



# Breast Lesions of Uncertain Malignant Potential

*Histopathology*. 2016 January ; 68(1): 45–56. doi:10.1111/his.12861.

## **Breast lesions of uncertain malignant nature and limited metastatic potential: Proposals to improve their recognition and clinical management**

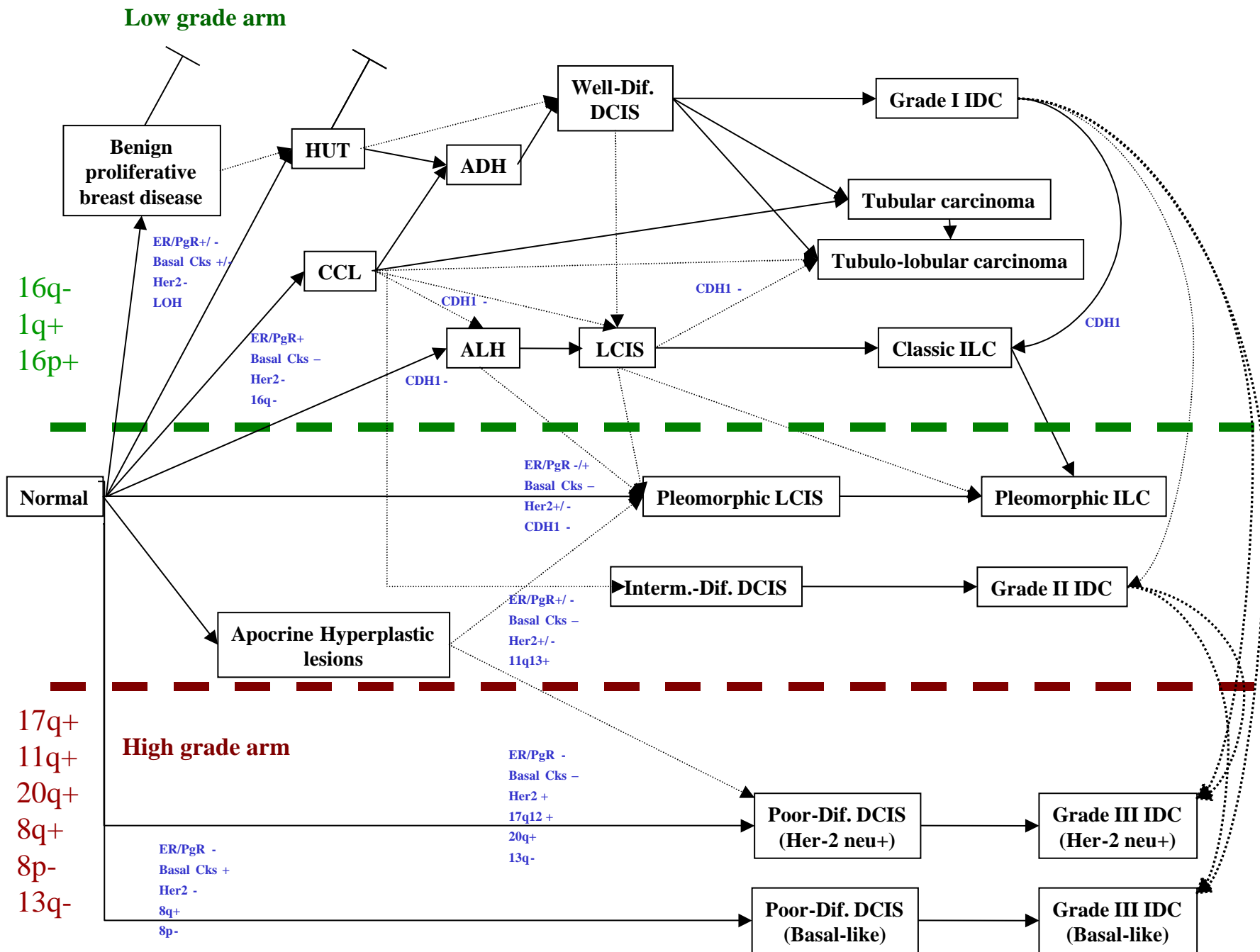
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# Breast Lesions of Uncertain Malignant Potential

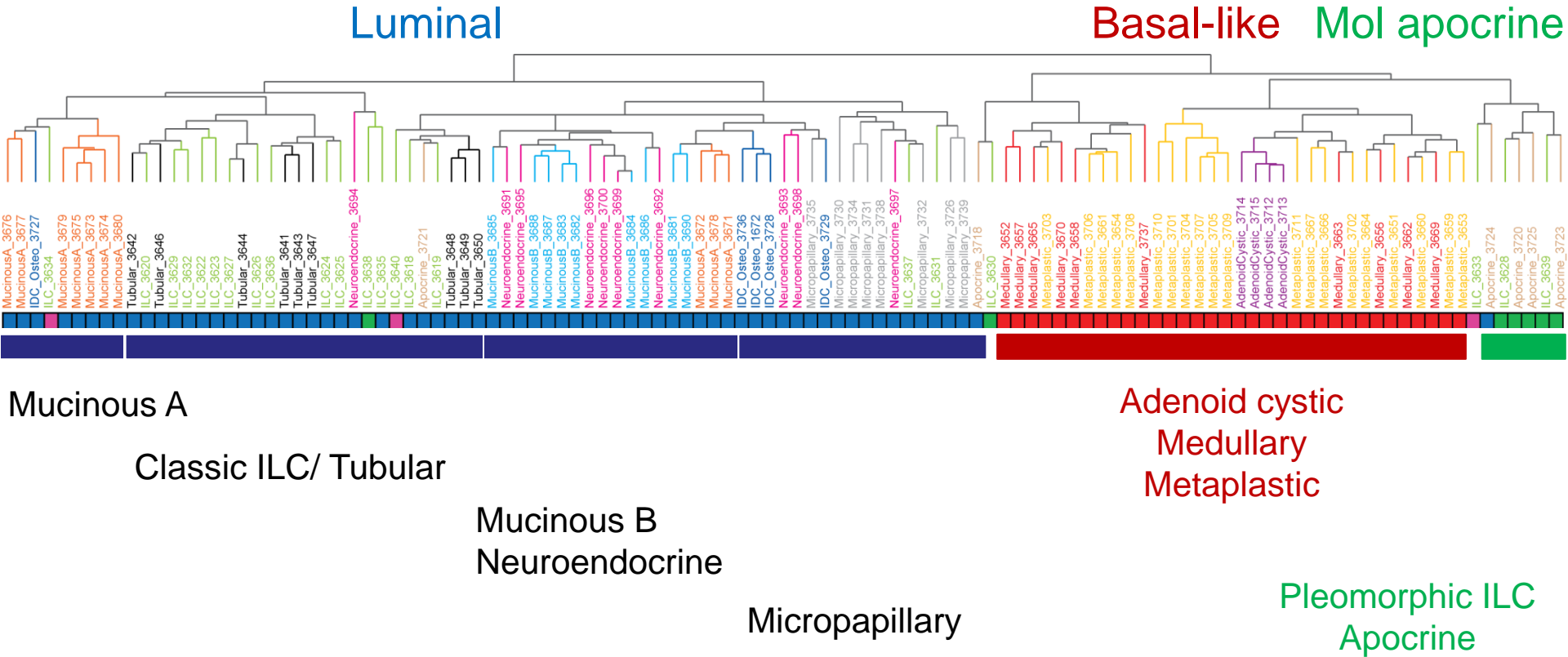
Lesions with uncertain malignant nature with show some features characteristic of malignancy such as infiltrative margins and absence of peripheral myoepithelial cells, but lack other features such as cytonuclear atypia, lymphovascular invasion or evidence of metastasis.

