DCIS Biology and Treatment

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Which in situ breast epithelial lesions are:

Hyperplastic

Neoplastic

     Benign   – "adenoma"

     Malignant   – "carcinoma in situ"

Which in situ breast epithelial lesions are:

Hyperplastic
> Usual Hyperplasia

Neoplastic

> "Benign" - adenoma / microfocal neoplasia / low grade
> > ? ADH / microfocal low grade DCIS
> > ? Lob Neoplasia
> > ? Columnar alteration

> "Malignant" - carcinoma in situ
> > ? "established" DCIS
> > ? some forms of LCIS

Neoplastic insitu breast epithelial lesions

Challenges:

Understanding molecular genetic pathogenesis

Identification of clinical relevance

Effective strategies for management

Development of reproducible criteria for routine classification

Risk and Epithelial Prolif.

Lesion	Risk	
Florid UEH	1.5 - 2	Minimal risk
ALH	4x	
ALH + family history	8 -10x	
ADH	4x	Bilateral risk
LCIS	10x	
LCIS + family history	10x	
DCIS low grade	10x	Ipsilateral risk

Lobular neoplasia risk most relevant in 5th decade

Slight preponderance of cancer in the ipsilateral breast for LN

Which in situ breast epithelial lesions are:

Hyperplastic = heterogeneous

Neoplastic = homogeneous / clonal

Benign - "adenoma"

Malignant - "carcinoma in situ"

Genetic alterations

LOH Studies

UDH   approx 10% (0-30%) usually one locus only

ADH   approx 50%

                similar loci to low grade DCIS and similar alterations found in subsequent inv ca of same breast

DCIS   50 – 80% numerous sites (similar to inv ca)

"……………..it is very questionable whether ADH represents a true histopathological entity"

Marc van de Vijver. Biological variables and prognosis of DCIS. The Breast 2005;14; 509-19

Grade of Invasive Cancers Developing Within DCIS

	Histological grade of invasive carcinoma			
DCIS	I	II	III	Total
Low grade	13 **(81%)**	3 (19%)	0	16
Intermed g	22 (24%)	63 **(70%)**	5 (6%)	90
High grade	3 (1%)	90 (42%)	119 **(56%)**	212
Cadman et al. The Breast (1997) 6, 132-137; Olubunmi et al (1994) Seminar in Diag Path 11, 215-222				318

DCIS

Relationship to invasive carcinoma

Summary

Morphological and molecular similarities

Clonal process

Analogous to epithelial in situ lesions elsewhere

High frequency of progression to invasive carcinoma if incompletely excised

Risk of invasive cancer after biopsy alone

	N		All	%
Lewis	1938	(8)	6	75
Farrow	1970	(25)	5	20
Haagensen	1971	(11)	8	73
Millis	1975	(8)	2	25
Rosen	1980	(15)	8	53
Eusebi	1994	(80)	11	14
Page	1995	(28)	9	32

Mean = 28 %

Natural history of low grade DCIS

- 28 patients with low grade identified from 1950-1968
- 30 yrs follow up
- 11 (39%) invasive cancer
- 5 (18%) breast cancer deaths
- 4 of the 5 breast cancer deaths occurred within 15 years

M Sanders D Page et al Cancer 2005

Natural history of low grade DCIS

D Page et al 2002

- Studies around this time where the DCIS was recognised found that the lesion was completely excised in 40% when mastectomy was performed
- If this was the case in this series, 17 would have had residual DCIS

Natural history of low grade DCIS

D Page et al 2002

- Revised invasive risk 61%
- Revised breast cancer death rate 29%
- 24% breast cancer death rate within 15 years
- Probably still a conservative estimate as residual lesions had been debulked

Mastectomy for DCIS - Results

	N	Recurrence	Follow-up (yrs)
Farrow et al '70	(181)	1	5 - 20
Ashikari et al '77	(74)	0	11
Sunshine et al '85	(68)	3	> 10
Schuh et al '86	(52)	1	5.5
Fisher et al '86	(28)	1	3.2
Kinne et al '89	(101)	1	11
Arneson et al '89	(28)	0	6.4
Silverstein et al '95	(167)	2	6.5

