Ductal Carcinoma In Situ with emphasis on pathology

classification
biomarkers

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Ductal carcinoma in situ (DCIS)

- Definition (WHO 2012)
  - A neoplastic proliferation of epithelial cells confined to the mammary ductal-lobular system and characterized by subtle to marked cytological atypia and an inherent but not necessary obligate tendency for progression to invasive breast cancer.

- Clinical Presentation:
  - Palpable mass
  - Pathological discharge from the nipple with or without a mass
  - Paget disease of the Nipple

- 80-85% of DCIS are detected mammographically in the absence of clinical findings primarily by the identification of microcalcifications.

DCIS, clinical course and prognosis

- DCIS is a non obligate precursor for invasive breast cancer and a heterogeneous disease

- Risk factors
  - Family history of breast cancer
  - Elevated BMI after menopause
  - Nulliparity, late age at first birth, late menopause
  - High mammographic breast density

- From 47%-86% of untreated DCIS will reportedly never progress to invasive disease

- Low breast cancer specific mortality among women with DCIS (1%-2.6% after 10 years).

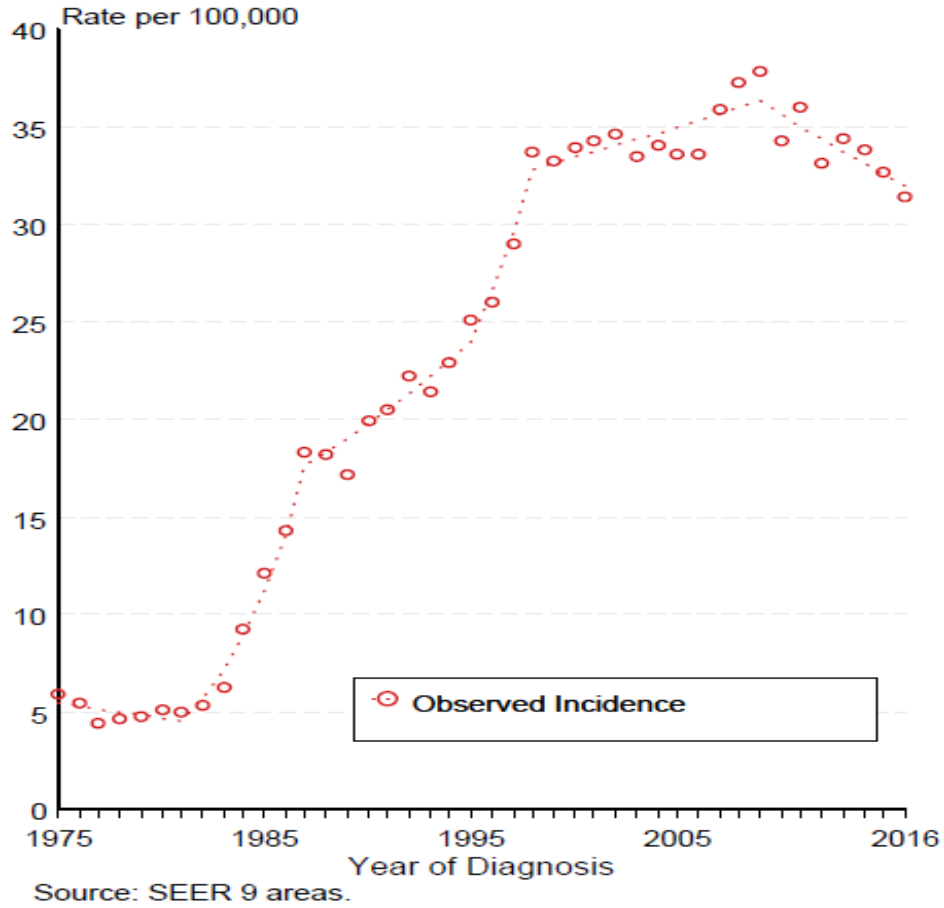
- Interval between DCIS and the development of invasive carcinoma is shorter for high grade DCIS (5 years) than low grade, slow growing DCIS (>15 years).

The incidence of DCIS increased after the advent of mammography screening

Before the introduction of mammography screening DCIS accounted for 2-3% of breast cancers.

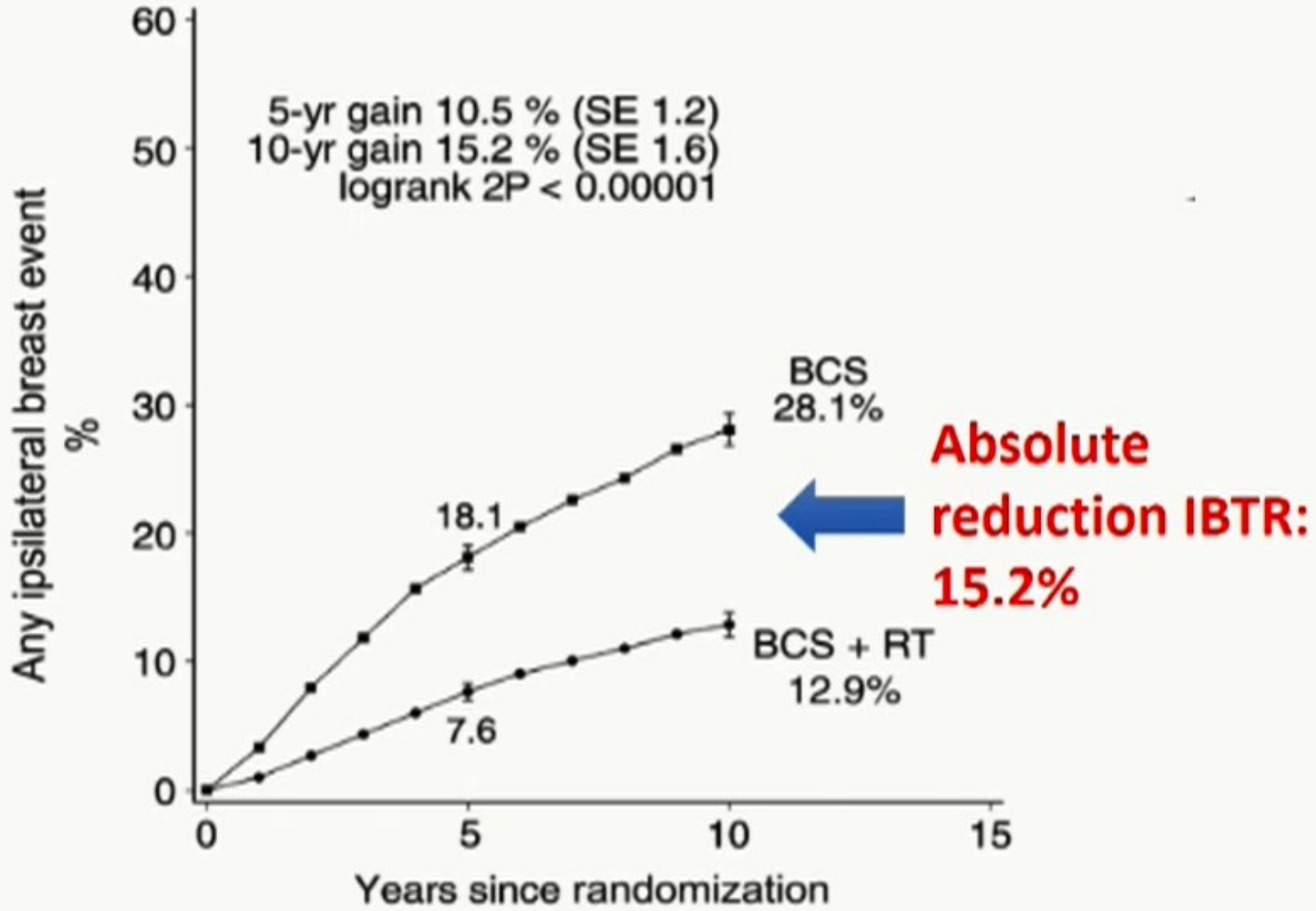
Presently, DCIS represents 13%
of the screen-detected malignant lesions in Denmark.
2017: app. 440 patients with DCIS (+/-screen-detected)
Danish Quality Database for Mammography Screening 2017
Danish Pathology Registry
DBCG

