



Toward Precision Extended Endocrine Therapy in Early HR+ Breast Cancer: Multimodal AI for Risk and Benefit Stratification

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Study Highlights

9.39% absolute 10-year EET benefit in LDR-B high patients (HR 0.41); no significant benefit in LDR-B low; treatment-by-LDR-B interaction P = 0.004

LDR-B high / LDR-R high patients (27.4%) derived significant EET benefit (absolute benefit 10.16%; HR 0.41; P < 0.001)

No molecular testing required — predictions from routine H&E images plus three clinical variables (age, nodal status, surgery type)

Background

- Hormone receptor-positive (HR+) early breast cancer carries persistent late distant recurrence (DR) risk.¹
- Extended endocrine therapy (EET; extended letrozole in NSABP B-42) reduces recurrence in some patients, but benefit must be weighed against toxicity, adherence and heterogeneous baseline risk.²
- Multigene assays (Oncotype DX, MammaPrint, Prosigna, EndoPredict, Breast Cancer Index [BCI]) are prognostic; BCI and MammaPrint have shown predictive signals for EET in trial cohorts, with modest absolute benefit or secondary-endpoint effects, and all require molecular testing.^{3–10}
- We previously developed and externally validated LDR-R, a prognostic model combining hematoxylin & eosin (H&E) images and clinical variables to predict late DR (10-year absolute risk difference 7.95%; hazard ratio [HR] 5.71; 95% confidence interval [CI] 3.50–9.32).¹¹
- Routine H&E images, combined with clinicopathologic factors, offer a way to identify EET benefit within the context of late DR risk without molecular testing.

Methods

- Multimodal artificial intelligence (AI) decision-support tool for EET selection (Figure 1), trained on 2,271 NSABP B-42 patients (postmenopausal HR+ early breast cancer, disease-free after 5 years of endocrine therapy, randomized to extended letrozole vs placebo) with 5-fold cross-validation (out-of-fold predictions); point estimates are from the primary run. Primary endpoint: late distant recurrence (DR), measured from randomization with 10-year follow-up.
- LDR-B (predictive): EET benefit from clinicopathologic features plus whole-slide image (WSI)-predicted expression of 11 genes. LDR-R (prognostic): late DR risk from image embeddings plus clinicopathologic features.
- Models are combined for individualized risk stratification and treatment guidance. During model development, different data-modality combinations (image-predicted molecular and clinical; Figure 4) and different foundation models (CTransPath, Prov-GigaPath, Virchow2, H-optimus-0) as tile encoders (Figure 5) were explored for the final LDR-B model, each summarized over 10 cross-validation repeats (model-high group defined at the 70th percentile threshold).