% Local Recurrence / annum after WLE alone

	N	All	Invasive
NSABP	403	4.7	2.4
EORTC	500	4.2	2.0
Milan	74	4.4	2.7
Florence	106	1.9	1.0
Manchester	127	4.5	1.0
Edinburgh	67	3.5	1.2
Nottingham	97	1.9	1.0
Philadelphia	233	4.4	1.3
Mean =		3.9	1.7

DCIS

Recurrence in remote quadrants

- 5% (2/43)

Adesson Fisher Zafrani

DCIS

Definitions

Unicentric
(1 duct system)

Multicentric
(>1 duct system)

Focal
continuous

Multifocal
discontinuous

Holland

DCIS

81 cases - 1 duct system

1 case - multiple ducts systems

Unicentric process

Holland Lancet 335, 519, 1990

DCIS
Grade and Recurrence

	Subtype	Nuclear grade	Necrosis	Architecture	Recurrences No	%
I	Comedo	High	+++	Solid	7/31	(23)
II	Crib/pap with necrosis	High	+++	Crib/pap	2/5	(40)
	Sub total				9/36	(25)
III	Cribriform/intermediate	Intermediate	+/-	Crib	1/10	(10)
IV	Micropapillary/non necrotic cribriform	Low	0	Micropap/crib	0/33	(0)

Lagios Surg Clin North Am 70, 853, 1990

Van Nuys Prognostic Index

Score	1	2	3
Size	<16mm	16 – 40mm	>40mm
Margin width	>9mm	1 – 9mm	<1mm
Pathology	Not high	Not high	High
	No necrosis	+/- Necrosis	Necrosis
Age	>60yr	40 – 60yr	<40yr
Van Nuys Score	4 - 6	7 - 9	10 - 12
10-year act LR free	96%	73%	37%

Silverstein '99

Margin	N	Mean size	High grade	Comedo	LR at 8 yrs
10mm	93	9mm	46%	23%	2.2%
1 – 10mm	124	8mm	32%	32%	18.9%
< 1mm	39	19mm	67%	74%	33.3%

Factors Predicting Local Recurrence after WLE alone

Close / incomplete margins

High grade / Comedo necrosis

Young age

(Size)

Univariate analysis for ipsilateral recurrence

Grading System		n	N of events	H.R.	95 % C.I.
Nuclear Grade	1	86	6 (7.0%)	0.51	0.22 - 1.15
	2	225	13 (5.8%)	0.41	0.23 – 0.72
	3	913	135 (14.8%)	1.00*	
Van Nuys Grade	1	99	5	0.39	0.16 - 0.94
	2	212	14	0.45	0.26 - 0.78
	3	913	135	1.00*	
Differentiation	1	90	6	0.38	0.22 - 0.66
	2	248	14	0.47	0.21 - 1.07
	3	886	134	1.00*	

Classification of DCIS

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- Low Nuclear Grade
- Intermediate Grade
- High Nuclear Grade
- Mixed Type
- Other (Rare) Variants