Data from the SEER database – National Cancer Institute (US) demonstrating the increase in DCIS from 1975 to in 2016 (rate/100.000)



https://seer.cancer.gov/csr/1975_2016/results

EBCTCG Overview of lumpectomy +/- RT for DCIS

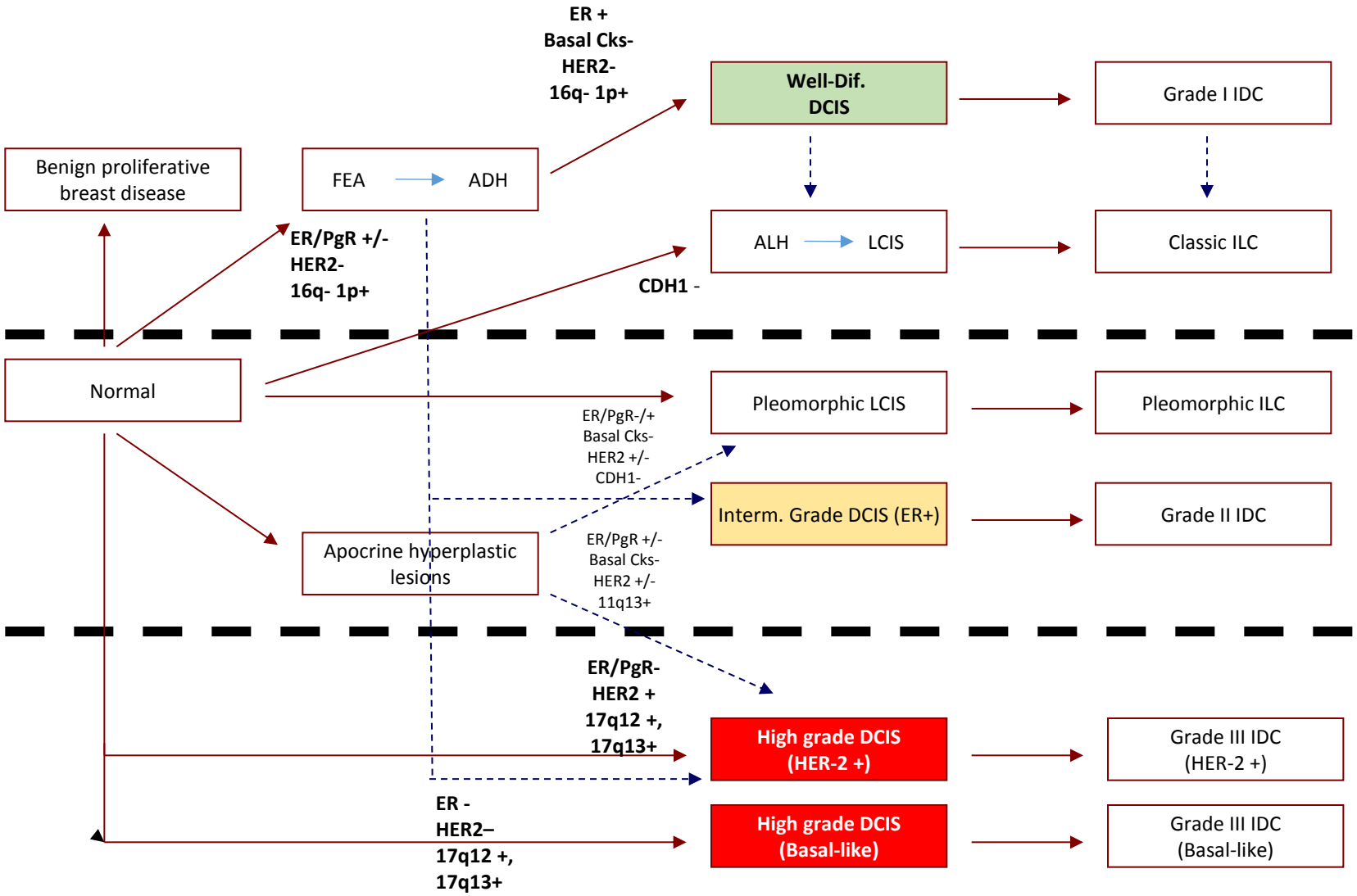


Absolute reduction IBTR: 15.2%

- Overall > 50% proportional reduction in ipsilateral events with radiation following lumpectomy
- Absolute magnitude of the reduction was dependent on baseline recurrence risk
- Benefit was independent of patient age, tumor size, margin status

EBCTCG. *J Natl Cancer Inst Monogr*. 2010.

