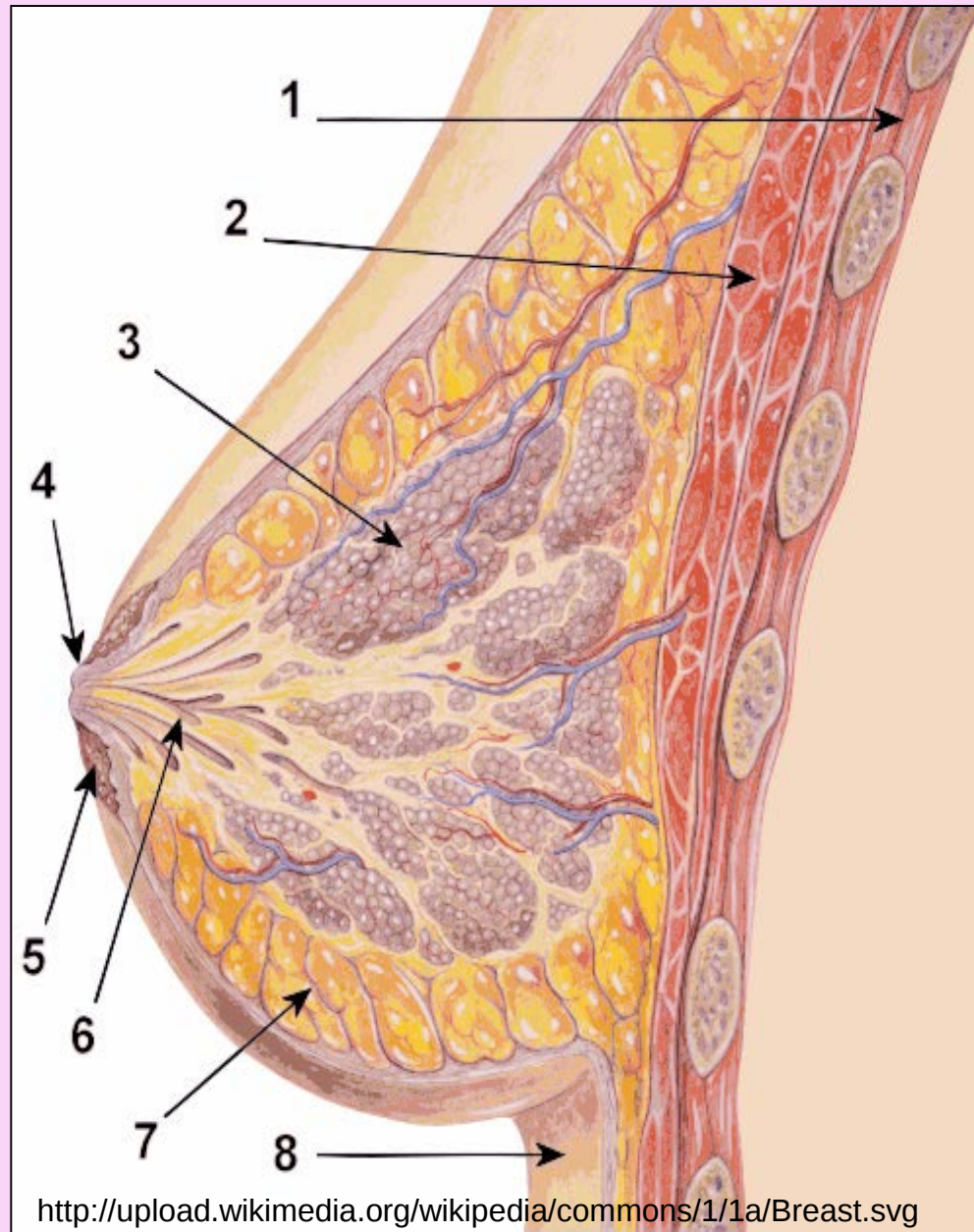


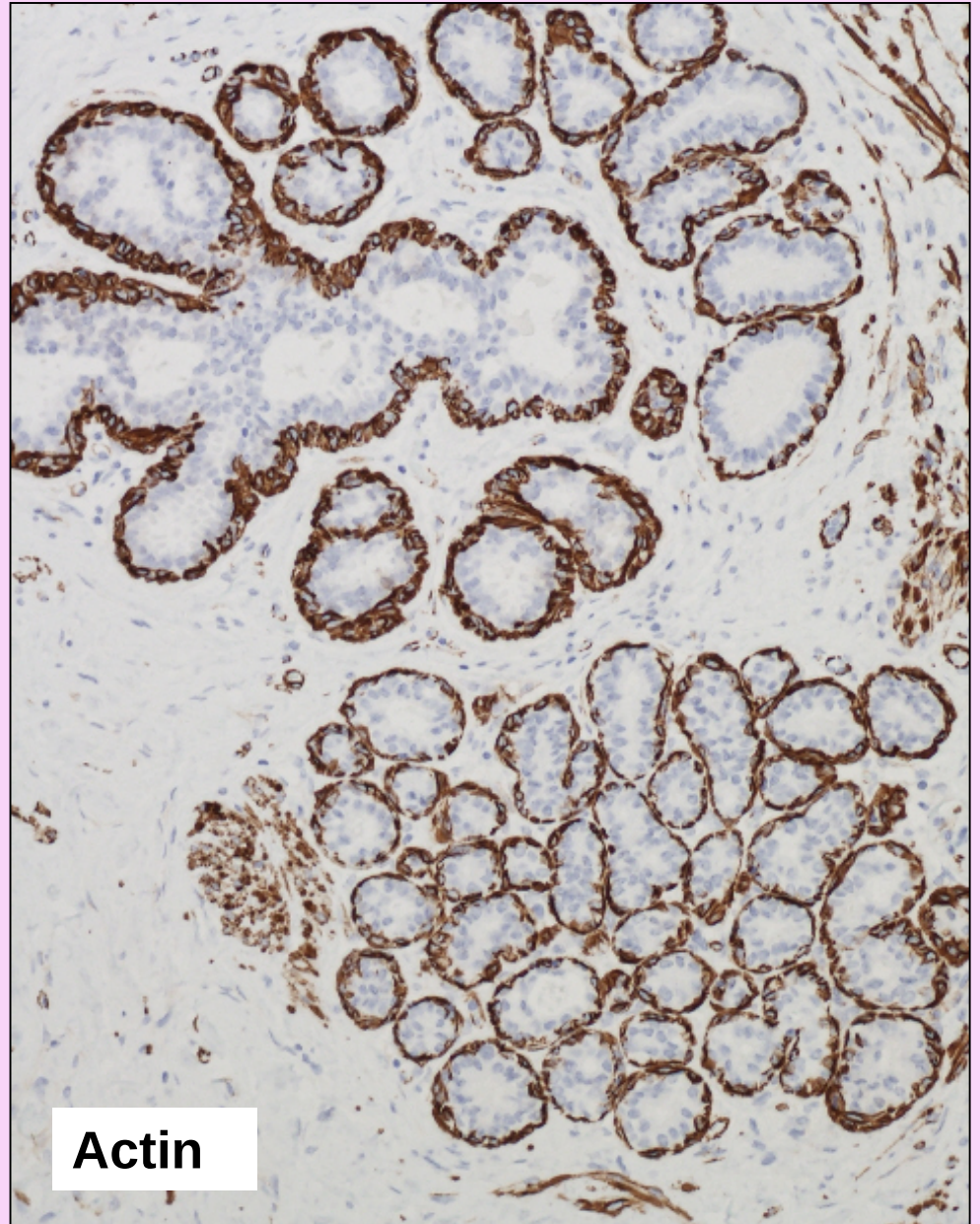
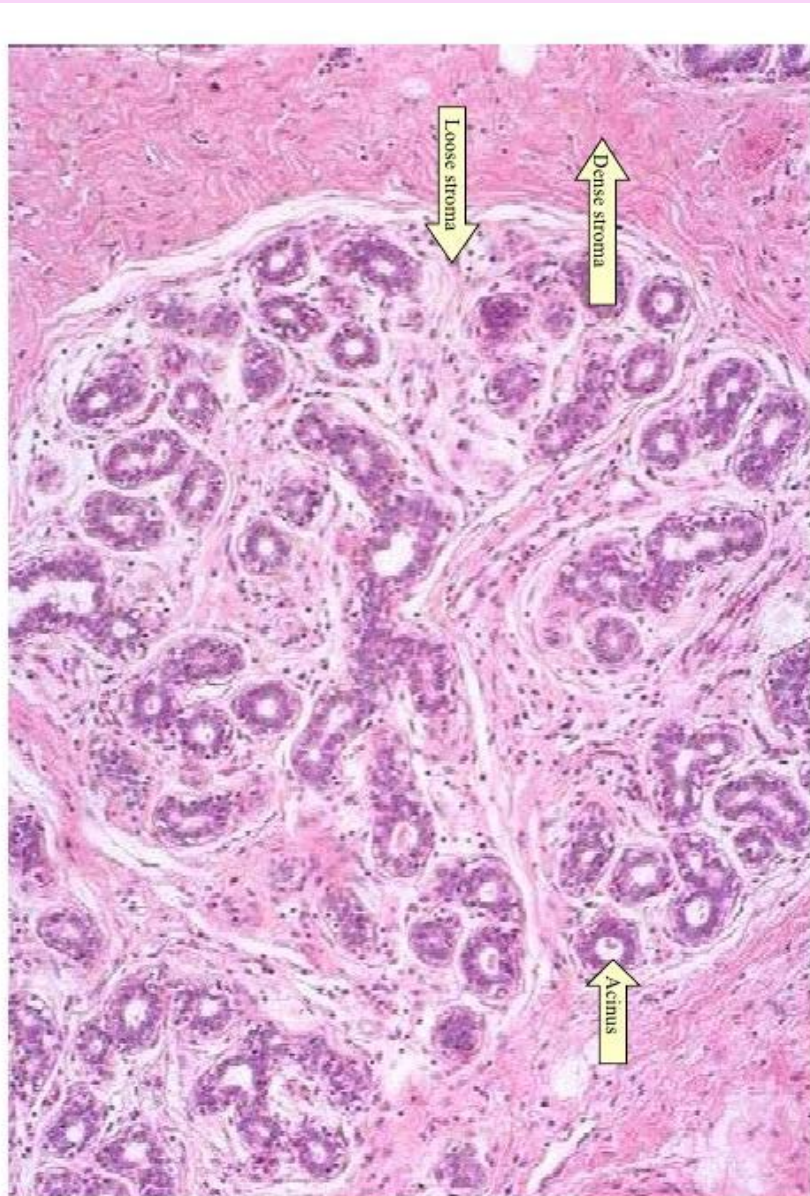
Breast cancer: IHC classification

Mogens Vyberg
Professor of Clinical Pathology
Director of NordiQC
Aalborg University Hospital,
Aalborg, Denmark

Breast



Breast

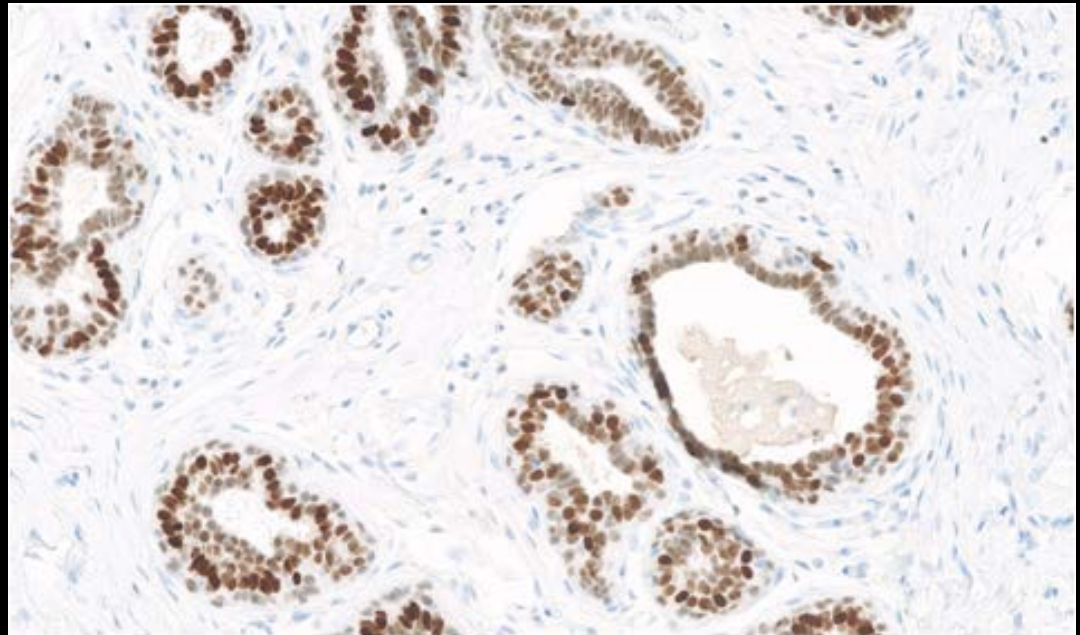


“Breast markers” for carcinoma diagnostics	Unknown Primary	Primary Breast	
GATA3	+	-	Dia- gnostic
GCDFP-15	+	-	
Mammaglobin	+	-	
Estrogen receptor α (ER)	+	+	Prognostic/ predictive
Progesteron receptor (PR)	-	+	
HER2	-	+	
Ki67	-	+	
E-Cadherin / p120	-	+	Sub- classification
CK5 / CK14	+	+	
p63 / p40	+	+	
Actin / Myosin	-	+	

GATA3

Transcription factor recognizing the **G-A-T-A nucleotide sequences** in target gene promoters, regulating genes involved in the development/maintenance of

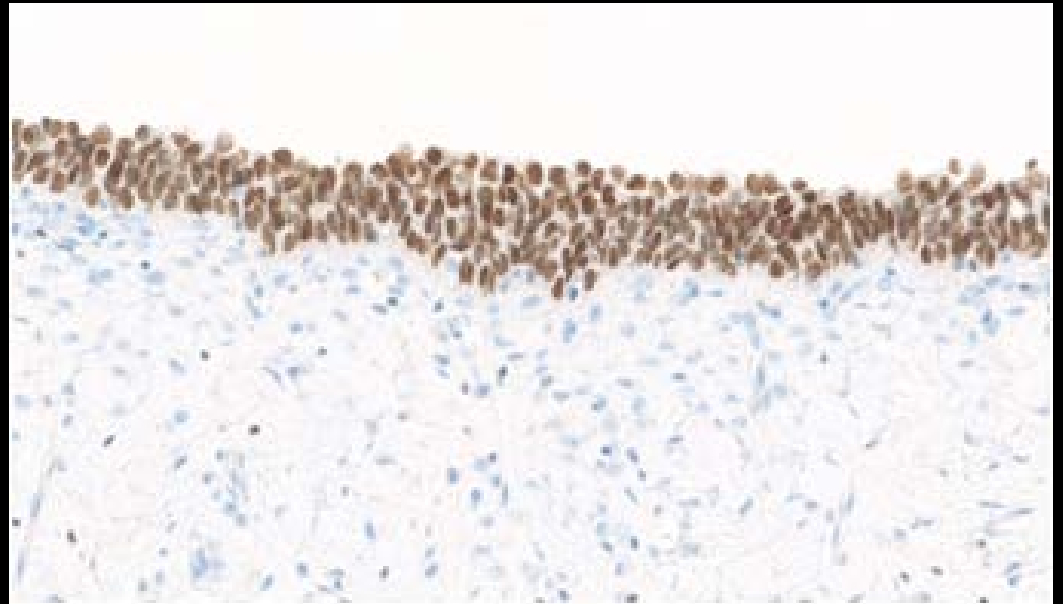
- T-cells
- breast epithelium
- urothelium →
- kidney
- skin
- trophoblast
- endothelia



GATA3

Transcription factor recognizing the **G-A-T-A nucleotide sequences** in target gene promoters, regulating genes involved in the development/maintenance of

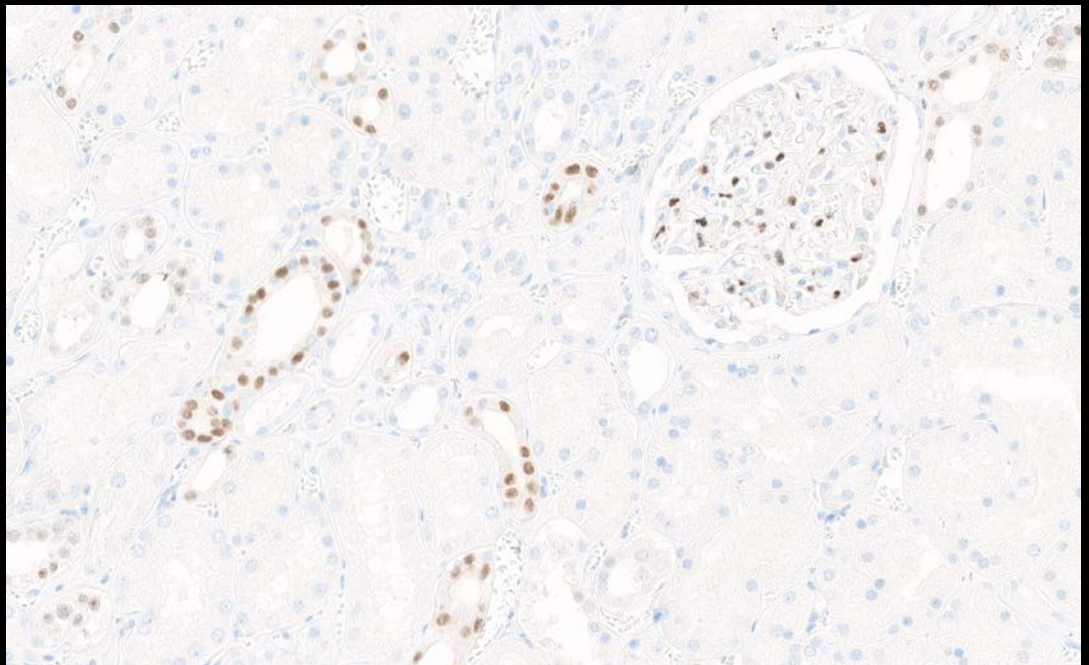
- T-cells
- breast epithelium
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- kidney
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- trophoblast
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GATA3

Transcription factor recognizing the **G-A-T-A nucleotide sequences** in target gene promoters, regulating genes involved in the development/maintenance of

- T-cells
- breast epithelium
- urothelium
- kidney
- skin
- trophoblast
- endothelia

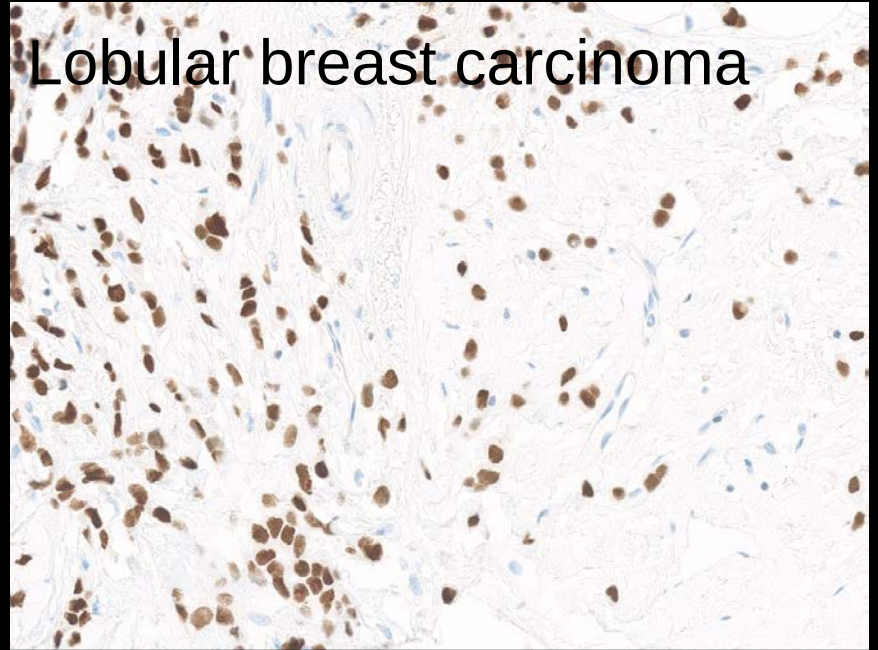


GATA3

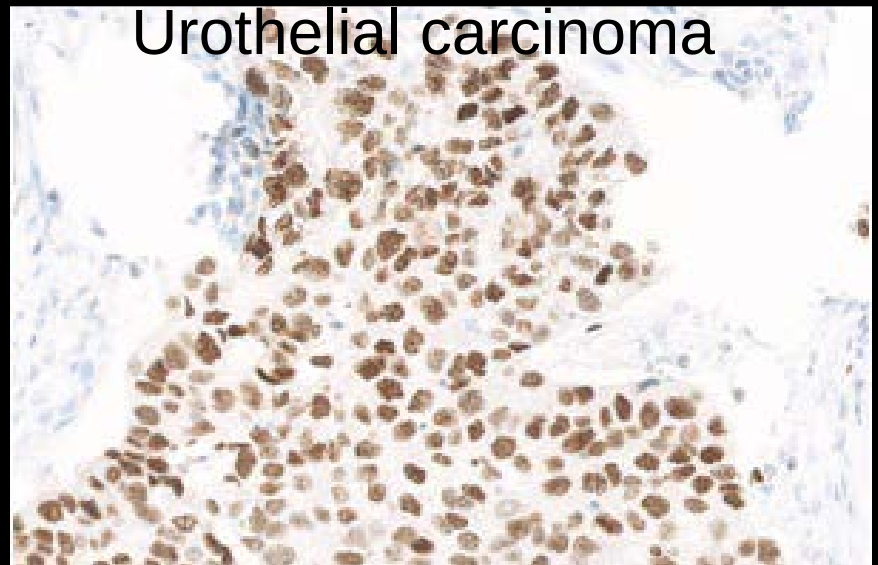
+

- Breast carcinoma
- Urothelial carcinoma
- Skin carcinoma
(squam., bas., adnex)
- Yolk sac tumour