Results

LDR-B: prediction of EET benefit

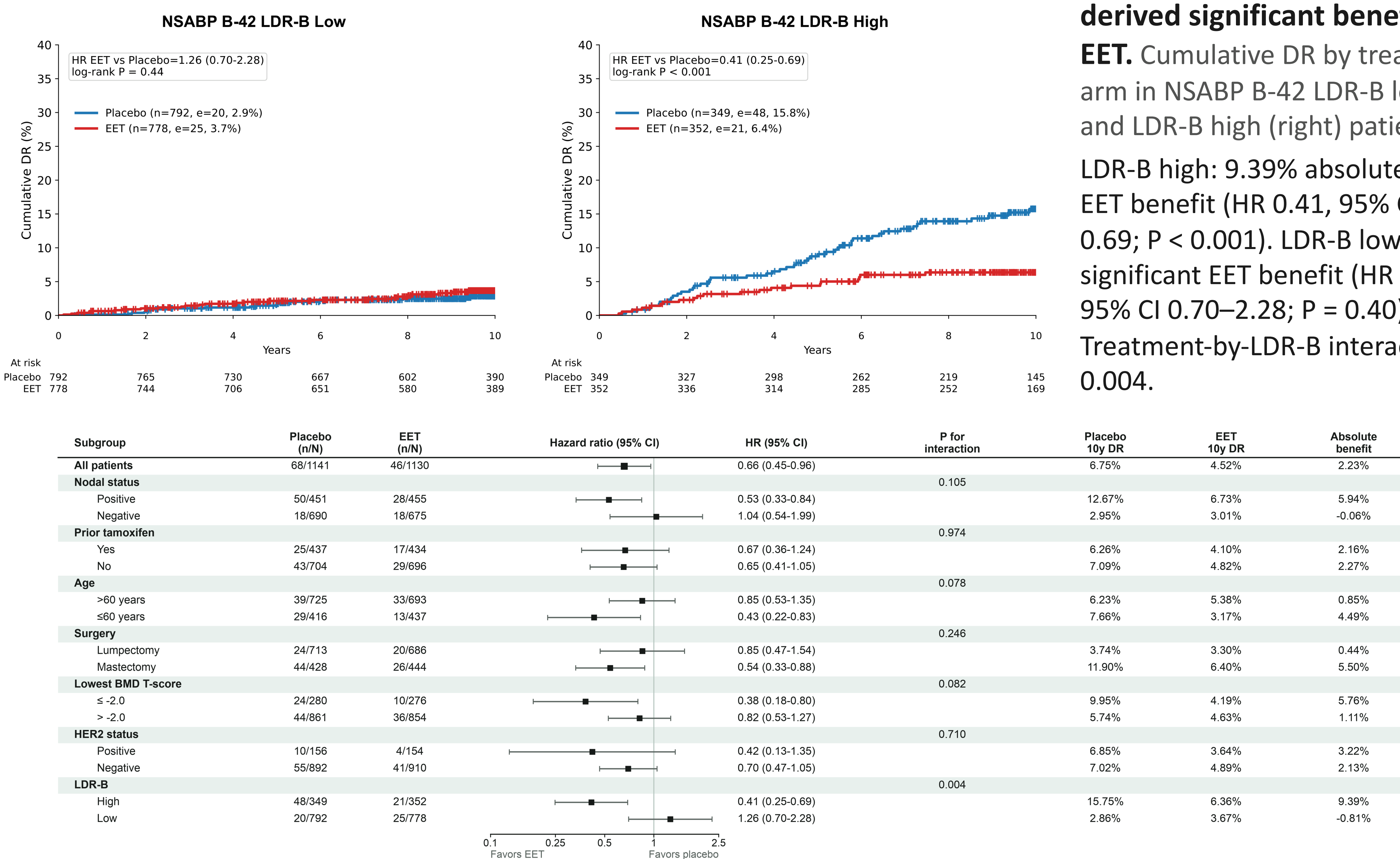


Figure 2. LDR-B high patients derived significant benefit from EET. Cumulative DR by treatment arm in NSABP B-42 LDR-B low (left) and LDR-B high (right) patients. LDR-B high: 9.39% absolute 10-year EET benefit (HR 0.41, 95% CI 0.25–0.69; P < 0.001). LDR-B low: no significant EET benefit (HR 1.26, 95% CI 0.70–2.28; P = 0.40). Treatment-by-LDR-B interaction P = 0.004.

