AJCC cancer staging – 8th Edition selected highlights

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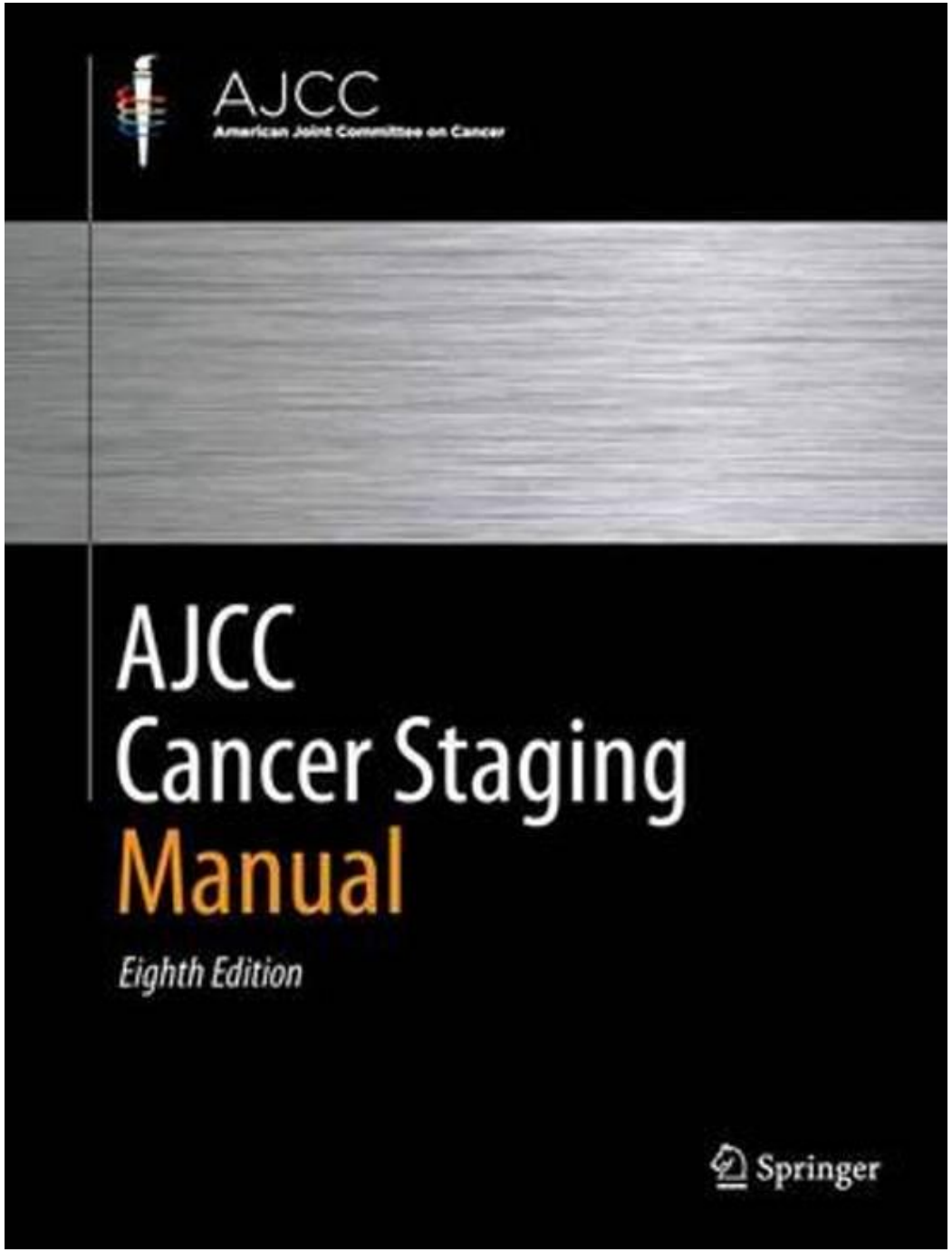

AJCC
American Joint Committee on Cancer
AJCC
Cancer Staging
Manual
Eighth Edition
Springer

Changes in AJCC-TNM8

- Changes in T, N, M definitions
- Post neoadjuvant therapy classification

- Two staging options
  - Anatomical staging (TNM categories)
  - Prognostic staging (included grade, ER, PR, HER2 and multigene panels)
    - Clinical prognostic stage: determined by TNM, tumor grade, HER2, ER and PR status based on physical examination, imaging studies and relevant biopsies
    - Pathological prognostic stage: based on clinical information, biomarker data and findings from resected tissue

TNM staging

- Tumor
- Node
- Metastasis

T category

- Rounding to the nearest mm
- Tumor >1 mm and <2 mm should be reported rounding to 2 mm (including those 1.0-1.5 mm in size)
- Microinvasion pT1mi : ≤1.0 mm
- Max invasive tumor size for estimate tumor volume
  - Small microscopic satellite foci of tumor not added to the max tumor size
- Multiple tumors - use dimension of the largest tumor
  - Size of multiple tumors is not added
  - Designated with the (m) modifier, i.e. pT1c(m) with a synchronous 1.5 cm and 0.6 cm tumor
- T4b satellite tumor nodules in the skin
  - Must be separate from primary tumor and macroscopically identified
  - Those identified only on microscopic examination do not qualify as T4b

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm).
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see section "Rules for Classification")

**Note:* Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the *AJCC Cancer Staging Manual, 8th Edition.*

LCIS

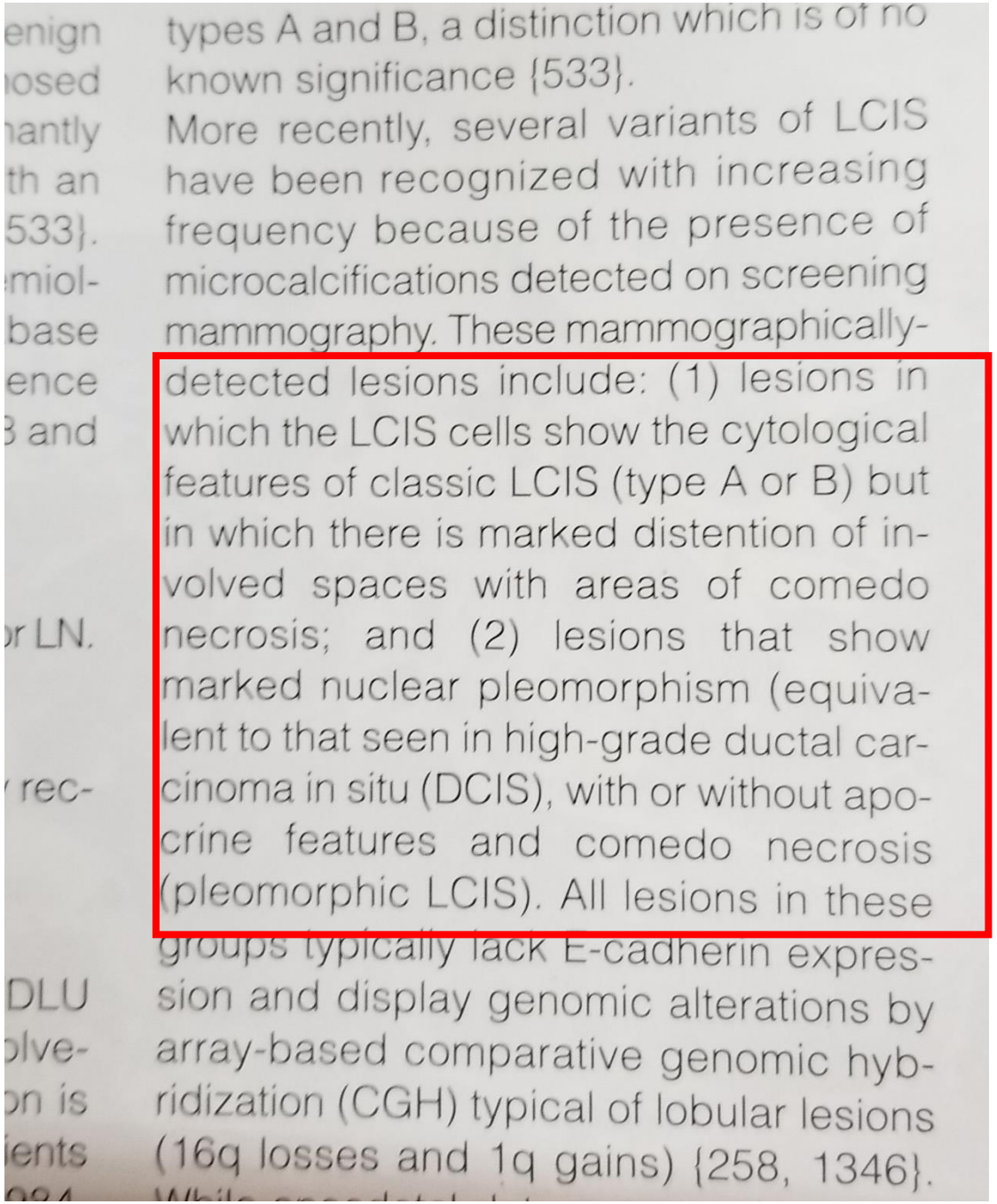
- LCIS perceived differently from DCIS
  - Extent not measured
  - B3 on CNB

- LCIS including variants (including pleomorphic) : excluded from pTis
  - Lack of level I evidence for its malignant character
  - Insufficient proof for the variants to be different
  - Now considered benign

  - (no evidence to indicate they are benign!)

