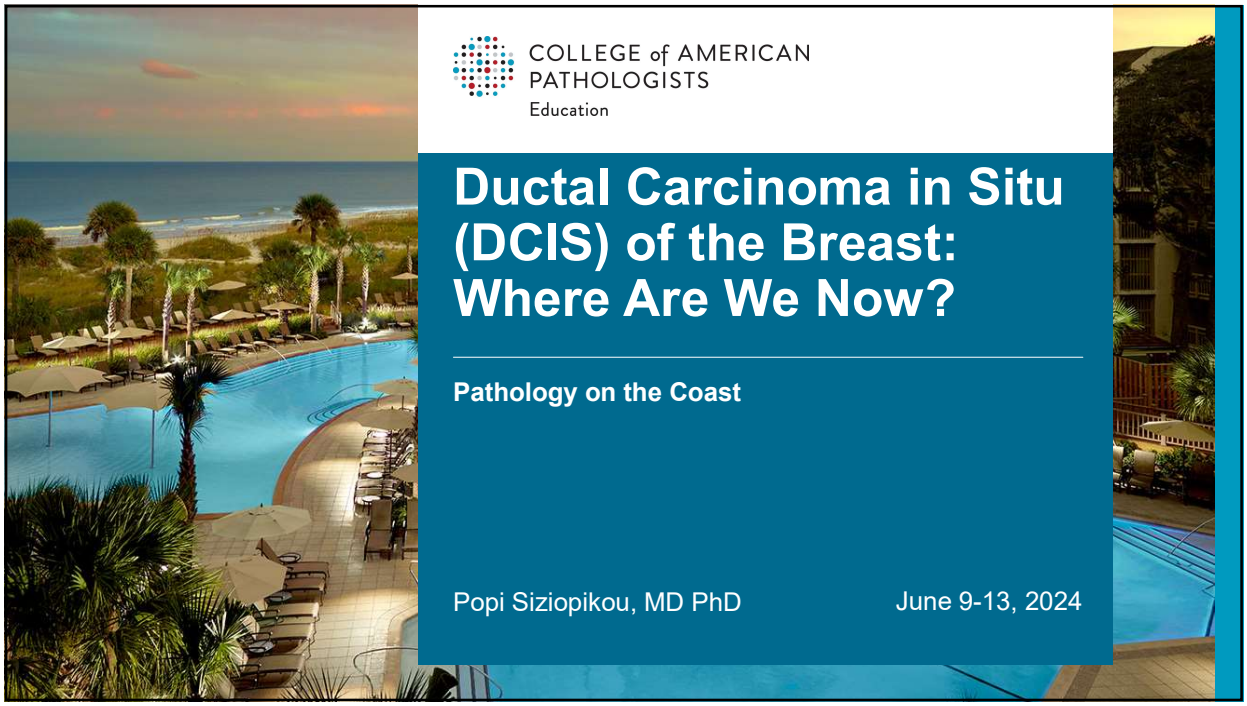


1

Objectives

- Define the histologic features of the different DCIS subtypes
- Evaluate histologic parameters of clinical significance in DCIS
- Identify molecular biomarkers in DCIS
- Discuss the possible differential diagnoses when considering a DCIS lesion
- Understand the various models of breast cancer progression

2

Outline

- Definition
- Incidence
- Clinical presentation
- Histologic parameters of clinical significance
- Differential diagnosis
- Molecular pathology/biomarkers in DCIS
- Models of breast cancer progression

3

Distribution of Histologic Types of Breast Cancer

	Total Cancers
In Situ Carcinoma	15% - 30%
Ductal carcinoma in situ	80%
Lobular carcinoma in situ	20%
Invasive Carcinoma	70% - 85%
Ductal carcinoma (no special type)	79%
Lobular carcinoma	10%
Tubular/cribriform carcinoma	6%
Colloid (mucinous) carcinoma	2%
Medullary carcinoma	2%
Papillary carcinoma	1%

4

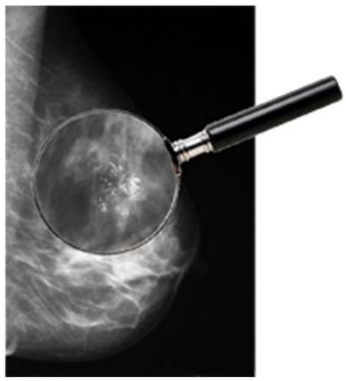
Ductal Carcinoma in Situ (DCIS) Definition

Ductal carcinoma-in-situ of the breast is characterized by tumor cells confined to the ductal system of the breast without light microscopic evidence of invasion through the basement membrane into the surrounding stroma.

5

DCIS Clinical Presentation

- Mammographic detection
  - Microcalcifications (76%)
  - Non-palpable breast mass (11%)
  - Both (13%)
- Incidental finding
- Palpable mass
- Nipple discharge
- Paget's disease of the nipple



6

Histologic Parameters of Clinical Significance in DCIS -*CAP Protocol for Reporting DCIS (2018)*

- Architectural patterns
- Nuclear Grade
- Necrosis
- Microcalcifications
- Size/extend of lesion
- Margin status

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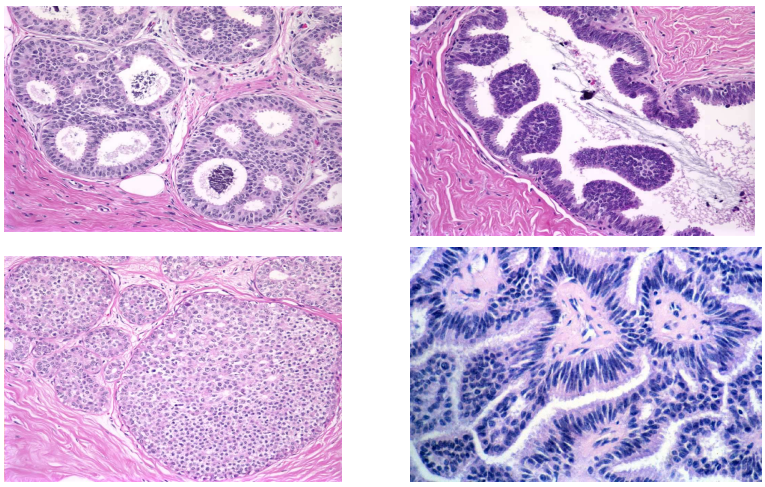
DCIS Architectural Subtypes

- Non-Comedo
  - Cribriform
  - Micropapillary
  - Solid
  - Papillary
  - Others (apocrine, hypersecretory)
- Comedo (prominent necrosis present)

8

Non-comedo DCIS



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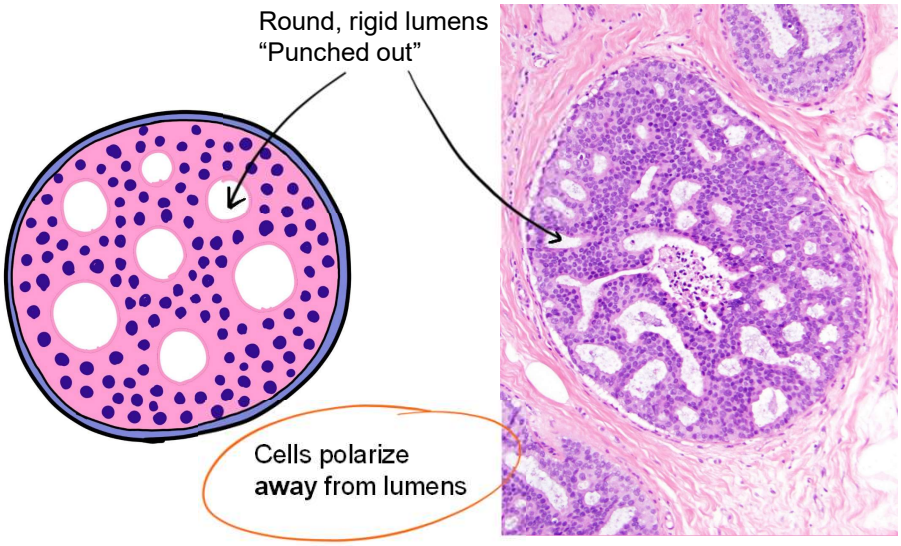
Cribriform DCIS



