JAMA Internal Medicine | Original Investigation | WOMEN'S HEALTH

Germline Pathogenic Variants Among Women Without a History of Breast Cancer

A Secondary Analysis of the WISDOM Randomized Clinical Trial

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IMPORTANCE The prevalence of pathogenic or likely pathogenic variants (PVs) in breast cancer susceptibility genes in the US population—regardless of family history risk factors—remains largely unknown because population-based genetic screening is not routinely performed.

OBJECTIVE To identify the prevalence of PVs in a large cohort of women offered criteria-independent genetic testing and to evaluate the relationship of test positivity to family history and other patient characteristics.

DESIGN, SETTING, AND PARTICIPANTS The Women Informed to Screen Depending on Measures of Risk (WISDOM) randomized clinical trial enrolled women without breast cancer aged 40 to 74 years between August 2016 and February 2023 in a pragmatic randomized screening trial comparing annual screening mammography with personalized risk-based screening. Data were analyzed from August 2023 to November 2025.

EXPOSURES All women in the personalized screening arm were offered germline testing for 9 breast cancer susceptibility genes: *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*, *CDH1*, *PTEN*, *STK11*, and *TP53*.

MAIN OUTCOMES AND MEASURES The prevalence of PVs in the trial and the distribution of self-reported demographic and family history data in this subpopulation of carriers.

RESULTS Among 23 098 women who completed germline genetic testing (mean [SD] age, 54.3 [9.6] years), 714 (3.1%) carried a PV. Excluding 109 who were previously aware of their PV, the detection rate was 2.6%. PVs were most common in *CHEK2* (337 [1.5%]) and *ATM* (101 [0.4%]) but less common in higher-penetrance genes (*BRCA1*, 33 [0.1%]; *BRCA2*, 82 [0.4%]; *PALB2*, 44 [0.2%]). PVs in the *CDH1*, *PTEN*, *STK11*, and *TP53* genes were rare (less than 0.1%). Notably, 180 of 605 women with PVs (29.8%) did not report a first-degree or second-degree female relative with breast or ovarian cancer, male relative with breast cancer, or Jewish ancestry.

CONCLUSIONS AND RELEVANCE In this secondary analysis of the WISDOM trial, criteria-independent genetic testing in a pragmatic trial identified a substantial number of women with clinically actionable results, many of whom would not have qualified for genetic testing under current guidelines. These findings support broader access to genetic testing as part of personalized breast cancer risk assessment.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02620852

Supplemental content

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JAMA Intern Med. 2026;186(3):344-352. doi:10.1001/jamainternmed.2025.7323
Published online December 12, 2025.

Genetic testing for breast cancer susceptibility genes (BCSGs) is becoming increasingly available, particularly with the advent of next-generation sequencing and multigene panels.[1] Yet current guidelines[2-6] recommend testing only for those with a personal or family history of breast and other cancers or Jewish ancestry, and most payors restrict coverage to guideline-directed testing. Operationalizing these clinical guidelines, however, has several challenges. Patients often have limited cancer family history information, and clinicians lack the time, training, and tools to collect and interpret this information.[7] Systematic differences in collecting family history information by race and ethnicity[8,9] and socioeconomic status[10] contribute to disparities[11] in who receives genetic testing. Even among women who do provide a thorough family history, many with pathogenic or likely pathogenic variants (PVs) in BCSGs do not meet guideline-directed requirements to be eligible for genetic testing.[12-15]

Unfortunately, many women with PVs in BCSGs are only identified after a cancer diagnosis,[12,13] a missed opportunity for the prevention or early detection of breast and other associated cancers. For example, among women with PVs in the *BRCA1* and *BRCA2* genes, cancer-related morbidity and mortality can be reduced through enhanced surveillance[16-18] and risk-reducing interventions.[19-22] Other rare BCSGs (eg, *CDH1*, *PTEN*, *STK11*, *TP53*) also have important implications for comprehensive cancer risk management and cascade testing[23] in families. Moreover, expanding germline testing to include moderate-penetrance genes (eg, *CHEK2* and *ATM*) may further refine individual risk assessments[24] and eventually aid in management of the associated cancer risks.[5,25]

Health systems, clinicians, payors, patients, and other stakeholders have an interest in efficiently identifying patients with PVs to improve patient outcomes and reduce costs. However, this task is perceived to be onerous because it requires building infrastructure for population-based testing.[26] The WISDOM (Women Informed to Screen Depending on Measures of Risk) randomized clinical trial is intended to pave a path forward as one of the first large-scale efforts to integrate germline BCSG testing into a personalized breast cancer screening strategy.[27,28] This analysis describes the prevalence of PVs in a large cohort of women offered criteria-independent genetic testing and the relationship of test positivity to family history and other participant characteristics.