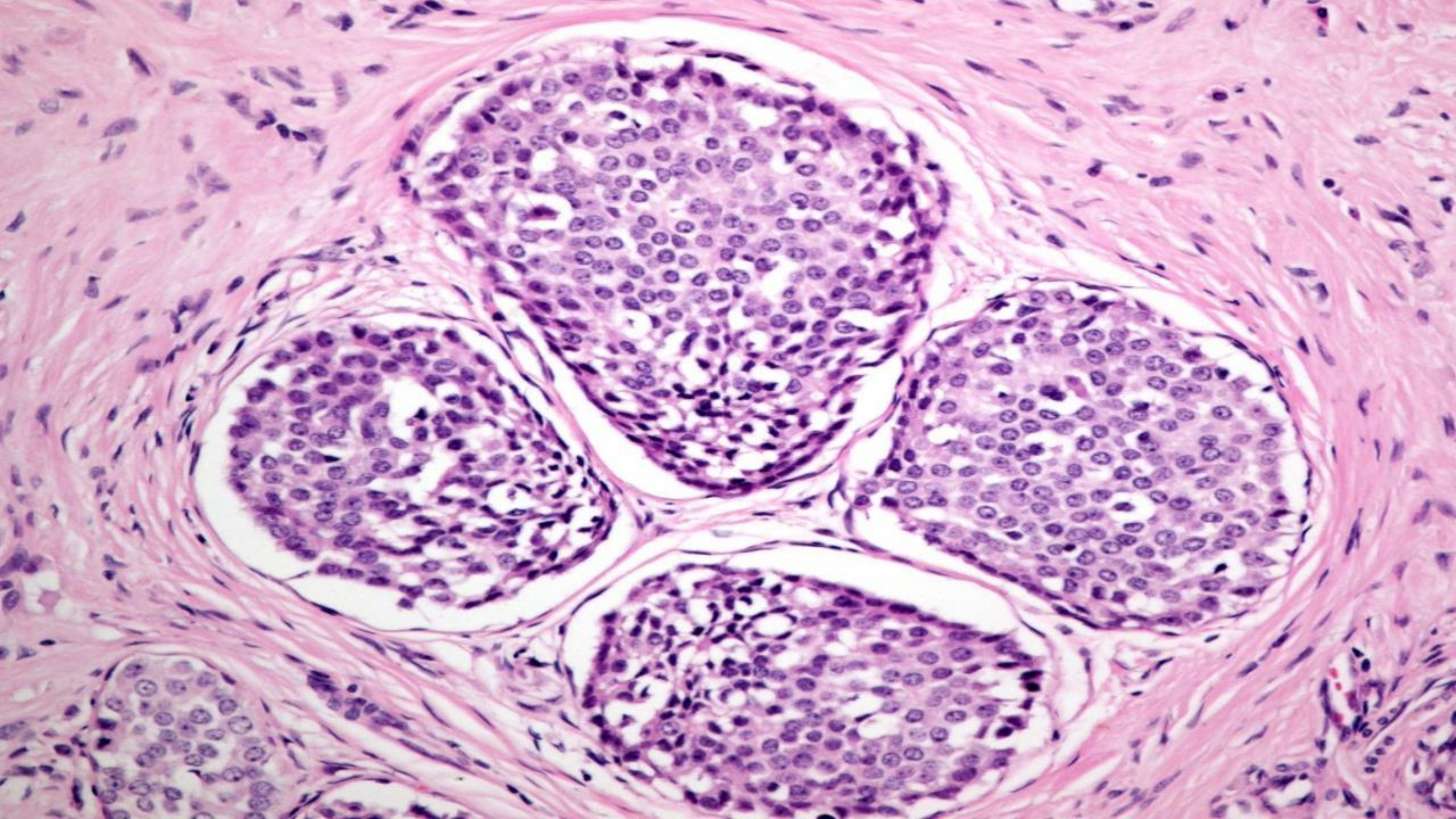
LCIS variants

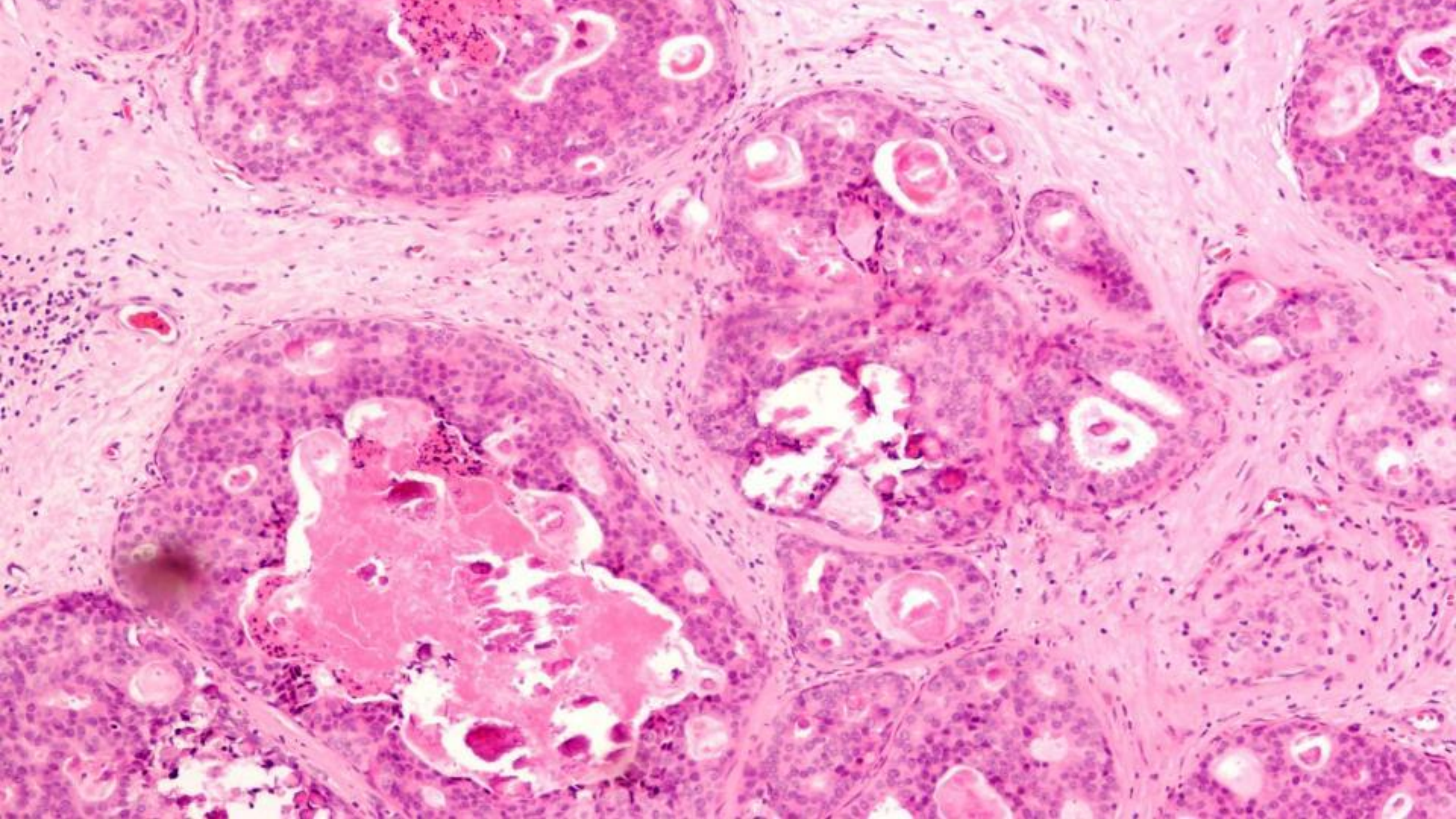
WHO 2012

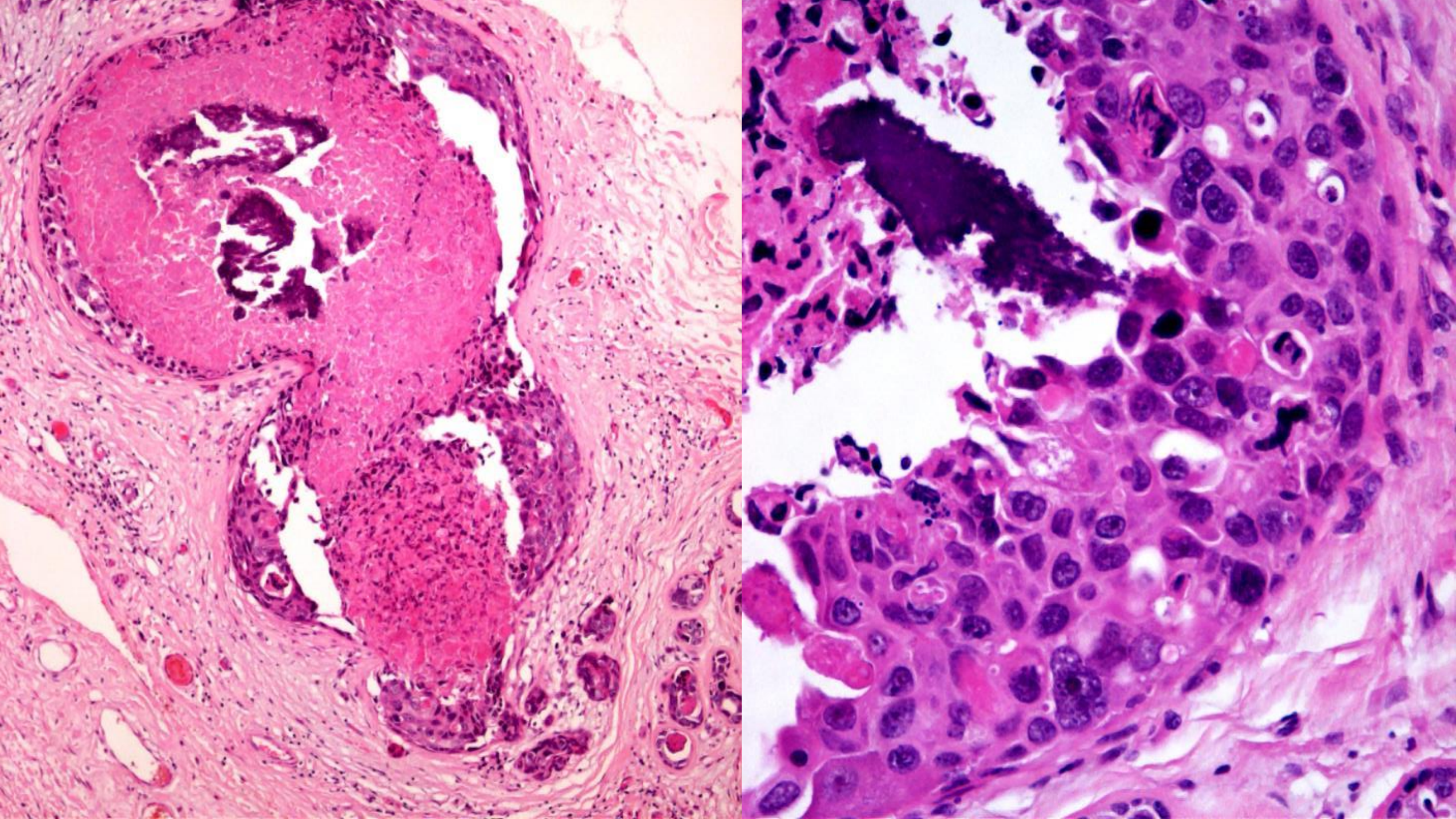


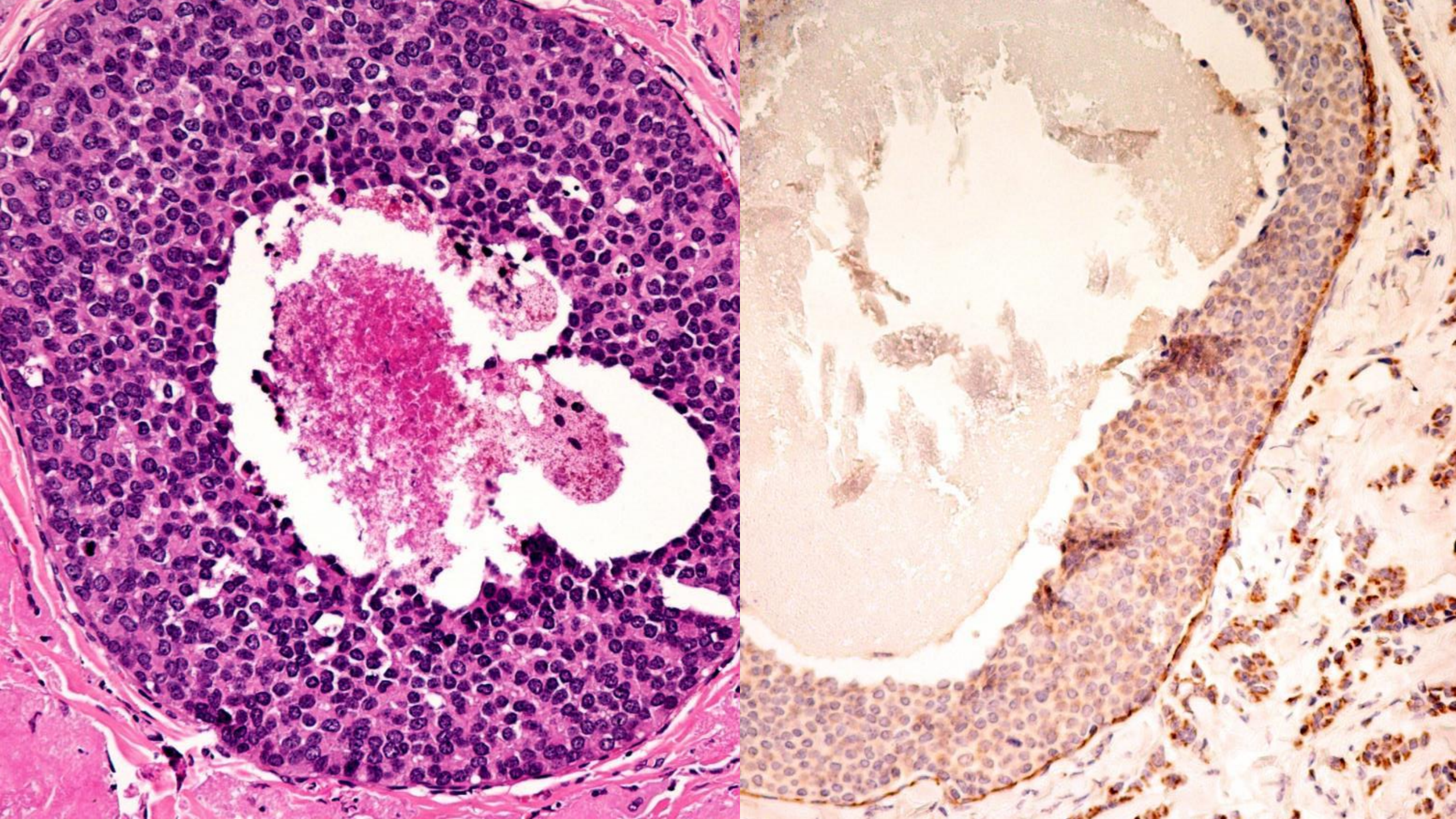
types A and B, a distinction which is of no known significance {533}.