- RCPath, NHS BSP and EU Pathology Reporting Guidelines 2005

DCIS

Allelic imbalance analysis suggests that low grade & high grade carcinomas follow different genetic pathways
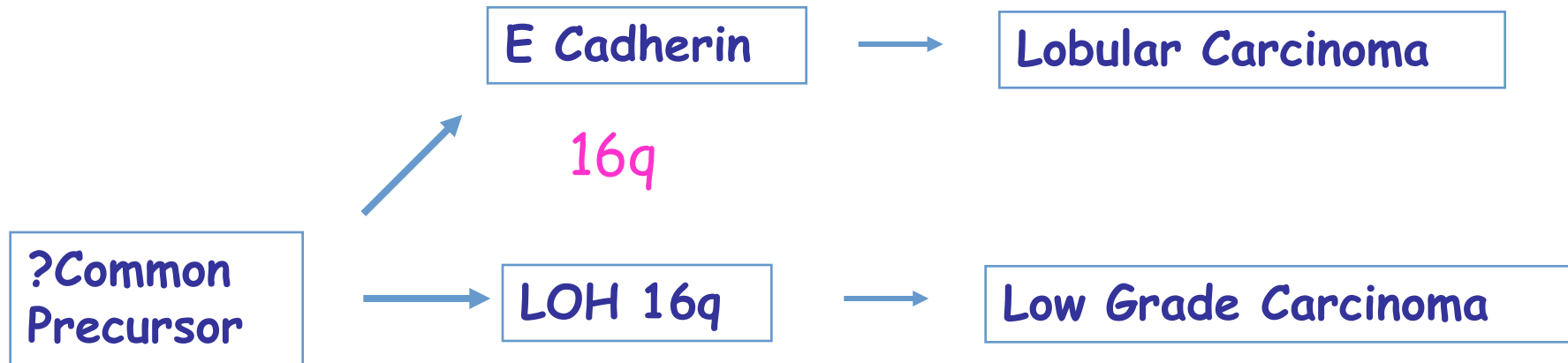
Roylance et al. J Pathol 2002; 196:32-36

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?Common Precursor → E Cadherin → Lobular Carcinoma

