San Antonio Breast Cancer Symposium 2025

Title: Validation of a multi-omic biosignature to predict locoregional recurrence risk and the benefit of adjuvant radiation therapy in women with early-stage invasive breast cancer treated with breast-conserving surgery and endocrine therapy.

Background: Randomized clinical trials demonstrate that radiotherapy (RT) after breast conserving surgery (BCS) significantly reduces risk of invasive locoregional recurrences (LRR) in women with early-stage hormone receptor positive (HR+) HER2 negative invasive breast cancer (IBC). However, RT de-escalation trials also demonstrate that some patients may omit RT based on clinicopathological factors. To better inform shared decision making, a multi-omic test was developed (n=939) to predict women's invasive LRR risk and RT benefit. Herein, we evaluate this test in a retrospective observational cohort treated at Royal Melbourne Hospital (RMH), Australia.

Methods: Women with HR+HER2- T1T2N0M0 IBC were treated at RMH with definitive BCS between 2006-2017 (n=526) and with adjuvant ± RT ± endocrine therapy (ET) ± chemotherapy (CT). Treatment and outcome were collected by RMH and transferred to a third-party biostatistics group (MCG, AUS). After RMH central pathology review, FFPE tumor samples were sent to a CLIA lab (Laguna Hills, CA) to assay protein expression by multiplex-immuno-fluorescence and RNA expression by targeted Next Generation Sequencing (blinded to treatment and outcome). The test combines multi-omic data using biosignatures to calculate a Decision Score (DS) to determine LRR prognosis and a Radio Resistance Index (RRI) to determine individualized RT benefit. Test results were transferred to and analyzed by MCG to validate the test using a pre-specified analysis plan. The association of continuous DS and RRI with LRR risk and RT benefit were analyzed in multivariable analysis. The absolute risk and RT benefit within Low and Elevated categorical risk groups were assessed using pre-specified thresholds (DS=5, RRI=5). Hazard ratios (HR)were determined using Cox proportional hazards analysis and the interaction of the RRI and RT benefit was assessed. Kaplan-Meier survival analysis was used to calculate absolute LRR risk.

Results: Complete biomarker and clinical information were available in 426 women treated with ET of whom 319 patients received RT. There were 43 invasive LRR and 22 contralateral breast events within 10-years. The study demonstrated that the test was prognostic for LRR risk, where increasing continuous DS was associated with higher invasive LRR risk (LRR HR=2.4 per 5 units, p<.001). The test was also predictive for RT benefit. Overall, patients substantially benefited from RT (HR=0.1, p<.001) but RT treated patients with increasing RRI had less RT benefit (LRR HR=5.9 per 5 units, RRI:RT interaction p<.001). For example, in a categorical analysis, in a Low Risk group (DS≤5, n=188), RT had no significant association with LRR (HR=0.6, p=.58), where mean 10-yr LRR was 8% without RT and 6.5% with RT. In contrast, the mean 10-yr LRR was 26% without RT in the Elevated Risk group (DS>5, n=238). In this group (DS>5), patients with RRI ≤5 substantially benefited from RT (HR=0.2, p=0.002), with a corresponding 18% reduction in 10-yr LRR risk; however, for patients with RRI>5, RT was not associated with a statistically significant decrease in LRR risk (HR=0.9, p=.8), where the10-yr LRR risk remained at 22% after RT.

Conclusions: Women diagnosed with early-stage HR+ HER2- IBC and treated with BCS and ET ±RT were stratified into those with lower and higher LRR risk and RT benefit using a multi-omic test. In this external blinded validation in a retrospective observational cohort, the test stratified women into those with low LRR risk who had no significant benefit from RT, those with elevated LRR risk who had a significant benefit from RT, and those with elevated LRR risk who had minimal therapeutic benefit from RT.

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Authors:

Bruce Mann, MD, PhD
The Royal Women's Hospital, Parkville, Australia

Karuna Mittal, PhD
PreludeDx, Laguna Hills, CA

Richard de Boer, MD
Royal Melbourne Hospital, Parkville, Australia

Caroline Maccallum
The Royal Women's Hospital, Parkville, Australia

Michael D. Alvarado, MD
UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Michael Christie, MD, PhD
Royal Melbourne Hospital, Parkville, Australia

Frank Vicini, MD
Michigan Healthcare Professionals, Farmington Hills, MI

Chirag Shah, MD
Cleveland Clinic, Cleveland, OH

Y. V. Zou
Genesis Care, Parkville, Australia

Mark Mentrikoski
PreludeDx, Laguna Hills, CA

Jess Savala, MD
PreludeDx, Laguna Hills, CA

David J. Dabbs, MD
PreludeDx, Laguna Hills, CA

Steven C. Shivers, PhD
PreludeDx, Laguna Hills. CA

Pat W. Whitworth, MD
Nashville Breast Center, Nashville, TN

Troy Bremer, PhD
PreludeDx, Laguna Hills, CA