- Microglandular Adenosis and Atypical MA
- Infiltrative Epitheliosis
- Skin adnexa-like and salivary gland-like tumours
  - non-cutaneous mammary pleomorphic adenoma and cylindroma



Simpson P, Reis-Filho JS, Gale T et al. J Pathol. 2005 Jan;205(2):248-54.

# Special types of breast cancer are more homogeneous at the transcriptome level



# Molecular Types of TNBC

Transcriptomic classification of TNBCs revised to four subtypes:

- Basal-like/immune-suppressed (BLIS),
- Basal-like/immune activated (BLIA),
- Luminal (AR)
- Mesenchymal (MES)

# High Grade Special Histological Types of TNBC

## 1. *Carcinoma with Medullary Features*

TP53, BRCA1 (germline) mutation

## 2. *Metaplastic Breast Carcinomas*

Chondroid & spindle cell preferentially MES subtypes. No MBC classified as IM or LAR

MBCs display enrichment for mutations affecting members of PI3K and Wnt pathways

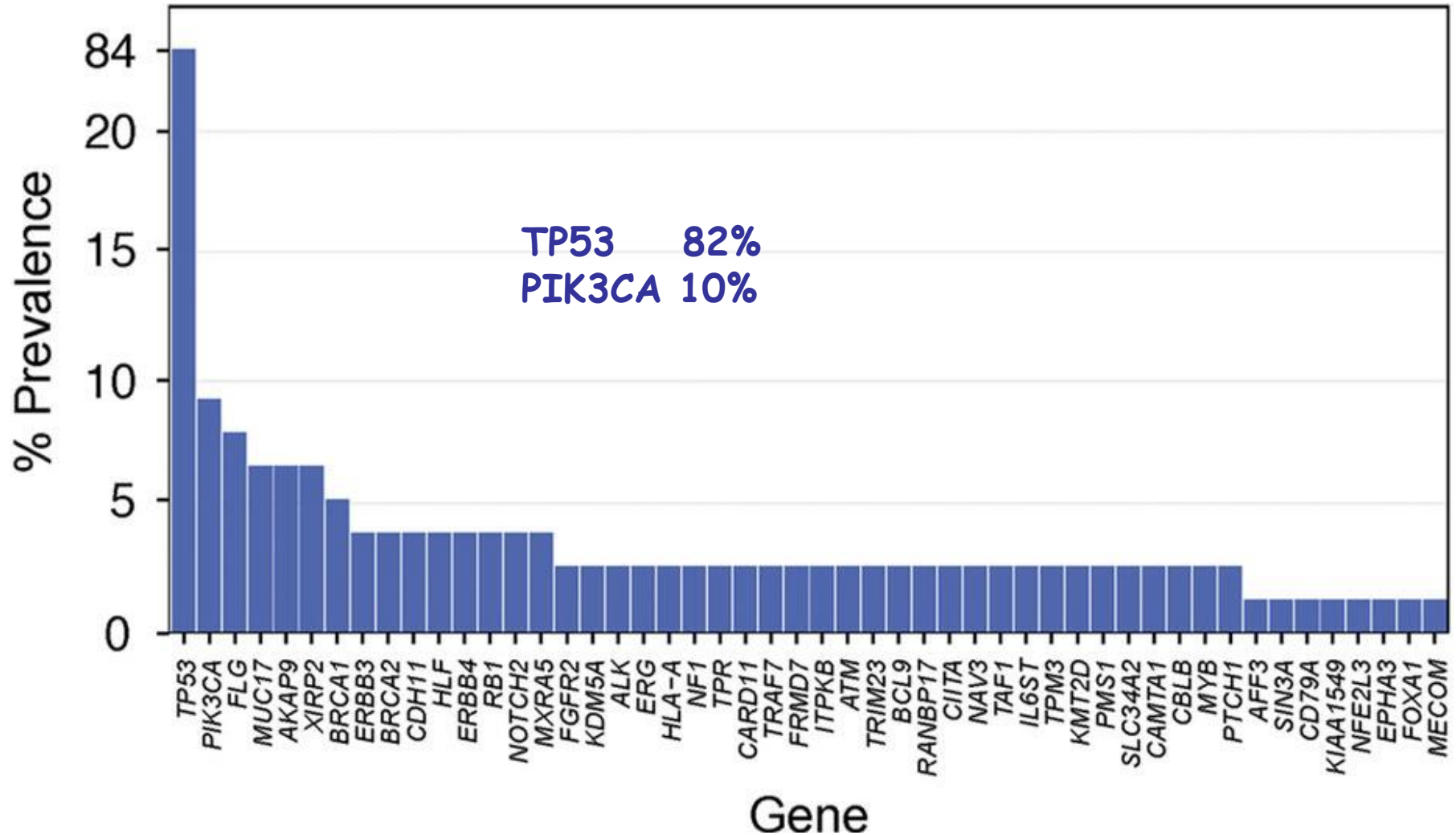
## 2. *Carcinoma with Apocrine Differentiation*