?Common Precursor → LOH 16q → Low Grade Carcinoma

?Common Precursor → C-erbB-2 & p53 → High Grade Carcinoma
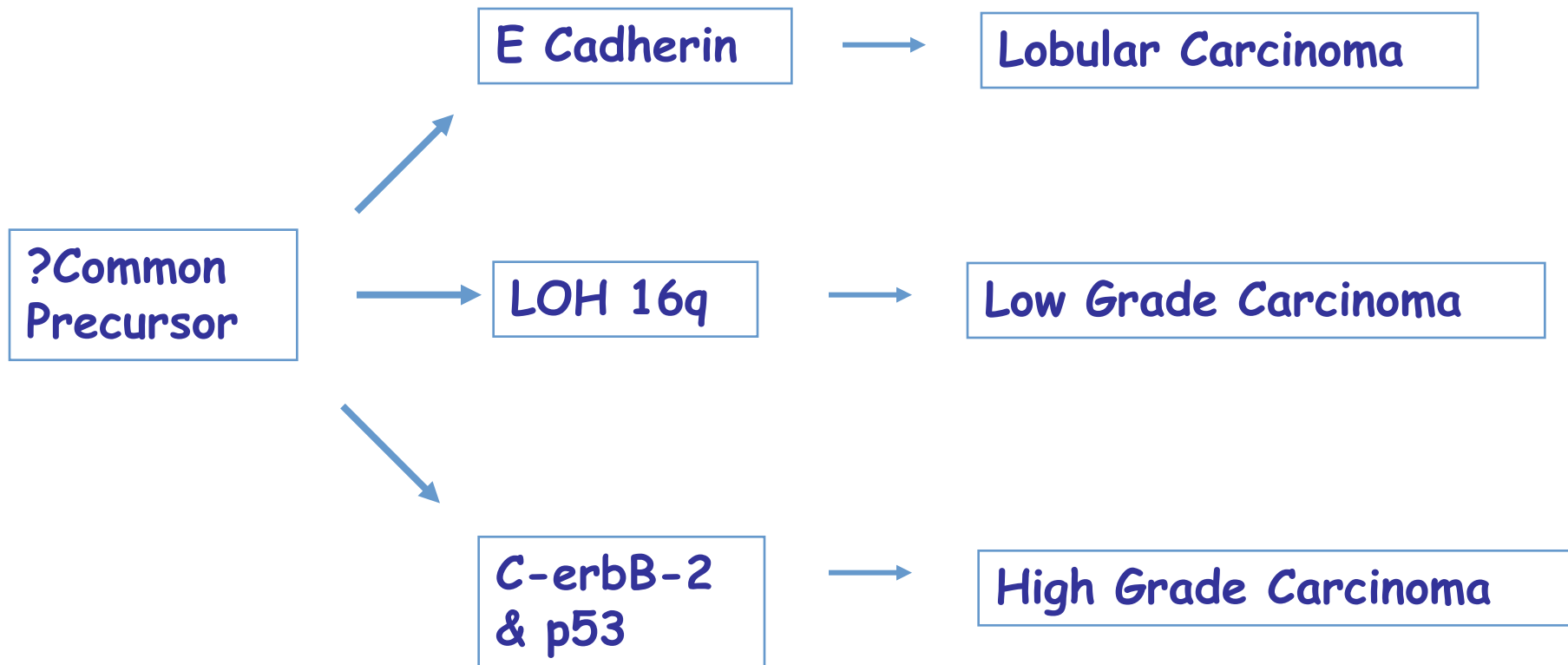
Other candidates: BRCA 1   17q   Medullary
                   BRCA 2   13q   Tub & Lob
