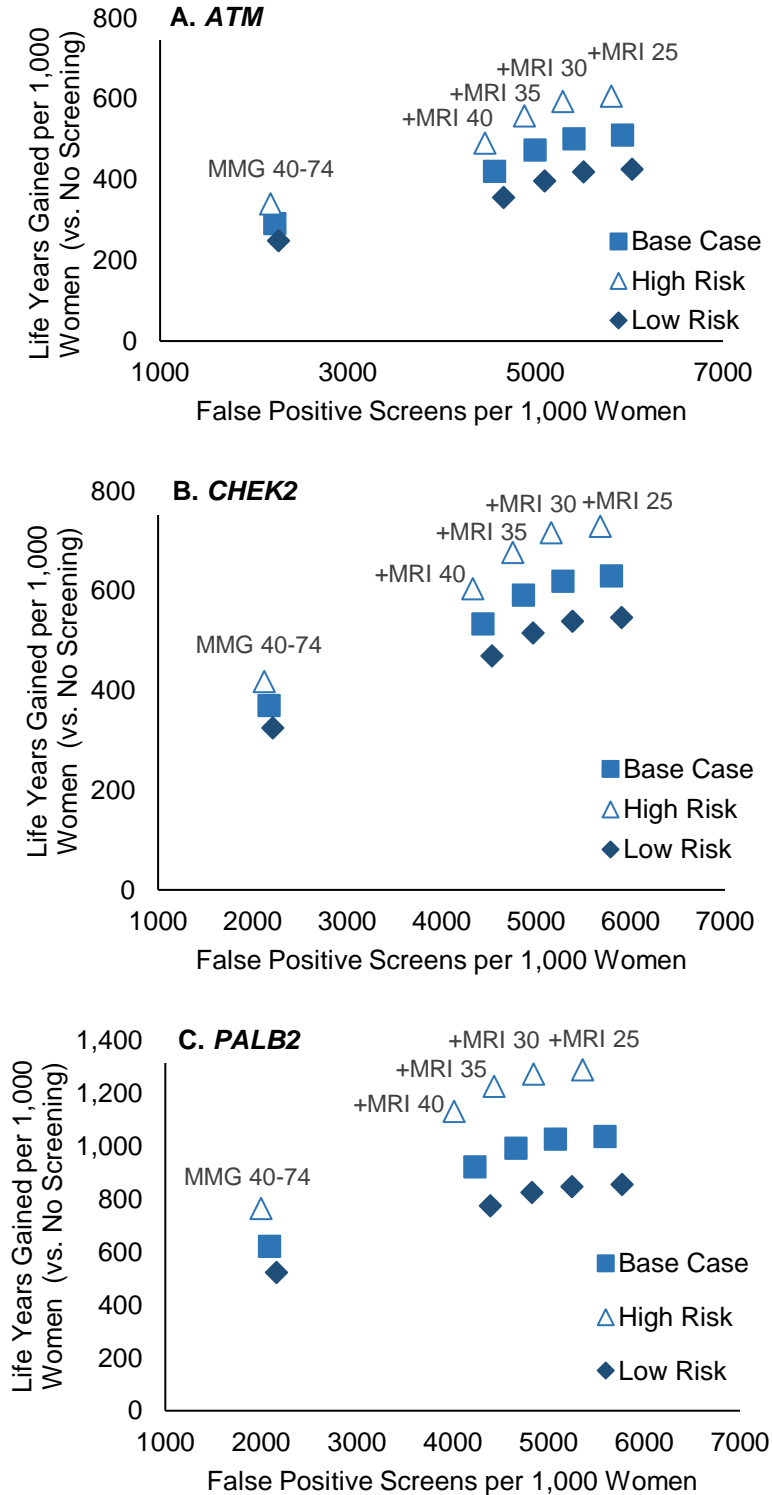
MMG, mammography; MRI, magnetic resonance imaging.

eTable 5. Sensitivity Analysis of Screening Outcomes Assuming Lower Breast Cancer Risk. Age-specific risk estimates from CARRIERS were decreased by one standard error (see eTable 1). Results are shown as model averages (ranges) of cumulative lifetime outcomes per 1,000 women screened across Model E and Model W-H.