Lobular breast carcinoma



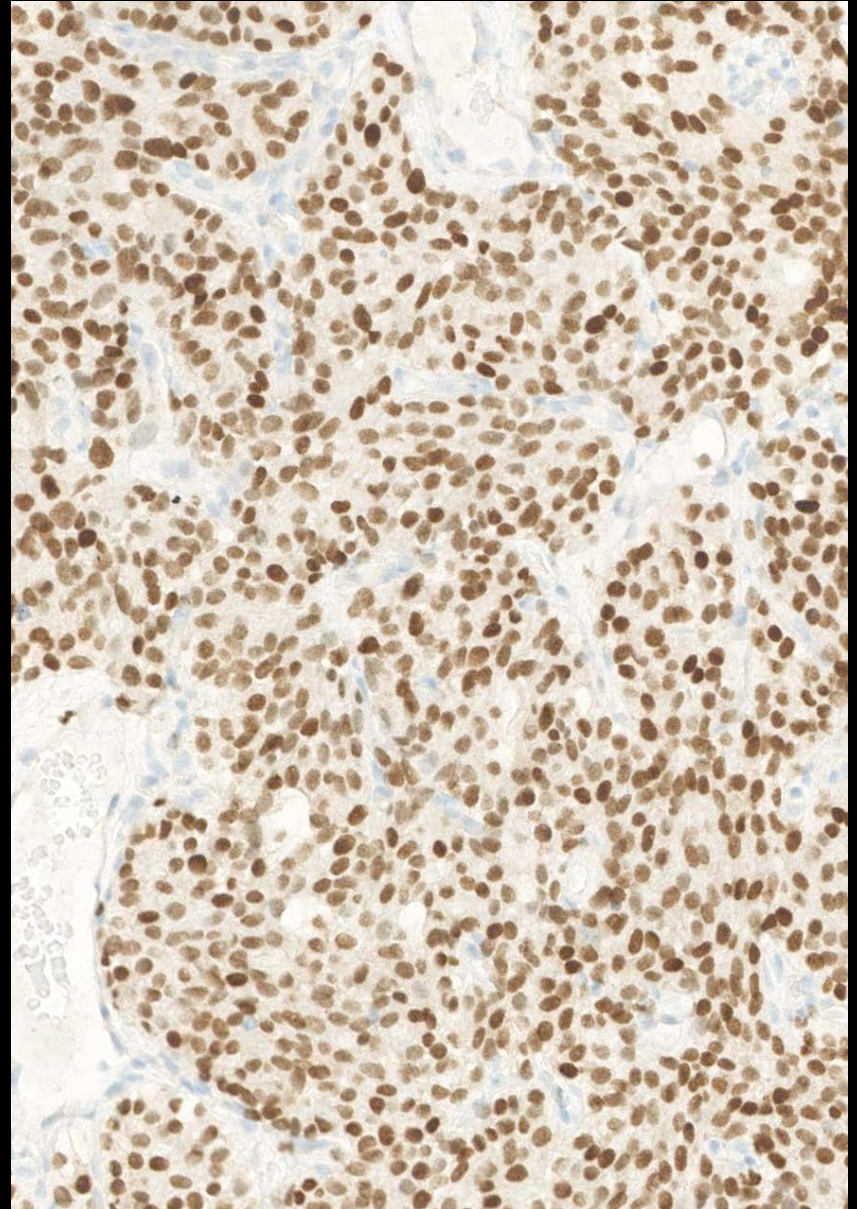
Urothelial carcinoma



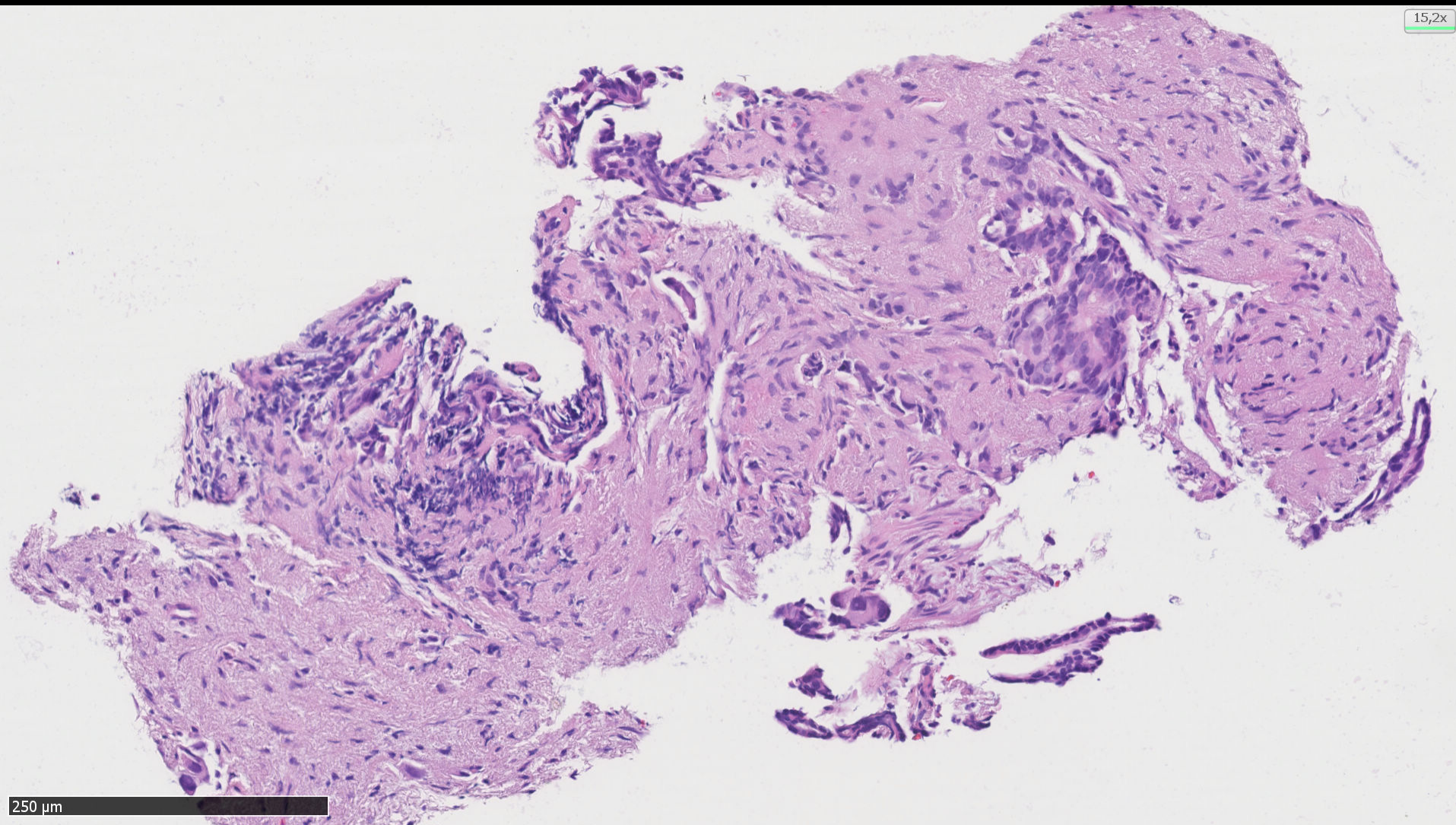
GATA3

+/-

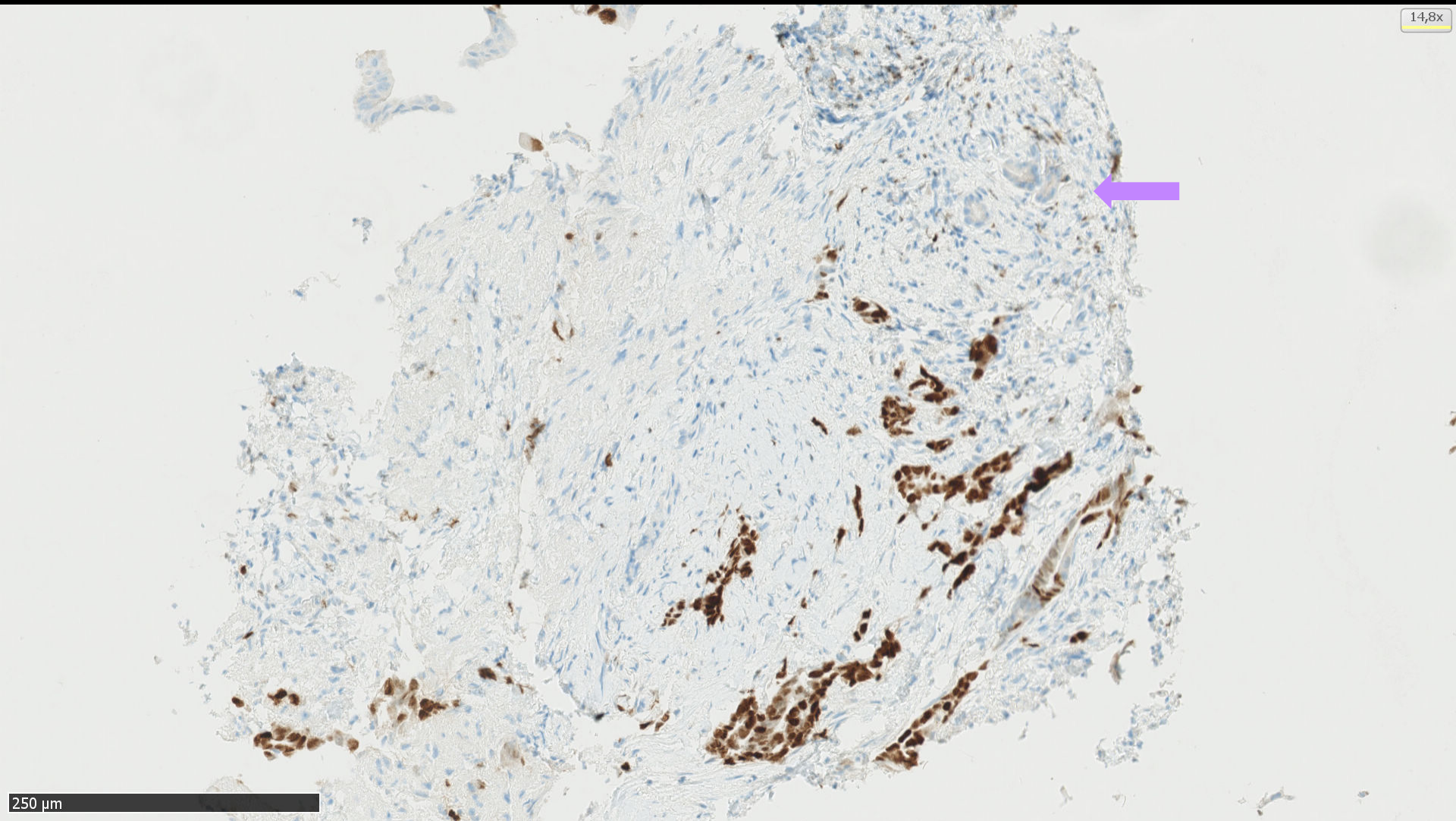
- Malignant mesothelioma
- Paraganglioma →
- Chromophobe renal cell carc.
- **Pancreas/biliary tract adenocarcinoma**



SPYBYTE biopsy choledochus



SPYBYTE biopsy choledochus – GATA3



GATA3

-/+

- Non-skin squamous cell carc.
- Salivary gland carcinomas
- Adrenal cortical carcinoma
- Embryonal carcinoma
- -(+)
Serous / endometrioid adenocarcinoma
- Colon / gastric adenocarcinoma
- Prostate adenocarcinoma
- Renal cell carcinoma (non-chrom.)
- Thyroid carcinoma
- Sarcomas

-

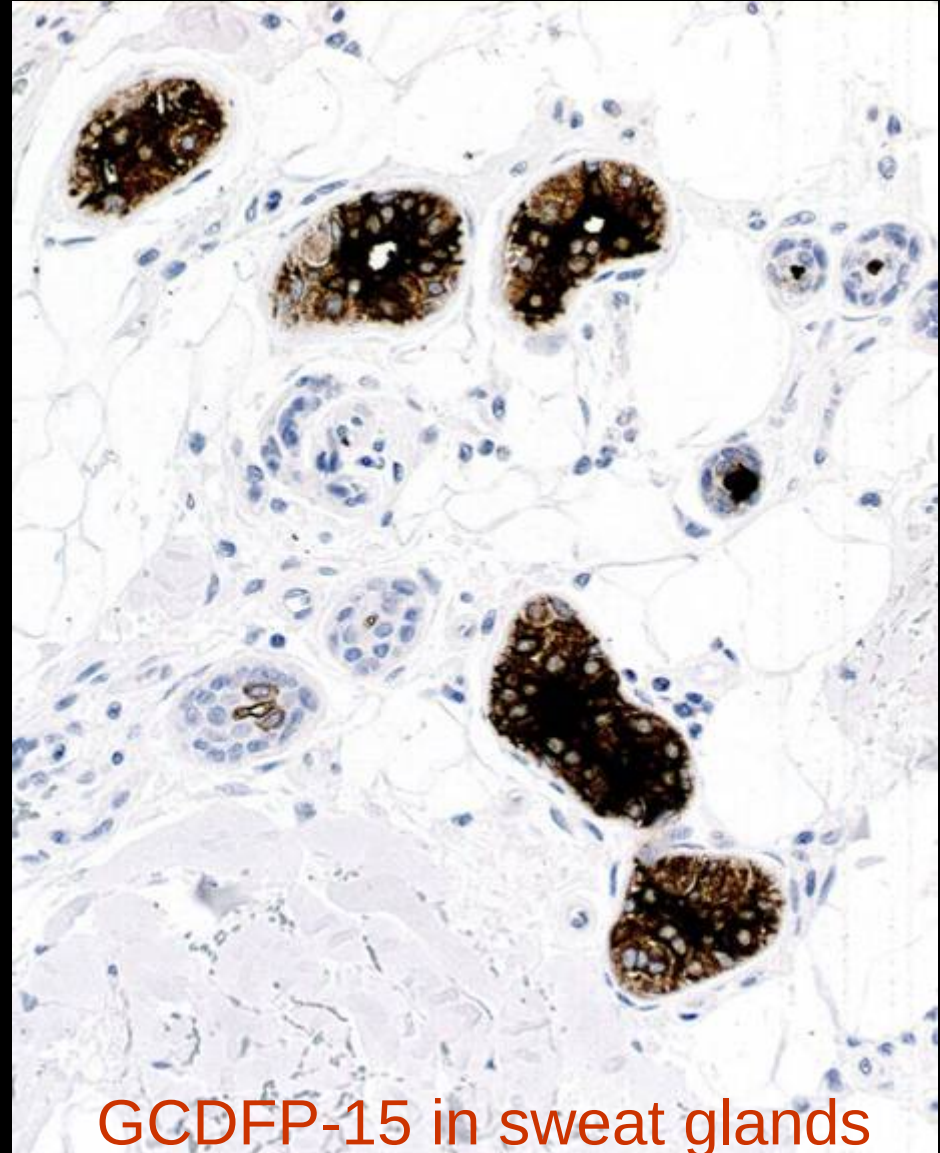
- Endocrine neoplasms
- Malignant melanoma
- Seminoma

GCDFP-15 (gross cystic disease fluid protein 15)

Prolactin induced
glycoprotein of apocrine cells

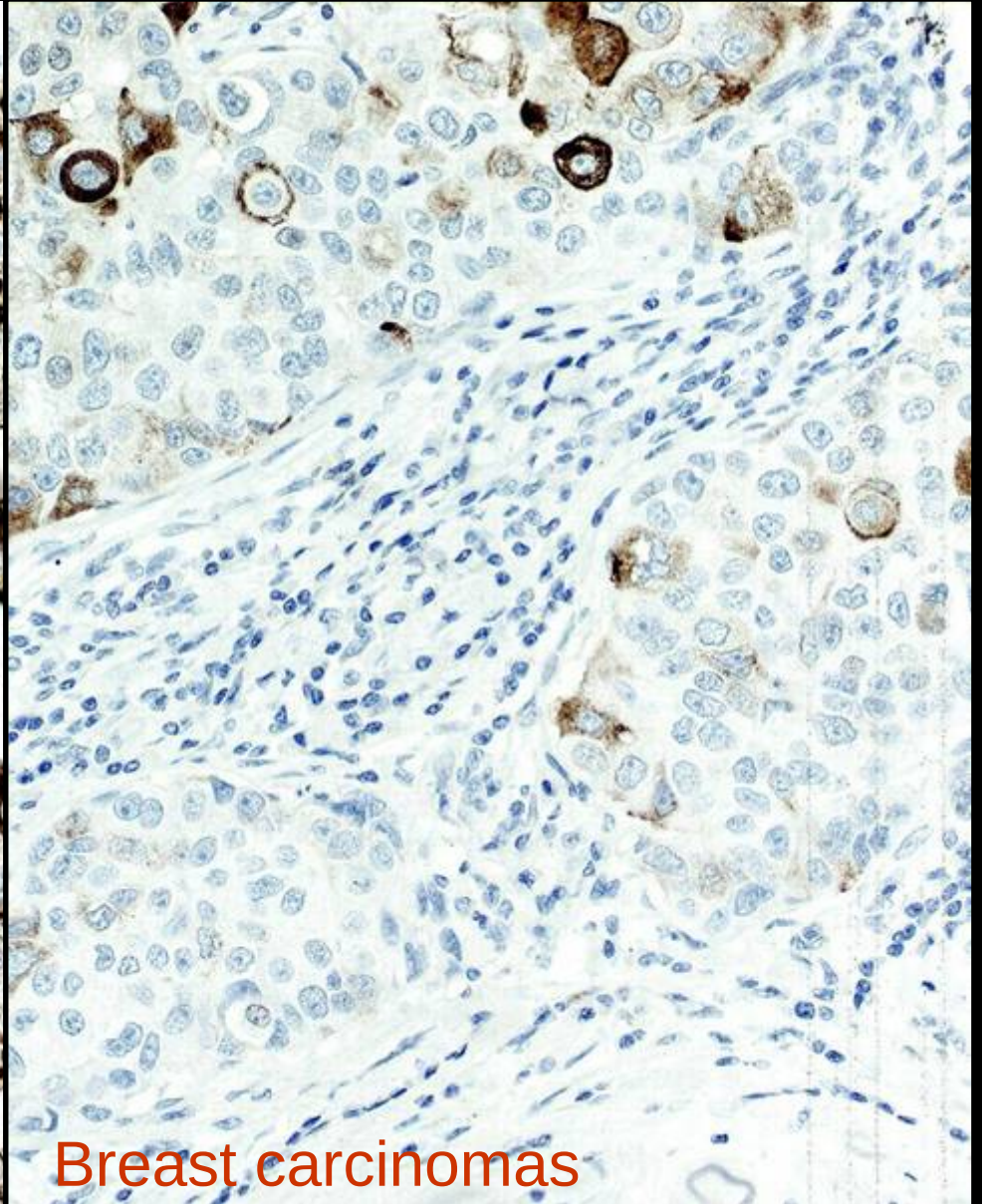
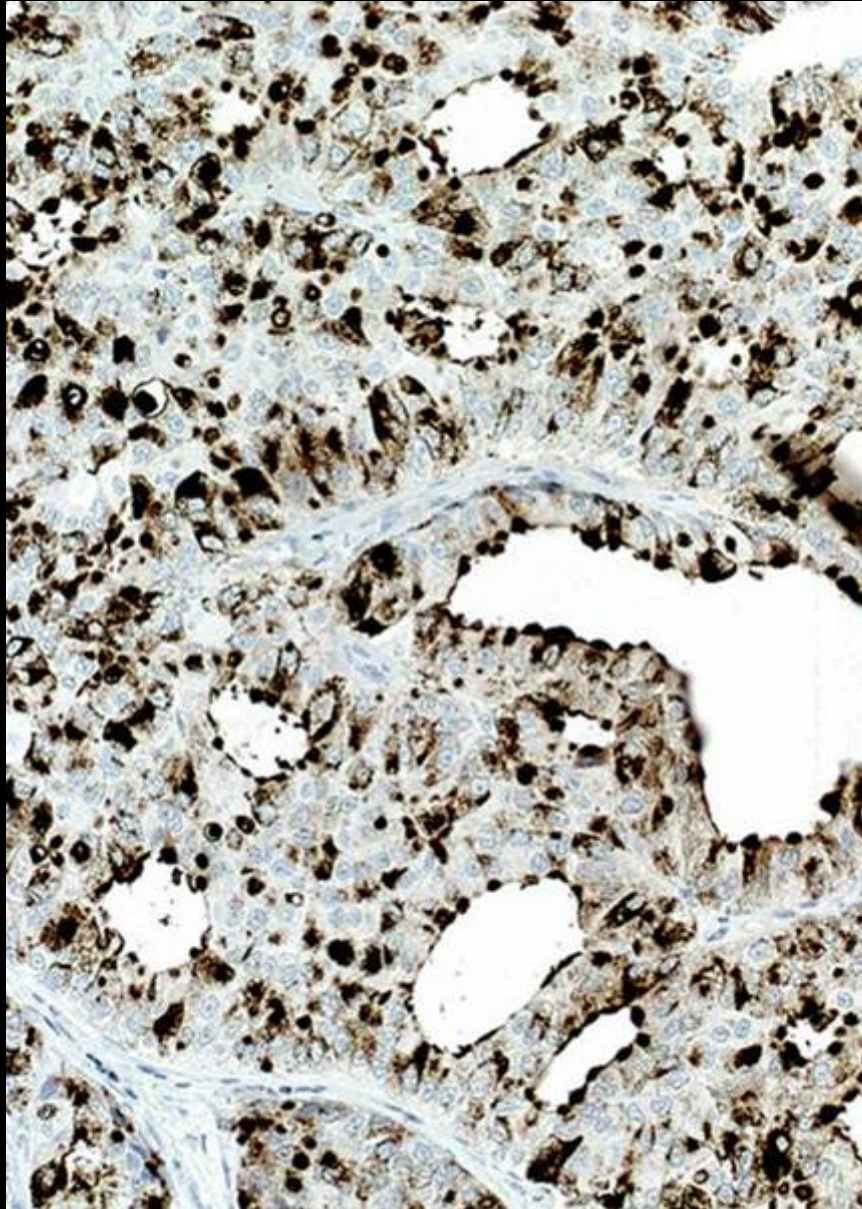
Adenocarcinomas

- Breast +/–
- Sweat gland +/–
- Salivary gland +/–
- Lung –(+)
- Renal cell –(+)
- Ovary –(+)



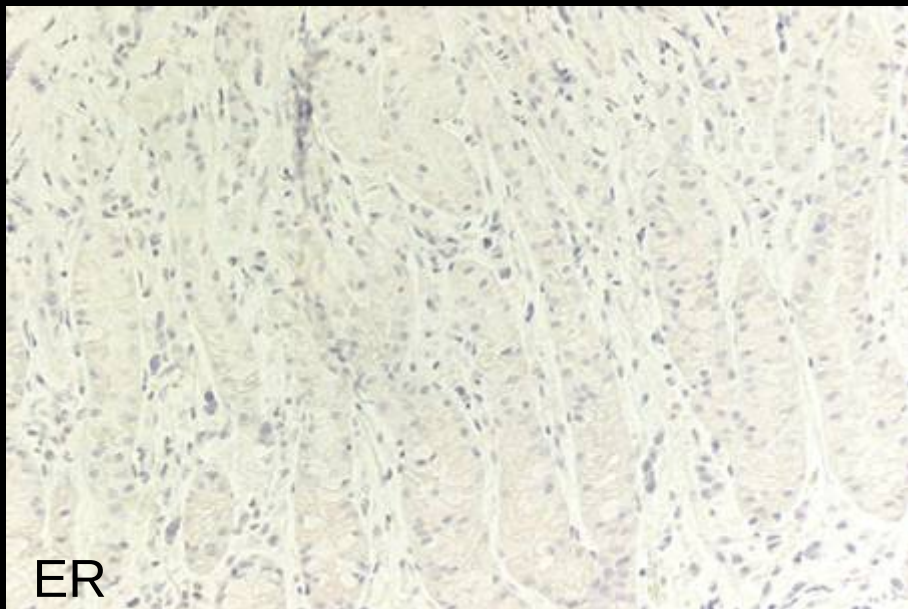
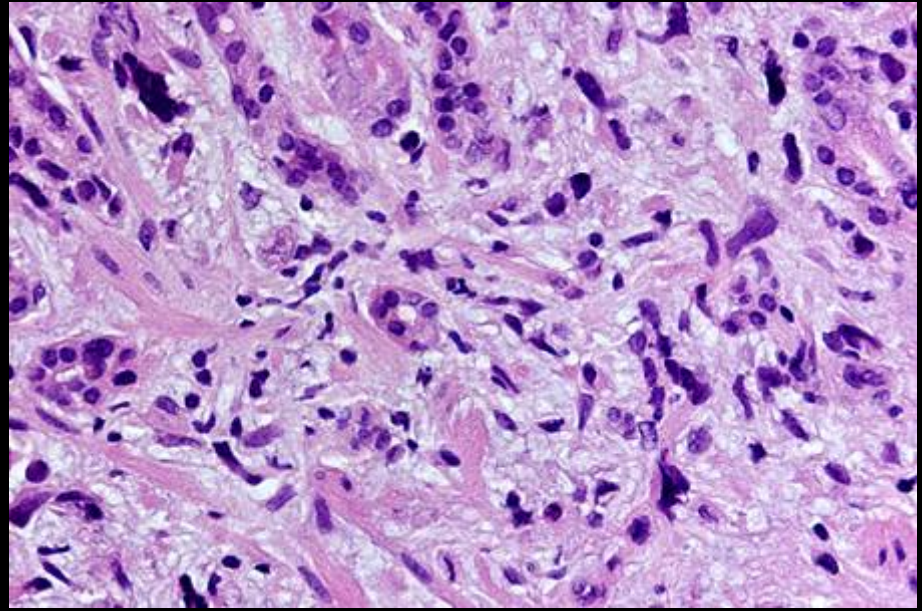
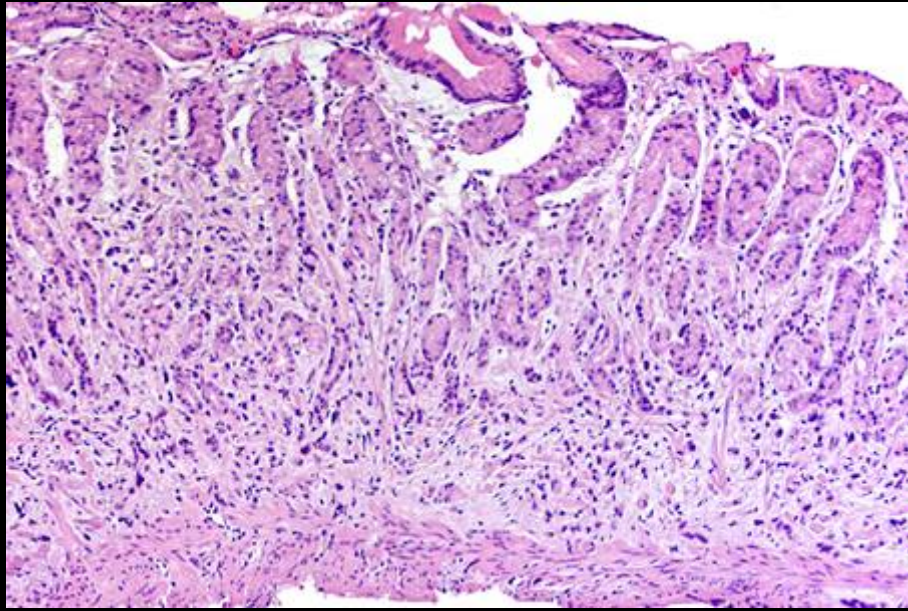
GCDFP-15 in sweat glands