Key Points

Question Among women without a history of breast cancer, what is the prevalence of pathogenic variants in breast cancer susceptibility genes, and what are the characteristics of women who have pathogenic variants in these genes?

Findings In the personalized arm (n = 23 098 women) of a large US breast cancer screening trial comparing annual screening mammography with personalized screening through clinical risk models and genetic testing, pathogenic variants were detected in 714 participants (3.1%; 2.6% of those previously unaware of their pathogenic variant). Approximately 30% of these carriers (180 of 605 women with PVs) did not report common family history risk factors that determine eligibility for germline testing.

Meaning Criteria-independent genetic testing yielded more women with high-penetrance and intermediate-penetrance breast cancer susceptibility genes who may benefit from changes in clinical management.

Methods

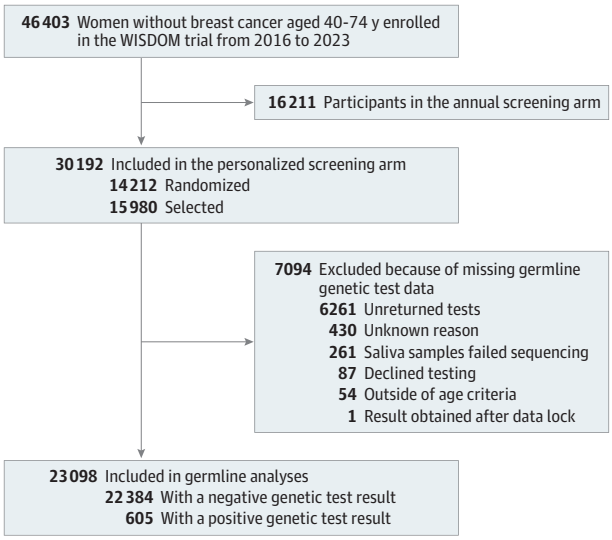
Study Population and Recruitment

The WISDOM trial (NCT02620852) is a large, pragmatic, preference-tolerant randomized clinical trial designed to compare annual screening mammography with a personalized, risk-based breast cancer screening strategy. The overall study protocol and risk assessment methods have been previously published[27,29]; the trial protocol can be found in Supplement 1, and a change log to the protocol can be found in Supplement 2. The results of the WISDOM trial have also been published.[30] Briefly, women aged 40 to 74 years with no personal history of breast cancer or ductal carcinoma in situ and no prior bilateral mastectomy were eligible to participate. Participants were recruited through multiple channels, including health systems, insurance carriers, employers, and direct outreach via the study website (thewisdomstudy.org). The study design allowed participants to either be randomized to the personalized or annual screening arm or self-select their preferred arm. All participants in the personalized arm were offered germline genetic testing with a 9-gene panel to inform screening recommendations. All participants provided written informed consent, and research protocols and participant questionnaires were approved by the University of California, San Francisco Institutional Review Board.

Germline Genetic Testing and Variant Classification

Color Genomics, a Clinical Laboratory Improvement Amendments–certified laboratory and accredited by the College of American Pathologists, conducted genetic testing according to previously described methods.[29] Briefly, DNA was extracted from saliva samples, with target enrichment using SureSelect XT probes (Agilent). Sequencing was then conducted with a NextSeq 500/550 kit (Illumina) for a panel including 9 BCSGs: *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *CDH1*, *PTEN*, *STK11*, and *TP53*. Variant classification followed American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) guidelines, and only PVs were reported. *CHEK2* variants were further subclassified based on estimated penetrance. Moderate-penetrance PVs included truncating variants (including the c.1100delC founder PV), splice site PVs, large rearrangements/deletions, and the R117G missense variant; low-penetrance *CHEK2* variants included I157T, S428F, and other missense variants, as described previously.[25] We report *CHEK2* low-penetrance (*CHEK2*LP) variants separately, as these are not recommended to be used in isolation in breast cancer risk assessment but are currently being reported out by commercial genetic testing laboratories. Participants with PVs received personalized screening assignments consistent with evidence-based guidelines and/or

Figure. CONSORT Diagram



CONSORT diagram for the participants in the WISDOM (Women Informed to Screen Depending on Measures of Risk) trial that received germline genetic testing. Only participants in the personalized screening arm who completed genetic testing were included. Participants with prior positive testing for germline pathogenic or likely pathogenic variants (n = 109) were removed for final estimate of prevalence.

the risk assessments provided by the WISDOM trial's screening review board.[3] Participants in the personalized arm also underwent genotyping for single-nucleotide variants selected based on prior genome-wide association studies to construct a polygenic risk score to further inform screening recommendations.[31,32]

Self-Reported Prior Genetic Testing

Baseline questionnaires asked participants whether they had previously undergone germline genetic testing and, if so, whether they had positive results and for which gene(s). Those reporting a positive test result in a gene matching their WISDOM trial test result were classified as being previously aware of their germline PV and excluded from analysis. Individuals reporting prior negative test results were also noted; however, it was not feasible to ascertain which of the 9 BCSGs were included in any participants' prior test. Therefore, these individuals were considered previously unaware in the primary analysis of PV detection rate.