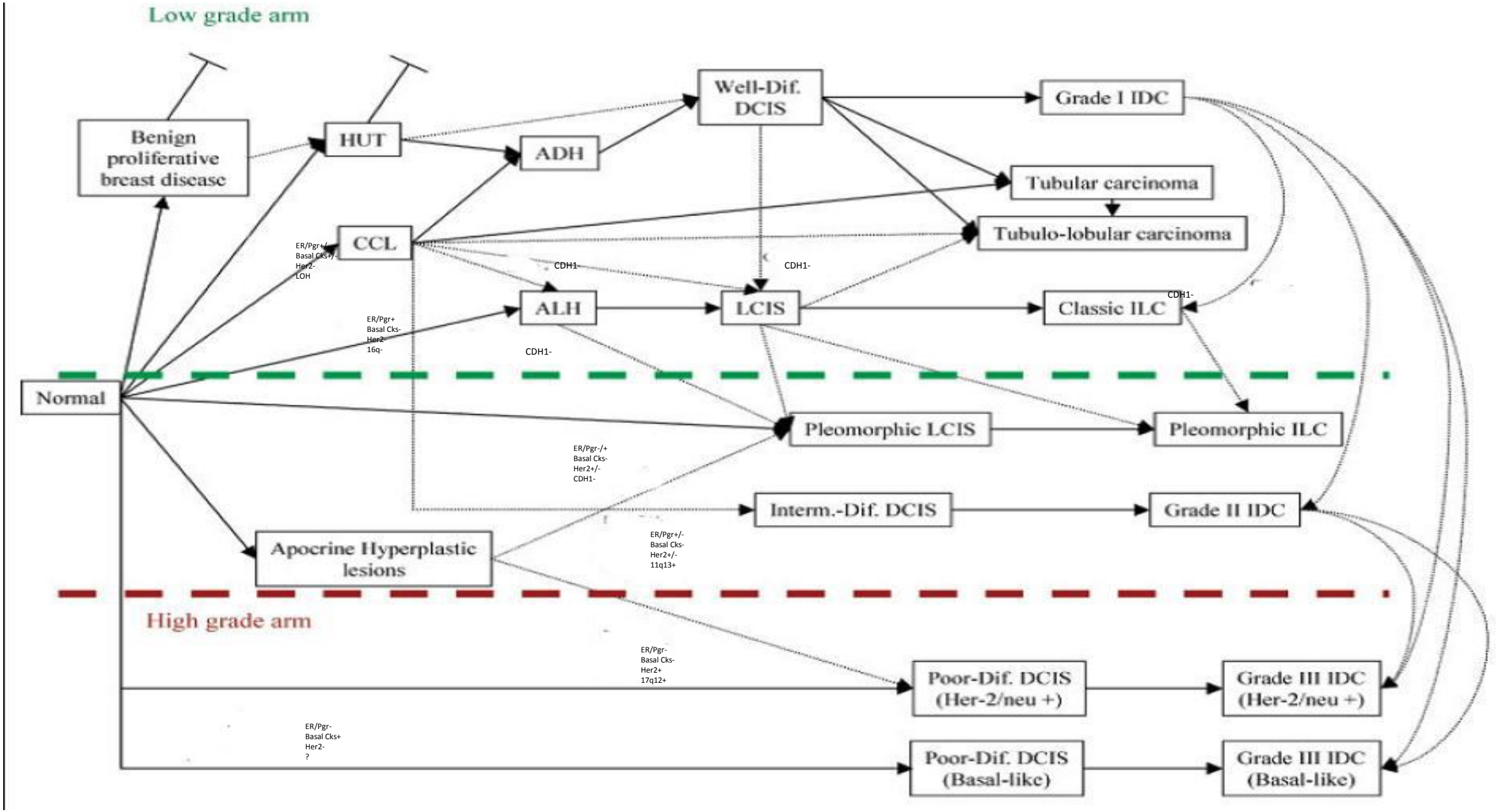
More recently, several variants of LCIS have been recognized with increasing frequency because of the presence of microcalcifications detected on screening mammography. These mammographically-detected lesions include: (1) lesions in which the LCIS cells show the cytological features of classic LCIS (type A or B) but in which there is marked distention of involved spaces with areas of comedo necrosis; and (2) lesions that show marked nuclear pleomorphism (equivalent to that seen in high-grade ductal carcinoma in situ (DCIS), with or without apocrine features and comedo necrosis (pleomorphic LCIS). All lesions in these groups typically lack E-cadherin expression and display genomic alterations by array-based comparative genomic hybridization (CGH) typical of lobular lesions (16q losses and 1q gains) {258, 1346}.



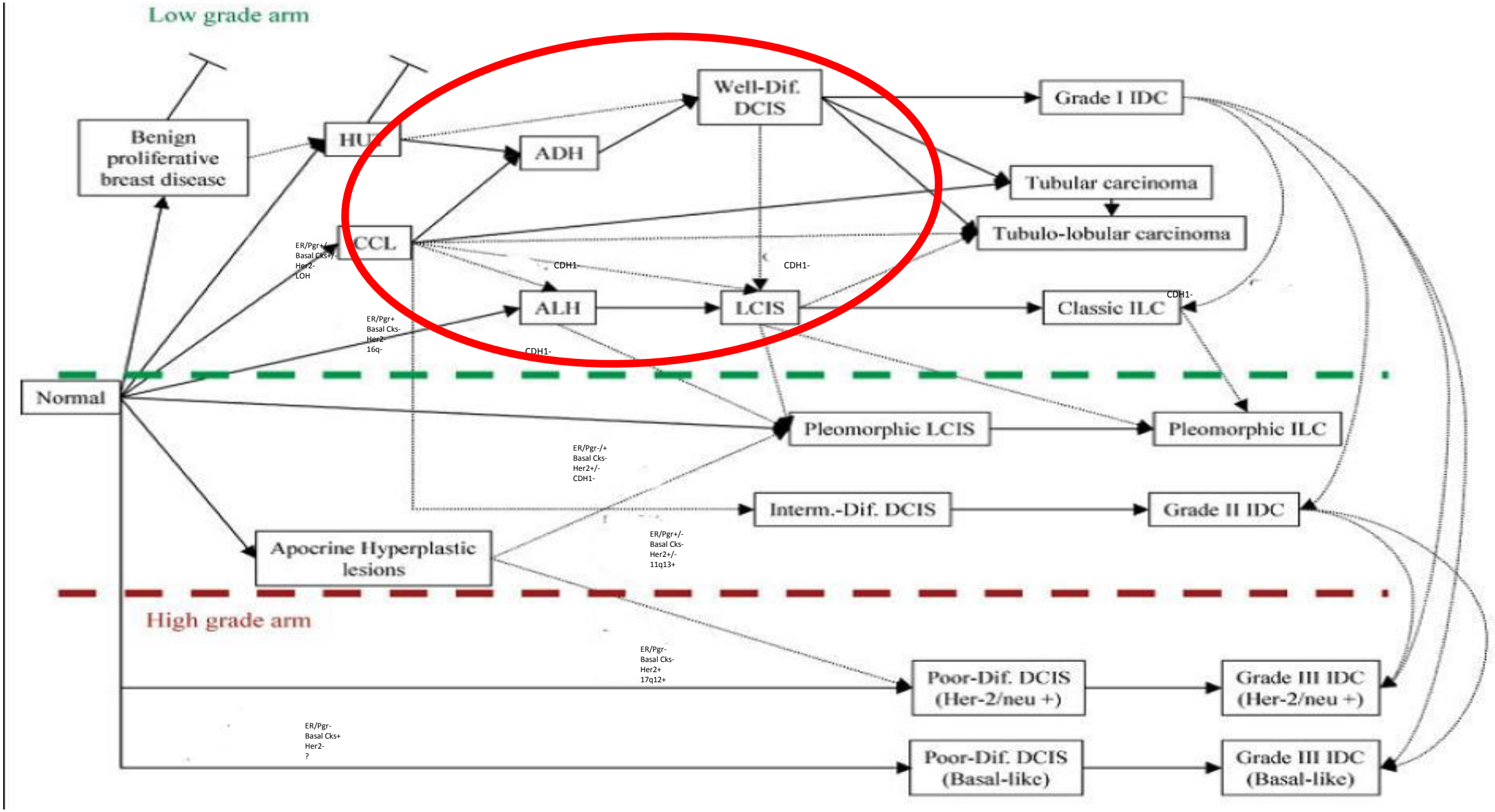








Multi-step model of breast cancer progression. Simpson PT, et al J Pathol 2005;205:248-254



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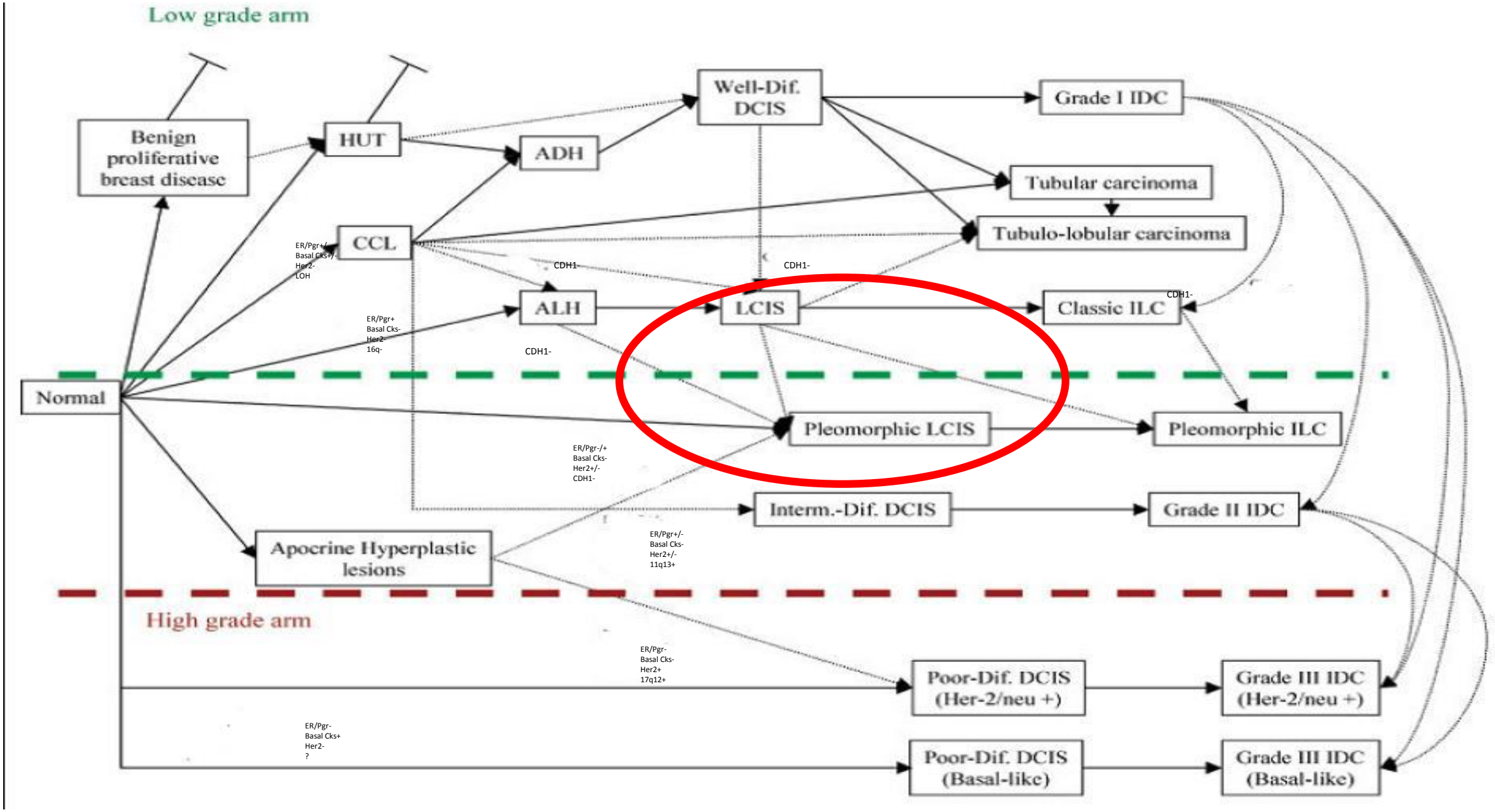


