

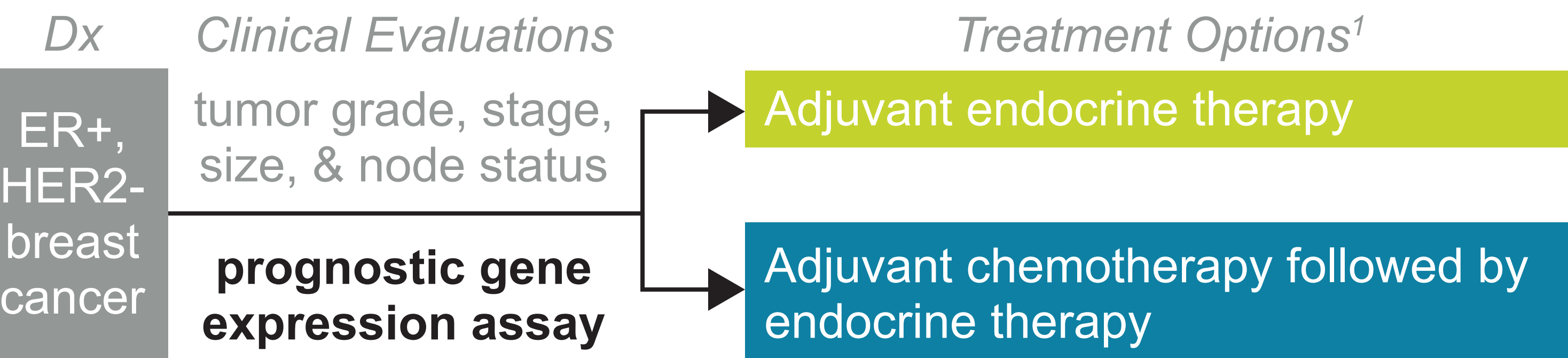
Predicting Expected Absolute Chemotherapy Treatment Benefit in Women with Early-Stage Breast Cancer using a 12-Gene Expression Assay

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BACKGROUND

- Many women with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer who have a low risk of distant recurrence can safely forgo adjuvant chemotherapy.¹
- Although risk of recurrence has traditionally been evaluated using clinical factors, a prognostic 12-gene expression assay has been previously validated as a superior predictor of the risk of distant recurrence in this population.²⁻⁵



- Here, we estimate the expected absolute chemotherapy benefit for women with early-stage ER+, HER2- breast cancer based on the 12-gene expression assay using a mathematical model.

METHODS

COHORT

- This cohort included treatment-naïve patients with ER+, HER2- breast cancer who were tested with the 12-gene expression assay between October 2014 and December 2017 (Myriad Genetic Laboratories or Myriad GmbH) as part of normal clinical operations (N=2,205).

12-GENE EXPRESSION ASSAY

- The RNA expression of 12 genes was measured by qRT-PCR in formalin-fixed paraffin-embedded breast resections.

3	5	3	1
Proliferation Target Genes	Hormone Receptor Target Genes	Normalization Genes	Marker of DNA Contamination

- A 12-gene molecular score was calculated as the linear combination of the normalized target gene expression.
- A molecular-clinical score (EPclin score) was calculated by combining the 12-gene molecular score with tumor size and the number of positive lymph nodes.
 - EPclin <3.3: low risk for distant recurrence
 - EPclin ≥3.3: high risk for distant recurrence

STATISTICAL METHODS

1. Risk of Distant Recurrence *Without* Chemotherapy

- The 10-year risk of distant recurrence in *patients treated with endocrine therapy only ('untreated')* was obtained from published results of the 12-gene expression assay in the ABCSG-6 and ABCSG-8 trials.²

2. Risk of Distant Recurrence *With* Chemotherapy

- The 10-year risk of distant recurrence in *patients treated with endocrine therapy and adjuvant chemotherapy ('treated')* was modeled using the overall chemotherapy treatment benefit to reduce recurrence in ER+, HER2- breast cancer from a meta-analysis by the EBCTCG (HR_{overall} = 0.7).^{6,7}

$$r_{\text{treated}} = 1 - (1 - r_{\text{untreated}})^{\text{HR}_{\text{treatment}}}$$
$$\log(\text{HR}_{\text{treatment}}) = \alpha - \beta(\text{EPclin} - 1)$$

r _{untreated}	Risk of 10-year distant metastasis in untreated patients from Part 1
r _{treated}	Risk of 10-year distant metastasis in treated patients
HR _{treatment}	Relative chemotherapy benefit for an EPclin score
α	Intercept
β	Strength of interaction between HR _{treatment} and EPclin
EPclin	Patient EPclin score

