SUPPLEMENTARY MATERIALS

Supplementary Methods

Model Erasmus University Medical Center (Model E)

Model E, also known as MISCAN-Fadia which is an acronym for Microsimulation Screening Analysis – Fatal Diameter is a breast cancer simulation model that uses continuous tumor growth to simulate the natural history of breast cancer.(1) The model simulates individual life histories from birth to death, with and without breast cancer, in the presence and in the absence of screening and treatment. Life histories are simulated according to discrete events such as birth, tumor inception, breast cancer metastasis, and death from breast cancer or death from other causes. Model E consists of four main components: demography, natural history of breast cancer, screening, and treatment. The impact of screening on the natural history of breast cancer is assessed by simulating continuous tumor growth and the "fatal diameter" concept. This concept implies that tumors diagnosed at a size that is between the screen detection threshold and the fatal diameter are cured, while tumors diagnosed at a diameter larger than the fatal tumor diameter metastasize and lead to breast cancer death. MISCAN-Fadia includes different natural histories for molecular subtypes based on a tumor's estrogen receptor (ER) status and human epidermal growth factor receptor (HER)-2 status.

Model Georgetown University-Albert Einstein College of Medicine (Model GE)

Model GE is a continuous-time, event-driven microsimulation of single-life histories of women utilizing a parallel universes approach.(2) The parallel universes approach starts with the generation of a basic life history for each simulated woman in the absence of any screening or adjuvant treatment. The effects of each screening and adjuvant treatment strategy under study are then simulated starting using the exact same basic life history. In this manner, the outputs for the different screening and adjuvant treatment strategies are matched pairs. The approach for simulating breast cancer natural history is phenomenological, relying on dates, stage, and age of clinical and screen detection for a tumor molecular subtype without explicitly modeling tumor growth. The model accommodates differences in natural history associated with ER and HER2 biomarkers, as well as conventional breast cancer risk factors. Breast cancer incidence depends on age, time period, and birth cohort, and is modified based on risk. The incidence includes a subset of ductal carcinoma in situ (DCIS) tumors that never surface clinically and eventually regress.

Prevalence and relative risk calculation for polygenic risk score groups (313-SNP PRS)

We modeled the distribution of risk relative to the average woman without a family history (RR*) as a function of polygenic risk and family history:

$$RR* = Lognormal\left(FHx\left(\mu_i + \frac{\sigma_i}{2}\right) - \left(\frac{\sigma_i}{2}\right)^2, \sigma_i\right)$$

Where FHx is an indicator for first degree family history of breast cancer (yes=1, no=0), μ_i is the log relative risk of family history (adjusted for polygenic effects), and σ_i is the log relative risk associated with a one standard deviation change in the polygenic risk score in age group i.

We used the following parameter values for μ_i and σ_i from Mavaddat (5).

References

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SUPPLEMENTARY TABLES

Supplementary Table 1. Model differences and similarities.

	Erasmus (Model E)	**Georgetown-Einstein (Model GE)**
Model type	Microsimulation of individual life histories	Microsimulation of individual life histories
Breast cancer natural history	Continuous tumor growth of invasive tumors	Stage transitions
Ductal carcinoma in situ	DCIS included	DCIS included
ER/HER2 tumor subtypes	Yes, different natural history by ER/HER2 status	Yes, different natural history by ER/HER2 status
Screen detection conditional on *	Age, density, screening modality and frequency	Age, density, screening modality and frequency
Screening benefit	Detection at smaller tumor sizes	Shift in distribution of stage at diagnosis
Overdiagnosis estimation†	Total number of cancers diagnosed in the presence of screening minus the number diagnosed in the absence of screening	Total number of cancers diagnosed in the presence of screening minus the number diagnosed in the absence of screening
Treatment benefit	Cure fraction among diagnosed cancer	Hazard reduction
Death from breast cancer	Breast cancer survival vs other cause survival	Breast cancer survival vs other cause survival

* Screening only occurs in the ages specified by the screening strategy. Outside of this screening window, cancers can only be diagnosed clinically due to symptoms. This means that cancers diagnosed on the last screen would be considered screen detected. After the last age of screening only clinical cases are diagnosed. Once a woman is diagnosed with DCIS or with invasive breast cancer, she does not continue screening.

† There is consensus in the literature that the majority of all overdiagnosed cases are among DCIS diagnoses. Since the natural history of DCIS cannot be directly observed and the true progression rate of DCIS is unknown, any differences in model estimates of overdiagnoses likely reflect the uncertainty about DCIS progression rates and its natural history.

Supplementary Table 2. Model setup and model input sources.