Molecular evolution of breast cancer

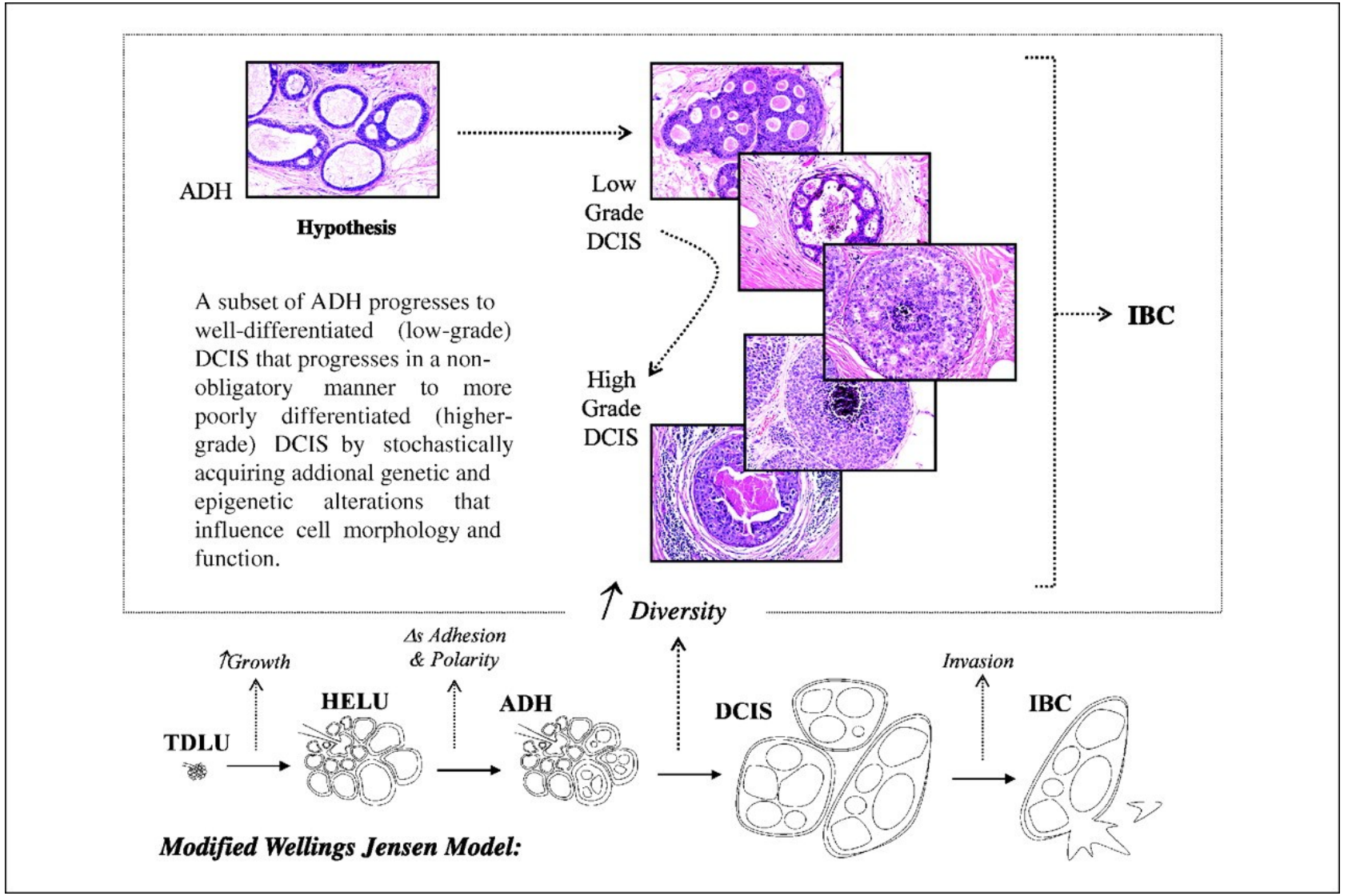


Low grade

High grade

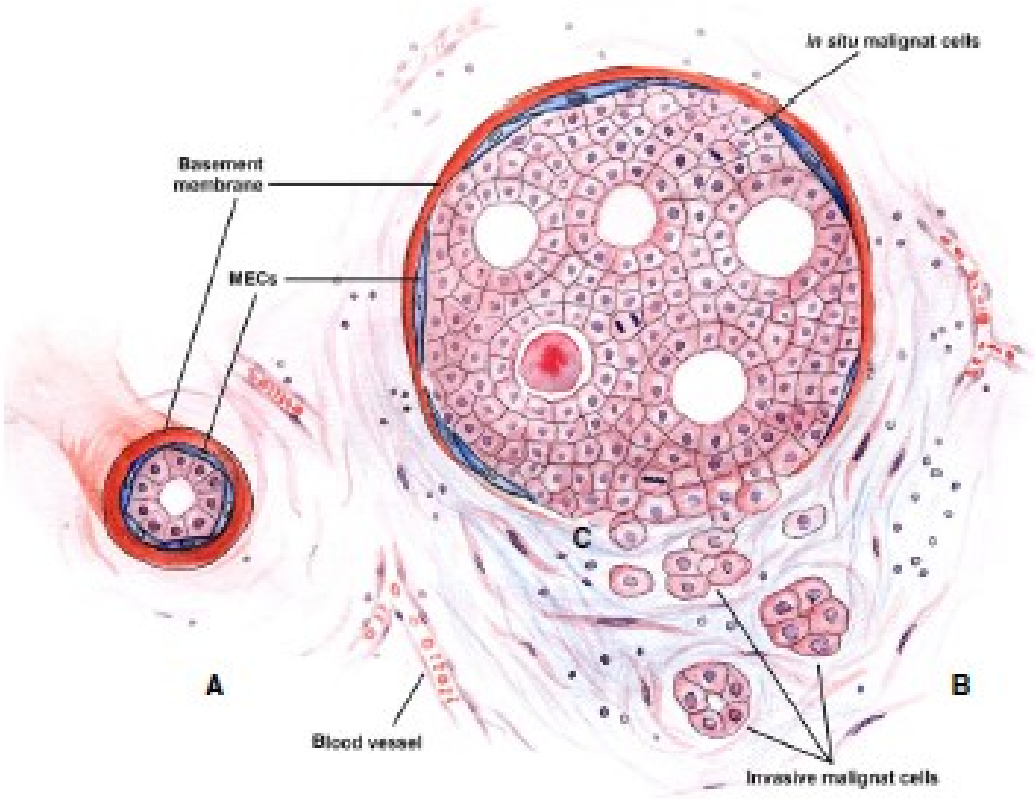
Adapted from Simpson et al. J Pathol 2005;205:248-254

Revised Wellings and Jensen model of human breast cancer evolution.