Demographic and Family History Data

Baseline questionnaires also included self-reported demographic information (eg, age, race and ethnicity, Jewish ancestry), health information (eg, height, weight, and personal history of cancers other than breast), and family history of breast and ovarian cancers. Race and ethnicity categories included Hispanic ethnicity; non-Hispanic American Indian, Alaska Native, Native Hawaiian, and Pacific Islander race (combined due to low numbers); non-Hispanic Asian race; non-Hispanic Black race; non-Hispanic White race; and non-Hispanic multiracial and other or unknown race. Family history data (eTable 1 in Supplement 3) included first-degree and second-degree relatives with breast, ovarian, and other cancers. Patients reporting a family history of breast or ovarian cancer were asked to separately identify each family member's status, including approximate age of onset, sex, and lineage (maternal or paternal). For multiple sisters and aunts, data collection focused on the relative with the youngest age of onset. Jewish ancestry was defined as having at least 1 grandparent with Jewish ancestry.

Statistical Analysis

Descriptive statistics were used to summarize the prevalence of PVs across genes and subgroups. χ^2 and Fisher exact tests were used to compare PV prevalence by study arm, age group, race and ethnicity, and family history. Analyses were stratified by whether participants were previously aware of their PV status. Participants with PVs in rarer BCSGs (*CDH1*, *PTEN*, *STK11*, and *TP53*) were excluded from subgroup tables due to small numbers. Significance was set at $P < .05$, and all P values were 2-tailed. All statistical analyses were conducted using SPSS version 29.0.2 (IBM) and R version 4.2 (The R Foundation).

Results

The WISDOM trial enrolled 30 192 women to the personalized screening arm (**Figure**): 14 212 (47.1%) were randomized to the personalized arm and 15 980 (52.9%) selected the personalized arm. Of the 23 098 participants who completed germline genetic testing, the mean (SD) age was 54.3 (9.6) years (**Table 1**). A total of 2156 participants (9.3%) were Hispanic (any race); 79 (0.3%) were American Indian or Alaska Native, Native Hawaiian, or Pacific Islander (combined due to low numbers); 1071 (4.6%) were Asian; 996 (4.3%) were Black; 17 866 (77.3%) were White; and 930 (4.0%) were multiracial or had other or unknown race. Additionally, 3393 (14.7%) had any Jewish ancestry and 19 705 (85.3%) had no Jewish ancestry. A total of 3127 (13.5%) reported a personal history of cancer other than breast cancer.

The 9 breast cancer-associated PVs were detected in 714 participants (3.1%). Excluding 109 participants who were previously aware of their PV prior to joining the study, the overall PV detection rate was 2.6% (**Table 2**).

Eight participants were found to be heterozygous for 2 different PVs: 2 had *ATM* and *CHEK2* PVs; 2 had *PALB2* and *CHEK2* PVs; 3 had *BRCA2* and *CHEK2* PVs and 1 had *BRCA1* and *CHEK2* PV. In all 8 cases, the *CHEK2* PV was either the I157T or S428F low-penetrance variant.

Genes Associated With Rare Cancer Syndromes

PVs in *CDH1* (n = 3), *PTEN* (n = 0), *STK11* (n = 0), and *TP53* (n = 5) were rare. Of the 5 women with *TP53* PVs (aged 45 to 69 years), none reported any personal cancer history. One reported multiple relatives with a variety of cancers, and 4 did not report any family history suggestive of Li-Fraumeni syndrome. Of the 3 women with a *CDH1* PV, 1 self-reported a personal history of gastric cancer (aged 46 years) and gastric and

Table 1. Baseline Characteristics of Women With Genetic Testing in the WISDOM Trial