	Description	Source
Population demographics		
Birth cohort	All women were born in 1985.	-
Life expectancy	For non-breast cancer patients all-cause mortality adjusted for breast cancer mortality determined life expectancy, among patients competing risk between breast cancer survival and other cause mortality determined life expectancy.	SEER Stat
Breast cancer natural history		
Incidence	Incidence in the absence of screening derived by Gangnon et al. is used as baseline incidence to estimate the effects of screening.	(3)
Sojourn time	Model-specific, based on tumor growth, progression and screening test sensitivity.	(1, 2)
Tumor behavior	Tumor growth or progression distribution was ER/HER2 subtype-specific and based on model calibration.	(4)
Risk levels		
Polygenic risk	7 polygenic risk groups spanning age-specific risk level between 0 and 10 times the population average. (0-0.5, 0.5-1.0, 1.0-1.5, 1.5-2.0, 2.0-3.0, 3.0-5.0, 5.0-10.0). Risk group upper and lower cut-off levels were self-chosen.	(5)
Family history	5 family history groups: women who learned in age ranges 30-39, 40-49, 50-64, 65-100 that they had a first-degree relative with breast cancer.	(6)
Risk-factor prevalence		
Polygenic risk	The prevalence was calculated by simulating the distribution of risk as a function of the PRS to match that of Mavaddat et al 2019. Using the cut-off risk levels of the seven defined groups, we calculated the number of women in each group.	(5)
Family history	The prevalence of the 5 family history groups: women who learned in age ranges 30-39, 40-49, 50-64, 65-100 that they had a first-degree relative with breast cancer.	(6)
Breast cancer screening		
Screening modality	Digital mammography	-
Screening performance	Age-, first-screen-, and screening interval-specific sensitivity and specificity, and distributions of stage at diagnosis distributions reported by the Breast Cancer Surveillance Consortium among women aged 30 to 74.	BCSC
Adherence	100% adherence to each screening strategy.	-
Breast cancer treatment		
Treatment types	Surgery followed by adjuvant hormone-, chemo- and/or trastuzumab therapy.	(7)
Treatment effects	Meta-analyses of clinical trials on breast cancer treatment effectiveness.	(8)
Adherence	100% adherence and receipt of age- stage- and ER/HER2 specific treatment.	-
Survival		
Breast cancer survival	Breast cancer survival before receipt of adjuvant treatment.	(4)
Other cause survival	Age- and cohort-specific all-cause mortality adjusted for breast cancer mortality.	(9)

Supplementary Table 3. Polygenic risk parameters used to calculate risk group prevalences.

	Sigma (σ)		
Age	**All cancers**	**ER+**	**ER-**
< 40	0.46 (0.38 – 0.53)	0.56 (0.47 – 0.65)	0.48 (0.36 – 0.59)
40-49	0.46 (0.42 – 0.50)	0.53 (0.48 – 0.57)	0.36 (0.29 – 0.43)
50-59	0.48 (0.45 – 0.51)	0.54 (0.50 – 0.57)	0.37 (0.32 – 0.43)
≥60	0.41 (0.38 – 0.43)	0.44 (0.41 – 0.47)	0.36 (0.31 – 0.42)
All ages	*0.44 (0.42 – 0.46)*	*0.49 (0.47 - 0.51)*	*0.37 (0.34 – 0.40)*

To model the distribution of risk relative to the population average, we consider RR = RR*/mean(RR*), where the mean of RR* is taken over the joint distribution of family history and polygenic risk in the population. The distributions of risk relative to the population average for various subgroups are displayed in the Supplementary figure 1:

Supplementary Table 4. Breast cancer risk and prevalence based on the 313-SNP polygenic risk score and breast cancer family history combined.

PREVALENCES	**Polygenic risk score groups** (low to high polygenic risk)						
FH group	**0.0-0.5**	**0.5-1.0**	**1.0-1.5**	**1.5-2.0**	**2.0-3.0**	**3.0-5.0**	**5.0-10.0**
30 < FH+ < 40	0.00%	0.19%	0.69%	0.95%	1.53%	1.10%	0.23%
40 < FH+ < 49	0.06%	0.91%	1.32%	0.91%	0.75%	0.23%	0.02%
50 < FH+ < 64	0.09%	1.27%	1.86%	1.28%	1.06%	0.32%	0.03%
65 < FH+ < 100	0.06%	0.65%	0.76%	0.44%	0.30%	0.08%	0.01%
No FH in life	17.06%	44.06%	16.07%	4.14%	1.41%	0.17%	0.00%
BREAST CANCER RISK	**Polygenic risk score groups** (low to high polygenic risk)						
FH group	**0.0-0.5**	**0.5-1.0**	**1.0-1.5**	**1.5-2.0**	**2.0-3.0**	**3.0-5.0**	**5.0-10.0**
30 < FH+ < 40	0.67	1.55	2.43	3.36	4.86	7.39	12.64
40 < FH+ < 49	0.53	1.23	1.93	2.67	3.86	5.86	10.03
50 < FH+ < 64	0.43	0.99	1.55	2.15	3.11	4.72	8.07
65 < FH+ < 100	0.41	0.95	1.49	2.06	2.98	4.52	7.74
No FH in life	0.24	0.56	0.87	1.21	1.75	2.66	4.55

Supplementary Table 5. Benefits and harms projections of mammography screening based on polygenic risk scores (313 SNPs). Outcomes for model E and model GE in () per 1,000 women screened.

