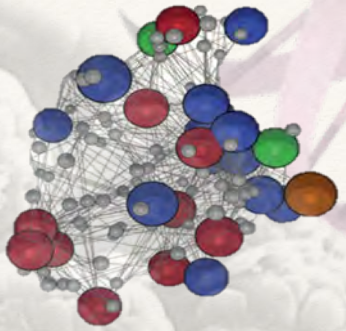

# *Lobular Neoplasia (ALH-LCIS) & management*

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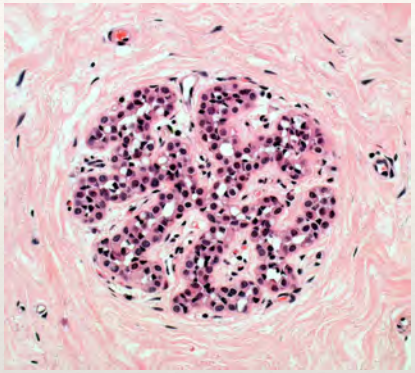
The University Of Queensland AUSTRALIA
Create change

pathology queensland

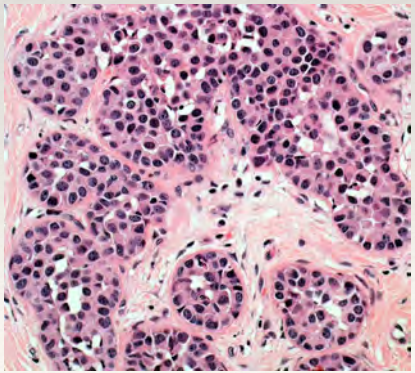
# Lobular Neoplasia

- Lobular neoplasia (LN) spectrum of atypical epithelial lesions originating in the terminal-duct lobular unit (TDLU), proliferation of small, non-cohesive cells, with or without pagetoid involvement.
- The designations “atypical lobular hyperplasia” and “lobular carcinoma in situ (LCIS)” are widely used to describe the variable extent of involvement of individual lobular units

ALH vs LCIS: Quantitative *not* Qualitative AND *Arbitrary*



ALH



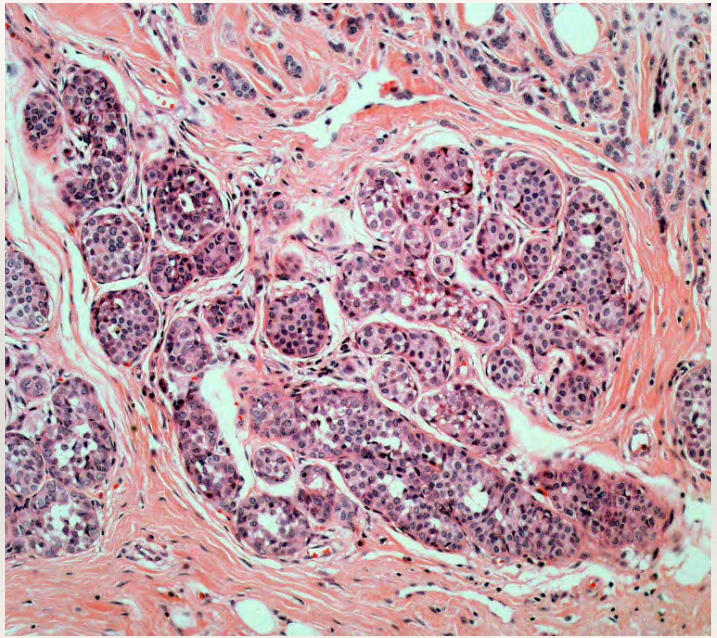
LCIS
classic type

*WHO Classification of Breast Tumours-5th Ed (2019)*

# LCIS - History

FOOTE AND STEWART

- Am J Pathol 1941
- A rare form of mammary cancer
- Incidental, Multicentric
- Invasive Ductal and Lobular



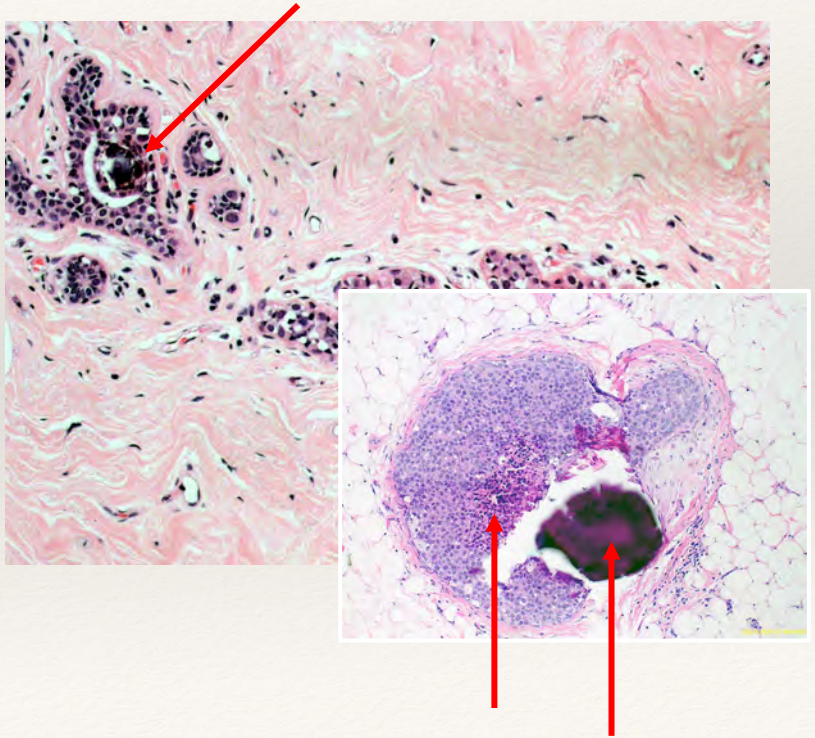
*Foote FW, Stewart FW. Lobular carcinoma in situ: A rare form of mammary cancer. Am J Pathol. 1941 Jul;17(4):491-496.3.*