Higher frequency of mutations in *PIK3CA* and other PI3K pathway genes

lower rate of *TP53* mutations and *MYC* gains

Geyer FC et al in preparation

# Somatic Mutations in TNBC (Cancer Genome Atlas)



# Low Grade TN BC

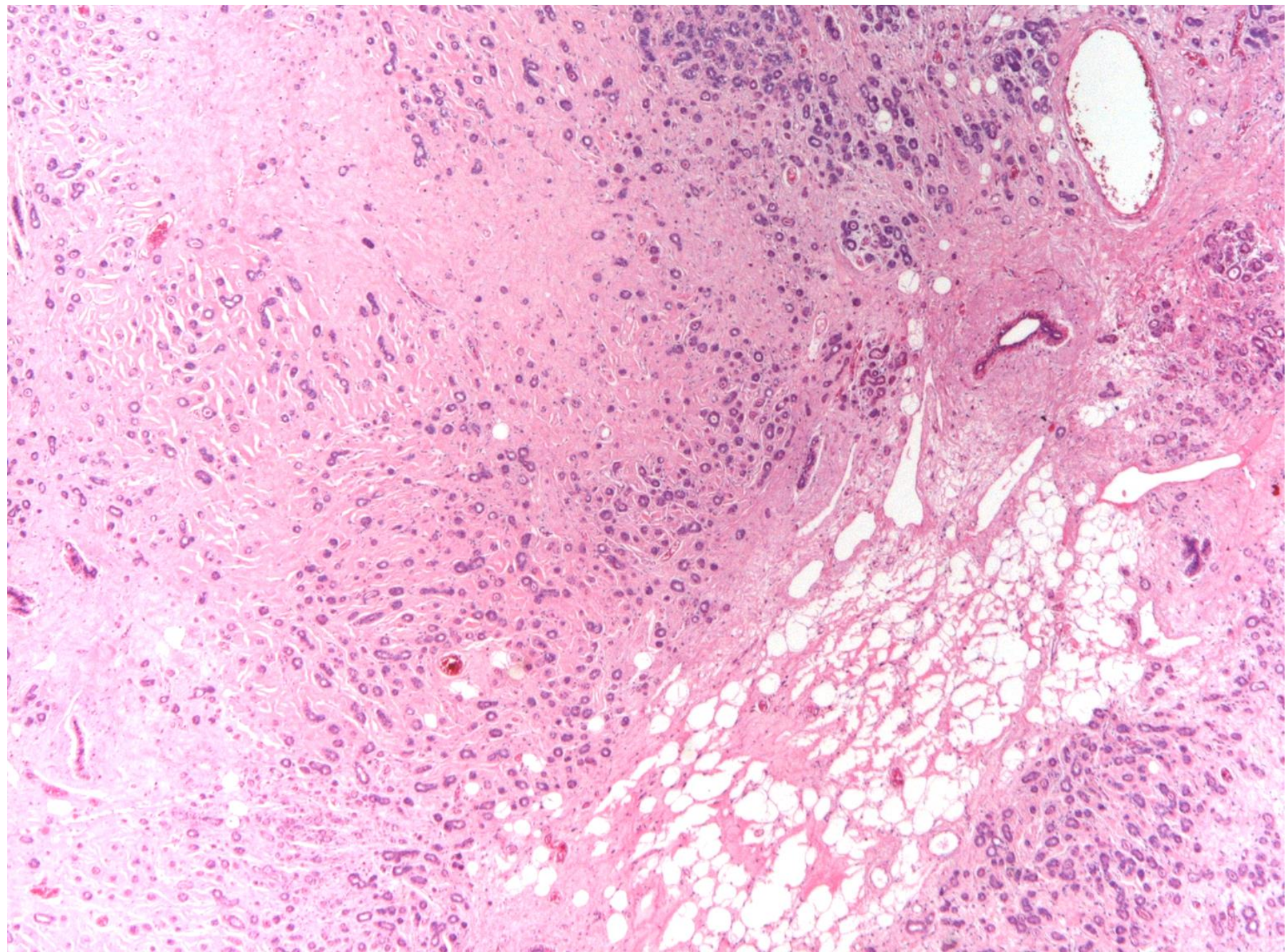
Low-grade TN breast neoplasia family

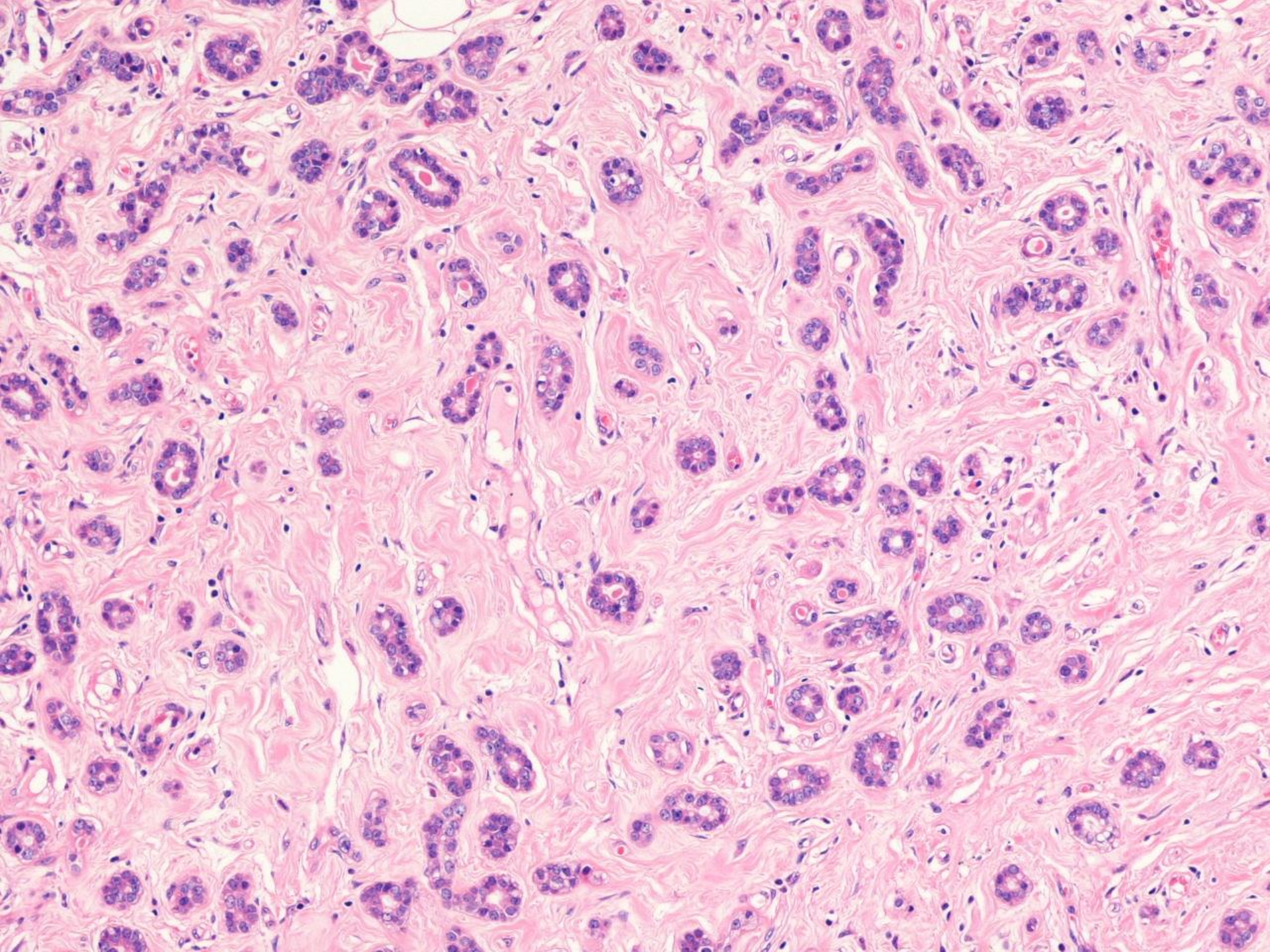
Microglandular adenosis (MGA)

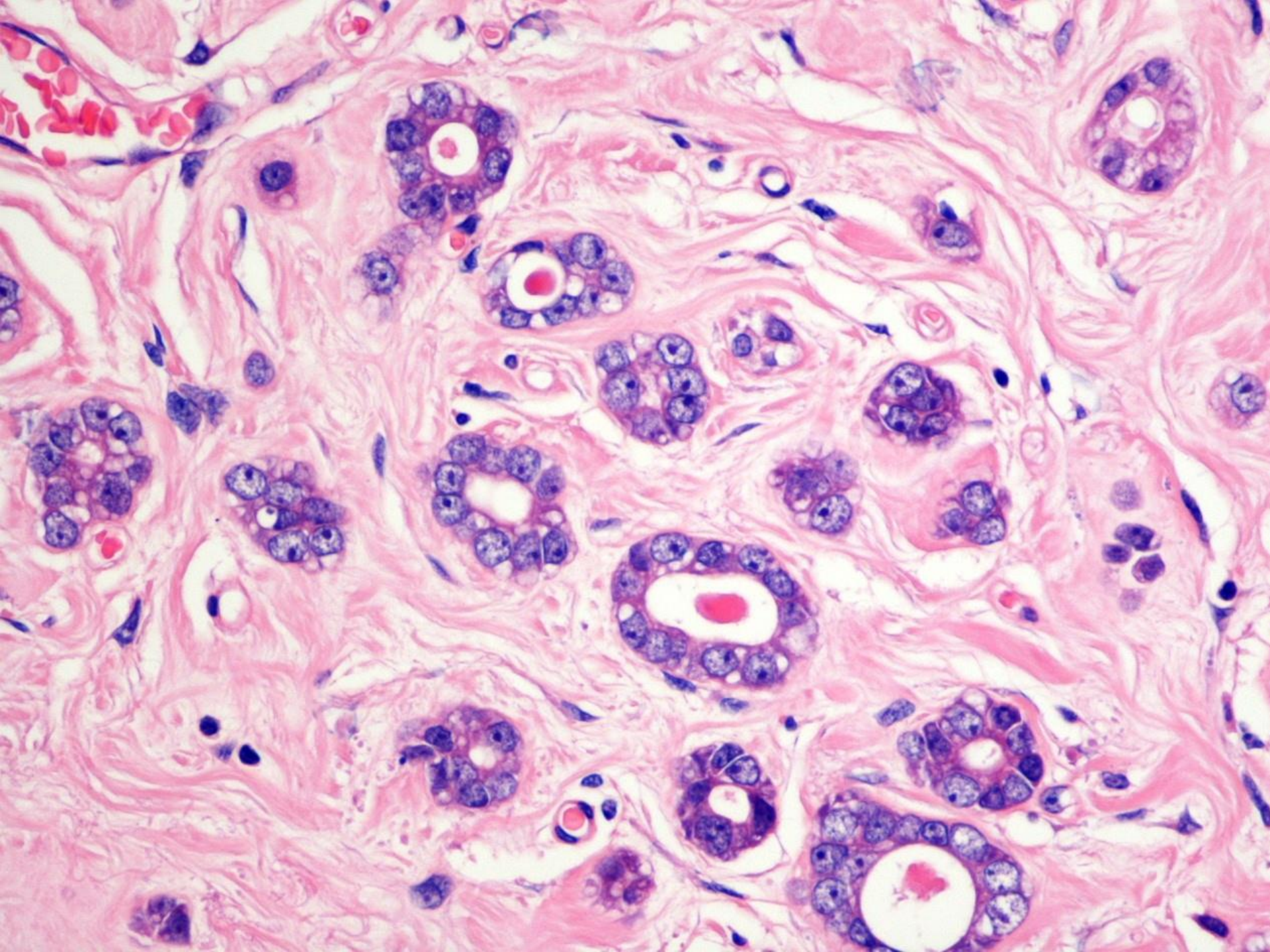
Atypical MGA (AMGA)