Screening guideline	Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
PRS group 7 (5.0 < RR < 10.0)						
USPSTF guideline	Biennial 50-74	9009 (8763)	361 (664)	21.3 (33.6)	44.4 (11.6)	750 (702)
ACS guideline	An 45-54, Bi 55-74	15246 (14861)	509 (860)	26.5 (39.7)	58.6 (11.8)	1441 (1366)
ACR guideline	Annual 40-74	25630 (25543)	677 (1048)	33.9 (46.9)	82.2 (14.2)	2463 (2401)
Risk-based (this study)	Annual 30-74	35105 (35323)	763 (1154)	36.1 (49.4)	91.9 (14.6)	3668 (3628)
PRS group 6 (3.0 < RR < 5.0)						
USPSTF guideline	Biennial 50-74	9889 (9905)	267 (436)	16.2 (22.4)	37.9 (11.7)	820 (802)
ACS guideline	An 45-54, Bi 55-74	16400 (16338)	363 (555)	19.4 (26)	47.1 (12.2)	1539 (1505)
ACR guideline	Annual 40-74	27841 (28173)	482 (673)	25 (30.6)	66.4 (14.3)	2648 (2639)
Risk-based (this study)	Annual 35-74	32616 (33054)	517 (715)	26 (31.7)	70.4 (14.7)	3255 (3252)
PRS group 5 (2.0 < RR < 3.0)						
USPSTF guideline	Biennial 50-74	10429 (10509)	200 (303)	12.2 (15.7)	30.2 (11.8)	863 (855)
ACS guideline	An 45-54, Bi 55-74	17085 (17106)	265 (385)	14.4 (18.1)	36.7 (12.5)	1596 (1577)
ACR guideline	Annual 40-74	29193 (29553)	352 (464)	18.6 (21.3)	51.8 (14.5)	2761 (2764)
Risk-based (this study)	An40-50,bi50-74	19165 (19982)	281 (436)	14.6 (19.8)	38.6 (13.8)	1930 (1979)
PRS group 4 (1.5 < RR < 2.0)						
USPSTF guideline	Biennial 50-74	10799 (10890)	148 (218)	9.1 (11.3)	23.5 (11.9)	892 (889)
ACS guideline	An 45-54, Bi 55-74	17547 (17585)	195 (273)	10.7 (13)	28 (12.8)	1635 (1623)
ACR guideline	Annual 40-74	30116 (30420)	260 (330)	13.9 (15.2)	39.6 (14.7)	2837 (2841)
Risk-based (this study)	Biennial 40-74	15604 (15688)	191 (292)	10.6 (13.6)	28.3 (14.1)	1467 (1458)
PRS group 3 (1.0 < RR < 1.5)						
USPSTF guideline	Biennial 50-74	11048 (11133)	113 (160)	7 (8.3)	18.4 (12)	912 (911)
ACS guideline	An 45-54, Bi 55-74	17855 (17890)	146 (202)	8.1 (9.5)	21.6 (13)	1660 (1651)
ACR guideline	Annual 40-74	30738 (30973)	195 (243)	10.5 (11.2)	30.7 (14.8)	2888 (2891)
Risk-based (this study)	Biennial 40-74	15889 (15957)	145 (215)	8.1 (10)	21.9 (14.4)	1490 (1483)
PRS group 2 (0.5 < RR < 1.0)						
USPSTF guideline	Biennial 50-74	11298 (11367)	75 (105)	4.7 (5.5)	12.6 (12.1)	932 (932)
ACS guideline	An 45-54, Bi 55-74	18161 (18181)	98 (131)	5.4 (6.3)	14.7 (13.3)	1686 (1679)
ACR guideline	Annual 40-74	31358 (31502)	130 (158)	7 (7.3)	20.9 (15)	2939 (2938)
Risk-based (this study)	Biennial 50-74	11298 (11367)	75 (105)	4.7 (5.5)	12.6 (12.1)	932 (932)
PRS group 1 (0.0 < RR < 0.5)						
USPSTF guideline	Biennial 50-74	11567 (11609)	34 (46)	2.1 (2.4)	5.8 (12.3)	953 (953)
ACS guideline	An 45-54, Bi 55-74	18486 (18481)	44 (57)	2.4 (2.7)	6.7 (13.6)	1713 (1707)
ACR guideline	Annual 40-74	32026 (32048)	59 (69)	3.2 (3.2)	9.6 (15.2)	2993 (2988)
Risk-based (this study)	Triennial 50-74	8005 (8035)	27 (41)	1.7 (2.1)	4.5 (12.1)	758 (651)

Supplementary Table 6. Benefits and harms projections of mammography screening based on polygenic risk scores and breast cancer family history combined. Outcomes for model E and model GE in () per 1,000 women screened.