GCDFP-15

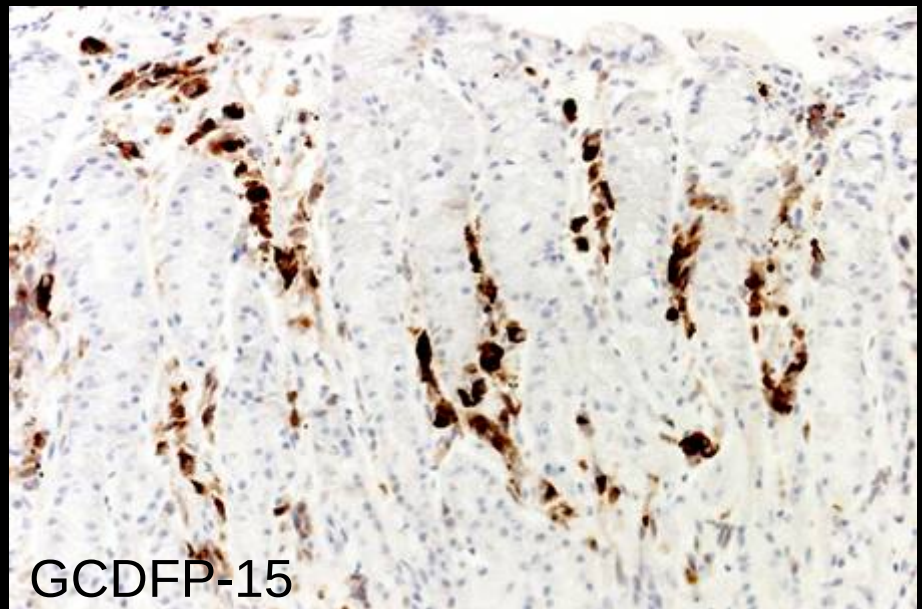


Breast carcinomas

Gastric biopsies, ♀ 43 y

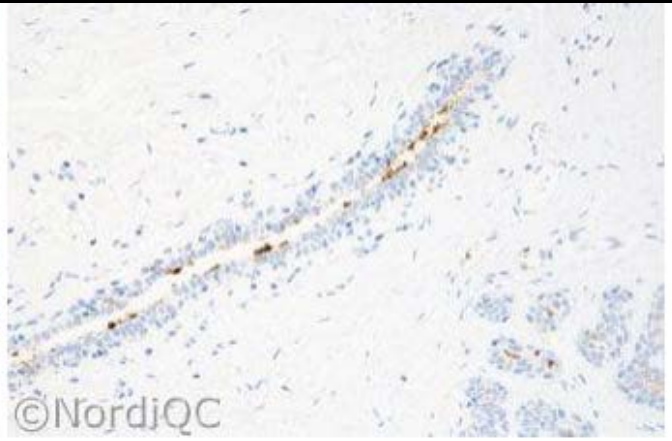


ER

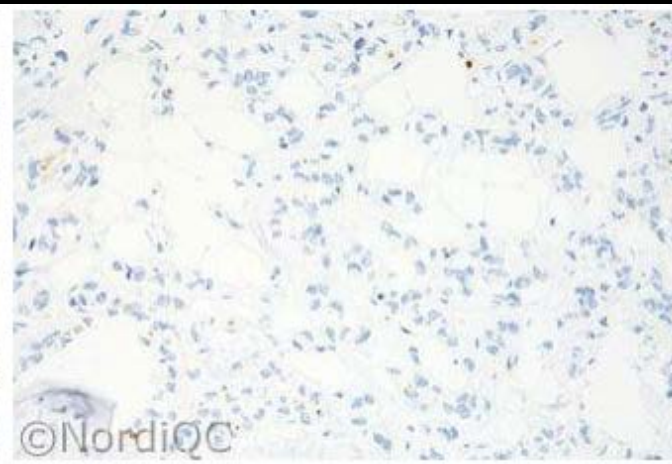
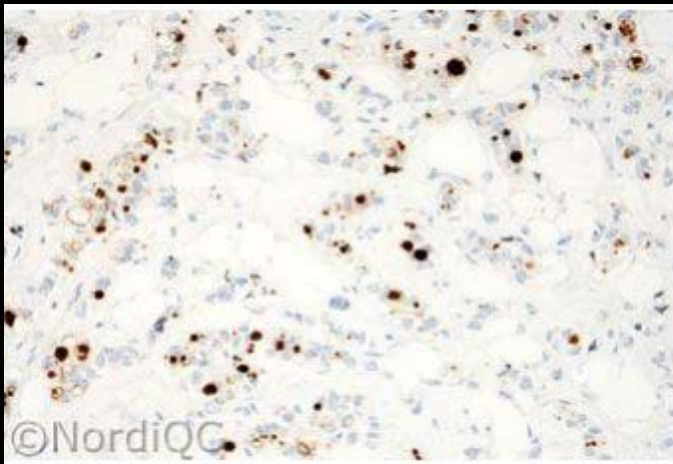


GCDFP-15

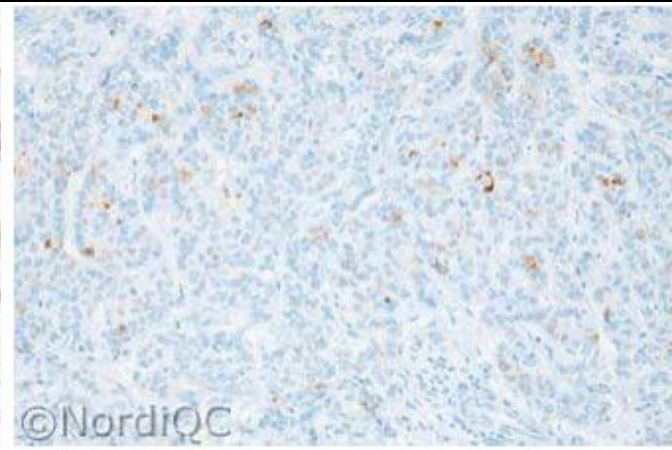
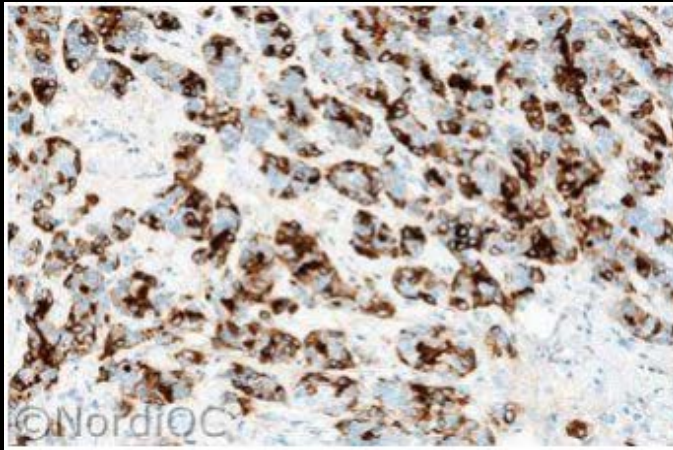
GCDFP15
Optimal



GCDFP15
Insufficient



Low Ab
conc.

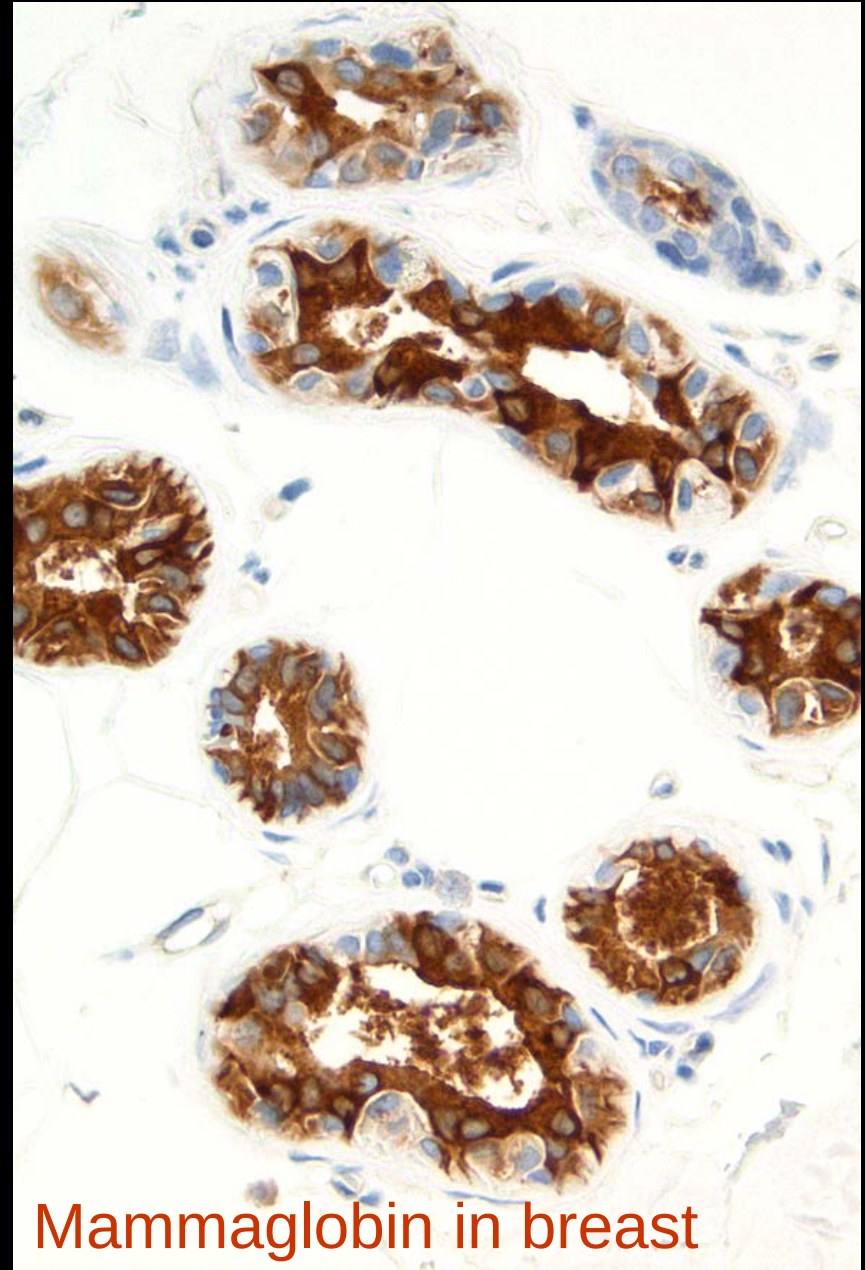


2-layer
detect.
system

Mammaglobin

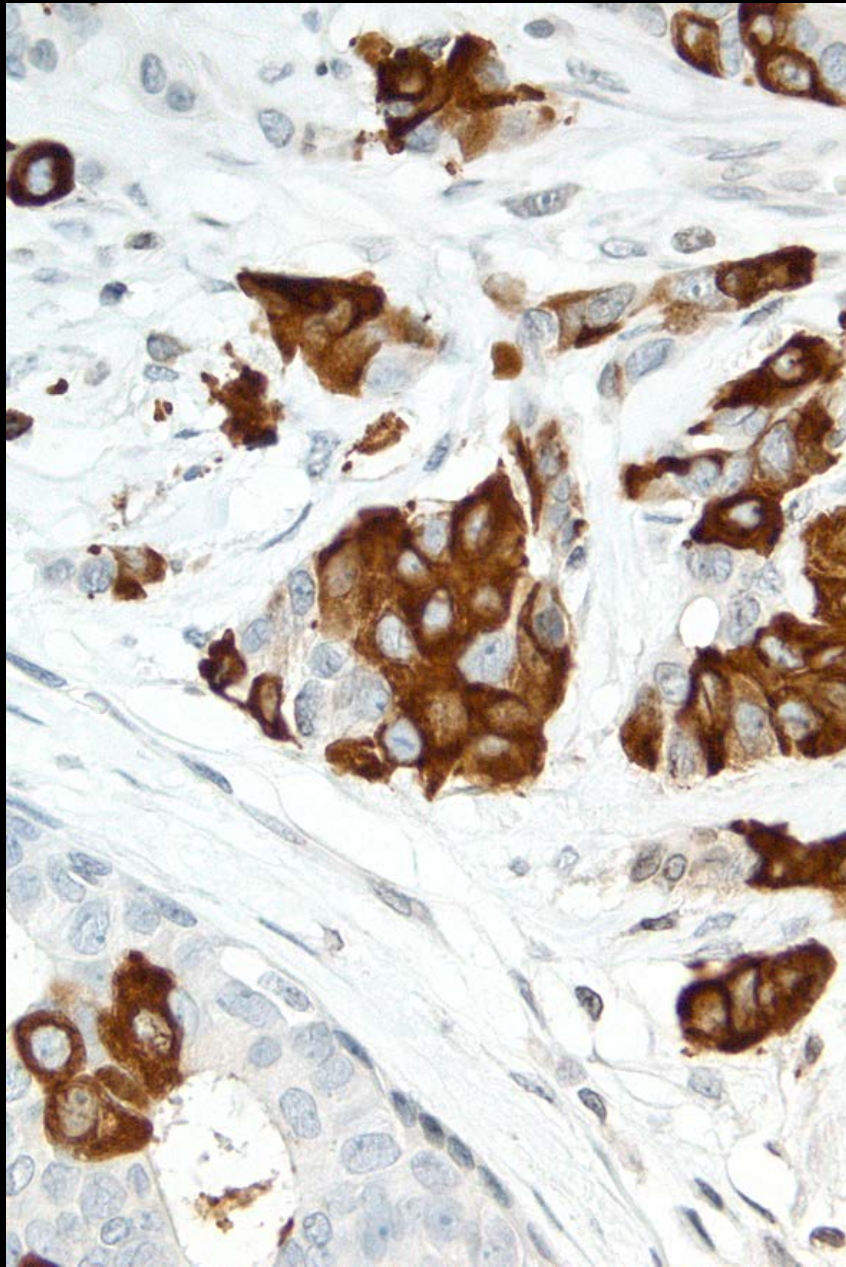
Mammary-specific member
of the uteroglobin family

- Adenocarcinomas
- Breast +/–
- Sweat gland +/–
- Salivary gland +/–
- Lung –/+
- Stomach, biliary,
thyroid, ovary, endom.
–(+)

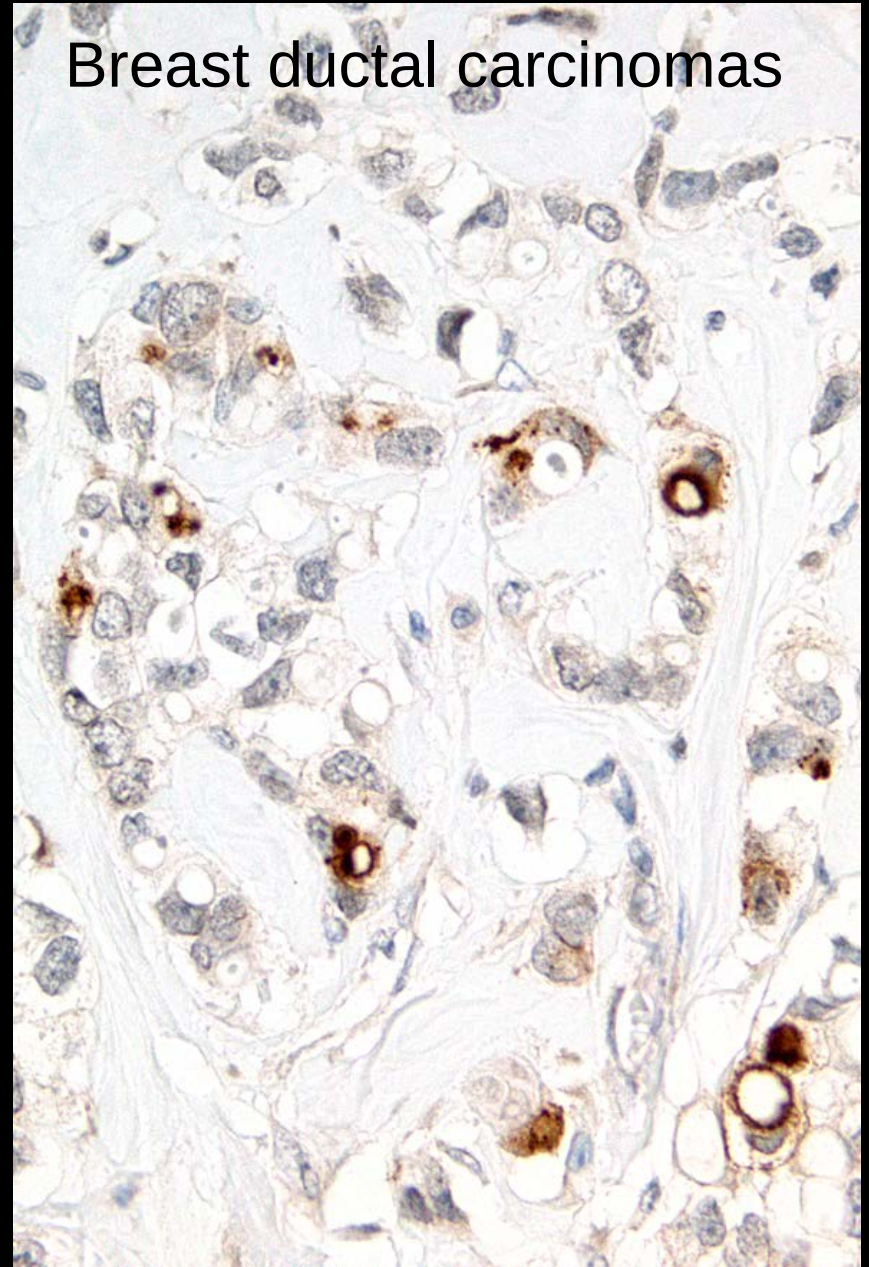


Mammaglobin in breast

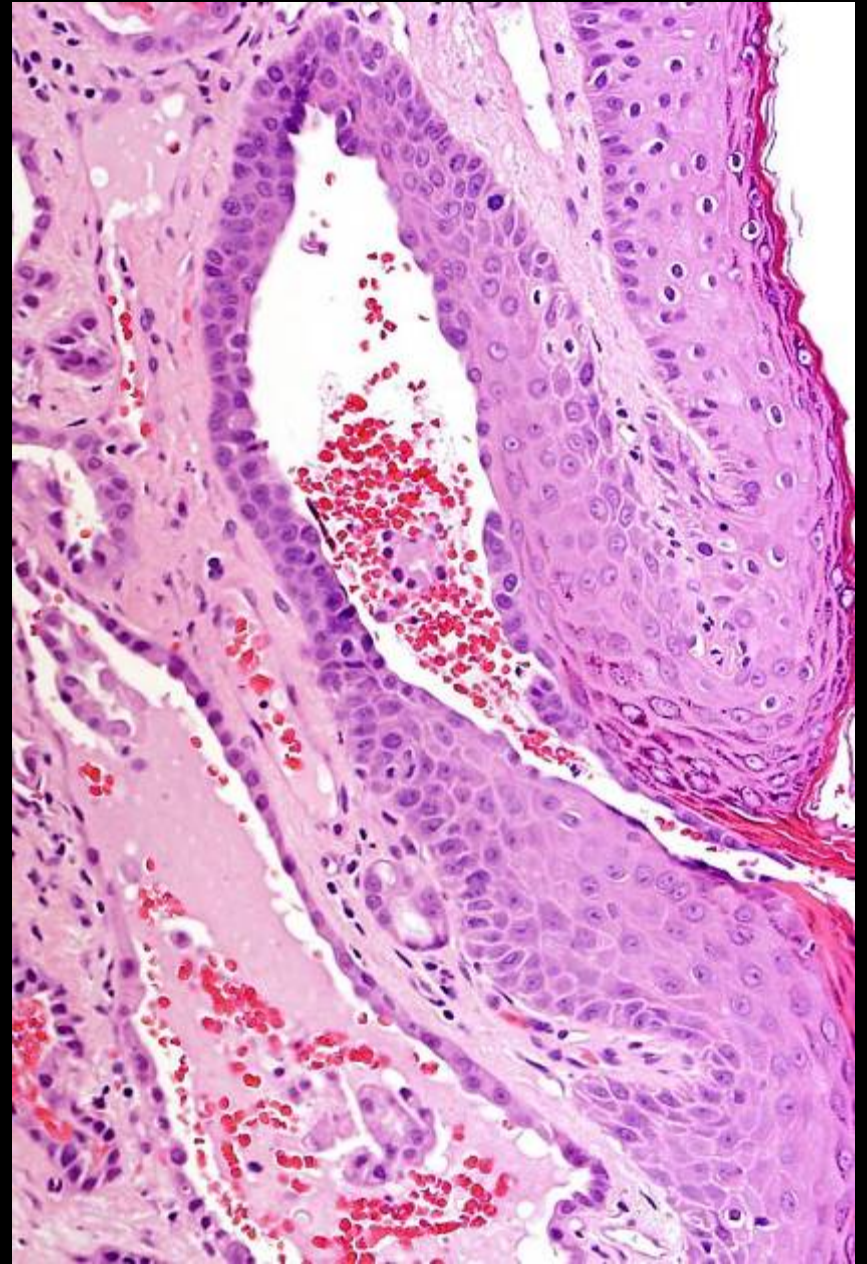
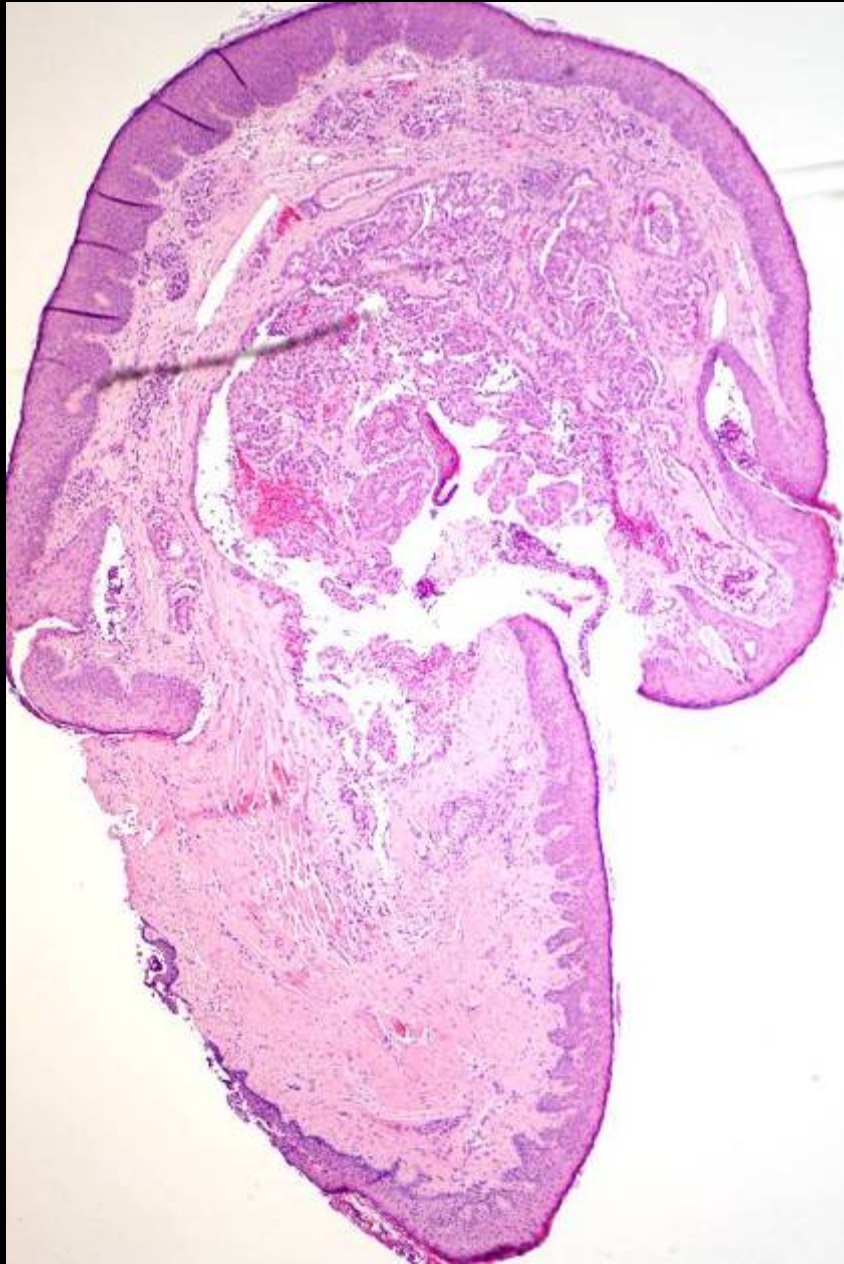
Mammaglobin