- A) Risk of recurrence modeled when there is no interaction between EPclin score and HR_{treatment}
- β = 0 (β_{min})
 - α calculated such that HR_{overall} = 0.7

- B) Risk of recurrence modeled for the maximum interaction between EPclin score and HR_{treatment}
- α = 0
 - β calculated such that HR_{overall} = 0.7 (β_{max})

- C) Risk of recurrence modeled when the interaction between EPclin score and HR_{treatment} is varied
- β varied from min (Part 2A) to max (Part 2B)
 - α calculated such that HR_{overall} = 0.7

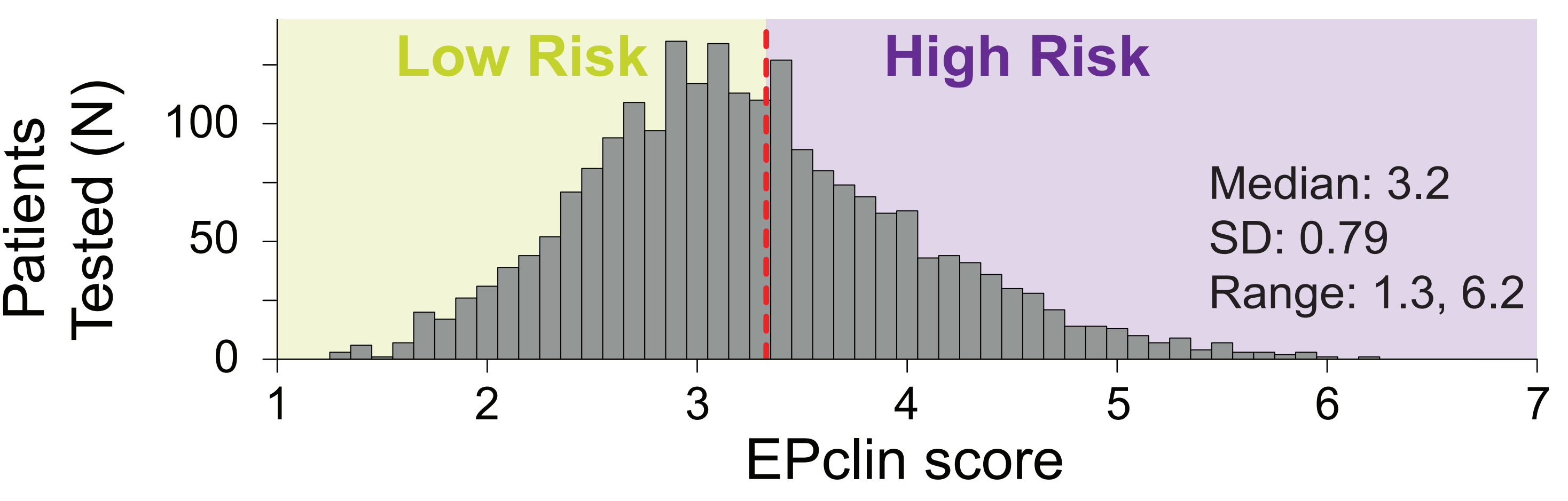
3. Absolute Benefit from Chemotherapy

$$\text{Absolute Benefit} = r_{\text{untreated}} - r_{\text{treated}}$$

- The EPclin scores for patients in this cohort ranged from 1.3 to 6.2 (Figure 1).

- 58% (1,286/2,205) were in the low risk category.
- 42% (919/2,205) were in the high risk category.