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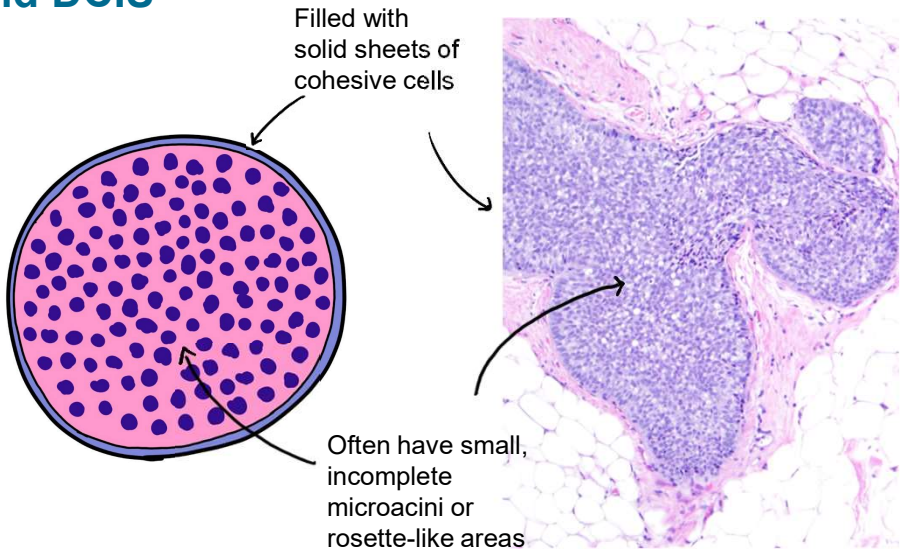
Solid DCIS



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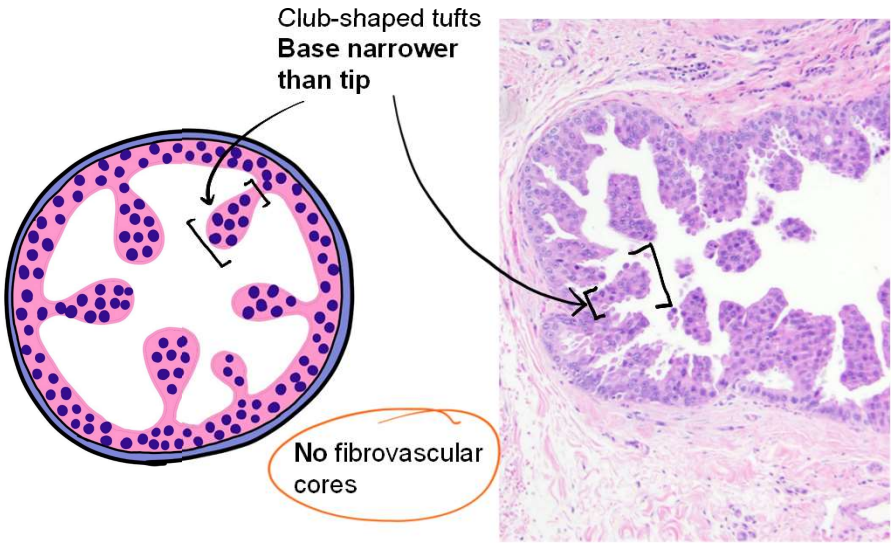
Micropapillary DCIS



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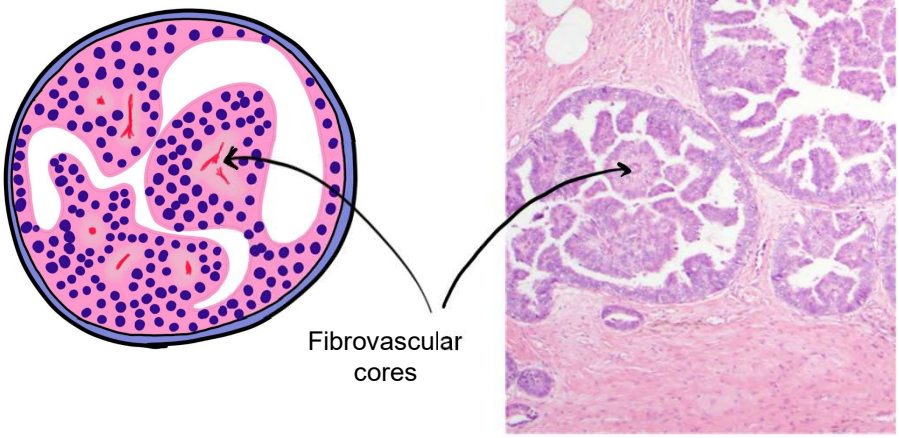
Papillary DCIS



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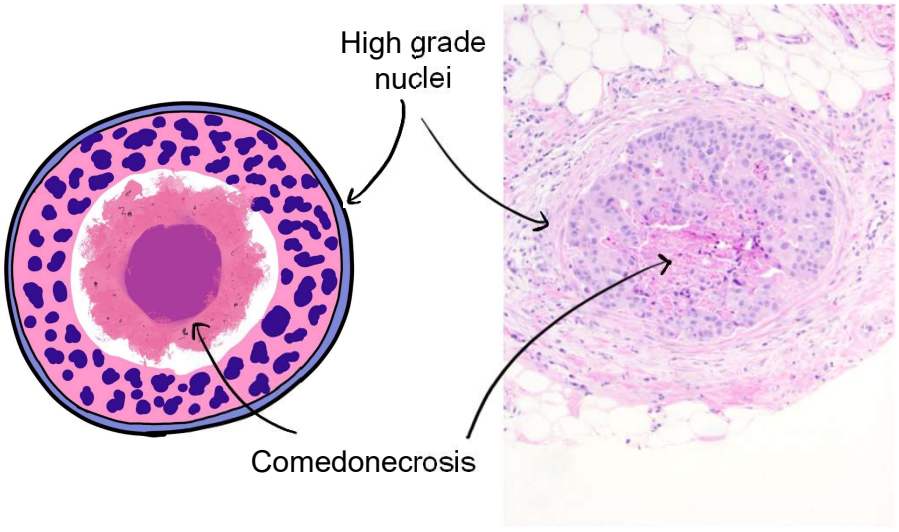
Comedo DCIS



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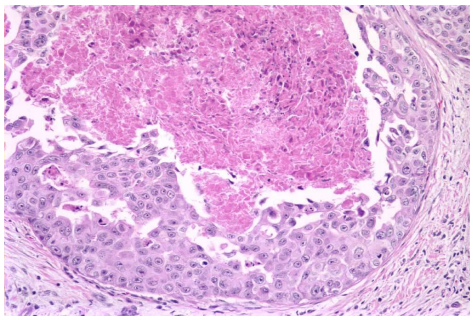
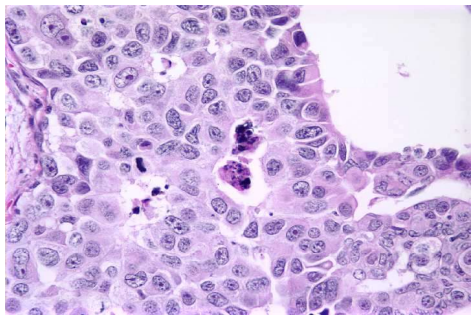
Comedo DCIS





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DCIS- Dichotomous Classification

	Non-comedo	Comedo
Cytology	low grade	high grade
ER	positive	negative
Aneuploidy	infrequent	frequent
Proliferative rate	low	high
HER2	infrequent	frequent
p53	uncommon	common
Microinvasion	uncommon	common
Angiogenesis	uncommon	common
Microcalcifications	low correlation	high correlation