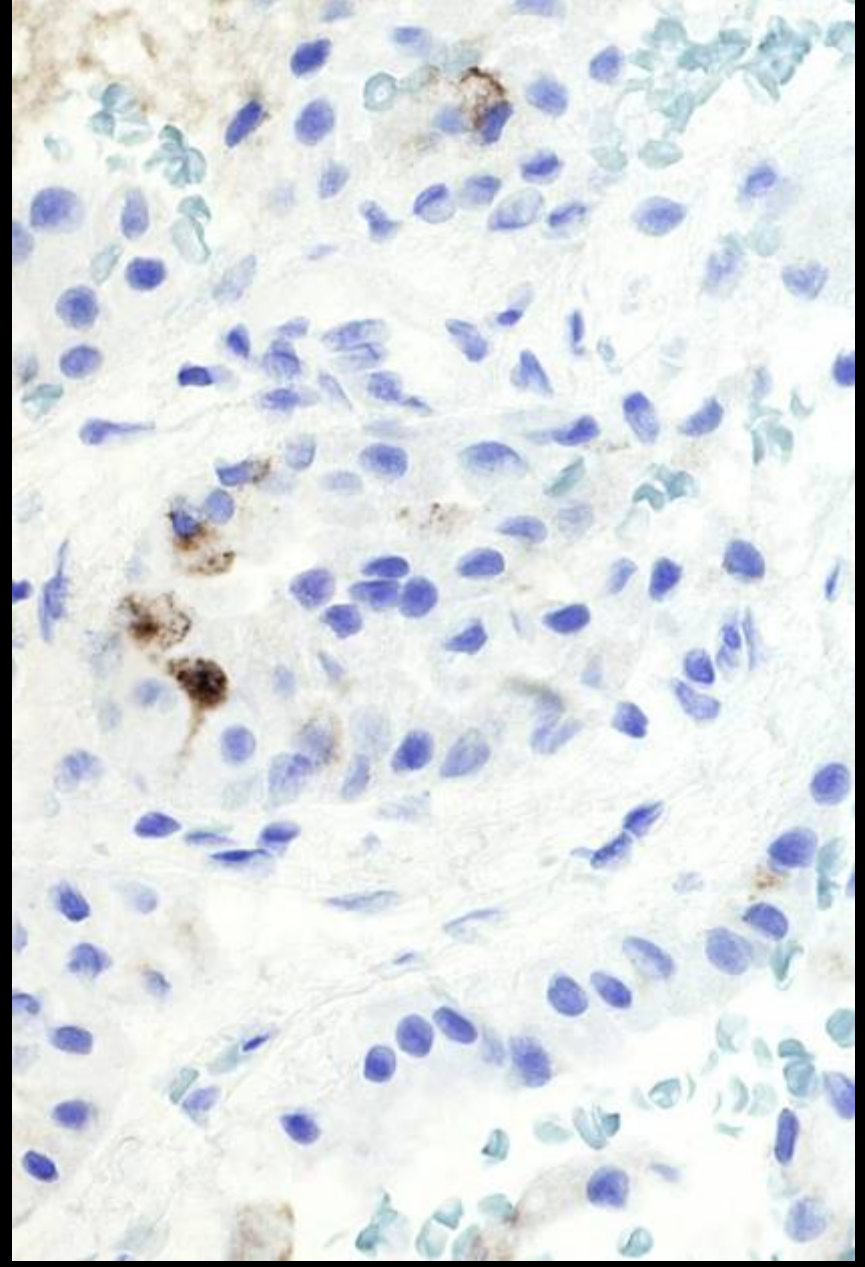
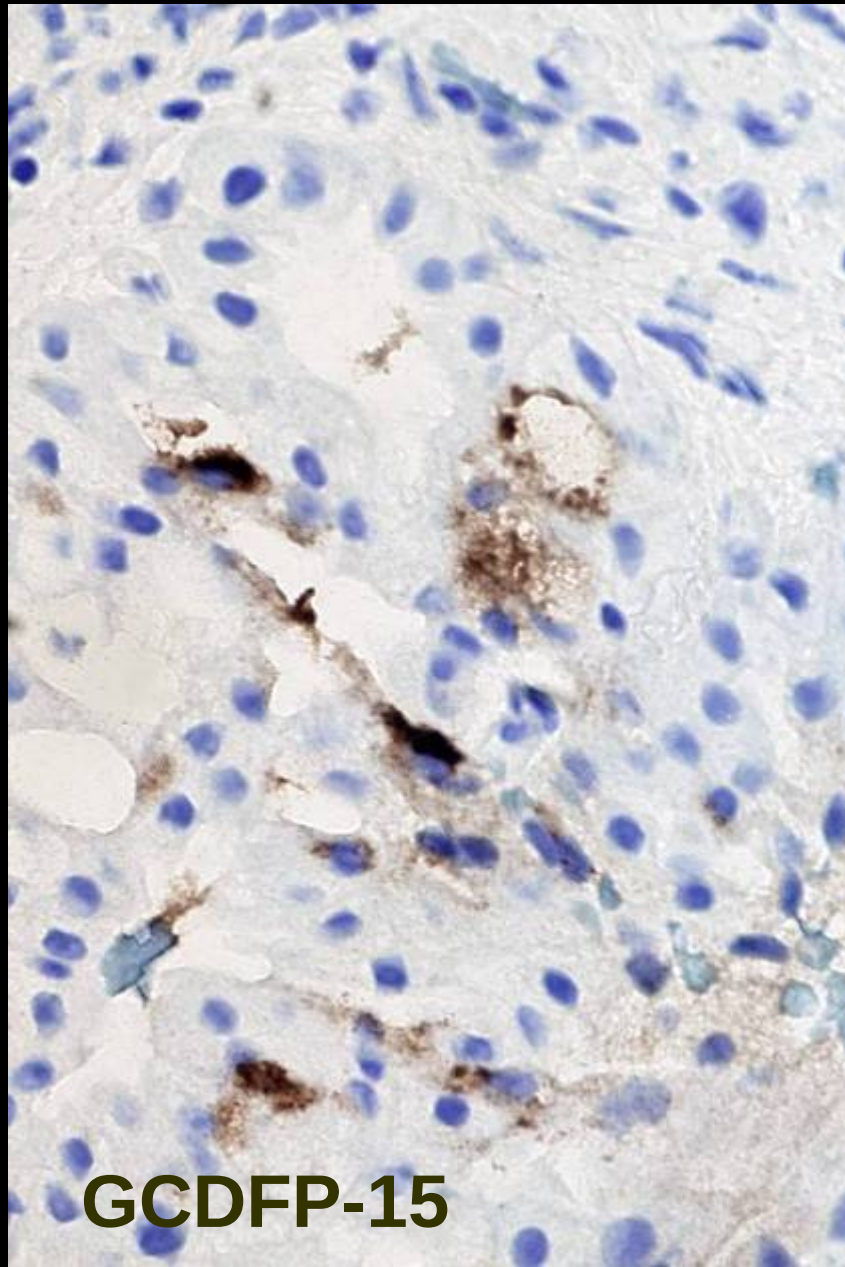
Breast ductal carcinomas



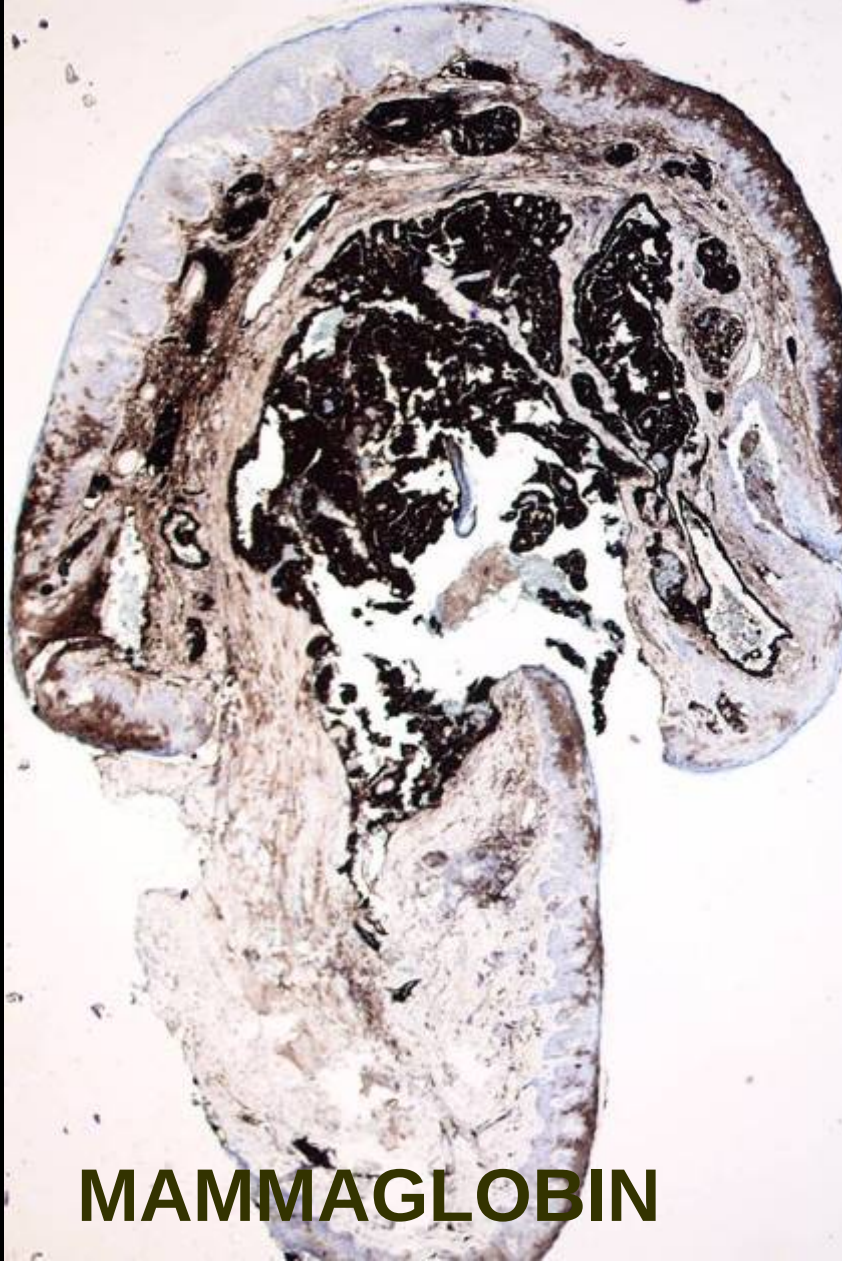
♂ 61, Metastatic adenocarcinoma UPT in the eye lid



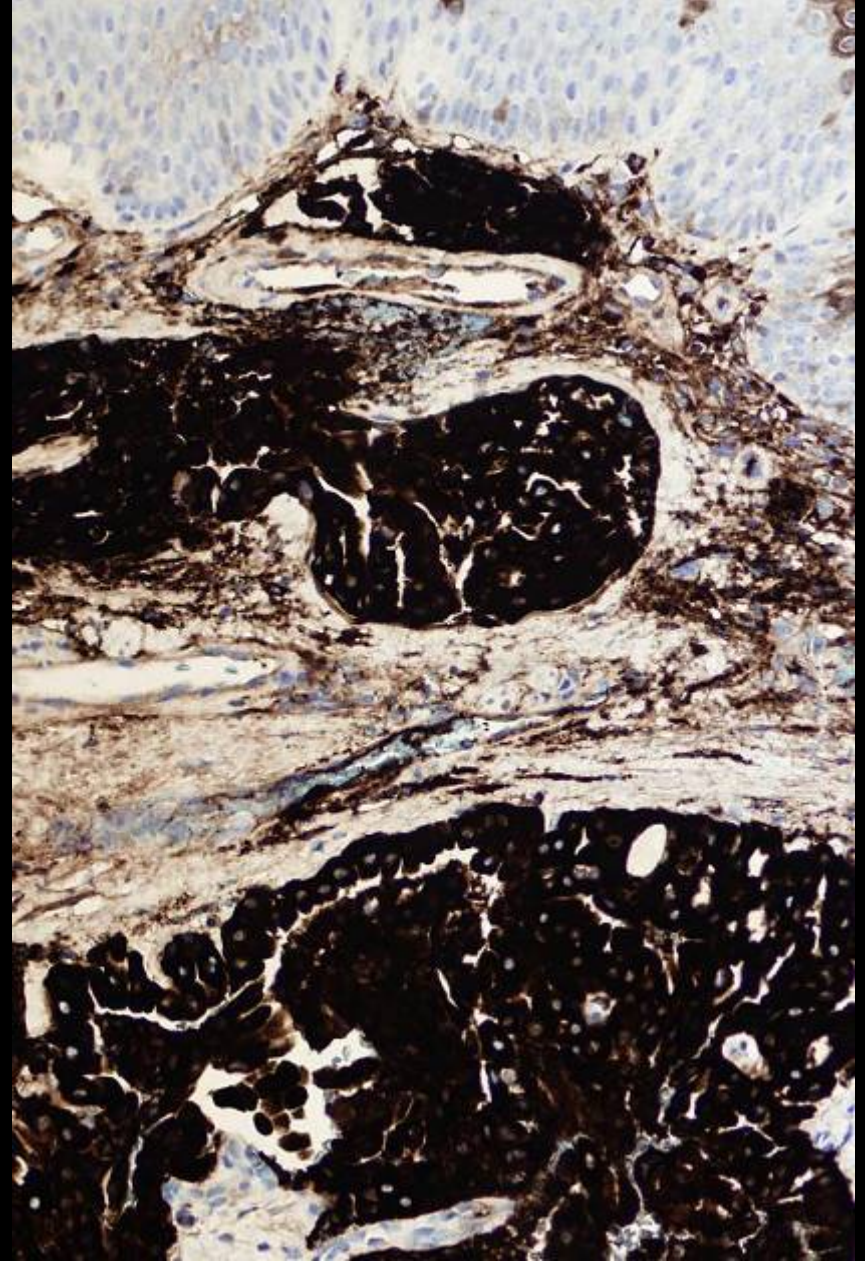
♂ 61, Metastatic adenocarcinoma UPT in the eye lid



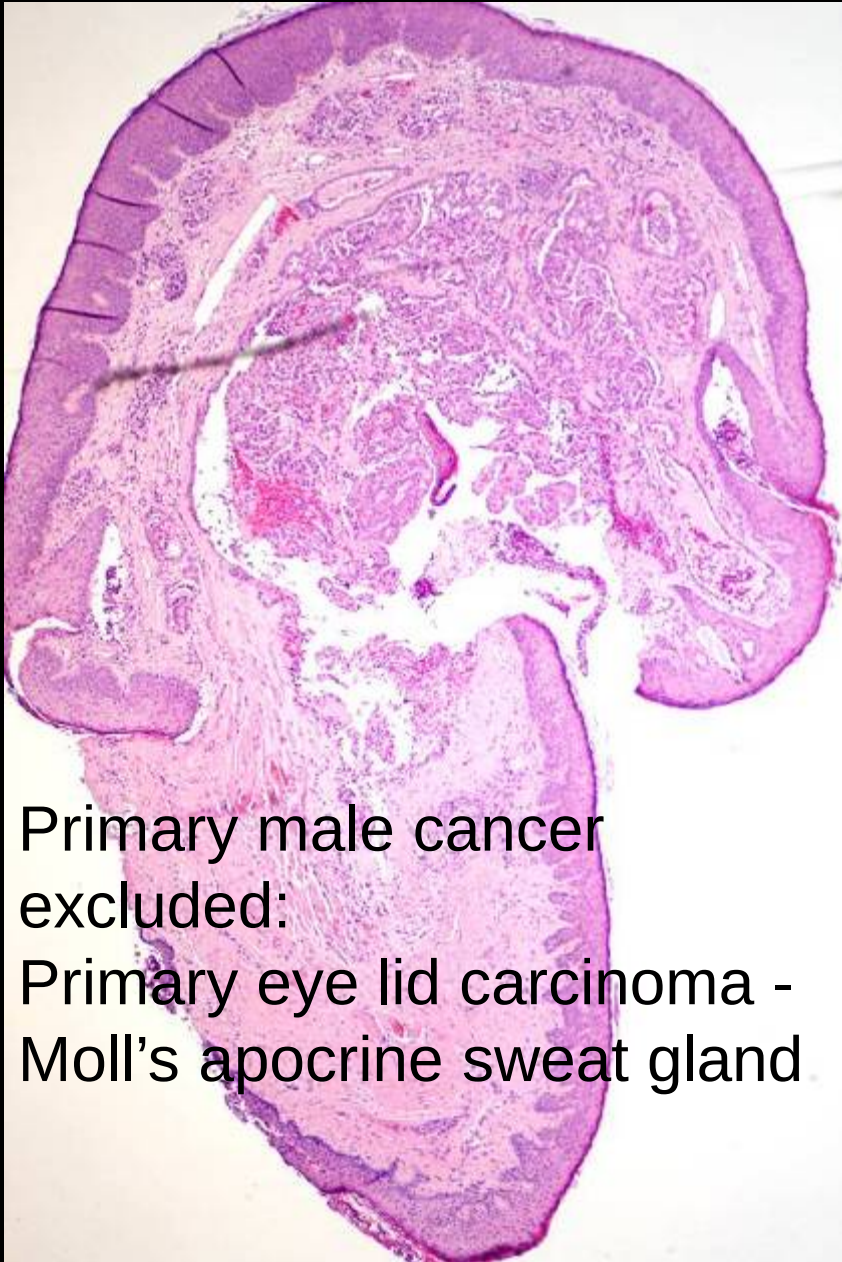
♂ 61, Metastatic adenocarcinoma UPT in the eye lid



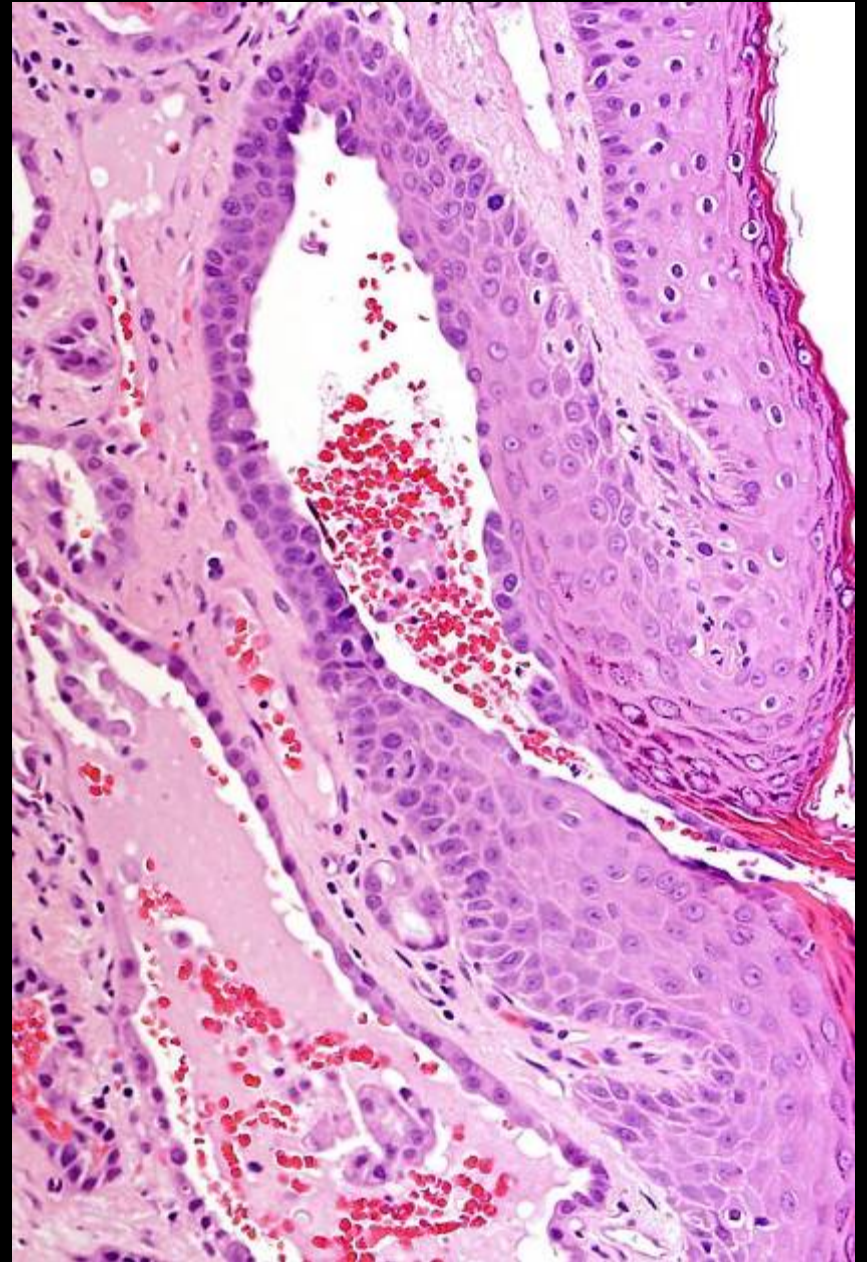
MAMMAGLOBIN



♂ 61, Metastatic adenocarcinoma UPT in the eye lid



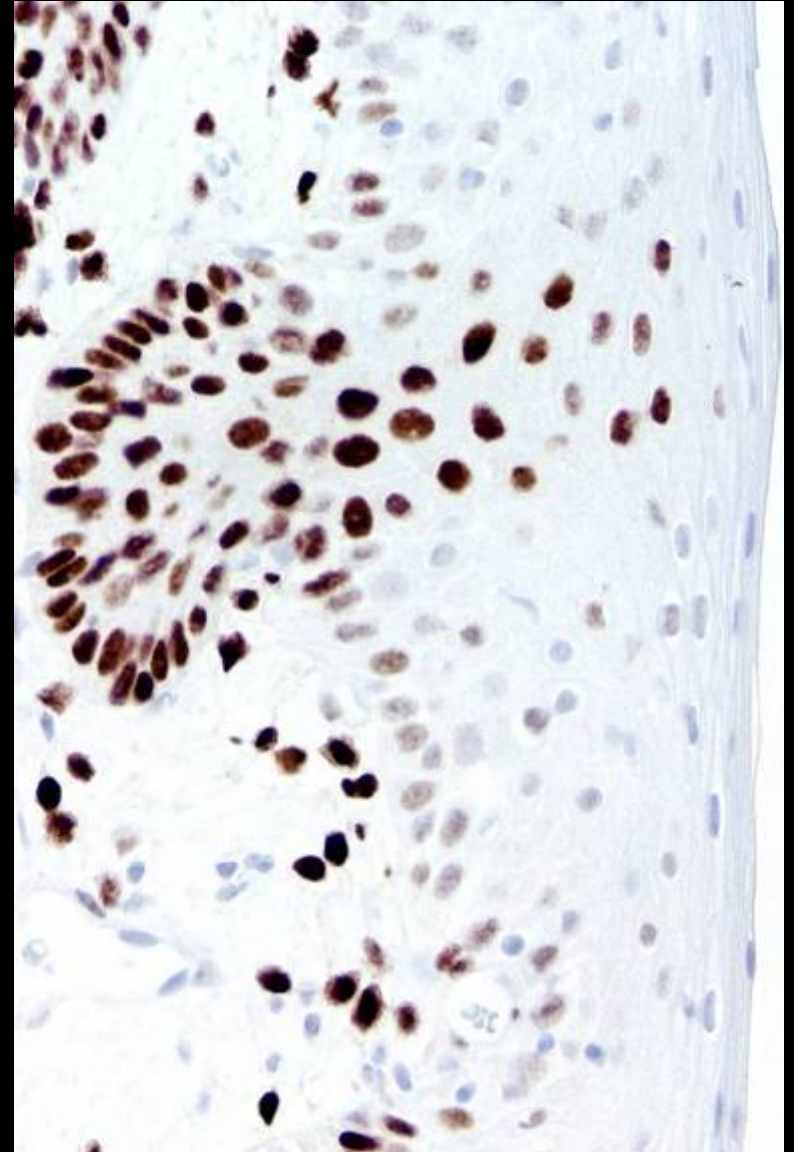
Primary male cancer
excluded:
Primary eye lid carcinoma -
Moll's apocrine sweat gland



Estrogen receptor alpha

Estrogen sensitive tissues:

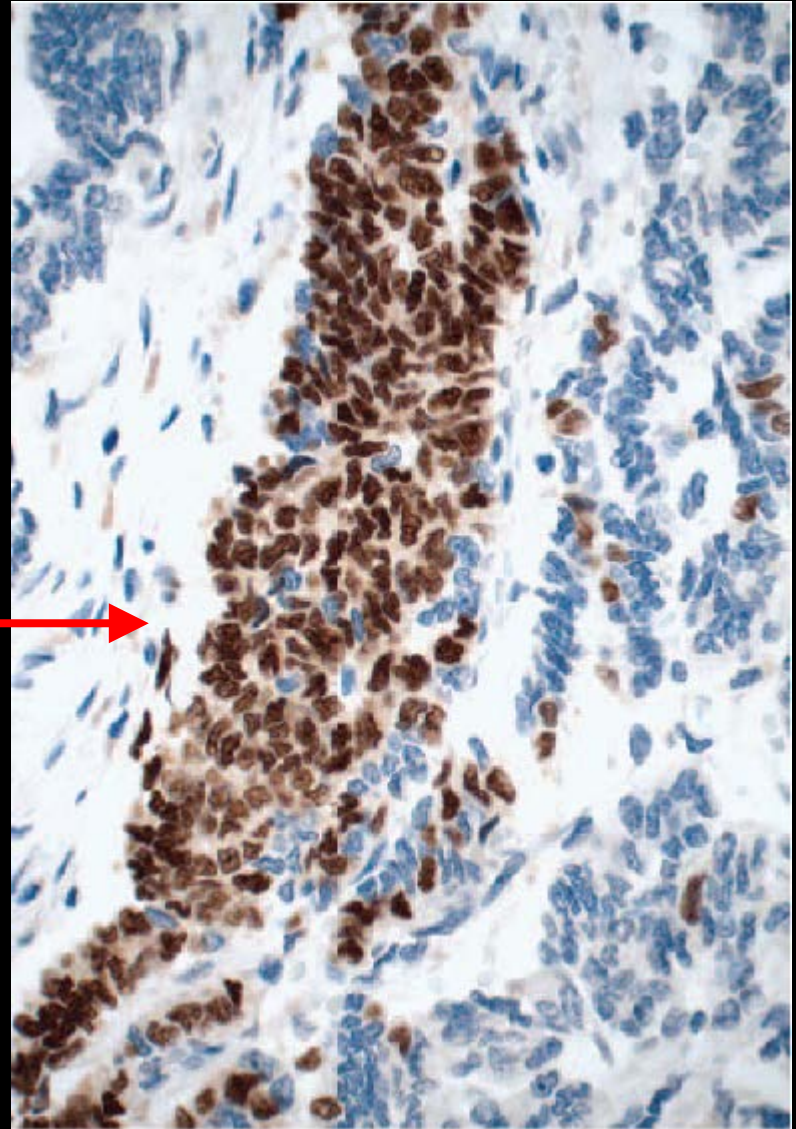
- Breast
- Ovarium
- Fallopian tube
- Endo- and myometrium
- Uterine cervix
- Thyroid gland
- Pituitary gland
- Pancreas
- Sweat gland
- Salivary gland
- Prostate, Liver



Estrogen receptor alpha

Adenocarcinomas

- Breast carcinoma +/–
- Ovarian (non-muc.) +/–
- Endometrial carc. +/–
- Cervix, lung, kidney, endocrine . . . –/+