	<i>Breast Cancer Mortality Reduction (%)</i>			<i>Life Years Gained</i>			<i>Deaths Averted</i>		
	<i>Model Average (Range)</i>			<i>Model Average (Range)</i>			<i>Model Average (Range)</i>		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	39.0 (38.4-39.7)	38.4 (38.3-38.6)	36.3 (35.1-37.5)	248 (229-266)	325 (290-360)	521 (454-589)	11.2 (7.8-14.7)	15.4 (10.3-20.5)	25.3 (17.7-32.8)
+MRI at 40	54.1 (53.7-54.5)	53.8 (53.7-54.0)	52.1 (51.7-52.5)	355 (338-372)	470 (430-510)	775 (709-840)	15.6 (10.9-20.2)	21.5 (14.4-28.6)	36.1 (26.1-46.0)
+MRI at 35	57.8 (57.4-58.2)	56.8 (56.1-57.6)	54.0 (53.8-54.1)	397 (383-410)	516 (481-551)	824 (766-883)	16.6 (11.9-21.3)	22.6 (15.4-29.8)	37.2 (27.3-47.1)
+MRI at 30	59.5 (58.8-60.3)	58.2 (57.1-59.3)	54.7 (54.2-55.1)	419 (406-431)	539 (506-573)	846 (792-901)	17.0 (12.3-21.8)	23.1 (15.9-30.3)	37.6 (27.8-47.5)
+MRI at 25	60.1 (59.1-61.0)	58.6 (57.3-59.9)	54.9 (54.4-55.4)	426 (415-437)	547 (515-579)	854 (802-907)	17.2 (12.4-21.9)	23.2 (16.1-30.4)	37.8 (28.0-47.6)

MMG, mammography; MRI, magnetic resonance imaging.

eFigure 2. False-Positive Screens Versus Life Years Gained for Screening Strategies for Women With Pathogenic Variants in *ATM* (panel A), *CHEK2* (panel B), and *PALB2* (panel C), Varying Breast Cancer Risk ± 1 Standard Error Based on CARRIERS Data. Results are shown as model averages of cumulative lifetime outcomes per 1000 women screened across Model E and Model W-H. MMG=Mammography; MRI=Magnetic resonance imaging. In all strategies, MMG is performed annually from ages 40-74; MRI varies in start age by strategy. MMG is performed annually from ages 40-74; MRI varies in start age by strategy.



eTable 6. Sensitivity Analysis of Screening Outcomes Assuming the Lower Confidence Limit of MRI Sensitivity. Results are shown as model averages (ranges) of cumulative lifetime outcomes per 1,000 women screened across Model E and Model W-H.

	<i>Breast Cancer Mortality Reduction (%)</i>			<i>Life Years Gained</i>			<i>Deaths Averted</i>		
	<i>Model Average (Range)</i>			<i>Model Average (Range)</i>			<i>Model Average (Range)</i>		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	37.3 (36.9-37.8)	37.1 (36.3-38.0)	35.2 (34.6-35.7)	281 (263-299)	356 (330-381)	599 (559-639)	12.7 (9.0-16.5)	16.6 (11.6-21.6)	28.5 (22.0-35.1)
+MRI at 40	50.5 (48.6-53.2)	50.4 (49.0-51.8)	49.0 (46.8-51.1)	393 (351-434)	498 (442-553)	854 (781-927)	17.5 (11.5-23.5)	22.9 (15.0-30.8)	39.9 (29.7-50.1)
+MRI at 35	53.9 (52.9-54.8)	53.3 (52.7-54.0)	50.8 (49.1-52.5)	437 (400-474)	548 (497-599)	915 (849-981)	18.6 (12.5-24.6)	24.1 (16.2-32.1)	41.4 (31.2-51.6)
+MRI at 30	55.5 (54.9-56.0)	54.6 (54.3-54.9)	51.6 (50.1-53.1)	462 (425-498)	573 (523-622)	942 (880-1004)	19.1 (13.0-25.1)	24.7 (16.7-32.7)	42.0 (31.8-52.1)
+MRI at 25	56.0 (55.6-56.5)	55.0 (54.8-55.1)	51.9 (50.5-53.3)	470 (435-505)	581 (533-629)	953 (892-1013)	19.3 (13.2-25.3)	24.8 (16.8-32.8)	42.2 (32.0-52.3)

