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Risk-Based vs Annual Breast Cancer Screening
The WISDOM Randomized Clinical Trial

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IMPORTANCE Individual breast cancer risk can guide screening initiation, frequency, use of supplemental imaging, and preventive measures to improve breast cancer screening by shifting resources from low-risk women to high-risk women.

OBJECTIVE To determine whether risk-based breast cancer screening is a feasible alternative to annual mammography.

DESIGN, SETTING, AND PARTICIPANTS Parallel-group, pragmatic, multicenter randomized clinical trial comparing risk-based (n = 14 212) with annual (n = 14 160) breast cancer screening. Women aged 40 to 74 years without prior diagnoses of breast cancer or ductal carcinoma in situ, or prophylactic bilateral mastectomy, were recruited from all 50 US states from September 2016 to February 2023, with follow-up through September 5, 2025 (median follow-up, 5.1 years). Statistical analysis was conducted between July and November 2025. All study procedures were conducted via an online platform. Women who declined randomization were enrolled in an observational cohort.

INTERVENTIONS Risk assessment included sequencing of 9 susceptibility genes, polygenic risk score, and the Breast Cancer Surveillance Consortium version 2 model. The risk-based group received 1 of 4 recommendations: (1) highest risk (≥6% 5-year risk, high-penetrance pathogenic variant): alternating mammography and magnetic resonance imaging (MRI) every 6 months and counseling; (2) elevated risk (top 2.5 risk percentile by age): annual mammography and risk-reduction counseling; (3) average risk: biennial mammography; and (4) low risk (aged 40-49 years and <1.3% 5-year risk): no screening until risk is 1.3% or greater or age 50 years.

MAIN OUTCOMES AND MEASURES The coprimary outcomes included noninferiority for stage ≥IIB cancers and superiority in reducing biopsy rates. Secondary outcomes included identification of stage ≥IIA cancers, mammogram rates, uptake of prevention strategies in higher risk cohorts, preference for screening group in the observational cohort, ductal carcinoma in situ, MRI, and stage-specific cancer rates.

RESULTS A total of 28 372 women were randomized. The mean (SD) age was 54 (9.6) years and the majority were non-Hispanic White (77%). The rate of stage ≥IIB cancers was noninferior in the risk-based compared with the annual group (risk-based: 30.0 [95% CI, 16.3-43.8] vs annual: 48.0 [95% CI, 30.1-65.5] per 100 000 person-years; rate difference, −18.0 per 100 000 person-years [95% CI, −40.2 to 4.1]). The rate of breast biopsies was not lower in the risk-based group (rate difference, 98.7 per 100 000 person-years [95% CI, −17.9 to 215.3]) despite fewer mammograms (rate difference, −3835.9 [95% CI, −4516.8 to −3154.9]). The cumulative incidence of cancer, biopsy, mammogram, and MRI increased as risk category increased. In the observational cohort, 89% of participants (15 980/18 031) chose risk based.

CONCLUSIONS Risk-based breast cancer screening that includes population-based genetic testing safely stratified risk and screening intensity, but did not reduce biopsy rates.

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Screening for breast cancer continues to be largely a one-size-fits-all, age-based approach grounded on data from screening trials conducted prior to the current understanding of the complexity of breast cancer. Today, it is known that breast cancer is not one disease; treatment tailored to tumor biology has been standard for more than 20 years. A woman's risk of developing breast cancer varies widely, as does her risk for different subtypes of breast cancer.[1] Breast cancer risk models now include breast density and combinations of single-nucleotide variants (SNVs) into polygenic risk scores (PRSs).[2,3] Additionally, moderate- and high-penetrance genes known to significantly increase lifetime breast cancer risk can be identified at low cost.[4]

Public health efforts to reduce breast cancer morbidity and mortality are focused on population-based screening. However, population-based screening has several shortcomings. First, with the introduction of mammography, there has been an increase in stage I disease, without a concomitant decrease in later-stage disease.[5] Additionally, there has been a large increase in in situ (stage 0) lesions, which has not been accompanied by an equivalent decrease in early-stage invasive cancers.[6-9] Second, higher-stage and molecularly high-risk cancers often present as symptomatic or interval cancers, arising between periodic screens.[10] In the I-SPY 1 trial for women with stage II or III breast cancers, 80% of cancers were not screen detected.[11] Third, false-positive rates are high, and 75% of screen-directed biopsies in the US are benign.[12,13] Fourth, screening as currently practiced is resource intensive. In the US, the aggregate annual cost of screening exceeds the US Centers for Disease Control and Prevention's core public health program budget, and projected costs vary 4-fold, depending on the guideline implemented.[14,15] Comprehensive risk profiling, including genetic risk, offers an opportunity to improve many of the current limitations of breast cancer screening[16] but is not routinely used. A risk-based intervention was designed to shift resources from low-risk women to high-risk women, with the aim of not increasing late-stage cancer diagnoses while reducing overall harms and costs. Risk-based screening has proponents and detractors, but it has not been tested in a randomized clinical trial.[17,18]

The WISDOM (Women Informed to Screen Depending on Measures of Risk) study was designed to reimagine and improve the approach to breast cancer screening, beginning with risk assessment to guide the frequency of, timing of, and modality for screening, and to direct breast cancer risk-reduction strategies. Here, the study approach and primary outcome results from WISDOM's randomized comparison of risk-based and annual screening are reported.

Key Points

Question Is risk-based breast cancer screening as safe, less morbid, and as acceptable to women as annual screening?

Findings Risk-based breast cancer screening, where screening intensity and risk-reduction counseling are tailored to individual risk, was noninferior to annual screening (rate difference, −18.0 per 100 000 person-years). Importantly, women in the highest risk category, assigned to screen every 6 months, had no stage ≥IIB cancers; no overall reduction in biopsies was observed, but the rates for cancer detection, biopsy, and mammograms increased with rising risk in the risk-based group.