Risk group based on PRS and age of Breast Cancer FH	Screening guideline	Screening strategy	Number of screens	Life years gained	Breast cancer deaths averted	Over diagnoses	False positives
PRS group 7 (5.0 < RR < 10.0)							
FH+ 30-39	USPSTF	Biennial 50-74	8093 (7417)	313 (774)	18.2 (38.6)	37 (10.9)	675 (589)
	ACS	Annual 30-74	32362 (31822)	903 (1550)	38.5 (62.5)	96.2 (13.7)	3419 (3293)
	ACR	An 45-54, Bi 55-74	23305 (22228)	736 (1334)	34.2 (57.4)	78.7 (13.4)	2257 (2095)
	Risk-based	Annual 30-74	13928 (12915)	520 (1057)	25.7 (47.6)	53.8 (11)	1323 (1184)
FH+ 40-49	USPSTF	Biennial 50-74	8413 (7716)	335 (805)	19.4 (40.2)	40.6 (11.3)	701 (612)
	ACS	Annual 30-74	33415 (32912)	826 (1513)	37.1 (62.7)	99 (14.2)	3522 (3407)
	ACR	An 45-54, Bi 55-74	24073 (23123)	732 (1391)	34.6 (59.8)	86.3 (14)	2330 (2179)
	Risk-based	Annual 30-74	14436 (13435)	538 (1097)	26.6 (49.3)	59.3 (11.5)	1371 (1231)
FH+ 50-64	USPSTF	Biennial 50-74	8876 (8289)	327 (865)	19.4 (43.2)	47.4 (12.2)	740 (658)
	ACS	Annual 30-74	34847 (34391)	720 (1381)	34.2 (60.4)	97.3 (15.1)	3650 (3550)
	ACR	An 45-54, Bi 55-74	25336 (24595)	641 (1283)	32.2 (58)	88.4 (14.8)	2441 (2321)
	Risk-based	Annual 30-74	15108 (14389)	475 (1096)	24.6 (50.5)	64.6 (12.2)	1431 (1322)
FH+ 65+	USPSTF	Biennial 50-74	9169 (8904)	288 (702)	17.5 (37.2)	46.5 (12.6)	763 (713)
	ACS	Annual 30-74	35564 (35681)	659 (1155)	31.5 (52.1)	93.4 (15.6)	3708 (3663)
	ACR	An 45-54, Bi 55-74	26053 (25886)	580 (1056)	29.5 (49.7)	84.4 (15.3)	2499 (2434)
	Risk-based	Annual 30-74	15489 (15115)	419 (872)	22.1 (42.2)	59.6 (12.5)	1462 (1389)
No BC FH	USPSTF	Biennial 50-74	9286 (9112)	263 (572)	15.7 (28.8)	39.6 (11.4)	772 (733)
	ACS	Annual 30-74	35837 (36112)	622 (1011)	29 (42.9)	83.5 (14.4)	3729 (3699)
	ACR	An 45-54, Bi 55-74	26327 (26325)	543 (911)	26.9 (40.5)	74.5 (14)	2520 (2471)
	Risk-based	Annual 30-74	15595 (15286)	395 (743)	20.3 (34.2)	52.5 (11.8)	1470 (1406)
PRS group 6 (3.0 < RR < 5.0)							
FH+ 30-39	USPSTF	Biennial 50-74	9117 (8979)	258 (545)	15.4 (27.6)	37.4 (11.2)	758 (723)
	ACS	Annual 30-74	35293 (35662)	663 (1030)	29.9 (42.8)	83.1 (14.2)	3678 (3653)
	ACR	An 45-54, Bi 55-74	25892 (25930)	561 (902)	27.3 (39.8)	72.2 (13.8)	2480 (2433)
	Risk-based	Annual 30-74	15337 (15039)	400 (722)	20.4 (33.1)	50.1 (11.5)	1446 (1383)
FH+ 40-49	USPSTF	Biennial 50-74	9365 (9188)	268 (557)	15.9 (28.2)	39.5 (11.4)	778 (740)
	ACS	Annual 30-74	31196 (31419)	587 (975)	28.2 (41.9)	81.8 (14.4)	3135 (3102)
	ACR	An 45-54, Bi 55-74	26499 (26534)	546 (922)	27.1 (40.6)	75.9 (14.1)	2536 (2489)
	Risk-based	Annual 35-74	15717 (15389)	403 (738)	20.6 (33.9)	53 (11.8)	1481 (1415)
FH+ 50-64	USPSTF	Biennial 50-74	9744 (9579)	250 (580)	15.3 (29.4)	43.1 (11.9)	809 (772)
	ACS	Annual 30-74	32308 (32409)	501 (875)	25.4 (39.7)	78.8 (14.9)	3233 (3198)
	ACR	An 45-54, Bi 55-74	27516 (27519)	469 (837)	24.6 (38.7)	75.1 (14.6)	2625 (2583)
	Risk-based	Annual 35-74	16253 (16018)	347 (718)	18.6 (33.7)	54.5 (12.2)	1528 (1475)
FH+ 65+	USPSTF	Biennial 50-74	9999 (9996)	215 (462)	13.4 (24.9)	40.5 (12.1)	829 (809)
	ACS	Annual 30-74	32925 (33282)	444 (717)	22.7 (33.6)	73.3 (15.1)	3282 (3274)
	ACR	An 45-54, Bi 55-74	28132 (28393)	412 (679)	21.8 (32.7)	69.7 (14.8)	2674 (2660)
	Risk-based	Annual 35-74	16569 (16501)	297 (565)	16.2 (27.8)	48.9 (12.4)	1553 (1520)
No BC FH	USPSTF	Biennial 50-74	10110 (10137)	190 (371)	11.6 (18.9)	32.2 (11.6)	838 (823)
	ACS	Annual 30-74	33186 (33572)	408 (617)	20.1 (27)	61.4 (14.7)	3302 (3299)
	ACR	An 45-54, Bi 55-74	28394 (28688)	376 (580)	19.3 (26.1)	57.7 (14.3)	2693 (2685)
	Risk-based	Annual 35-74	16667 (16614)	274 (476)	14.5 (22.1)	40.7 (12.3)	1561 (1531)
PRS group 5 (2.0 < RR < 3.0)							
FH+ 30-39	USPSTF	Biennial 50-74	9812 (9849)	204 (392)	12.4 (20)	32.8 (11.4)	814 (799)
	ACS	Annual 30-74	37225 (37764)	496 (722)	23.1 (30.4)	68 (14.6)	3845 (3848)
	ACR	An 45-54, Bi 55-74	27641 (27967)	427 (637)	21.3 (28.4)	60.6 (14)	2628 (2618)
	Risk-based	Annual 30-74	16258 (16193)	306 (513)	15.9 (23.8)	42.1 (12)	1525 (1492)
FH+ 40-49	USPSTF	Biennial 50-74	10005 (9999)	207 (398)	12.6 (20.3)	34 (11.6)	829 (811)
	ACS	Annual 30-74	28112 (28395)	411 (647)	20.9 (28.9)	62.5 (14.2)	2671 (2658)
	ACR	An 45-54, Bi 55-74	28112 (28395)	411 (647)	20.9 (28.9)	62.5 (14.2)	2671 (2658)
	Risk-based	Annual 40-74	16545 (16440)	304 (521)	15.9 (24.1)	43.6 (12.2)	1551 (1515)
FH+ 50-64	USPSTF	Biennial 50-74	10301 (10277)	191 (409)	11.8 (20.9)	35.8 (11.9)	854 (834)
	ACS	Annual 30-74	19055 (19772)	269 (546)	14.2 (25.3)	44.5 (13.7)	1922 (1959)

