**Title:**
Integration of the stem cell biology-based genomic tool, StemPrintER, with clinicopathological parameters for the prediction of distant recurrence in ER+/HER2- breast cancer patients.

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**Background**
The StemPrintER risk score (SPRS) is a 20 gene-based predictor that estimates the "degree of stemness" of the primary tumor and provides additional prognostic information regarding distant metastasis (DM) risk in early stage ER+/HER2- breast cancer (BC) patients beyond that obtained from standard clinicopathological parameters. Here we describe a further refined model, that combines prognostic information from SPRS with tumor size (pT) and nodal status (pN), termed SPARE (SPRS for Personalized Adjuvant therapy in Receptor-Expressing patients). SPARE was compared to the clinical treatment score (CTS) for 10-year risk of DM in a consecutive-retrospective ER+/HER2- BC patient cohort (n=1,827) with 15-year complete follow-up from the European Institute of Oncology (IEO) in Milan.

**Methods**
The SPARE model was developed in patients randomly assigned to a training set (n=609), using the ridge-penalized Cox regression, and tested in an independent validation set (n=1,218). Likelihood $\chi^2$ ($LR\chi^2$) and Kaplan-Meier survival analysis were used to compare the prognostic information from SPARE and CTS (based on age, pN, pT, endocrine treatment). Comparative analyses were made for the DM risk over the 10-year follow-up, as well as in the early (0-5 years) or late (5-10 years) interval, according to nodal status.

**Results**
SPARE outperformed CTS in providing prognostic information for 10-year DM risk ($LR\chi^2$: SPARE = 141.2, $P$<0.0001; CTS=118.1, $P$<0.0001), with even greater differences in node-negative patients ($LR\chi^2$: SPARE=47.6, $P$<0.0001; CTS=27.5, $P$<0.0001) and in 1-3 node-positive patients ($LR\chi^2$: SPARE=30.6, $P$<0.0001; CTS=15.1, $P$<0.0001). When reciprocally adjusted for each other, SPARE added prognostic information to CTS ($\Delta LR\chi^2$: CTS+SPARE *vs.* CTS = 25.2; $P$<0.0001), while CTS did not provide any statistically significant information to SPARE (SPARE+CTS *vs*. SPARE = 2.1, $P$=0.14). Using predefined cut-offs to stratify chemo-naïve patients clinically estimated at low recurrence risk, SPARE identified low, intermediate and high risk patients based on their annual rate of DM in the early (low, 0.2%, intermediate, 0.8%, high, 3.3%) and late (low, 0.3%, intermediate, 0.9%, high, 1.6%) interval.

**Conclusion**
SPARE represents a more refined clinical tool, compared to standard clinicopathological parameters, that could be used for personalized therapeutic decision making in ER+/HER2- BC patients.

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