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# Magnetic Resonance Imaging and a 12-Gene Expression Assay to Optimize Local Therapy for Ductal Carcinoma In Situ: 5-year clinical outcomes of ECOG-ACRIN 4112

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# Disclosure Information

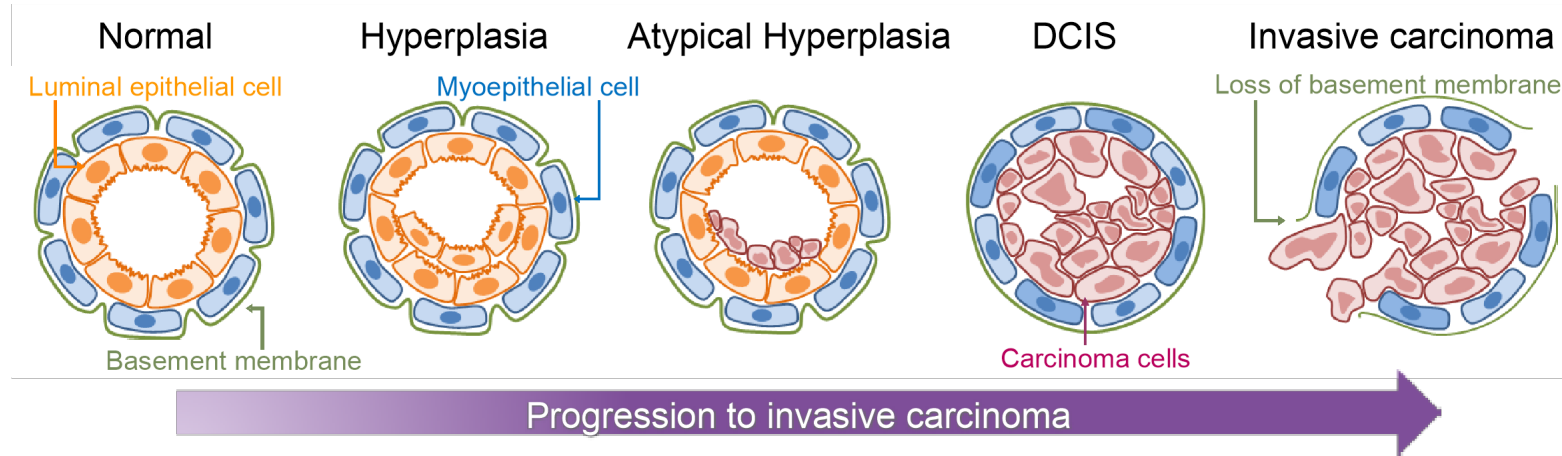
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## Seema Ahsan Khan

I have no financial relationships to disclose

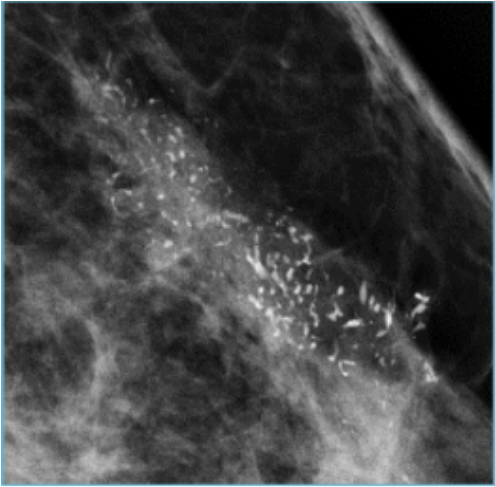
# Ductal Carcinoma in Situ (DCIS)



A non-obligate precursor of invasive breast cancer with variable biology and natural history

- Comprises 20% of screen-detected malignancy.
- Its main adverse outcome is subsequent invasive breast cancer.
- The standard of care includes surgical resection for all, radiotherapy if the breast is conserved, and endocrine therapy if DCIS is ER+.
- Women with DCIS remain at higher risk of breast cancer death in the U.S.

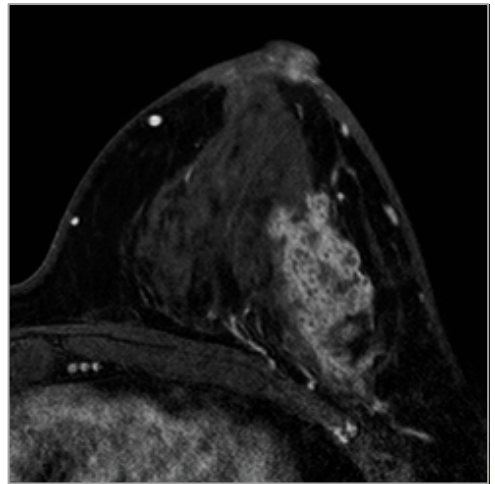
# Surgical decisions for DCIS



Lesion detected on Mammogram  
DCIS diagnosed on core needle biopsy

Breast conserving resection?