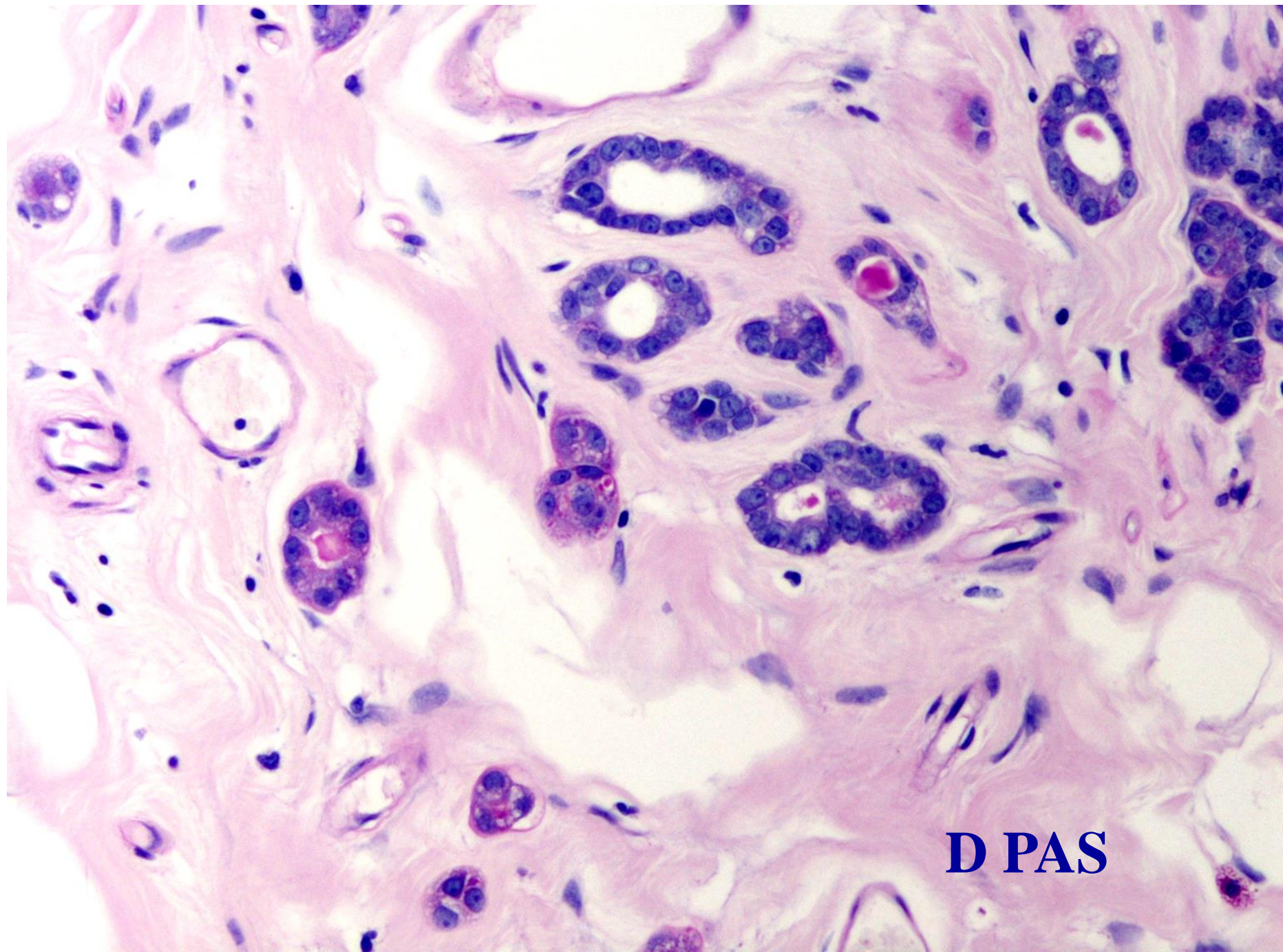
Acinic cell like carcinoma (ACC)