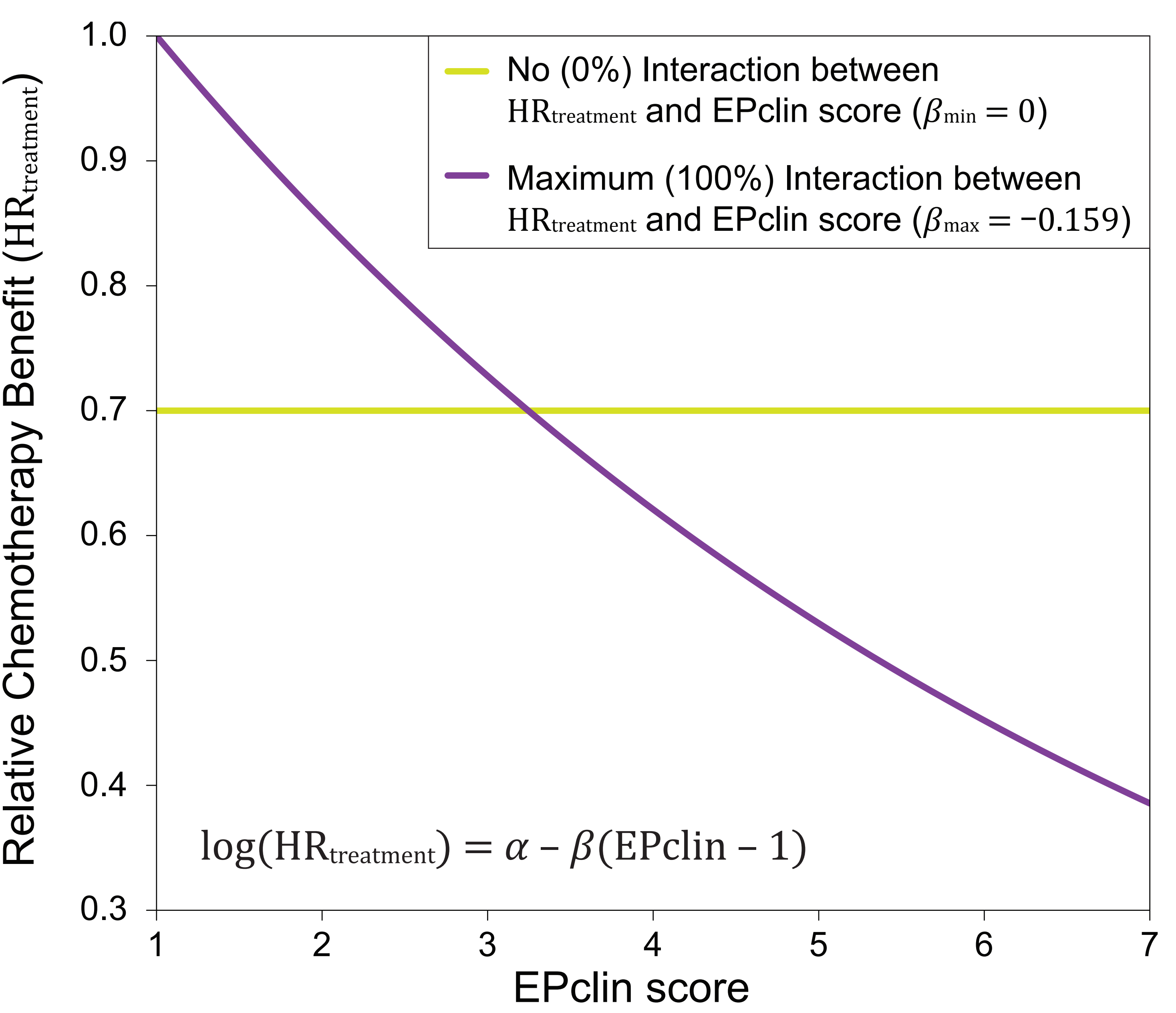
Figure 1. Distribution of EPclin Scores



- HR_{treatment} as a function of EPclin score is given in Figure 2 when:

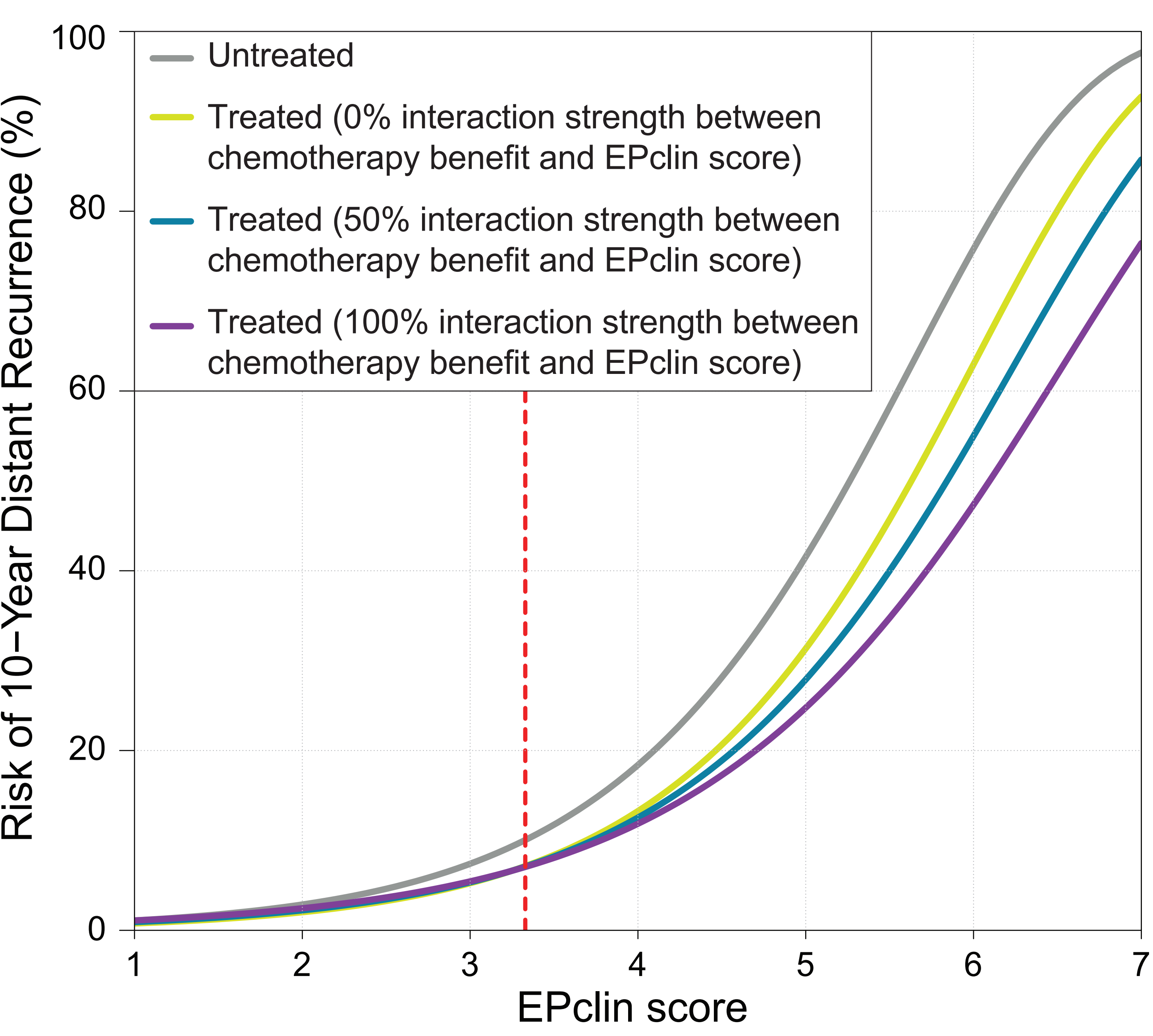
- There is no assumed interaction between treatment benefit and EPclin (0% interaction strength, β_{min}).
- The interaction between treatment benefit and EPclin is maximized (100% interaction strength, β_{max}).

Figure 2. Relative Patient Benefit from Chemotherapy



RESULTS

Figure 3. Risk of Distant Recurrence According to EPclin Score as a Function of Interaction Strength



- The risk of distant metastasis was calculated for a variety of interaction strengths between HR_{treatment} and EPclin score (Figure 3).
 - There was little separation between the treated and untreated risk curves for low EPclin scores.
 - There was much more separation between the treated and untreated risk curves for high EPclin scores.
- The effect of interaction strength on absolute chemotherapy benefit was rather moderate (Figure 4).
- The absolute chemotherapy benefit in high risk patients ranged from 7.3% (β_{max}) to 5.3% (β_{min}) (Figure 4).
 - This corresponded with mean 10-year risks of distant recurrence ranging from 14.7% (β_{max}) to 12.8% (β_{min}).
- The absolute chemotherapy benefit in low risk patients ranged from 1.5% (β_{max}) to 1.8% (β_{min}) (Figure 4).
 - This corresponded with mean 10-year risks of distant recurrence ranging from 4.6% (β_{max}) to 4.3% (β_{min}).

SUMMARY

- A mathematical model was used to estimate the expected absolute chemotherapy benefit among patients with early-stage ER+, HER2- breast cancer based on the test results of a 12-gene expression assay.
- This was done using the overall adjuvant chemotherapy benefit as determined in a meta-analysis by the EBCTCG in order to overcome the potential bias inherent to individual trials that result in variable observed treatment benefits.
- In this analysis, the 12-gene expression assay was estimated to predict absolute benefit from adjuvant chemotherapy in women with ER+, HER2- early stage breast cancer, regardless of which EPclin score cohorts accrued maximal relative treatment benefit.

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