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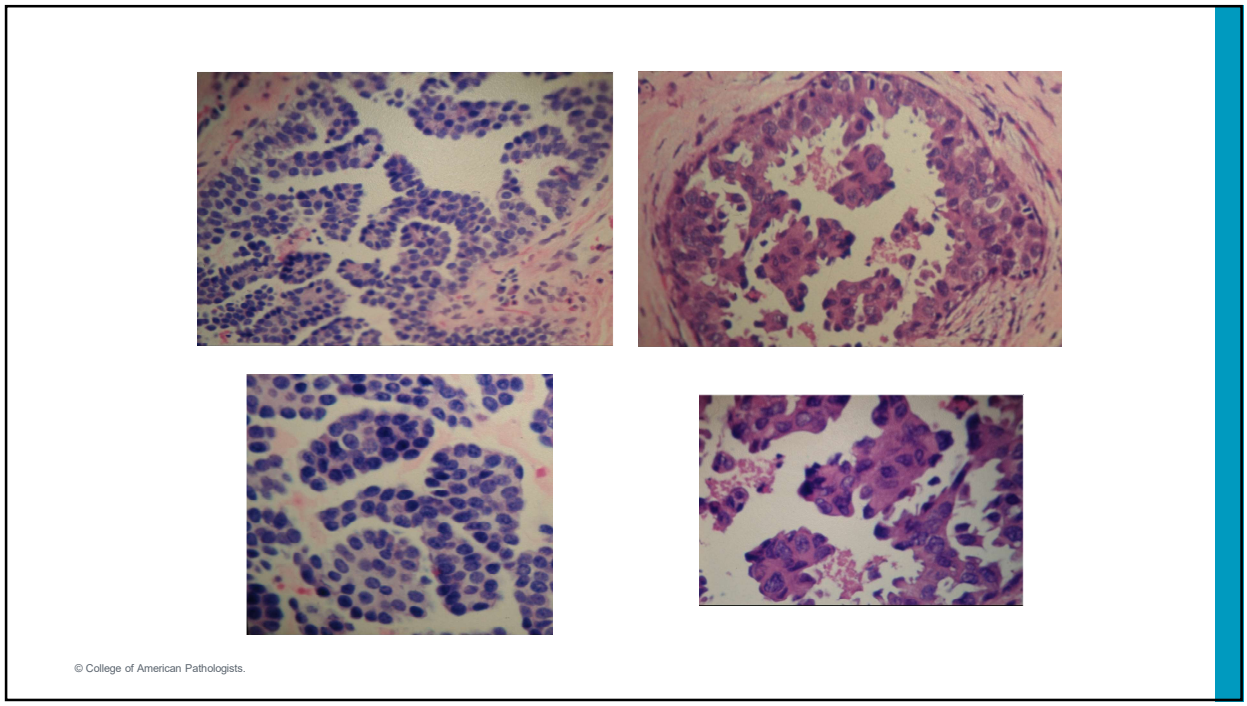

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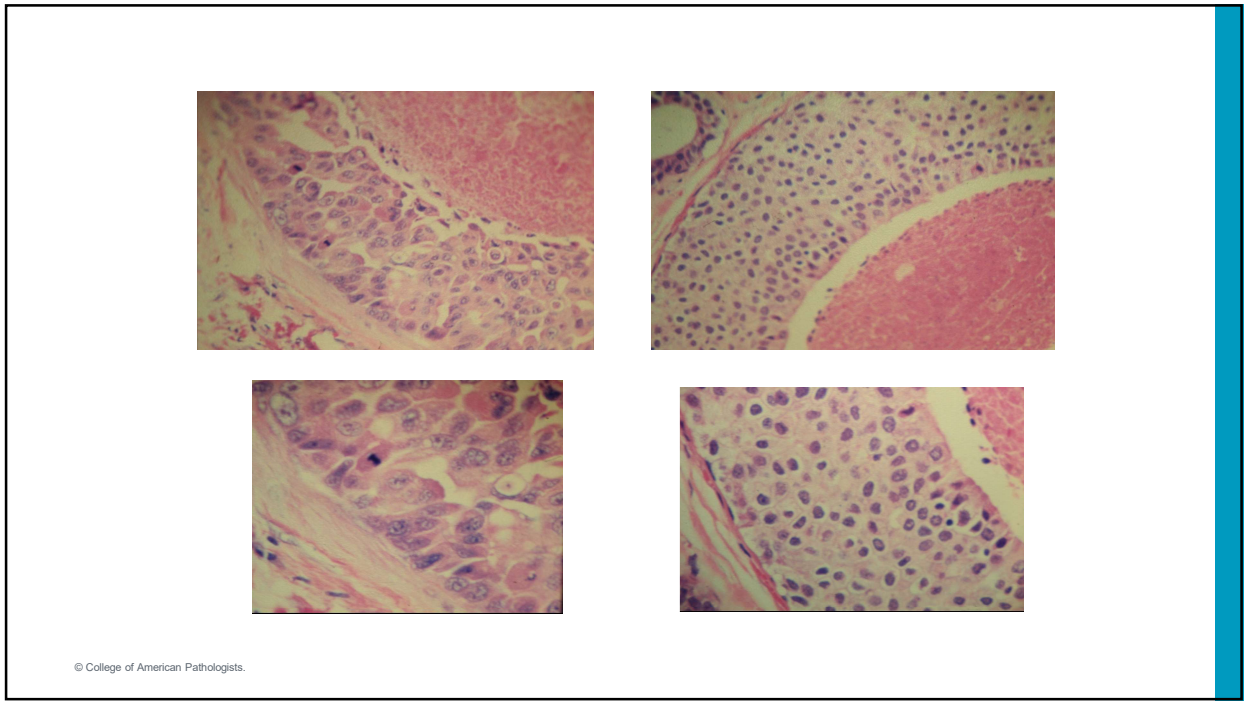

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Other DCIS Proposed Classification Systems

Lagios	Nottingham	European
Micropapillary/ cribriform	DCIS without necrosis	Well differentiated
Cribriform with anaplasia	DCIS with necrosis (non-pure comedo)	Intermediately differentiated
Comedo with necrosis	Pure comedo	Poorly differentiated

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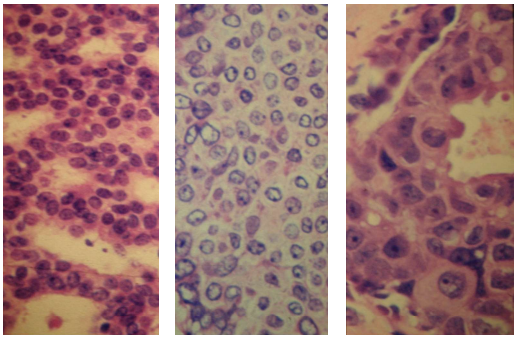
DCIS Nuclear Grade

- Low (grade 1)
- Intermediate (grade 2)
- High (grade 3)



Grade 1 **Grade 2** **Grade 3**

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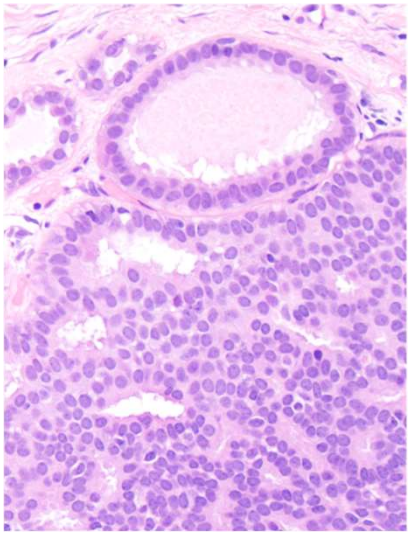
Low Grade (Grade 1)

- Well defined cell membranes
- Uniform size, shape, and placement
- Small, homogeneous chromatin distribution, inconspicuous nucleoli
- Subtle increase in nuclear-cytoplasmic ratio
- Mitotic figures are rare



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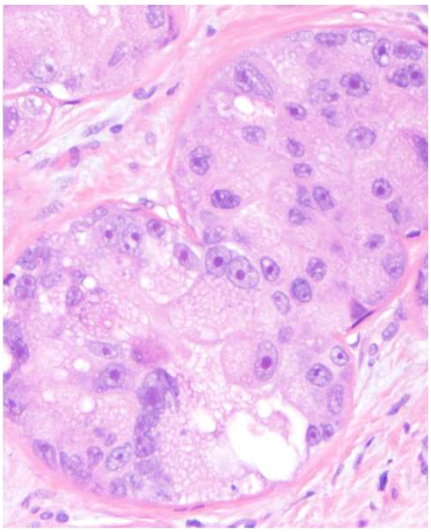
High Grade (Grade 3)

- Large, pleomorphic nuclei
- Vesicular/coarse chromatin, prominent nucleoli
- Mitoses frequent ± atypical
- Comedo necrosis often present.
- Amorphous , linear calcifications
- Periductal desmoplasia, chronic inflammation, angiogenesis often seen
- May produce mass like presentation



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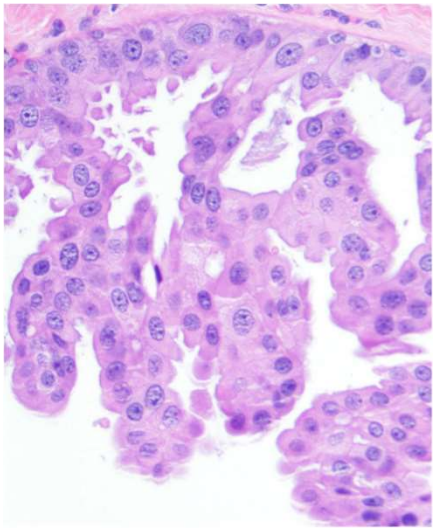
Intermediate Grade (Grade 2)

- Cells don't fulfill criteria of grade 1 or 3
- Mild-moderate variability in nuclear size, shape, placement
- Nucleoli variably conspicuous
- Tends to mimic usual ductal hyperplasia