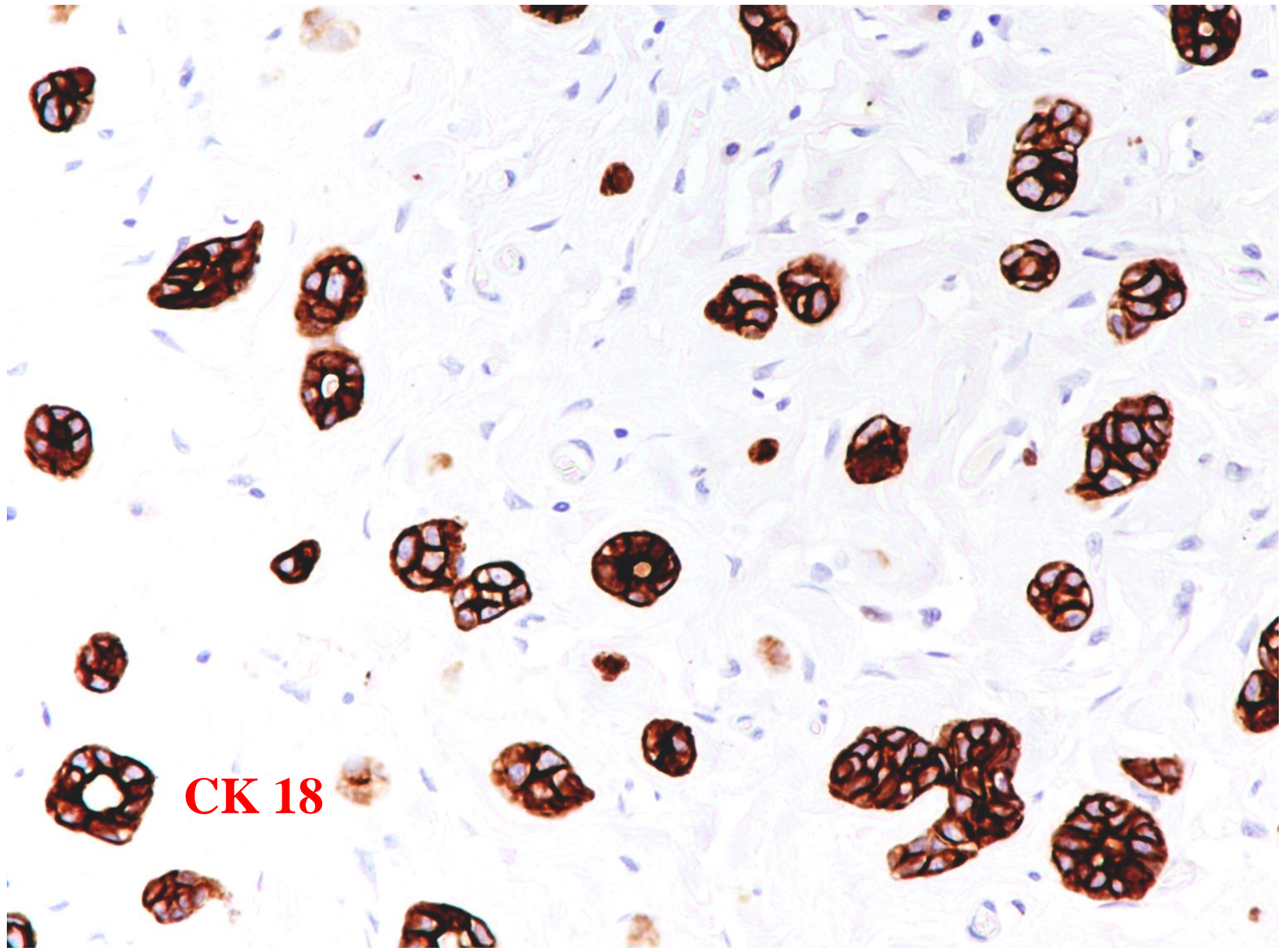


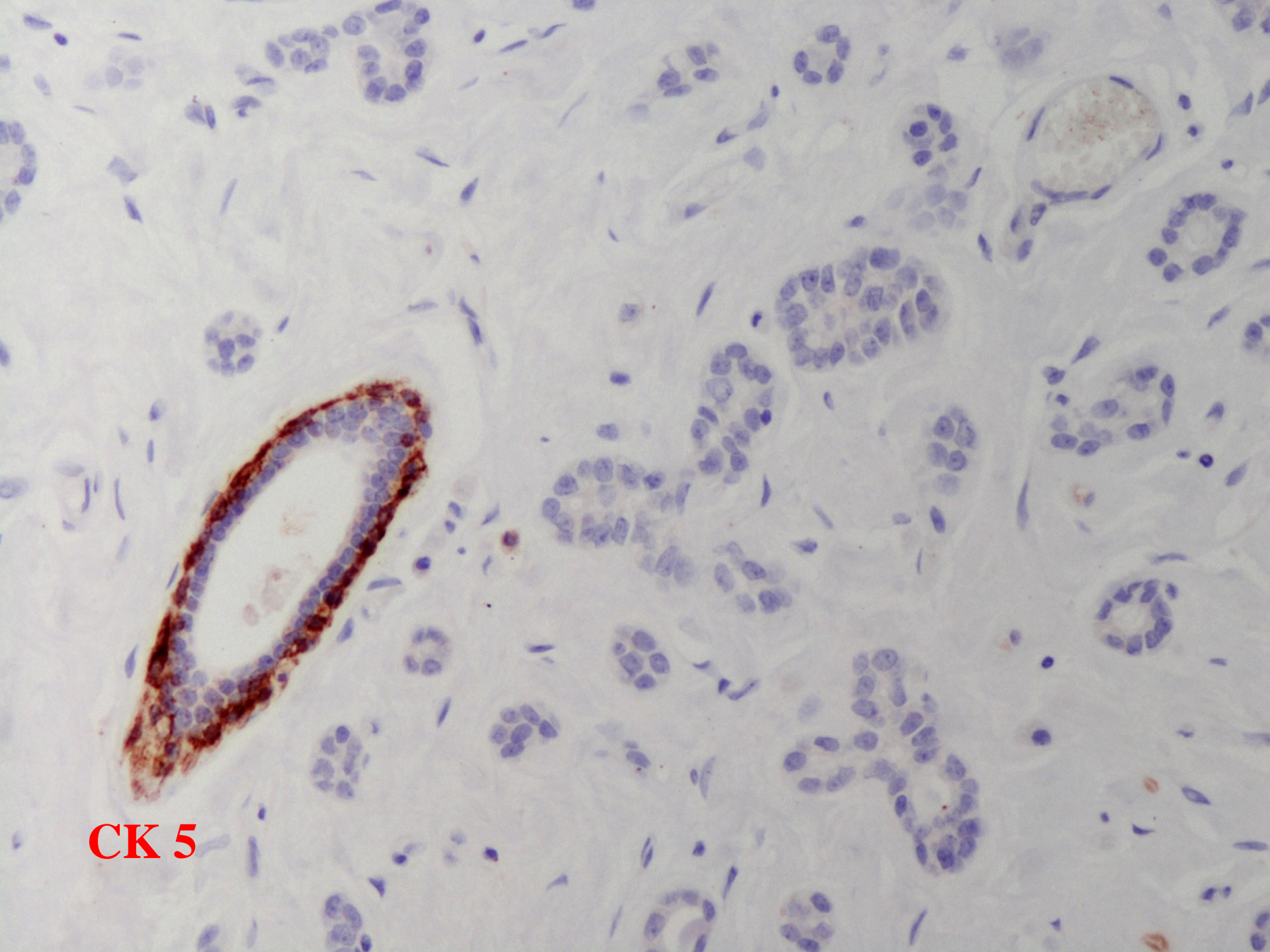