Mastectomy?

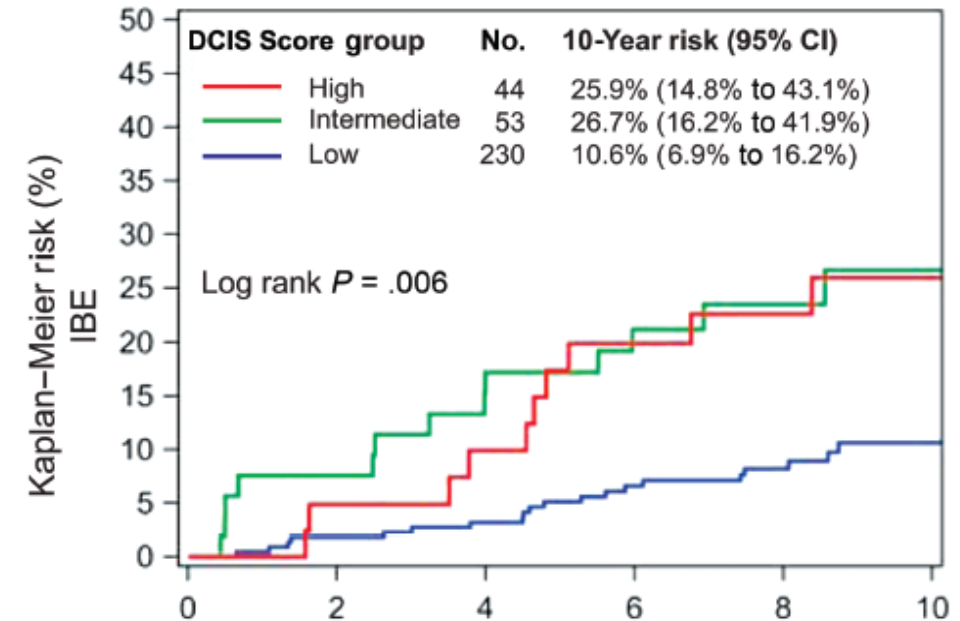
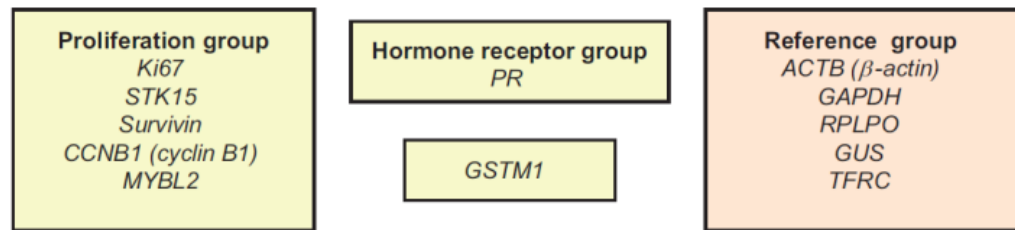


- MRI more sensitive for DCIS detection than mammography<sup>1</sup>
  - Better for higher grade than for low grade DCIS
- More accurate for identification of additional occult disease<sup>2</sup>
- Utilization is variable across sites
- Conflicting data on mastectomy and re-excision rates<sup>3,4,5,6</sup>

# Radiotherapy decisions for DCIS

## DCIS Score estimates risk of ipsilateral breast events

-12-gene assay derived from 21-gene recurrence score (Oncotype)



- Initially evaluated in 327 participants of ECOG 5194, a Phase II single arm trial of DCIS patients undergoing WLE alone. Solin LJ et. al., *JNCI* 2015
- Subsequently validated in a population-based cohort to show independent prognostic value for risk of DCIS and invasive recurrence. Rakovitch E et. al. *Breast Cancer Res Treat* 2015



# ECOG-ACRIN E4112

## Goals

- Among patients with DCIS who are candidates for wide local excision based on standard mammographic imaging and physical examination, to determine the proportion of patients undergoing mastectomy following MRI
    - Published, Lehman et. al., JAMA Oncol 2016
  - **To estimate 5 and 10 year ipsilateral breast event (IBE) rates** in patients treated with wide local excision for DCIS after MRI-guided surgery, and selective use of post operative radiotherapy.
    - **Low DCIS Score : recommendation to omit radiation**
    - **Intermediate-high DCIS score: recommendation to undergo radiation**
- current analysis, reporting 5-year IBE rates**