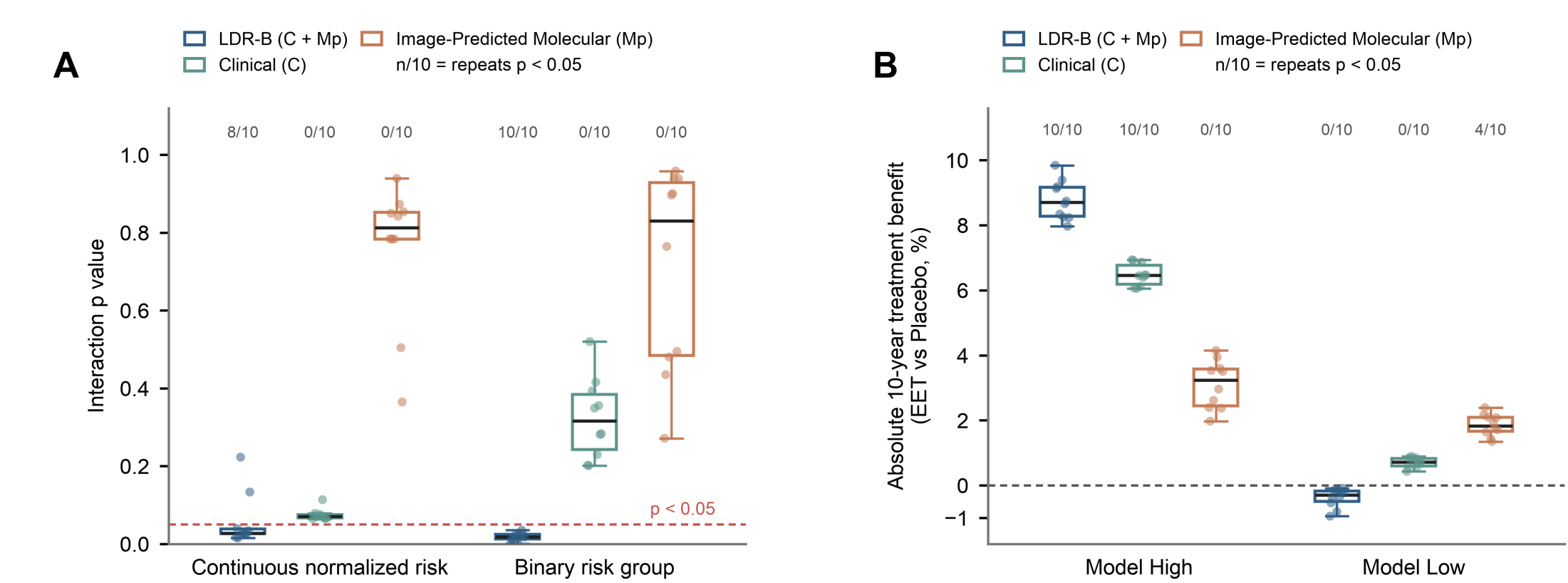


Figure 4. Clinical plus image-predicted molecular features are both required for benefit prediction. Treatment-by-risk interaction P values (A) and 10-year absolute EET benefit (B) by data modality over 10 cross-validation repeats. Only the combined model showed consistent treatment interactions (A); significant in 10/10 repeats with the binary risk groups and 8/10 with the continuous score) and the largest benefit in model-high patients (median 8.70%; B).