Meaning Risk-based breast cancer screening is safe and acceptable, offering an opportunity to modernize screening in the precision medicine era.

Methods

Study Design

WISDOM is a pragmatic randomized clinical trial comparing annual breast cancer screening beginning at age 40 years with risk-based screening (NCT02620852). Women aged 40 to 74 years with no prior diagnoses of breast cancer or ductal carcinoma in situ (DCIS), and no prior prophylactic bilateral mastectomy, were eligible. In addition to a randomized cohort, women who chose not to randomize could self-select a group as part of an observational cohort (eFigure 1 in Supplement 1). The primary objective of WISDOM was to demonstrate safety, measured as a noninferior rate of stage ≥IIB breast cancers, with risk-based screening compared with annual screening. The coprimary end point was to demonstrate fewer interventions, measured by a reduction in biopsy rates. These are reported for the randomized group. Results from the observational cohort, with the exception of preference for group, will be reported elsewhere. Secondary end points included stage ≥IIA cancers; DCIS; mammograms; magnetic resonance imaging (MRI); stage-specific cancer rates, comprising stage ≥IIA or symptomatically detected cancers; preference for group; and uptake of prevention interventions.

Enrollment

Recruitment was open to all women across the US and strategies, described elsewhere, included direct invitation from study sites (eTable 1 in Supplement 1) and outreach through advocacy organizations, media reports, social media, and physicians.[19] Participation was virtual, with sign-up, informed consent, enrollment, and follow-up conducted through the study website.

Study Workflow

Women could choose either to be randomized or self-select a group as part of an observational cohort. Consenting participants who agreed to randomization were asked to complete a breast health questionnaire (Supplement 2), and then randomized to undergo either annual screening beginning at age 40 years or the risk-based group. Those in the risk-based group were mailed genetic testing kits (Color Health).

Participants were asked to complete breast health and other questionnaires yearly to identify changes in risk factors, and report mammograms, breast biopsies, and cancer diagnoses. Mammogram data were collected by participant upload of mammography reports or by obtaining records directly from providing institutions or offices. All cancers were self-reported, after which study coordinators collected medical records with participant consent. Stage and mode of detection

were centrally reviewed by breast surgeons. Cancer registry linkages were used for additional verification (eMethods in Supplement 1).[19,20]

Study Oversight

The WISDOM study was designed and implemented by study investigators after consultation with a wide array of stakeholders. All participants provided electronic informed consent. The WISDOM protocol was approved by the University of California, San Francisco Institutional Review Board and overseen by a data and safety monitoring board (DSMB). WISDOM complied with all local and national regulations regarding human study participants and was conducted in accordance with the criteria set by the Declaration of Helsinki.[21]

Risk Models and Screening Assignments

The WISDOM risk model was based on the Breast Cancer Surveillance Consortium (BCSC) version 2 model,[22] incorporating a PRS that changed over the course of the trial, beginning with 75 SNVs and ending with 118 to 126 SNVs, described previously.[23,24]

The 4 risk-based categories were highest (5-year risk ≥6% or carrier of high-penetrance pathogenic variant), assigned to undergo screening every 6 months, alternating MRI and mammograms; elevated (top 2.5% by age[25]), assigned to undergo annual mammograms beginning at age 40 years; average, assigned to undergo biennial screening beginning at age 50 years; and lowest, women younger than 50 years with a risk of less than 1.3%, assigned to undergo no screening at this time (eTable 2 in Supplement 1). Yearly questionnaire responses were used to reclassify risk and update screening recommendations, adjusting for changes in risk factors and screening algorithm refinements. Women in the annual group filled out questionnaires. If they met high-risk BCSC criteria of 5-year risk of 5% or higher, they were sent an elevated risk report, but screening assignments were not changed. Women were sent an annual screening assignment to their online portal (eMethods in Supplement 1).

Risk Counseling and Breast Health Decisions

Our Breast Health Decisions tool was automated to include individual risk information for WISDOM participants in the risk-based group, explaining risk factors and putting risk in context.[25-27] It included recommendations for risk reduction (lifestyle and endocrine risk-reducing medication). A certified genetic counselor reached out to women with pathogenic variants in 1 of the 9 high-risk genes. Women in the top 2.5% of risk by age were contacted by a breast health specialist.

Statistical Analysis

Statistical analysis was conducted between July and November 2025. Randomization was 1:1 between the risk-based and annual groups, stratified by site, age younger than 50 years, prior mammogram, and BCSC risk score. The WISDOM trial was originally planned to randomize 65 000 women and be completed after 5 years to provide a median of approximately 3 years of exposure time in each randomized group, resulting in 80% power to show a noninferior rate of stage ≥IIB breast cancers in the risk-based compared with the annual group (assuming the same rate of stage ≥IIB cancer in the 2 groups and a 1-sided 2.5% α) and 90% or greater power to show a 25% difference in biopsy rate (with a 2-sided 5% α). The noninferiority margin, jointly decided upon by radiologists, breast surgeons, general care practitioners, advocates, and statisticians, was set to 50 stage ≥IIB cancers per 100 000 person-years (a difference of 1 stage ≥IIB cancer for every 2000 women screened). Due to slow initial accrual, trial duration was extended to up to 10 years, enabling a sample size reduction with maintained statistical power and the same noninferiority margin. The accrual goals were updated and approved by the DSMB and Patient-Centered Outcomes Research Institute. Under updated projections of accrual and follow-up, the randomized cohort was expected to yield approximately 72 000 person-years of exposure per group to yield 87% power to show noninferiority of stage ≥IIB cancer and 95% or greater for a 25% difference in biopsy rates (eMethods in Supplement 1).