# E4112 Schema & Eligibility

March 2015-Apr 2016

## Inclusion

Women with core biopsy-proven unilateral DCIS within the past 4 months

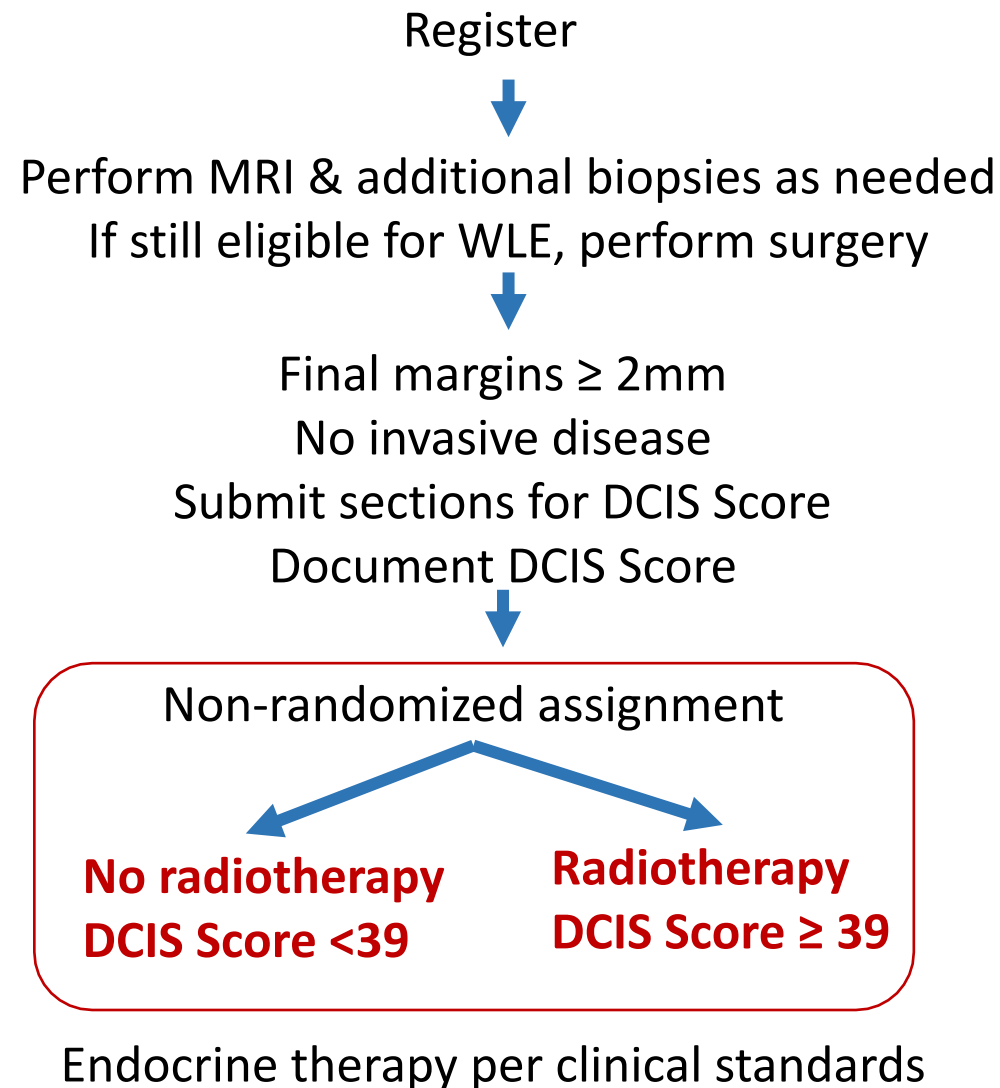
No microinvasion

Breast conservation was feasible based on conventional imaging

Disease resectable in a single specimen

No prior history of invasive breast cancer or DCIS

No use of anti-estrogens in prior 3 months

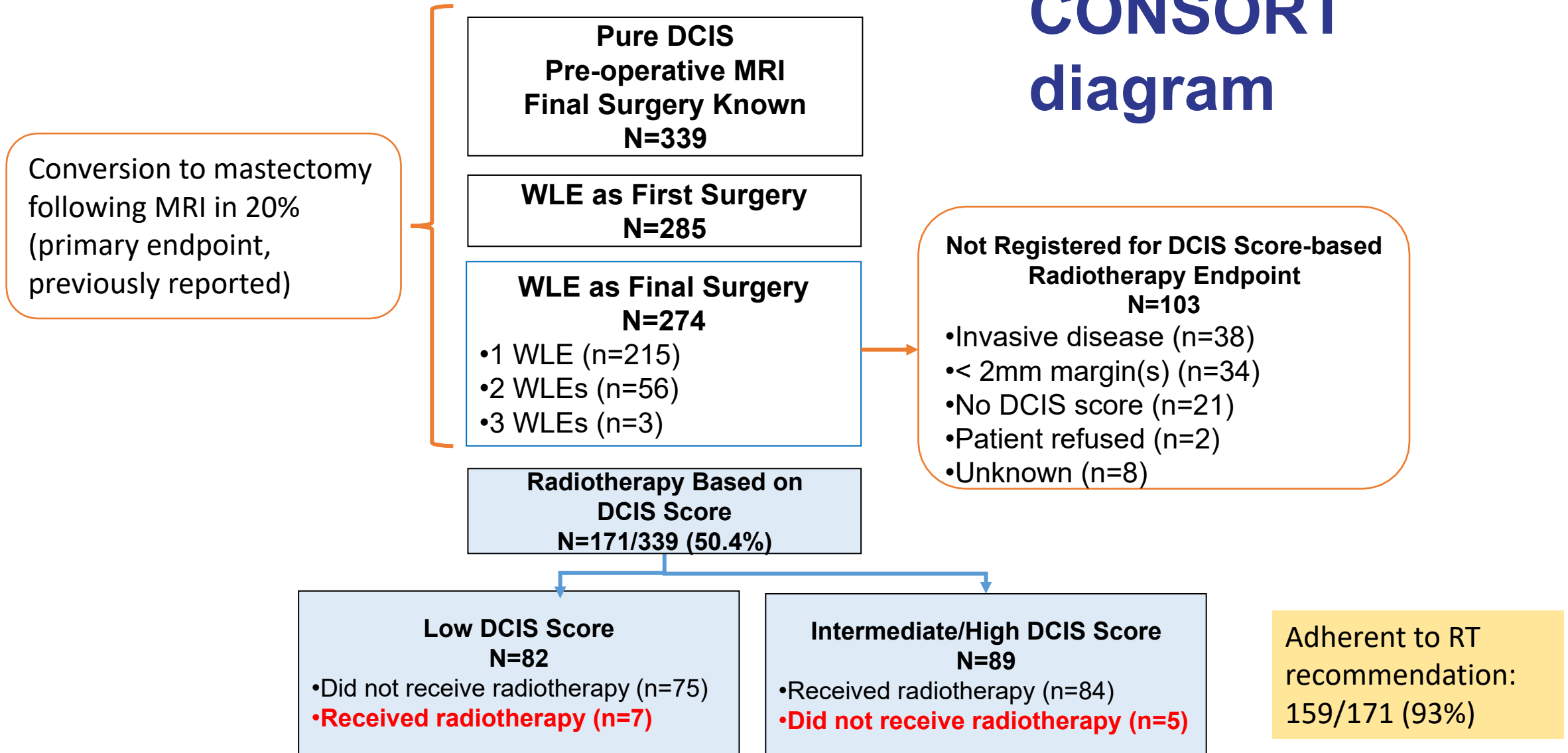


# Statistical Methods for IBE analysis

- Kaplan-Meier survival curves for the time-to-IBE
- Point estimates of the 5-year IBE rate with 95% CIs
- Analyses performed on
  - **All 171 participants** whose final surgery was WLE, margins  $\geq 2$  mm, and DCIS score was available for RT recommendation.
  - **Participants adherent** to DCIS Score-based RT recommendation,
  - **Subsets defined by age** at the time of DCIS diagnosis (<50 years versus  $\geq 50$  years)