Characteristic	Women, No. (%)[a]				*P* value
	High-penetrance and syndromic PV (n = 167)[b]	Moderate-penetrance PV (n = 248)[c]	*CHEK2* low-penetrance PV (n = 190)[d]	No PVs (n = 22 384)	
Study arm					
Randomized	71 (43)	106 (43)	87 (46)	10 595 (47)	.29
Self-selected	96 (57)	142 (57)	103 (54)	11 789 (53)	
Age at baseline, y					
40-49	73 (44)	95 (38)	65 (34)	8653 (39)	.02
50-59	56 (34)	81 (33)	51 (27)	6819 (30)	
60-69	32 (19)	57 (23)	51 (27)	5582 (25)	
70-74	6 (4)	15 (6)	23 (12)	1330 (6)	
Race and ethnicity[e]					
Hispanic	22 (13)	16 (6)	9 (5)	2101 (9)	<.001
Non-Hispanic American Indian, Alaska Native, Native Hawaiian, and Pacific Islander	0 (0)	0 (0)	0 (0)	79 (0)	
Non-Hispanic Asian	5 (3)	5 (2)	0 (0)	1058 (5)	
Non-Hispanic Black	11 (7)	6 (2)	1 (1)	976 (4)	
Non-Hispanic White	124 (74)	215 (87)	175 (92)	17 256 (77)	
Non-Hispanic multiracial and other or unknown race	5 (3)	6 (2)	5 (3)	914 (4)	
Jewish ancestry					
Any Jewish grandparent	28 (17)	25 (10)	66 (35)	3249 (15)	<.001
No Jewish grandparent	139 (83)	223 (90)	124 (65)	19 135 (85)	

Abbreviation: PV, pathogenic or likely pathogenic variant.

[a] Excludes the 109 women previously aware of their PV.

[b] High-penetrance and syndromic genes included *BRCA1*, *BRCA2*, *PALB2*, *CDH1*, and *TP53*. For women with 2 PVs, the higher-penetrance variant was counted.

[c] Moderate-penetrance genes included *ATM* and *CHEK2* c.1100delC carriers and the R117G missense PV, truncating and splice site variants, and large deletions.

[d] Low-penetrance variants included *CHEK2* I157T and S428F plus other missense variants.

[e] Race and ethnicity data were collected by self-report; participants could select 1 or more prespecified categories as listed or choose unknown or multiracial. The American Indian, Alaska Native, Native Hawaiian, and Pacific Islander categories were combined due to low numbers.

breast cancers in paternal relatives. Another woman with *CDH1* PV self-reported a personal history of thyroid cancer.

Impact of Study Arm Self-Selection

There was no statistically significant difference in PV proportions in self-selected vs randomized participants (341 [2.8%] vs 264 [2.4%]; *P* = .07). Interestingly, 91 participants in the self-selected group (0.7%) self-reported prior positive genetic test findings compared with 18 (0.2%) in the randomized group.

Participant Characteristics Associated With PVs

Several demographic variables were associated with having a PV. Younger age groups had a higher proportion of high-penetrance PVs in BCSGs than older age groups (40-49 years, 73 [0.8%]; 50-59 years, 56 [0.8%]; 60-69 years, 32 [0.1%]; 70-74 years, 6 [0.4%]; *P* = .02) (Table 1), with the important context that women with any personal history of breast cancer were ineligible to participate. PVs in most genes were found in the 4 largest racial and ethnic groups (non-Hispanic Asian, non-Hispanic Black, Hispanic [any race], and non-Hispanic White), and no PVs were found in the non-Hispanic American Indian, Alaska Native, Native Hawaiian, or Pacific Islander group. A higher proportion of *CHEK2* PVs was identified in White individuals (308 of 17 770 [1.7%]) compared with all other racial and ethnic groups (29 of 5219 [0.6%]) (*P* < .001), not surprising given that founder PVs in *CHEK2* are associated with European ancestry (eTable 2 in Supplement 3). We also detected a higher proportion of *PALB2* PVs in non-Hispanic Black individuals (6 of 994 [0.6%]) compared with other groups (38 21 995 [0.2%]) (*P* = .01).

Table 2. Overall Frequency of Germline Pathogenic or Likely Pathogenic Variants (PVs) in the WISDOM Trial

PV	Frequency	
	WISDOM trial participants with a PV	Comparison rates from other studies[a]
High-penetrance breast cancer genes		
BRCA1	0.14% (1 in 697)	0.09% (1 in 1134)
BRCA2	0.36% (1 in 280)	0.25% (1 in 400)
PALB2	0.19% (1 in 522)	0.14% (1 in 726)
Lower-penetrance breast cancer genes		
ATM	0.44% (1 in 228)	0.35% (1 in 287)
CHEK2[b]	0.64% (1 in 156)	0.58% (1 in 172)
CHEK2 low penetrance[c,d]	0.83% (1 in 121)	NA
Syndromic breast cancer genes		
CDH1	0.01% (1 in 7663)	0.02% (1 in 6658)
PTEN	0	0.01% (1 in 14 902)
STK11	0	<0.01% (1 in 46 733)
TP53	0.02% (1 in 4597)	0.01% (1 in 13 606)
Total	2.63% (1 in 38)	0.92% (1 in 109)

Abbreviation: NA, not applicable.

