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To interview Per Karlsson, please contact Julia Gunther at [julia.gunther@aacr.org](mailto:julia.gunther@aacr.org) or 770-403-7690. For a photo of Karlsson, please click [here](#).

## **Genetic Profiling May Identify Patients with Breast Cancer Who Can Safely Omit Radiation Therapy After Breast-conserving Surgery**

SAN ANTONIO – Patients with invasive breast cancer who had low scores on an investigational gene molecular signature had similar rates of local recurrence whether or not they received adjuvant radiation therapy after breast-conserving surgery, according to results of a meta-analysis presented at the [San Antonio Breast Cancer Symposium](#), held December 6-10, 2022.

Patients with [breast cancer](#) who undergo breast-conserving surgery are recommended to receive adjuvant radiation therapy to reduce the risk of local recurrence. “However, many patients will not experience a local recurrence even without radiation therapy,” said [Per Karlsson, MD](#), a professor of oncology at the Sahlgrenska Comprehensive Cancer Center and the University of Gothenburg in Sweden.

“Currently, we do not have any reliable predictive classifiers to identify patients who might be able to skip radiation therapy,” he added. “Since radiation therapy can be associated with problematic side effects in some patients, it is of clinical importance to identify those patients for whom radiation therapy can be safely omitted.”

In this study, Karlsson and colleagues evaluated the predictive potential of POLAR (Profile for the Omission of Local Adjuvant Radiotherapy), an investigational 16-gene molecular signature that was developed based on gene expression differences between patients with and without local recurrence after breast-conserving surgery. Genes included in the signature have known roles in cellular proliferation and the immune response.

The researchers performed a meta-analysis of 623 patients with lymph node-negative, estrogen receptor-positive, HER2-negative breast cancer who were enrolled in one of three randomized clinical trials examining the efficacy of breast-conserving surgery with and without local breast radiation therapy. The clinical trials included in the meta-analysis were the Swedish [SweBCG91RT](#) trial, the [Scottish Conservation Trial](#) (SCT), and a [trial from the Princess Margaret Hospital](#) (PMH) in Canada. Among the 623 patients in the meta-analysis, 354 were from SweBCG91RT, 137 from SCT, and 132 from the PMH trial.

To evaluate the predictive capability of POLAR, the researchers analyzed gene expression in patient breast tumor samples to assign each patient a POLAR score; they then examined the impact of radiation therapy for patients with high and low POLAR scores. Among the 429 patients with high POLAR scores, those who received adjuvant radiation therapy after breast-conserving surgery had a 63 percent reduction of local recurrence compared with those who did not receive adjuvant radiation therapy, suggesting that adjuvant radiation therapy was beneficial for these patients.

In contrast, for the 194 patients with low POLAR scores, there was no significant difference in local recurrence rate between those who received adjuvant radiation therapy and those who did not. After 10 years, 5 percent of patients who received radiation therapy experienced a local recurrence, compared with 7 percent of those who did not receive radiation therapy.

“In a patient-level meta-analysis of three independent randomized clinical trials, the POLAR gene profile successfully predicted which patients would and would not benefit from local radiation therapy, thereby identifying a group of breast cancer patients where radiation therapy may be safely omitted after breast-conserving surgery,” summarized Karlsson.

“Although only a minority of patients experience severe side effects to breast radiation, this adds up to a fair number of patients once you consider how prevalent breast cancer is,” he added. “The POLAR gene profile may, therefore, help mitigate toxicities and improve quality of life for many patients.” Karlsson noted that the POLAR gene profile will need further validation and additional streamlining before it could be used in the clinic.

Future research from Karlsson and colleagues will examine whether the POLAR gene profile can also identify patients who could safely avoid regional radiation therapy, which is associated with more severe toxicities than local radiation therapy.

A limitation of the study is its retrospective design. Additionally, the POLAR gene profile was developed using samples from patients who did not receive currently available endocrine therapies; however, validation trials included patients who received such therapies.

The study was supported by funds from the Swedish Cancer Society, the Swedish Research Council, the King Gustaf V Jubilee Clinic Foundation, the ALF Agreement of the Swedish government, PFS Genomics, and Exact Sciences.

Karlsson has pending patents with and receives royalties from Exact Sciences and PreludeDX.

## **Abstract**

### **GS4-03**

#### **Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in a meta-analysis of three randomized controlled trials of breast conserving surgery +/- radiotherapy**

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**Background:** There are currently no commercially available tests to identify early stage breast cancer patients treated with breast conserving surgery (BCS) and systemic therapy at low risk of locoregional recurrence (LRR) for whom postoperative radiotherapy (RT) may be safely omitted. Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) is a 16-gene molecular signature developed to identify invasive breast cancer patients who may be candidates for RT omission after BCS. In this work, we seek to validate POLAR in a meta-analysis of three RCTs of BCS +/- RT: SweBCG91RT, Scottish Conservation Trial (SCT) and Princess Margaret Hospital (PMH). **Methods:** A patient-level meta-analysis was performed in 623 node-negative breast cancer patients with ER+/HER2-negative tumors who were enrolled in the three RCTs and for whom primary tumor material was available for analysis. Contributions from each cohort were as follows: SweBCG91RT N=354 (57%), SCT N=137 (22%), and PMH N=132 (21%). Numbers of LRR events in each cohort were as follows: SweBCG91RT N=72 (20%), SCT N=28 (20%), and PMH N=16 (12%). There was a mix of systemic therapy used (no systemic therapy for SweBCG91RT, chemotherapy or adjuvant endocrine therapy, but not both, in SCT, and tamoxifen but no chemotherapy for PMH). Median follow-up time for the patients who did not have LRR was 13.3 years for SweBCG91RT, 21.1 years for SCT, and 8.6 years for PMH. A multivariable Cox proportional hazards

model on time to LRR, including the continuous standardized POLAR score, RT, and interaction, stratified by cohort, was used to test the interaction between the continuous POLAR score and RT. Additional Cox models tested the association between treatment arms separately for patients with a low and high POLAR score using a pre-specified cut point. Cumulative incidences were computed, with distant metastasis and death without recurrence considered as competing events. **Results:** The test for interaction between RT treatment and POLAR was statistically significant ( $p = 0.022$ ). Patients with a high POLAR score ( $N=429$  [69%]) had a large benefit from RT (10-year cumulative incidence of LRR: 20% [15%-26%] for those not treated with RT vs 7% [4%-11%] for those treated with RT; hazard ratio for RT vs no RT: 0.37 [0.23-0.60],  $p < 0.001$ ), whereas there was no evidence of benefit from RT for patients with a low POLAR score ( $N=194$  [31%], 10-year cumulative incidence of LRR: 5% [2%-11%] for those not treated with RT vs 7% [3%-14%] for those treated with RT; hazard ratio for RT vs no RT: 0.92 [0.42-2.02],  $p = 0.832$ ). **Conclusions:** To our knowledge, POLAR is the first genomic classifier that is not only prognostic for LRR but also predictive, showing a significant interaction between RT and the classifier. Patients with a high POLAR score should be recommended radiotherapy while patients with a low score may be candidates for omission of radiotherapy after breast conserving surgery.

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