# CONSORT diagram

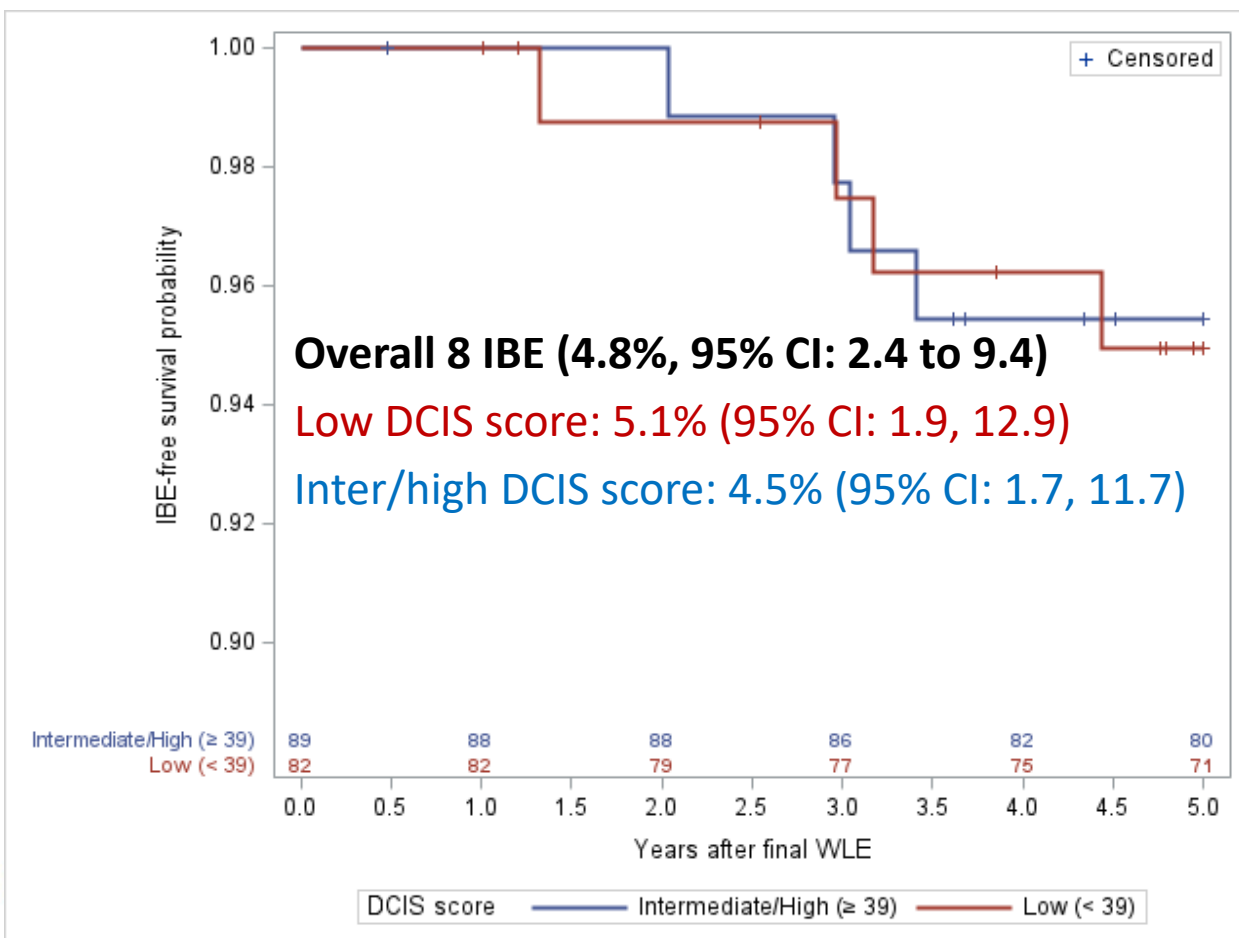


# Participant Characteristics stratified by DCIS Score

Variable	Participants who received a radiotherapy recommendation based on DCIS score (N=171)	
	DCIS score < 39(N=82)	DCIS score ≥ 39 (N=89)
Median age , N (%)	59 (51-68)	61 (54-66)
Median MRI size (IQR), mm	15 (10-23) <sup>a</sup>	19 (14-26) <sup>b</sup>
ER positive, N (%)	72 (87.8)	65 (73.0)
PR Positive, N (%)	66 (80.5)	43 (48.3)
DCIS nuclear grade, N (%)		
Low	17 (20.7)	3 (3.4)
Intermediate/high	49 (59.8)	78 (87.6)
Received endocrine therapy, N (%)		
Yes	61 (74.4)	49 (55.1)
No	16 (19.5)	31 (34.8)
Not reported	5 (6.1)	9 (10.1)