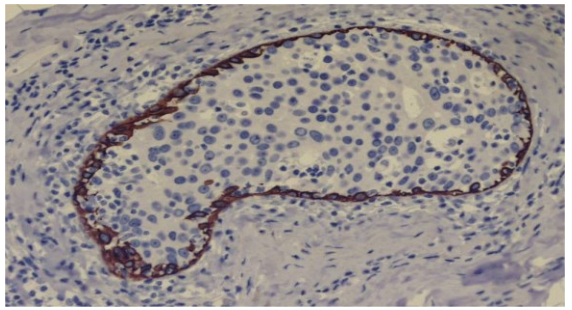


D. Craig Allred et al. Clin Cancer Res 2008;14:370-378

The epithelial-stroma interaction in tumor progression (cross talk) is an important feature of invasion



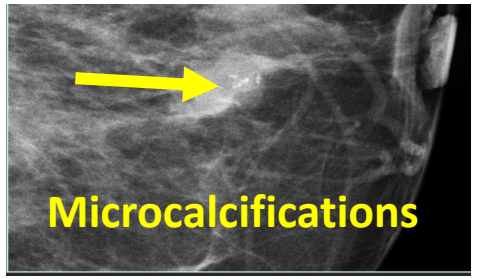
The myoepithelial cell (MEC) layer is intact in DCIS.
Identification of MEC by immunohistochemistry.

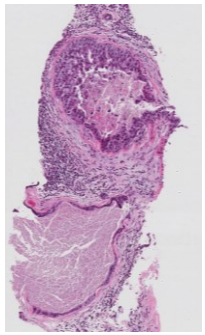


MECs have natural tumor suppressor functions and express several tumor suppressor proteins.
Rakha et al. Histopathology 2018, 72, 1075-1083

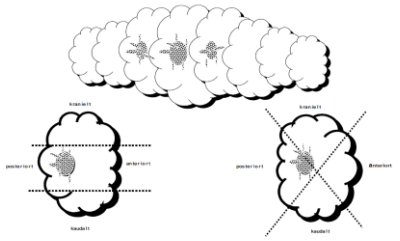
Molecular properties that differentiate DCIS and IDC involve the microenvironment.
Subtype-specific gene signatures may have the potential to predict invasiveness, hence prognosis.
Lesurf et al., 2016, Cell Reports 16, 1166–1179

Diagnostic procedure and processing in the pathology lab.



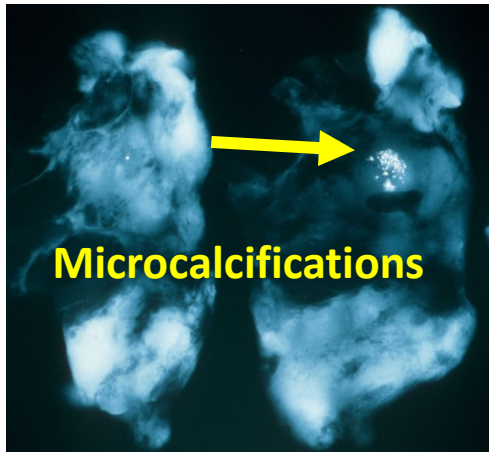


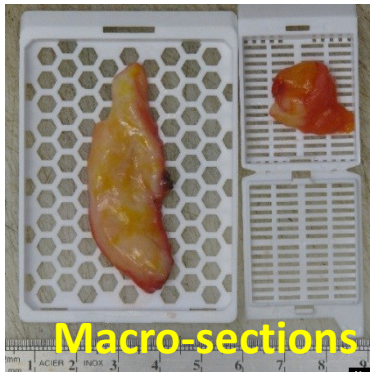
Core needle biopsy



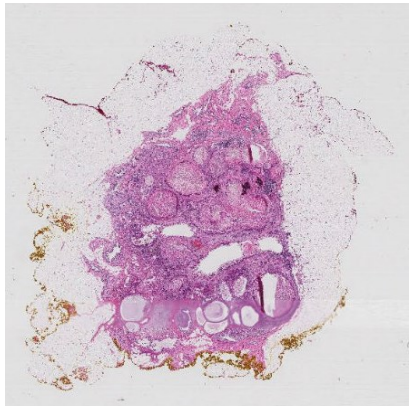
BCS specimen processed prior to fixation – correct orientation and standardized sectioning mandatory

