

COST-EFFECTIVENESS OF MONO- AND POLYGENIC RISK-GUIDED BREAST CANCER SCREENING IN THE US

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Background

- Two genetic tests can personalize breast cancer (BC) care. Polygenic risk scores (PRS) estimate BC risk from common genetic variants and identify women for more intensive screening. Hereditary breast and ovarian cancer (HBOC) panels detect rare high-risk mutations like *BRCA1/2* and identify candidates for both intensified screening and risk-reducing mastectomy (RRM) and salpingo-oophorectomy (RSO).¹⁻⁴
- Intensified mammography and MRI screening for high-risk women catches some cancers earlier but does not prevent them. The added screening also brings more cost, more false positives, more biopsies, and more DCIS overdiagnosis.^{5,6}
- Whether the added screening is worth it at the population level, alone or combined with HBOC testing, has not been evaluated in the US.

Objective

To evaluate whether risk-stratified breast cancer screening can improve health outcomes and cost-effectiveness versus existing guideline-based approaches in the US healthcare setting.

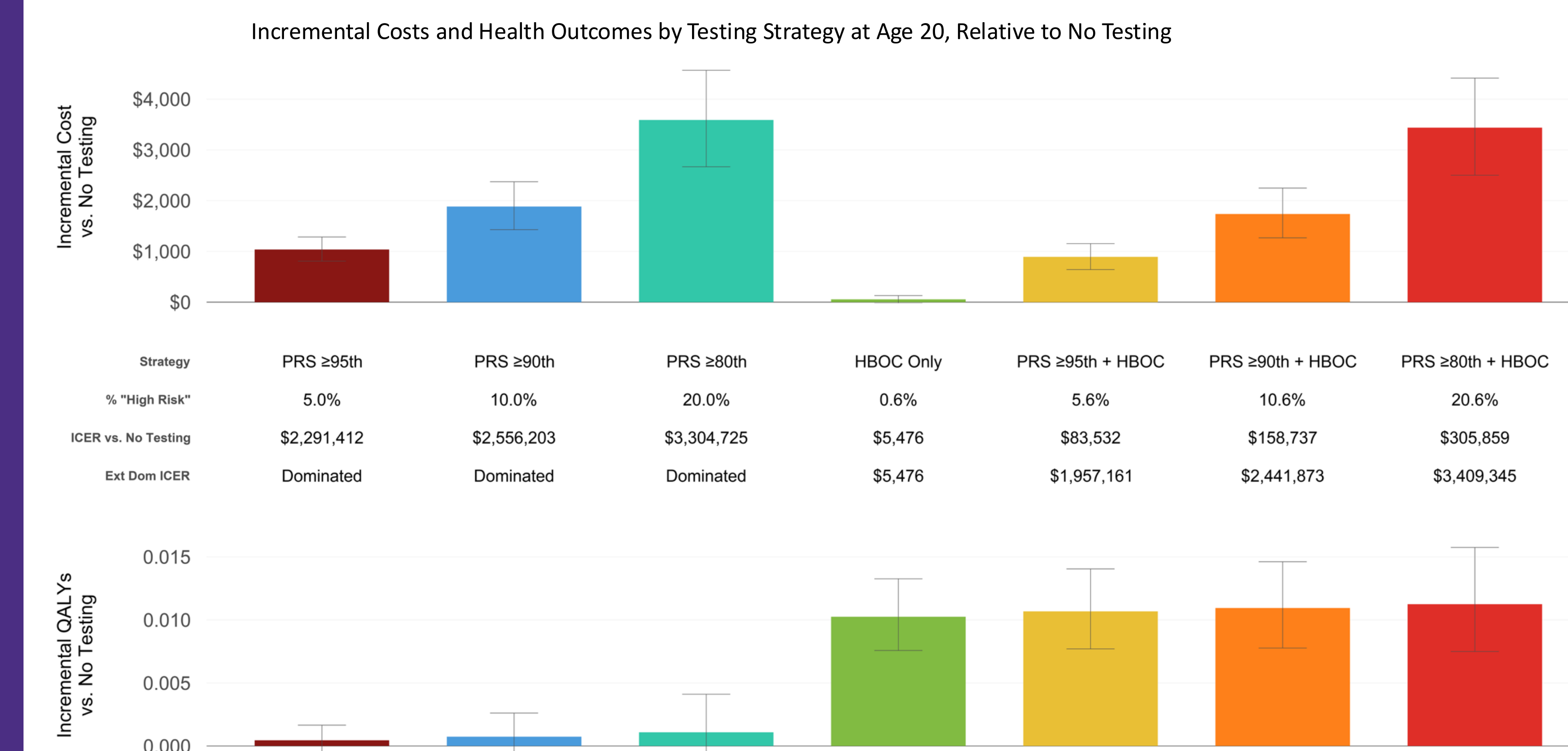
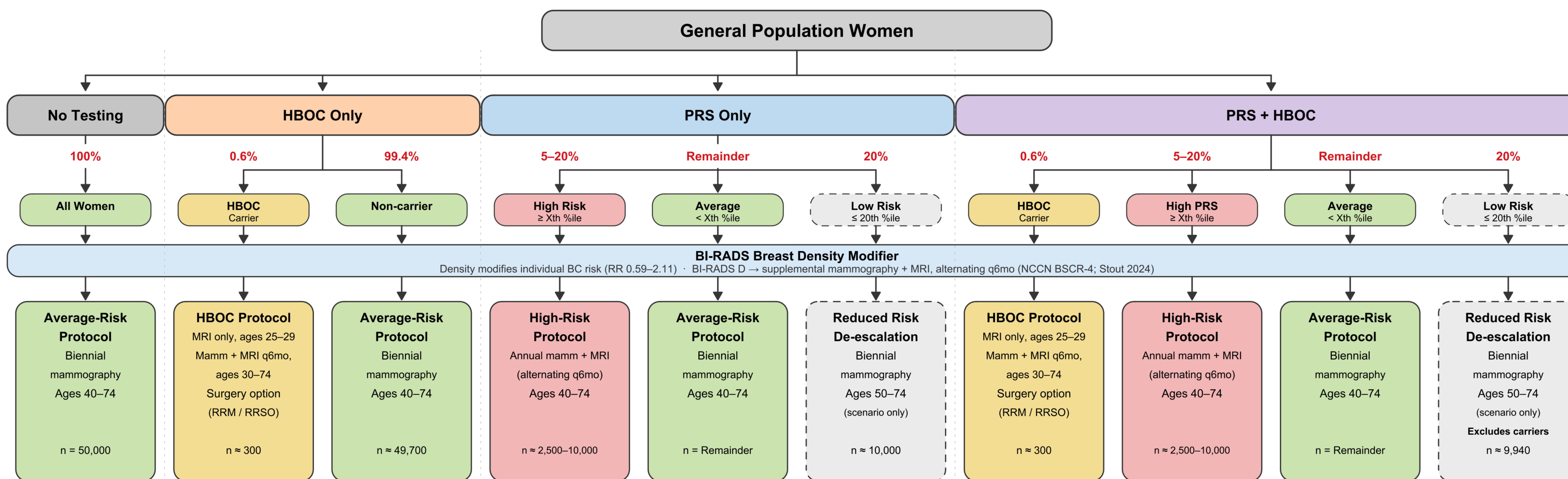
Methods