# Clinical Features

Classic LCIS:
- no specific clinical features
- usually incidental finding

Rare cases (< 2%)
- calcifications or
- heterogeneous non–mass-like enhancement MRI

Pleomorphic LCIS and florid LCIS:
- usually associated with Ca++



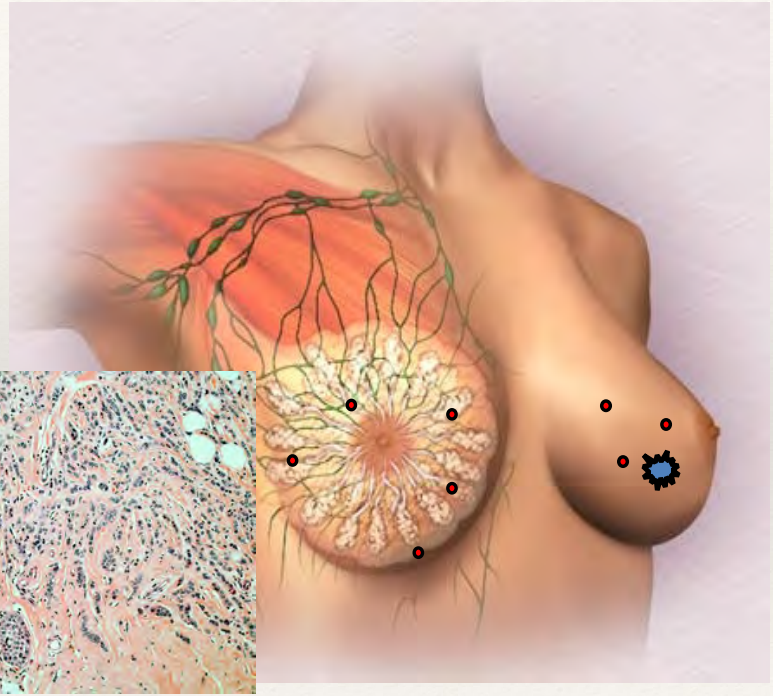
# Epidemiology

- LCIS: rare: 0.5–3.6% of benign breast biopsies & 0.04–1.2% of reduction mammoplasty specimens
- Predominantly in premenopausal women (mean age: ~50 years)
- Pleomorphic LCIS and florid LCIS - postmenopausal women (mean age: ~60 years)

*Francisco Acevedo et al Breast Cancer Research and Treatment (2019) 173:201–207; Beute BJ, et al. AJR Am J Roentgenol. 1991 157(2):257-65 Desouki MM, et al. Hum Pathol. 2013 44(9):1877-81; Chen YY, Hwang ES, Roy R, et al. Am J Surg Pathol. 2009 Nov;33(11):1683-94.*