Estrogen receptor alpha

Lung adenocarcinomas

	ER, No. Positive/Total (%)	
Beattie et al, ³¹ 1985	6/15	(40.0)
Cagle et al, ³² 1990	3/18	(16.7)
Canver et al, ¹¹ 1994	62/64	(96.9)
Dabbs et al, ⁹ 2002	30/45	(66.7)
DiNunno et al, ⁴⁴ 2000	0/248	(0)
Ollayos et al, ³³ 1994	3/42	(7.1)
Radzikowska et al, ⁵¹ 2002	2/32	(1 adca, 1 squamous)
Su et al, ³⁴ 1996	3/49	(6.1)

Estrogen receptor alpha: The influence of antibody selection

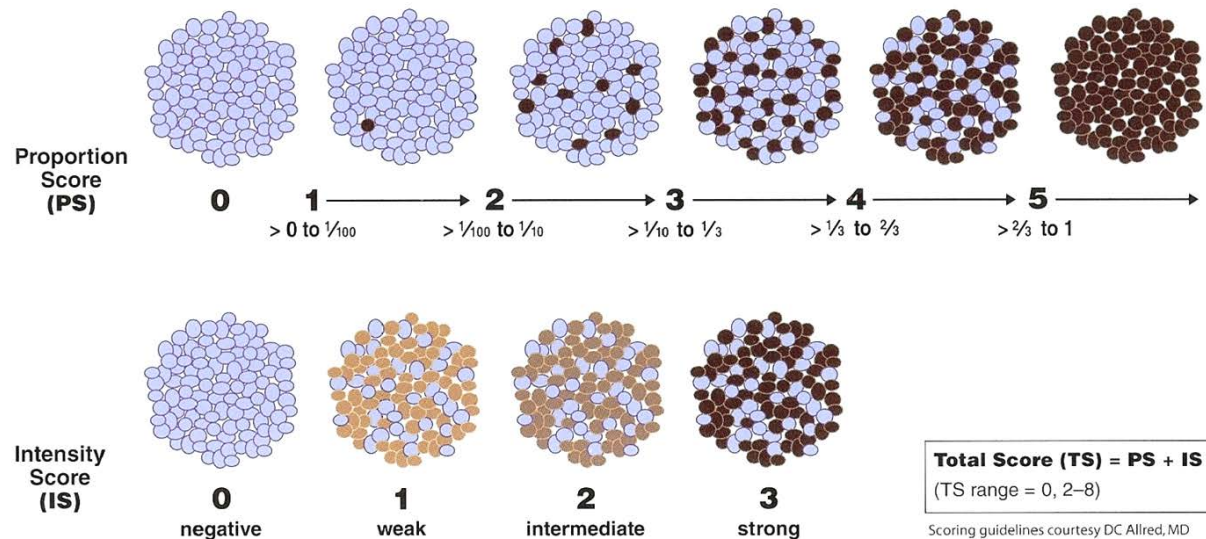
92 lung adenocarcinomas

ER+ ($\geq 1\%$ pos. cells)

- 1D5: 8%
- 6F11: 14%
- SP1: 27%

Scoring hormone receptors

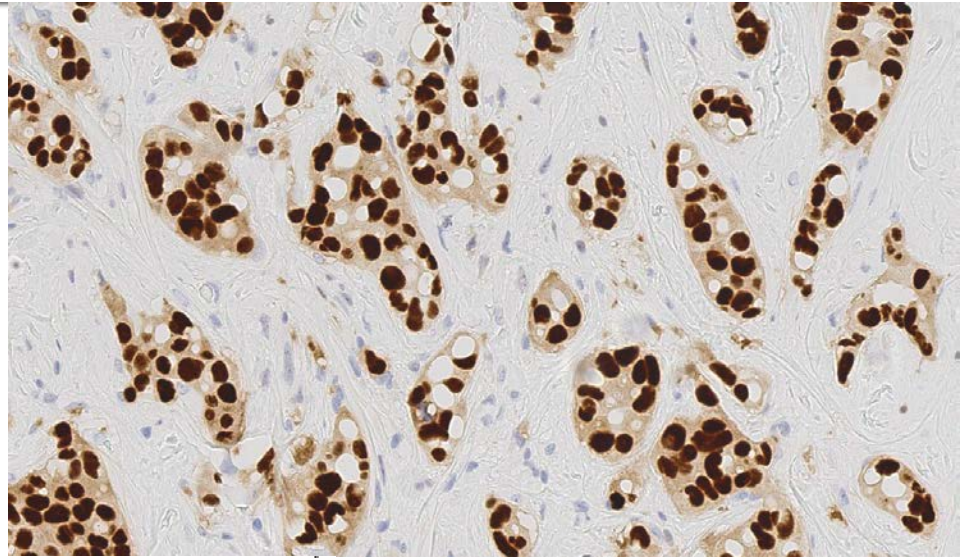
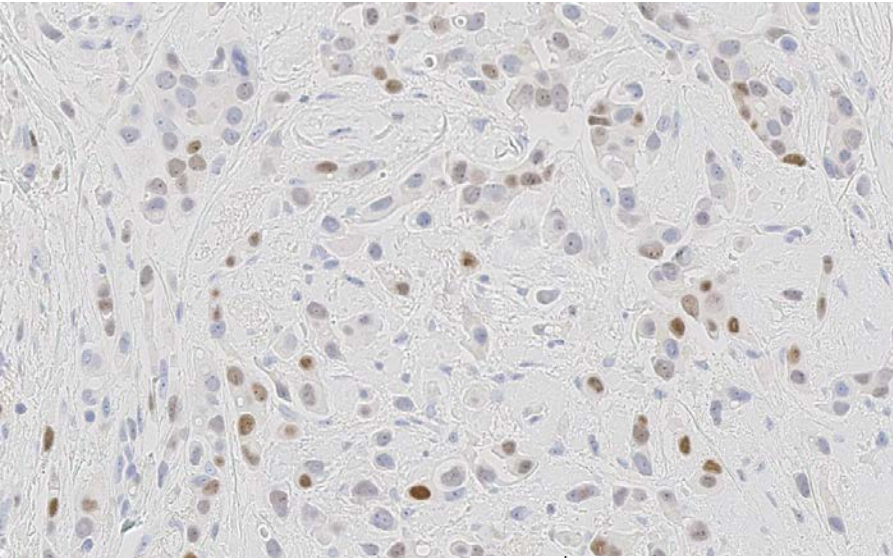
Allred Scoring System



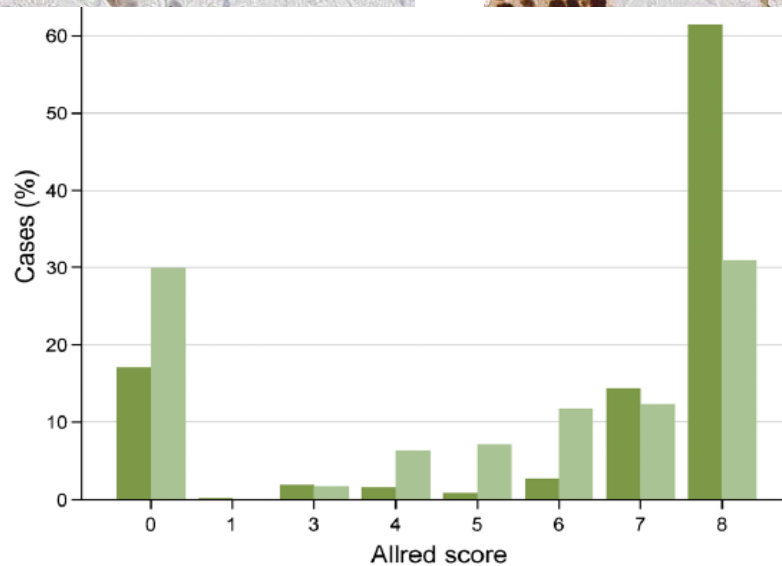
ER/PR pharmDx Scoring Guidelines

Proportion Score (PS) Proportion of tumor cells with positive nuclear staining	PS Observation	Intensity Score (IS) Average intensity of all positive tumor cells	IS Observation
0	None	0	None
1	> 0 to $1/100$	1	Weak
2	$> 1/100$ to $1/10$	2	Intermediate
3	$> 1/10$ to $1/3$	3	Strong
4	$> 1/3$ to $2/3$		
5	$> 2/3$ to 1		

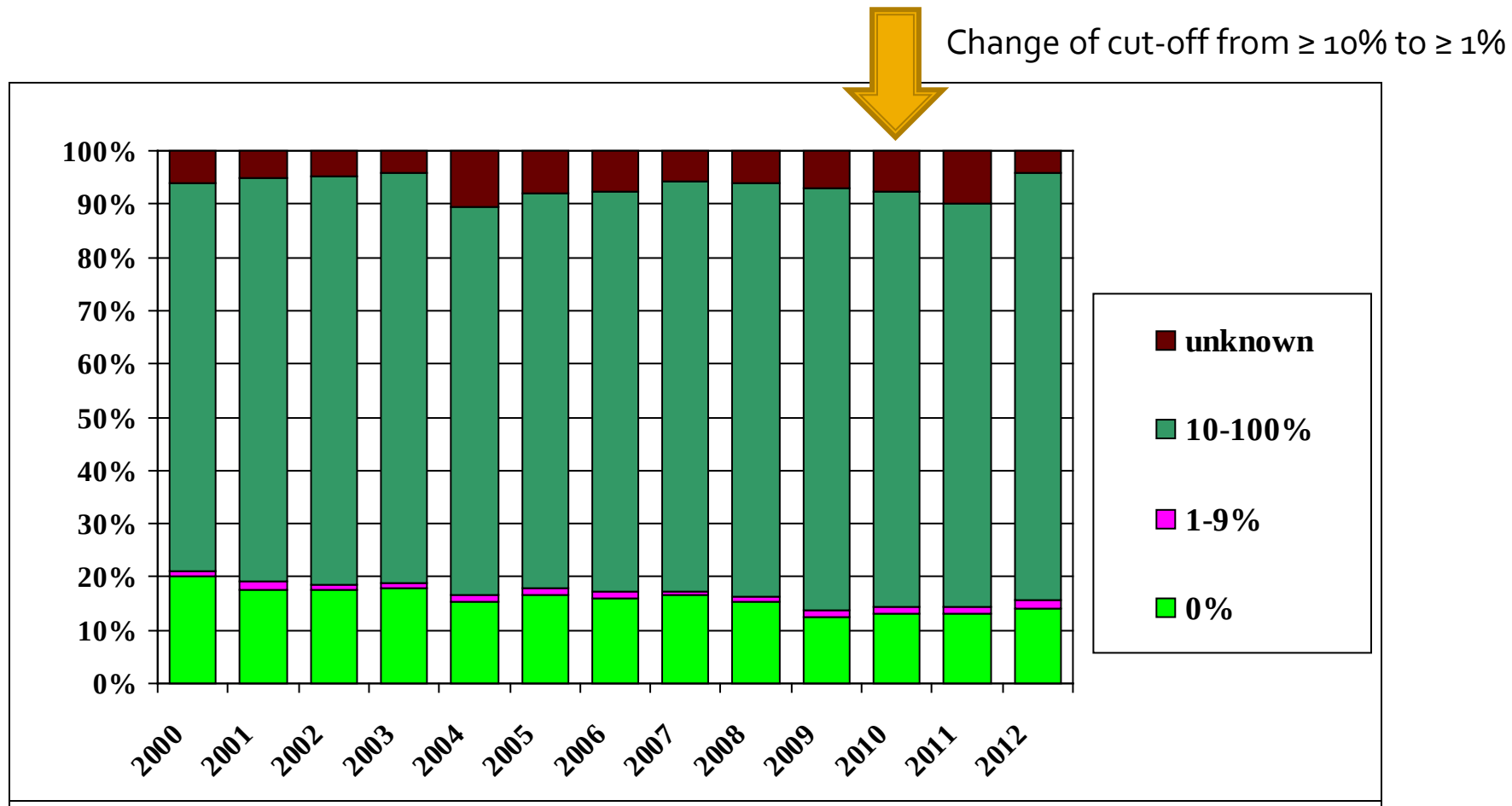
Interpretation of ER



Gándara-Cortes et al.



ER status Denmark 2000-2012



Danish Breast Cancer Cooperative
Group

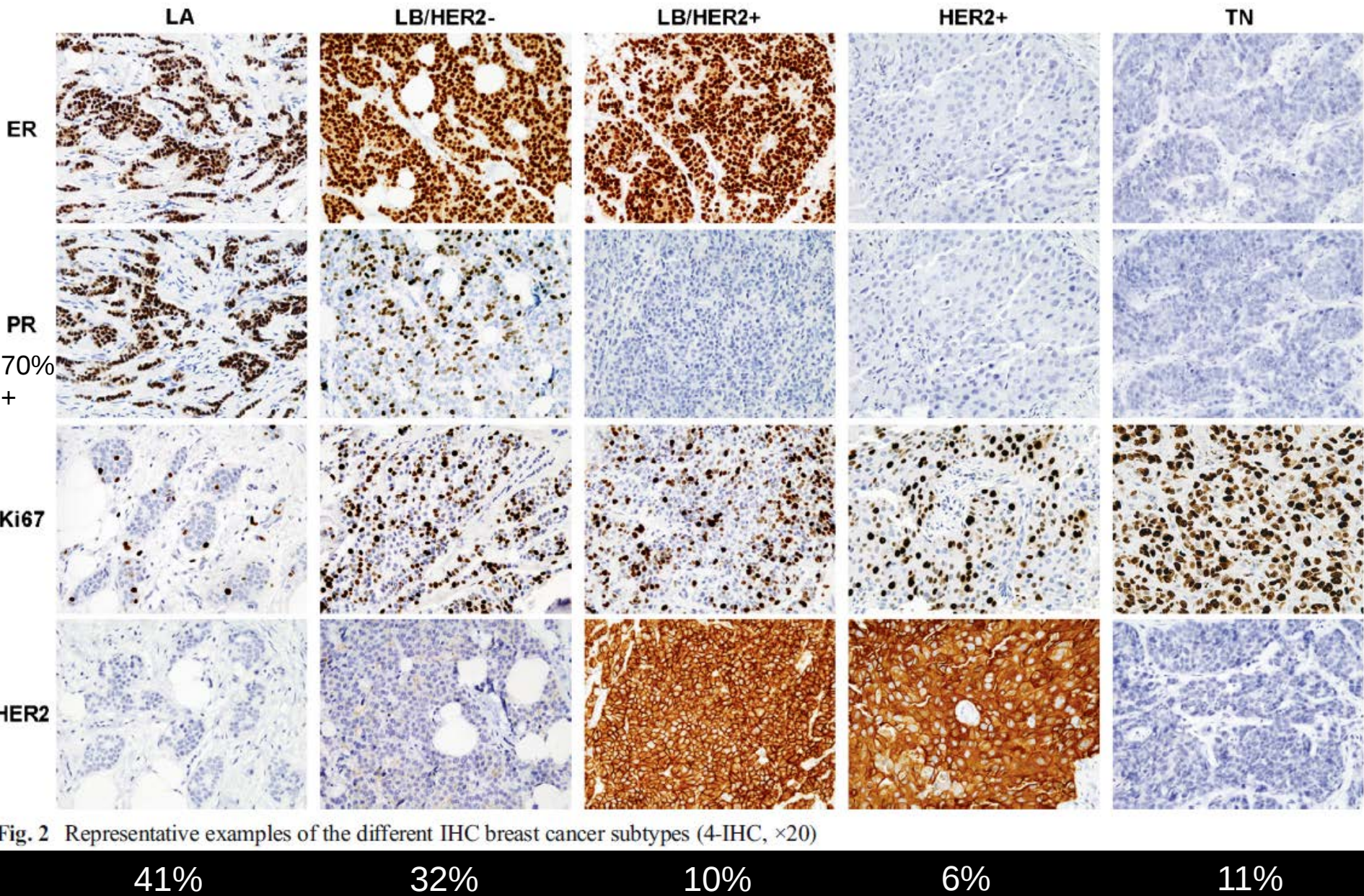


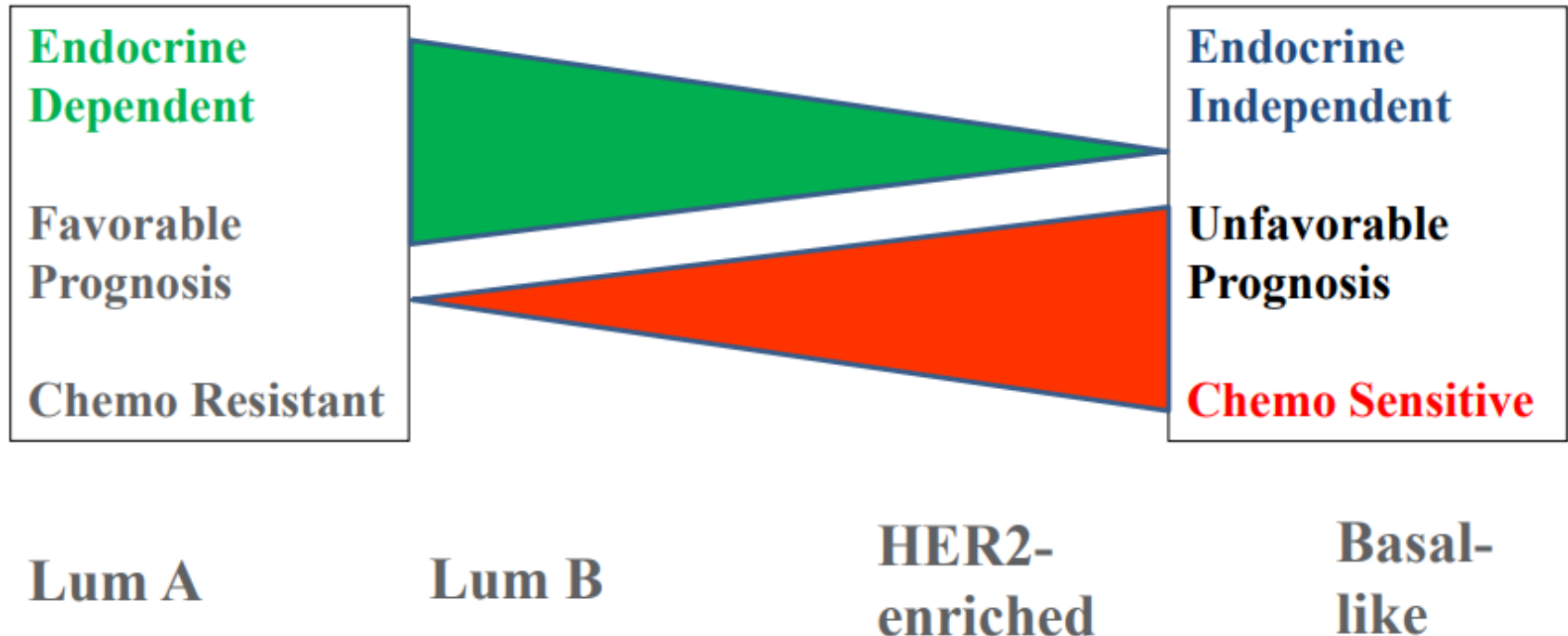
Fig. 2 Representative examples of the different IHC breast cancer subtypes (4-IHC, ×20)

**Immunohistochemical surrogates
for the gene defined intrinsic subtypes
St Gallen International Expert Consensus 2011**

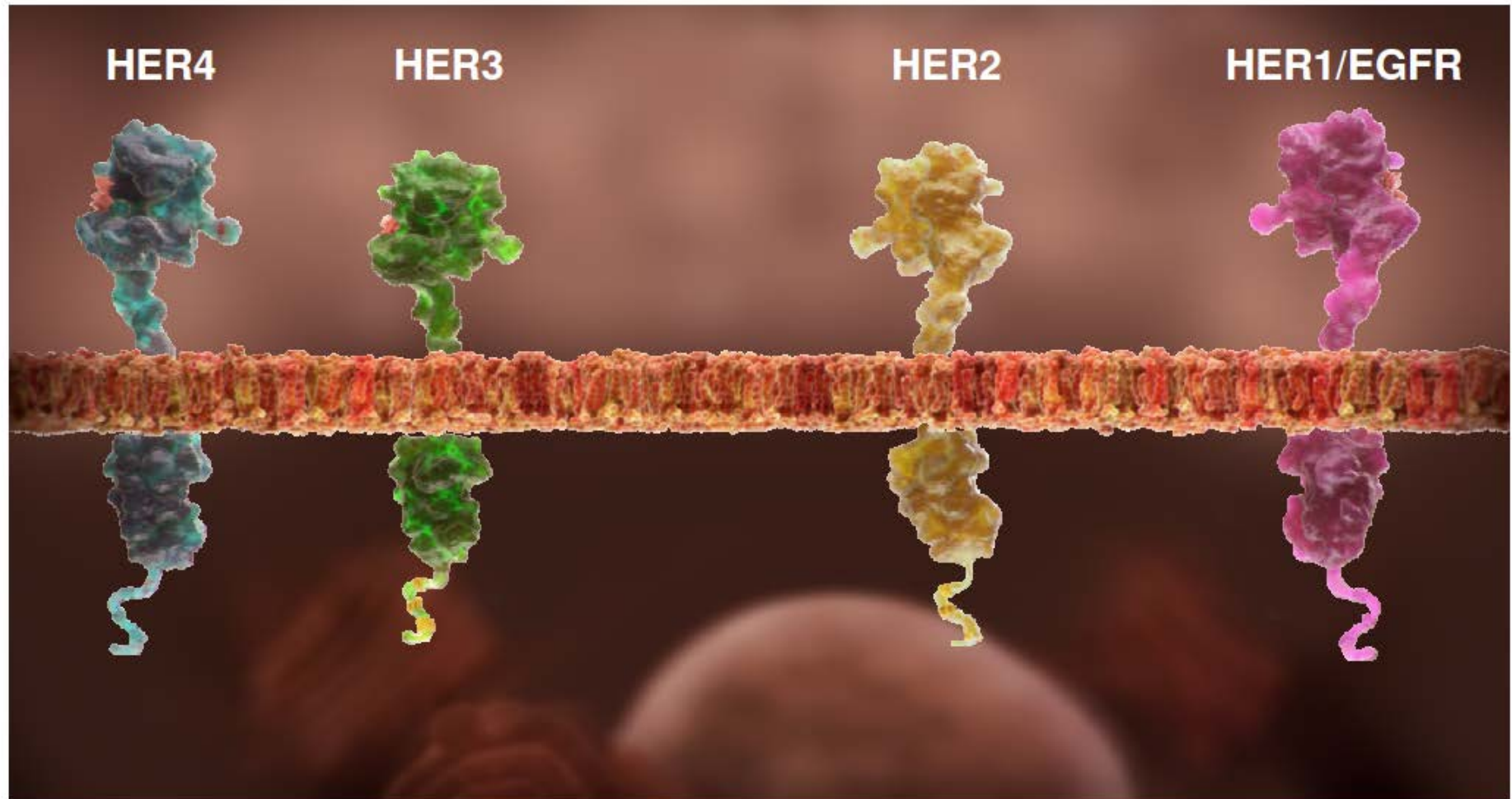
Annals of Oncology 2011; 22:1736-1747

- Luminal A: ER-positive, HER2-negative, Ki67- low and
- Luminal B: ER-positive, HER2-negative, Ki67> 14% or
- Luminal B: ER-positive, HER2-overexpressed or amplified, any Ki67
- HER2-positive (non luminal): HER2 overexpressed or amplified and ER negative
- Triple-negative: ER-negative, (PR-negative), HER2-negative

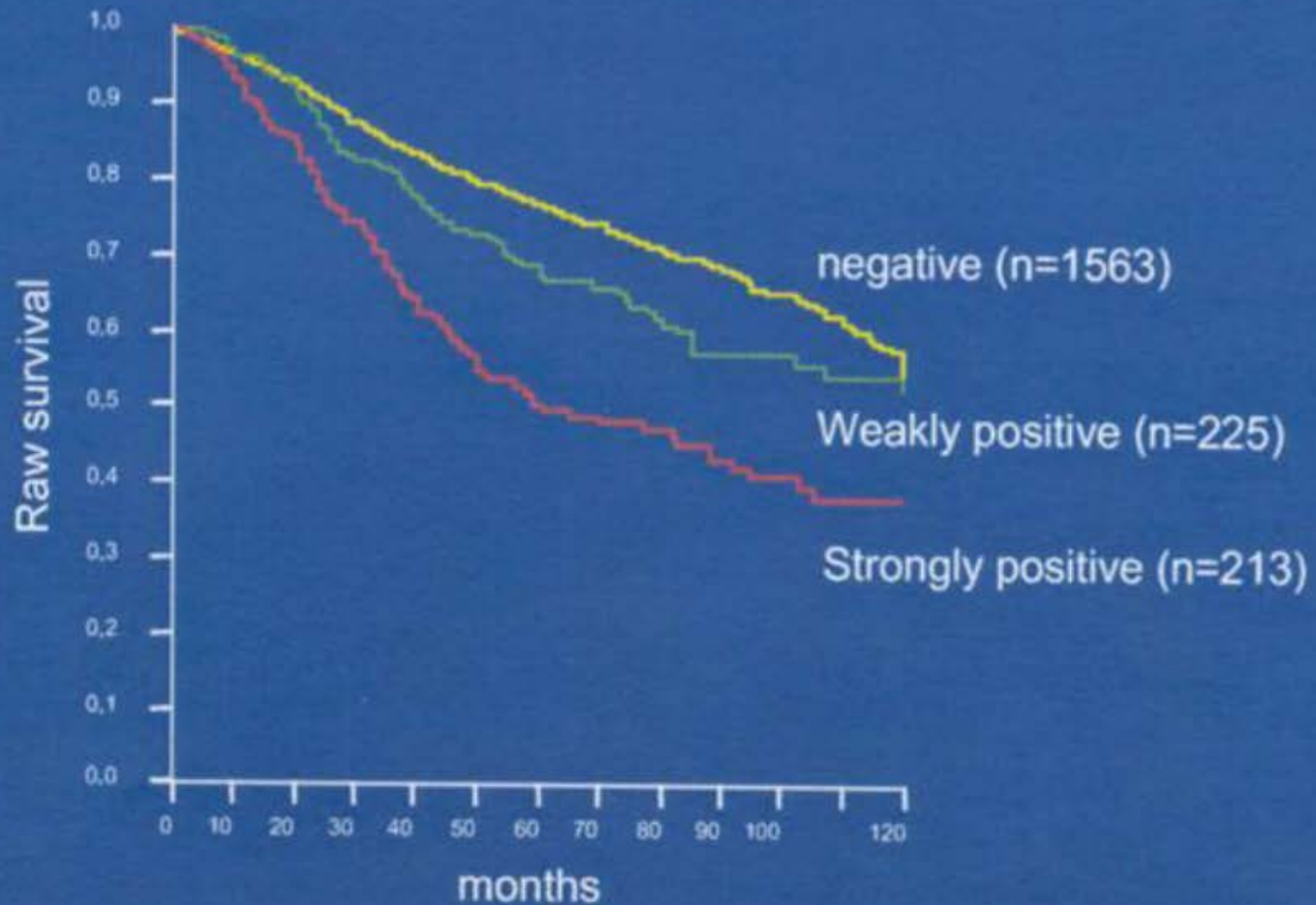
Breast cancer – Molecular intrinsic subtypes