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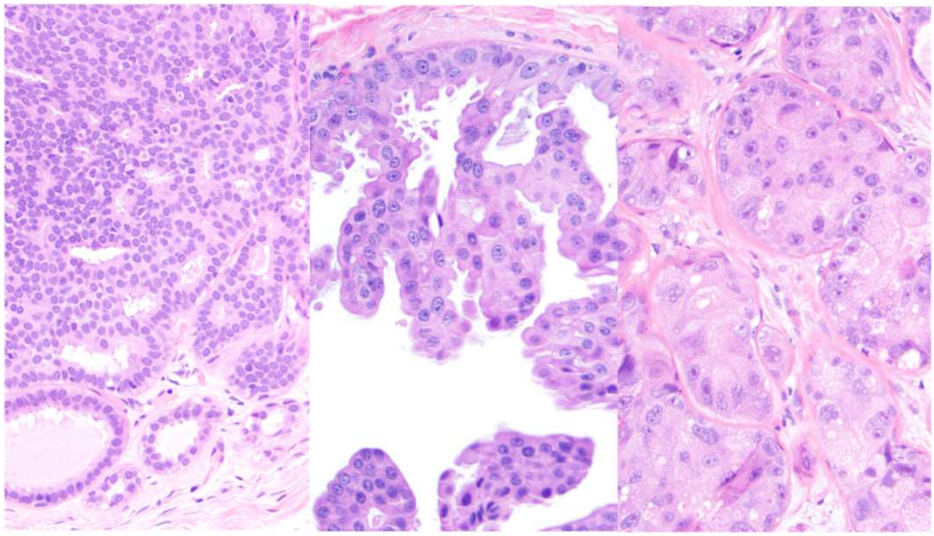
DCIS - Nuclear Grade



Grade 1 **Grade 2** **Grade 3**

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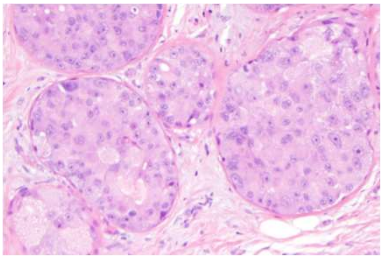
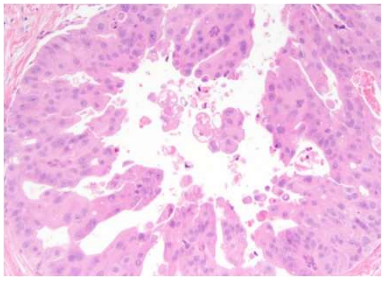
DCIS with Apocrine Features Special Types

- Abundant, eosinophilic cytoplasm, prominent nucleoli, grades 1-3
- High grade - straightforward
- Low grade – difficult to distinguish from apocrine metaplasia: has architectural features of DCIS
- Triple negative





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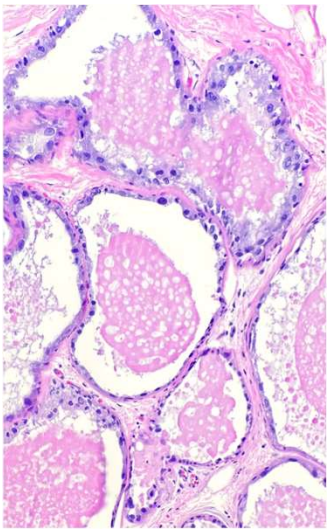
Cystic Hypersecretory DCIS Special Types

- Rare - Multiple cyst-like structures with homogeneous eosinophilic material resembling thyroid colloid
- Grade 2-3: Micropapillary pattern common – solid, cribriform, clinging
- Some cases coexist with cystic hypersecretory change (flat, benign), cystic hypersecretory hyperplasia (stratified), and stratified/ micropapillary epithelium with cytology atypical *(atypical cystic hypersecretory hyperplasia)*



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Studies on Multicentricity in DCIS

- Study by Holland et al (119 mastectomy specimens): DCIS distribution is contained in a specific quadrant
- Study by Faverly et al (60 mastectomy specimens)

Overall: 50% continuous growth
50% discontinuous growth ("gaps")
Continuous growth by grade:
30% of grade
45% of grade II
90% of grade III

- Studies on clonality
- Magnification views and careful pathology/radiology correlation very important

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NSABP - B17
8-year Recurrence Rates

	Type of Local Recurrence		
	All	**Non-invasive**	**Invasive**
Excision	26.8%	13.4%	13.4%
Excision + RT	12.1%	8.2%	3.9%
% Reduction	55%	39%	71%

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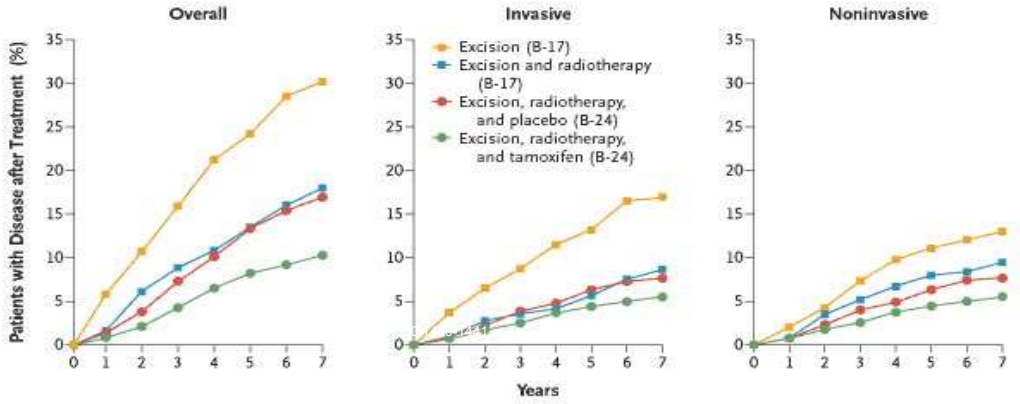
The Risk of Ipsilateral or Contralateral Breast Tumor after Surgical Excision among Patients with Ductal Carcinoma in Situ Who Were Treated with Excision Alone; Excision and Radiotherapy; Excision, Radiotherapy, and Tamoxifen; or Excision, Radiotherapy, and Placebo



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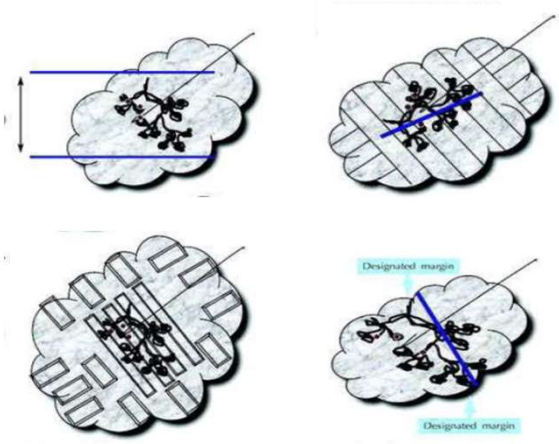
Size/Extent of DCIS



Lester et al., Arch Pathol Lab Med, 133: 15-25, 2009

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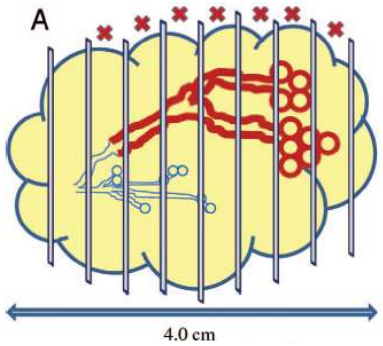
Size/Extent of DCIS



7 slices x (4.0 cm / 10) = 2.8 cm

- Optimal method is slice mapping
  - DCIS size = Slices with DCIS x average slice thickness (length/# slices)
- Block method (# blocks with DCIS x average thickness) underestimates size in most cases (72%) with an average reduction of 33%
  - Using 0.4 cm as multiplication factor improves concordance

(Lester et al. 2009)
(Damanesh et al, 2009)

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Size/extent of DCIS reporting

- Present on one slide:
  - largest diameter: x cm
- Present on more than one slide:
  - # of slides with DCIS
  - # of slides examined
  - largest single diameter of DCIS on a slide
- Overall estimate of DCIS (based on the number of slices involved and thickness of the blocks)

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Definition of Margin Status

- Ink margins with 6 colors; measure distance on the slides
- Free: >0.2 cm
- Close: 0.1-0.2 cm
- Involved: Cross-sectioned: re-excision
- When margin is <0.2 cm away, we give a quantitation of surface area