# Pathology & Natural History

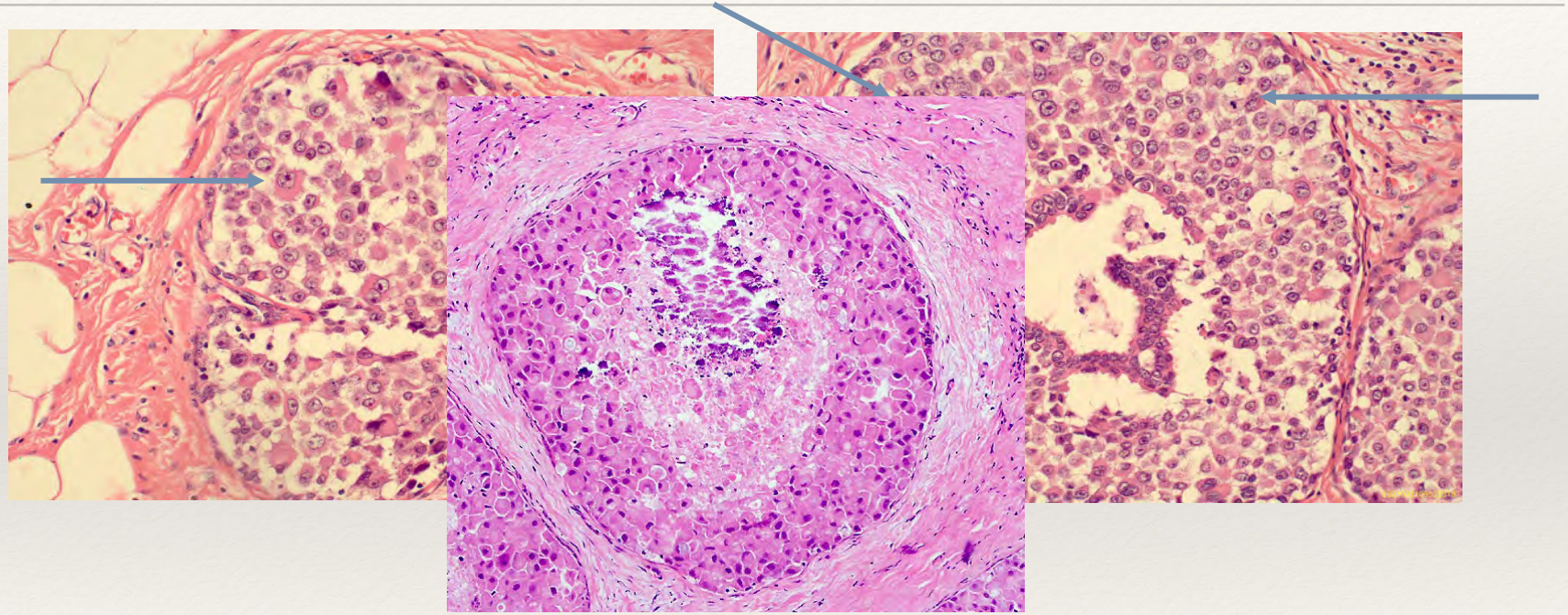
- Multifocal & Bilateral (Classic)
- Risk of ILC – 1-2% per year
- Risk bilateral, with IDC & ILC
- Risk > in Ipsilateral breast
- Risk > for ILC
- Risk for PLCIS unclear





*Rosen PP, et al. Am J Surg Pathol. 1978 Sep;2(3):225-51; Fisher ER, et al. 2004 Jan;100(2):238-44.; King TA,, et al. . J Clin Oncol. 2015 Nov;33(33):3945-52..; Ansquer Y, Delaney S, Santulli P, et al.. Eur J Surg Oncol. 2010 Jul;36(7):604-9.;Malone KE,, et al., 1988-2001. Cancer. 2006 May;106(10):2104-12.; Wheeler JE et al,. 1976;11:161-88.*