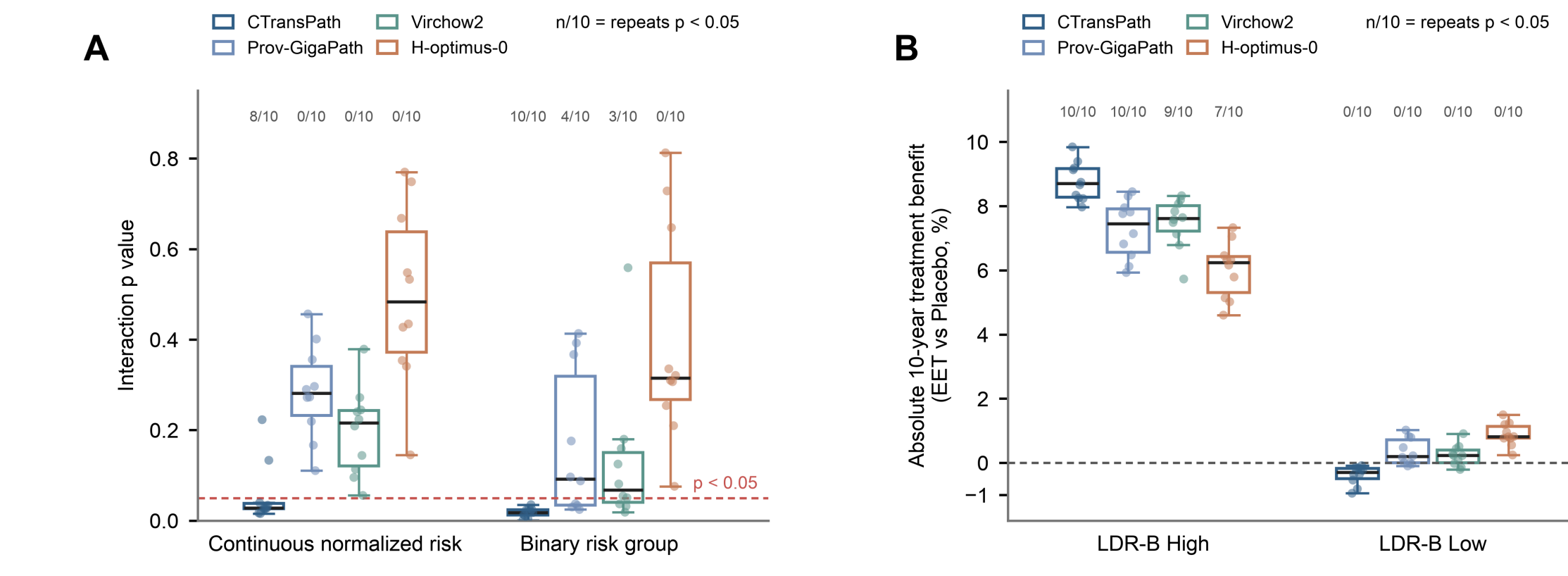


Figure 5. The LDR-B variant built on the CTransPath-based tile encoder showed the strongest EET-benefit stratification. Treatment-by-risk interaction P values (A) and 10-year absolute EET benefit (B) in LDR-B high vs low, for LDR-B variants built on four foundation models. Only the CTransPath-based variant reached consistently significant treatment interactions (A) and showed the largest EET benefit in LDR-B high patients (median 8.70%; B).

