COST-EFFECTIVENESS OF POLYGENIC RISK SCORE–GUIDED BREAST CANCER SCREENING IN THE US

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BACKGROUND

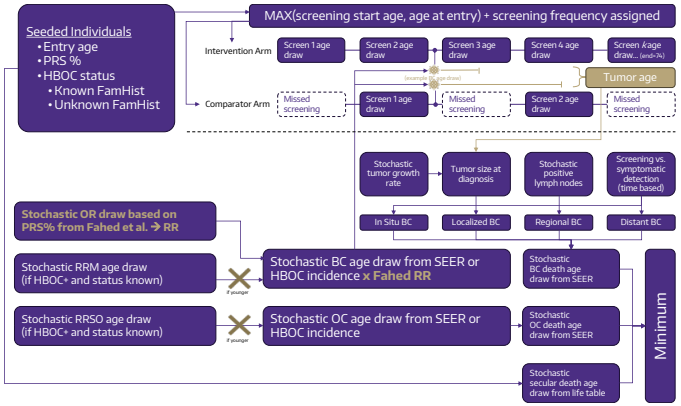
- Polygenic risk score (PRS) testing estimates breast cancer (BC) risk based on common genetic variants, while hereditary breast and ovarian cancer (HBOC) testing detects rare, high-risk mutations in genes like *BRCA1/2;* both offer opportunities to personalize BC screening based on individual risk.
- Population-wide HBOC testing is marginally cost-effective in isolation[1] but cost-effective when paired with other rare hereditary diseases.[2]
- Enhanced screening with PRS may improve outcomes for high-risk individuals, but the cost-effectiveness of population-wide PRS testing strategies remains unclear.

METHODS

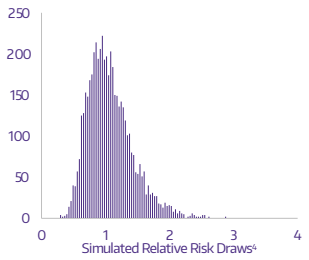
- We developed a preliminary, Excel-based discrete event simulation (DES) model to evaluate the cost-effectiveness of population-level breast cancer (BC) risk testing strategies.
- A U.S. birth cohort of 5,000 women was simulated over their lifetimes.
- Four strategies were compared: PRS+HBOC testing, PRS only, HBOC only, and no testing; all genetic testing cost $250.
- High PRS (top 20%) triggered annual mammography from age 30; HBOC carriers received annual mammography and MRI from age 20; others followed USPSTF biennial screening from age 40.[3]
- PRS risks (ORs converted to RRs) were based on Fahed et al.[4] and applied to SEER[5] or Kuchenbaecker et al.[6] BC incidence rates for HBOC carriers, assuming independent risks.
- Age-dependent adherence and screening drift were modeled.
- Tumor growth and detection followed CISNET methods;[7] diagnosis stage depended on detection timing, and informed survival and costs.
- Ovarian cancer was modeled for all, with elevated risk and preventive surgery options (RRM/RRSO) for HBOC carriers.[8]
- Outcomes included BC incidence, mortality, costs, QALYs, and ICERs.
- We performed probabilistic sensitivity analysis over 3,000 iterations.

Table 1. Model Parameters	Description
Screening Guidelines	Followed USPSTF recommendations based on age and risk profile[3]
Cancer Incidence	Modeled baseline breast and ovarian cancer incidence by age using SEER population data[5]
Tumor Growth & Stage	Simulated tumor growth using CISNET (Wisconsin model);[4] stage at diagnosis calibrated to SEER data[5]
Cancer Survival	Applied 5-year relative survival by stage for breast and ovarian cancer from SEER[5]
Health State Utilities	Derived from published literature on quality-of-life impacts[various]
Cancer Costs	Used stage-specific breast cancer costs at diagnosis from Grady et al.[9]

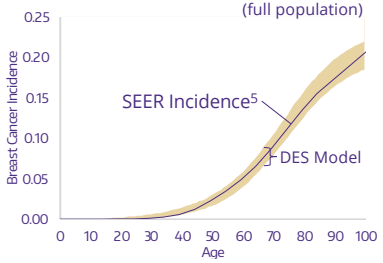
Discrete Event Simulation Model



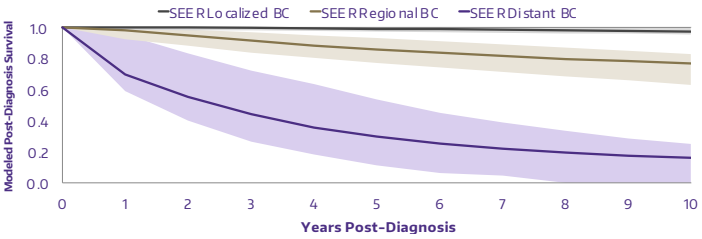
Modeled PRS-Adjusted Risk



Cumulative BC Incidence and Uncertainty



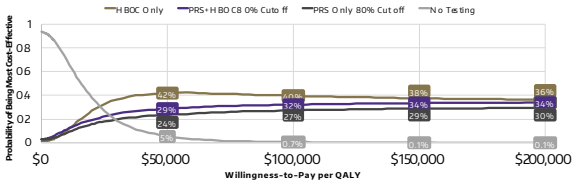
Breast Cancer Post-Diagnosis Survival and Modeled Uncertainty



RESULTS

Table 2. Model Results

Strategy	PRS Cutoff	Avg Cost	Avg QALYs	ΔCost vs No Testing	ΔQALYs vs No Testing	ICER vs No Testing
PRS+HBOC	80%	$5,348	29.5340	$932	0.0053	$174,292
PRS+HBOC	95%	$5,356	29.5333	$939	0.0046	$202,084
PRS+HBOC	90%	$5,370	29.5332	$953	0.0045	$211,547
HBOC Only	--	$4,514	29.5331	$98	0.0045	**$21,881**
PRS Only	90%	$5,383	29.5306	$966	0.0019	$497,236
PRS Only	80%	$5,388	29.5287	$971	0.0001	$16,191,021
No Testing	--	$4,417	29.5287	--	--	reference
PRS Only	95%	$5,392	29.5285	$975	-0.0002	dominated



- PRS + HBOC testing increased QALYs but at higher cost, resulting in ICERs near upper cost-effectiveness thresholds.
- PRS alone produced relatively small or negative health gains with similar costs, yielding high/dominated ICERs and low value.
- Most health gains in the combined strategies were attributable to HBOC testing; HBOC testing alone was cost-saving.
- **Due to platform limitations, the model compared testing strategies pairwise with No Testing only, so PSA samples were not matched across all 8 arms--introducing some noise into average results; model conversion to R will enable simultaneous comparison for cleaner head-to-head estimates.**

CONCLUSIONS

- Our preliminary model shows that PRS testing added only marginal health benefits relative to its additional cost.
- The modest impact stemmed from the low baseline breast cancer risk in the general population, limiting the absolute risk increase even for those with high PRS.
- Population-wide PRS testing may become more valuable if applied to multiple conditions simultaneously.

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