Confirmation of microcalcifications by image analysis





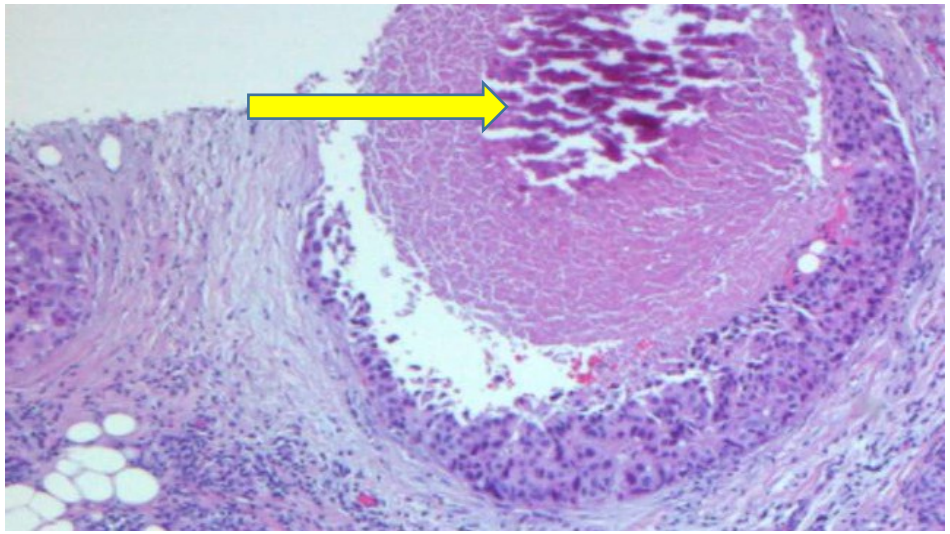
Microscopy



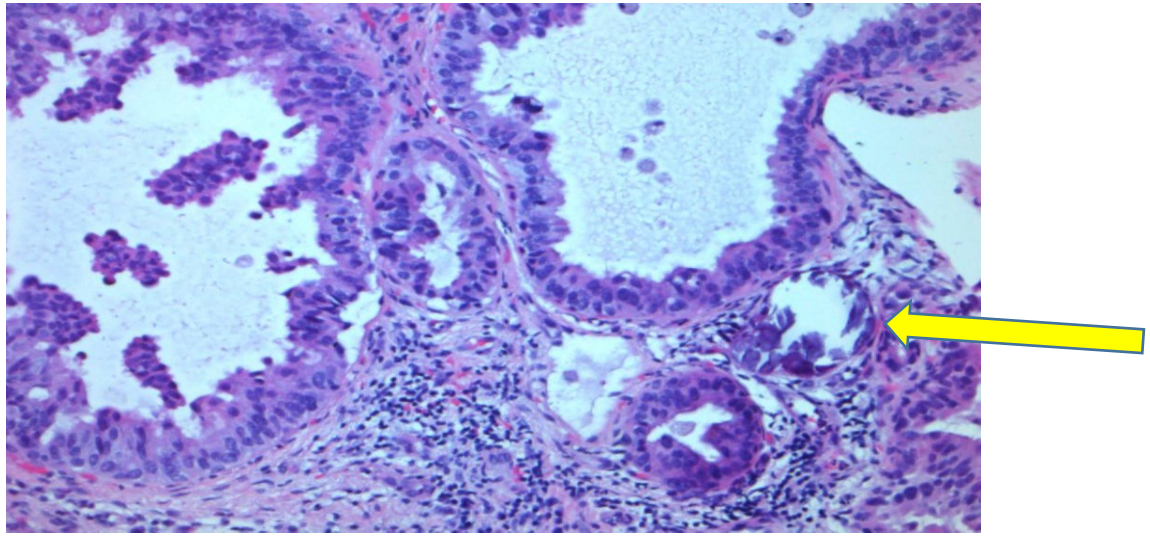
Pathology Report:

- **Identification of microcalcifications**
- **Classification**
- **Size**
- **Association to margins**
- **(no invasion)**

Identification of calcifications both in the neoplastic ducts and in the surrounding stroma

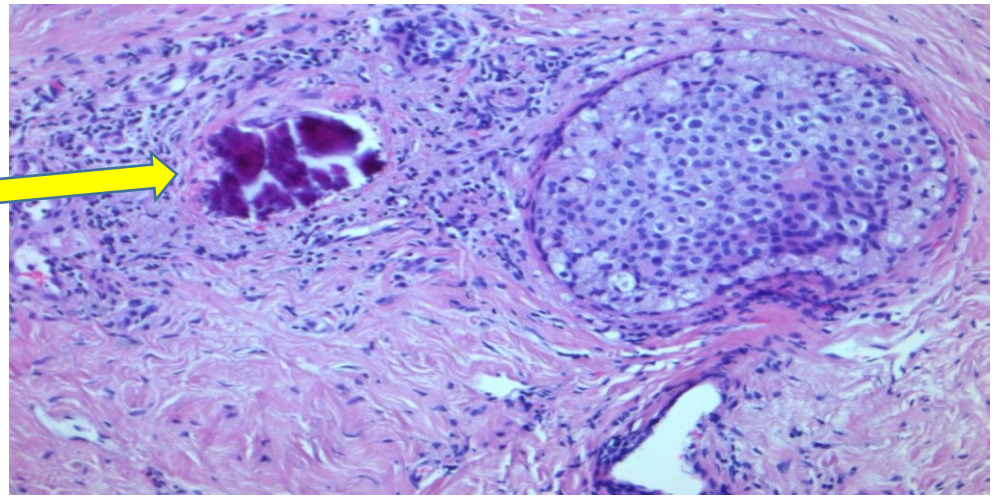


High grade DCIS



Micropapillary DCIS with calcifications

Calcification



Low grade DCIS

Diagnostic agreement among pathologist?

- 240 randomly selected cases into 4 groups of 60 cases
- 115 pathologists each randomized to 1 group of 60 cases
- Pathologists´ diagnosis compared to consensus of 3 experts

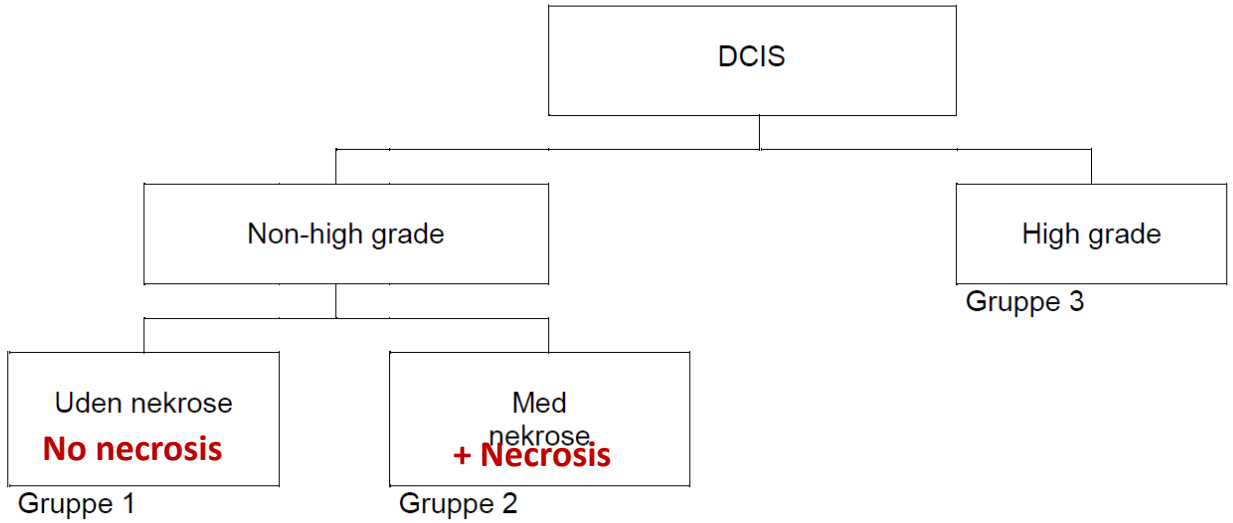
	Pathologist Interpretation vs Consensus-Derived Reference Diagnosis, % (95% CI)			
Consensus Reference Diagnosis	No. of Interpretations	Overall Concordance Rate	Overinterpretation Rate	Underinterpretation Rate
Benign without atypia	2070	87 (85-89)	13 (11-15)	
Atypia	2070	48 (44-52)	17 (15-21)	35 (31-39)
DCIS	2097	84 (82-86)	3 (2-4)	13 (12-15)
Invasive carcinoma	663	96 (94-97)		4 (3-6)

