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Clinical and economic impact of the 21-gene assay for guiding treatment in patients with HR+/HER2- early breast cancer across racial and ethnic subgroups in the US.

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Background

- In patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2-), axillary lymph node–negative (N0), or node-positive (N1) early-stage breast cancer, adjuvant chemotherapy (CT) may be administered prior to endocrine therapy (ET) to enhance the reduction in risk of distant recurrence, although it is associated with substantial toxicity.
- Reliance on clinicopathologic factors such as tumor grade, size, and nodal burden to guide chemotherapy use has historically led to both over- and undertreatment.(1)
- The 21-gene assay refines risk stratification by generating a Recurrence Score® result (RS; 0–100), estimating distant recurrence risk and predicting adjuvant chemotherapy benefit in HR+/HER2- early-stage breast cancer, with its clinical utility validated in the TAILORx and RxPONDER randomized trials.(2, 3)
- Racial and ethnic disparities in treatment and outcomes persist among breast cancer patients in the US.(4, 5) No economic evaluations to date have addressed the assay's value across racial and ethnic subgroups.(6-9)

Aim

- **The aim of this study was to assess the clinical and economic value of the 21-gene assay compared to relying on clinical-pathologic risk factors alone among women with HR+/HER2- N0 and N1 early-stage breast cancer from a US perspective, stratified by racial and ethnic subgroup.**

Methods and Materials

- A validated cost-effectiveness model of the 21-gene assay, which followed best practice guidelines, was adapted to reflect patients with N0 or N1 HR+/HER2− early breast cancer across four US racial and ethnic subgroups: non-Hispanic Black (NHB), non-Hispanic White (NHW), Asian, and Hispanic.(10, 11)
- A decision-tree model stratified patients by genomic risk (RS result) and adjuvant treatment, followed by a Markov model with five health states: recurrence-free, distant recurrence, long-term chemotherapy-related adverse events (AEs; acute myeloid leukemia [AML] or congestive heart failure [CHF]), and death.
- The model assessed lifetime costs and health outcomes, comparing use of the 21-gene assay to clinical-pathologic risk factors alone, by nodal status and by racial and ethnic subgroup.
- The analysis was conducted from a US societal perspective, incorporating Medicare expenditures, patient out-of-pocket costs related to chemotherapy, and productivity losses due to chemotherapy and distant recurrence, applying a 3% annual discount rate.(11)
- Table 1 presents the data sources of the model inputs. Subgroup-specific assumptions were reviewed and validated by US clinical experts.
- Model outcomes were reported as incremental cost-effectiveness ratios (ICERs), calculated as the incremental costs per incremental quality-adjusted life year (QALY). Cost-effectiveness was assessed by comparing the ICERs against a chosen reference willingness-to-pay (WTP) threshold of $100,000 per QALY gained.(12)
- Model uncertainty was evaluated using deterministic sensitivity analysis (DSA), probabilistic (5,000 simulations) sensitivity analysis (PSA) and scenario analysis.

Table 1. Overview of data sources.

Type of inputs	Source
Clinical inputs	Published studies (TAILORx(3, 7), RxPONDER(2, 6), and a SEER database analysis(13))
Health-related quality of life	Published literature(10, 14), with subgroup-specific estimates used where available
Cost inputs	Estimated based on the original published model(10), aligned with US clinical practice and 2021 USD costs

Results

- The 21-gene assay was dominant (cost-saving with greater QALY gains) compared to clinical-pathologic risk factors alone across all assessed racial and ethnic subgroups in both N0 and N1 populations (Table 2). Model outcomes varied across racial and ethnic subgroups, largely attributable to subgroup-specific clinical trial inputs.

- N0 findings
  - N0 NHB and Asian subgroups showed the greatest QALY gains and cost savings, driven by chemotherapy use directed towards patients with high RS results, which reduced progression to advanced disease, lowered treatment costs in the recurrent setting, and improved overall survival and quality of life.
  - N0 NHW and Hispanic subgroups had smaller cost savings in advanced disease treatment due to lower distant recurrence risk observed in clinical trial data.(7)

- N1 findings
  - N1 Asian subgroup had the greatest cost-savings from reduced chemotherapy use, while N1 NHB subgroup had the lowest cost savings. This was driven by a higher progression risk and lower chemotherapy benefit on disease progression, both reported from clinical trial data, resulting in higher distant recurrence costs.(6, 13)
  - N1 NHW and Hispanic subgroups showed comparable results to the N1 overall population.

Table 2. Base case cost-effectiveness results and breakdown of incremental cost: 21-gene assay versus Clinical-pathologic risk factors alone.

