

# San Antonio Breast Cancer Symposium 2014

**Publication Number:** P4-11-17

**Title:** Validation of a multi-marker test that predicts recurrence in patients diagnosed with ductal carcinoma in situ (DCIS) treated with breast-conserving surgery (BCS)

Steven P Linke<sup>1</sup>, Troy M Bremer<sup>1</sup>, Pat Whitworth<sup>8</sup>, Alfred Lui<sup>3</sup>, Jess Savala<sup>3</sup>, Yelina Noskina<sup>3</sup>, Todd Barry<sup>6</sup>, Stephen Lyle<sup>2</sup>, Stephanie C Walters<sup>2</sup>, Cherie Taglienti<sup>2</sup>, Karl Simin<sup>2</sup>, Wenjing Zhou<sup>4</sup>, Karin Jirström<sup>5</sup>, Rose-Marie Amini<sup>4</sup> and Fredrik Wärnberg<sup>4</sup>. <sup>1</sup>Prelude Corporation, Laguna Hills, CA; <sup>2</sup>University of Massachusetts Medical School, Worcester, MA; <sup>3</sup>PersonalizeDx, Lake Forest, CA; <sup>4</sup>Uppsala University, Uppsala, Sweden; <sup>5</sup>Lund University, Lund, Sweden; <sup>6</sup>Spectrum Pathology, Mission Viejo, CA and <sup>7</sup>Nashville Breast Center, Nashville, TN.

**Background:** DCIS is diagnosed in ~54,000 women/year in the US. Identifying patients who are most likely to recur has been deemed one of the most important unmet needs in breast cancer treatment. The goal of this study was to develop and blindly validate a multi-marker risk stratification test in DCIS patients treated with BCS.

**Material and Methods:** A variety of clinical, pathological, immunohistochemical, and in situ hybridization data were derived from a set of patients diagnosed with DCIS (without evidence of invasive breast cancer) between 1986 and 2004 in Uppland and Västmanland, Sweden—the Uppsala University Hospital (UUH) patient set. Separate models to predict DCIS and invasive event risk were developed using statistical pattern recognition and modeling methods on UUH patients treated with BCS in the absence of adjuvant therapy (n=200). In addition, an “overall” risk model was created by combining the DCIS and invasive models. The risk models consist of algorithms that combine data on p16/INK4A, Ki-67, COX-2, PR, HER2, FOXA1, SIAH2, CD31, patient age, necrosis, tumor size, palpability, and/or margin status, along with predefined thresholds that create low, intermediate, and high risk groups (“elevated” risk groups combine the intermediate and high risk groups). The models were then tested blindly on a set of patients diagnosed with DCIS and treated with BCS from 1999 through July 2008 at the University of Massachusetts Memorial Hospital, Worcester, MA (UMass patient set). Molecular marker data was collected with CLIA-validated assays and Board-certified pathologists, and other data was collected from medical records. Testing was done according to a predefined statistical analysis plan in the UMass patients equivalent to those in the UUH patient training set—those with complete marker data and treated with BCS, and were either PR-negative or not treated with hormone therapy (n=155). Event rates were assessed for up to 10-year outcome using Kaplan-Meier survival analysis. Hazard ratios (HRs) were determined using Cox proportional hazards analysis.

**Results:** The 10-year overall event rate in the full population was 12% (6% invasive plus 6% DCIS). For the invasive risk model, the low (n=29) and elevated (n=97) risk groups had 0% and 7% 10-year invasive event rates, respectively. For the DCIS risk model, the low (n=76) and elevated (n=50) risk groups had 2% and 15% 10-year DCIS event rates, respectively. For the overall risk model (combined risk of DCIS or invasive events), the low (n=20), intermediate (n=65), and high (n=41) risk groups had 0%, 7%, and 22% overall 10-year event rates, respectively (HR=8.0/bin, p=0.001). The overall risk model maintained significance when adjusted for nuclear grade, tumor size, patient age, necrosis, and margin status, while none of these clinicopathologic factors demonstrated significance in the presence of the model.

**Discussion:** This study indicates that the present approach to risk stratification modeling can accurately identify patients at risk for DCIS or invasive events after a primary DCIS diagnosis. The models presented here are the basis of a comprehensive multi-marker panel undergoing formal validation.