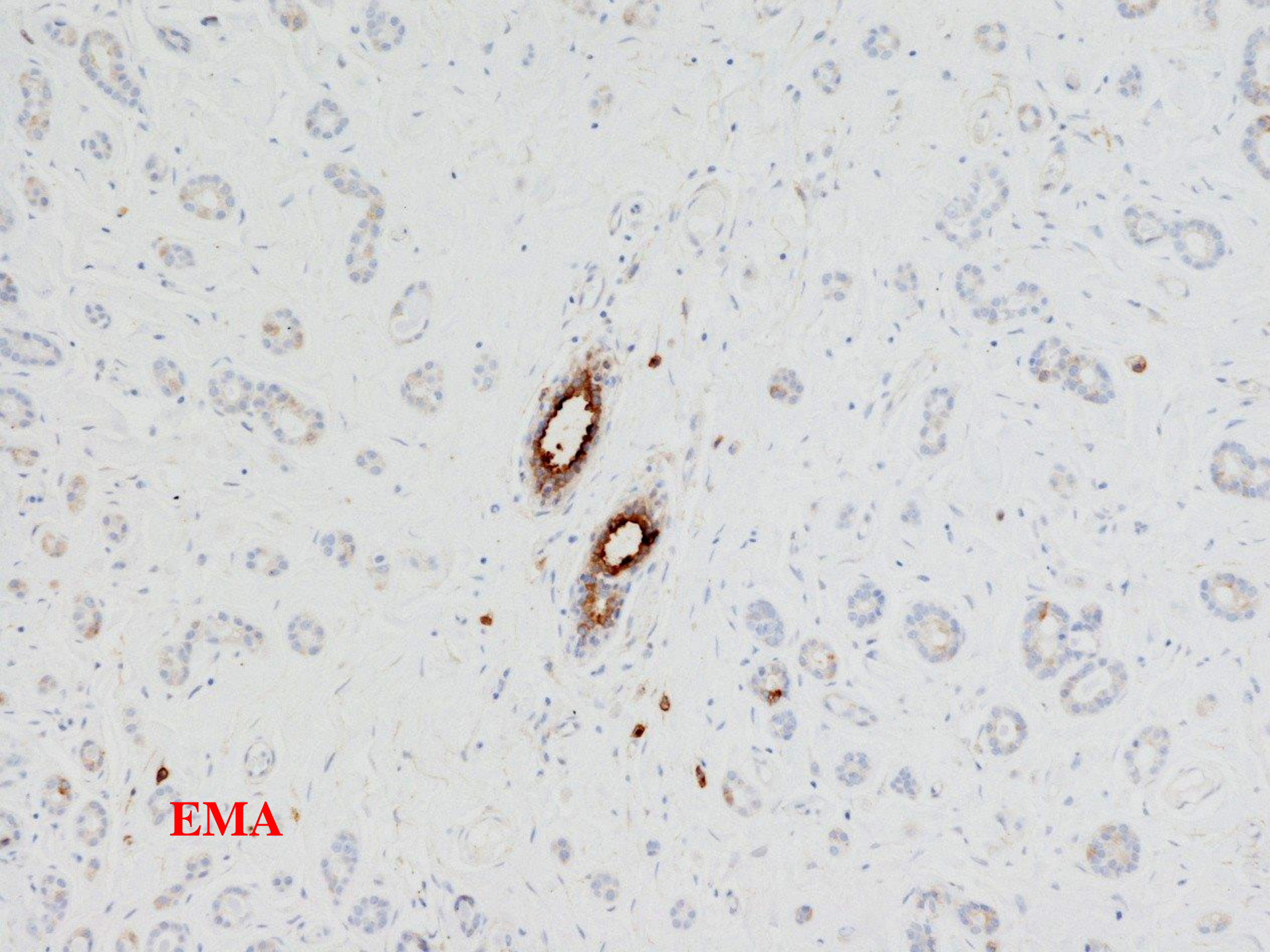
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**CK 18**