Multi-step model of breast cancer progression. Simpson PT, et al J Pathol 2005;205:248-254

pT4d: more restrictive criteria

- Inflammatory breast cancer (IBC) is a clinical-pathological diagnosis based on diffuse erythema or edema of one-third or more of the breast
- Tumor must have a rapid evolution with less than 6 months from the first symptoms to diagnosis of breast cancer
  - Aims to separate IBC from locally advanced breast cancer producing inflammatory and skin changes in the later course of the disease
- Dermal lymphatic invasion is common in IBC
  - Not necessary for its diagnosis
  - When present alone, without other IBC clinical symptoms - insufficient to make Dx
- When all features of IBC were present but <1/3 of breast was not involved - classified as T4bi or T4c (7th Ed)

N category

- No major changes
- cN0 assigned when evaluation of nodes by physical exam or imaging are negative
- cNx should be rarely used : only valid if nodal basin removed and cannot be examined by imaging or physical examination
- Stressed on the use pathological confirmatory methods (FNA, CNB) of nodal involvement before the removal of primary tumor results in clinical N category
- Qualifiers added behind to reflect this degree of confidence and contrast with staging by palpation or imaging
  - FNA/CNB (f)
  - Sentinel node biopsy (sn)
  - cN1(f) or cN1(sn) Vs cN1

cN Category	cN Criteria
cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases;
	or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (Level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes;
	or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

- Microscopic measurement of node metastases are more clearly defined
- Largest contiguous tumor deposit used for pN
- Do not use dimension of area containing several or multiple tumor deposits

N category : ITC

- Isolated tumor cell (ITC) clusters and micro-metastases are likely to be present as multiple tumor deposits
- ITC definition:
  - small clusters of cells not larger than 0.2mm, or
  - single tumor cells or few than 200 cells in a single histologic cross section
- ITC only are tabulated in the report but do not contribute to overall N classification

pM

- No changes have been implemented
- Valid M categories for clinical and pathological staging
  - cM0: no signs or symptoms of distant metastasis
  - cM1: signs, symptoms or imaging evidence of distant metastases
  - pM1: microscopic confirmation of distant metastasis
- No pM0 and Mx
- cM0(i+) is used if there is no clinical or imaging evidence of distant disease but here is molecular or microscopic evidence of circulating tumor cells or disseminated tumor cell deposits no larger than 0.2 mm in bone marrow or other non-regional LN

M Category	M Criteria
M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

*Note that imaging studies are not required to assign the cM0 category

Anatomical stage group

- Based on anatomical extent of the tumor
- Defined by T, N and M categories
- Only use in settings where biomarker analysis is not available

Anatomical staging subgroups

1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are staged using the N1 category.
4. M0 includes M0(i+).
5. The designation pM0 is not valid; any M0 is clinical.
6. If a patient presents with M1 disease prior to neoadjuvant systemic therapy, the stage is Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
7. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression, and provided the patient has not received neoadjuvant therapy.
8. Staging following neoadjuvant therapy is denoted with a "yc" or "yp" prefix to the T and N classification. There is no anatomic stage group assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Post NAT: ypT and ypN

- ypT category
  - The largest focus of viable appearing residual tumor is used for classification
  - Treatment related fibrosis or necrotic not included
  - When multiple foci present, add (m) modifier to the ypT
- ypN category
  - The size of the largest focus of residual tumor is used
  - Treatment associated fibrosis near nodal tumor is not included

- The pathology report should include a description of the residual tumor in the breast and regional LN that explains the basis of the ypT and ypN classification
- When possible, the report should include the pretreatment cT and cN classification
- Residual DCIS after NAT is classified as ypTis

Post NAT: complete pathological response (pCR)

- Now further defined as
  - No viable invasive tumor
  - No viable in situ tumor
  - No lympho-vascular tumor emboli

- If a cancer is categorized M1 prior to or during NAT, the cancer is categorized as M1 following NAT (regardless of the observed response to therapy)

Examples of Pathologic response evaluation systems after NAT

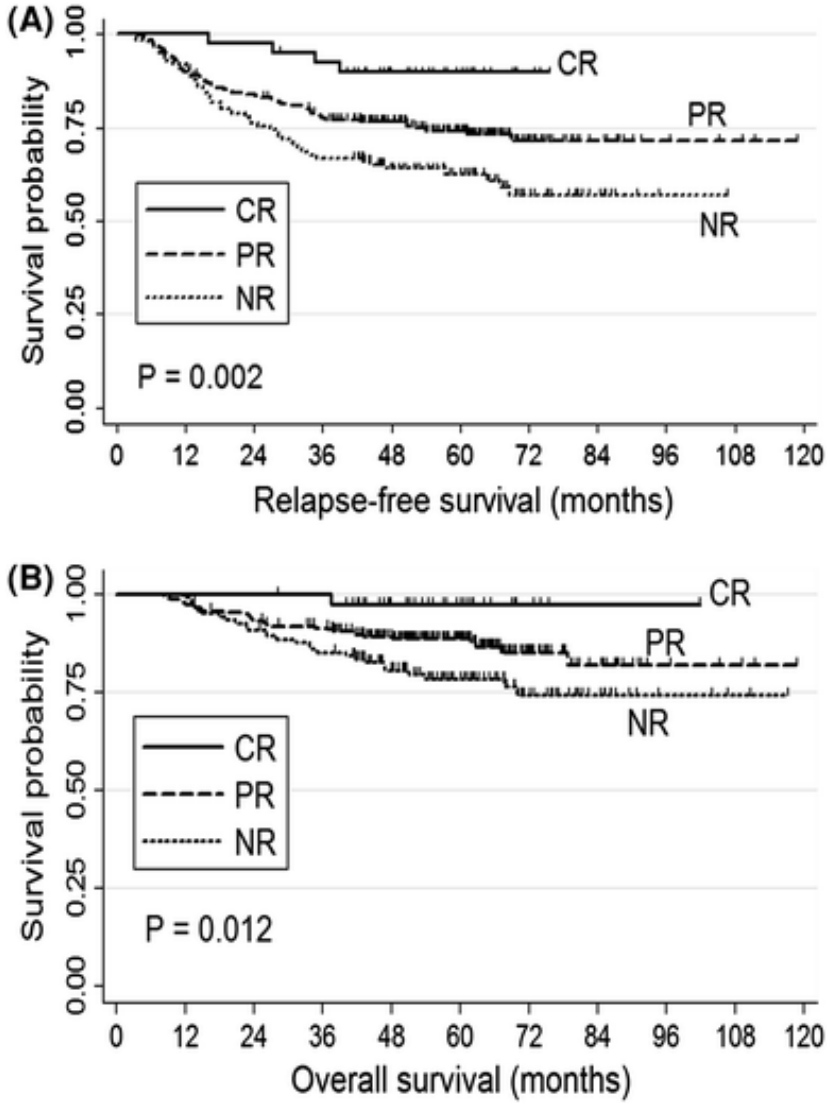
System	Included variable	Definition of pCR	Reference
AJCC (y)	Size of invasive carcinoma	No invasive carcinoma in breast, lymph node and lymphovascular channels	Boughey et al. [8]
	Lymph nose status (the number of metastatic lymph node and size of metastatic deposit)		
B-18	Treatment effect in invasive carcinoma	No invasive carcinoma in breast and lymph node	Diaz et al. [24]
	Lymph nose status (the number of metastatic lymph node and size of metastatic deposit)		
Miller-Payne	Presence of invasive carcinoma	No invasive carcinoma in breast	Mamounas et al. [9]
	Tumor cellularity		
MNPI	Size of invasive carcinoma	No invasive carcinoma in breast and lymph node	Carey et al. [10]
	Tumor grade		
	Lymph nose status (the number of metastatic lymph node)		
Pinder	Tumor proportion (%) in remaining breast	No invasive carcinoma in breast and lymph node	Ogston et al. [11]
	Lymph nose status (presence of evidence of response)		
Residual Cancer Burden (RCB)	Size of tumor bed in two dimension	No invasive carcinoma in breast and lymph node	Abrial et al. [12]
	Tumor cellularity		
	Lymph node status (the number of metastatic lymph node and size of metastatic deposit)		

pCR, pathologic complete response; AJCC, American Joint Committee on Cancer; MNPI, Modified scores from Nottingham Prognostic Index; MSBR grade, Modified Scarff Bloom Richardson grade; RCB, residual cancer burden.

AJCC 7ed

- Staging after NAT is indicated by a ‘y’ descriptor
- T and N uses the same criteria as before treatment
- pCR
  - absence of invasive cancer in breast and LN
- Partial response
  - a decrease in either or both yT and yN stage compare to pretreatment and no increase in either yT or yN
- No response
  - no apparent changes in yT and yN
  - increase in T or N categories at time of pathologic evaluation

AJCC response criteria related to outcome



Keam B et al Ann Surg Oncol 2013

Miller-Payne

- Compare cancer cellularity in pre-treatment sample to resected tumor
- The system does not include response in LN

Grade 1: No change or some alteration to individual malignant cells but no reduction in overall cellularity.

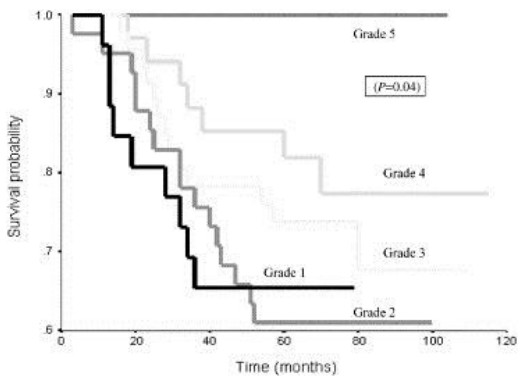
Grade 2: A minor loss of tumour cells but overall cellularity still high; up to 30% loss.

Grade 3: Between an estimated 30% and 90% reduction in tumour cells.

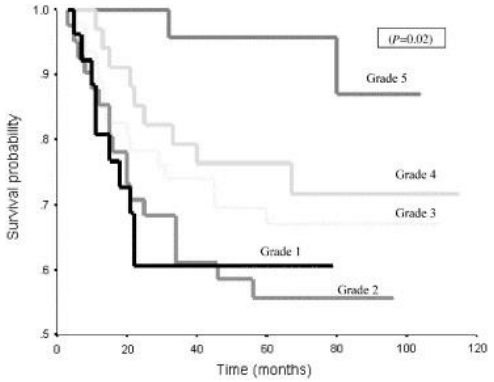
Grade 4: A marked disappearance of tumour cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumour cells.

Grade 5: No malignant cells identifiable in sections from the site of the tumour; only vascular fibroelastotic stroma remains often containing macrophages. However<comma> ductal carcinoma in situ (DCIS) may be present.