                   1q 3p 11q 13q 17q   Tubular
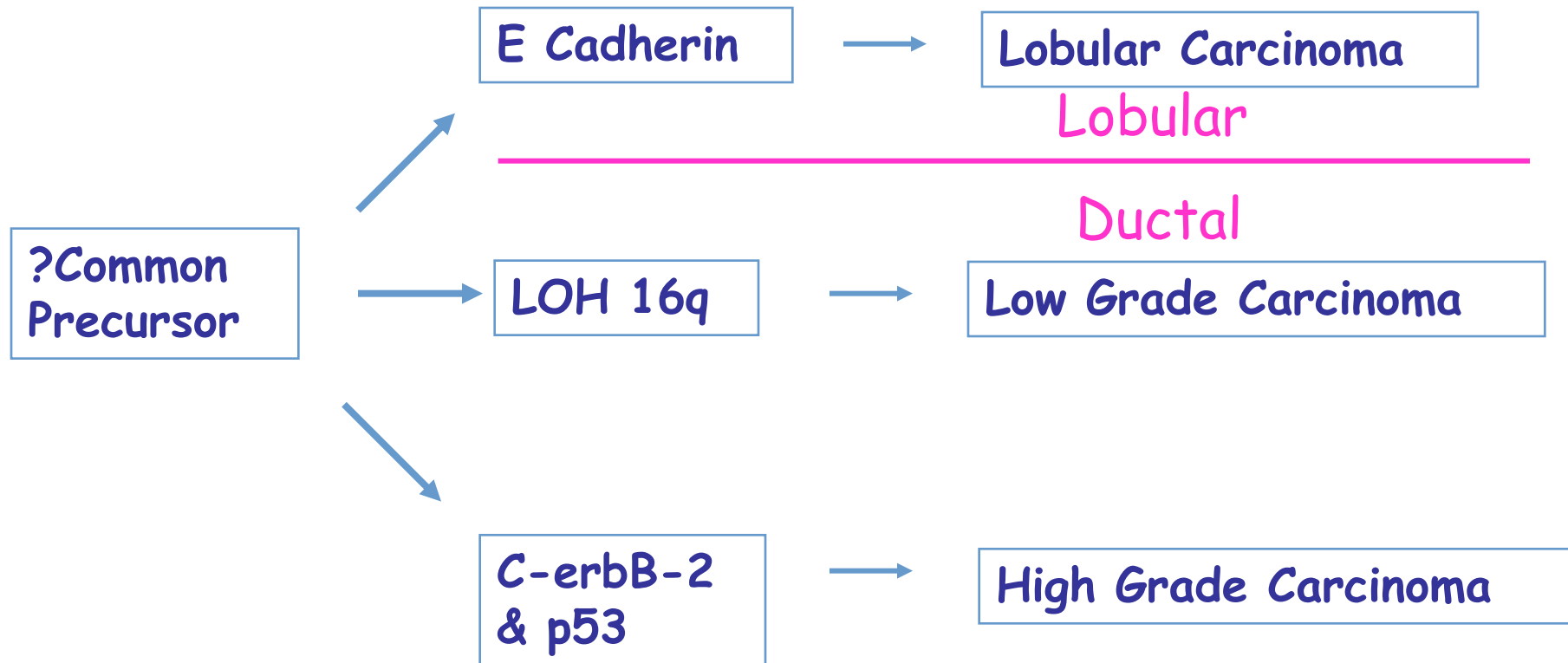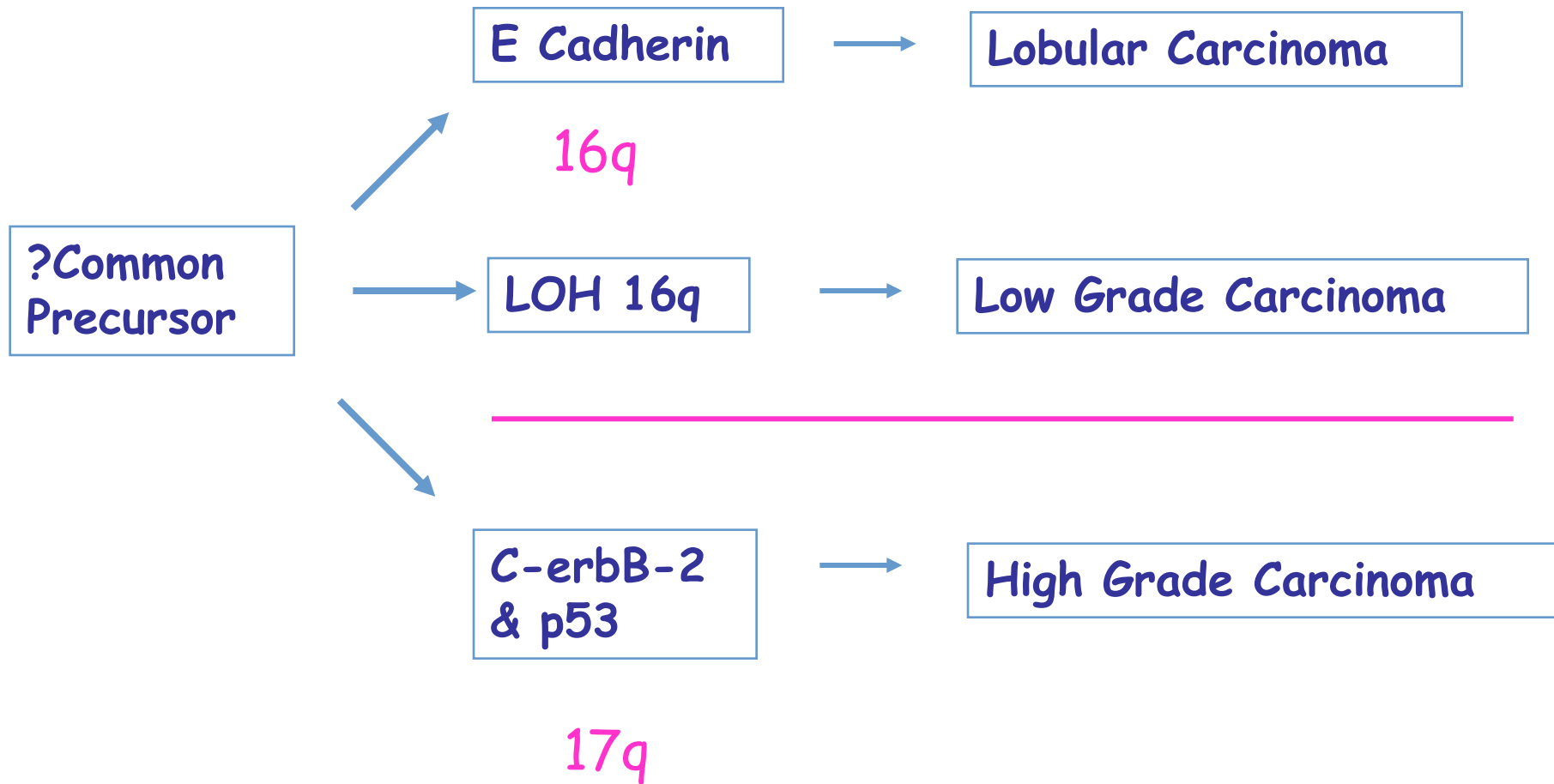