MMG, mammography; MRI, magnetic resonance imaging.

eTable 7. Sensitivity Analysis of Screening Outcomes Assuming the Lower Confidence Limit of the MRI Specificity. Results are shown as model averages (ranges) of cumulative lifetime outcomes per 1,000 women screened across Model E and Model W-H.

	Breast Cancer Mortality Reduction (%)			Life Years Gained			False-Positive Screens			Benign Biopsies		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	38.5 (37.8-39.2)	38.4 (38.0-38.8)	36.4 (34.6-38.2)	291 (263-319)	370 (330-409)	621 (559-684)	2224 (2222-2227)	2174 (2172-2175)	2092 (2085-2099)	296 (296-297)	290 (290-290)	279 (278-280)
+MRI at 40	53.6 (52.9-54.3)	53.6 (53.3-53.9)	52.3 (51.4-53.1)	420 (388-452)	533 (489-577)	921 (876-967)	4772 (4757-4787)	4638 (4636-4640)	4421 (4401-4441)	1249 (1245-1253)	1214 (1213-1215)	1157 (1152-1163)
+MRI at 35	57.6 (57.2-58.0)	57.0 (56.3-57.7)	54.4 (54.2-54.7)	473 (447-498)	591 (555-627)	992 (959-1025)	5232 (5209-5255)	5096 (5086-5106)	4878 (4850-4905)	1432 (1425-1438)	1396 (1393-1399)	1339 (1332-1347)
+MRI at 30	59.5 (58.5-60.4)	58.4 (57.2-59.6)	55.4 (55.3-55.4)	501 (478-523)	620 (587-652)	1025 (998-1051)	5673 (5649-5696)	5536 (5499-5573)	5318 (5298-5337)	1601 (1589-1613)	1565 (1550-1581)	1508 (1498-1519)
+MRI at 25	60.2 (58.9-61.2)	58.9 (57.5-60.3)	55.7 (55.5-55.8)	510 (489-531)	630 (599-661)	1037 (1013-1061)	6223 (6196-6249)	6086 (6073-6100)	5867 (5837-5898)	1811 (1819-1804)	1776 (1772-1780)	1719 (1710-1727)

MMG, mammography; MRI, magnetic resonance imaging.

eTable 8. Sensitivity Analysis of Screening Outcomes of Screening Strategies Assuming the Upper Confidence Limit of the MRI Specificity. Results are shown as model averages (ranges) of cumulative lifetime outcomes per 1,000 women screened across Model E and Model W-H.