OS

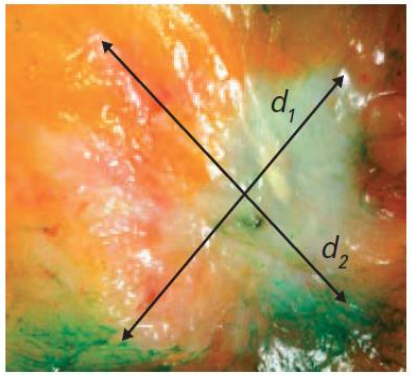


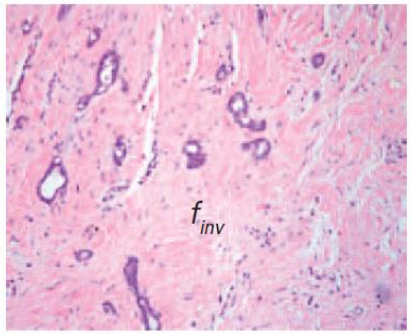
DFS

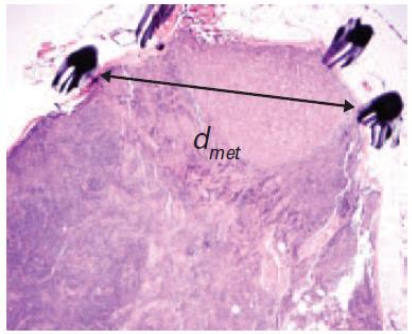


Ogston K et al 2003 Breast

RCB Index

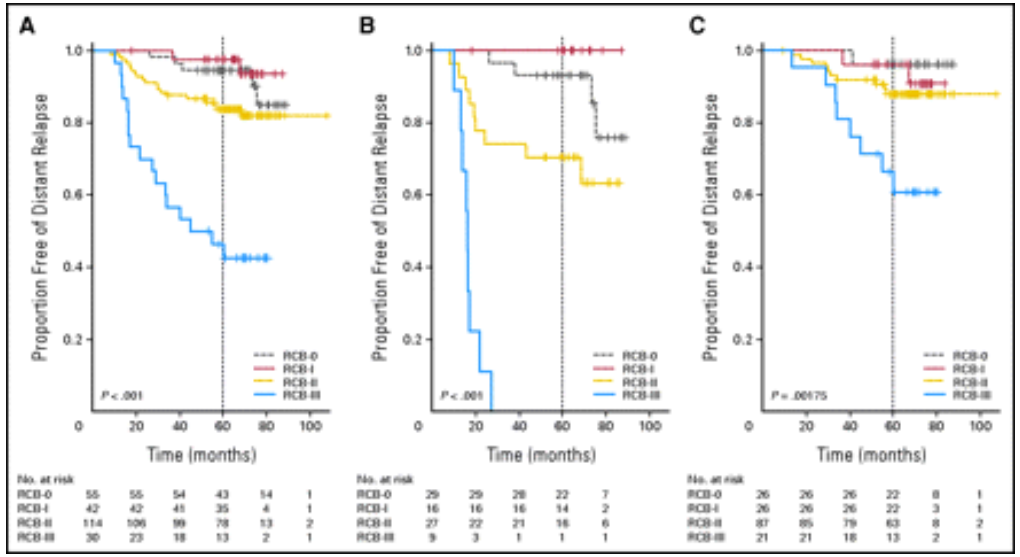






Parameters associated with higher distant relapse

Variable	Hazard Ratio (95% CI)	P
Primary tumor bed dimensions ($\sqrt{d_1 d_2}$)	1.24 (1.04 to 1.48)	.02
Cellularity fraction of invasive cancer (f_{inv})	7.37 (2.16 to 25.1)	.001
Size of largest metastasis (d_{met})	1.17 (0.99 to 1.38)	.06
No. of positive lymph nodes	1.11 (1.04 to 1.19)	.002



$$RCB = 1.4(f_{inv} d_{prim})^{0.17} + [4(1 - 0.75^{LN}) d_{met}]^{0.17}$$

RCB-0: no carcinoma in breast and LN
RCB-I: minimal residual disease (RD)
RCB-II: moderate RD
RCB-III: extensive RD

- Cutoffs between RCB I to III were selected as the quantile that maximized the profile log-likelihood of a Cox Model

Symmans WD et al 2007 JCO

Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area: _____ (mm) X _____ (mm)

Overall Cancer Cellularity (as percentage of area): _____ (%)

Percentage of Cancer That Is *in situ* Disease: _____ (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: _____

Diameter of Largest Metastasis: _____ (mm)

Reset Calculate

Residual Cancer Burden: _____

Residual Cancer Burden Class: _____

- Largest two dimension of residual tumor bed
- Multicentric disease, measure largest tumor bed

- Both in situ and invasive
- 0%, 1%, 5%, 10%, 10% increment thereafter
- Scan across tumor and estimate average cellularity from different microscopic field

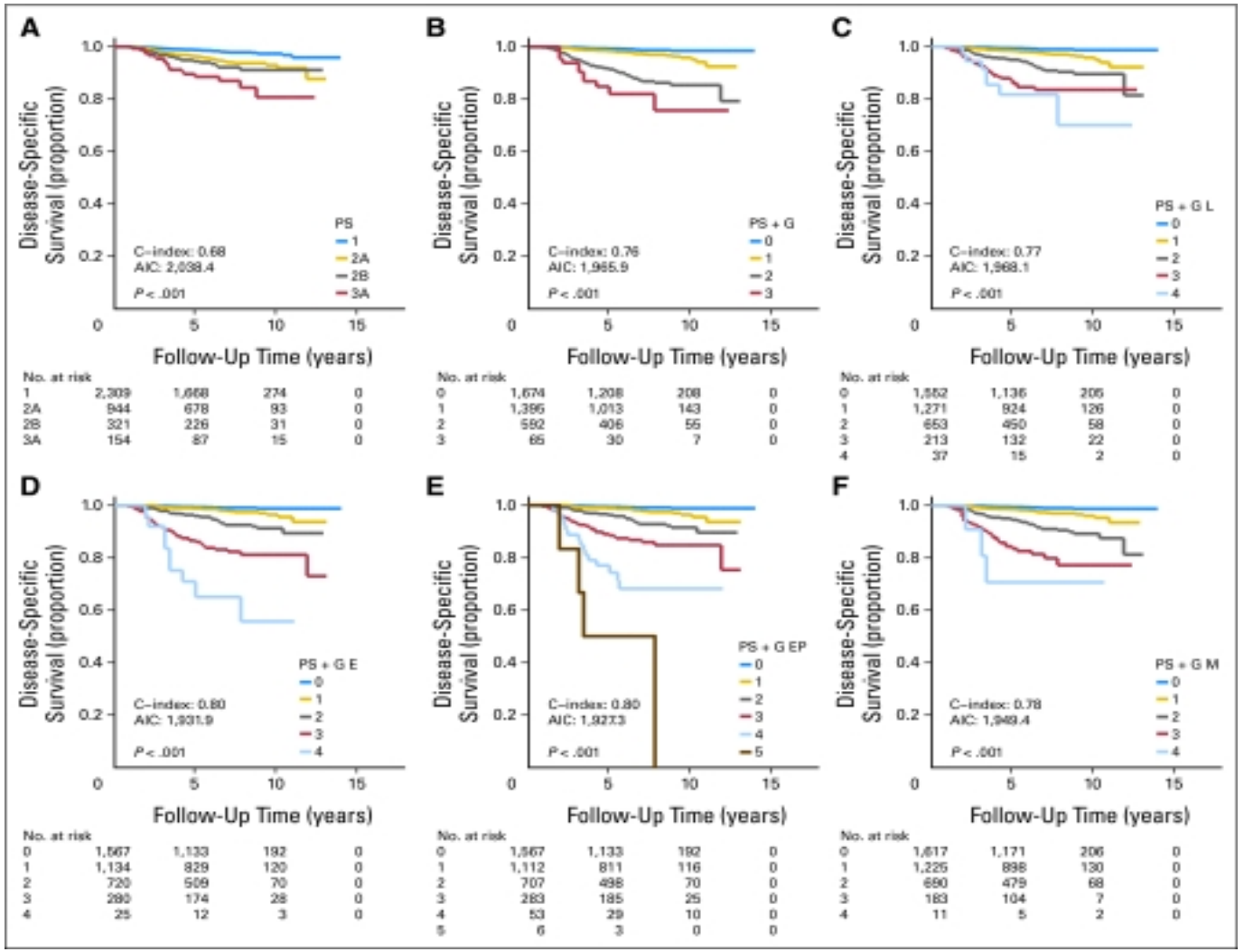
- Similar evaluation as overall cellularity

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Revision of TNM staging 7th edition

MD Anderson staging system

- 3728 patients who were treated between 1997-2006 from MD Anderson
- Grade and ER with pathological stage showed improved stratification with disease specific survival compared to pathological stage alone
- Validated with SEER database
- No HER2 targeted therapy used in the cohort
- An updated study from the investigators using cohort with HER2 positive cancer patients treated with Trastuzumab
  - inclusion of HER2 status along with ER, grade and AJCC pathological stage further refined risk stratification



PS-pathological stage
G- grade
E- ER
P- PR
M- ER, PR and HER2 status

Yi M et al 2011 J Clin Oncol

MD Andersen staging: Bioscore

- Points assigned for each biologic factor and TNM stage based on the hazard ratio magnitude determined on multivariate analysis
- Bioscore from 0 to 7 : 5 year DSS of 100-33%

- Limitation : relatively small cohort; thus not included into AJCC staging
- However, the data strongly supported the incorporation of biomarkers into TNM staging

Mittendorf EA et al 2017 Ann Surg Oncol

TABLE 6. The University of Texas MD Anderson Cancer Center Univariate and Multivariate Analyses for Clinicopathologic Factors Associated With Disease-Specific Survival

		UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS		
FACTOR	5-YEAR DSS, %	HR	*P*	HR	*P*	BIOSCORE POINTS ASSIGNED
Pathologic stage						
IA/IB	99.1	Referent		Referent		0
IIA	98.0	2.8	.002	2.3	.01	1
IIB	95.6	4.8	< .0001	4.0	< .0001	2
IIIA	95.4	6.8	< .0001	7.2	< .0001	3
IIIC	79.5	26.6	< .0001	19.9	< .0001	4
ER status						
Positive	98.8	Referent		Referent		0
Negative	92.9	4.9	< .0001	2.5	.001	1
PR status						
Positive	98.8	Referent		Referent		
Negative	95.2	4.0	< .0001		NS	
HER2 status						
Positive	97.5	Referent		Referent		0
Negative	98.0	0.8	.5	2.2	.04	1
Nuclear grade						
1	99.8	Referent		Referent		0
2	98.9	5.0	.1	4.0	.2	0
3	95.3	25.0	.001	13.0	.01	1

Abbreviations: DSS, disease-specific survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NS, nonsignificant; PR, progesterone receptor. Source: Personal communication, E.A. Mittendorf (unpublished data).

Biological factors incorporated in AJCC staging

- Grade
- Hormone receptor (ER and PR)
- HER2
- Multigene prognostic/ predictive panels

Grade

- A key proxy for the biologic character of a cancer is tumor differentiation
- Histological grade : Nottingham modification Bloom-Richardson grading

- Semi-quantitative evaluations for tubules, nuclear pleomorphism and mitotic activity with a score from 1 to 3 for each
- Grade equate by totaling scores
  - Grade 1 (score 3-5): Favorable
  - Grade 2 (score 6-7): intermediate
  - Grade 3 (score 8-9): unfavorable
  - GX: grade cannot be assessed

ER and PR expression

- ER and PR expression : by IHC
- Any staining of 1% of cells or more is considered positive

HER2

- By either IHC (protein) or ISH (gene amplification)

- 2013 ASCO guideline for sequential performance of tests
- IHC
  - Negative: 0 or 1+ staining
  - Equivocal: 2+ staining
  - Positive: 3+ staining
- ISH
  - Negative: HER2:CEP17 <2.0 AND HER2 copy <4
  - Equivocal: HER2:CEP17 <2.0 AND HER2 copy ≥4 but <6
  - Positive: HER2: CEP17 ≥2.0 by ISH or HER2 copy ≥6 regardless of ratio by ISH

- Categorize HER2 equivocal by ISH as HER2 negative for assigning stage in prognostic stage group

Multigene panels

- Prognostic and predictive models should not be part of the staging without knowledge of ER, PR and HER2
- Panels should only be included into the staging system for certain subsets of breast cancer
- Obtaining genomic profiles is NOT required for assigning Pathological Prognostic Stage

