The traditional key feature in DCIS shared decision-making, nuclear grade, is unreliable; central vs local pathologist inter-observer reproducibility analysis in a prospective trial.

S. Willey[1], K.E. Rojas[2], C. Shah[3], F. Vicini[4], F.S. Heinemann[5], D. Dabbs[6], J. Savala[6], A. Daily[6], P.W. Whitworth[6], K. Mittal[6], S. Shivers[6], T. Bremer[6]

[1]Inova Schar Cancer Institute, Fairfax, VA; [2]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; [3]Allegheny Health Network, Pittsburgh, PA; [4]Michigan Healthcare Professionals, Farmington Hills, MI; [5]Department of Pathology, Hoag Hospital, Newport Beach, CA; [6]PreludeDx, Laguna Hills, CA

Background

20% to 30% of patients with ductal carcinoma in-situ (DCIS) who undergo a lumpectomy without radiation,will recur within 10 years without adjuvant radiation therapy (RT), which reduces the risk of recurrence by half. Adjuvant radiation reduces the risk of recurrence by half, however overview of the randomized control trials shows no survival advantage. Therefore, the primary treatment goal for DCIS Is to prevent the development of invasive breast cancer.

Unlike systemic adjuvant treatment decisions for invasive breast cancer, DCIS radiation treatment recommendations still rely on traditional clinicopathologic features, especially grade 3 vs grade 1-2.

The National Comprehensive Cancer Network (NCCN) guidelines require nuclear grade 1-2 to identify low-risk patients for consideration of omission of radiotherapy. Reliable grade assessment for every patient is thus critical for shared decision-making until a tumor-specific, validated biomarker is widely utilized.

Nuclear grade concordance studies have demonstrated significant inter-observer variability. This study assesses the concordance of local nuclear grade reported for patients in the prospective PREDICT I seven-gene biosignature clinical utility study compared to a central pathology review with consensus assessment.

Methods

Concordance of nuclear grade reported by pathologists from individual sites in the PREDICT I study was compared to nuclear grade from a central pathology review with consensus (PreludeDx).

During central review, nuclear grade was assessed independently by two pathologists, and when scoring differed, a third pathologist was used to obtain a consensus result. Concordance was reported for local versus central Grade 1 or 2 vs Grade 3.

RTOG 9804 "good risk"	7 gene biosignature
Grade 1or 2, Screen Detected, non-palpable, Margins > 2 mm, Size < 2.5 cm.	Age, Palpability, margin status, extent, COX2, HER2, SIAH2, FOXA1, PR, Ki67, P16

Table 1: Features used to determine NCCN recommended RTOG-9804 "good risk" and 7-gene biosignature Decision Score (DS) categories.

- RTOG 9804 "good-risk" criteria are the current NCCN recommended standard by which decisions to omit RT are made with nuclear grade as a major component.
- **24%** of patients had discordant scoring of nuclear grade between clinical sites and central review.
- **43%** of patients assigned grade 3 by clinical sites were assessed as grade1/2 by central review.

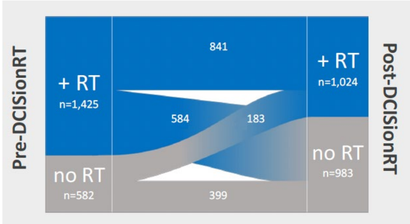

Figure 1: Change in RT recommendations for patients enrolled in PREDICT I based on DS alone as reported in Shah et. al. 2024.