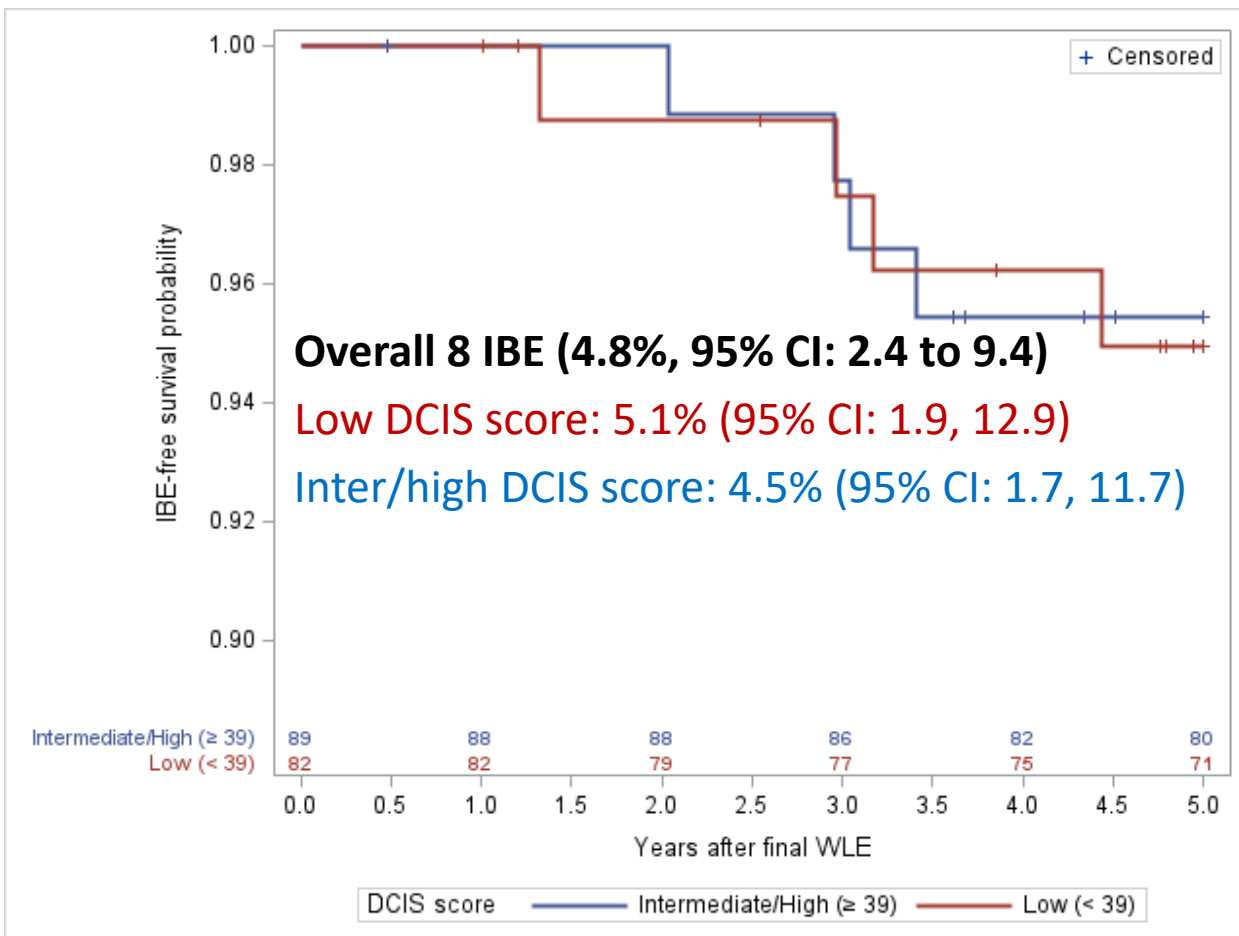
# Ipsilateral breast events at median follow-up of 5 years

Participants who received a radiotherapy recommendation based on DCIS score (N=171)