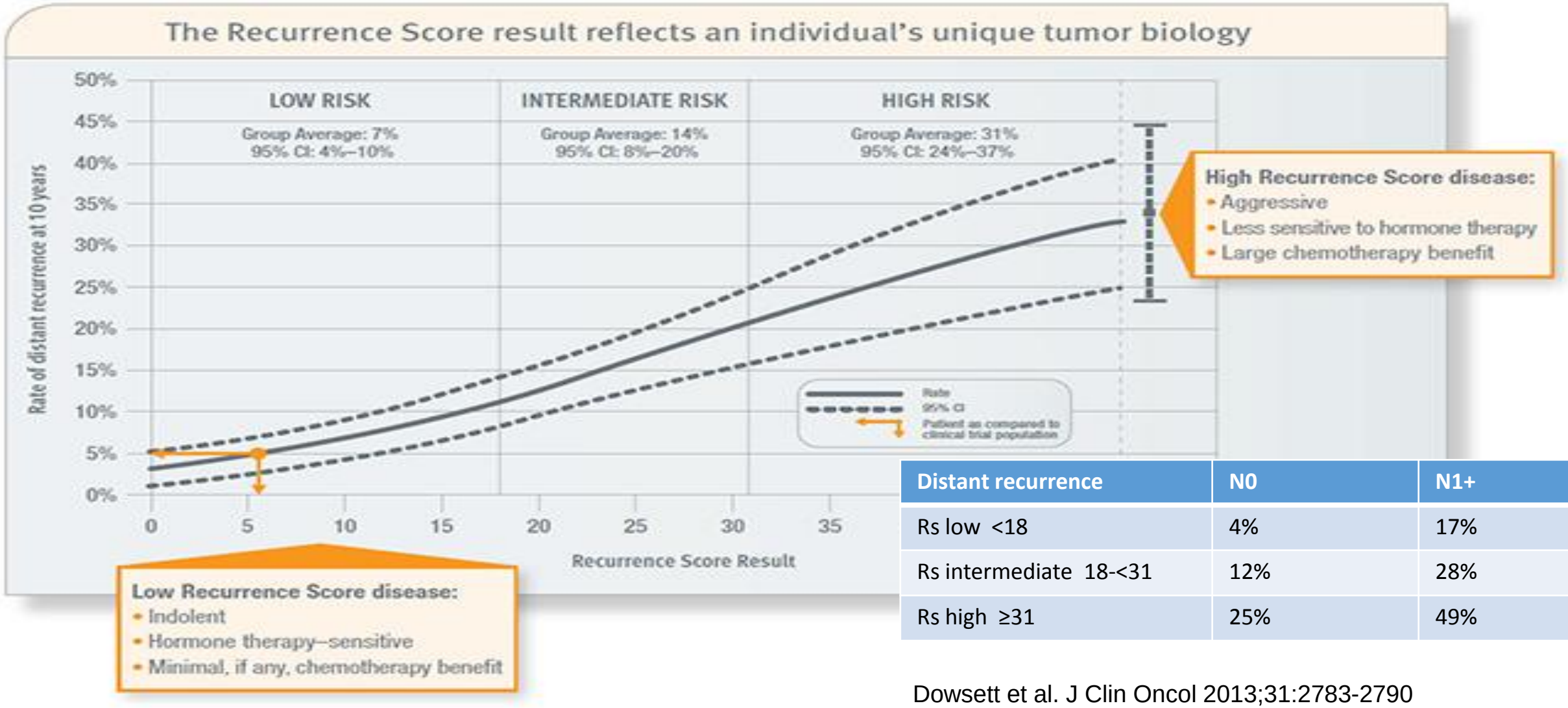
Multigene panel: Oncotype Dx

- The only multigene panel included to classify pathologic prognostic stage because prospective Level I data supports for patients with score <11
- Oncotype Dx not performed, not available or score ≥11
  - Group assigned based on anatomical and biomarker categories
- Applicable for assigning stage of patients with T1-2 N0 M0, ER+ and HER2- and recurrence score <11, the case should be assigned Pathological Prognostic Stage Group IA
  - Down-staging of biologically low risk T2N0 form stage II to I

Oncotype Dx

- By Genomic Health Inc
- FFPE samples in a central laboratory
- 21 gene expression assay
  - 16 cancer related genes in proliferation, invasion, HER2 pathway and ER pathways as well as 5 normalised genes
- Recurrence risk of early stage (I-II), hormone receptor positive breast cancer
- Predictive for adjuvant chemotherapy

Oncotype Dx



Distant recurrence	N0	N1+
Rs low <18	4%	17%
Rs intermediate 18-<31	12%	28%
Rs high ≥31	25%	49%

Dowsett et al. J Clin Oncol 2013;31:2783-2790

Other multigene panels?

- Results from MINDACT study showed that for women with a Mammaprint low genomic risk of recurrence but a high clinical risk with ER+HER2- cancers might spared chemotherapy
- However, the clinical risk was estimated with Adjuvant!OnLine (July 2017) currently not been available online for use
  - Panel decided not to be included in the pathological prognostic staging
- Other multigene panels (ProSigna, Breast Cancer index, EndoPredict and IHC, etc) also provide similar prognostic information with Level II evidence
- AJCC Panels makes no representation that one or another of the genomic profiles should or should not be used in defining prognosis
- Further updates to the staging based on the then available evidence
- Clinicians and patients should make decision based on the evidence at the time of treatment

Agreement between different prognostic tests

- Similar proportion of patients identified as low, intermediate or high risk in different tests
- Marked differences for categorization of individual patients
  - 39.4% showed concordance in all tests

No. of other tests agreed with test	Oncotype DX No. (%)	Prosigna No. (%)	MammaPrint No. (%)	IHC4 No. (%)	IHC4-AQUA No. (%)
4	119 (39.4)	119 (39.4)	119 (39.4)	119 (39.4)	119 (39.4)
3	84 (27.8)	77 (25.5)	73 (24.2)	67 (22.2)	75 (24.8)
2	54 (17.9)	52 (17.2)	47 (15.6)	36 (11.9)	33 (10.9)
1	31 (10.3)	33 (10.9)	34 (11.2)	25 (8.3)	27 (9.0)
0	13 (4.3)	18 (6.0)	25 (8.3)	10 (3.3)	17 (5.6)
Missing	1 (0.3)	3 (1.0)	4 (1.3)	45 (14.9)	31 (10.3)

OPTIMA trial: prospective test of effectiveness of multiparameter testing to identify patients insensitive to adjuvant CT (n=302)

Bartlett J et al 2016 JNCI 108:djw050

Prognostic staging

- *National cancer database* analyses were used to establish clinical and pathological prognostic stage groups
- Patients with breast cancer that have offered and mostly treated with *appropriate endocrine and/or systemic chemotherapy*
- For each prognostic stage group, *3 year overall survival* was computed. Using the same data, 7th edition staging criteria were used to generate survival benchmark and ranges for new stage assignment
- Over 35% of patients results in stage reassignment compared to 7th Ed

Clinical Prognostic Staging

- Based on history, physical examination, any imaging performed, biopsies and biomarkers (grade, ER, PR and HER2)
- Genomic profile is not included
- Relevant to all patients, including those who will receive pre-operative treatments
- Determined prior to any treatment
- Allows determination of changes between baseline and pre-operative treatments
- Allows comparison between groups treated with surgery first or other treatment modalities

Pathological prognostic staging

- Based on clinical staging plus pathological findings at definitive surgery and biomarkers (Grade, ER, PR, HER2 and multigene prognostic panels)
- Relevant to all patients treated with surgery as initial treatment BUT not for those with neoadjuvant treatment
- Recommended staging system for use in the USA by all tumor registries

Changes in staging

TNM Stage	Anatomical stage	Pathological Prognostic stage
T1N0M0	IA	IA
		IB
T1N1M0	IIA	IA
		IB
		IIA
T3N0M0	IIB	IA
		IB
		IIA
		IIB
		IIIA
T3N2M0	IIIA	IA
		IB
		IIA
		IIB
		IIIA

Prognostic staging

Differences in clinical and Pathological staging

*Downstage *Upstage

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB *
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB *
			Negative	Positive	IB *
				Negative	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA*
			Negative	Positive	IIA*
				Negative	IIA
		Negative	Positive	Positive	IB *
				Negative	IIA*
			Negative	Positive	IIA*
				Negative	IIA
	G2	Positive	Positive	Positive	IB *
				Negative	IIA*
			Negative	Positive	IIA*
				Negative	IIA
		Negative	Positive	Positive	IB *
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB*
	G3	Positive	Positive	Positive	IB *
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA*
				Negative	IIB*
			Negative	Positive	IIB*
				Negative	IIB*

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB *
				Negative	IIA *
			Negative	Positive	IIA *
				Negative	IIB
		Negative	Positive	Positive	IIA *IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIA *
			Negative	Positive	IIA *
				Negative	IIB
		Negative	Positive	Positive	IIA *
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB *IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB *
				Negative	IIIA *
			Negative	Positive	IIIA *
				Negative	IIIB *

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA *
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA *
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB *
	G2	Positive	Positive	Positive	IIA *
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA *
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB *
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA *
				Negative	IIIB *
			Negative	Positive	IIIB *
				Negative	IIIC

Prognostic staging

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB *
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC *
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB *
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Any T Any N M1	Any	Any	Any	Any	IV

'T1 Includes T1mi.
'*N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.
'**N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

T	N	M	G	HER2	ER	PR	SEVENTH EDITION ANATOMIC STAGE/ PROGNOSTIC GROUP	EIGHTH EDITION PROGNOSTIC STAGE GROUP
Biomarkers								
1	0	0	1	−	−	−	IA	IIA
1	0	0	3	−	+	−	IA	IIA
3	1-2	0	1	+	+	+	IIIA	IB
Oncotype DX recurrence score- < 11 for ER-positive tumors								
2	0	0	Any	−	+	Any	IIA	IB

Abbreviations: −, negative; O+, positive; ER, estrogen receptor; G, grade; HER2, human epidermal growth factor receptor 2; M, metastasis classification; N, lymph node classification; PR, progesterone receptor; T, tumor classification.

Giuliano AE etal 2017 CA Cancer J Clin

The NEW ENGLAND JOURNAL of MEDICINE

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Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, E.A. Perez, J.A. Olson, Jr., J.A. Zujewski, T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.N. Atkins, J.L. Berenberg, and G.W. Sledge

ABSTRACT

BACKGROUND

Prior studies with the use of a prospective–retrospective design including archival tumor samples have shown that gene-expression assays provide clinically useful prognostic information. However, a prospectively conducted study in a uniformly treated population provides the highest level of evidence supporting the clinical validity and usefulness of a biomarker.

METHODS

We performed a prospective trial involving women with hormone-receptor–positive, human epidermal growth factor receptor type 2 (HER2)–negative, axillary node–negative breast

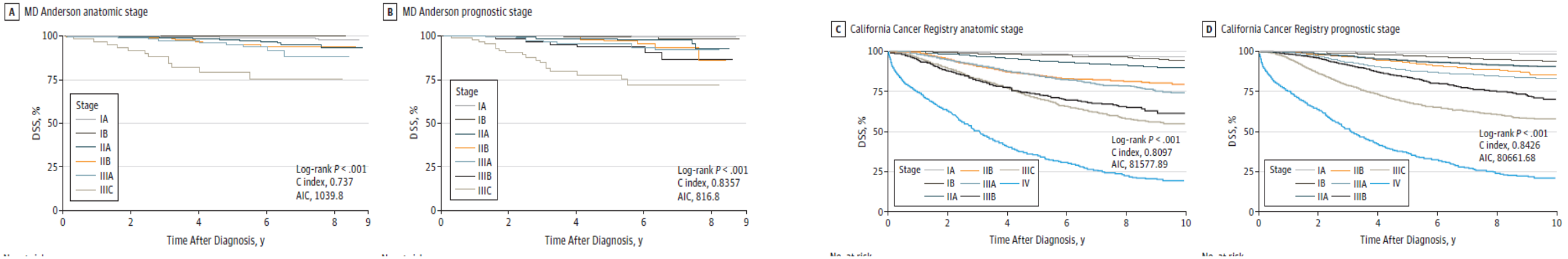
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sparano at the Department of Oncology, Montefiore Medical Center, 1695 Eastchester Rd., Bronx, NY 10461, or at jsparano@montefiore.org.

This article was published on September 28, 2015, at NEJM.org.

RS < 11 used to indicate a group with very low risk of recurrence

Validation study

- Included 3327 stage I to III patients from MD Anderson Cancer Center and 54727 stage I to IV patients from California Cancer Registry
- MD Anderson cohort
    - Upstage-29.5%
    - Downstage-28.1%
    - Prognostic (C index 0.8347; AIC 816.8) Vs anatomical stage (C index 0.737; AIC 1039.8)
- California Cancer Registry
    - Upstage-31.0%
    - Downstage-20.6%
    - Prognostic (C index 0.8426; AIC 80661.68) Vs anatomical stage (C index 0.8197; AIC 81577.89)
- Prognostic Staging provides more accurate prognostic information than the anatomical staging



Weiss A et al 2018 JAMA Oncol

Summary

- T – addressed issue of multiple foci
- pT4d – better defined
- LCIS – not pTis anymore
- ypT, ypN and pCR better defined
- N - addressed issue of multiple foci
- Staging options
  - Anatomical staging (TNM categories)
  - Prognostic staging (included grade, ER, PR, HER2 and multigene panels)
    - Clinical prognostic staging
    - Pathologic prognostic staging


Thank you !