	Breast Cancer Mortality Reduction (%)			Life Years Gained			False-Positive Screens			Benign Biopsies		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	38.5 (37.8-39.2)	38.4 (38.0-38.8)	36.4 (34.6-38.2)	291 (263-319)	370 (330-409)	621 (559-684)	2224 (2222-2227)	2174 (2172-2175)	2092 (2085-2099)	296 (196-197)	290 (290-290)	279 (178-280)
+MRI at 40	53.6 (52.9-54.3)	53.6 (53.3-53.9)	52.3 (51.4-53.1)	420 (388-452)	533 (489-577)	921 (876-967)	4367 (4353-4380)	4244 (4242-4246)	4045 (4027-4064)	1141 (1138-1145)	1110 (1109-1110)	1058 (1053-1063)
+MRI at 35	57.6 (57.2-58.0)	57.0 (56.3-57.7)	54.4 (54.2-54.7)	473 (447-498)	591 (555-627)	992 (959-1,025)	4773 (4752-4794)	4649 (4640-4658)	4449 (4424-4474)	1303 (1298-1309)	1271 (1268-1274)	1219 (1212-1226)
+MRI at 30	59.5 (58.5-60.4)	58.4 (57.2-59.6)	55.4 (55.3-55.4)	501 (478-523)	620 (587-652)	1025 (998-1051)	5165 (5145-5186)	5040 (5008-5073)	4841 (4824-4858)	1454 (1444-1465)	1422 (1408-1435)	1370 (1361-1379)
+MRI at 25	60.2 (58.9-61.2)	58.9 (57.5-60.3)	55.7 (55.5-55.8)	510 (489-531)	630 (599-661)	1,037 (1013-1061)	5655 (5631-5680)	5531 (5519-5543)	5331 (5303-5358)	1642 (1635-1649)	1609 (1606-1613)	1557 (1550-1565)

MMG, mammography; MRI, magnetic resonance imaging.

eTable 9. Sensitivity Analysis of Screening Outcomes Using Age-Specific MRI Specificity from the Breast Cancer Surveillance Consortium. Results are shown as model averages (ranges) of cumulative lifetime outcomes per 1,000 women screened across Model E and Model W-H.

	Breast Cancer Mortality Reduction (%)			Life Years Gained			False-Positive Screens			Benign Biopsies		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	38.5 (37.8-39.2)	38.4 (38.0-38.8)	36.4 (34.6-38.2)	291 (263-319)	370 (330-409)	621 (559-684)	1871 (1867-1875)	1837 (1835-1838)	1781 (1773-1788)	256 (256-257)	252 (251-252)	244 (243-245)
+MRI at 40	53.6 (52.9-54.3)	53.6 (53.3-53.9)	52.3 (51.4-53.1)	420 (388-452)	533 (489-577)	921 (876-967)	4225 (4209-4241)	4124 (411-4131)	3960 (3938-3981)	1108 (1104-1112)	1082 (1080-1084)	1039 (1033-1045)
+MRI at 35	57.6 (57.2-58.0)	57.0 (56.3-57.7)	54.4 (54.2-54.7)	473 (447-498)	591 (555-627)	992 (959-1025)	4805 (4781-4828)	4702 (4687-4716)	4537 (4508-4565)	1344 (1337-1351)	1317 (1313-1321)	1274 (1266-1282)
+MRI at 30	59.5 (58.5-60.4)	58.4 (57.2-59.6)	55.4 (55.3-55.4)	501 (478-523)	620 (587-652)	1025 (998-1051)	5375 (5338-5412)	5271 (5224-5317)	5106 (5073-5138)	1563 (1546-1580)	1536 (1517-1555)	1493 (1477-1508)
+MRI at 25	60.2 (58.9-61.2)	58.9 (57.5-60.3)	55.7 (55.5-55.8)	510 (489-531)	630 (599-661)	1037 (1013-1061)	6082 (6055-6109)	5978 (5960-5996)	5812 (5781-5844)	1834 (1826-1841)	1807 (1801-1812)	1764 (1755-1772)