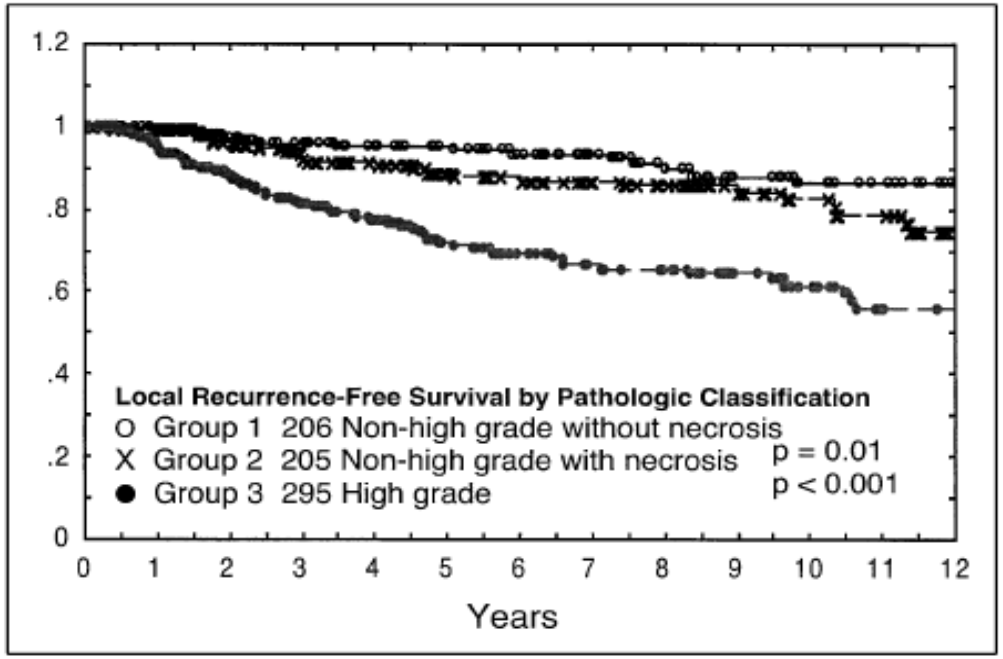
Factors associated with disagreement:
Diagnostic challenge of low grade cases
Lack of experience

Elmore et al, JAMA 2015; 313:122-32
Onega T et al, Eur J Cancer 2017; 80:39-47

Challenges associated with the ”less is more” treatment approach in DCIS

Introduction of DCIS in the DBCG guidelines in 1982 with the presently applied classification from 2004





Silverstein MJ. The American journal of Surgery 186 (2003) 337-343

The classification is based on the Van Nuys prognostic index with emphasis on nuclear atypia and the identification of intraluminal necrosis

www.dbcg.dk

Histo-pathological DCIS classification systems have documented inferior reproducebility

- In general the classification systems are based mainly on the extent of cytonuclear atypia

- 23 pathologists evaluated 33 cases of DCIS according to 5 different systems
    - Van Nuys classification highest overall kappa value: 0.42
    - The classification system based solely on the presence of necrosis had the lowest kappa value: 0.34

      Hum Pathology 1998; 29:1056-1062

- Even poorer reproducebility has been reported when focusing on growth pattern alone

  Sloane JP et al. Eur J Cancer 30A:1414-1419

- A significant inter and intra-laboratory variation in DCIS grading has been reported in the Netherlands
    - Annual benchmarking of histologic grading has been considered by the Dutch Society for Pathology

  Dooijeweert C . Breast Cancer Research and Treatment (2019) 174:479–488

Identification of subgroups who could be spared radiotherapy?

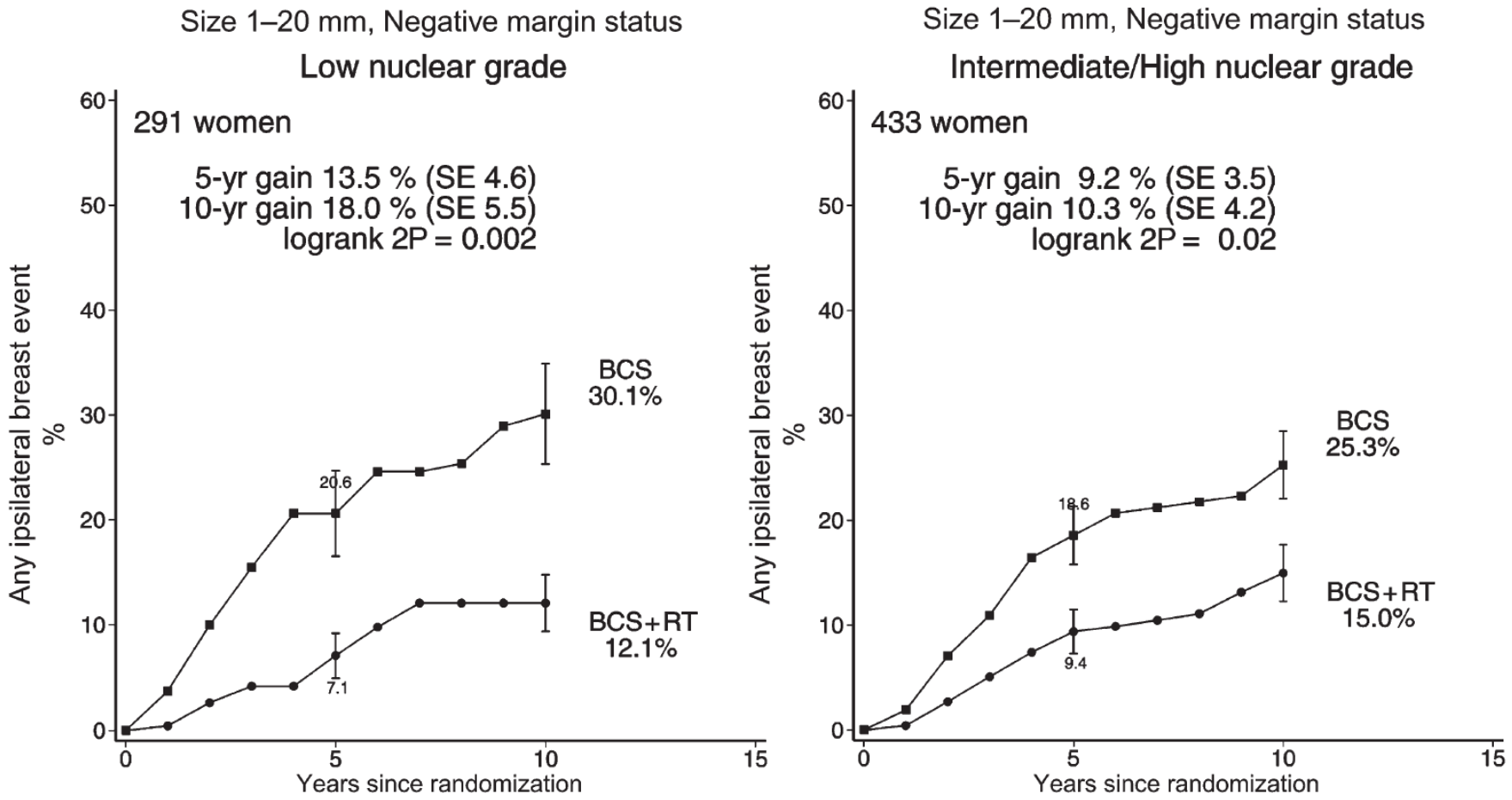


Figure 10. Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 724 women with negative margin status and pathological tumor size 1–20 mm according to nuclear grade: 10-year cumulative risks of any ipsilateral breast event.