Assessment of HER2 status: IHC and ISH

HER2 status	2013 recommendations		2018 changes	
	IHC	ISH	IHC	ISH
HER2 positive	3+ (>10 % of invasive tumor cells with uniform intense membrane staining)	Dual probes: **HER2/CEN17 of ≥2 with any copy numbers or HER2/CEN17 of <2.0 with an average HER2 copy number ≥ 6.0 per cell** Single probe: Average HER2 copy number ≥ 6.0 per cell		**A definite diagnosis required additional workup**
HER2 equivocal	**2+ (>10 % of invasive tumor cells with incomplete or weak membrane staining OR ≤10 % of invasive tumor cells with intense membrane staining)**	**Dual probes: HER2/CEN17 of <2.0 with an average HER2 copy number ≥ 4.0 and <6.0/cell or Single probe: Average copy number ≥ 4.0 and <6.0 per cell**	**>10 % of invasive tumor cells with weak to moderate complete membrane staining** ≤10 % of invasive tumor cells with intense membrane staining is uncommon. Such cases may be considered as IHC 2+ equivocal but additional testing may reveal different percentage	**A definite diagnosis required additional workup**

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Assessment of HER2 status: IHC and ISH

HER2 status	2013 recommendations		2018 changes	
	IHC	ISH	IHC	ISH
HER2 positive	3+ (>10 % of invasive tumor cells with uniform intense membrane staining)	Dual probes: **HER2/CEN17 of ≥2 with any copy numbers or HER2/CEN17 of <2.0 with an average HER2 copy number ≥ 6.0 per cell** Single probe: Average HER2 copy number ≥ 6.0 per cell		**A definite diagnosis required additional workup**
HER2 equivocal	**2+ (>10 % of invasive tumor cells with incomplete or weak membrane staining OR ≤10 % of invasive tumor cells with intense membrane staining)**	**Dual probes: HER2/CEN17 of <2.0 with an average HER2 copy number ≥ 4.0 and <6.0/cell or Single probe: Average copy number ≥ 4.0 and <6.0 per cell**	**>10 % of invasive tumor cells with weak to moderate complete membrane staining** ≤10 % of invasive tumor cells with intense membrane staining is uncommon (no need to be specified). Such cases may be considered as IHC 2+ equivocal but additional testing may reveal different percentage.	**A definite diagnosis required additional workup**

1.ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; CEN17, chromosome 17 centromere; ISH, *in situ* hybridization

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Additional workup:HER2/CEP17≥2.0 but average HER2 signals/ cell is <4.0

- If IHC has been assessed by the laboratory, perform IHC testing on the same section used for ISH
  - IHC3+: positive
  - IHC2+: recount ISH by different observer
    - if counts remains the same, diagnosis is HER2 negative with a comment
  - IHC0/1+: negative with a comment
  - Comment:
    - Evidence is limited on the efficacy of HER2 targeted therapy in this small subset of cases.
    - In the first generation of adjuvant trastuzumab trials, patients in this subgroup treated with trastuzumab did not show improvement in DFS and OS but there were too few cases to draw definitive conclusions

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Additional workup: HER2 signal / cell>=6.0 with HER2/CEP17<2.0

- If IHC has been assessed by the laboratory, perform IHC testing on the same section used for ISH
  - IHC3+: positive
  - IHC2+: recount ISH by different observer
    - if counts remains the same, diagnosis is HER2 positive
  - IHC0/1+: HER2 negative with a comment
  - Comment:
    - There are insufficient data on the efficacy of HER2 targeted therapy in cases with a HER2 ratio of <2.0 in the absence of protein overexpression because such patients were not eligible for the first generation of adjuvant trastuzumab clinical trials

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Additional workup: HER2/CEP17 ratio<2.0 with an average HER2 copy number of ≥4.0 and <6.0 per cell

- If IHC has been assessed by the laboratory, perform IHC on the same ISH section
  - IHC3+: positive
  - IHC2+: recount ISH by different observer
    - if counts remains the same, diagnosis is HER2 negative with comment
  - IHC0/1+: HER2 negative with a comment
  - Comment
    - IT is uncertain whether this group of patients benefits from HER2 targeted therapy in the absence of protein overexpression. If the specimen test result is close to the ISH ratio threshold for positive, there is a high likelihood that repeat testing will result in different results by chance alone. Therefore when IHC results are not 3+ positive, it is recommended that the sample be considered HER2 negative without additional testing on the same specimen

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HER2 test discordance

- HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on excision biopsy if
  - Tumor is grade 3
  - Amount of invasive cancer in core biopsy is small
  - Resection specimen contains high grade cancer that is morphologically distinct from that in the core
  - Core biopsy result is equivocal for both IHC and ISH
  - There is doubt about handling of core biopsy or test is suspected by a pathologist to be negative on the basis of testing error

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HER2 test discordance

- Reorder HER2 test if the following histopathologic findings occur and initial HER2 test was positive
  - Histological grade 1 tumor (at least 90% pure) of
    - ER/PR+ IDC
    - ER/PR+ ILC
    - Tubular
    - Mucinous
    - Cribriform
    - Adenoid cystic carcinoma

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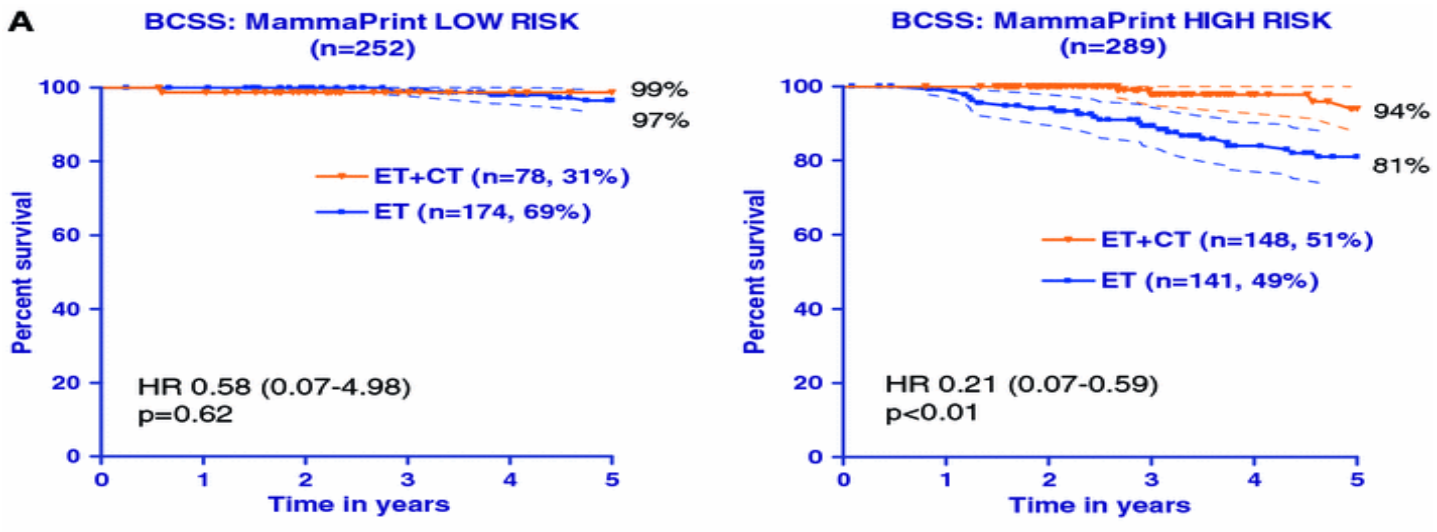
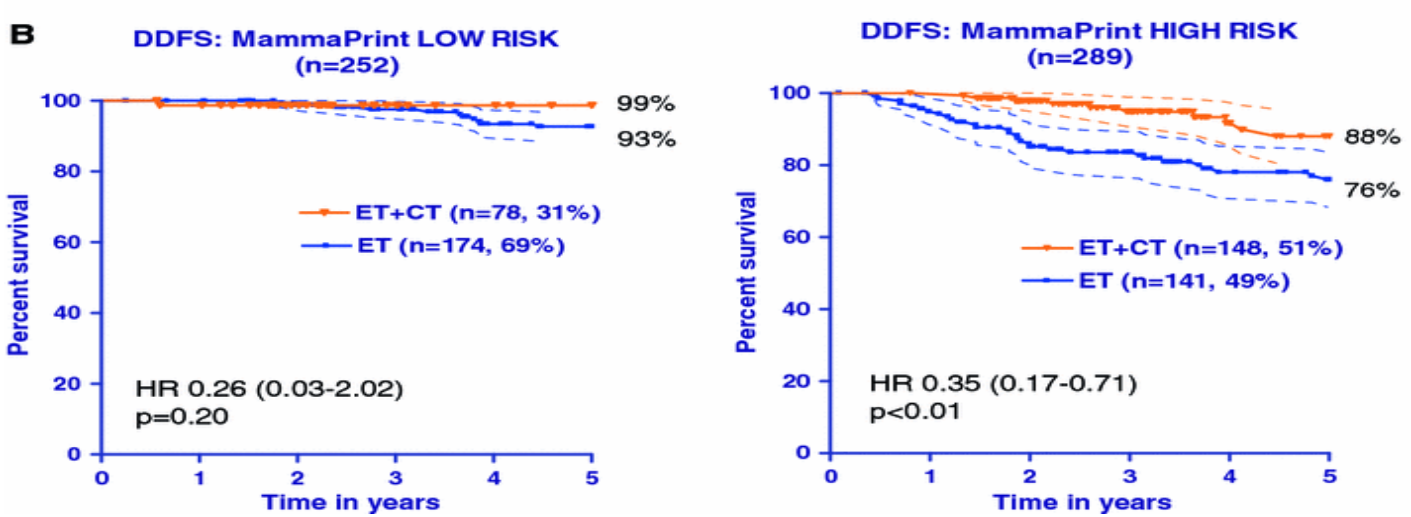
Mammaprint

- Reported as risk Score
  - +1 to -1;
  - binary stratification
- 5 year breast specific survival
  - Low risk:97%
  - High risk:87%
- 5 year distant disease free survival
  - Low risk:95%
  - High risk:82%