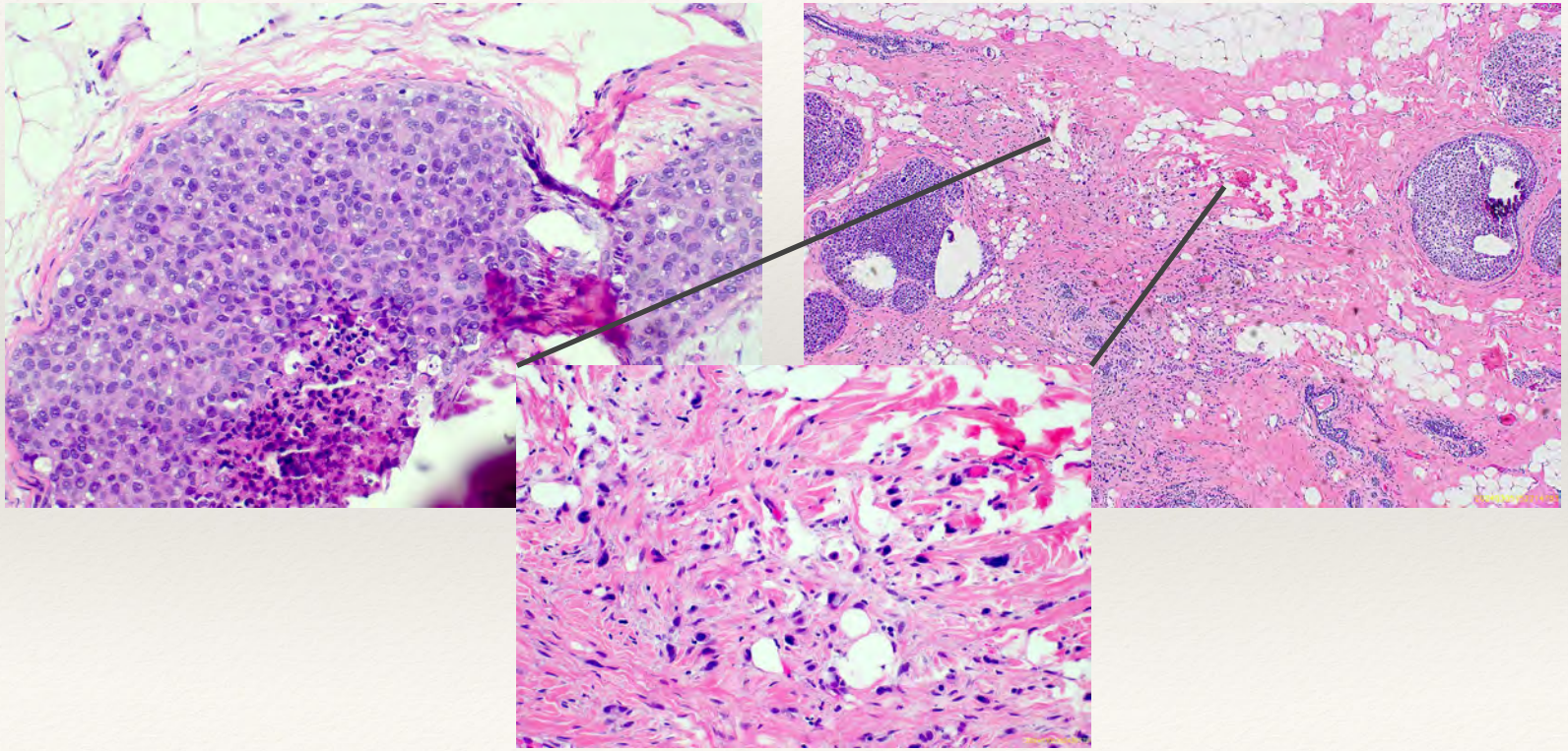
# Subtype - Pleomorphic



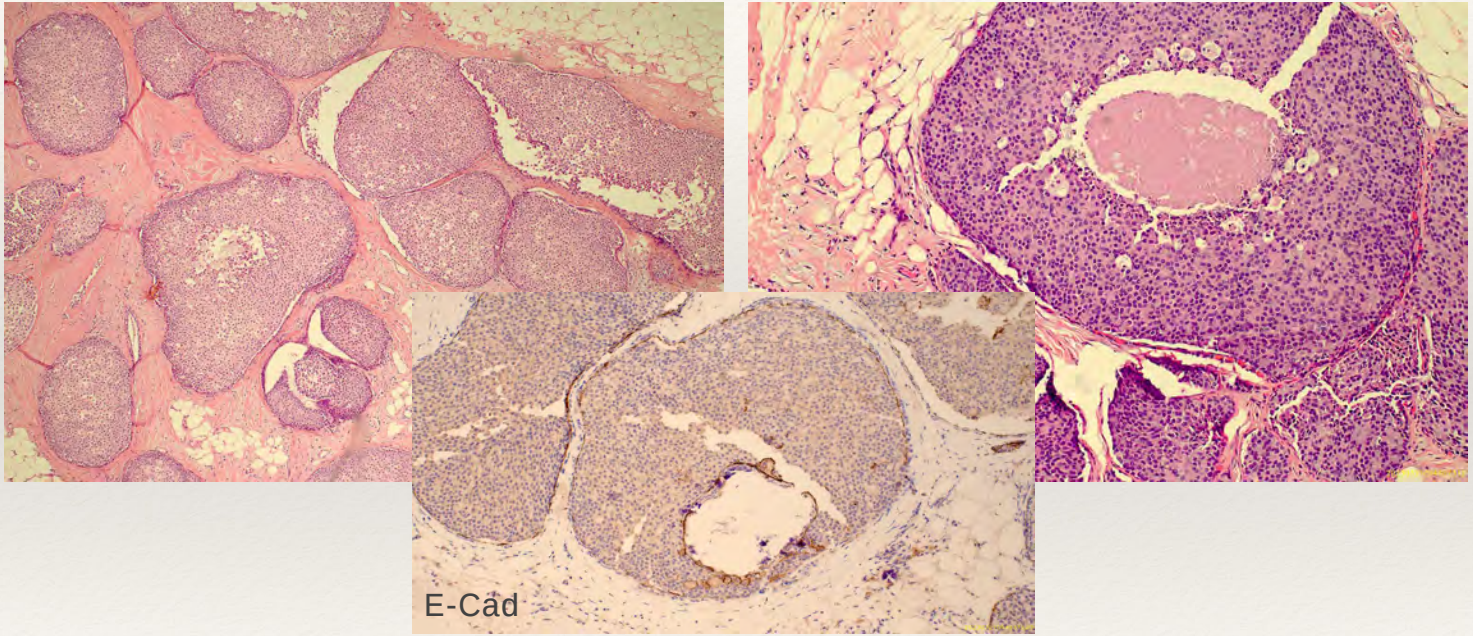
Marked Nuclear Pleomorphism – similar to high grade DCIS