There are four receptors in the HER family

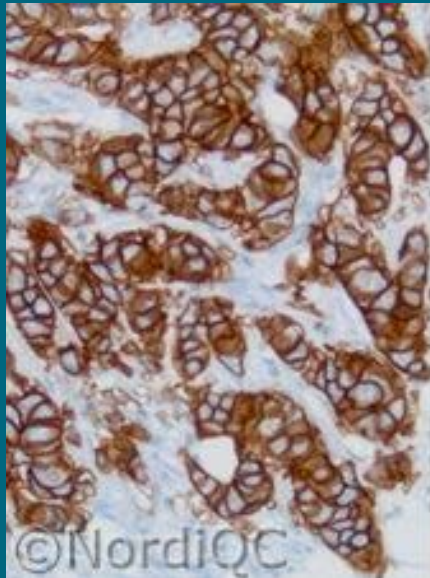


HER2 and Breast Cancer Progression

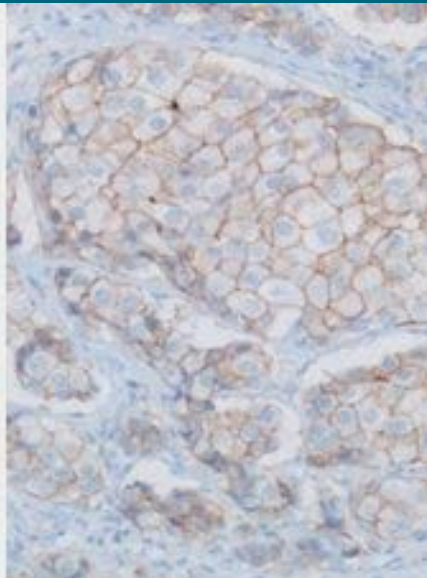


Science, Vol 235, 1987

NordiQC runs for HER2 IHC



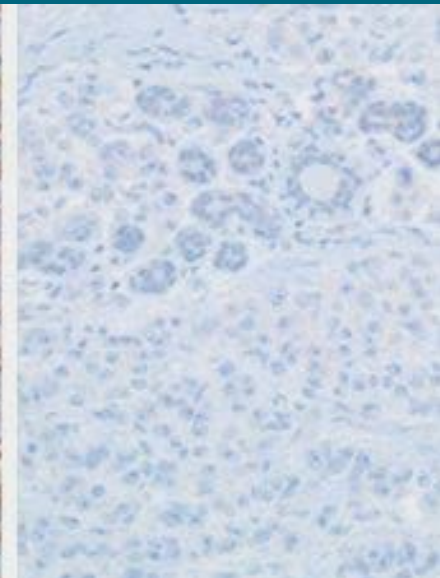
Ampl. 3+



Ampl. 2+



Unampl. 2+



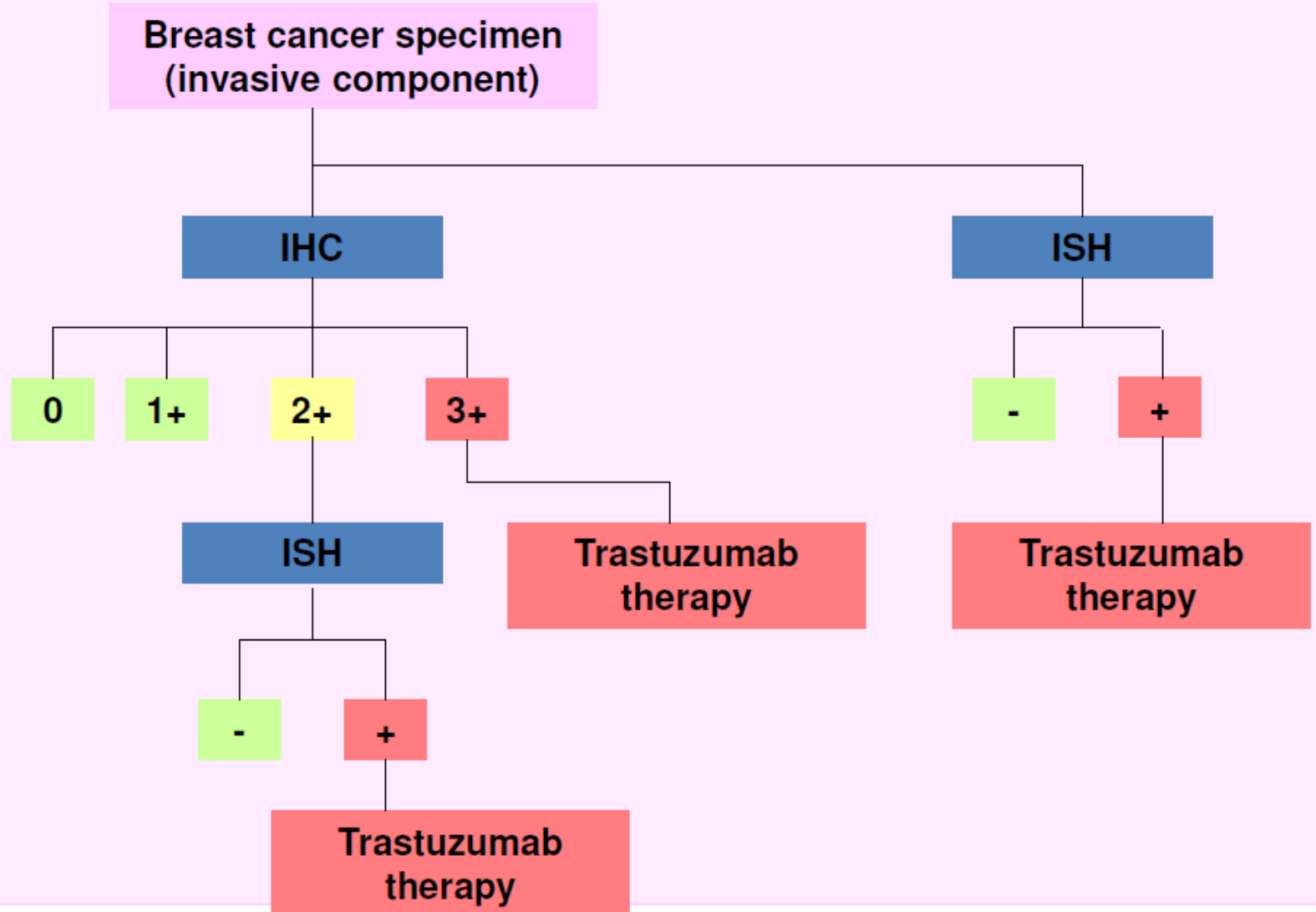
Unampl. 0

[J Clin Oncol](#). 2013 Nov 1;31(31):3997-4013. doi: 10.1200/JCO.2013.50.9984. Epub 2013 Oct 7.

Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.

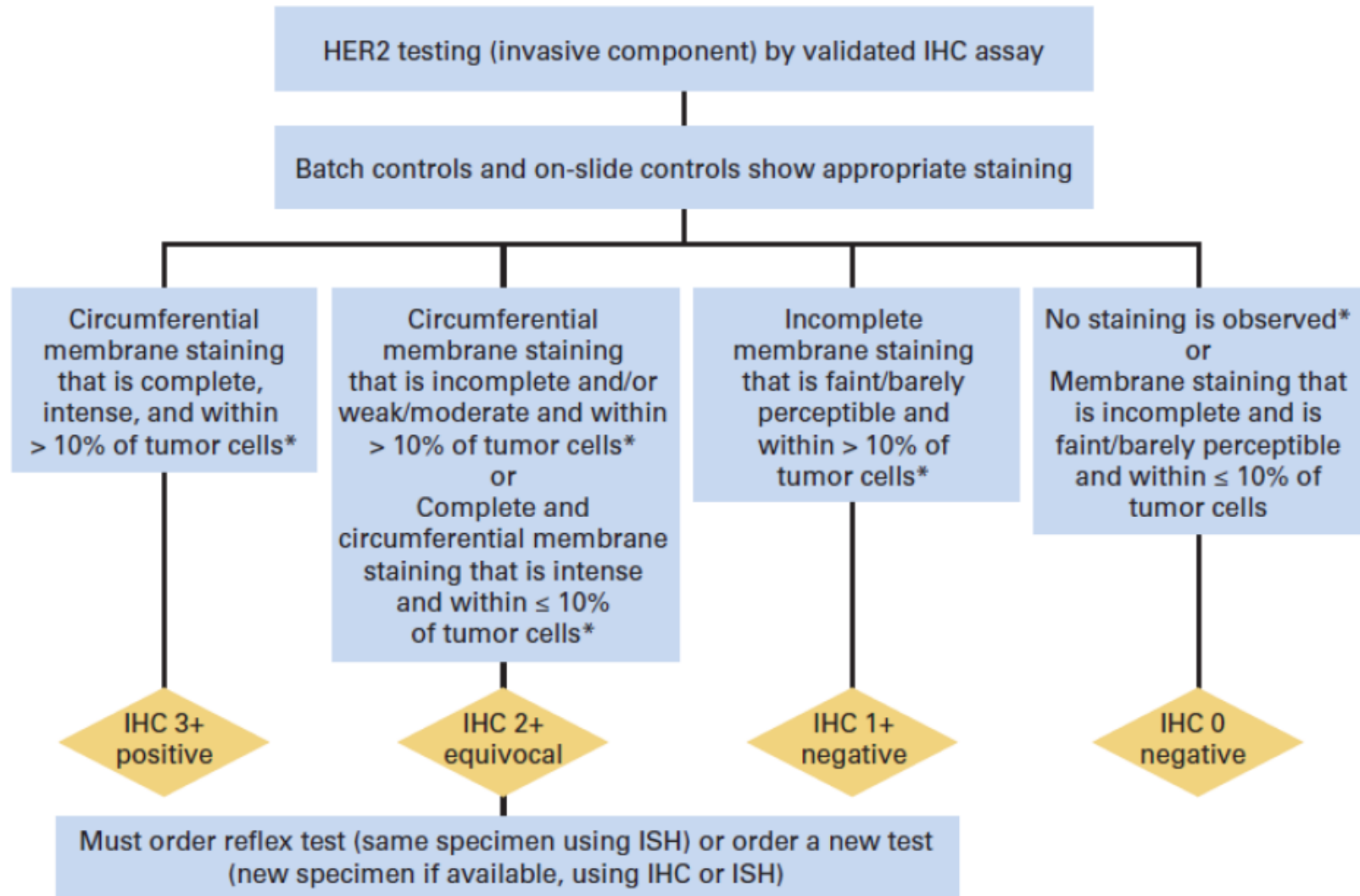
[Wolff AC](#)¹, [Hammond ME](#), [Hicks DG](#), [Dowsett M](#), [McShane LM](#), [Allison KH](#), [Allred DC](#), [Bartlett JM](#), [Bilous M](#), [Fitzgibbons P](#), [Hanna W](#), [Jenkins RB](#), [Manqu PB](#), [Paik S](#), [Perez EA](#), [Press MF](#), [Spears PA](#), [Vance GH](#), [Viale G](#), [Hayes DF](#); American Society of Clinical Oncology; College of American Pathologists.

HER2 Algorithm

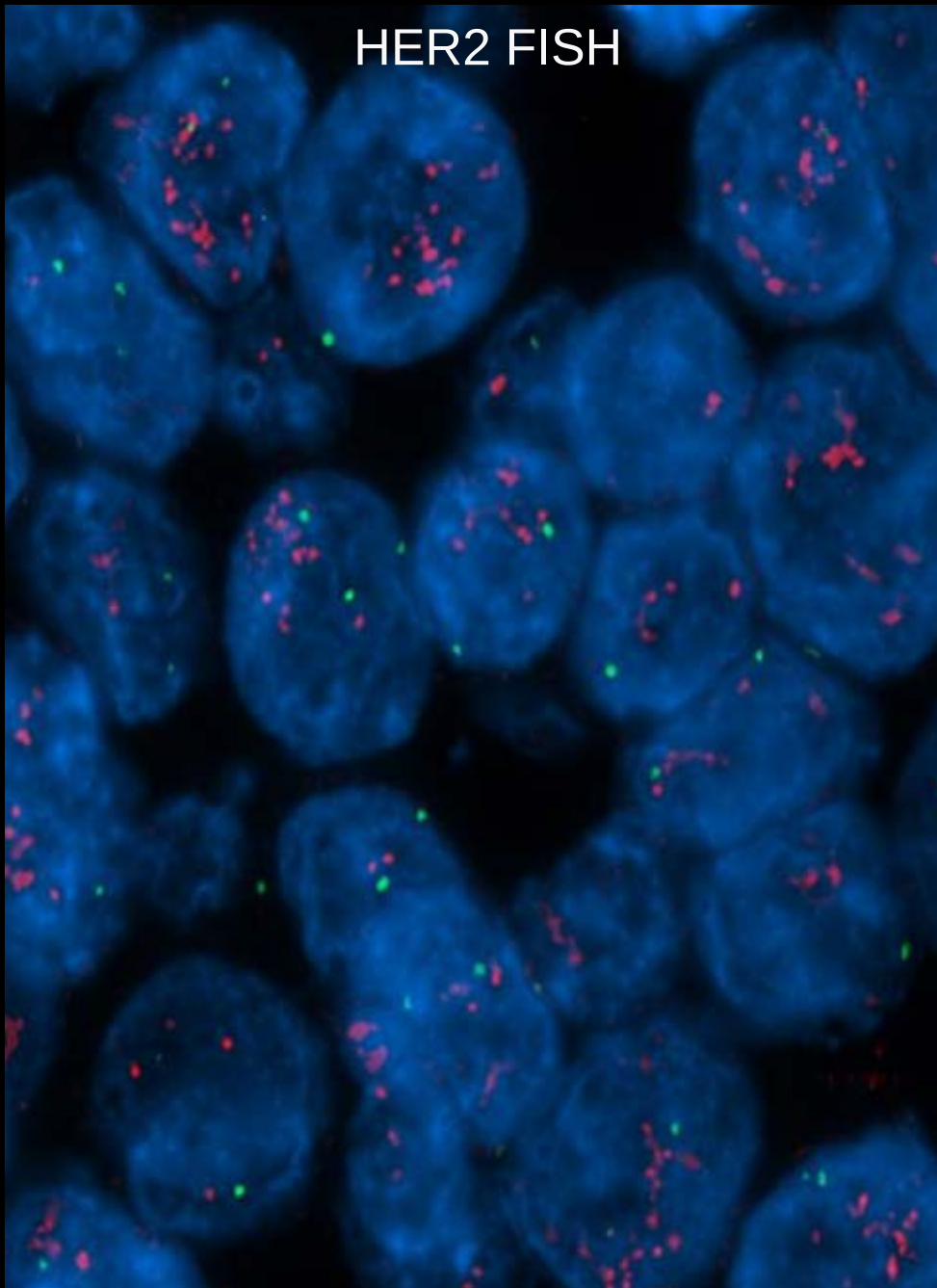


HER2 Testing IHC

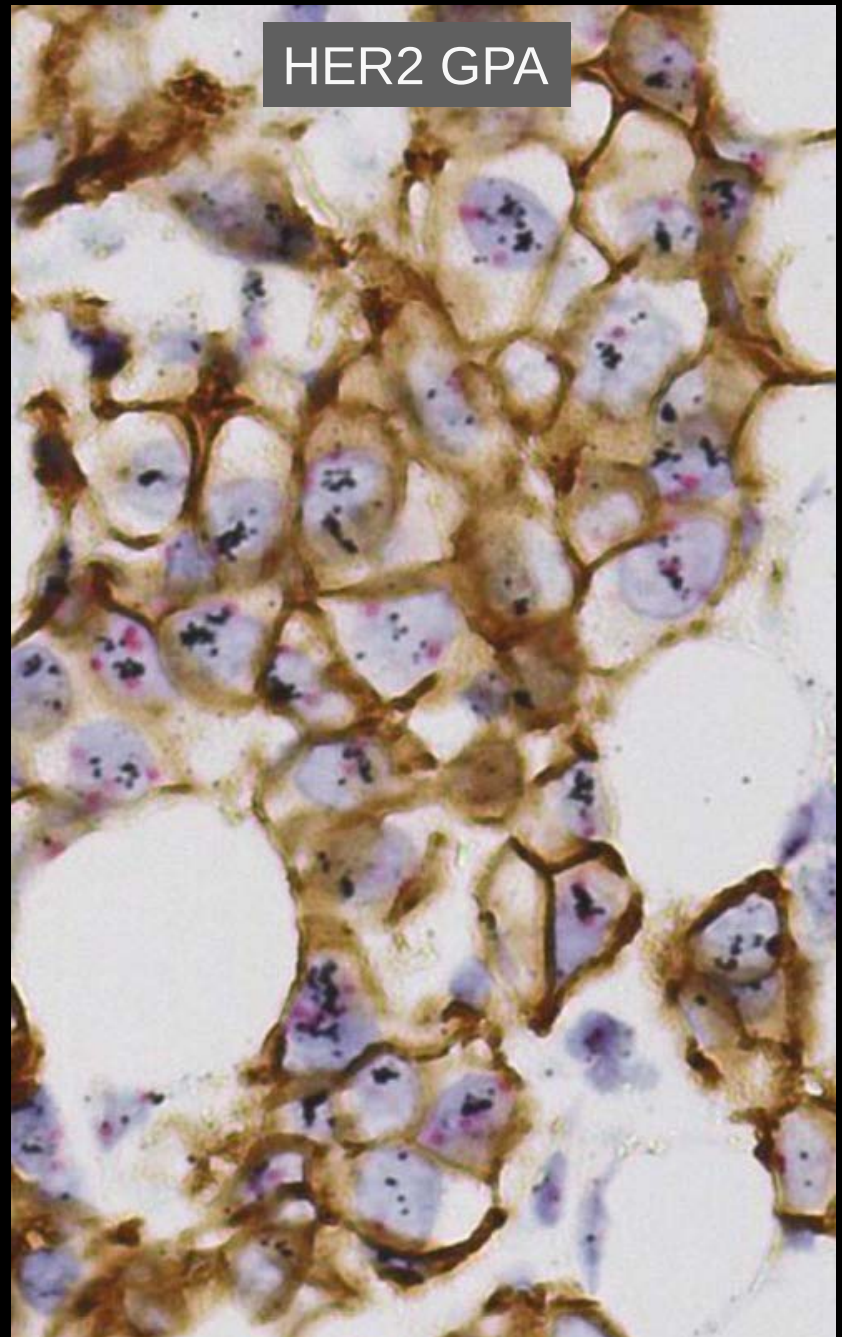
www.asco.org/guidelines/ © American Society of Clinical Oncology®. All rights reserved.