[a] Data from Rowlands et al[33]; rates from combined control groups from the BRIDGES and CARRIERS studies and UK Biobank. Low-penetrance missense variants I157T and S428F were not included.

[b] Includes c.1100delC carriers and the R117G missense PV, truncating and splice site variants, and large deletions.

[c] Includes the I157T and S428 lower-penetrance PVs plus other missense variants.

[d] Participants with 2 PVs (n = 8) were classified according to their higher-penetrance PV.

Table 3. Prevalence of Germline Pathogenic or Likely Pathogenic Variants (PVs) According to Family History of Breast or Ovarian Cancer

Family history	Total, No.	Women, No. (%)			
		Any (n = 605)	High-penetrance and syndromic PV (n = 167)[a]	Moderate-penetrance PV (n = 248)[b]	*CHEK2* low-penetrance PV (n = 190)[c]
No family history of breast or ovarian cancer	10 144	229 (2.3)	53 (0.5)	101 (1.0)	75 (0.7)
1 Female relative with breast cancer ≥50 y	5208	133 (2.6)	39 (0.7)	54 (1.0)	40 (0.8)
1 Female relative with breast cancer <50 y	1437	43 (3.0)	11 (0.8)	15 (1.0)	17 (1.2)
≥2 Female relatives with breast cancer any age	3555	117 (3.3)	32 (0.9)	53 (1.5)	32 (0.9)
≥1 Female relative with ovarian cancer	1052	29 (2.8)	7 (0.7)	11 (1.0)	11 (1.0)
≥1 Female relative with ovarian cancer and ≥1 female relative with breast cancer	1445	48 (3.3)	22 (1.5)	12 (0.8)	14 (1.0)
≥1 Male relative with breast cancer	148	6 (4.1)	3 (2.0)	2 (1.4)	1 (0.7)

[a] High-penetrance and syndromic genes included *BRCA1*, *BRCA2*, *PALB2*, *CDH1*, and *TP53*. For women with 2 PVs, the higher-penetrance variant was counted.

[b] Moderate-penetrance genes included *ATM* and *CHEK2* c.1100delC carriers and the R117G missense PV, truncating and splice site variants, and large deletions.

[c] *CHEK2* low-penetrance PVs includes I157T and S428F plus other missense variants other than R117G.

Prevalence of PVs According to Family History

The prevalence of PVs among women with no family history of breast or ovarian cancer was 2.3% (229 of 10 144) overall and 1.5% (154 of 10 144) for high-penetrance and moderate-penetrance genes (**Table 3**). In comparison, women with at least 2 female relatives with breast cancer had a PV prevalence of 3.3% (117 of 3555), with 2.4% (85 of 3555) having a PV in a high-penetrance or moderate-penetrance gene. The highest prevalence of PVs (6 of 148 [4.1%]) was among those with a male relative with breast cancer, although this group was comparatively small and many of these women (108 [73.0%]) also had at least 1 female relative with breast cancer.

Overall, 180 of 605 (29.8%) reported none of the composite family history risk factors, including no first-degree or second-degree family member with a history of breast or ovarian cancer, no male relative with breast cancer, and no Jewish ancestry (eTable 3 in Supplement 3). This included 44 of 159 women with *BRCA1*, *BRCA2*, or *PALB2* PVs (27.7%) and 135 of 438 with a PV in *ATM* or *CHEK2* (30.8%).

Most women with a PV reported no family history of ovarian cancer specifically, including 21 of 33 women with a *BRCA1* PV (63.6%) and 72 of 82 with a *BRCA2* PV (87.8%) (eTable 4 in Supplement 3). Few women had a male relative with breast cancer: 6 with a PV and 142 without a PV. Of note, 548 women (2.4%) who received genetic testing results reported being adopted.

Self-Reported Jewish Ancestry

Overall, 3393 women receiving genetic testing (14.7%) reported having at least 1 grandparent with Jewish ancestry. Excluding those who were aware of their PV prior to joining the WISDOM trial, 119 of 3368 individuals with Jewish ancestry (3.5%) had a PV. Only 53 of these individuals (1.6%) had a PV in high-penetrance and moderate-penetrance genes, while 57 (1.7%) had the founder *CHEK2* S428F variant.