+/- Apocrine differentiation, necrosis, calcification

# Subtype - Pleomorphic



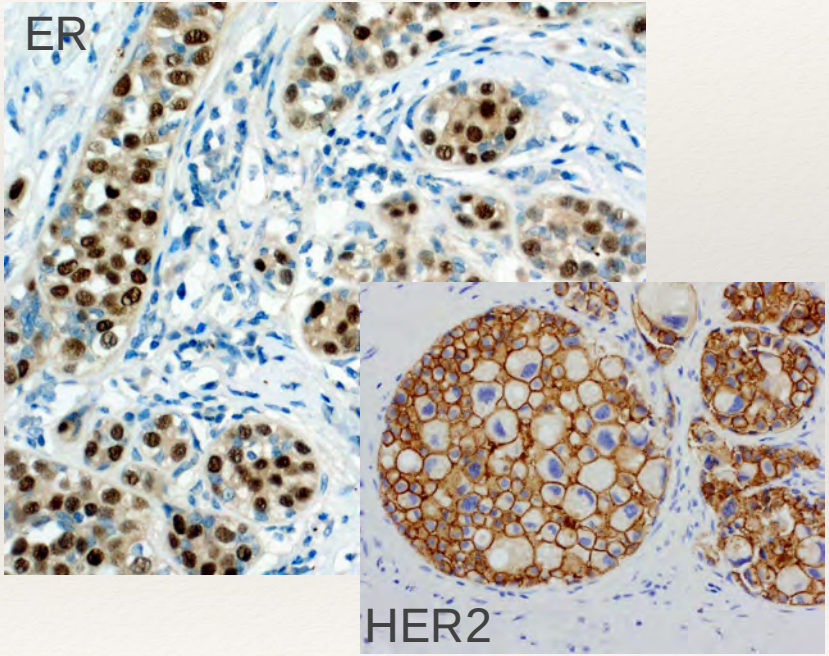
# Subtype - Florid




Classic LCIS – marked distention - confluent growth, +/- necrosis and Ca++

# LCIS: Biomarker profile

- ER: Positive
- PR: Positive
- Her2: Negative



# LCIS: a non-obligate precursor

## Loss of heterozygosity in lobular carcinoma in situ of the breast

S R Lakhani, N Collins, J P Sloane, M R Stratton

**Abstract**

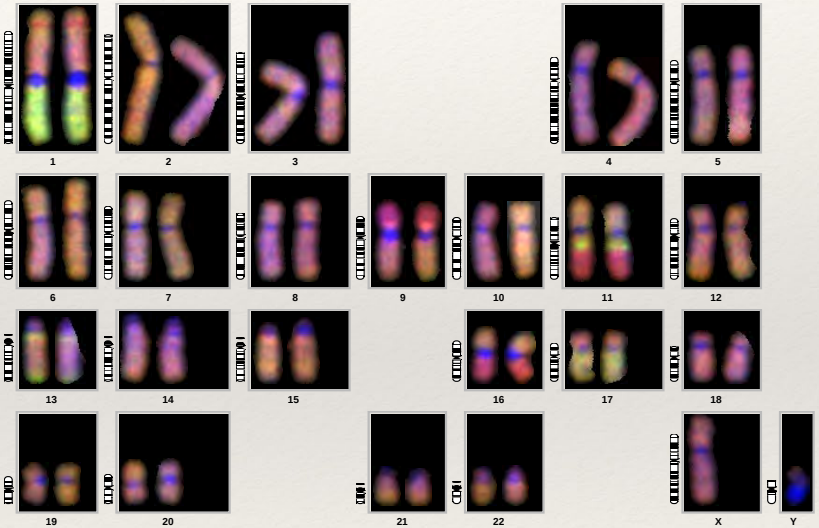
***Aims*—(1) To investigate whether loss of heterozygosity identified at various loci in invasive breast carcinoma or is present in lobular carcinoma in situ (LCIS). (2) To investigate whether LCIS is a monoclonal (neoplastic) or a polyclonal (hyperplastic) proliferation.**

***Methods*—Forty three cases of LCIS (30 with associated invasive carcinoma or in situ ductal carcinoma (DCIS) and 13 cases of pure LCIS) were investigated for loss of heterozygosity on chromosomes 16q, 17q, 17p, and 13q using a microdissection technique, polymorphic DNA markers, and the polymerase chain reaction (PCR).**

***Results*—Loss of heterozygosity was detected in both subgroups of LCIS at all the loci examined. There was no significant difference in the frequency of the loss between the group associated with invasive carcinoma and the pure LCIS group. The frequency of loss of heterozygosity ranged**

of age, usually as an incidental finding in a biopsy taken for other palpable or mammography detected benign or malignant lesions. LCIS is not palpable and rarely visible on mammography.[2] Over the 25 years following diagnosis, approximately one fifth of patients with LCIS will develop invasive cancer.[3-7] Invasive cancers are equally likely to occur in the contralateral breast and in the breast known to contain LCIS. This is in contrast to partially resected DCIS in which the invasive cancer usually develops in the same quadrant of the same breast as the DCIS.[8] Approximately 50% of invasive cancers developing upon a background of LCIS are lobular in type, the remainder being a mixture of ductal-NST (no special type), tubular, and others.[4]