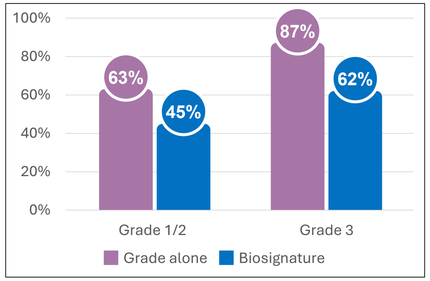

Figure 2: Change in RT recommendations for PREDICT I based on local grade. RT was recommended to 87% of grade 3 patients were compared to 63% of grade1/2 patients. When incorporating the 7-gene biosignature, RT recommendations shifted to 62% of grade 3 patients and 45% of grade 1/2 patients. (Shah et. al. 2024)

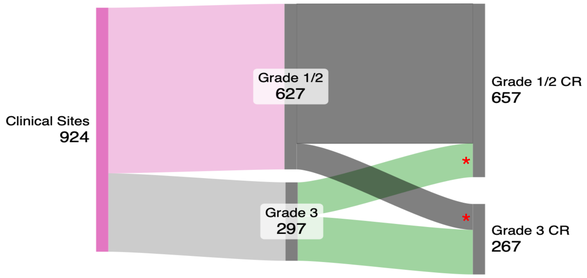

Figure 3: Distribution of grade received from clinical sites compared to central review in cohort of 924 patients from the PREDICT I study.
*Indicates unreliable discrimination of risk, potentially leading to over or undertreatment.

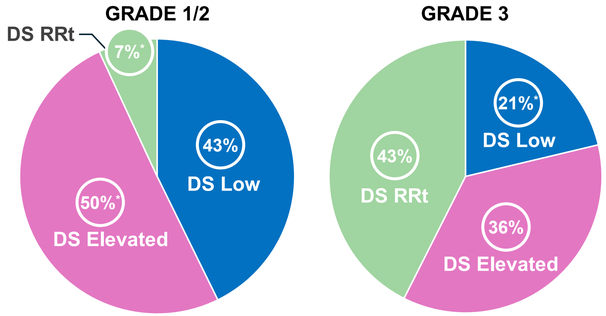

Figure 4: Percentage of DS Low, Elevated, and Residual Risk Type (RRt) by local Grade 1/2 and grade 3 of the 924 patient subset from the PREDICT I registry.
*Indicates unreliable discrimination of risk, potentially leading to over or undertreatment.

Results

Nuclear grade was compared for 924 archived patients. Overall, 24% of patients (226/924) had discordant scoring of nuclear grade between clinical sites and central review.

Of the 68% (627/924) of patients defined grade 1-2 by clinical sites, 16% (98/627) were assessed as grade 3 by central review, while 43% of patients (128/297) assessed as grade 3 by local grade were assessed as Grade 1 or 2 by central grade.

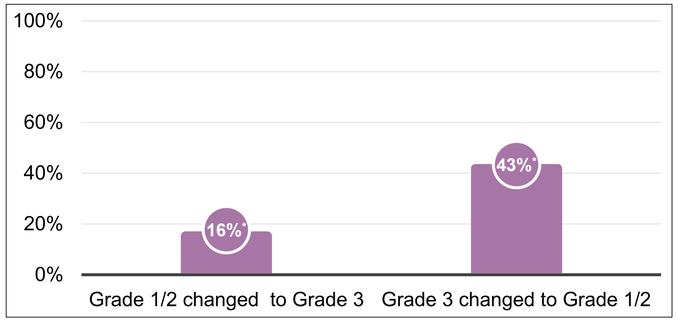

Figure 5: Overall change between clinical sites and central review.
*Indicates unreliable discrimination of risk, potentially leading to over or undertreatment.

Conclusions

This study demonstrates that nuclear grade assessment has poor concordance among pathologists. Given that nuclear grade is a prognostic factor for local relapse, the reliability of the assessment of nuclear grade for individual patients is inadequate, particularly given the reliance on this pathologic factor in treatment guidelines. Use of nuclear grade as part of assessing "low-risk" will lead to misclassification of patient risk and under- or over-treatment.

Due to the discordance of nuclear grading, the use of additional methods such as an individualized, validated biomarker may better inform shared decision-making for DCIS patients, as has been utilized for invasive breast cancer for over a decade.

Contact: Troy Bremer tbremer@preludedx.com

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