Breast cancer specific survival



Distant disease free survival



Knauer M et al Breast Cancer Res Treat

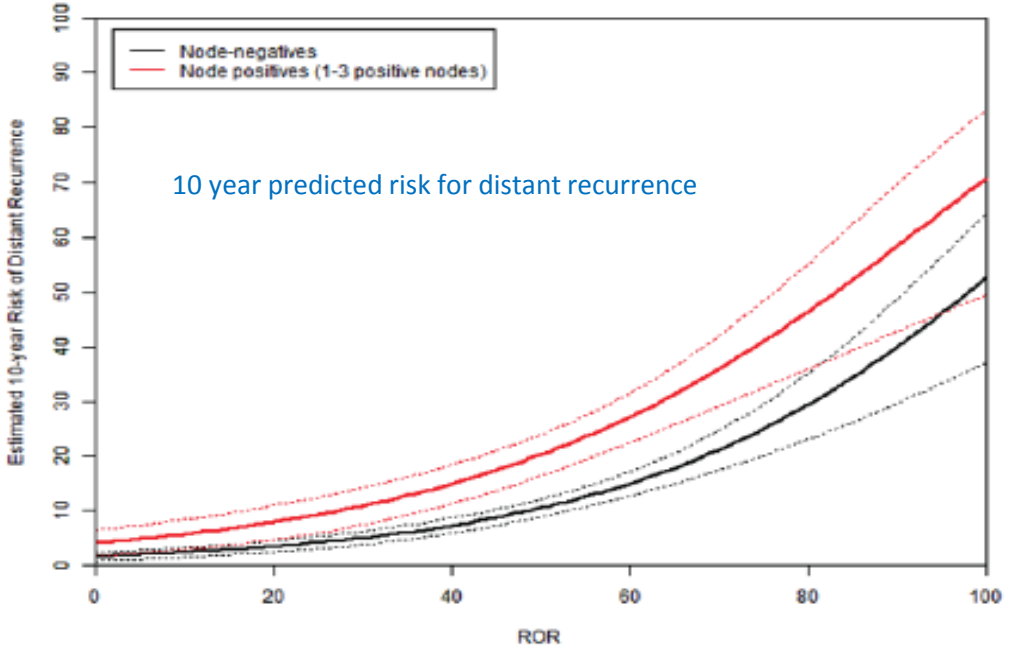
ET-endocrine therapy; CT-chemotherapy

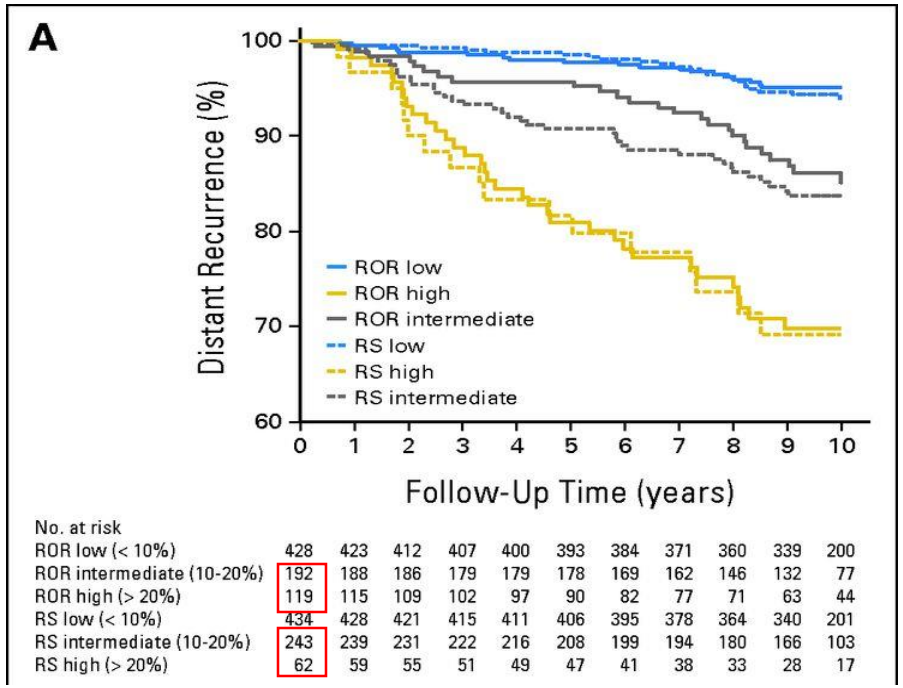
Prosigna

- Based on the PAM50 gene expression assay for intrinsic subtyping by Perou's group
- In kit format performed on nCounter ® analysis system by Nanostring technologies
- FDA approved to estimate distant recurrence free survival for stage I-II (including 1-3 positive nodes), ER positive breast cancer in postmenopausal women treated with adjuvant endocrine therapy
- The score also based on tumor size and nodal stage with special weighting given to a set of proliferation genes
- Intrinsic subtyping included in St. Gallen's guidelines

Prosigna

- Three-tiered stratification of risk of recurrence (ROR) based on nodal status
- Node negative
  - Low risk: 0-40
  - Intermediate risk: 41-600
  - High risk: 61-100
- Node positive
  - Low risk: 0-40
  - High risk: 41-100





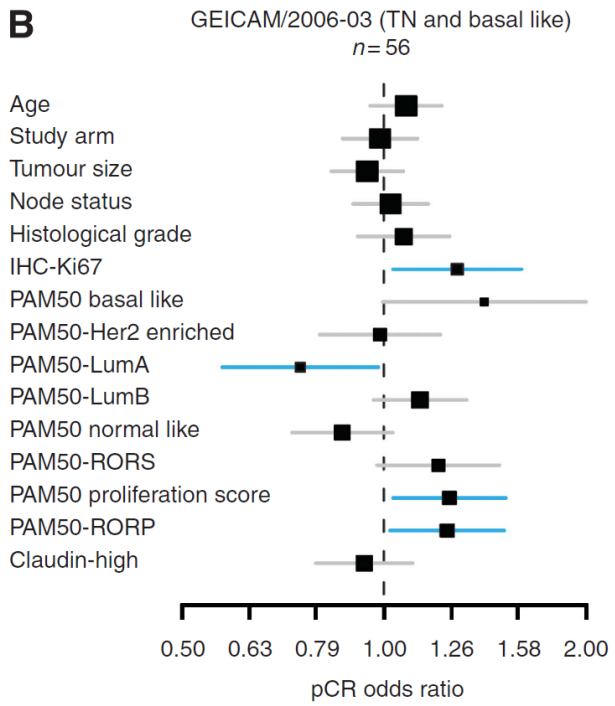
No. at risk											
ROR low (< 10%)	428	423	412	407	400	393	384	371	360	339	200
ROR intermediate (10-20%)	192	188	186	179	179	178	169	162	146	132	77
ROR high (> 20%)	119	115	109	102	97	90	82	77	71	63	44
RS low (< 10%)	434	428	421	415	411	406	395	378	364	340	201
RS intermediate (10-20%)	243	239	231	222	216	208	199	194	180	166	103
RS high (> 20%)	62	59	55	51	49	47	41	38	33	28	17

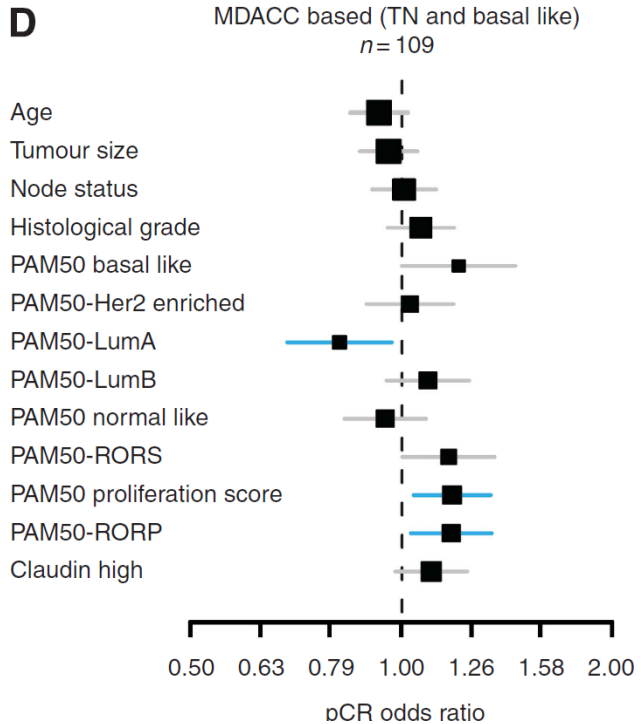
- ROR Vs RS
- Prosigna identified fewer patients in the intermediate group but more in high risk group
- Low risk and high risk groups identified by each test showed similar outcomes

Dowsett et al. J Clin Oncol 2013;31:2783-2790

PAM50 ROR score predicting pCR after chemotherapy in BLBC subtype

- Proliferation score and luminal A signature significant associated with pCR
- ROR score predict pCR for BLBC cancers within TNBC



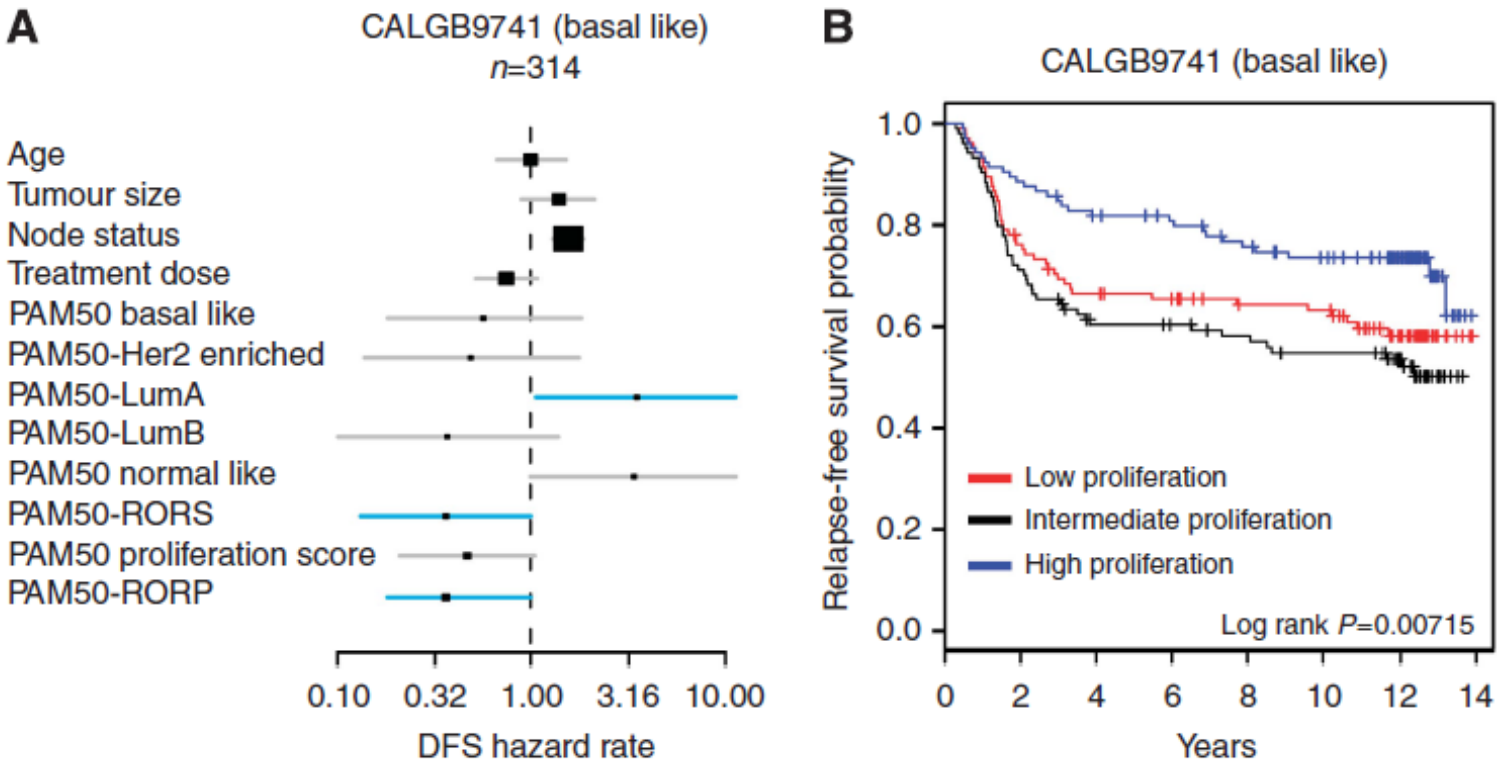


Data Set	GEICAM2006-03	MDACC based
Type of cohort	Core Basal[a]	Triple negative
Clinical setting	Neoadjuvant	Neoadjuvant
Systemic treatment	Chemo	Chemo
Chemoregimen	EC→D+/−Carbo	Anthracycline/taxane based
Primary end point	pCR breast	pCR breast/axila
No. of patients	69	188
Mean age	49.9	49.6
Node positivity	31 (44.9%)[b]	—
Tumour size >2 cm	62 (89.9%)	179 (95.2%)
Genomic Platform	nCounter	Microarray
Intrinsic subtype distribution		
Basal like	56 (81.2%)	109 (58%)
Claudin low	7 (10.1%)	47 (25%)
HER2 enriched	4 (5.8%)	14 (7.4%)
Luminal A	0	3 (1.6%)
Luminal B	0	6 (3.2%)
Normal like	2 (2.9%)	9 (4.8%)

Prat A et al 2014 Br J Cancer 111:1532

ROR predicting DFS within TNBC of BLBCs

- 314 BLBC patients
- Treated with adjuvant anthracycline/taxane based chemotherapy
- Better DFS associated with low expression of lum A and high proliferation signature



Prat A et al 2014 BJC 111:1532