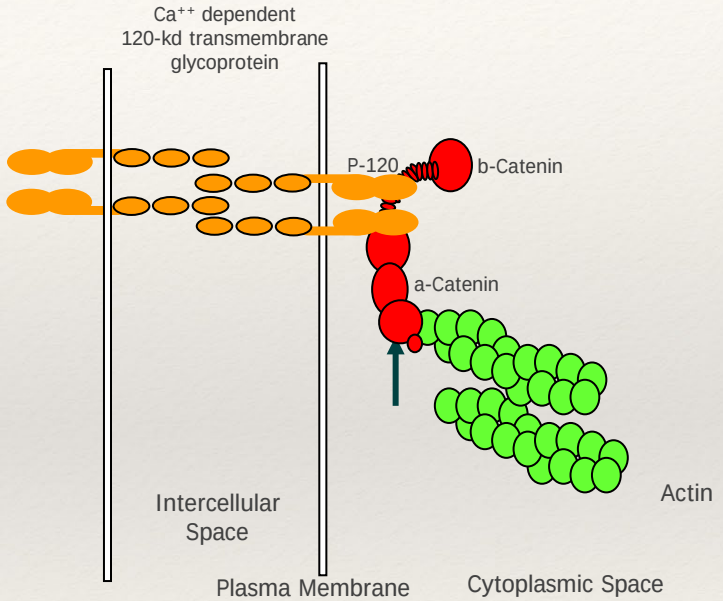
The biological nature of LCIS and its relationship to invasive carcinoma are ill defined. LCIS has been regarded solely as a risk indicator for invasive cancer.[9,10] By this hypothesis, the presence of LCIS indicates that the whole breast epithelium is at increased risk




*Lakhani et al. Clin Mol Pathol 1995. 48(2): M74–M78*
*Lu et al: Can Res 1998 58(20) 4721-7*

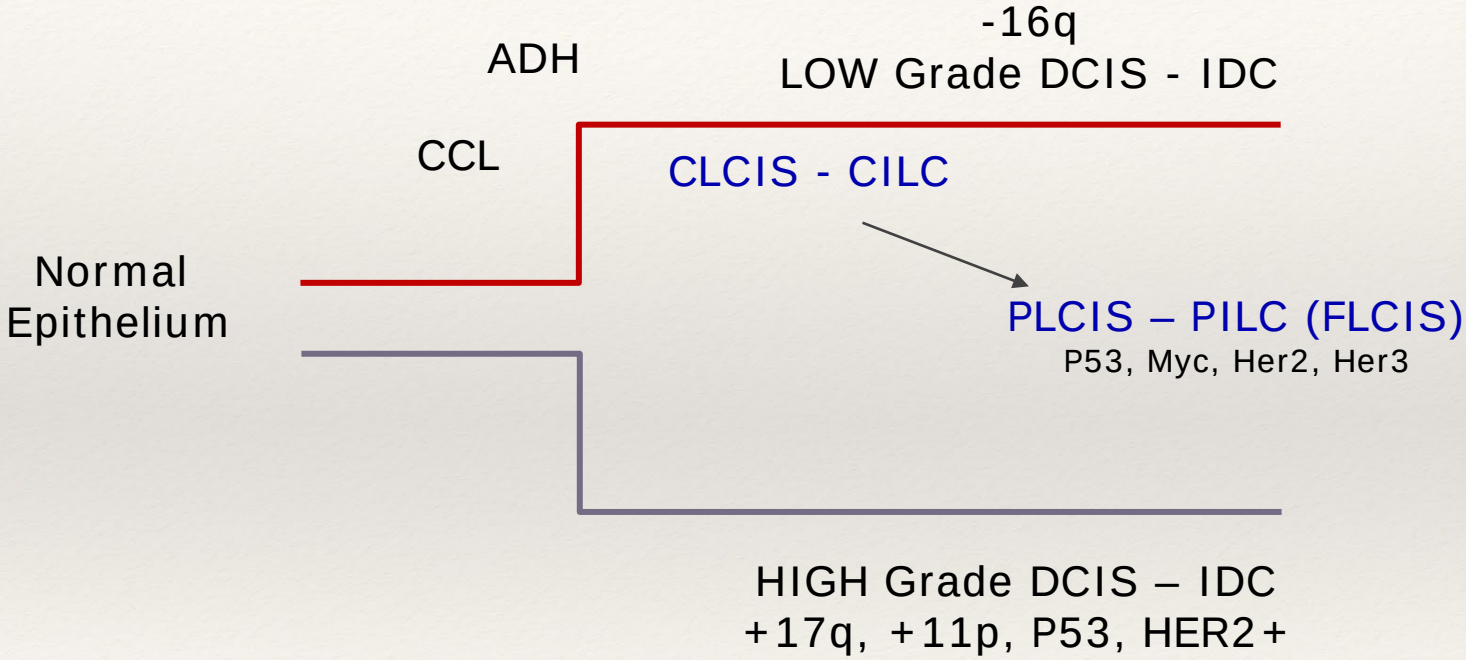
# LCIS: E-Cadherin

- *CDH1* cloned in 1995, 16 exons, 16q22.1
- Approx 60-80% ILC mutations
- LCIS and ILC from same pt showed same mutation