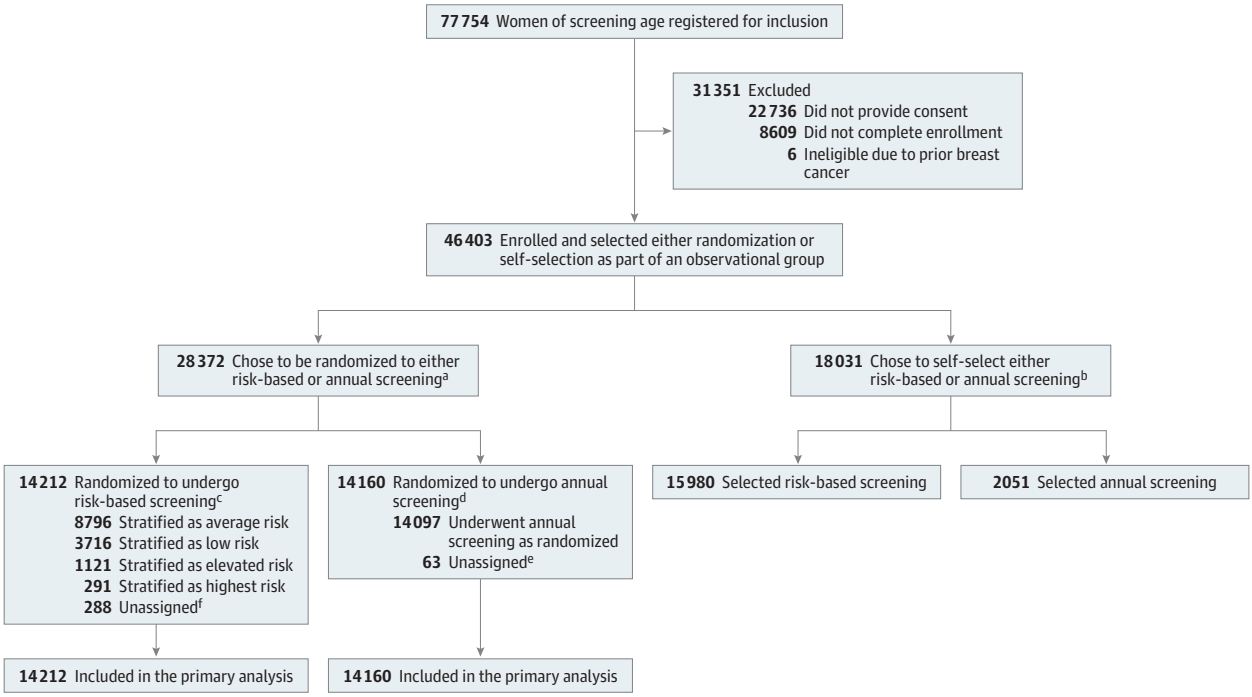
The primary analysis population was the as-randomized population. The absolute risk difference and 95% Wald CI of stage ≥IIB cancers between the randomized groups were estimated using an exponential regression model adjusted for stratification factors. If the higher boundary for the 2-sided 95% CI in the absolute difference of stage ≥IIB cancer rate between the risk-based group and the annual group was smaller than 50 per 100 000 person-years, the risk-based group would be deemed noninferior; if the lower boundary was smaller than 0, the risk-based group would be deemed superior. For the morbidity end point, we modeled biopsy events as recurrent outcomes with Poisson regression to estimate absolute differences in biopsy rates and 95% Wald CI. Inverse probability of censoring weights were used in both models to account for informative censoring due to differences in disease verified exposure time induced by differences in screening intensity; censoring weights were estimated using Cox regression, with BCSC risk score and randomization stratification factors as covariates. Analyses without inverse probability of censoring weights were performed as sensitivity analyses. Analyses of stage ≥IIA cancers, DCIS, and stage ≥IIB or symptomatically detected cancers (combined) followed the same general framework as primary end points.

Stage-specific breast cancer incidence was estimated using the Aalen-Johansen estimator.[28] Cumulative mean numbers of mammograms, MRIs, and breast biopsies were estimated using the nonparametric method proposed by Ghosh and Lin.[29] Censoring rules and handling of competing risks and missing data are described in the eMethods in Supplement 1.

We calculated adherence by study year as the percentage of study participants who followed their screening recommendation for a given study year (specified as imaging within 3 months of time assigned for women assigned to undergo imaging).

All analyses were prespecified. *P* values are reported for the primary outcomes, a 1-sided *P* value for noninferiority for the difference in stage ≥IIB breast cancer rate and a 2-sided *P* value for the difference in biopsy rates. For all other outcomes, 2-sided 95% CIs are provided without multiplicity

Figure 1. Flow of Participants in a Trial of Risk-Based vs Annual Breast Cancer Screening



BCSC indicates Breast Cancer Surveillance Consortium.

[a]Randomization was stratified by clinical site, age younger than 50 years, mammogram on file (no prior mammogram, mammogram but not on file, mammogram on file), and BCSC risk score (3 categories) to ensure similar population distributions in both groups.

[b]Participants who were not interested in being randomized were offered the opportunity to be part of an observational group in which they could self-select either risk-based or annual screening. Other than preference, results for that group will be reported elsewhere.

[c]Risk groups were assigned based on the BCSC version 2 risk model, supplemented by polygenic risk and 9 high-penetrance pathogenic variants. Risk-based screening recommendation letters and genetic test results were delivered to the study portal, with email notification when documents were ready to view.

[d]Risk was assessed using the BCSC version 2 risk model. Those in the top 5% of risk by age were given an elevated risk report indicating their increased risk. Annual screening recommendation letters were delivered to the study portal, with email notification when recommendations were ready to view.

[e]Participants who did not receive a screening assignment were included in the analysis and were not assigned due to a system error wherein missing density was not imputed, which was required for assignment in all study groups.

