Cancer Screening and Prevention **2026** vol. 5(2) | 83–85
DOI: 10.14218/CSP.2026.00008

Editorial

The WISDOM Trial and the Evidence Base for Risk-based Breast Cancer Screening

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Received: June 04, 2026 | **Revised:** June 18, 2026 | **Accepted:** June 22, 2026 | **Published online:** June 29, 2026

Breast cancer screening recommendations continue to rely largely on age, despite substantial variation in individual risk. Advances in risk prediction, including the incorporation of breast density, polygenic risk scores (PRS), and germline susceptibility variants, have renewed interest in screening strategies that adapt screening intensity according to individual risk rather than age alone. However, evidence supporting risk-based screening has largely been derived from observational studies and simulation models. In this issue, Esserman and colleagues report the results of the Women Informed to Screen Depending on Measures of Risk (WISDOM) randomized clinical trial, providing the first large-scale randomized evaluation of a comprehensive risk-based screening strategy.[1]

The trial enrolled 28,372 women aged 40–74 years and compared annual mammography with a screening approach based on clinical risk factors, breast density, PRS, and testing for nine breast cancer susceptibility genes. Women classified as being at highest risk underwent alternating mammography and magnetic resonance imaging (MRI), whereas those at average or low risk received less intensive screening recommendations. After a median follow-up of 5.1 years, the incidence of stage IIB or higher breast cancer, the primary safety endpoint, was not increased in the risk-based group.[1]

The interpretation of these findings should be considered in the context of previous work (Table 1).[1–8] Most evidence supporting personalized screening has originated from modeling studies rather than prospective trials. Pashayan and colleagues estimated that risk-stratified screening could improve the balance between benefits and harms while reducing costs.[2] Similar conclusions emerged from Cancer Intervention and Surveillance Modeling Network analyses, which suggested that women at lower risk could safely undergo screening at longer intervals with fewer false-positive findings and unnecessary procedures.[3,4] These studies provided a theoretical basis for personalized screening but could not address real-world implementation.

Other prospective studies have evaluated intensified screening in selected high-risk populations rather than risk stratification across the general screening population. The Dense Tissue and Early Breast Neoplasm Screening trial demonstrated that supplemental MRI reduced interval cancers among women with extremely dense breasts.[5] The Familial MRI Screening trial reported improved detection of early-stage cancers among women with a strong familial risk.[6] WISDOM differs from these studies by evaluating a population-level strategy integrating multiple risk components to determine screening intensity (Table 1).

The primary finding of WISDOM is that reducing screening intensity among lower-risk women was not associated with an increase in advanced-stage disease during the study period. The incidence of stage IIB or higher breast cancer was similar between the risk-based and annual-screening groups, supporting the medium-term safety of the personalized approach.[1] However, the second coprimary endpoint deserves equal consideration. Despite a reduction in mammography utilization, biopsy rates were not significantly lower in the risk-based group.[1]

This observation is relevant because one of the principal arguments supporting personalized screening has been the expectation that fewer examinations in lower-risk women would translate into fewer downstream investigations.[2–4] That outcome was not observed. Several aspects of the study may explain this result. Adherence to assigned screening recommendations was incomplete and declined during follow-up. Women assigned to lower-intensity screening frequently underwent additional imaging, while women assigned to annual screening often received fewer mammograms than intended by the protocol.[1] Consequently, the actual difference in screening exposure between the study groups was smaller than planned.

These findings highlight an issue that extends beyond the performance of risk models themselves. Accurate risk prediction is necessary for personalized screening, but implementation also depends on physician recommendations, patient preferences, and local screening practices. The discrepancy between predicted and observed reductions in biopsy rates illustrates the importance of these factors when evaluating screening interventions. These implementation challenges are consistent with the broader transition toward precision screening strategies integrating imaging, genetic, and individualized risk assessment approaches recently discussed in the literature.[9]

The ongoing My Personal Breast Screening trial was designed to evaluate risk-stratified screening in a large population in Europe and Israel.[7] Although outcome data are not yet available, a recent ancillary study among healthcare professionals participating in My Personal Breast Screening identified broad support for

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How to cite this article: Poirot M, de Médina P, Silvente-Poirot S. The WISDOM Trial and the Evidence Base for Risk-based Breast Cancer Screening. *Cancer Screen Prev* 2026;5(2):83–85. doi: 10.14218/CSP.2026.00008.