- We simulated the lifetimes of 50,000 US women, each with individual genetic risk, breast density, screening adherence, and competing causes of death, and calibrated a CISNET⁷ approach to tumor growth and stage at diagnosis to SEER⁸ population targets.
- We compared eight strategies at testing ages 20, 30, 40, and 50: no testing; HBOC alone; PRS alone at the 80th, 90th, or 95th percentile; and combined PRS+HBOC at each threshold.
- We modeled high-risk women on alternating mammography and MRI every 6 months from age 40,⁹ HBOC carriers additionally on MRI from age 25 with eligibility for risk-reducing surgery,^{10,11} and all other women on biennial mammography.¹²
- We performed a de-escalation scenario analysis that allowed women confirmed at low polygenic risk (≤ 20 th percentile, non-carrier, non-BI-RADS D) to defer the start of biennial mammography from age 40 to 50, based on the recent WISDOM trial.²
- We used a US health-care sector perspective, discounted costs (2025 USD) and QALYs at 3%, ran 3,000 probabilistic uncertainty iterations, and compared strategies against a \$100,000 per QALY threshold.

Results

- HBOC testing was optimal at every testing age. At age 20, HBOC yielded 0.0103 incremental QALYs (95% CR, 0.0076 to 0.0133) at \$56 incremental cost (CR, -\$17 to \$129) versus no testing, primarily due to cancer prevention via risk-reducing surgery among identified carriers; ICER \$5,476/QALY (100% probability cost-effective at \$100,000/QALY).
- HBOC ICERs at ages 30, 40, and 50 were \$890, cost-saving, and \$8,799/QALY. PRS-only produced <0.002 QALYs (CRs spanning zero) at \$1,037 to \$3,589 incremental cost, and was strictly dominated by HBOC at every age.
- Adding PRS to HBOC produced 0.0004 to 0.0010 additional QALYs at \$836 to \$3,383 additional cost, with extended-dominance ICERs of \$1.96 to \$3.41 million/QALY versus HBOC alone.
- HBOC Only remained the optimal strategy across all probabilistic and one-way sensitivity analyses.
- In the de-escalation scenario, deferring biennial mammography for confirmed low-PRS women saved \$164-\$306 per woman with negligible QALY change, but this did not make PRS testing variants cost-effective.

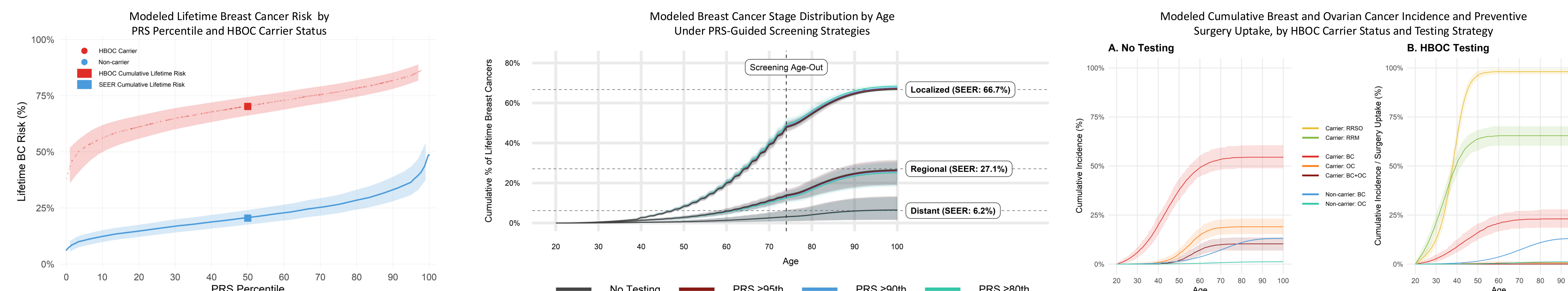
Model Schematic: Testing Strategy and Risk-Stratified BC Screening Framework



Conclusions

- Population-based HBOC testing was highly cost-effective or cost-saving across testing scenarios.
- Population-based PRS-guided screening, alone or in combination with HBOC, yielded small incremental health gains but was not cost-effective.
- For a US clinician weighing whether to integrate genetic testing into average-risk breast screening, HBOC panel testing offers meaningful clinical benefit and is a good economic value; PRS screening does neither.

Modeled Cancer Risk and Calibration



References

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