	ACR	An 45-54, Bi 55-74	28904 (29087)	348 (583)	18.7 (27.3)	60.5 (14.6)	2739 (2724)
	Risk-based	An 40-50, Bi 50-74	16957 (16880)	257 (504)	14 (23.8)	43.7 (12.5)	1587 (1556)
FH+ 65+	USPSTF	Biennial 50-74	10507 (10572)	161 (323)	10.2 (17.5)	32.9 (12)	870 (860)
	ACS	Annual 30-74	19275 (20084)	235 (440)	12.4 (21.1)	40.2 (13.8)	1940 (1988)
	ACR	An 45-54, Bi 55-74	29398 (29707)	302 (470)	16.3 (22.8)	55.2 (14.7)	2779 (2778)
	Risk-based	An 40-50, Bi 50-74	17206 (17219)	218 (391)	12 (19.4)	38.5 (12.5)	1607 (1588)
No BC FH	USPSTF	Biennial 50-74	10599 (10671)	140 (256)	8.6 (13.1)	25.2 (11.8)	876 (870)
	ACS	Annual 30-74	19356 (20174)	214 (373)	10.9 (16.8)	32.8 (13.9)	1946 (1997)
	ACR	An 45-54, Bi 55-74	29617 (29913)	270 (397)	14.1 (18)	44.1 (14.5)	2795 (2796)
	Risk-based	An 40-50, Bi 50-74	17287 (17297)	197 (328)	10.5 (15.3)	31 (12.6)	1613 (1596)
PRS group 4 (1.5 < RR < 2.0)							
FH+ 30-39	USPSTF	Biennial 50-74	10319 (10412)	158 (285)	9.7 (14.7)	27.1 (11.6)	854 (848)
	ACS	Annual 30-74	28744 (29630)	309 (492)	14.1 (20.6)	41.9 (14.3)	3146 (3196)
	ACR	An 45-54, Bi 55-74	28911 (29277)	323 (459)	16.4 (20.6)	48.7 (14.3)	2735 (2737)
	Risk-based	An 30-50, Bi 50-74	16913 (16930)	232 (372)	12.2 (17.3)	33.9 (12.4)	1581 (1561)
FH+ 40-49	USPSTF	Biennial 50-74	10466 (10521)	159 (288)	9.7 (14.8)	27.8 (11.7)	866 (857)
	ACS	Annual 30-74	19196 (19997)	246 (438)	12.4 (19.4)	37.3 (13.8)	1933 (1979)
	ACR	An 45-54, Bi 55-74	29271 (29585)	310 (465)	16 (20.9)	49.7 (14.4)	2767 (2766)
	Risk-based	An 40-50, Bi 50-74	17128 (17108)	228 (375)	12.1 (17.5)	34.7 (12.5)	1600 (1577)
FH+ 50-64	USPSTF	Biennial 50-74	10694 (10722)	145 (295)	9 (15.2)	28.5 (11.9)	885 (873)
	ACS	Annual 30-74	15501 (15530)	184 (372)	10.4 (17.6)	33.5 (13.9)	1459 (1443)
	ACR	An 45-54, Bi 55-74	29880 (30083)	260 (418)	14.2 (19.7)	47.5 (14.7)	2819 (2813)
	Risk-based	Biennial 40-74	17443 (17422)	191 (361)	10.6 (17.1)	34.1 (12.7)	1627 (1607)
FH+ 65+	USPSTF	Biennial 50-74	10855 (10935)	121 (231)	7.7 (12.5)	25.9 (12)	897 (892)
	ACS	Annual 30-74	15672 (15745)	159 (296)	9 (14.6)	30.2 (14.1)	1473 (1463)
	ACR	An 45-54, Bi 55-74	30264 (30529)	224 (335)	12.2 (16.3)	42.7 (14.8)	2850 (2852)
	Risk-based	Biennial 40-74	17634 (17666)	161 (280)	9 (13.9)	29.7 (12.8)	1642 (1630)
No BC FH	USPSTF	Biennial 50-74	10928 (11006)	103 (183)	6.4 (9.4)	19.3 (11.9)	903 (900)
	ACS	Annual 30-74	15746 (15812)	141 (249)	7.7 (11.4)	23.5 (14.2)	1478 (1469)
	ACR	An 45-54, Bi 55-74	30439 (30677)	198 (281)	10.4 (12.8)	33.3 (14.7)	2863 (2864)
	Risk-based	Biennial 40-74	17699 (17721)	144 (232)	7.7 (10.9)	23.4 (12.9)	1647 (1636)
PRS group 3 (1.0 < RR < 1.5)							