[f]Due to low risk (<1.3% 5-year risk), age 70 years or older, 5-year risk of 2.2% or less, and comorbidities with predicted 50% or greater risk of mortality in 10 years.

adjustments; therefore, caution should be applied when evaluating their joint statistical level. All statistical analyses were performed using R version 4.4.2 (R Foundation).

Results

From September 31, 2016, through February 28, 2023, 46 403 women enrolled, with 28 372 (61%) choosing randomization (**Figure 1**). The characteristics of the randomized participants at baseline were similar in the 2 groups (**Table**). Mean (SD) age was 54 (9.6) years and the majority were non-Hispanic White (77%). Additional baseline characteristics are published elsewhere.[19] The proportions of participants in the risk-based group assigned to the highest, elevated, average, and lowest risk categories were 2%, 8%, 63%, and 27%, respectively.

Primary End Points

The last follow-up date was September 5, 2025; median follow-up was 5.1 years. A total of 523 cancers occurred in the randomized cohort, 408 (78%) invasive and 115 (22%) stage 0 (DCIS) (**Figure 2**) (eTables 3 and 4 in Supplement 1). The rate of stage ≥IIB cancers met the noninferiority end point ($P < .001$), with non-statistically significant lower numbers of stage ≥IIB cancers in the risk-based group (21 vs 31; rate difference, −18.0 per 100 000 person-years [95% CI, −40.2 to 4.1]; $P = .11$) (**Figure 3**). Stage ≥IIB cancer rates increased as risk category increased from low to elevated; however, there were no stage ≥IIB cancers in the highest risk category. The cumulative incidence functions of cancers by stage in the annual vs risk-based screening groups and by risk category are shown in **Figure 4**A, B.

Biopsy rates, a coprimary end point, were not significantly different between groups (943 vs 1029; rate difference, 98.7 per 100 000 person-years [95% CI, −17.9 to 215.3]; $P = .10$) (Figure 2, **Figure 5**A, B). Rates varied markedly across screening assignments in the risk-based group, with rates for highest, elevated, average, and lowest risk categories being 6647, 3207, 1173, and 981 per 100 000 person-years, respectively. The total number of biopsies (1972) was 4-fold higher than cancers reported (523).

Table. Baseline Participant Demographics and Risk Factors

Characteristic	No./total No. (%)	
	Risk-based screening group (n = 14 212)	Annual screening group (n = 14 160)
Age, No. (%), y		
40-49	5202 (37)	5197 (37)
50-59	4407 (31)	4305 (30)
60-69	3657 (26)	3687 (26)
70-74	912 (6)	939 (7)
≥75	20 (<1)	20 (<1)
Race and ethnicity[a]		
Hispanic	1312/14 153 (9)	1236/14 081 (9)
Non-Hispanic Asian	560/14 153 (4)	583/14 081 (4)
Non-Hispanic Black or African American	808/14 153 (6)	807/14 081 (6)
Non-Hispanic multiracial	419/14 153 (3)	432/14 081 (3)
Non-Hispanic Native Hawaiian or other Pacific Islander/American Indian or Alaska Native	67/14 153 (<1)	69/14 081 (<1)
Non-Hispanic White	10 927/14 153 (77)	10 891/14 081 (77)
Other[b]	60/14 153 (<1)	63/14 081 (<1)
Educational attainment		
High school graduate or less	477/14 156 (3)	459/14 115 (3)
Some college or technical school	2805/14 156 (20)	2863/14 115 (20)
College graduate or more	10 874/14 156 (77)	10 793/14 115 (77)
Age at menarche, y		
<12	2472/11 820 (20)	2424/11 836 (21)
12-13	6398/11 820 (54)	6486/11 836 (55)
≥14	2857/11 820 (24)	2852/11 836 (24)
Don't know	93/11 820 (<1)	74/11 836 (<1)
Age at first birth, y		
Nulliparous	2869/11 695 (25)	2957/11 703 (25)
<20	1052/11 695 (9)	990/11 703 (9)
20-24	2123/11 695 (18)	2148/11 703 (18)
25-29	2455/11 695 (21)	2457/11 703 (21)
30-34	1892/11 695 (16)	1917/11 703 (16)
>34	1304/11 695 (11)	1234/11 703 (11)
Prior biopsy reported at baseline, No. (%)[c]	3234 (23)	3110 (22)
Self-reported atypia biopsy finding at baseline, No. (%)[c]	129 (4)	119 (4)
Family history of breast cancer		
No family history of breast cancer	6413/14 006 (46)	6448/13 933 (46)
First-degree relative only	1725/14 006 (12)	1698/13 933 (12)
Second-degree relative only	3440/14 006 (25)	3399/13 933 (24)
Both first- and second-degree relatives	1160/14 006 (8)	1126/13 933 (8)
Don't know	1268/14 006 (9)	1262/13 933 (9)
Chemoprevention at baseline		
None	10 399/10 584 (98)	10 389/10 550 (98)
≥1	185/10 584 (2)	161/10 550 (2)

(continued)

Table. Baseline Participant Demographics and Risk Factors (continued)

Characteristic	No./total No. (%)	
	Risk-based screening group (n = 14 212)	Annual screening group (n = 14 160)
Breast density (highest recorded), No. (%)[d]		
Almost entirely fatty	545 (5)	497 (4)
Scattered fibroglandular densities	4996 (41)	4727 (41)
Heterogeneously dense	5364 (44)	5179 (44)
Extremely dense	1219 (10)	1271 (11)
No response/missing	2074 (15)	2474 (18)
Screening history at baseline		
I've never had a mammogram	893/14 131 (6)	890/14 091 (6)
Less than 2 y ago	12 010/14 131 (85)	11 941/14 091 (85)
2 to 3 y Ago	717/14 131 (5)	735/14 091 (5)
4+ y Ago/I've stopped getting mammograms	447/14 131 (3)	448/14 091 (3)
Don't know	64/14 131 (<1)	77/14 091 (1)
Breast cancer genetic test, No. (%)		
Gene panel test completed	10 884 (77)	NA
No pathogenic variant	10 601 (97)	NA
Moderate-risk pathogenic variant[e]	204 (2)	NA
High-risk pathogenic variant[f]	79 (<1)	NA

Abbreviation: NA, not applicable.