Discussion

Initial results from the WISDOM trial, a first-in-kind large-scale deployment of personalized screening for breast cancer, shed new light on the feasibility and positive yield of criteria-independent germline testing for BCSGs. Notably, most non-randomized women chose the personalized arm with genetic testing instead of the annual screening arm. Of those who completed genetic testing who were previously unaware of their PV, 605 (2.6%) had a PV detected, which is higher than previous estimates,[12,34] even when considering the WISDOM trial's enrichment for family history risk factors. Importantly, 30% of women with PVs reported no first-degree or second-degree relative with breast cancer, ovarian cancer, or Jewish ancestry, suggesting that a substantial number of these women would be unlikely to be offered genetic testing under current guidelines.[3]

The identification of *BRCA1*, *BRCA2*, and *PALB2* PV carriers without a family history of breast cancer highlights an important implementation gap in testing guidelines. The steadily decreasing cost of genetic testing[35] offers new opportunities for broader application,[36,37] especially given the younger mean age of diagnosis and risk of fast-growing and aggressive cancers in many of these PV carriers.[14,15,38,39]

Lower-than-expected proportions of family history risk factors in these carriers could have several explanations. These genes have incomplete penetrance, and patients may have incomplete or limited family structure (eg, have fewer first-degree or second-degree relatives surviving beyond age 45 years).[40] Other possibilities include small family size, undisclosed nonpaternity events, male-dominant family structures, competing mortality, and poor communication about cancer diagnoses within families. Criteria-independent testing should thus be seen as a complementary approach to indication-based testing. This notion is consistent with DNA-based screening and population guidance from the ACMG in their points to consider statement.[41] It remains unknown whether the breast cancer incidence differs if women with high-penetrance PVs are stratified by reported family history status, and the WISDOM trial is poised to answer this question as we follow up these women prospectively.

Regarding moderate-penetrance *CHEK2* variants and *ATM* variants, which have a range of risk estimates of approximately 20% lifetime risk of breast cancer, [24,42] where breast magnetic resonance imaging is recommended for high-risk surveillance, carriers may benefit from a comprehensive risk assessment that incorporates their PV-associated risk along with family history, breast density, and polygenic risk score. Although there is still a lack of outcomes data regarding the

potential benefits or harms of identifying individuals with moderate-penetrance and low-penetrance PVs in a population setting, recent ACMG guidance recommends a holistic approach to risk assessment in this population that is consistent with the WISDOM trial's personalized approach.[25,41] Our results also highlight that a significant proportion of positive genetic test results are low-penetrance *CHEK2LP* variants, which are not clinically actionable in isolation.[24] Stakeholders could consider including or excluding *CHEK2LP* variants in program planning given that their prevalence is relatively common compared with PVs in the higher-penetrance genes and have unknown clinical utility in a population setting. In addition, while individuals with PVs in syndromic genes—eg, *CDH1*, *PTEN*, *STK11* and *TP53*—were rare, the opportunity for personalized counseling and cascade familial testing has important clinical implications for these individuals and their families. All PV carriers are offered a consultation with a breast health specialist genetic counselor and are strongly recommended to meet with a local cancer genetic counselor or high-risk clinic to obtain an individualized and guideline-informed management plan.

The WISDOM trial population is enriched for family history of breast cancer compared with published population rates in control arms of several large case-control studies.[33] The WISDOM trial's pragmatic design may attract individuals concerned about their breast cancer risk due to family history and/or personal risk factors or for those seeking to integrate genetic test results into their personalized risk assessment. Nevertheless, the prevalence of PVs detected in the WISDOM trial likely represents a real-world situation where personal experiences and perceived risk may influence the decision to pursue germline testing for BCSGs. The WISDOM trial also used several strategies to increase recruitment and participation of women in racial and ethnic minority populations to counteract historical inequities in access to and knowledge of genetic testing[43] and noted PVs in all genes in multiple racial and ethnic groups, including a higher prevalence of *PALB2* PVs in non-Hispanic Black participants.

The WISDOM trial is continuing to enroll since 2023 as WISDOM 2.0 but no longer includes randomization, aiming to improve our ability to predict risk and engage high-risk women in breast cancer screening and prevention. In WISDOM 2.0, women can continue to choose an annual vs personalized approach; eligibility has been lowered to age 30 years, in response to the findings of the present analysis. A goal of risk-based screening should be to identify women at highest risk when they are likely to benefit most. Given that genetic testing can be performed at any age and is typically a one-time test and that women with high-penetrance PVs often develop breast cancer in their 30s, our goal is to identify PV carriers who can benefit from increased surveillance or risk-reducing interventions in this younger age range. One of the strengths of the WISDOM trial is its large, prospective design with built-in mechanisms to iteratively review lessons learned and implement updated risk-assessment strategies over time.