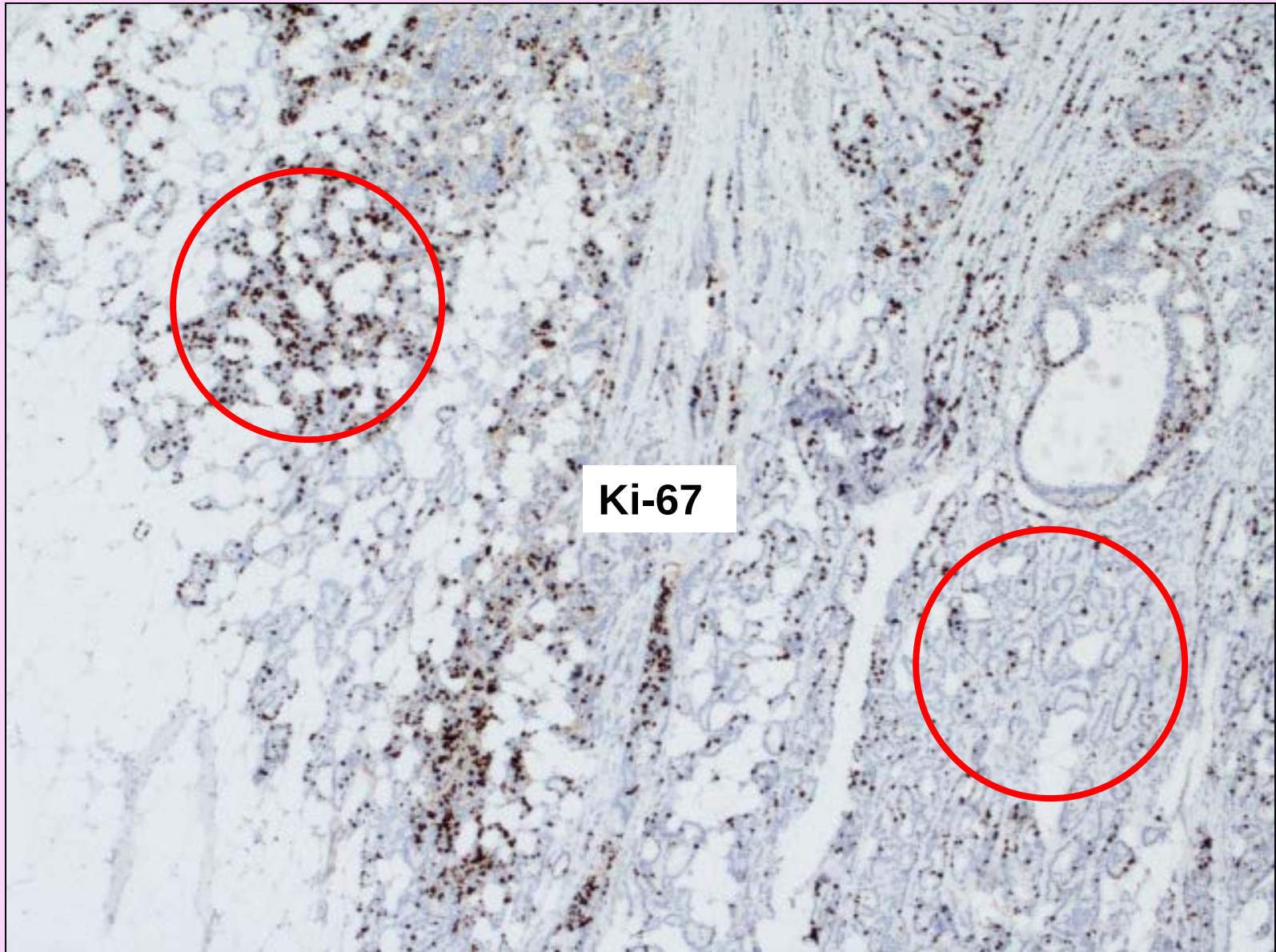
HER2 FISH

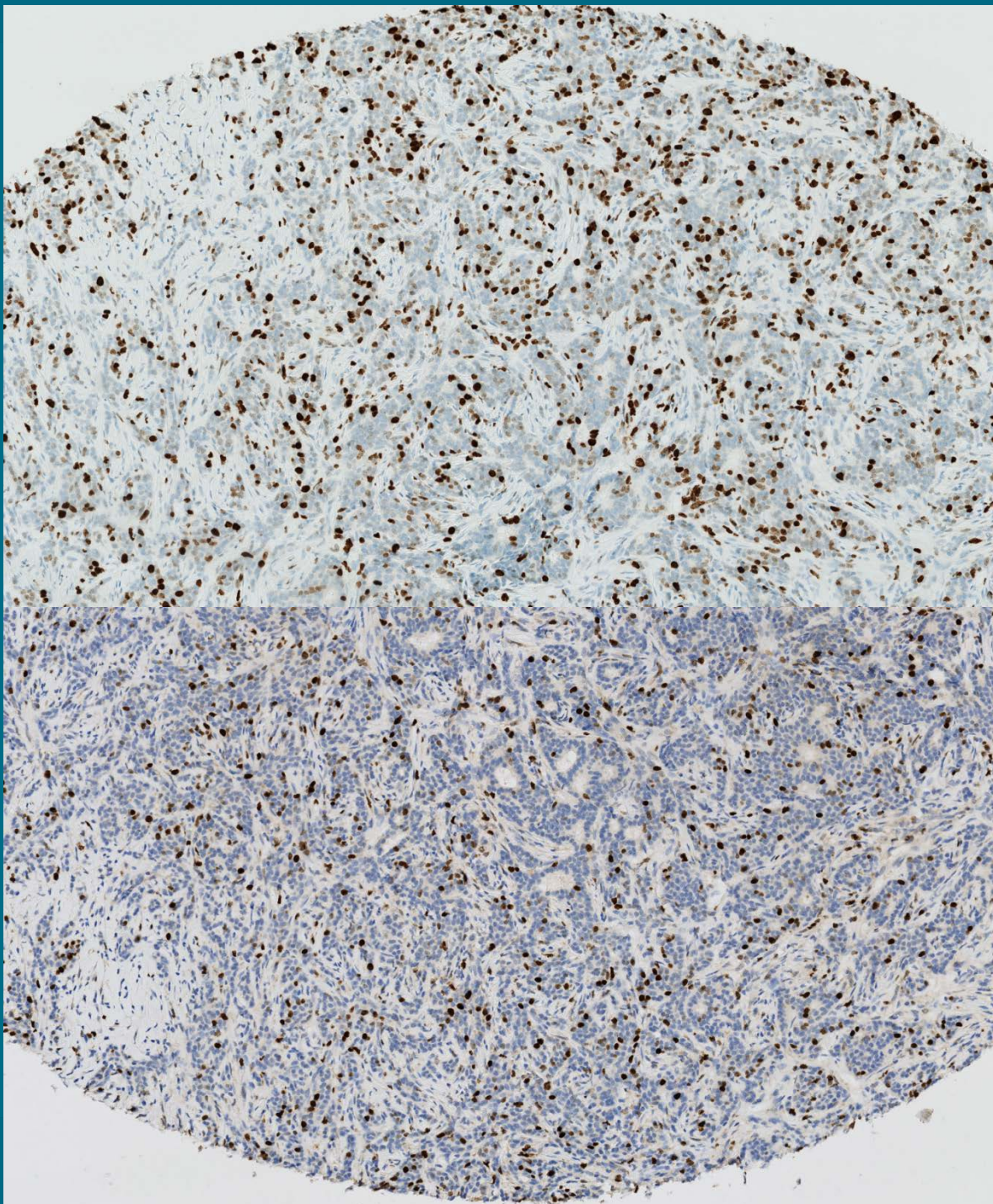


HER2 GPA



Prognosis and proliferation





Ki67 immunoassay Digital image analysis

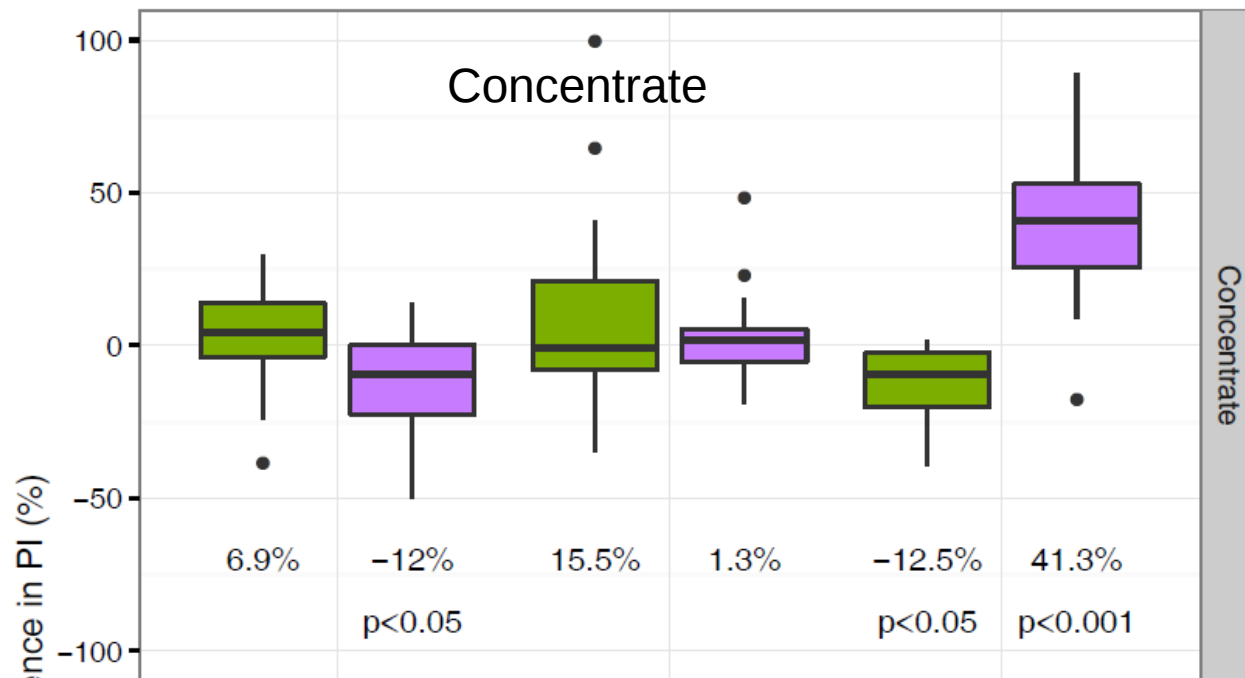
Clone **SP6**
concentrate
Ventana
platform

Prolif.index
38 %

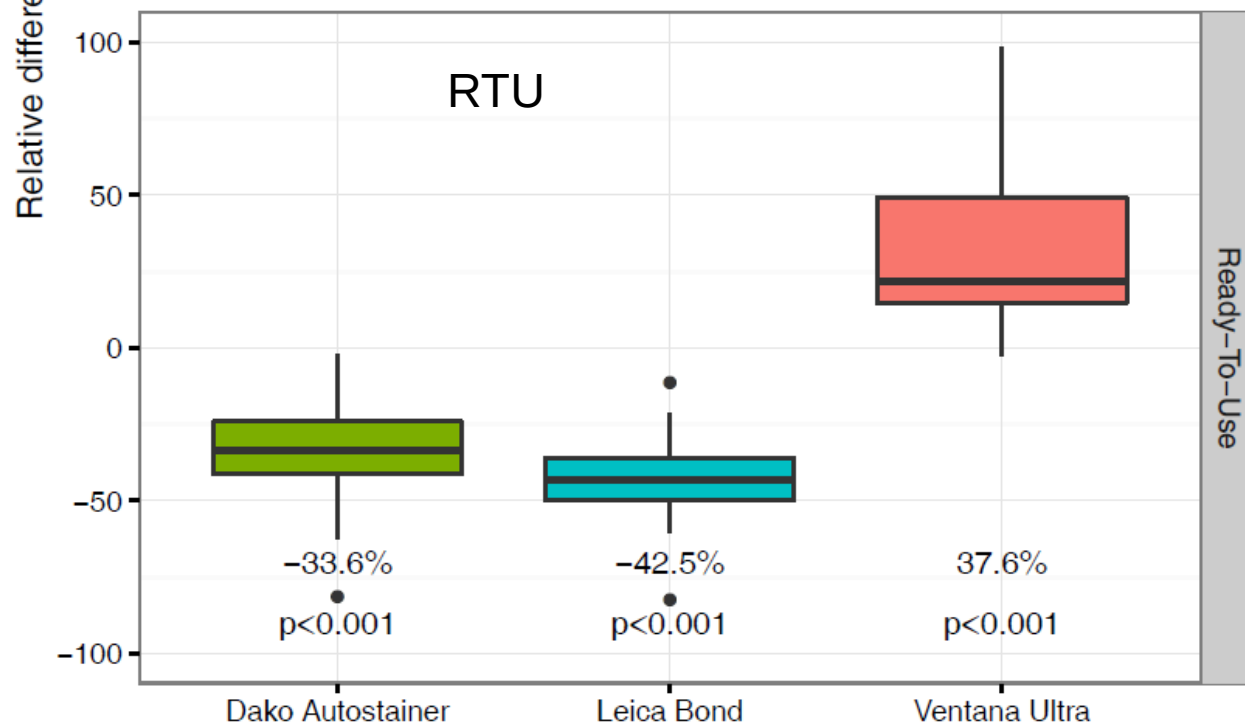
Clone **MM1**
RTU
Leica platform

Prolif.index
12 %



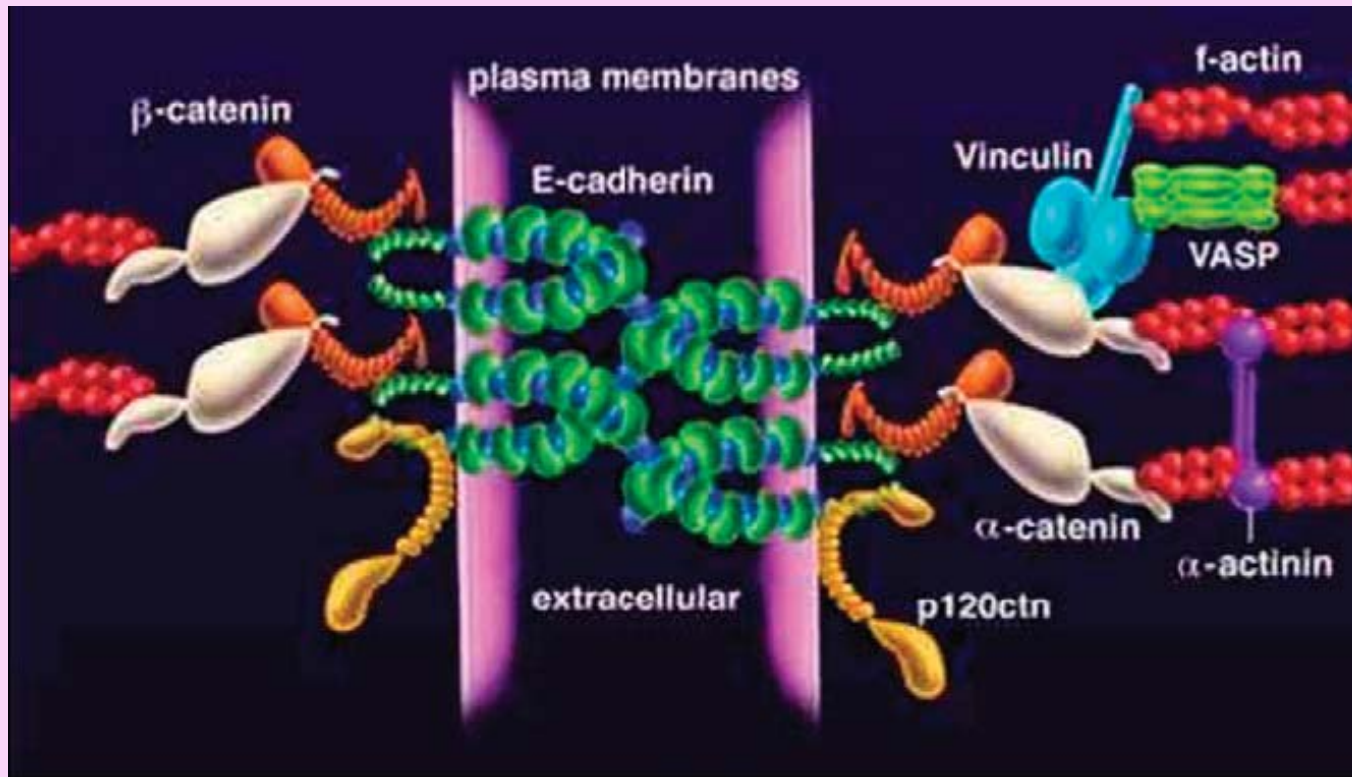


Mib1 as
concentrate
in optimized
protocols on
3 platforms



E-Cadherin and E-cadherin complex

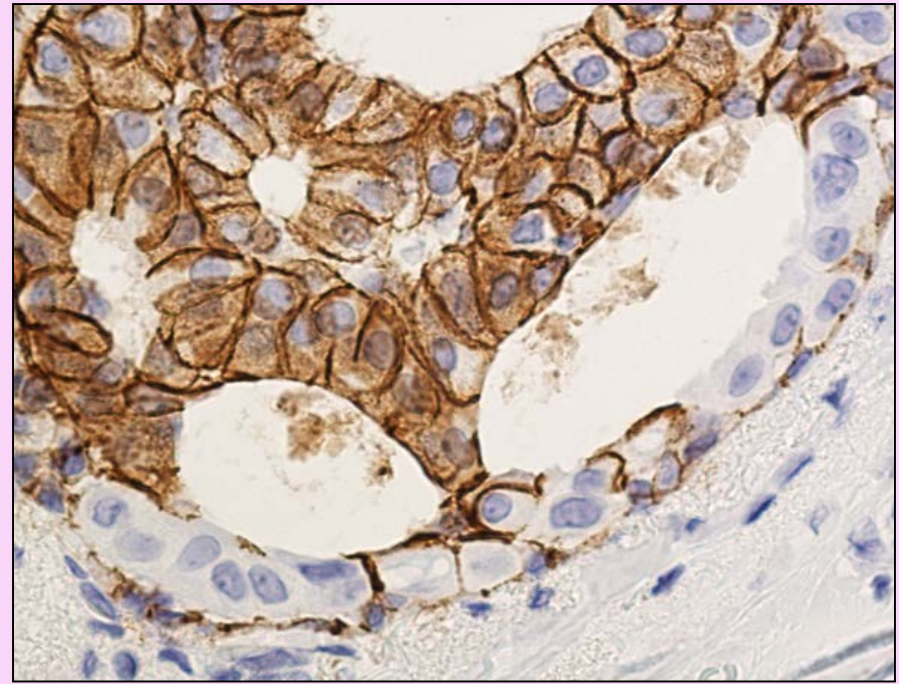
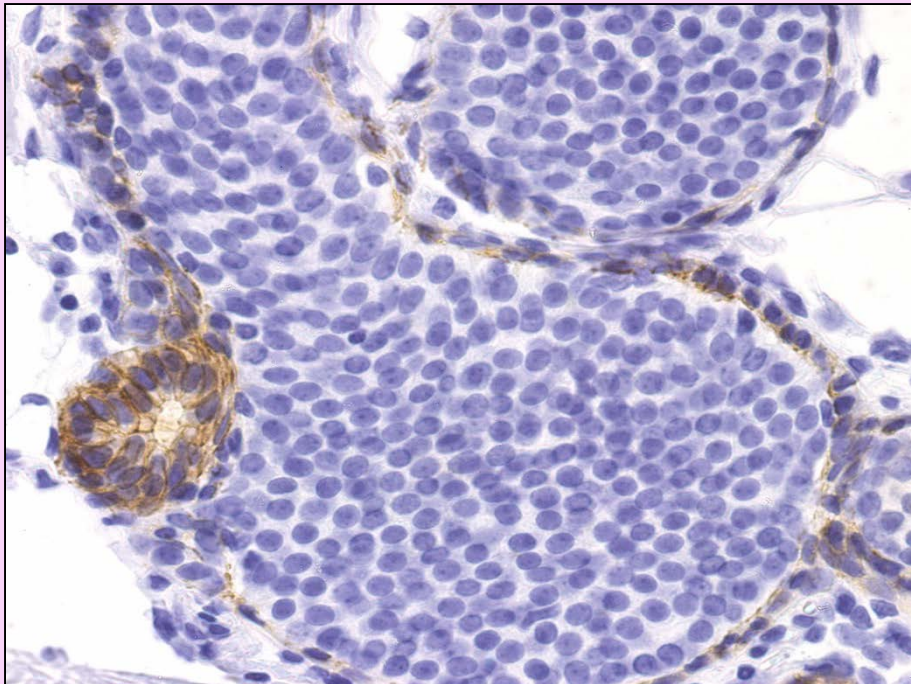
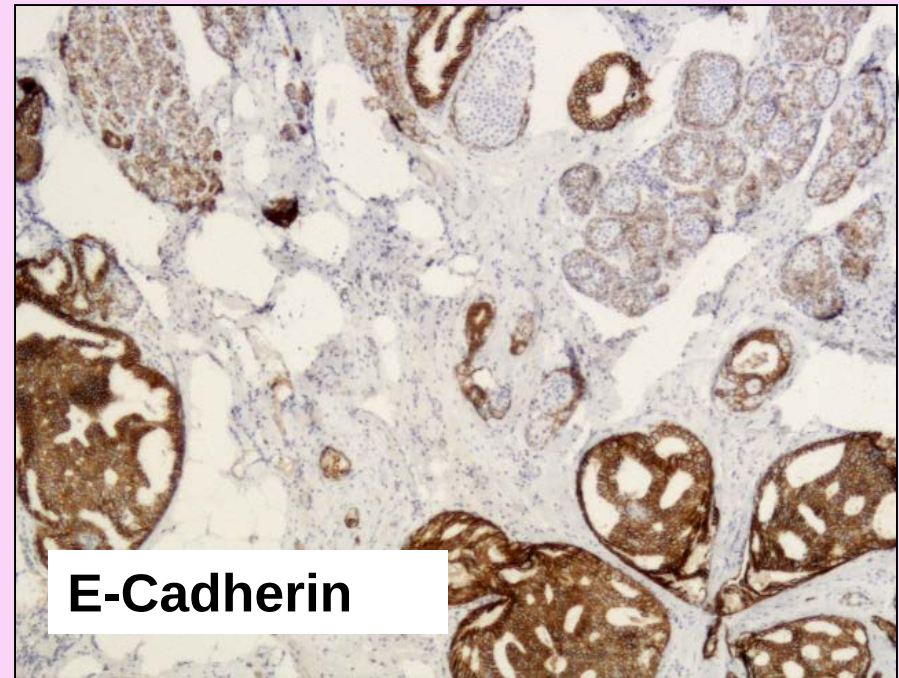
E-Cadherin and p120



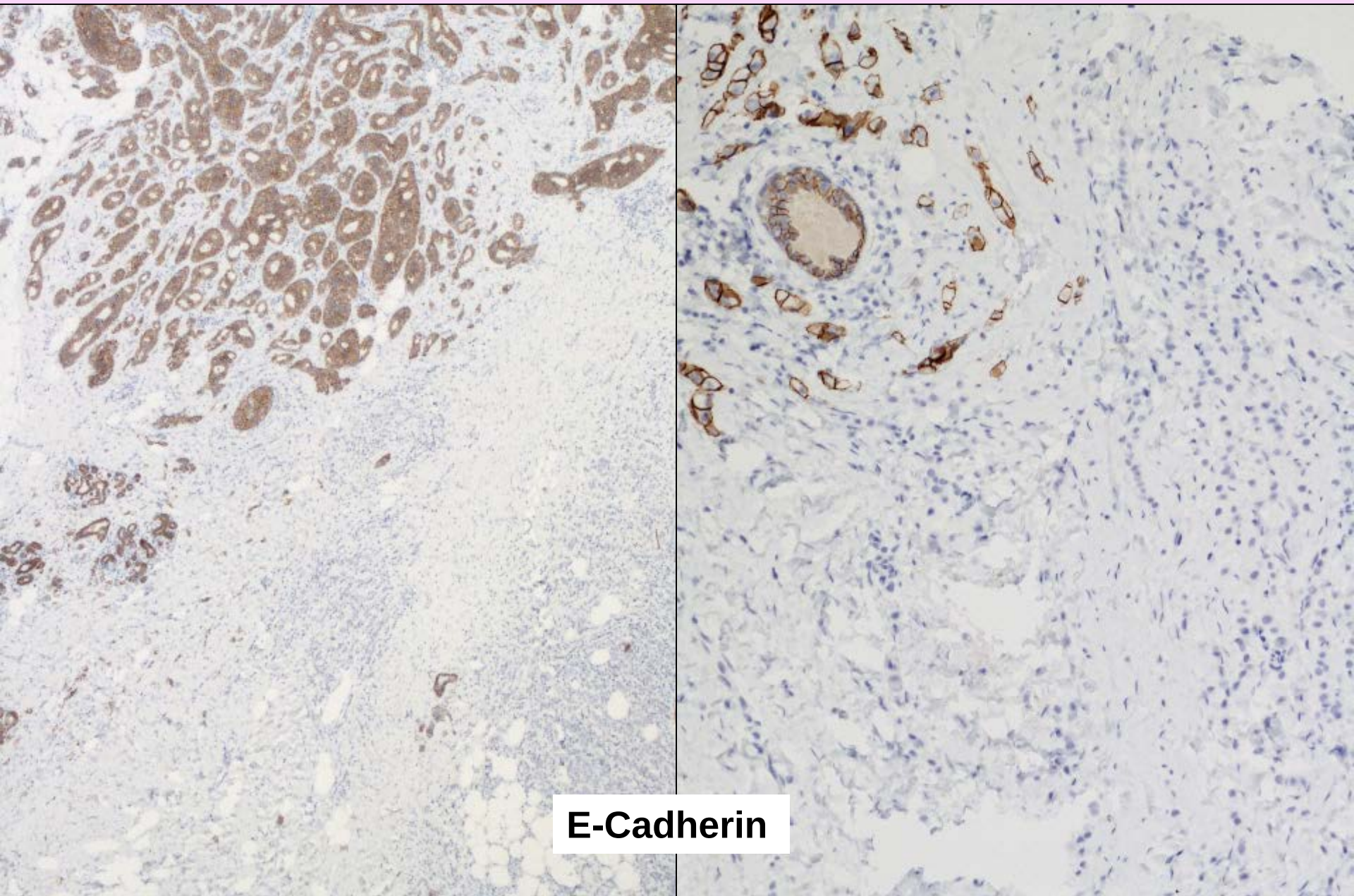
From Dabbs J.D. et al. Am J Surg Pathol 2007, 31; 427-37