[a] Race and ethnicity were self-reported and collected due to their inclusion as risk factors in the Breast Cancer Surveillance Consortium version 2 risk model.

[b] Not listed or do not know.

[c] Previous biopsy reported on baseline questionnaire, including biopsy result response to follow-up question: "Have any of your breast biopsies (e.g., needle biopsies, surgeries) showed proliferative changes with atypia sometimes called atypia, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH)?"

[d] Breast Imaging Reporting and Data System density score extracted from clinical mammogram report by study staff (not participant reported). Density was imputed for participants whose breast density was missing or who had no prior mammogram.

[e] Moderate-penetrance genes included *ATM* and *CHEK2*.

[f] High-penetrance and syndromic genes included *BRCA1*, *BRCA2*, *PALB2*, *CDH1*, *TP53*, *PTEN*, and *STK11*. For women with 2 pathogenic variants, the higher-penetrance variant was counted.

Secondary End Points

Rates of stage ≥IIA cancers (Figure 4C, D) met the noninferiority end point (risk difference, -28.6 per 100 000 person-years [95% CI, −64.5 to 7.3]; noninferiority margin, 100 per 100 000 person-years). Rates of all invasive and DCIS diagnoses were similar across the 2 groups (Figure 4E, H). Cumulative incidence functions for any cancer and stage ≥IIB or symptomatically detected cancers are shown in eFigures 2 and 3 in Supplement 1. Cancer rates increased as risk increased. For example, invasive cancer rates were 1279, 428, 233, and 169 per 100 000 women per year in the highest, elevated, average, and lowest risk categories, respectively.

The number of mammograms was lower in the risk-based group, but varied significantly by risk assignment (Figure 2, Figure 5C, D). Overall use of mammograms was lowest for women in their 40s, where the majority (70.9%) were

Figure 2. Coprimary and Secondary End Point Analyses Comparing the Risk-Based and Annual Screening Groups

	Risk-based group (n = 14 212 [75 004 person-years])		Annual group (n = 14 160 [73 703 person-years])		Rate difference per 100 000 person-years (95% CI)[a]	Rate ratio (95% CI)[a]	log(RR) (95% CI)	P value
	No. of events	Rate per 100 000 person-years (95% CI)	No. of events	Rate per 100 000 person-years (95% CI)				
Coprimary end points								
Stage ≥IIB	21	30.0 (16.3 to 43.8)	31	48.0 (30.1 to 65.5)	-18.0 (-40.2 to 4.1)	0.62 (0.35 to 1.12)	-0.48 (-1.05 to 0.11)	<.001[b]
Biopsy	1029	1371.0 (1289.7 to 1450.3)	943	1272.2 (1193.6 to 1356.1)	98.7 (-17.9 to 215.3)	1.08 (0.99 to 1.18)	0.08 (-0.01 to 0.17)	.10
Secondary end points								
Any cancer	260	423.6 (371.9 to 475.3)	263	410.9 (360.4 to 461.5)	12.7 (-59.6 to 85.0)	1.03 (0.87 to 1.23)	0.03 (-0.14 to 0.21)	NA
Stage ≥IIA	57	88.7 (65.1 to 112.3)	74	117.3 (90.9 to 144.4)	-28.6 (-64.5 to 7.3)	0.76 (0.53 to 1.07)	-0.27 (-0.63 to 0.07)	NA
Stage ≥IIB or symptomatically detected	41	63.1 (43.2 to 82.9)	43	68.2 (47.6 to 88.9)	-5.2 (-33.8 to 23.5)	0.92 (0.60 to 1.43)	-0.08 (-0.51 to 0.36)	NA
DCIS	56	90.7 (66.7 to 114.7)	59	92.4 (68.5 to 116.3)	-1.6 (-35.5 to 32.2)	0.98 (0.68 to 1.42)	-0.02 (-0.39 to 0.35)	NA
MRI	891	1187.1 (1111.7 to 1267.7)	589	794.7 (733.0 to 861.5)	392.4 (291.5 to 493.4)	1.49 (1.34 to 1.66)	0.40 (0.29 to 0.51)	NA
Mammogram	32 332	43 083.7 (42 616 to 43 569.6)	34 751	46 919.5 (46 429.5 to 47 415.3)	-3835.9 (-4516.8 to -3154.9)	0.92 (0.9 to 0.93)	-0.08 (-0.11 to -0.07)	NA
Stage I	134	226.2 (188.4 to 264.0)	120	187.1 (153.0 to 221.1)	39.1 (-11.8 to 90.0)	1.21 (0.94 to 1.55)	0.19 (-0.06 to 0.44)	NA
Symptomatically detected	32	49.6 (32.0 to 67.3)	25	40.3 (24.5 to 56.2)	9.3 (-14.4 to 33.1)	1.23 (0.72 to 2.09)	0.21 (-0.33 to 0.74)	NA

DCIS indicates ductal carcinoma in situ; MRI, magnetic resonance imaging; NA, not applicable.
[a]Rate ratios and differences were estimated using an exponential regression model adjusted for stratification factors. Inverse probability of censoring weights were used to account for informative censoring due to differences in disease verified exposure time induced by differences in screening intensity.
[b]P value for stage ≥IIB cancers is for noninferiority. The noninferiority margin was set to 50 stage ≥IIB cancers per 100 000 person-years.

in the group assigned not to screen until age 50 years (3694/5209) and 69 (1.3%), 646 (12.4%), 710 (13.6%), and 90 (1.7%) were assigned to the highest, elevated, or average at baseline risk groups or unassigned, respectively. Among participants in the risk-based group, MRI screening was used most frequently in the highest risk category (Figure 2, Figure 5E, F).