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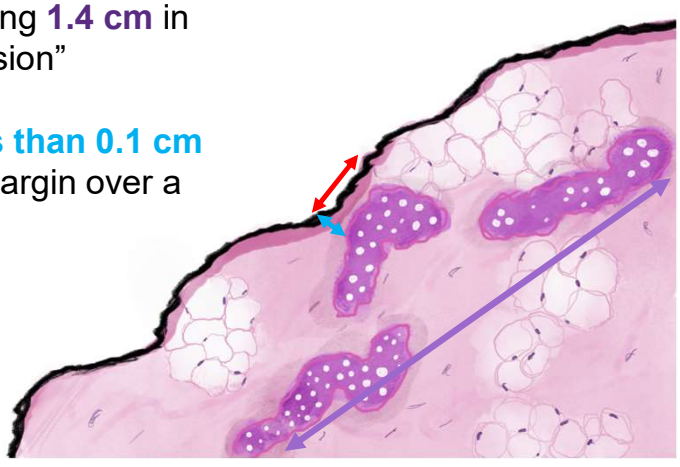
Example of Surface Area Quantitation

"DCIS, measuring **1.4 cm** in greatest dimension"

"Closest at **less than 0.1 cm** from the final margin over a **0.1 cm area**"



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DCIS at the Margin; Extent of Margin Involvement

- Focal (DCIS at the margin in a <0.1 cm area in 1 block)
- Minimal/moderate (between focal and extensive)
- Extensive (DCIS at the margin in an area >1.5 cm or 5 or more low power fields and/or 8 or more blocks)

Lester et al., Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast; Archives of Pathology and Lab Medicine, 133:15, 2009.

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Differential Diagnosis of DCIS Lesions

- UDH
- ADH
- DCIS with microinvasion
- Invasive cancer
- DCIS extending into benign structures
- LVI
- LCIS

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Differential Diagnosis of DCIS Lesions

- **UDH**
- ADH
- DCIS with microinvasion
- Invasive cancer
- DCIS extending into benign structures
- LVI
- LCIS

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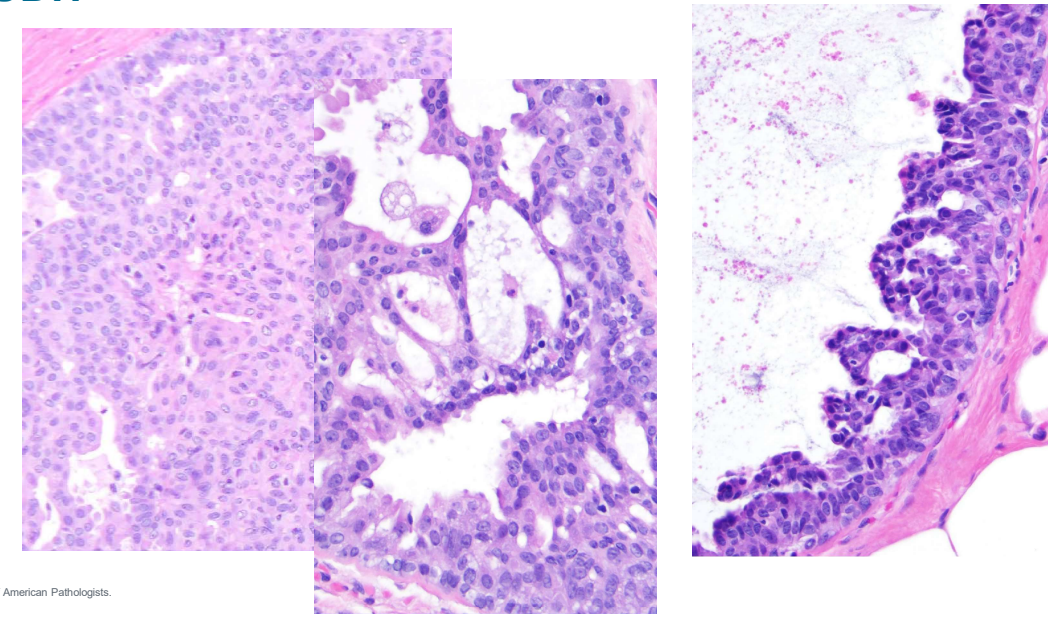
UDH



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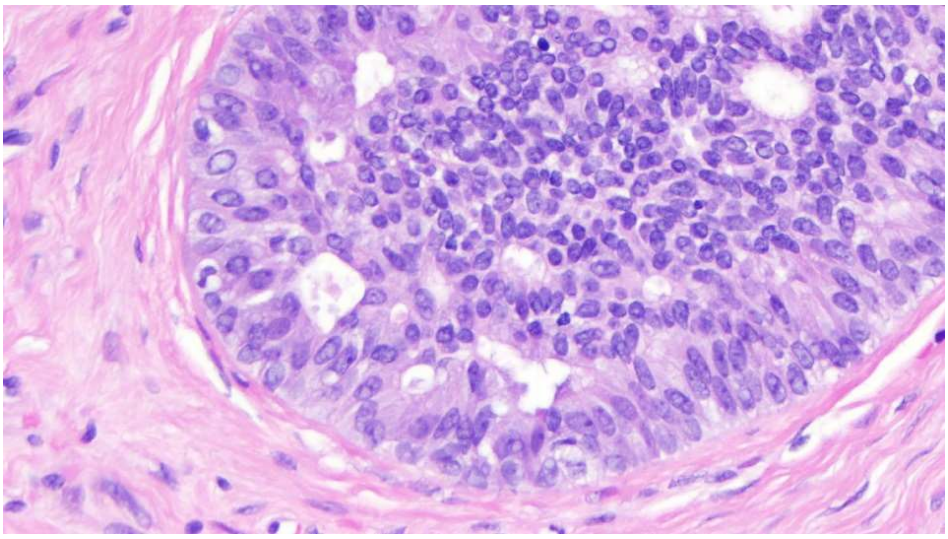
UDH



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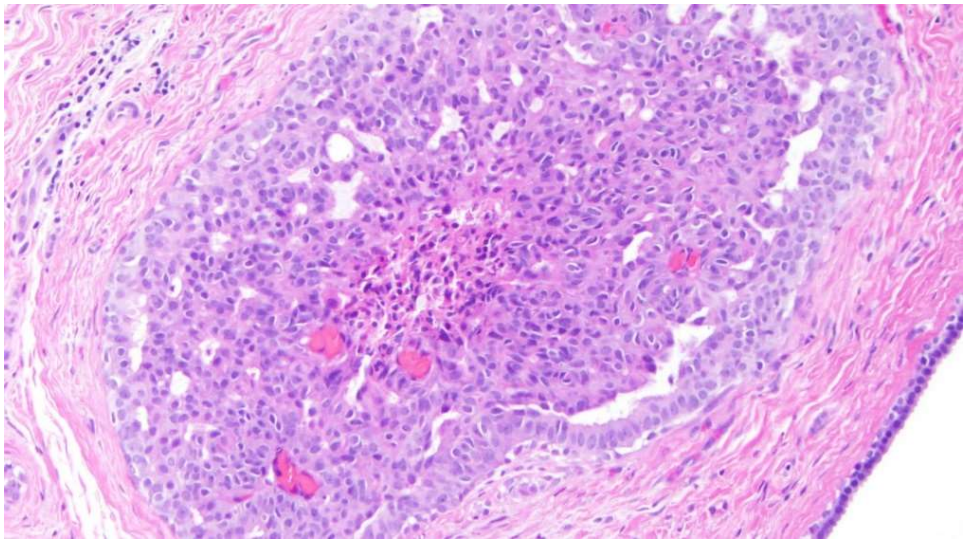
UDH



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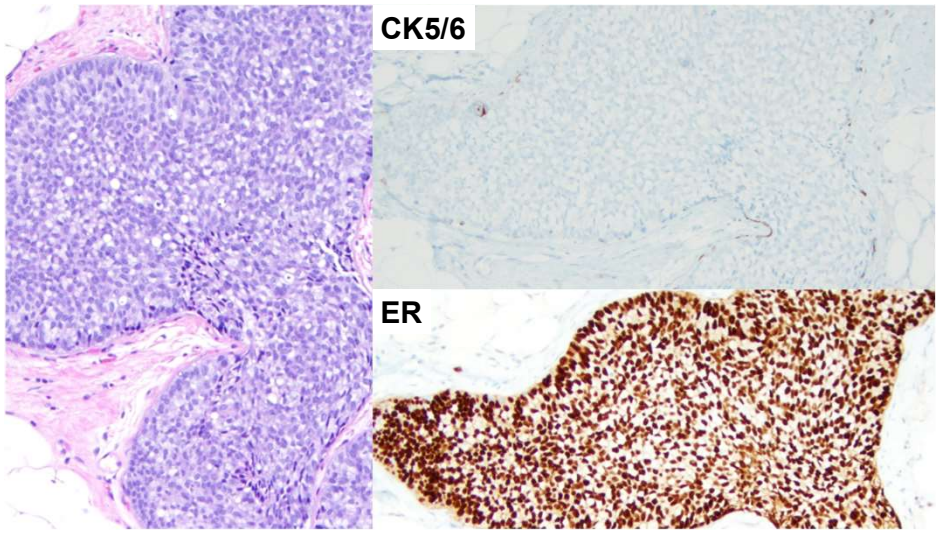
DCIS