There have been several studies examining the risks and benefits and workflows involved with unrestricted germline testing for cancer risk genes.[44,45] In general, studies have not identified major harms and have consistently identified individuals with clinically significant PVs who would not have otherwise qualified for germline testing. However, it should be noted that many of these programs had workflows that had genetic counselors involved at all stages to ensure that individualized interpretation and management recommendations were provided to participants and their health care professionals. We also note that the inclusion of moderate-penetrance and low-penetrance variants introduces the possibility for confusion and conflicting recommendations; qualitative research from participants with an *ATM* or *CHEK2* PV in the WISDOM trial[46] found that participants were broadly grateful to have a PV identified that they were previously unaware of and had a good understanding of the limited clinical utility of many *ATM* and *CHEK2* test results.

Limitations

We note several important limitations with this analysis. Variant calls were all determined at a single clinical laboratory, and it is possible that some PVs might be called as variants of uncertain significance at other laboratories or vice versa. However, this would not be likely to alter our findings substantively. Any self-reported prior testing was not confirmed and so it is possible that some participants may have had germline testing with a PV result but chose not to report this to the WISDOM trial. Limited family structure, especially among women with relatives who died of other causes, likely contributes to lower-than-expected prevalence of family history of breast cancer. Family history of cancer, moreover, was not confirmed with medical records and relies on the self-report of participants; however, this is typical for large population-based studies, and breast cancer reporting is relatively accurate compared with other cancer types.[47] We did not collect data on family history of pancreas, prostate, or other cancers, some of which are incorporated into current testing criteria. However, it is unlikely that having these additional data elements would have substantively altered our findings (particularly since not all of the panel genes are associated with elevated actual risks of other cancer types). The WISDOM trial also includes several classes of variants that may not have been identified or reported in the BRIDGES, CARRIERS, or UKBiobank studies, including large deletions and low-penetrance PVs in *CHEK2*, for example, which presumably contributed to the higher PV rate observed in the WISDOM trial.[33] At the time that the WISDOM trial was being designed, the *BARD1*, *RAD51C* and *RAD51D* genes were not yet confirmed as BCSGs and thus were not included in our panel. These genes (along with 17 additional general cancer susceptibility genes) are now included in the WISDOM 2.0 panel. Finally, for the rarer *TP53* variants, supplemental testing to determine the origin of the *TP53* variant (germline vs somatic mosaicism vs clonal hematopoiesis of indeterminate potential) was not performed through the WISDOM trial.

Conclusions

The WISDOM trial's pragmatic design offers a model for integrating genetic testing into routine breast cancer risk assess-

ment. These findings support the feasibility and acceptability of criteria-independent genetic testing for a diverse group of women. While we identified high-penetrance PVs in women who otherwise would not have qualified for germline testing, the most common PVs identified in our population were moderate-penetrance or low-penetrance variants, which require a nuanced and holistic risk assessment approach that deserves careful planning prior to implementing unrestricted genetic testing. These and other WISDOM trial findings will provide helpful data for stakeholders in a variety of health care settings to evaluate the potential clinical utility and opportunities for cancer prevention and early detection. Our results demonstrate that relying on a reported family history of cancer has limitations in identifying women who carry a PV, and criteria-independent testing would broaden the group who could benefit from evidence-based cancer surveillance and risk-reduction interventions.

ARTICLE INFORMATION

Accepted for Publication: November 2, 2025.