Vertical lines indicate 1 SE above or below the 5 and 10 year percentages.

EBCTCG overview 2010 JNCI Monogr.

Upgrade to high grade DCIS or upstage to invasive cancer

- DCIS N=307 on core needle biopsy, then surgically removed

	Upgrade rate to a higher nuclear grade**	*p* value	Upstage rate from DCIS to invasive disease	*p* value
Total	12% (13/110)		18% (54/307)	
Age (year)		0.34		0.78
≤50	18% (3/17)		19% (11/57)	
>50	11% (10/93)		17% (43/250)	
Race		0.66		0.86
Caucasian	10% (7/71)		18% (35/198)	
Black	14% (5/37)		17% (16/96)	
Other	50% (1/2)		21% (3/14)	
Nuclear grade		0.09		<0.01*
Low	27% (4/15)		7% (1/15)	
Intermediate	9% (9/95)		7% (7/95)	
High	N/A		23% (46/197)	
ER		0.55		<0.01*
Positive	11% (11/103)		14% (36/249)	
Negative	29% (2/7)		31% (18/58)	
PR		0.51		<0.01*
Positive	10% (10/98)		11% (24/216)	
Negative	25% (3/12)		33% (30/91)	

Data are expressed as row percentage with fraction in parentheses

* *p* value <0.05

** Among cases of low or intermediate nuclear grade at core needle biopsy

ER estrogen receptor; *PR* progesterone receptor; *N/A* not applicable

Ann Surg Oncol. 2017 November ; 24(12): 3534–3540.

Upstage to invasive cancer

- DCIS N= 1271 by CNB followed by surgical excision (10 year retrospective analysis)

Table 2. Summary of Studies Evaluating Ductal Carcinoma In Situ (DCIS) Nuclear Grade on Core Needle Biopsy With Upgrade to Invasion on Follow-up Surgery

Source, y	Total DCIS on CNB	Overall Upgrade Rate, %	Grade of DCIS on CNB, No. (%)			Grade of DCIS With Upgrade, No./Total (%)			DCIS Grade Significantly Correlates With Upgrade	Characteristics of Invasion Associated With LG DCIS
			LG	IG	HG	LG	IG	HG		
Present study	1271	8	200 (16)	649 (51)	422 (33)	10/200 (5)	43/649 (7)	52/422 (12)	Yes	All well or moderately differentiated IMC 6 of 10 ER+, all HER2− All pT1, 1 case with positive lymph nodes

Upstage rate: **5%** **7%** **12%**

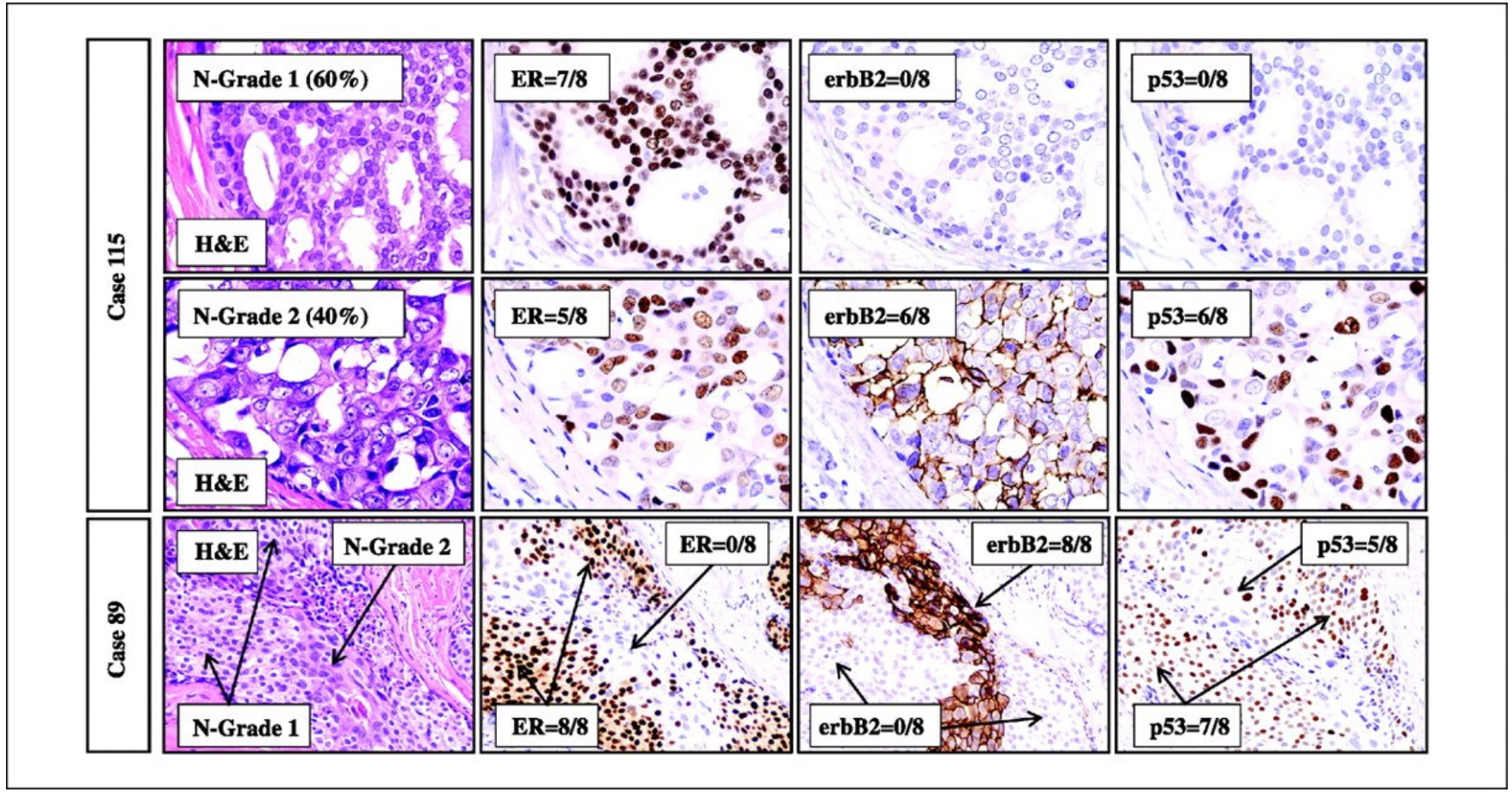
Podoll et al Arch Pathol Lab Med. 2018 Sep;142(9):1120-1126