*Berx G, Van Roy F. The E-cadherin/catenin complex: an important gatekeeper in breast cancer tumorigenesis and malignant progression. Breast Cancer Res. 20013(5):289-93.*
*Vos et al E-cadherin inactivation in lobular carcinoma in situ of the breast: an early event in tumorigenesis. BJC 1997 76;1131-3*

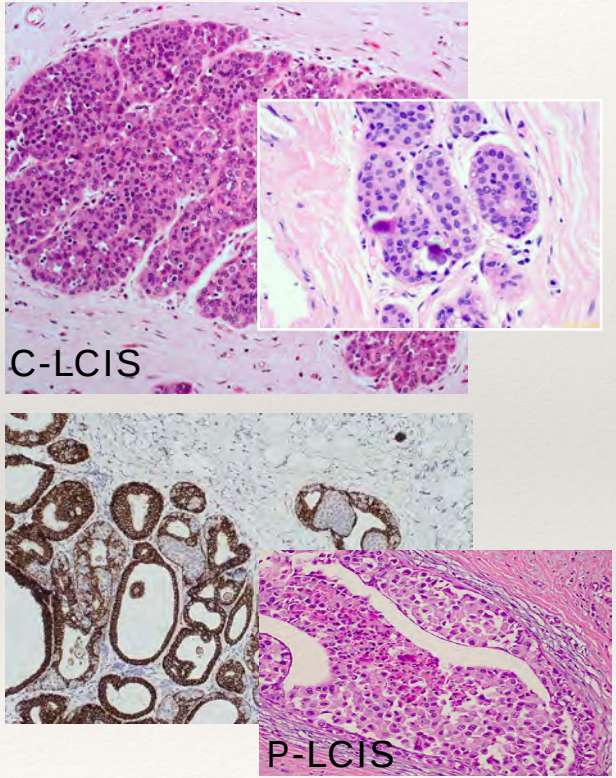
# Multistep Model




*Reis-Filho et al J Pathol 2005 207(1) 1-13; Simpson et al. J Pathol 2005 205(2) 248-54; Simpson et al J Pathol 2008 215(2) 248-54; Boldt V, et al. Genes Chromosomes Cancer. 2010 49(5):463-70. ; Chen YY, et al. Am J Surg Pathol. 2009 Nov;33(11):1683-94. ; Etzell JE, et al. Hum Pathol. 2001 Mar;32(3):292-6. ; Shin SJ, et al. Hum Pathol. 2013 Oct;44(10):1998-2009; Shamir et al, Mod Pathol (2019) 43: 39-408; Harrison et al Mod Pathol 2020* 33(7):1287-1297

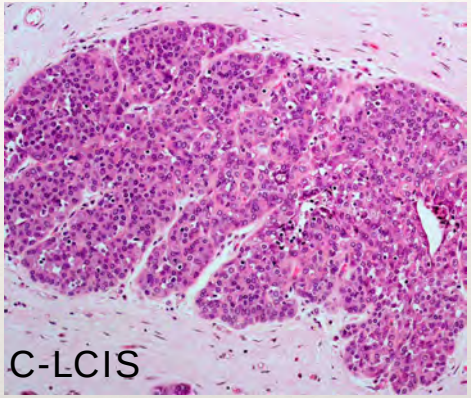
# Management implications – Core biopsies

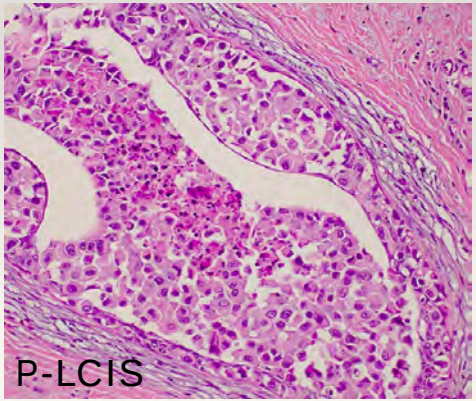
- Still Controversial, Some – excision – even cLCIS
- Most would not excise for incidental CLCIS
- Excision if index lesion or discordance between radiology-pathology
- Presence of another lesion (ADH/DCIS)
- Mixed/indeterminate features
- PLCIS/FLCIS



# Management implications – Excision Specimen

- CLCIS – size, margins not relevant and not recorded
- FLCIS and PLCIS – margin status is recorded to allow discussion @ MDT
- Overall, MDTs tend to treat PLCIS like DCIS, FLCIS more variable