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Differential Diagnosis of DCIS Lesions

- UDH
- **ADH**
- DCIS with microinvasion
- Invasive cancer
- DCIS extending into benign structures
- LVI
- LCIS

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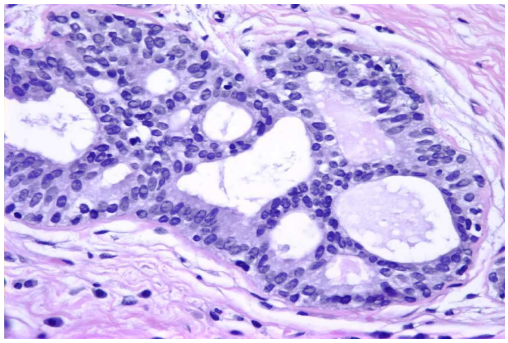
Histologic Criteria for Atypical Ductal Hyperplasia (ADH)

- Lesions have some of the architectural and cytologic features of DCIS, such as:
  - Nuclear monomorphism,
  - Regular cell placement, and
  - Round regular spaces *in at least part of the involved space*



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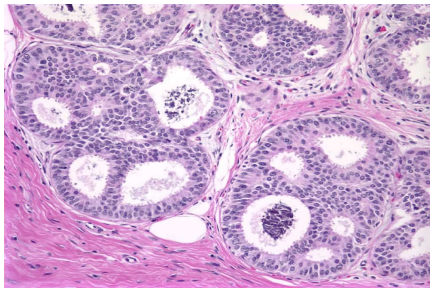
Histologic Criteria for Low Grade (Grade I) DCIS

- Uniform cell population
- "Punched out", neatly rounded geometric spaces
- Bulbous, well defined papillary fronds
- Round, hyperchromatic, monotonous nuclei
- Area bound by basement membrane



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ADH vs. DCIS Quantitative Criteria

- At least 2 spaces of uniformly present atypical cells (Page et al.)
- 2mm rule (Tavassoli and Norris)
  - Only applies to low grade lesions
  - Need for identification of reliable biologic markers

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Comparison between ADH and Low Grade DCIS

Magnitude of risk:

- ADH: 4-5x
- DCIS: 8-10x

Laterality of risk:

- ADH: either side
- DCIS: ipsilateral

Type of subsequent cancer:

- ADH: any histology, any grade
- DCIS: grade similar to DCIS

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Differential Diagnosis of DCIS Lesions

- UDH
- ADH
- **DCIS with microinvasion**
- Invasive cancer
- DCIS extending into benign structures
- LVI
- LCIS

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Microinvasion: Definition

- T1mic: AJCC Cancer Staging Manual, 7th edition, 2010
- Microinvasion is the extension of cancer cells beyond the basement membrane with no focus larger than 0.1 cm
- When multiple foci of microinvasion are present:
  - Note their presence in the report
  - Report the dimension of only the largest one

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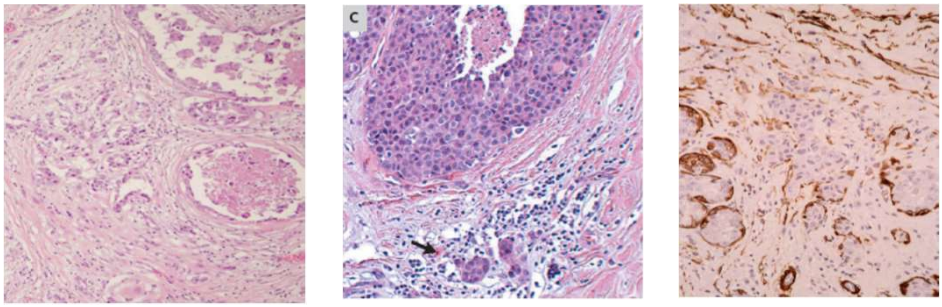
Microinvasion



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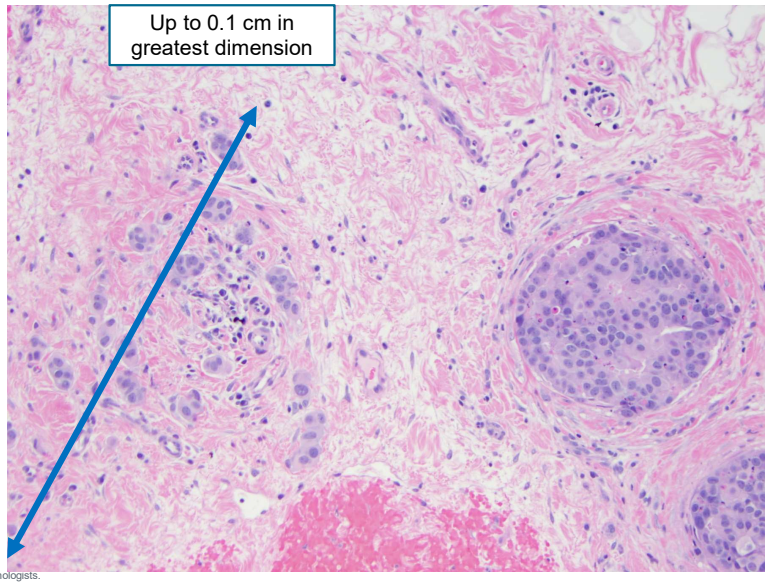
Microinvasion



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DCIS and Microinvasion

- DCIS lesions <2.5 cm 0/29
- DCIS lesions >2.5 cm 11/25 (44%)
- DCIS lesions >5 cm 9/13 (70%)

Sourse: Lagios et al., Cancer 1982.

Association of microinvasive carcinoma with DCIS

- Increased risk : large extent, high nuclear grade, necrosis, comedo architecture
- Size <3.2 cm = 38%
  >3.2 cm = 62%

Source: Kim et al, 2018

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Differential Diagnosis of DCIS Lesions

- UDH
- ADH
- DCIS with microinvasion
- **Invasive cancer**
- DCIS extending into benign structures
- LVI
- LCIS

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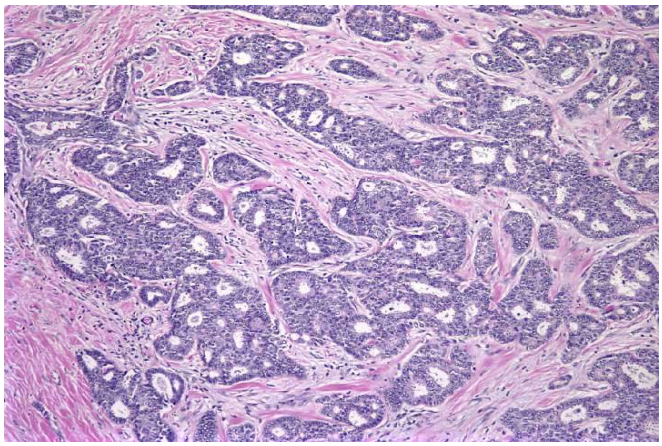
Cribriform Ca



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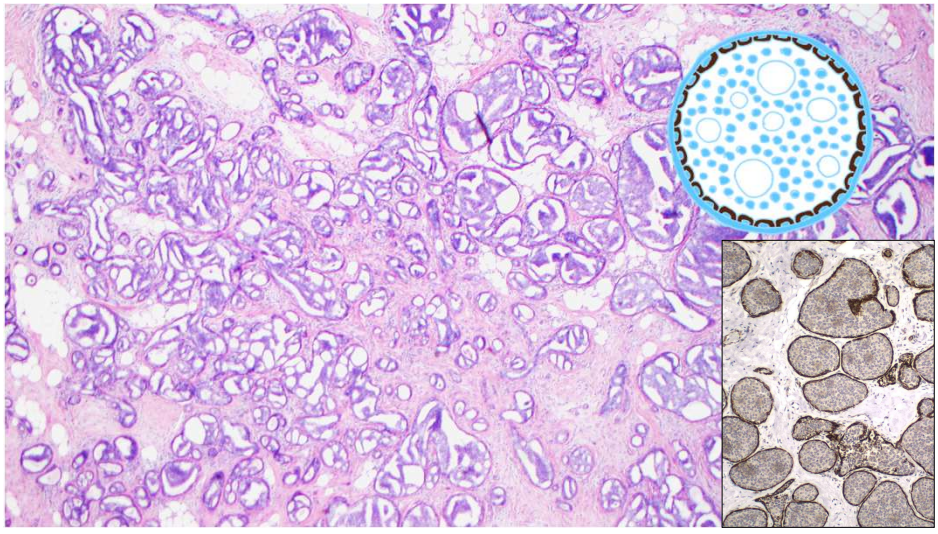
DCIS: SMMS IHC



