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Title: A DCIS biosignature integrated with a novel biologic subtype was predictive for RT benefit and for elevated recurrence risk despite BCS and RT

Background: Randomized studies in breast ductal carcinoma in situ (DCIS) patients treated with breast conserving surgery (BCS) have failed to identify those at 'low risk' who do not benefit from radiation therapy (RT) or those at 'elevated risk' despite BCS with RT. The DCIS biosignature, DCISionRT® (PreludeDx™, Laguna Hills, CA), has been validated in multiple studies to be prognostic for 10-year risk of ipsilateral breast recurrence (IBR) after BCS and predictive for RT benefit. The goal of this study was to validate DCISionRT with a novel, integrated Residual Risk subtype (RRt) biosignature (DCISionRT+RRt) to identify patients at higher risk following BCS with RT.

Methods: The DCISionRT+RRt integrated biosignature was evaluated for 926 women with pure DCIS treated with definitive BCS with or without RT from a multinational cohort: Uppsala University Hospital, Sweden (1986-2004), University of Massachusetts, Worcester, MA (1999-2008), Kaiser Permanente Northwest, Portland, OR (1990-2007), and Royal Melbourne Hospital, Australia (2006-2011). Central pathology review and biosignature testing was performed on formalin-fixed paraffin embedded tissue at a CLIA-certified lab (Laguna Hills, CA), providing a unique "decision score" (DS⁺) for each specimen. Individual patient outcome and biosignature results were analyzed independently (McCloud Consulting). Clinical utility of the integrated biosignature was assessed in three patient groups **a)** Low Risk (DS⁺≤2.8), **b)** Elevated Risk (DS⁺>2.8 without RRt) and **c)** Residual Risk (DS⁺>2.8 with RRt).

Results: The integrated biosignature classified women into three groups: Low Risk (n=338, 37%), Elevated Risk (n=399, 43%), and Residual Risk (n=189, 20%) (Table 1). In patients with Low DS⁺, the average 10-year IBR risk was 5.1% and no difference was observed between those treated with and without RT (HR=0.8, p=0.7, Δ=0.8%). Patients in the Elevated Risk group had elevated risk (20.6%) without RT and a significant RT risk reduction to 4.9% 10-year IBR risk after RT (p<0.001). However, the Residual Risk group had high 10-year IBR risk without RT (42.1%) and elevated residual risk after BCS with RT (14.7%, p=0.005) compared to those without RRt. Patients derived similar relative risk reduction from RT in both the Elevated Risk and Residual Risk groups. Overall, women treated with BCS without RT with DS⁺>2.8 had a 10-year IBR risk of 25.7% and benefited significantly from RT (HR=0.26 and Δ=17.7%), and they had a higher RT benefit than those in the Low Risk group (multiplicative interaction p=0.05, additive interaction p<0.001).

Conclusions: The integrated biosignature was prognostic for 10-year IBR risk and predictive for RT benefit. This biosignature now identifies 3 distinct groups of women: **(1)** Low Risk with a low 10-year IBR risk after BCS without RT and no benefit from adjuvant RT; **(2)** Elevated Risk with increased 10-year IBR risk without RT but low 10-year IBR risk with RT; and **(3)** Residual Risk with high 10-year IBR risk after BCS without RT and elevated 10-year IBR risk after BCS with RT. The biosignature can identify patients with elevated recurrence risk after RT where additional therapies may be warranted.

Table 1. 110-year total IBR risks (95% confidence intervals)

	Low Risk Group (DS ⁺ ≤ 2.8) n=338, events=15	Elevated Risk Group (DS ⁺ > 2.8 without RRt) n=399, events=33	Residual Risk Group (DS ⁺ > 2.8 with RRt) n=189, events=29
BCS without RT	5.6% (2.5% - 12.1%)	20.6% (13.7% - 30.3%)	42.1% (25.9% - 63.0%)
BCS with RT	4.8% (2.5% - 9.1%)	4.9% (2.8% - 8.6%)	14.7% (8.8% - 24.1%)
RT (absolute difference)	0.8% (-4.6% - 6.2%)	15.7% (7.0% - 24.3%)	27.4% (7.0% - 47.7%)
RT HR	0.8 (0.3 - 2.3)	0.2 (0.1 - 0.5)	0.2 (0.1 - 0.4)

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