Published Online: December 12, 2025. doi:10.1001/jamainternmed.2025.7323

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Obtained funding: Scheuner, van 't Veer, Fiscalini, Borowsky, L. Esserman.
Administrative, technical, or material support: Blanco, Shieh, Olopade, Goodman, Harvey, DeRosa, Silver, Fiscalini, Sabacan, Petruse, Borowsky, Naeim, Park, Parker, Anton-Culver, Madlensky.
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Conflict of Interest Disclosures: Dr Fergus reported grants from the American Society of Clinical Oncology and National Cancer Institute during the conduct of the study. Ms Ross reported grants from the National Cancer Institute during the conduct of the study; and grants from Mount Zion Health Fund outside the submitted work; is a member of the National Society of Genetic Counselors and Genetic Counseling Experience Initiative; and is a genetic counselor workplace representative for union UPTE CWA 9119. Dr Scheuner reported grants from the National Cancer Institute and the Veterans Affairs Health Systems Research during the conduct of the study; and had a patent for US 8,719,045 issued with no royalties received and a patent for US 7,951,078 B2 issued with no royalties received. Ms Blanco reported grants from Patient-Centered Outcomes Research Institute during the conduct of the study. Dr Tice reported grants from the National Cancer Institute and Patient-Centered Outcomes Research Institute during the conduct of the study. Dr Ziv reported grants from the National Cancer Institute and Department of Defense Breast Cancer Research Program during the conduct of the study. Dr Shieh reported grants from the National Cancer Institute outside the submitted work. Dr van 't Veer reported personal fees from Agendia NV as a part-time employee and stockholder outside the submitted work. Dr Olopade reported grants from Color Genomics; served on the scientific advisory board for TempusAI; and is cofounder of CancerIQ outside the submitted work. Dr Goodman reported grants from Patient-Centered Outcomes Research Institute, Breast Cancer Research Foundation, and National Cancer Institute during the conduct of the study. Mr Tong reported grants from Patient-Centered Outcomes Research Institute and Breast Cancer Research Foundation during the conduct of the study. Ms Harvey reported grants from Patient-Centered Outcomes Research Institute during the conduct of the study. Ms DeRosa reported grants from Patient-Centered Outcomes Research Institute during the conduct of the study. Ms Silver reported grants from Patient-Centered Outcomes Research Institute during the conduct of the study. Dr Kaster reported grants from Rising Tide outside the submitted work. Ms Fiscalini reported grants from National Cancer Institute, Patient-Centered Outcomes Research Institute, and Breast Cancer Research Foundation during the conduct of the study. Ms Blum reported grants from the National Cancer Institute and US Department of Defense during the conduct of the study. Ms Sabacan reported grants from the National Cancer Institute and Patient-Centered Outcomes Research Institute during the conduct of the study. Ms Heditsian reported grants from Patient-Centered Outcomes Research Institute, National Institutes of Health, and BrightPink.org during the conduct of the study. Ms Brain reported grants from Patient-Centered Outcomes Research Institute, National Institutes of Health, and BrightPink.org during the conduct of the study. Dr Eklund reported grants from Patient-Centered Outcomes Research Institute and National Cancer Institute during the conduct of the study. Dr Borowsky reported grants from National Institutes of Health, Patient-Centered Outcomes Research Institute, and Breast Cancer Research Foundation during the conduct of the study. Dr Naeim reported grants from Patient-Centered Outcomes Research Institute during the conduct of the study and is cofounder of Invista Health outside the submitted work. Dr Park reported grants from Patient-Centered Outcomes Research Institute and Breast Cancer Research Fund during the conduct of the study. Dr LaCroix reported grants from Patient-Centered Outcomes Research Institute and Breast Cancer Research Foundation during the conduct of the study. Dr Parker reported grants from Patient-Centered Outcomes Research Institute and Breast Cancer Research Foundation during the conduct of the study. Dr Lancaster reported grants from the National Cancer Institute, Breast Cancer Research Foundation, and

Patient-Centered Outcomes Research Institute during the conduct of the study. Dr J. Esserman reported grants from the National Cancer Institute during the conduct of the study. Dr Wenger reported grants from Patient-Centered Outcomes Research Institute during the conduct of the study. Dr Arasu reported grants from the National Cancer Institute and Kaiser Permanente/The Permanente Medical Group during the conduct of the study. Dr L. Esserman reported grants from Patient-Centered Outcomes Research Institute and Breast Cancer Research Foundation during the conduct of the study; is on the Blue Cross Medical Advisory Panel; is an uncompensated board member of Quantum Leap Healthcare Collaborative; and is an investigator for a trial funded by Moderna. Dr Madlensky reported grants from the National Cancer Institute and Patient-Centered Outcomes Research Institute during the conduct of the study. No other disclosures were reported.

Funding/Support: Dr Fergus received salary support from an American Society of Clinical Oncology Young Investigator Award (2023YIA-9977333099). Dr L. Esserman received funding from the National Cancer Institute (R01CA237533), Patient-Centered Outcomes Research Institute (PCS-1402-10749), and the Breast Cancer Research Foundation (SPEC-22-018, SPEC-24-026). Dr Shieh received funding from the National Cancer Institute (K08CA237829). Dr van 't Veer received funding from the US Department of Defense (13922076-BC230196). We thank the Robert Wood Johnson Pioneer Pitch Award, BrightPink.org, Mt Zion Health Fund, Safeway Foundation, Salesforce, and V Foundation for their support.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: This study was presented at the San Antonio Breast Cancer Symposium; December 12, 2025; San Antonio, Texas.

Data Sharing Statement: See Supplement 4.

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