

Head-to-head and combined performance of an AI-based H&E biomarker and the 21-gene recurrence score for distant recurrence in HR+/HER2- early breast cancer: validation in TAILORx

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Background

In HR+/HER2- early breast cancer (EBC), the 21-gene recurrence score (RS) is a reference genomic prognostic tool, yet residual heterogeneity persists within RS-defined risk strata, particularly for late distant recurrence¹⁻². RlapseRisk BC (RR) is a CE-IVDR AI biomarker integrating H&E morphologic features with age, tumor size, and nodal status. RR was developed using >6,000 patients from 7 retrospective cohorts and its clinical validity was subsequently established in independent validation cohorts comprising the prospective-retrospective analysis of NSABP B-28 (n=731, node-positive randomized trial) and a multi-institutional retrospective case series (n=936), spanning diverse geographic regions and laboratory settings. We evaluated the histology-only component (RR-H) in TAILORx, head-to-head and in combination with RS.

Objectives

- Compare RR-H head-to-head with the 21-gene RS as stand-alone prognostic scores for DR, on top of clinicopathologic factors.
- Quantify the added prognostic value of combining RR-H with RS (likelihood-ratio test, C-index, time-dependent AUC at 5 and 10 years).
- Assess the consistency of the RR-H effect across treatment populations (endocrine-only vs chemo-endocrine arms).
- Exploratory: 10-years DR and RRBC × RS cross-classification.

References and acknowledgment

1. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111-121.
2. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377:1836-1846.

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Conclusions

- In TAILORx, the H&E-only score RR-H showed stand-alone discrimination similar to the 21-gene RS.
- RR-H and RS were complementary: combined, they gave the highest discrimination, with the largest gain at 10 years.
- Exploratory: RR-H kept its prognostic value for late distant recurrence (>5 years), where the RS effect attenuated.

Method

- Design: prospective-retrospective analysis of TAILORx (NCT00310180); RRBC and RR-H was locked before analysis
- Scores: RR-H = histology-only component of RRBC (continuous, per 1 SD); RRBC = multimodal score (RR-H + age, tumor size, nodal status; binary at locked cut-off); RS = 21-gene RS (per 1 SD, or 0-25 / 26-100)
- Population: n=7,584 with evaluable WSI, RS and clinicopathologic data; 532 DR events; arms A+B endocrine-only (n=3,922), C+D chemo-endocrine (n=3,662).
- Endpoint: DRFI (STEEP 2.0); Kaplan-Meier estimates shown as 10-year DR risk.
- Analysis:
 - Cox models Base (age, tumor size, grade, histologic subtype) ± RS ± RR-H; LR test; Harrell's C-index; time-dependent AUC at 5 and 10 years; RR-H × treatment interaction.
 - RRBC × RS cross-classification (arms A, B, D; n=5,028);
 - late-DR landmark in patients DR-free at 5 years (n=6,458; 355 events).

Results - Head-to-head and combined discrimination

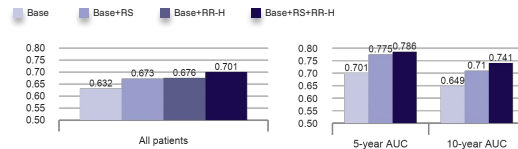


Fig 1. Harrell's C-index of nested Cox models for DRFI (all patients, n=7,584)

Fig 2. Time-dependent AUC for DR at 5 and 10 years (Base+RR-H not reported)

- Head-to-head: added to Base clinical, RR-H and RS gave similar discrimination (C-index 0.676 vs 0.673; Base alone 0.632).
- Combined: RR-H added significant information beyond Base+RS (LR $\chi^2 = 53.6$, $p = 2.5 \times 10^{-13}$ (not show on figures); Base+RS+RR-H reached the highest C-index (0.701).
- Time horizons: the gain from adding RR-H to Base+RS was larger at 10 years (AUC 0.710 → 0.741, +0.031) than at 5 years (0.775 → 0.786, +0.011).

Results

Independent and complementary prognostic information

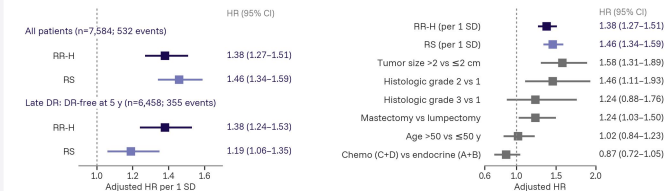


Fig 3. Adjusted HR per 1 SD, RR-H vs RS: all patients vs late DR

Fig 4. Multivariable Cox model for DRFI, all patients

- Independent effects (Fig 4): RR-H and RS were weakly correlated (Spearman $\rho = 0.15$) and both remained prognostic, with similar HRs per 1 SD: RR-H 1.38 (1.27-1.51), RS 1.46 (1.34-1.59). The RR-H effect was consistent across treatment: HR 1.34 (1.19-1.51) endocrine-only vs 1.52 (1.36-1.70) chemo-endocrine; interaction $p = 0.92$.
- Late Distant Recurrence (Fig 3): in patients DR-free at 5 years, HR per 1 SD was 1.38 (1.24-1.53) for RR-H vs 1.19 (1.06-1.35) for RS; adding RR-H to Base+RS raised the C-index from 0.605 to 0.648.

Discordance between RRBC and RS (binary scores, exploratory)

10-yr DR risk, % (95% CI); n	RS 0-25 (n=3,922)	RS 26-100 (n=1,106)	RRBC alone
RRBC-low (n=3,614)	4.1 (3.4-5.0) n=2,985	8.8 (5.9-12.9) n=629	4.8 (4.1-4.7)
RRBC-high (n=1,414)	9.0 (7.2-11.3) n=937	21.5 (16.3-28.1) n=477	12.1 (10.3-14.3)
RS alone	5.3 (4.6-6.2)	14.4 (11.4-18.0)	n=5,028

Table 1. 10-year DR risk, % (95% CI), by RRBC × RS (arms A, B, D; n=5,028)

RRBC and RS often disagreed: RRBC classified 24% of RS 0-25 patients as high risk and 57% of RS 26-100 patients as low risk. Discordance was prognostic: 10-year DR risk was 9.0% (RS 0-25/RRBC-high) vs 4.1% (concordant low), and 8.8% (RS 26-100/RRBC-low) vs 21.5% (concordant high). Combined, 10-year DR risk ranged from 4.1% to 21.5%, wider than with either score alone (RS 5.3-14.4%; RRBC 4.8-12.1%).

All RS 26-100 patients received chemotherapy