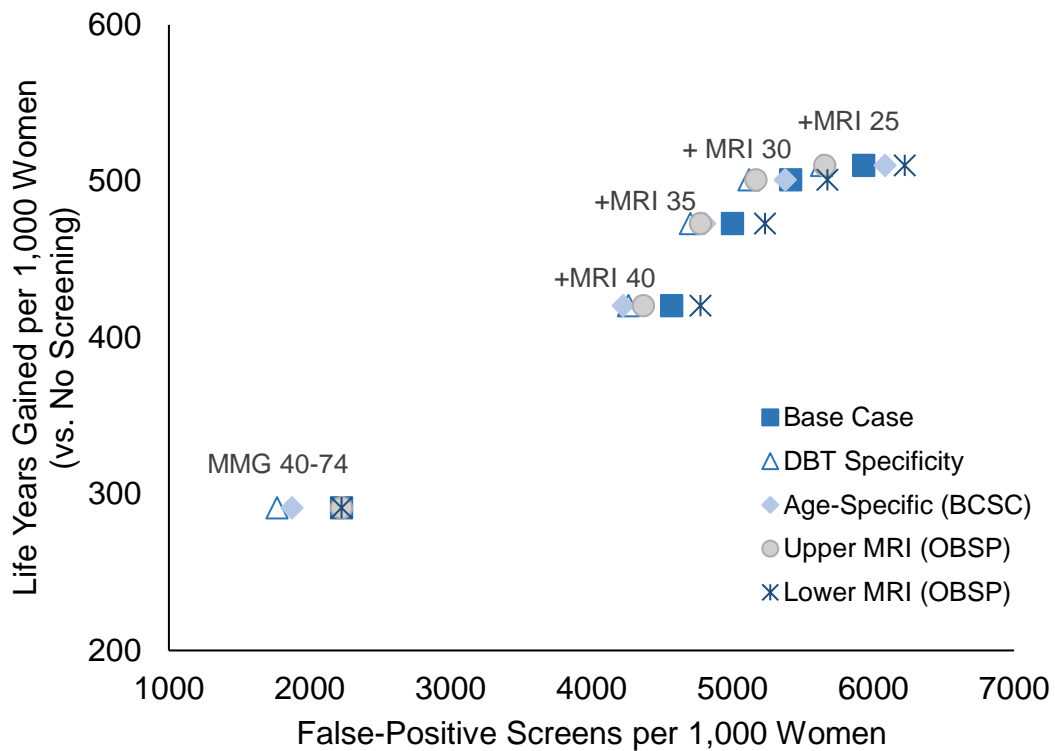
MMG, mammography; MRI, magnetic resonance imaging.

eTable 10. Sensitivity Analysis of Screening Outcomes Assuming the Use of Digital Breast Tomosynthesis for Mammography Screening. Results are shown as model averages (ranges) of cumulative lifetime outcomes per 1,000 women screened across Model E and Model W-H.