The distribution of screen-detected vs symptomatic cancers showed higher proportions of symptomatically detected cancers with increasing stage (eTable 5 in Supplement 1). Rates of use of endocrine risk-reducing therapy increased among high risk categories over time in the risk-based group compared with baseline (eFigure 4 in Supplement 1).

Of participants in the observational cohort who chose their own screening approach, 89% opted for risk-based (Figure 1).

Survey Completion and Adherence

Average annual completion rates were 60% (57% and 65%) and 57% (52% and 61%) of participants completing a survey within 12 months of the study end date for the annual and risk-based groups, respectively. A total of 72% (76% risk-based and 68% annual) initiated a follow-up survey after baseline. At least 10% of participants with cancer contacted the study to report their cancer, even if they had not filled out a follow-up survey (eTable 6 in Supplement 1). Adherence to assigned screening was higher in the first years (45%-60%) and lower in later years (20%-30%), depending on risk category and study year (eTable 7 in Supplement 1).

Discussion

The WISDOM results show that the rate of stage ≥IIB cancers in the risk-based group was noninferior to annual screening, demonstrating that stratifying screening intensity, modality, and age to start screening by individual risk is safe. Additionally, the WISDOM approach stratified risk for developing breast cancer (Figure 2D, F), providing a critical foundation for improving and refining risk-based screening approaches.

Given the sharp demarcation in survival outcomes for stage >IIA breast cancers, no increase in stage ≥IIB cancers was the safety end point selected for the primary outcome.

A coprimary end point, biopsy rate, was selected as a proxy for morbidity. Although the risk-based approach did not reduce the number of biopsies overall, biopsy rates decreased as risk classification decreased, as did MRI and mammography usage. Although models have demonstrated that adherence to risk-based screening recommendations will reduce overall biopsy rates,[30,31] in WISDOM, women and health care professionals were more reticent to

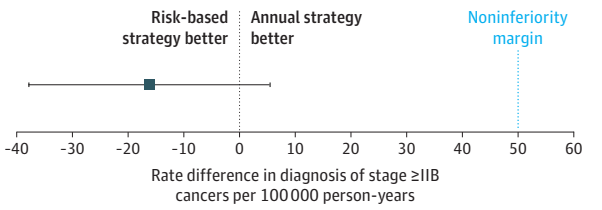
screen less. The overall reduction in mammograms in the risk-based group was less than anticipated because those randomized to the risk-based group and assigned to the average (biennial screening) and lowest risk categories (no screening) screened more often than recommended. Increased MRI use in women assigned to elevated risk was also observed, even though it was not recommended. Under current guidelines, women with a 20% lifetime risk for breast cancer based on family history are recommended MRI.[32,33] Although WISDOM applies more stringent criteria, participants may have heeded other advice to follow current guidelines. Furthermore, participants randomized to the annual group, on average, screened less often than annually, reducing differences in mammography and biopsy rates between the annual and risk-based groups.

Secondary end points included no increase in stage ≥IIA cancers because this stage represents a small increase in the hazard for disease-specific mortality, so it was also included as a secondary end point. This end point was met. The secondary end point of acceptability can be assessed in 2 ways. First, it was shown that 61% of women were willing to be randomized to risk-based screening. Second, in the observational cohort, where women could self-select their screening approach, 89% chose risk-based, regardless of age or geography. An additional secondary end point was the rate of uptake of preventative interventions in high-risk women. The Breast Health Decisions tool[26,27] was used to educate participants in the risk-based group on their personal risk and prevention options, along with direct outreach to those at high risk. The use of endocrine risk-reducing medications was doubled from 5% to 10% in the highest risk group. WISDOM, one of the first studies to utilize population-based genetic assessment for breast cancer risk with no pretest counseling, supports the notion that identifying those at highest risk enables better prevention uptake.[24-27]

A key takeaway is that genetic testing (including pathogenic variants and PRS) integrated with a well-established clinical risk model is feasible and impactful at the population level.[34,35] It was previously reported that 30% of WISDOM participants with high-penetrance pathogenic variants reported no family history, demonstrating that family history alone is not sufficient to identify those at highest risk.[36] The use of PRS changed risk assignments in 10% to 14% of women.[24] Three-quarters of participants completed genetic testing using kits mailed to their homes, higher than completion in many reports of women with cancer (46%-90%) and similar to studies of women without cancer invited to test.[37-40]

The now-routine inclusion of breast density in mammogram reports has prompted supplemental screening that has not been prospectively tested and will substantially increase the aggregate cost of annual screening.[41-44] The risk-based WISDOM approach already incorporates density but has the potential to significantly reduce aggregate cost[15,17,45,46] without increasing stage ≥IIB cancers. There is another prospective, risk-based randomized screening trial in Europe, MyPeBS, which will report out in 2027, and provide complementary data.[47] Plans to pool data should further improve risk assignment.

Figure 3. Rate Difference per 100 000 Person-Years and Depiction of Noninferiority



The difference is defined as the rate of stage ≥IIB cancers in the risk-based group − the rate of stage ≥IIB cancers in the annual group. CI whiskers do not cross the noninferiority line, meaning that the hypothesis that risk-based screening is inferior to annual screening is rejected.