FH+ 30-39	USPSTF	Biennial 50-74	10319 (10778)	158 (213)	9.7 (11)	27.1 (11.8)	854 (880)
	ACS	Annual 30-74	19926 (20478)	263 (327)	13 (14.3)	37.9 (14.7)	2037 (2065)
	ACR	An 45-54, Bi 55-74	29799 (30125)	247 (341)	12.7 (15.4)	38.8 (14.5)	2809 (2813)
	Risk-based	Biennial 30-74	17365 (17405)	178 (276)	9.4 (12.9)	27 (12.7)	1619 (1606)
FH+ 40-49	USPSTF	Biennial 50-74	10466 (10859)	159 (216)	9.7 (11.1)	27.8 (11.9)	866 (887)
	ACS	Annual 30-74	15212 (15656)	220 (304)	11.8 (13.8)	35.2 (14.1)	1435 (1455)
	ACR	An 45-54, Bi 55-74	30078 (30353)	236 (344)	12.3 (15.5)	39.3 (14.6)	2834 (2835)
	Risk-based	Biennial 40-74	17529 (17537)	174 (279)	9.3 (13)	27.4 (12.8)	1633 (1618)
FH+ 50-64	USPSTF	Biennial 50-74	10694 (11009)	145 (218)	9 (11.2)	28.5 (12)	885 (899)
	ACS	Annual 30-74	13370 (13063)	171 (253)	10.2 (12.2)	32.8 (12.9)	1199 (1167)
	ACR	An 45-54, Bi 55-74	30547 (30722)	198 (308)	10.8 (14.5)	37.3 (14.8)	2874 (2870)
	Risk-based	Biennial 45-74	17771 (17769)	145 (266)	8 (12.7)	26.7 (12.9)	1654 (1640)
FH+ 65+	USPSTF	Biennial 50-74	10855 (11166)	121 (171)	7.7 (9.3)	25.9 (12.1)	897 (913)
	ACS	Annual 30-74	13551 (13217)	145 (196)	8.8 (9.9)	29.5 (12.9)	1213 (1181)
	ACR	An 45-54, Bi 55-74	30847 (31053)	168 (246)	9.3 (12)	33.2 (14.9)	2897 (2898)
	Risk-based	Biennial 45-74	17920 (17949)	121 (206)	6.8 (10.3)	23 (13)	1666 (1657)
No BC FH	USPSTF	Biennial 50-74	10928 (11219)	103 (135)	6.4 (6.9)	19.3 (12.1)	903 (918)
	ACS	Annual 30-74	13635 (13259)	126 (162)	7.3 (7.7)	22.6 (13.1)	1219 (1185)
	ACR	An 45-54, Bi 55-74	30986 (31162)	148 (207)	7.8 (9.4)	25.5 (14.9)	2908 (2908)
	Risk-based	Biennial 45-74	17971 (17990)	107 (171)	5.8 (8)	17.9 (13.2)	1670 (1661)
PRS group 2 (0.5 < RR < 1.0)							
FH+ 30-39	USPSTF	Biennial 50-74	11041 (11133)	85 (141)	5.2 (7.3)	15.7 (12)	911 (911)
	ACS	Annual 30-74	18652 (18051)	132 (205)	6.9 (9.1)	21.2 (14.6)	1833 (1777)
	ACR	An 45-54, Bi 55-74	30714 (30946)	168 (223)	8.7 (10.1)	27.3 (14.8)	2884 (2888)
	Risk-based	Biennial 35-74	17826 (17864)	120 (183)	6.4 (8.6)	19 (13.1)	1657 (1649)
FH+ 40-49	USPSTF	Biennial 50-74	11117 (11187)	84 (141)	5.2 (7.3)	15.8 (12)	918 (916)
	ACS	Annual 30-74	15964 (16017)	113 (198)	6.2 (9)	19.4 (14.4)	1496 (1489)
	ACR	An 45-54, Bi 55-74	30903 (31095)	160 (224)	8.4 (10.2)	27.5 (14.9)	2901 (2902)
	Risk-based	Biennial 40-74	17938 (17950)	117 (183)	6.3 (8.5)	19.2 (13.1)	1667 (1657)
FH+ 50-64	USPSTF	Biennial 50-74	11238 (11285)	75 (143)	4.7 (7.4)	15.8 (12.1)	927 (924)
	ACS	Annual 30-74	11238 (11285)	75 (143)	4.7 (7.4)	15.8 (12.1)	927 (924)
	ACR	An 45-54, Bi 55-74	31223 (31337)	133 (200)	7.3 (9.5)	25.8 (15)	2929 (2925)