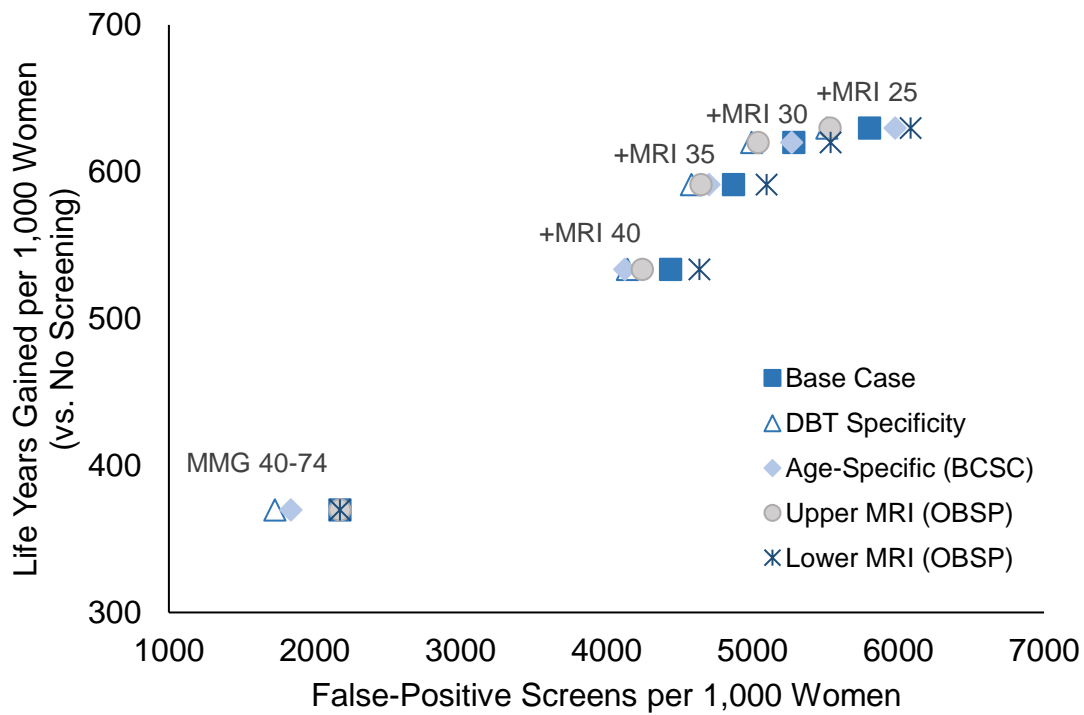
	Breast Cancer Mortality Reduction (%)			Life Years Gained			False-Positive Screens			Benign Biopsies		
	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>ATM</i>	<i>CHEK2</i>	<i>PALB2</i>
MMG at 40	38.5 (37.8-39.2)	38.4 (38.0-38.8)	36.4 (34.6-38.2)	291 (263-319)	370 (330-409)	621 (559-684)	1766 (1764-1768)	1726 (1725-1727)	1661 (1656-1667)	237 (236-237)	232 (231-232)	223 (222-224)
+MRI at 40	53.6 (52.9-54.3)	53.6 (53.3-53.9)	52.3 (51.4-53.1)	420 (388-452)	533 (489-577)	921 (876-967)	4263 (4250-4277)	4144 (4142-4146)	3950 (3932-3967)	1115 (1111-1118)	1083 (1083-1084)	1033 (1028-1038)
+MRI at 35	57.6 (57.2-58.0)	57.0 (56.3-57.7)	54.4 (54.2-54.7)	473 (447-498)	591 (555-627)	992 (959-1025)	4827 (4681-4722)	4580 (4571-4589)	4385 (4360-4410)	1288 (1283-1294)	1257 (1254-1259)	1206 (1199-1213)
+MRI at 30	59.5 (58.5-60.4)	58.4 (57.2-59.6)	55.4 (55.3-55.4)	501 (478-523)	620 (587-652)	1025 (998-1051)	5411 (5093-5140)	4995 (4959-5030)	4800 (4780-4819)	1448 (1437-1459)	1416 (1402-1431)	1365 (1355-1376)
+MRI at 25	60.2 (58.9-61.2)	58.9 (57.5-60.3)	55.7 (55.5-55.8)	510 (489-531)	630 (599-661)	1037 (1013-1061)	5634 (5610-5658)	5513 (5525-5500)	5317 (5290-5344)	1646 (1639-1653)	1614 (1611-1688)	1563 (1556-1571)