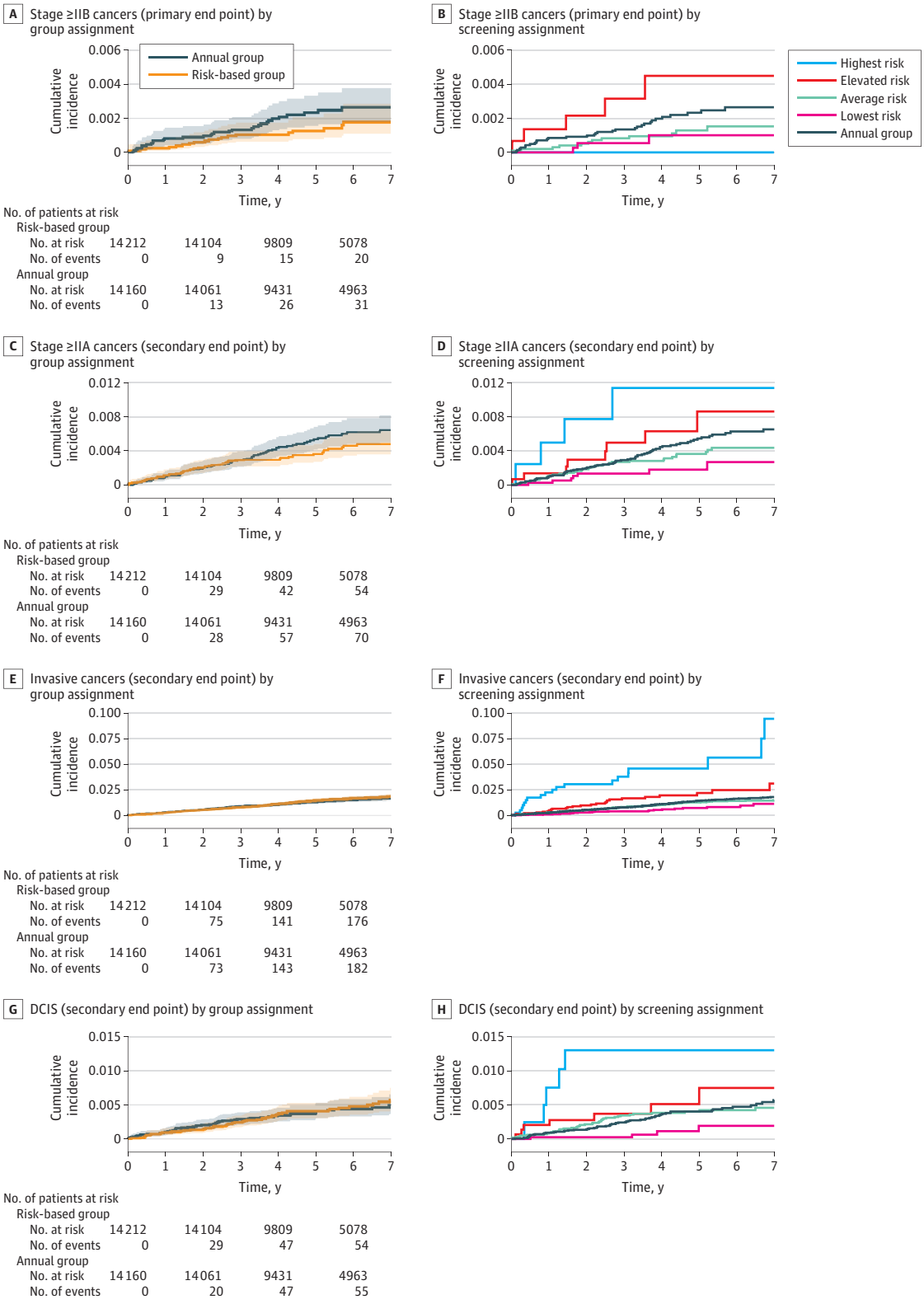
Limitations

This study has limitations. Many limitations are related to the pragmatic design. First, adherence to screening recommendations was not optimal. Women get screening advice from many sources—multiple guidelines,[48] public health messaging,[49] and mammography result letters urging annual mammograms, etc—all likely impacted adherence. Study engagement was high, with 72% of participants completing a survey after baseline. Study retention was not as high as a traditional randomized clinical trial, but much higher than healthy population-based studies, such as All of Us.[50,51] The COVID-19 pandemic occurred in the middle of this trial; its potential impact on the study is currently being evaluated. Second, the study relied on self-reporting of cancers, biopsies, and imaging procedures. However, it was confirmed that self-reporting identified 95% of cancer diagnoses at the University of California centers and cross-referenced with the cancer registry, suggesting that few cancers were missed[20] and pathology of 95% of participants was verified. Self-report of biopsies appeared close to expectation, as 27% of women with biopsies (523/1972) had a cancer diagnosis, consistent with cancer and biopsy rates in the US.[52] Third, the number of stage ≥IIB cancers was small, leading to a higher probability that results were impacted by stochastic noise. Fourth, the study population was enriched with college-educated White women compared with the general US population, which may limit generalizability. Fifth, cancer screening is often dictated by primary care physicians, but WISDOM brought screening directly to the individual, which may have limited adherence. With better engagement of health care teams, improved ways to get risk assessment integrated into the clinical workflow, and more confidence in the value of risk-based screening, improvements to adherence are anticipated.