Clinical framework: LDR-B + LDR-R

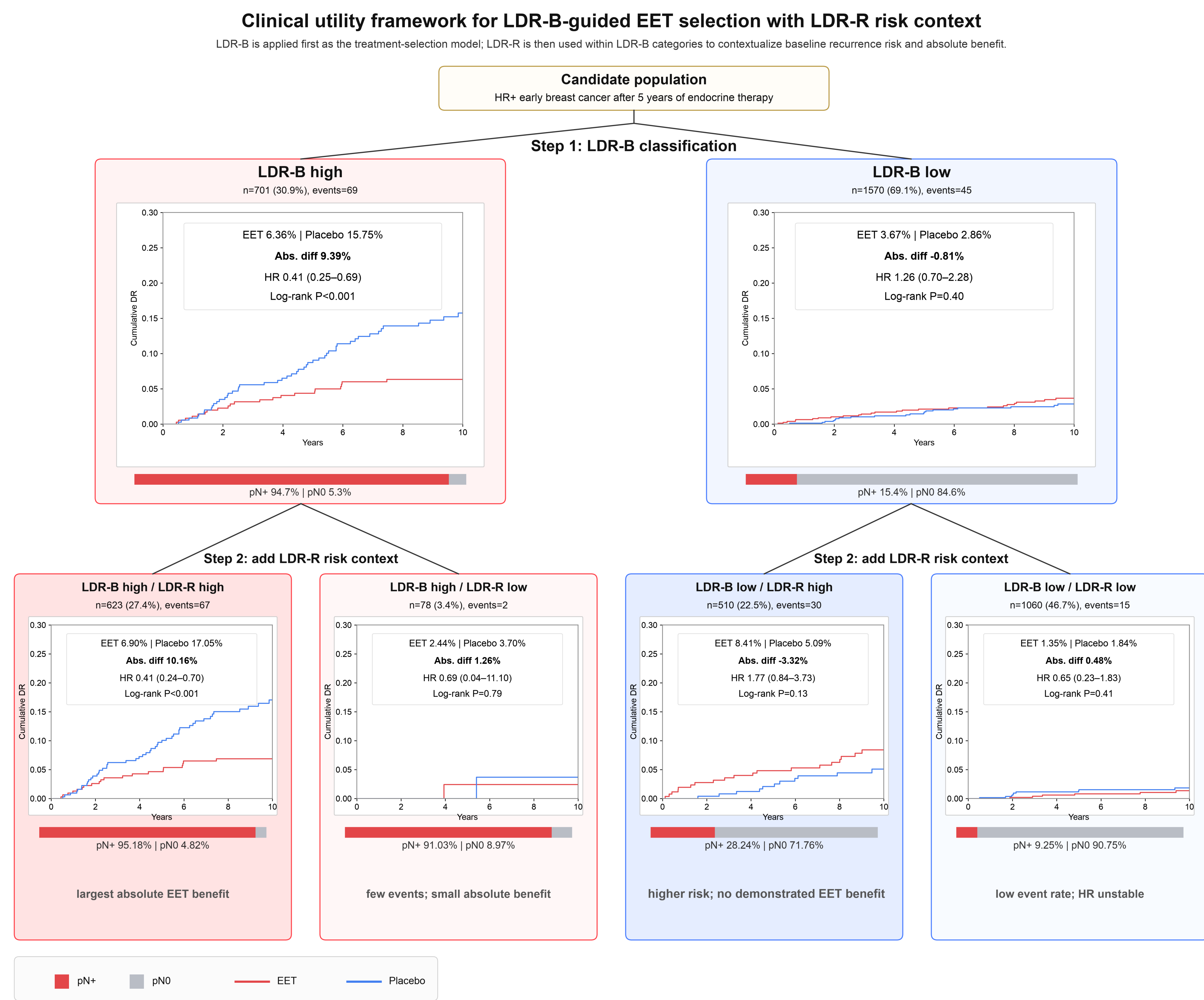


Figure 6. LDR-B high / LDR-R high patients (27.4%) derived significant EET benefit (absolute benefit 10.16%). LDR-B is applied first (treatment selection); LDR-R adds risk context within each LDR-B class. Bars: pN+/pN0 (pathological node-positive/negative).

- Four subgroups: LDR-B high / LDR-R high 27.4%; LDR-B high / LDR-R low 3.4%; LDR-B low / LDR-R high 22.5%; LDR-B low / LDR-R low 46.7%.
- LDR-B high / LDR-R high: significant EET benefit (absolute benefit 10.16%; HR 0.41, 95% CI 0.24–0.70; P < 0.001);** these patients were predominantly node-positive (95.18% pN+ vs 39.89% overall).
- LDR-B low: no significant EET benefit in either LDR-R group;** LDR-R high: –3.32% (HR 1.77, 95% CI 0.84–3.73; P = 0.13); LDR-R low: 0.48% (HR 0.65, 95% CI 0.23–1.83; P = 0.41). High late-DR risk alone did not identify EET benefit.

Conclusion

- Using routine H&E images and three clinical variables, this multimodal AI tool identifies patients most likely to benefit from EET within the context of late DR risk and may enable more individualized EET decisions in early HR+ breast cancer.
- These retrospective, cross-validated findings support prospective validation of LDR-B as an EET decision-support tool.

Figure 1. The LDR framework: one H&E workflow feeds two complementary models. Shared preprocessing tiles the WSI and extracts CTransPath embeddings. LDR-R (multimodal transformer) outputs a continuous late-DR risk score; LDR-B predicts the 11 BCI genes with a GEP model (trained on 9,003 Caris breast cancer patients), concatenates them with age, nodal status and surgery type, and outputs a continuous benefit score. Both trained in NSABP B-42 (n = 2,271).

GEP, gene expression prediction; MLP, multilayer perceptron; BMD, bone mineral density; px, pixels; LDR, late distant recurrence (LDR-R, risk model; LDR-B, benefit model); CTransPath, pathology foundation model used as the tile encoder; NSABP, National Surgical Adjuvant Breast and Bowel Project.

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