Biomarkers in DCIS

Biological features of normal, preinvasive and invasive breast lesions

Characteristic	% Average TDLU	ADH	DCIS (Total)	DCIS (Low grade)	DCIS (High grade)	IBC	Reference(s)
ER-positive cells	25–30	90	50–75	39–90	16–74	65	Arpino 2005[36]; Irvine & Fentiman 2007[37] Chaudhuri 1993[47]
PR-positive cells	15–25	—	62	64–80	56–74	63	Arpino 2005[36]; Irvine & Fentiman 2007[37]
Erb-B2/HER-2 oncogene or protein	0	1	32	19	56	14–25	Hoque 2002[48]
EGFR	—	—	8–63	—	—	25–36	Kelloff & Sigman 2004[49]; Livasy 2007[50]; Truica 2003[51]
p53 abnormal gene or protein	0	0	20–30	0–21	3–67	40	Arpino 2005[36]; Nofech-Mozes 2005[41]
bcl-2 positive	—	—	48–56†	—	Loss of *bcl-2*	75	Quinn 1998[52‡]; Nofech-Mozes 2005[41]
Cox-2	23	—	50–67	—	—	36–63	Boland 2004[53]; Shim 2003[54]
Ki-67 overexpression (positive if > 10%)‡	—	—	—	0	33	Variable	Molino 1997[55]
Hsp-27 expression	7.4	25	61	—	—	63	Storm 1995[103]; Ioachim 2003[57]

Coexistence of multiple histological grades and biomarker phenotypes within the same DCIS



Allred DC et al. Clin Cancer Res 2008, 14:370-378

Prognostic and predictive biomarkers in DCIS

- ER+ DCIS and adjuvant endocrine treatment

- Investigational biomarkers with potential prognostic information, not ready for clinical application, i.e.:

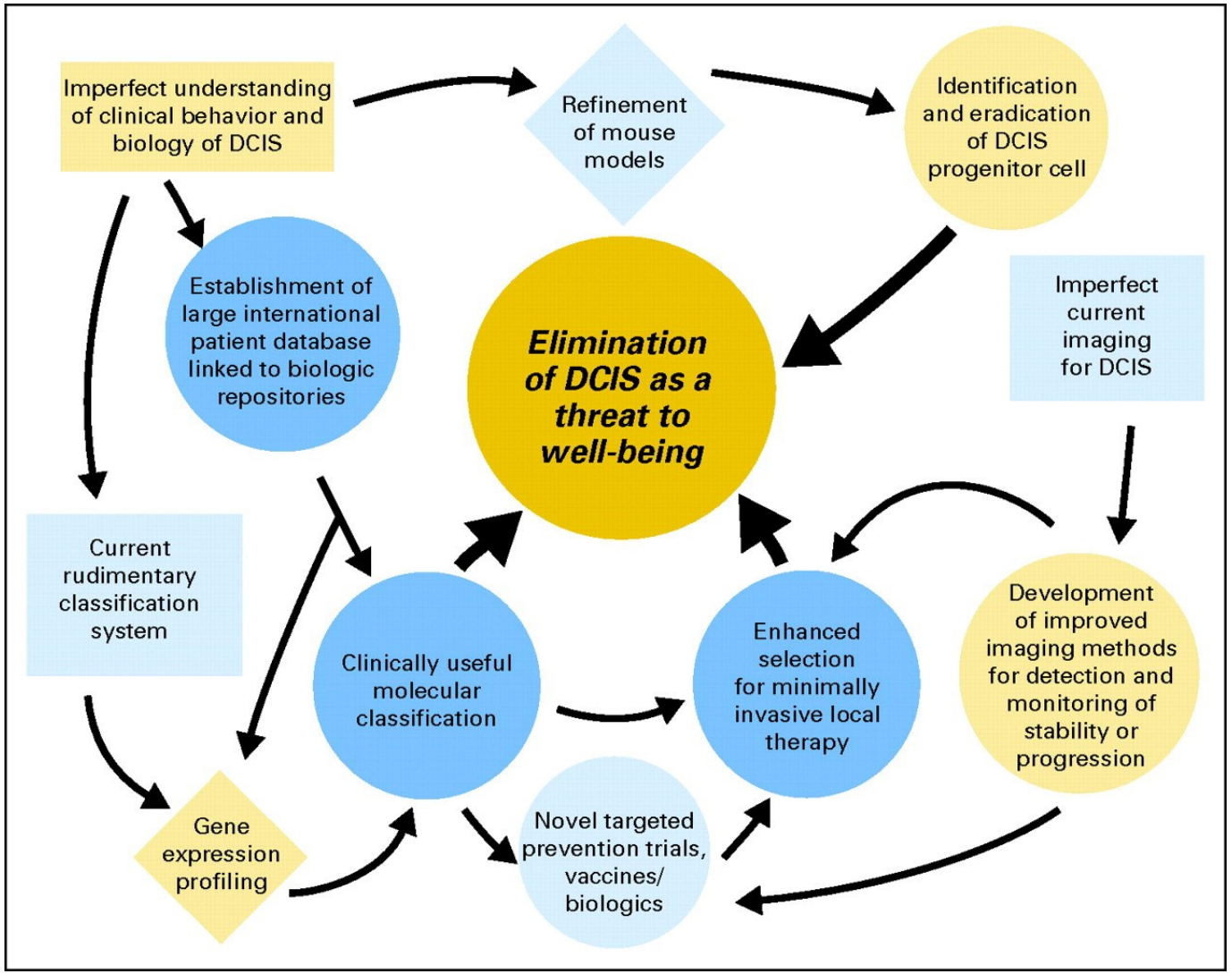
  - HER2+ (Borgquist S et. al 2015, BMC Cancer Jun 11; 15:468)
  - TILs (Diecia, M.V., Seminars in Cancer Biology (2017)
  - Ki67 (lack of analytical validity)
  - Androgen receptor

  - Genomic profiling
    - Intrinsic molecular subtype classification

- Oncotype DX Breast DCIS score

State of the science and roadmap to advance the field of ductal carcinoma in situ

Improved prognostic tools for DCIS patients are warranted to tailor therapy on an individual level



Established prognostic risk factors for any recurrence:

Young age at primary diagnosis
Family history of breast cancer
Size
Margins
Nuclear grade
Comedo necrosis

Kuerer HM. Et al. JCO 2008; 27:279-288

THANK YOU