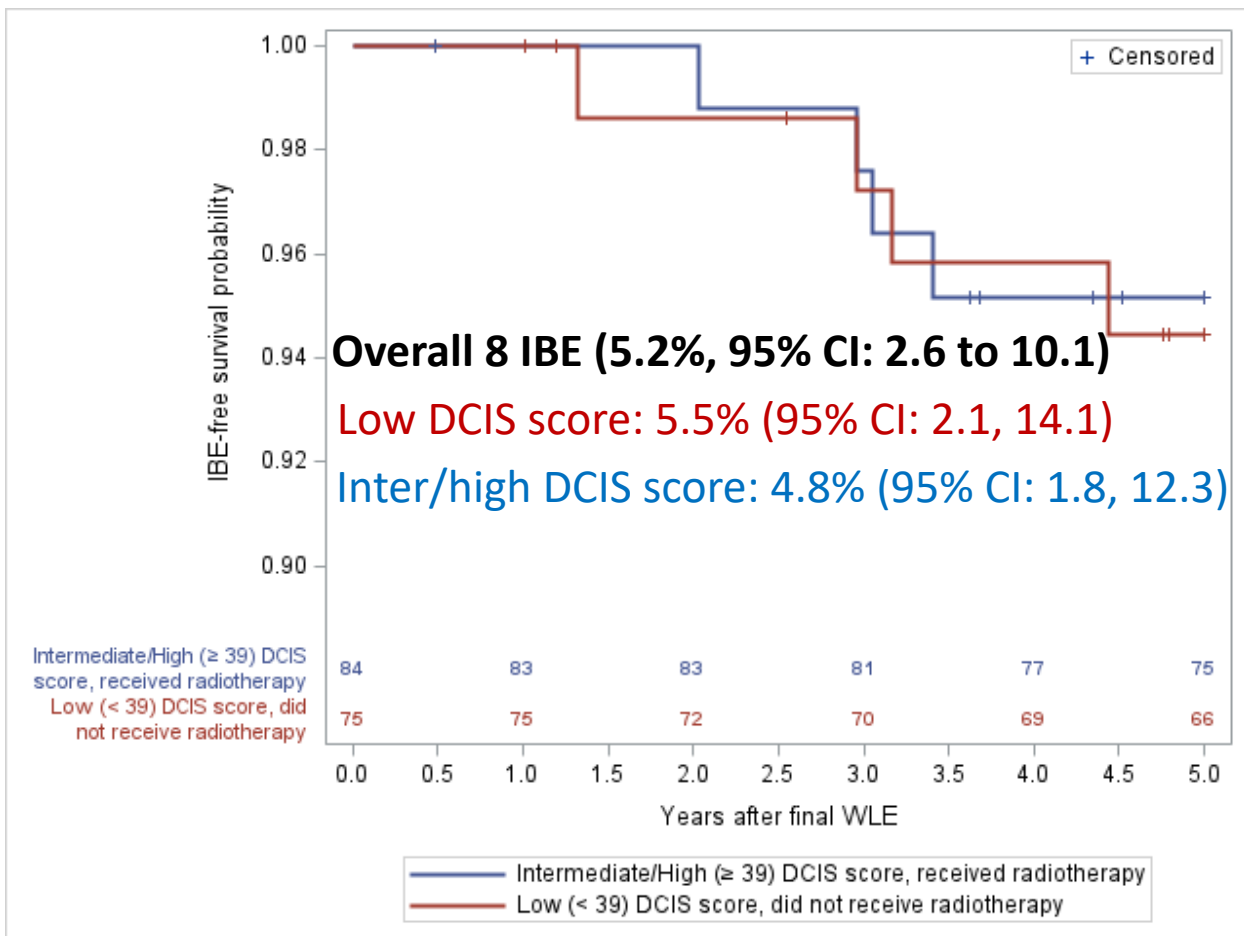


# Ipsilateral breast events at median follow-up of 5 years

Participants who received a radiotherapy recommendation based on DCIS score (N=171)



Participants who adhered to their DCIS score-based radiotherapy recommendation (N=159)



# Results: Ipsilateral breast events (IBE) by age

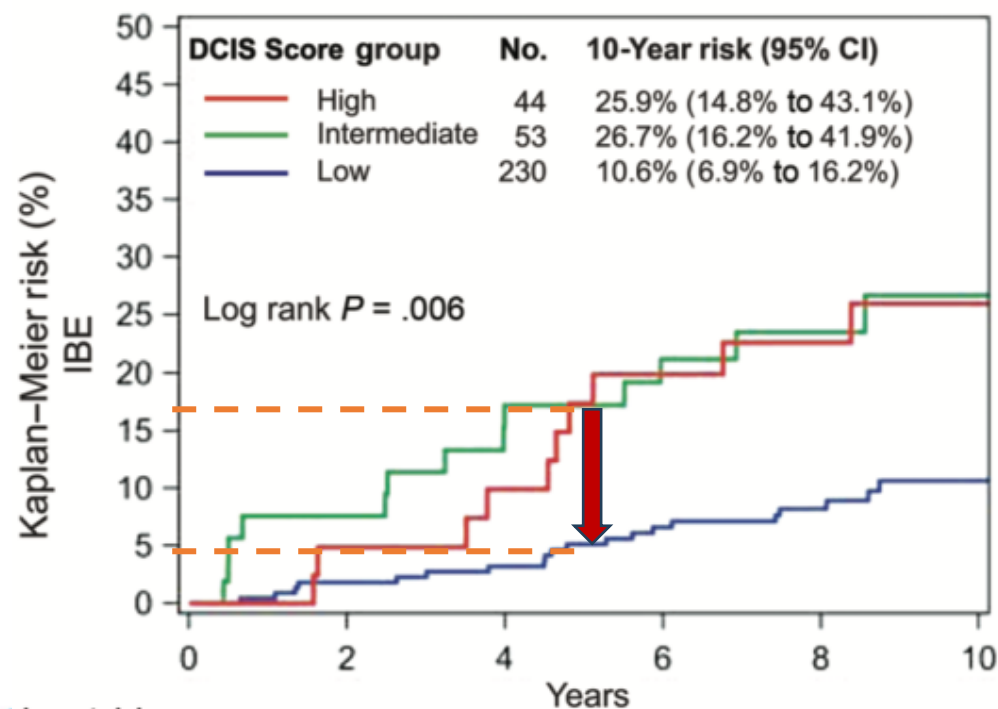
Age < 50 years (N=33)					Age ≥ 50 years (N=138)				
5-year IBE	Low DCIS score		Intermediate/High DCIS score		Low DCIS score		Intermediate/High DCIS score		Total
	6.7% (95% CI 1.0, 38.7).		5.6% (95% CI 0.8, 33.4)		4.7% (95% CI 1.5, 13.8)		4.3% (95% CI 1.4, 12.7).		
	No RT	RT	No RT	RT	No RT	RT	No RT	RT	
Yes	1	0	0	1	3	0	0	3	8
Histology	Invasive			Invasive	1 invasive			1 invasive	
No	12	2	3	14	59	5	2	66	163
Total	13	2	3	15	62	5	2	69	171