MMG, mammography; MRI, magnetic resonance imaging

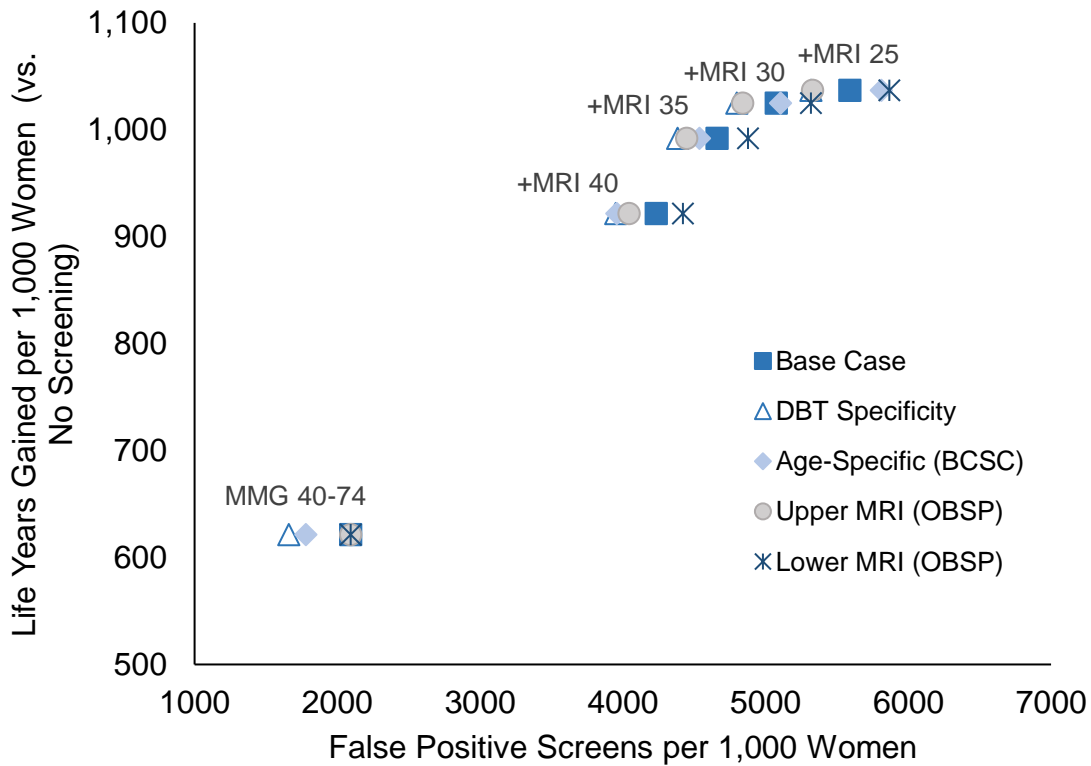
eFigure 3A. False-Positive Screens Versus Life Years Gained for Screening Strategies for Women With Pathogenic Variants in *ATM* Under Varying Assumptions for Screening Specificity. In the base case, screening specificity estimates were based on published data from the Ontario Breast Screening Program (OBSP). MRI specificity was varied across the 95% CI. Specificity estimates from the Breast Cancer Surveillance Consortium (BCSC) stratified by age group and screening round were also considered. Improved mammography specificity due to digital breast tomosynthesis (DBT) was estimated based on published data. Results are shown as model averages of cumulative lifetime outcomes per 1000 women screened across Model E and Model W-H. MMG=Mammography; MRI=Magnetic resonance imaging. In all strategies, MMG is performed annually from ages 40-74; MRI varies in start age by strategy.



eFigure 3B. False-Positive Screens Versus Life Years Gained for Screening Strategies for Women With Pathogenic Variants in *CHEK2* Under Varying Assumptions for Screening Specificity. In the base case, screening specificity estimates were based on published data from the Ontario Breast Screening Program (OBSP). MRI specificity was varied across the 95% CI. Specificity estimates from the Breast Cancer Surveillance Consortium (BCSC) stratified by age group and screening round were also considered. Improved mammography specificity due to digital breast tomosynthesis (DBT) was estimated based on published data. Results are shown as model averages of cumulative lifetime outcomes per 1000 women screened across Model E and Model W-H. MMG=Mammography; MRI=Magnetic resonance imaging. In all strategies, MMG is performed annually from ages 40-74; MRI varies in start age by strategy.



eFigure 3C. False-Positive Screens Versus Life Years Gained for Screening Strategies for Women With Pathogenic Variants in *PALB2* Under Varying Assumptions for Screening Specificity. In the base case, screening specificity estimates were based on published data from the Ontario Breast Screening Program (OBSP). MRI specificity was varied across the 95% CI. Specificity estimates from the Breast Cancer Surveillance Consortium (BCSC) stratified by age group and screening round were also considered. Improved mammography specificity due to digital breast tomosynthesis (DBT) was estimated based on published data. Results are shown as model averages of cumulative lifetime outcomes per 1000 women screened across Model E and Model W-H. MMG=Mammography; MRI=Magnetic resonance imaging. In all strategies, MMG is performed annually from ages 40-74; MRI varies in start age by strategy.



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