DCIS vs. LCIS

E-Cadherin

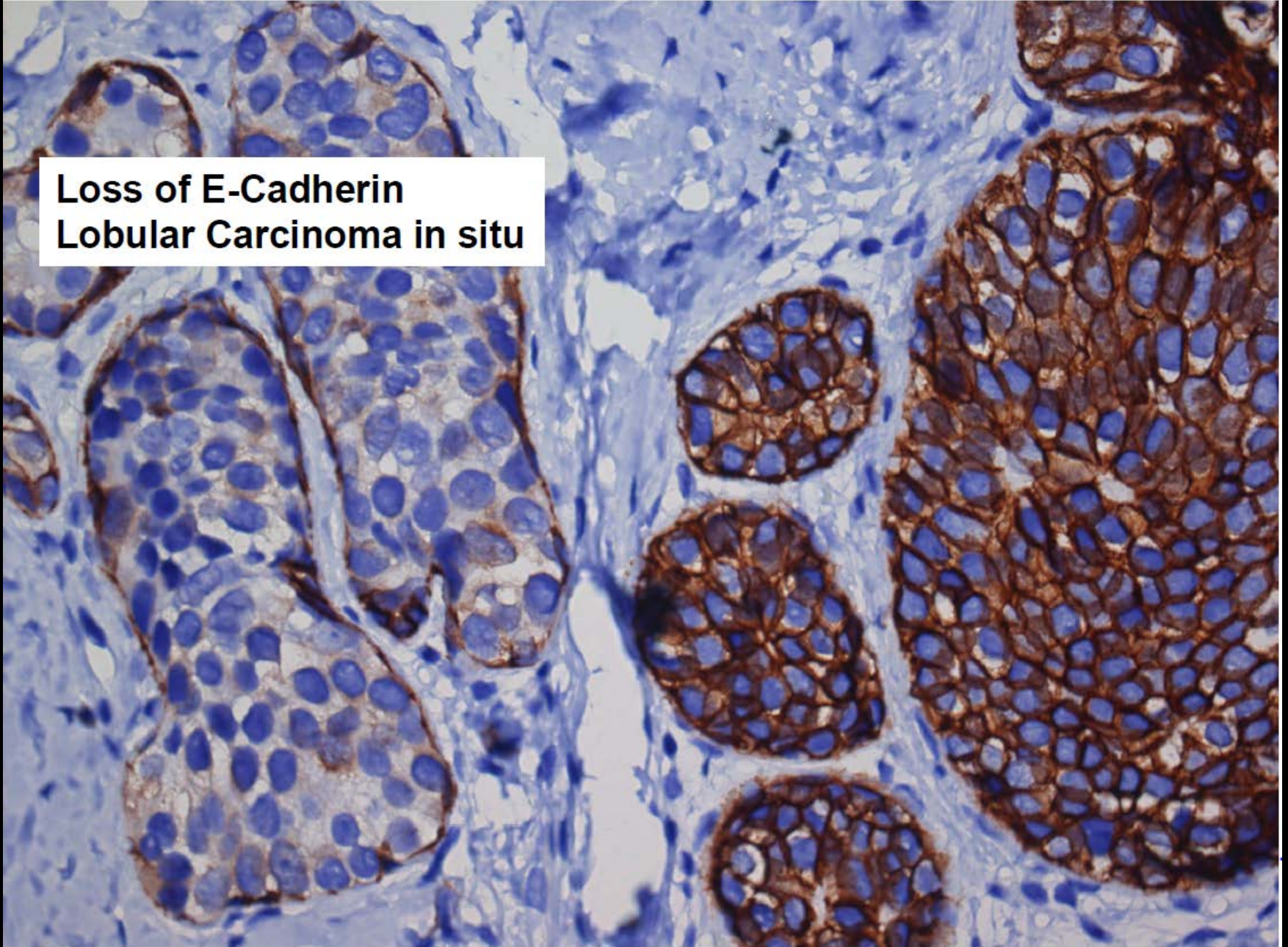


“Collision” carcinoma

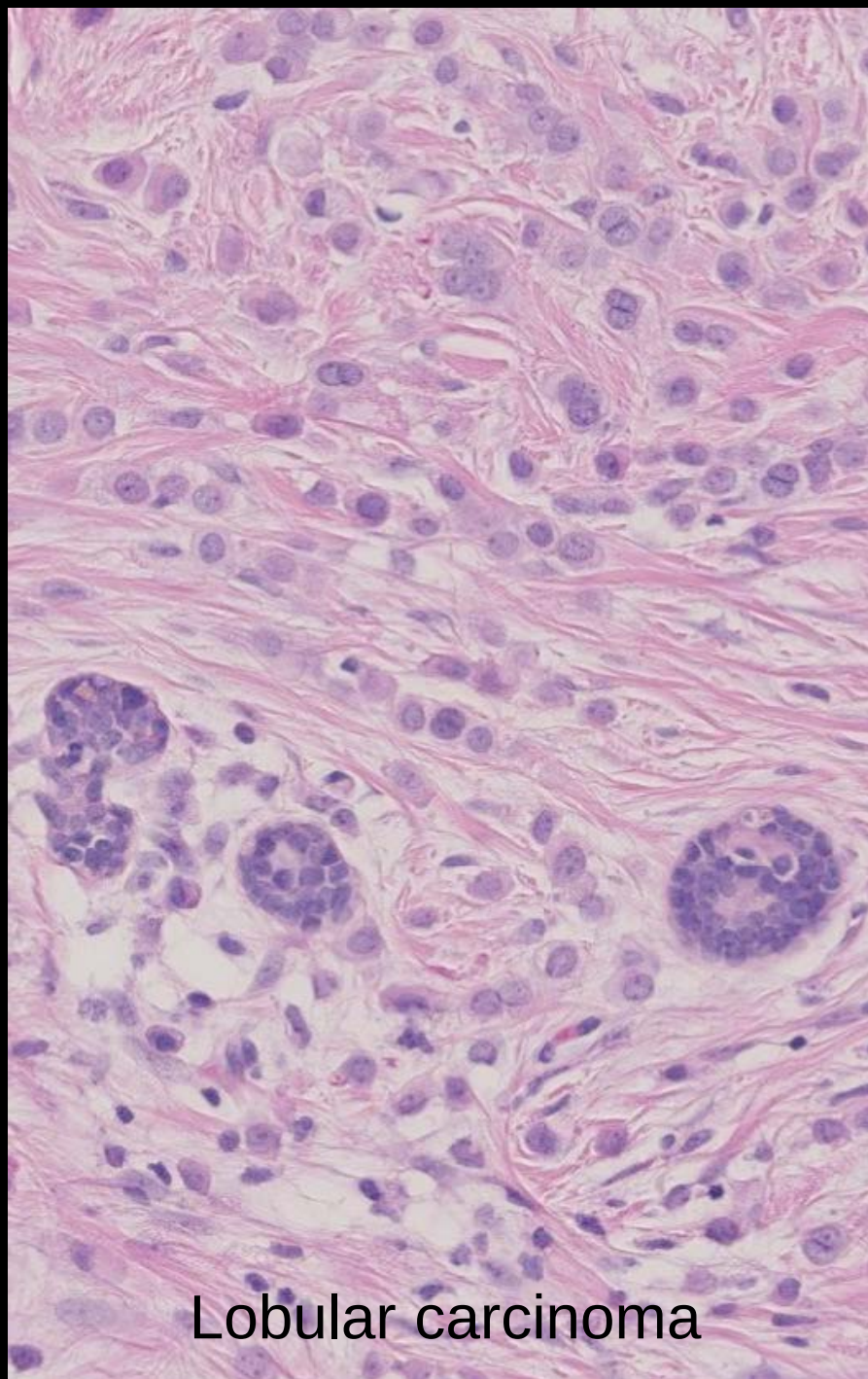


E-Cadherin

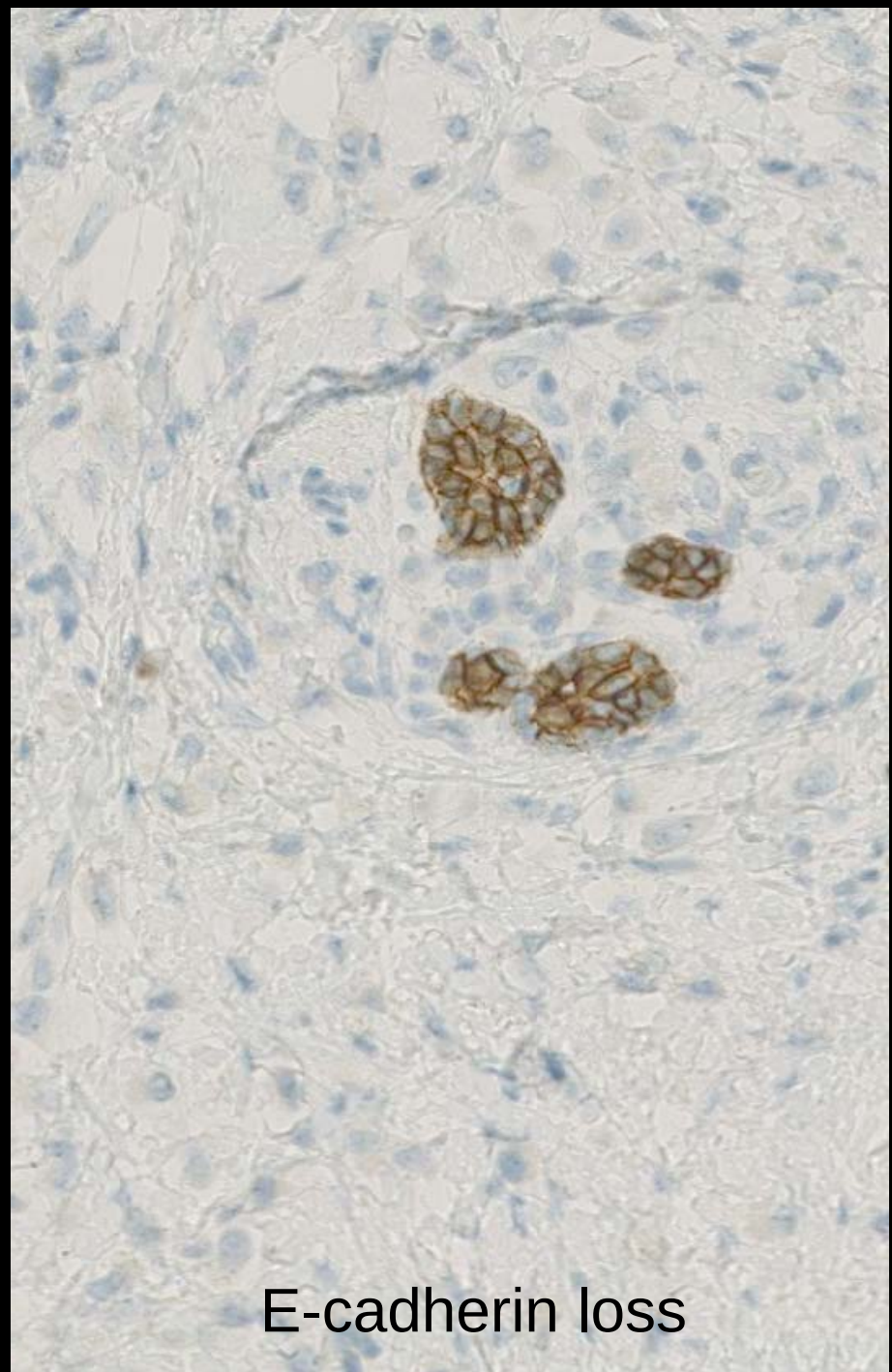
**Loss of E-Cadherin
Lobular Carcinoma in situ**



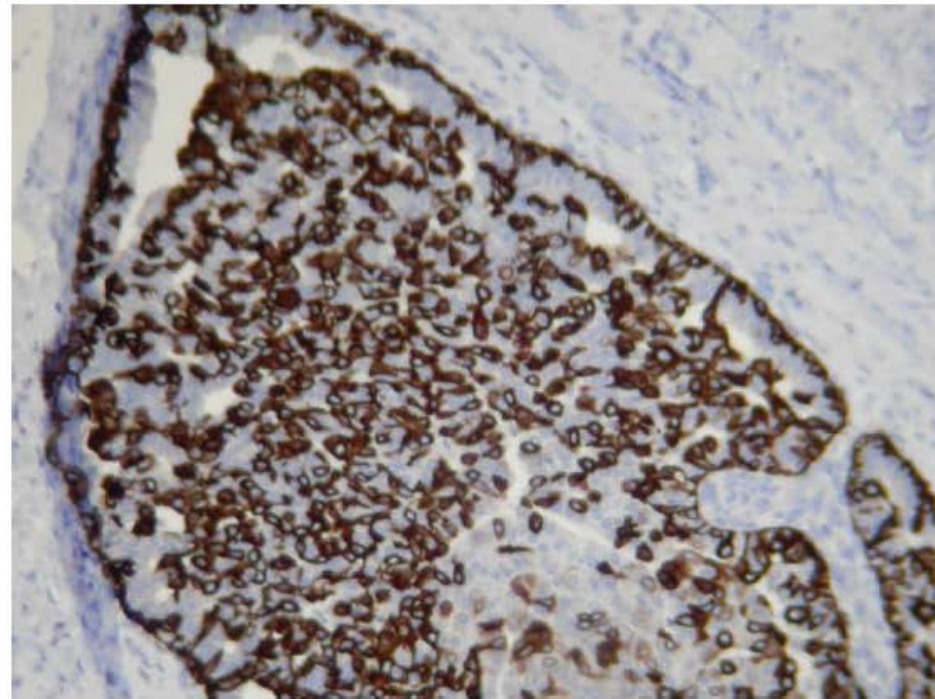
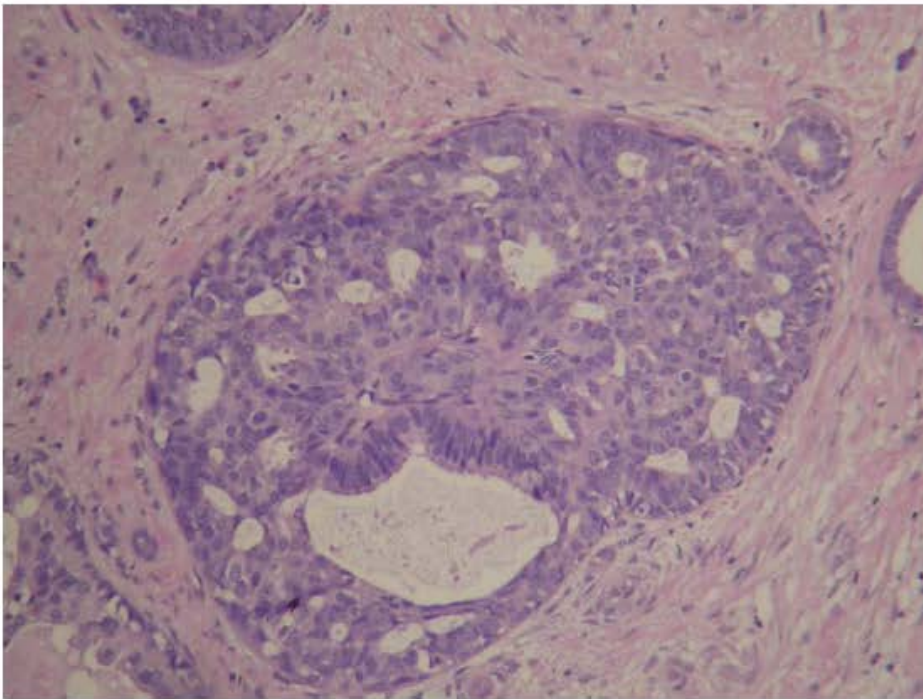
E-cadherin: Cell Adhesion Molecule



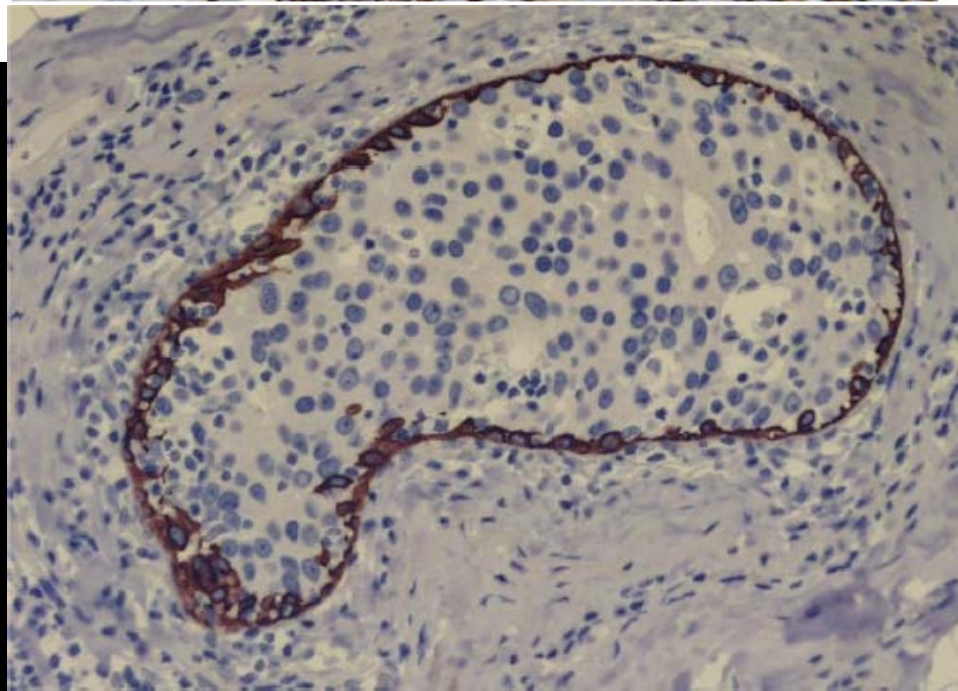
Lobular carcinoma



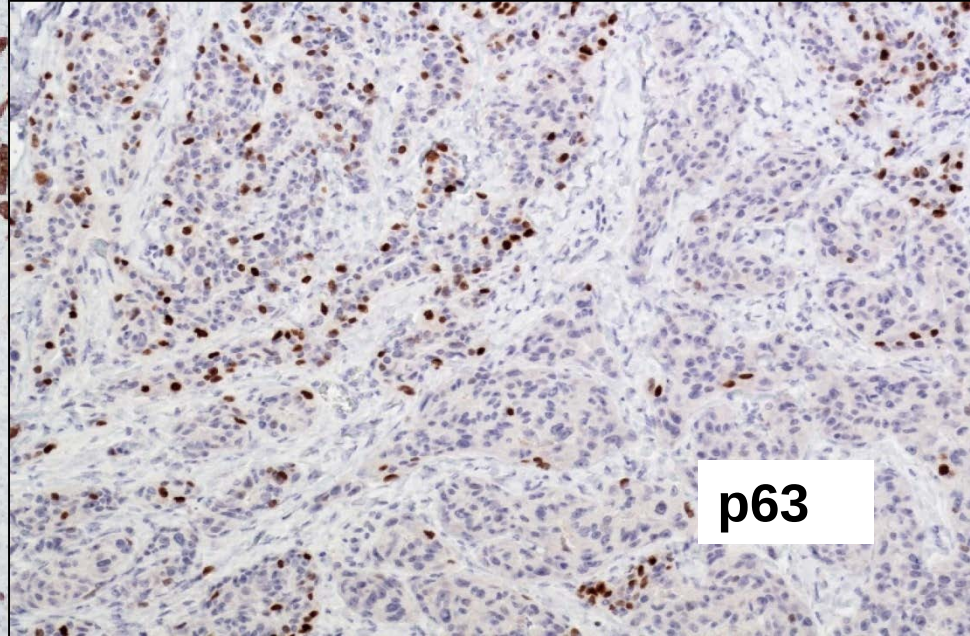
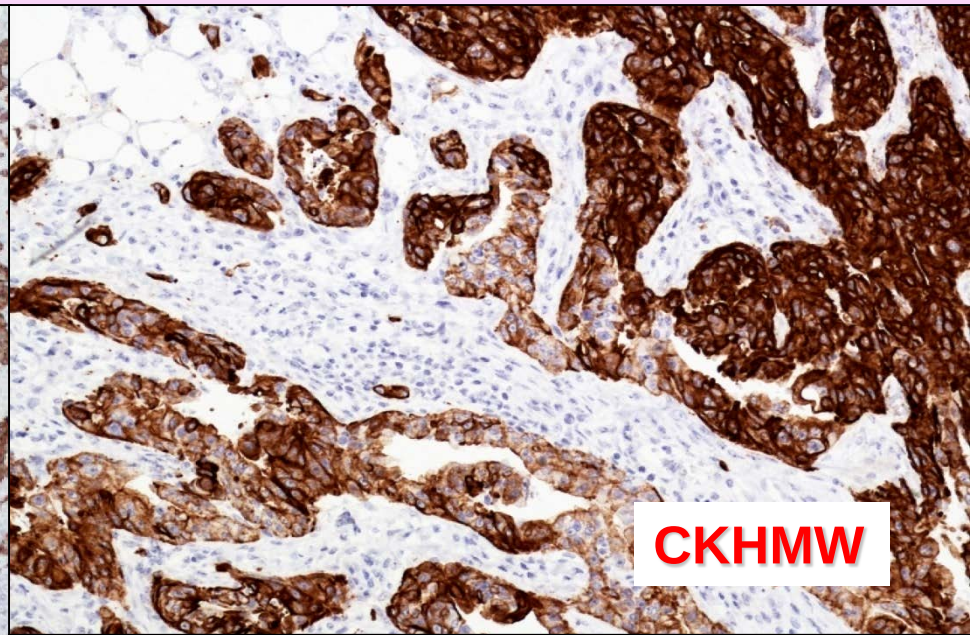
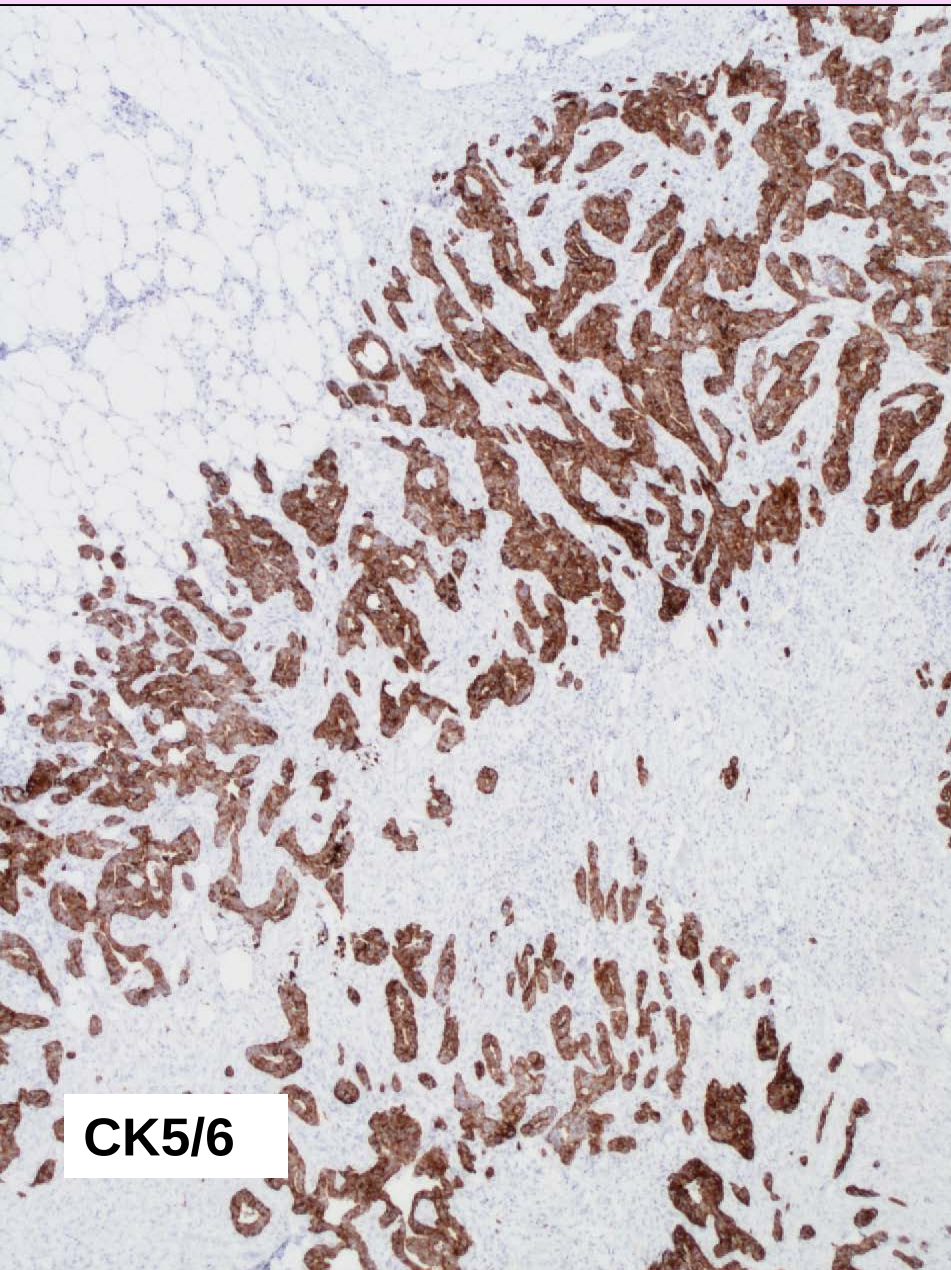
E-cadherin loss



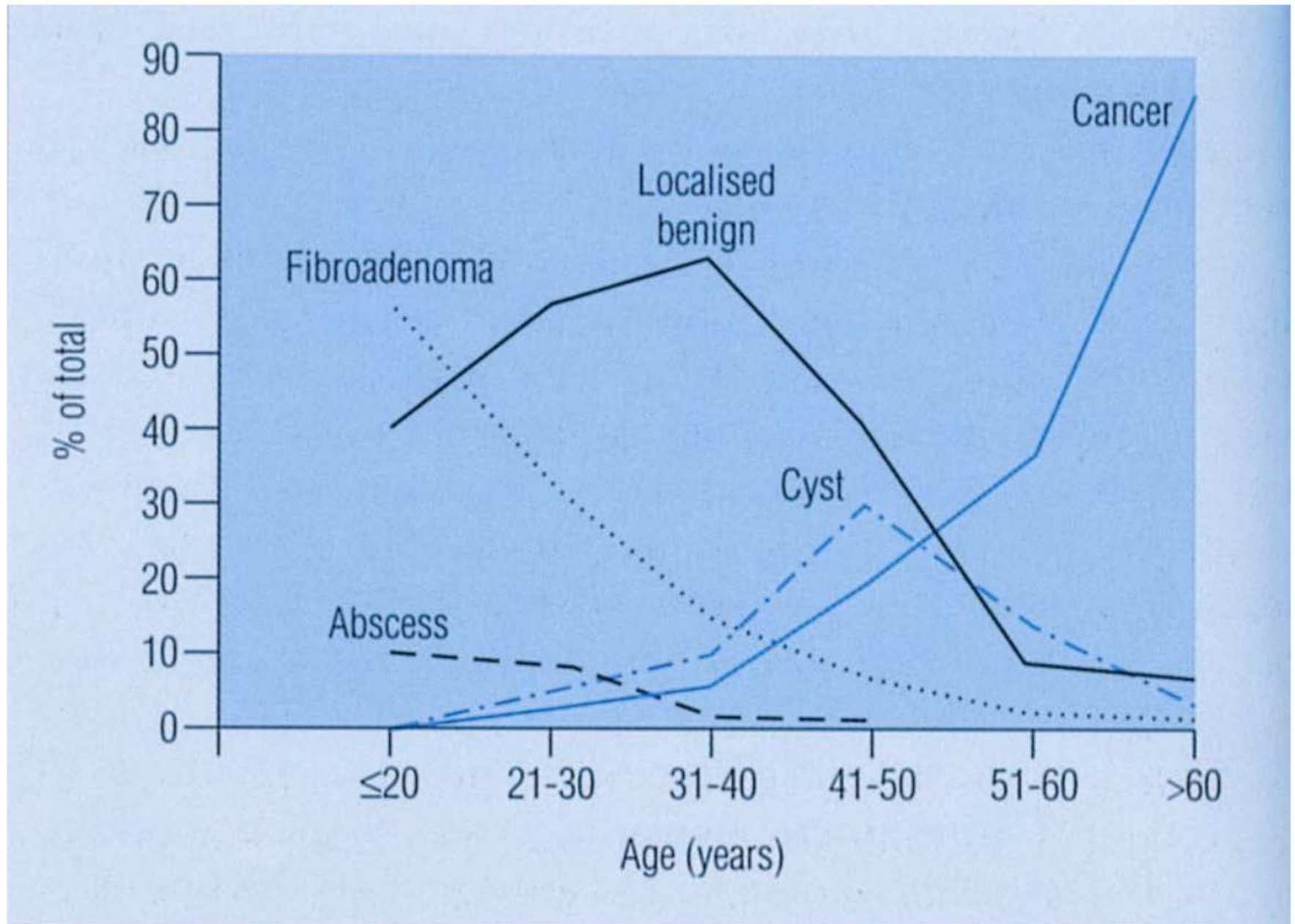
CK5 /CK14
Ductal hyperplasia vs.
Ductal carcinoma in situ



Breast carcinoma - basal like



Breast tumours according to age



Breast cancer: IHC classification

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