Population	N0					N1				
Subgroups	**Overall**	**NHB**	**NHW**	**Asian**	**Hispanic**	**Overall**	**NHB**	**NHW**	**Asian**	**Hispanic**
Δ Costs	**-$10,886**	-$18,018	-$9,380	-$12,917	-$9,104	**-$4,921**	-$2,107	-$4,771	-$5,810	-$4,454
Δ QALYs	**0.154**	0.169	0.156	0.228	0.153	**0.076**	0.050	0.063	0.102	0.072
ICER* per QALY	**Dominant†**	Dominant	Dominant	Dominant	Dominant	**Dominant**	Dominant	Dominant	Dominant	Dominant
Cost categories										
21-gene assay cost	**$3,873**	$3,873	$3,873	$3,873	$3,873	**$3,873**	$3,873	$3,873	$3,873	$3,873
Adjuvant treatment [a]	**$258**	-$199	$431	$63	-$440	**-$5,671**	-$5,660	-$5,496	-$6,030	-$5,974
Short- and long-term chemotherapy AEs [b]	**$66**	-$117	$117	$4	-$152	**-$1,288**	-$1,846	-$1,229	-$1,557	-$1,455
Recurrence-free	**$140**	$212	$122	$195	$134	**$57**	$67	$54	$94	$67
Local and distant recurrence	**-$11,022**	-$15,370	-$10,235	-$12,088	-$8,593	**$1,578**	$4,017	$1,428	$1,619	$2,426
Terminal care	**-$323**	-$486	-$267	-$504	-$303	**-$112**	-$118	-$108	-$214	-$139
Patient out-of-pocket costs	**$75**	-$64	$127	$16	-$134	**-$1,294**	-$1,291	-$1,254	-$1,376	-$1,363
Lost productivity cost	**-$3,952**	-$5,869	-$3,548	-$4,475	-$3,490	**-$2,065**	-$1,149	-$2,039	-$2,218	-$1,890

Notes: * ICER = incremental lifetime costs per incremental QALY; † Dominant = higher QALYs and lower cost; [a] includes adjuvant CT and ET; [b] includes short-term AEs, AML and CHF.

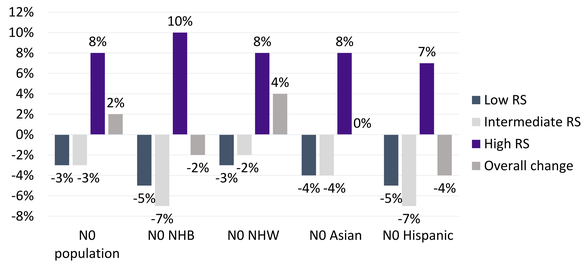


Chart 1. Change in chemotherapy allocation: N0 population and subgroups.
Note: Low RS: 0-10 (N0); Intermediate RS: 11-25 (N0); High RS: 26-100 (N0).

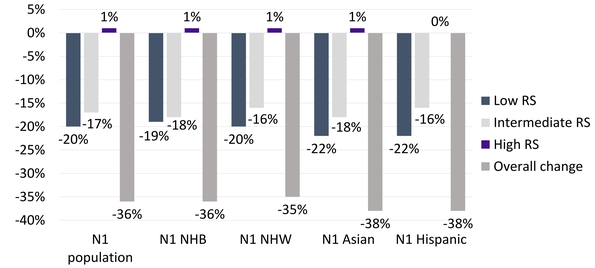


Chart 2. Change in chemotherapy allocation: N1 population and subgroups.
Note: Low RS: 0-13 (N1); Intermediate RS: 14-25 (N1); High RS: 26-100 (N1).

- In the N0 population and subgroups, compared to clinical-pathologic risk alone, the 21-gene assay increased chemotherapy use among patients with high RS results (by 7–10%), while reducing chemotherapy use in low and intermediate RS categories (Chart 1).
- In the N1 population and subgroups, the test significantly reduced chemotherapy use in low and intermediate RS categories (by 35–38%) (Chart 2).
- Across N0 and N1 population and subgroups, the deterministic sensitivity analysis indicated that distant recurrence rates for endocrine and chemo-endocrine therapy, chemotherapy benefit in the RS >25 group, discount rates for outcomes and costs, and health state utility in recurrence-free were the most influential inputs on the results.
- The probabilistic sensitivity analysis showed that the 21-gene assay had a probability of being cost-effective exceeding 96% in N0 and N1 populations and subgroups, except for the N1 NHB subgroup (83%), at a $100,000 per QALY threshold.
  - This supports a high degree of certainty in the dominant conclusion of the base case.
  - The N1 NHB subgroup differed from the overall N1 population; this could not be validated due to limited published data for distant recurrence risk.
- Scenario analyses, exploring age at diagnosis, genomic risk distributions, chemotherapy allocation, distant recurrence rate and drug costs, showed the 21-gene assay was dominant versus clinical-pathologic risk factors alone in N0 and N1 populations and subgroups, except in the N1 NHB subgroup where it was cost-effective (ICER $44,186/QALY) tested with chemotherapy use from claims data.

Conclusions

- **In US practice, the use of the 21-gene assay would be associated with lower costs and more QALYs compared to using clinical-pathologic risk factors alone across racial and ethnic subgroups among patients with HR+/HER2- N0 and N1 early-stage breast cancer.**
- **Some differences driven by the clinical inputs used were observed among the racial and ethnic subgroups explored.**
- **The study was limited by data gaps and uncertainty of evidence used:**
  - **Reliance on SEER registry data based on clinical practice up to 2019, with some uncertainty in age at diagnosis and chemotherapy allocation.**
  - **Limited data for subgroup-specific distant recurrence risk (notably in N1 racial and ethnic subgroups).**
  - **Scenario analyses using alternative data sources to address data limitations confirmed the robustness of the base case results.**

Take-home message

- **These findings support the clinical and economic value of the 21-gene assay across racial and ethnic subgroups with HR+/HER2- early-stage breast cancer, demonstrating its potential to guide more appropriate chemotherapy use and improve value-based, equitable treatment decision-making.**

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