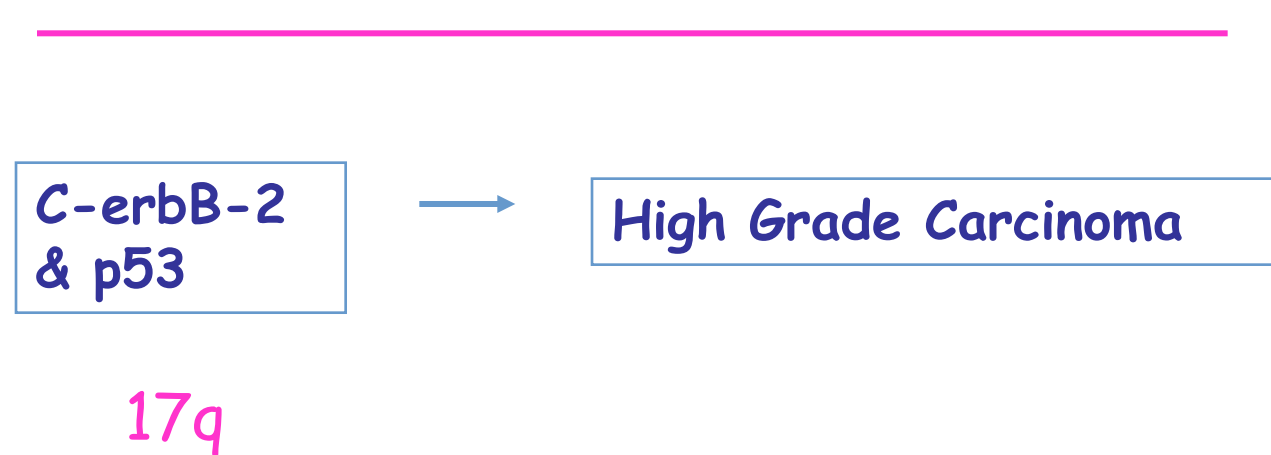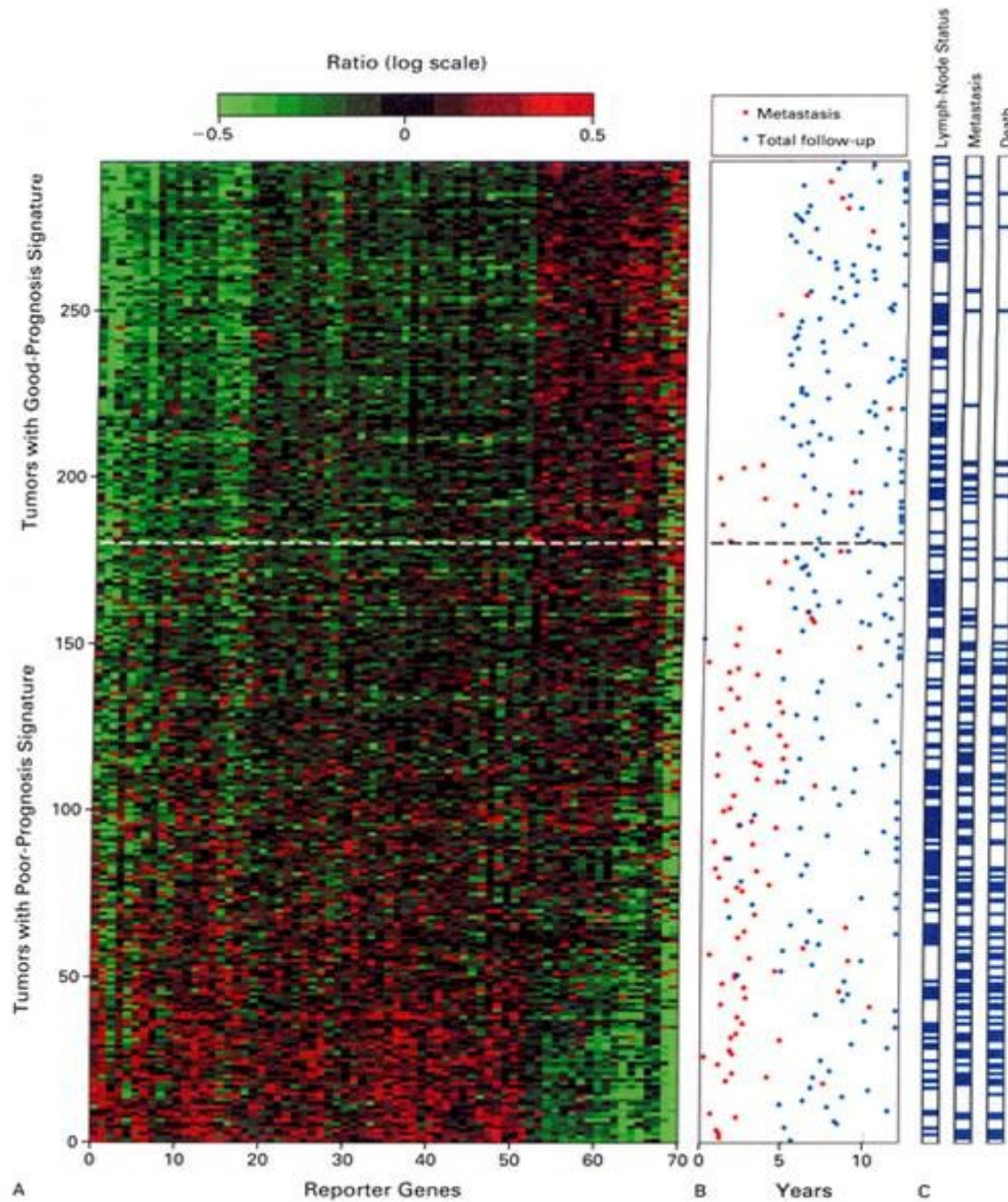
Expression Arrays