	Risk-based	Biennial 50-74	18102 (18102)	98 (173)	5.5 (8.3)	18.3 (13.2)	1682 (1671)
FH+ 65+	USPSTF	Biennial 50-74	11325 (11389)	62 (111)	4 (6.1)	14.1 (12.2)	934 (933)
	ACS	Annual 30-74	11325 (11389)	62 (111)	4 (6.1)	14.1 (12.2)	934 (933)
	ACR	An 45-54, Bi 55-74	31430 (31554)	112 (160)	6.3 (7.9)	22.9 (15)	2945 (2944)
	Risk-based	Biennial 50-74	18203 (18220)	80 (134)	4.5 (6.7)	15.8 (13.2)	1690 (1682)
No BC FH	USPSTF	Biennial 50-74	11365 (11423)	52 (87)	3.2 (4.5)	10.1 (12.2)	937 (936)
	ACS	Annual 30-74	11365 (11423)	52 (87)	3.2 (4.5)	10.1 (12.2)	937 (936)
	ACR	An 45-54, Bi 55-74	31527 (31625)	98 (133)	5.2 (6.1)	17.2 (15)	2952 (2950)
	Risk-based	Biennial 50-74	18239 (18246)	71 (110)	3.9 (5.2)	12.1 (13.4)	1692 (1685)
PRS group 1 (0.0 < RR < 0.5)							
FH+ 30-39	USPSTF	Biennial 50-74	11447 (11505)	39 (62)	2.4 (3.2)	7.6 (12.2)	944 (944)
	ACS	Annual 30-74	14742 (14019)	47 (76)	2.5 (3.4)	7.8 (14.9)	1724 (1431)
	ACR	An 45-54, Bi 55-74	31728 (31803)	77 (98)	4 (4.5)	13 (15.1)	2968 (2965)
	Risk-based	Annual 30-74	18333 (18341)	56 (80)	3 (3.8)	9 (13.5)	1700 (1694)
FH+ 40-49	USPSTF	Triennial 30-74	11483 (11529)	39 (62)	2.4 (3.2)	7.6 (12.2)	946 (946)
	ACS	Annual 30-74	10983 (10986)	38 (74)	2.1 (3.4)	6.7 (14.3)	1218 (1044)
	ACR	An 45-54, Bi 55-74	31815 (31869)	73 (99)	3.8 (4.5)	13 (15.1)	2976 (2971)
	Risk-based	Triennial 40-74	18384 (18379)	53 (80)	2.9 (3.8)	9 (13.5)	1704 (1698)
FH+ 50-64	USPSTF	Biennial 50-74	11538 (11572)	35 (63)	2.2 (3.3)	7.4 (12.3)	951 (950)
	ACS	Annual 30-74	7987 (8012)	26 (56)	1.7 (2.9)	5.7 (12.1)	756 (649)
	ACR	An 45-54, Bi 55-74	31962 (31976)	61 (88)	3.4 (4.2)	12 (15.2)	2988 (2982)
	Risk-based	Triennial 50-75	18459 (18446)	44 (76)	2.5 (3.6)	8.5 (13.5)	1711 (1704)
FH+ 65+	USPSTF	Biennial 50-74	11578 (11618)	28 (49)	1.8 (2.7)	6.6 (12.3)	954 (954)
	ACS	Annual 30-74	8012 (8042)	22 (43)	1.4 (2.4)	5 (12.1)	758 (652)
	ACR	An 45-54, Bi 55-74	32057 (32071)	51 (69)	2.8 (3.4)	10.6 (15.2)	2996 (2990)
	Risk-based	Triennial 50-75	18505 (18498)	36 (58)	2.1 (2.9)	7.3 (13.6)	1714 (1709)
No BC FH	USPSTF	Biennial 50-74	11597 (11633)	24 (38)	1.5 (2)	4.6 (12.3)	955 (955)
	ACS	Annual 30-74	8024 (8051)	18 (34)	1.1 (1.7)	3.6 (12.1)	759 (653)
	ACR	An 45-54, Bi 55-74	32103 (32102)	44 (58)	2.3 (2.7)	7.8 (15.2)	2999 (2993)
	Risk-based	Triennial 50-75	18522 (18509)	32 (48)	1.7 (2.3)	5.4 (13.6)	1716 (1710)