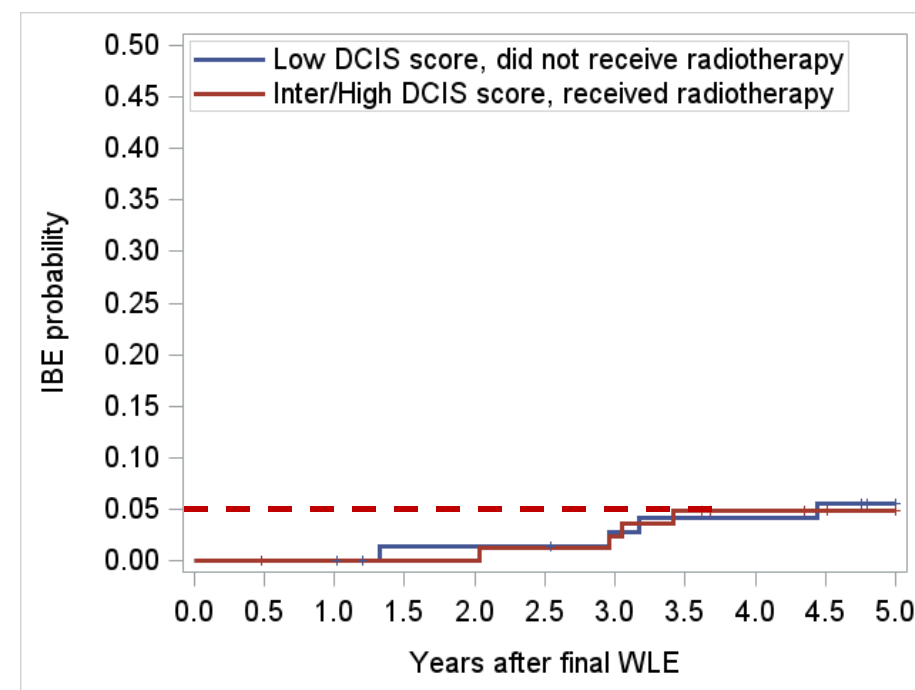
# E4112 in the context of previous data

## Size and grade for DCIS therapy vs. DCIS Score

E5194: 5-year IBE rate stratified by DCIS Score



E4112: 5-year IBE rate stratified by DCIS Score



# Limitations

- In this phase 2 trial, powered to test feasibility of DCIS decision-making based on advanced imaging and a molecular score, **IBEs are infrequent and confidence intervals for these are correspondingly wide.**
- We projected that about 250 patients will reach the radiotherapy/no radiotherapy decision node in this trial. **Attrition following completion of wide local excision was higher than expected.**
- The **potential reduction in IBE rate with radiotherapy in the low DCIS Score group cannot be estimated within E4112.**
- The **small number of women aged <50 years** limits the applicability of data to this age group.
- **Lesion size was under 2.5 cm for 75% of patients in this trial**, therefore our results apply best when DCIS size is under 2.5 cm.

# Conclusion

- DCIS Score identified ~50% as eligible for omission of radiation therapy following MRI and successful BCS.
  - Adherence to RT recommendations was 93% (159/171)
- Women with intermediate/high Score DCIS who received radiotherapy experienced an IBE rate that was approximately two-thirds lower than previously reported.
- When DCIS Score was low, 5-year IBE rate was ~5%, as in prior studies where RT omission was based on low-grade or low Score DCIS.
- Analysis of 10-year IBE outcomes from E4112 is planned, and larger prospective studies are under consideration.

# Acknowledgments

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  - Connie Lehman, MD – Breast Committee Imaging Chair at inception and study PI
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  - In memoriam – Larry Solin, MD



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