DCIS: SMMS IHC

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Differential Diagnosis of DCIS Lesions

- UDH
- ADH
- DCIS with microinvasion
- Invasive cancer
- **DCIS extending into benign structures**
- LVI
- LCIS

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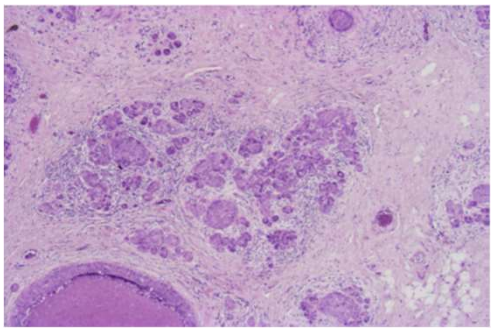
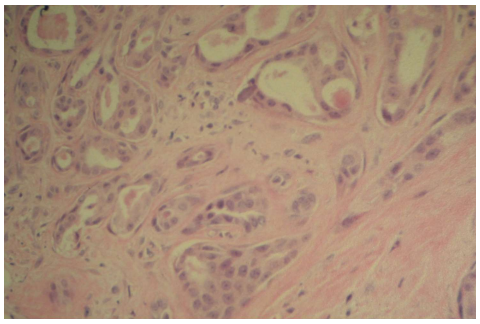
DCIS Extending into Benign Structures



DCIS in lobules



DCIS in adenosis

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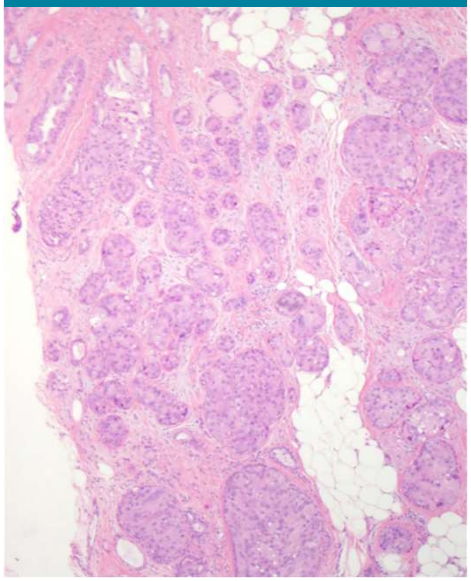
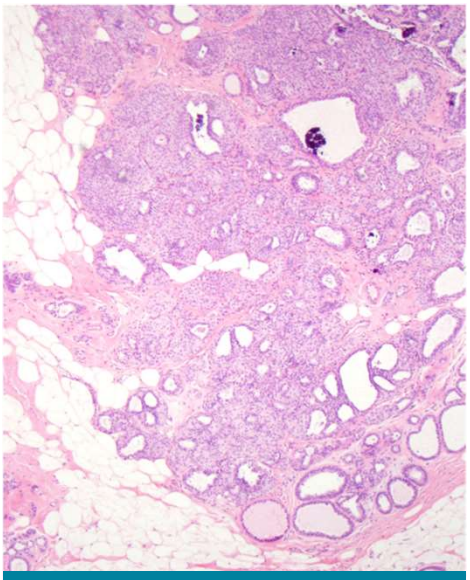
Lobular extension





Involving sclerosing adenosis

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Differential Diagnosis of DCIS Lesions

- UDH
- ADH
- DCIS with microinvasion
- Invasive cancer
- DCIS extending into benign structures
- **LVI**
- LCIS

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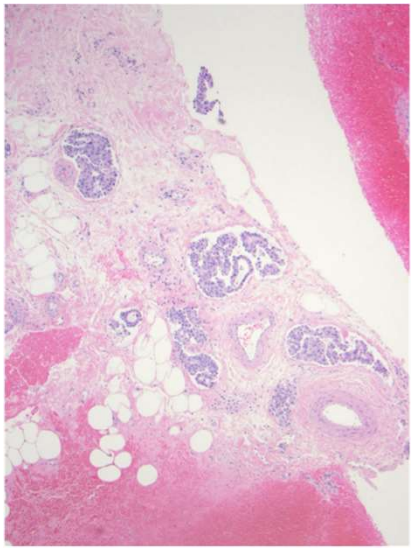
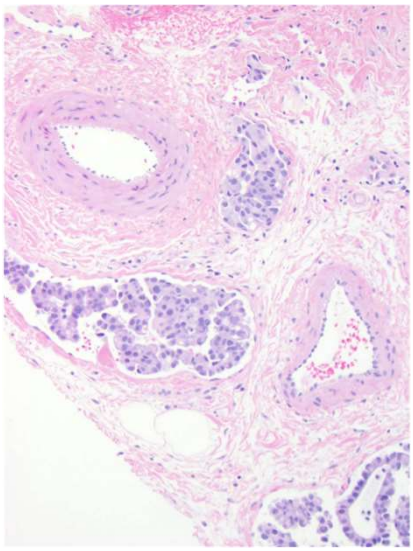
LVI





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IHC Stains Helpful for the Diagnosis of LVI

Differential	P63/SMM	D2-40
DCIS	+	-
IDC	--	-
LVI	-	+

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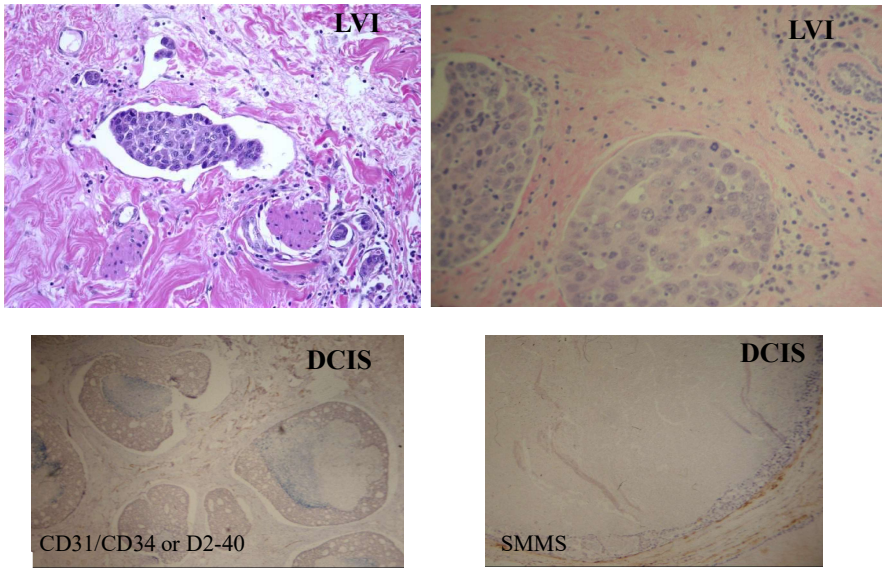
LVI vs DCIS



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Differential Diagnosis of DCIS Lesions

- UDH
- ADH
- DCIS with microinvasion
- Invasive cancer
- DCIS extending into benign structures
- LVI
- **LCIS**

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Lobular Carcinoma in Situ (LCIS)

- Involves lobules
- Occasionally extends into larger ducts (pagetoid spread)
- 50-70% bilaterality (marker of disease propensity)

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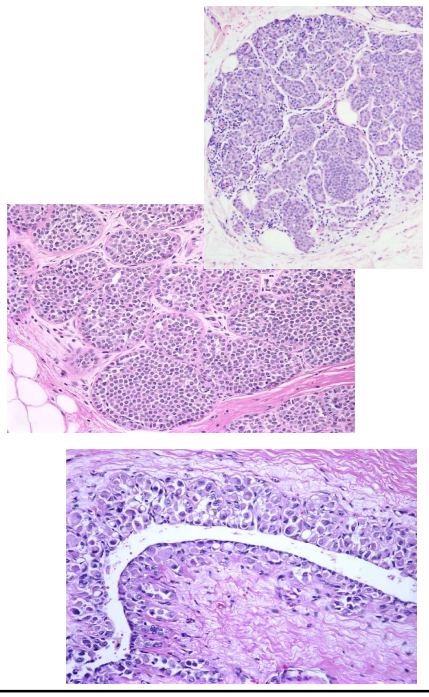
Histologic Criteria for LCIS