Supplementary Table 7. Benefits and harms projections of mammography screening based on breast cancer family history. Outcomes for model E and model GE in () per 1,000 women screened.

Risk group based on family history (FH) of breast cancer	Screening guideline	Screening strategy	Nr. of screens	Life years gained *	Breast cancer deaths averted *	Over diagnoses	False positives
Positive FH ages 30-39	USPSTF guideline:	Biennial 50-74	10754 (10875)	142 (195)	8.6 (10)	21.2 (11.9)	889 (895)
	ACS guideline:	An 45-54, Bi 55-74	17467 (17531)	192 (251)	10.3 (11.7)	25.7 (12.8)	1627 (1618)
	ACR guideline:	Annual 40-74	29996 (30349)	259 (310)	13.5 (14)	36.7 (14.6)	2825 (2834)
	Risk-based (this study)	Biennial 30-74	20466 (20590)	212 (297)	10.9 (13)	28.5 (14.9)	2083 (2076)
Positive FH ages 40-49	USPSTF guideline:	Biennial 50-74	10859 (10949)	141 (195)	8.6 (10.1)	21.4 (12.1)	897 (906)
	ACS guideline:	An 45-54, Bi 55-74	17619 (17650)	189 (252)	10.2 (11.8)	26 (12.9)	1641 (1629)
	ACR guideline:	Annual 40-74	30255 (30556)	248 (311)	13.1 (14.1)	37.1 (14.7)	2848 (2853)
	Risk-based (this study)	Biennial 40-74	15670 (15755)	183 (274)	10 (12.5)	26.4 (14.1)	1472 (1464)
Positive FH ages 50-64	USPSTF guideline:	Biennial 50-74	11025 (11084)	126 (197)	7.9 (10.2)	21.6 (12.1)	911 (906)
	ACS guideline:	An 45-54, Bi 55-74	17846 (17860)	158 (240)	8.9 (11.5)	25.1 (13)	1660 (1649)
	ACR guideline:	Annual 40-74	30692 (30891)	209 (279)	11.6 (13.2)	35 (14.8)	2885 (2885)
	Risk-based (this study)	Biennial 50-74	11025 (11084)	126 (197)	7.9 (10.2)	21.6 (13)	911 (1649)
Positive FH ages 65+	USPSTF guideline:	Biennial 50-74	11143 (11227)	104 (154)	6.6 (8.4)	19.3 (12.1)	920 (919)
	ACS guideline:	An 45-54, Bi 55-74	17984 (18024)	131 (185)	7.4 (9.3)	21.7 (13.1)	1671 (1664)
	ACR guideline:	Annual 40-74	30975 (31191)	177 (222)	9.9 (10.9)	31.1 (14.9)	2908 (2911)
	Risk-based (this study)	Biennial 50-74	11143 (11227)	104 (154)	6.6 (8.4)	19.3 (12.1)	920 (919)
No BC FH in lifetime	USPSTF guideline:	Biennial 50-74	11197 (11275)	88 (122)	5.4 (6.2)	14.1 (13.1)	924 (1664)
	ACS guideline:	An 45-54, Bi 55-74	18032 (18060)	116 (154)	6.3 (7.2)	16.8 (13.2)	1675 (1668)
	ACR guideline:	Annual 40-74	31105 (31289)	155 (186)	8.3 (8.5)	23.8 (14.9)	2918 (2919)
	Risk-based (this study)	Biennial 50-74	11197 (11275)	88 (122)	5.4 (6.2)	14.1 (12.1)	924 (923)

SUPPLEMENTARY FIGURES

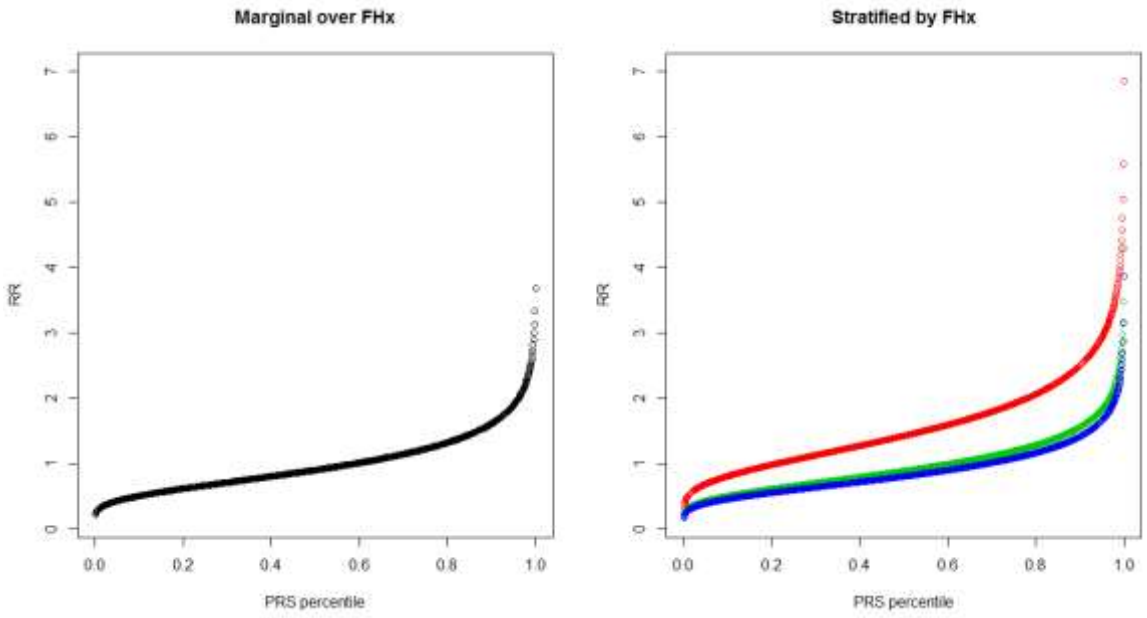

Figure 1: Distribution of breast cancer relative risk as a function of PRS (left) and family history + PRS (right). Red represents FH+ < age 40 women, green: FH+ between ages 40 and 65, blue: no FH in life.