Table 1. Selected studies relevant to risk-based breast cancer screening

Study	Design	Population	Risk factors used	Main outcome	Key finding	Registration
Esserman *et al*., 2026 (WISDOM)[1]	Randomized clinical trial	28,372 women, United States	Clinical risk factors, breast density, PRS, 9 susceptibility genes	Stage ≥IIB breast cancer	Noninferior to annual screening; fewer mammograms but no reduction in biopsy rates	NCT02620852
Roux *et al*., 2022 (MyPeBS protocol)[7]	Randomized clinical trial (ongoing)	~85,000 women, Europe and Israel	Clinical risk factors, breast density, PRS	Advanced breast cancer incidence	Ongoing evaluation of risk-stratified screening	NCT03672331
Roux *et al*., 2025 (MyPeBS ancillary study)[8]	Cross-sectional survey of healthcare professionals	198 professionals from 6 countries	Risk communication and implementation practices	Acceptability of risk-based screening	Broad support for risk-based screening; concerns regarding training and implementation	NCT03672331
Pashayan *et al*., 2018[2]	Modeling study	Simulated population	Risk-stratified screening	Benefit-to-harm ratio	Predicted improved efficiency of screening	Not applicable
Trentham-Dietz *et al*., 2016[3]	CISNET modeling study	Women ≥50 years	Breast density and clinical risk factors	Screening outcomes	Extended intervals feasible in lower-risk women	Not applicable
van Ravesteyn *et al*., 2021[4]	CISNET modeling study	Low-risk women	Risk-based interval assignment	Harms and benefits	Fewer false-positive findings with less intensive screening	Not applicable
Bakker *et al*., 2019 (DENSE)[5]	Randomized trial	Women with extremely dense breasts	Breast density	Interval cancer rate	Supplemental MRI reduced interval cancers	NTR2499
Saadatmand *et al*., 2019 (FaMRIsc)[6]	Randomized trial	Women with familial risk	Family history	Stage at diagnosis	MRI improved early detection	NTR3689

CISNET, Cancer Intervention and Surveillance Modeling Network; DENSE, Dense Tissue and Early Breast Neoplasm Screening; FaMRIsc, Familial MRI Screening; MRI, magnetic resonance imaging; MyPeBS, My Personal Breast Screening; NCT, National Clinical Trial number; NTR, Netherlands Trial Register; PRS, polygenic risk score; WISDOM, Women Informed to Screen Depending on Measures of Risk.

risk-based screening together with concerns regarding risk communication, professional training, and implementation in population-based programs.[8] These observations are consistent with findings from WISDOM and suggest that implementation may become a major determinant of the effectiveness of personalized screening strategies.

The study also contributes to the growing literature on population-based genetic risk assessment. Previous analyses from the WISDOM cohort demonstrated that a substantial proportion of women carrying high-penetrance pathogenic variants would not have been identified using family history–based testing criteria alone.[10] In addition, incorporation of PRS modified screening assignments for a proportion of participants.[11] Whether broader integration of genetic testing into screening programs will improve outcomes sufficiently to justify implementation at scale remains uncertain.

Several limitations should be considered when interpreting the results. The number of stage IIB cancers was relatively small, resulting in limited precision around some estimates. The study population was predominantly White and highly educated, which may limit generalizability. This limitation is particularly relevant for PRS, whose predictive performance may vary across ancestral populations because most derivation cohorts have been of European ancestry. In addition, unequal access to MRI, genetic counseling, and risk communication resources could complicate implementation of personalized screening strategies in underserved populations. Follow-up also remains relatively short for an intervention intended to influence long-term cancer outcomes. Adherence to assigned screening recommendations was lower than anticipated, further complicating interpretation of differences between study groups.[1]

The WISDOM trial provides randomized evidence that a comprehensive risk-based screening strategy can be implemented without an observed increase in advanced-stage breast cancer during medium-term follow-up.[1] The results also indicate that achieving reductions in screening-related harms may be more difficult than anticipated from modeling studies, and that implementation, equity, and long-term outcome evaluation will be critical determinants of the future role of risk-based screening in population programs. From a clinical perspective, implementation of personalized screening will require standardized approaches for physician training and patient risk communication. From a research perspective, longer-term follow-up and validation in diverse populations remain essential. From a health policy perspective, future screening programs will need to address equitable access to MRI, genetic testing, and supporting infrastructure before large-scale adoption can be considered. Further evidence from ongoing trials and longer follow-up will be necessary before determining the role of risk-based screening within future population screening programs.

Acknowledgments

None.

Funding

No funding was received for this work.

Conflict of interest

MP is an Associate Editor of *Cancer Screening and Prevention*. The authors declare no other conflicts of interest.

Author contributions

Manuscript drafting and writing (MP, PDM, SSP), table conception and preparation (MP), conception and design of the work (MP). All authors have approved the final version of the manuscript.

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