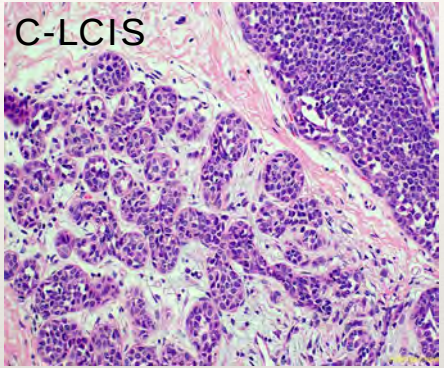

C-LCIS

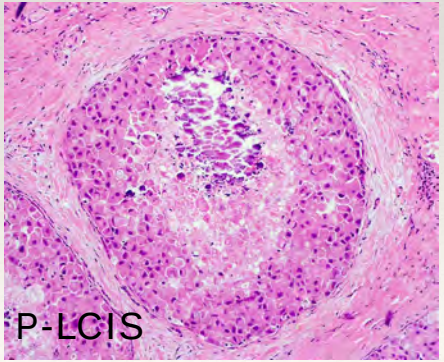

P-LCIS

# Role for Radiotherapy

- No evidence for role in risk reduction for CLCIS

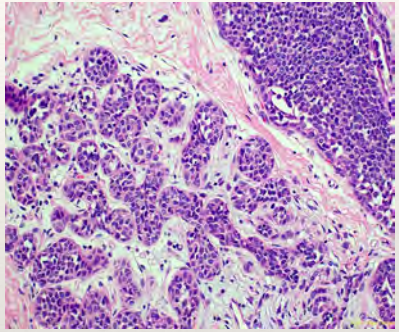
- Since PLCIS is treated like DCIS, logical to consider its use, but there is no evidence to support this

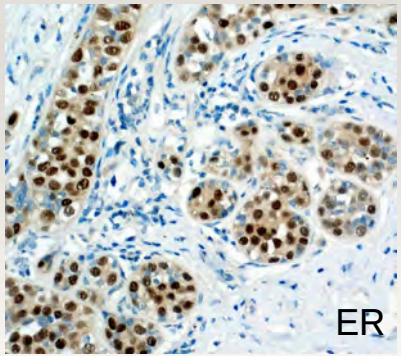


# Risk reducing medication

- LCIS mostly ER+ve
- Evidence for 50% reduction in recurrence with use of anti-oestrogens Rx
- No survival benefit demonstrated
- MDT discussion for risk-benefit-side effects

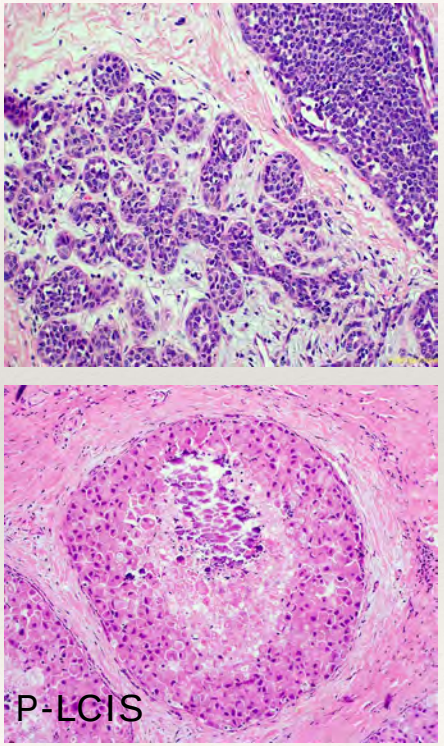





*Allison et al 2020 J Clin Oncol (38) 1346. ASCO-CAP Guidelines for ER/PR Testing*

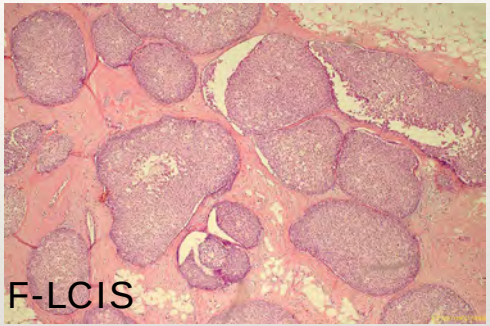
# Risk reducing surgery & surveillance

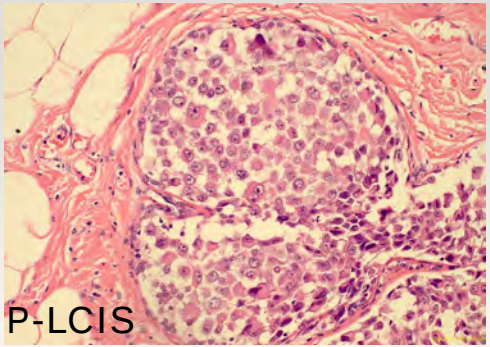
- Prophylactic bilateral mastectomy not recommended for most women
- Option for some women - needs genetic and MDT discussion
- Surveillance is also an issue (yes/no and modality) for MDTs



# Summary

- Risk lesion and non-obligate precursor (like DCIS)
- Molecular data – P-LCIS/F-LCIS similar to high grade DCIS
- Evidence of natural history and data for therapeutic intervention weak or incomplete
- Management decisions partly evidence based, partly pragmatic
- MDT discussions therefore become very important – so management is in context


F-LCIS


P-LCIS

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