- Characteristic, small uniform cells
- Filling of all the acini (no spaces between cells)
- Marked *expansion* of at least one-half of the acini in the lobular unit
- Pagetoid spread into ducts



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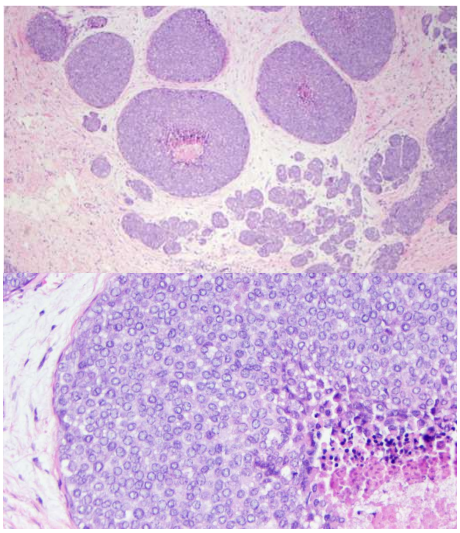
Florid LCIS

- Morphologic features of classic LCIS
- Acini markedly distended with larger cells and foci of comedo-like necrosis may be present
- Managed and reported as DCIS?



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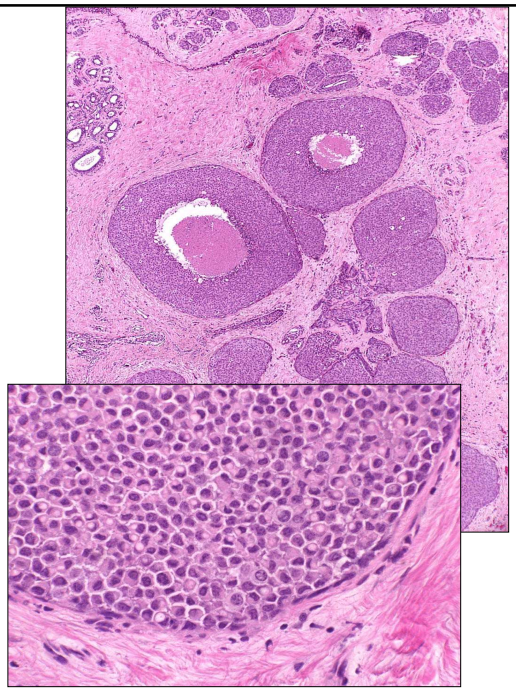
LCIS pleomorphic type

- Lobulocentric growth
- Discoherant cell population
- E-cadherin negative
- Central necrosis
- Nuclear pleomorphism
- Moderate to abundant cytoplasm, signet ring features
- Usually ER positive, GCDFP positive, and HER2 negative



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Biomarkers & Genetics

- Most important biomarker of clinical importance – ER
  - Chemoprevention (use of Tamoxifen/other SERMs)
  - Significant reduction of local recurrence
- Percentage cutoffs
  - <1% = negative
  - 1-9% = low positive
  - ≥10% = positive

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Molecular Pathology Biomarkers in DCIS

- ER/PR
- HER-2/neu
- p53
- Tumor proliferative rate
- Apoptotic markers (e.g. bcl-2)
- Angiogenesis markers
- Cell adhesion molecules (e.g. e-cadherin)
- Extracellular matrix proteins (e.g.MMP-13, tenascin-c)

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Recent Genetic Studies

- Usual ductal hyperplasia has few similarities to ADH, DCIS or invasive cancer
- ADH has many similarities to low grade DCIS
- Low grade DCIS and high grade DCIS appear to be genetically distinct lesions that lead the development of distinct forms of invasive breast cancer
  - LG: losses at 16q, 17p, gains @ 1q
  - HG: genomic instability: losses at 11q, 14q, 8p, and 13q, gains at 17q, 8q, 5p
  - HER2 overexpression, p53 mutations
- Implications on the paradigm of breast cancer progression

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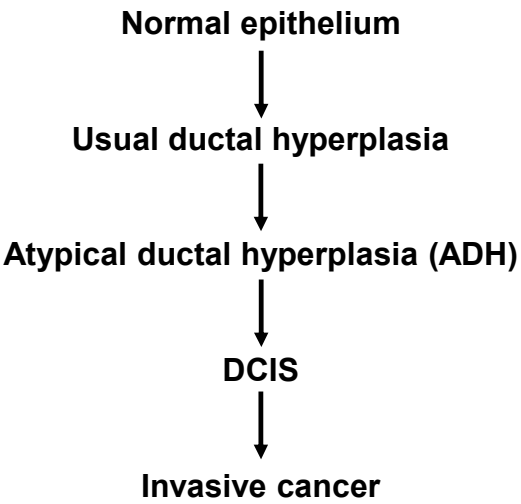
Traditional Breast Cancer Progression Model



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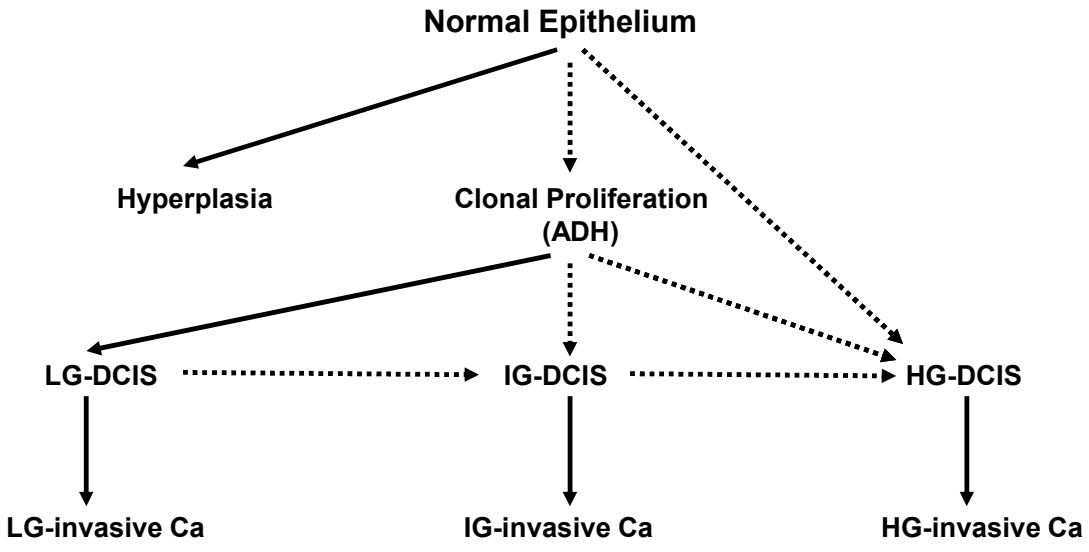
Current Breast Cancer Progression Model



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DCIS Subclasses

- 61% luminal A (ER+, HER-2-)
- 9% luminal B (ER+, HER-2+)
- 16% HER-2 positive (ER-, HER-2+)
- 8% basal-like (ER-, HER-2-, EGFR+, CK5/6+)
- 6% unclassified (neg for all markers)

Livasy et al, Hum Pathol, 38:197-204, 2007

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DCIS Treatment Options

- Breast conserving surgery followed by radiation therapy
- Simple mastectomy
- Unclear role for sentinel lymph node biopsy (high grade DCIS, mastectomy, palpable mass)

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Prognosis

- Extremely good; Cancer deaths due to:
  - Undetected invasive carcinoma at time of diagnosis
  - Recurrence as invasive disease (50% of the time)
- Increased risk of recurrence post-breast conservation
  - Young age
  - Large lesions
  - High grade
  - Comedo necrosis
  - Positive margins

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Summary

- Definition
- Incidence
- Clinical presentation
- Histologic parameters of clinical significance
- Differential diagnosis
- Molecular pathology/biomarkers in DCIS
- Models of breast cancer progression

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Summary

In DCIS, new classifications, new technology and new treatments continue to challenge our pre-existing concepts and understanding of DCIS and are expected to lead to improved patient outcomes.

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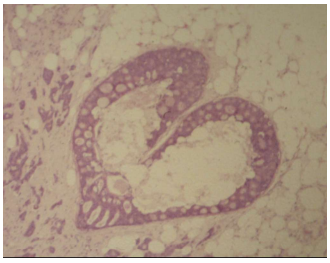
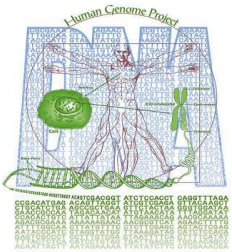
Thank you!





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Questions?

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