Classification of breast cancer

Distinct subgroups identified

Basal epithelial

Luminal epithelial

   ER positive A & B

   HER amplified

Prognostic differences

Perou et al.,2000; Sorlie et al.,2001; van 't Veer 2002

Markers in DCIS

Gene expression patterns in DCIS & invasive & metastatic tumors with serial analysis of gene expression (SAGE) (8 DCIS cases grouped)

16,430 transcripts analyzed

mRNA ISH to examine gene expression (18 tumours) & IHC on TMAs (769 cases)

No universal "in situ" or "invasive" signature

Porter D. Mol Cancer Res. 2003;1:362-75

Translation of cDNA studies

- Distinct sub classes of breast cancer can be identified by expression of proteins of known relevance in breast cancer

- These sub classes are comparable to those identified by cDNA expression array technology

- Molecular classification of breast cancer based on protein expression potentially offers further refinement of traditional methods of classification

- A modern clinically relevant breast cancer classification based on molecular genetic, phenotypic and morphological characteristics appears realistic

Abd El-Rehim DM etal Int J Cancer. 2005, 116:340-50.

NSABP P-1

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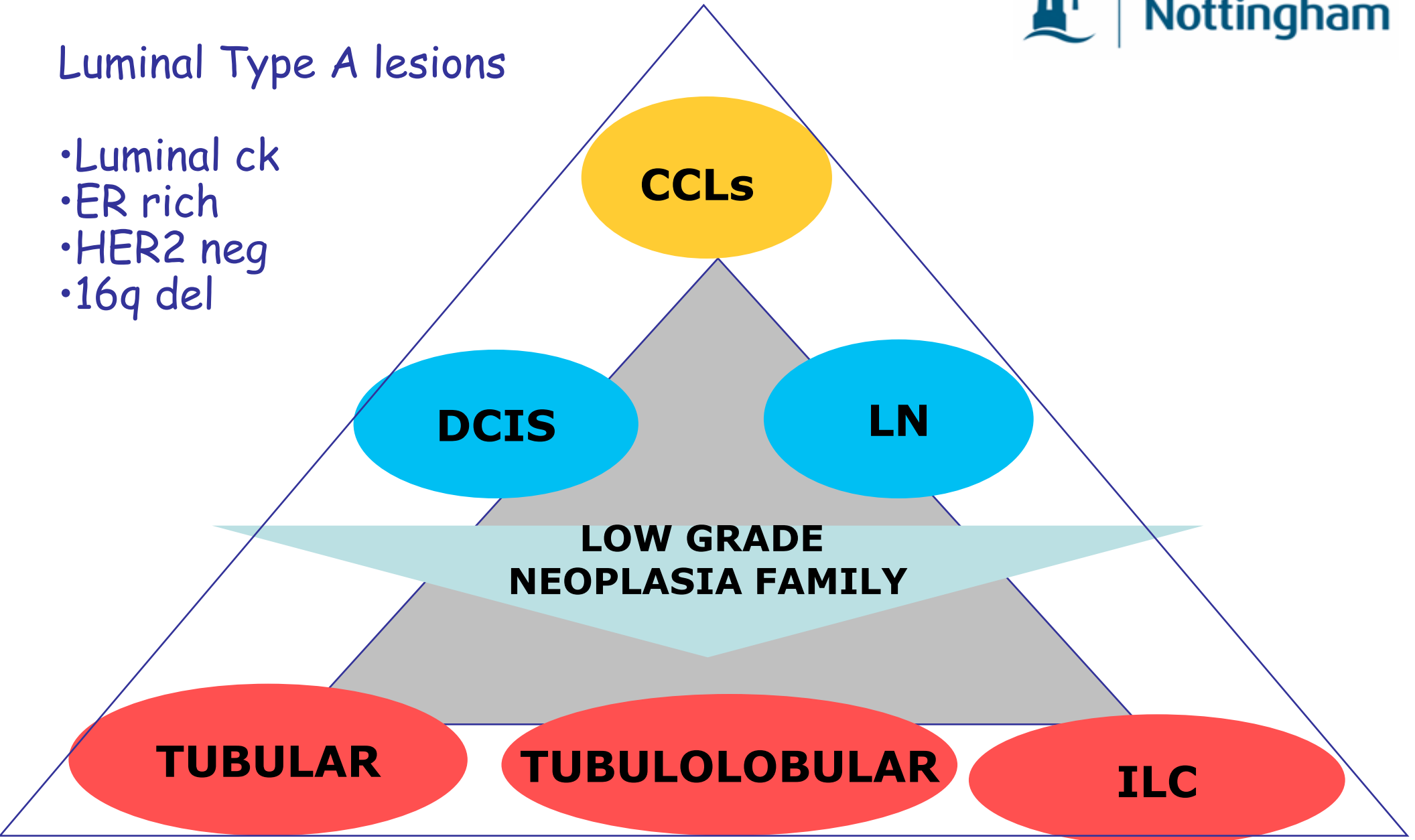
- Women (No = 13,388) at increased risk for breast cancer as they
    a) were 60 years or older
    b) were 35-59 with a 5-year predicted risk   of at least 1.66%
    c) had a history of LCIS
- Received placebo or 20 mg/day tamoxifen for 5 years
- Tamoxifen reduced the risk of invasive breast cancer by 49%
- Decreased risk occurred in women aged 49 years or younger (44%), 50-59 years (51%) and 60 years or older (55%)
- Risk reduced in women with a history of LCIS (56%) or atypical hyperplasia (86%)
- Tamoxifen reduced the occurrence of ER-positive tumours by 69%, no difference in the occurrence of ER-negative tumours

Fisher B et al. J NCI. 1998; 90; 1371-1388

In situ Lesions of the Breast

Future classifications systems

- Reflect underlying molecular genetics

- Based on objective morphological and/or protein expression criteria

- Take account of disease extent

- Take account of risk