Conclusions

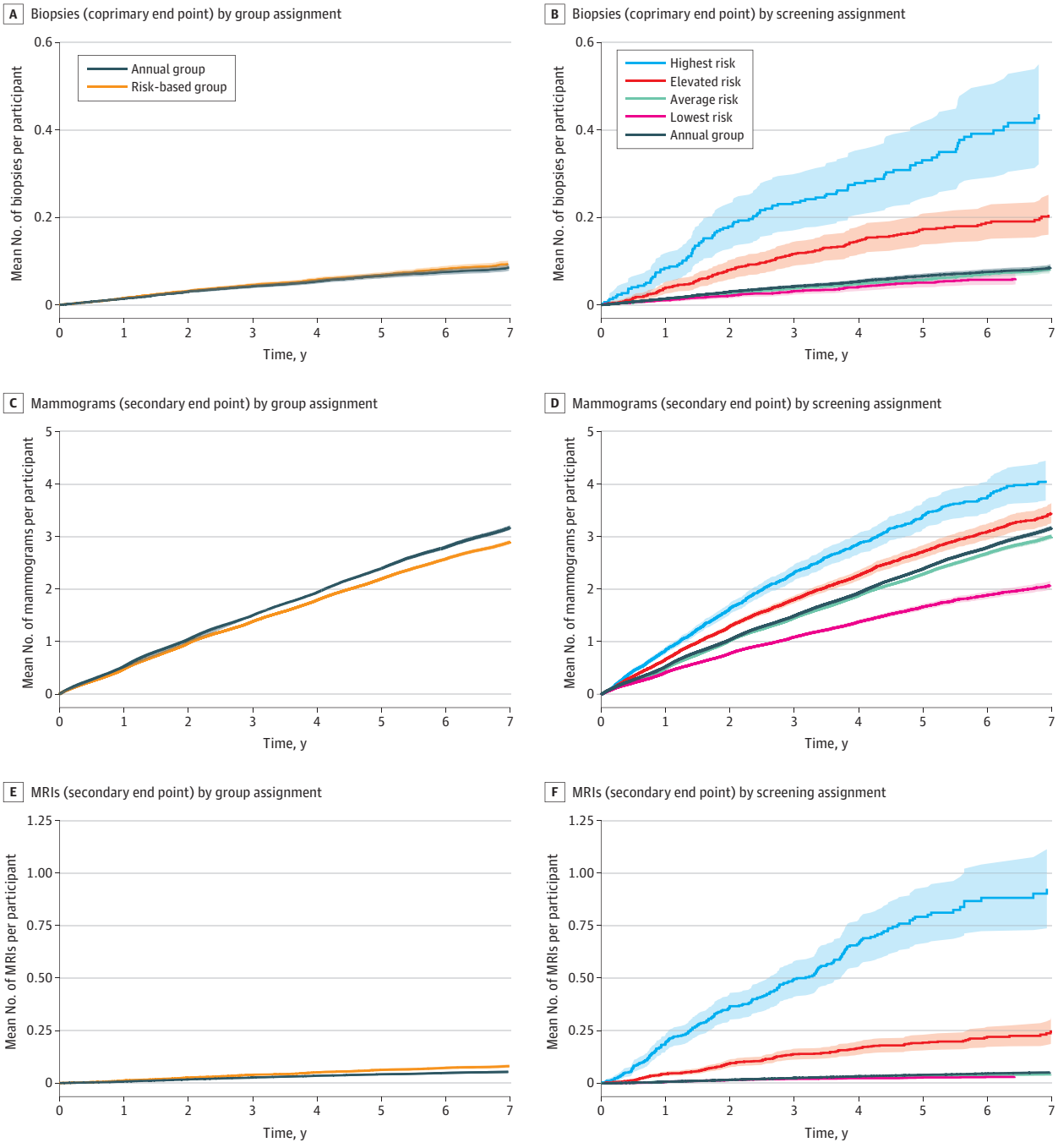
The WISDOM study demonstrated that a risk-based approach successfully stratifies the population for breast cancer risk and is safe and acceptable to women. Development of better risk models and risk-reducing recommendations hold promise for future improvements, as does more effective risk communication to patients and health care professionals to promote

Figure 4. Cumulative Incidence of Breast Cancer Stage at Detection



Shaded areas represent 95% CIs. Cumulative incidence by screening assignment in the risk-based group was computed with screening assignment as a time-varying exposure because participants could switch screening assignment after updated risk assessment. Risk model was based on the Breast Cancer Surveillance Consortium version 2 model,[22] with a polygenic risk score. The median (IQR) follow-up was 5.2 (3.8-6.9) years in the risk-based group and 5.0 (3.7-6.9) years in the annual group. For information on risk level categories and cancer stages, see notes to Figure 5. DCIS indicates ductal carcinoma in situ.

Figure 5. Biopsies, Mammograms, and Magnetic Resonance Imaging (MRI)



Mean cumulative numbers by screening assignment within the risk-based group were computed with screening assignment as a time-varying exposure because participants could switch screening assignment after updated risk assessment. The biopsy rates were higher in the risk-based groups (B), but the main contributor was the significantly higher rate of procedures in the highest and elevated risk groups (A). Mammograms were lower overall in the risk-based group (D), but the mean number varied by risk group (C). MRIs were higher in the risk-based group (F), but the main contributor to the mean number of MRIs was from the highest and elevated risk groups. Risk levels in the risk-based group were determined by stratifying 5-year breast cancer risk into 4 categories: highest (5-year risk ≥6%), elevated (top 2.5% by age[25]), average (women aged ≥50 years with a risk of <6% and below the top 2.5th percentile by age), and lowest (women aged <50 years with a risk of <1.3%). The risk model was based on the Breast Cancer Surveillance Consortium version 2 model,[22] together with a polygenic risk score. Ductal carcinoma in situ: noninvasive cancer confined to ducts (stage 0); invasive: cancer that has spread into breast tissue; stage IIA: invasive tumor 2 to 5 cm without nodal spread or smaller than 2 cm with 1 to 3 positive nodes; stage IIB: invasive tumor larger than 5 cm without nodal spread or 2 to 5 cm with 1 to 3 positive nodes. Shaded areas indicate the 95% CIs. The median (IQR) follow-up was 5.2 (3.8-6.9) years in the risk-based group and 5.0 (3.7-6.9) in the annual group. The lowest risk lines are truncated in panels B and F because no biopsies were taken in that category between 6.4 and 7 years.

informed, shared decision-making. Work is ongoing in the next platform iteration, WISDOM 2.0, to utilize PRS for subtype-specific and ancestry-based risk assessment, along with radiographic (AI) measures of risk.

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