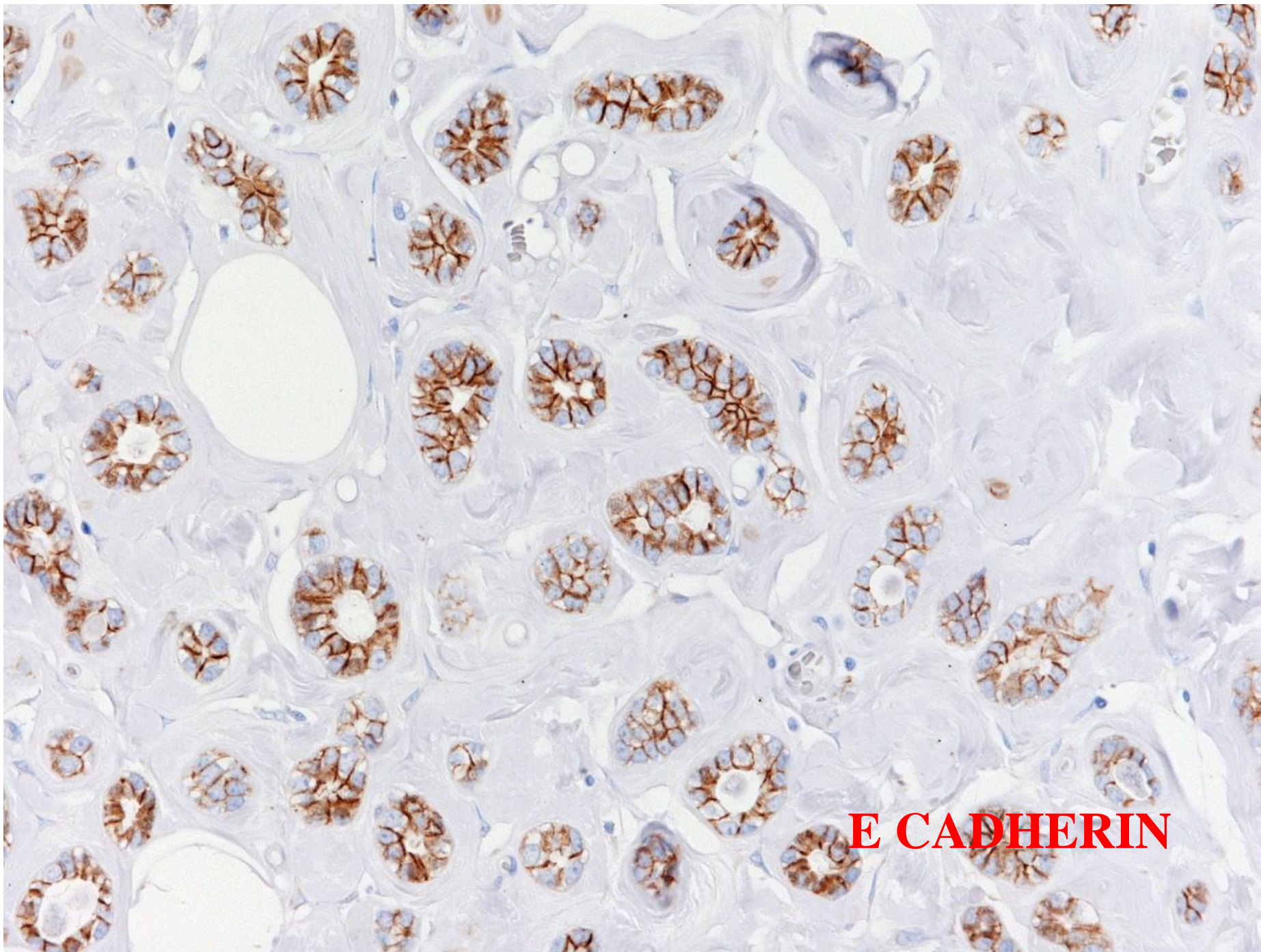




**CK 5**

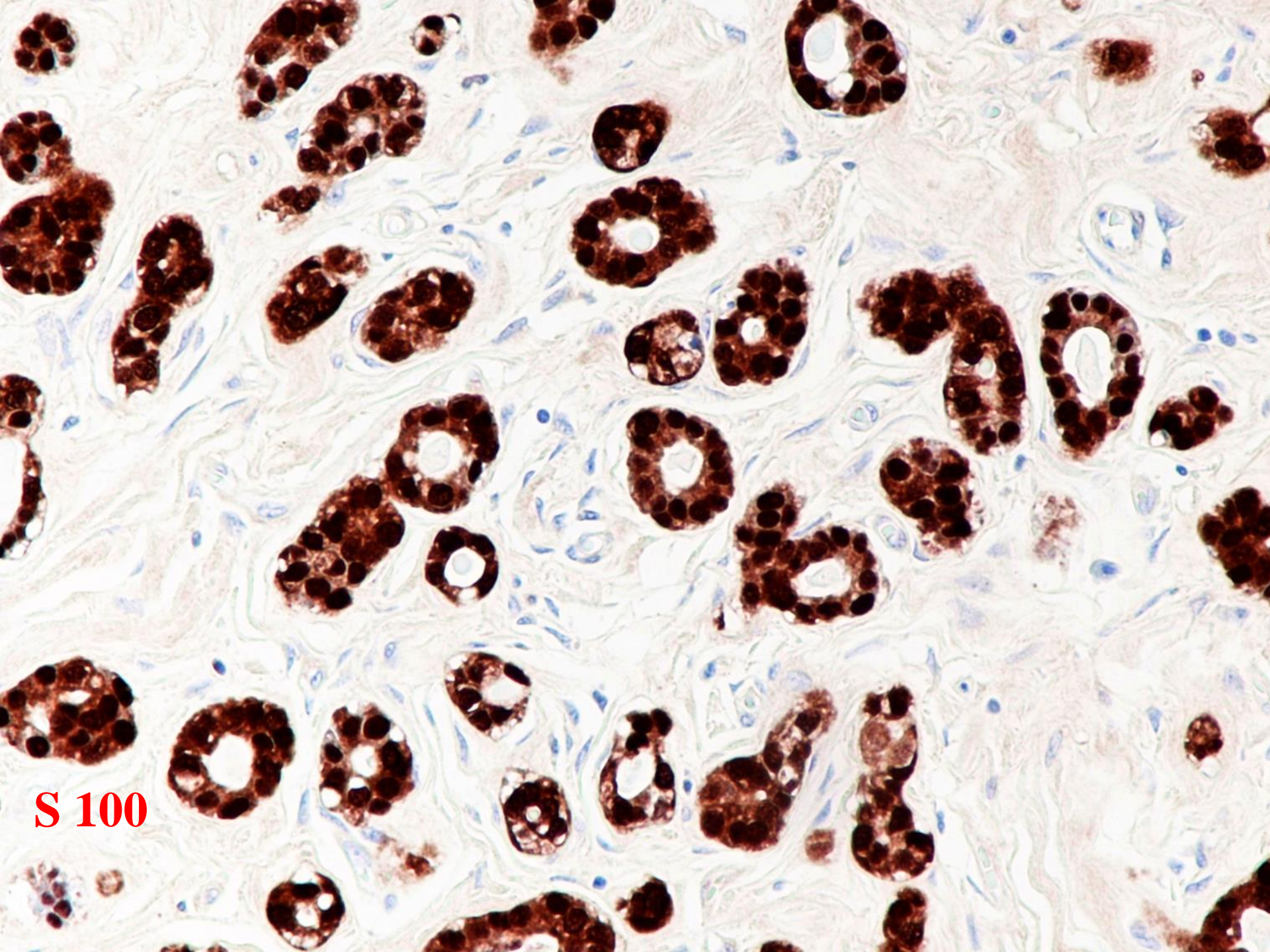


**EMA**

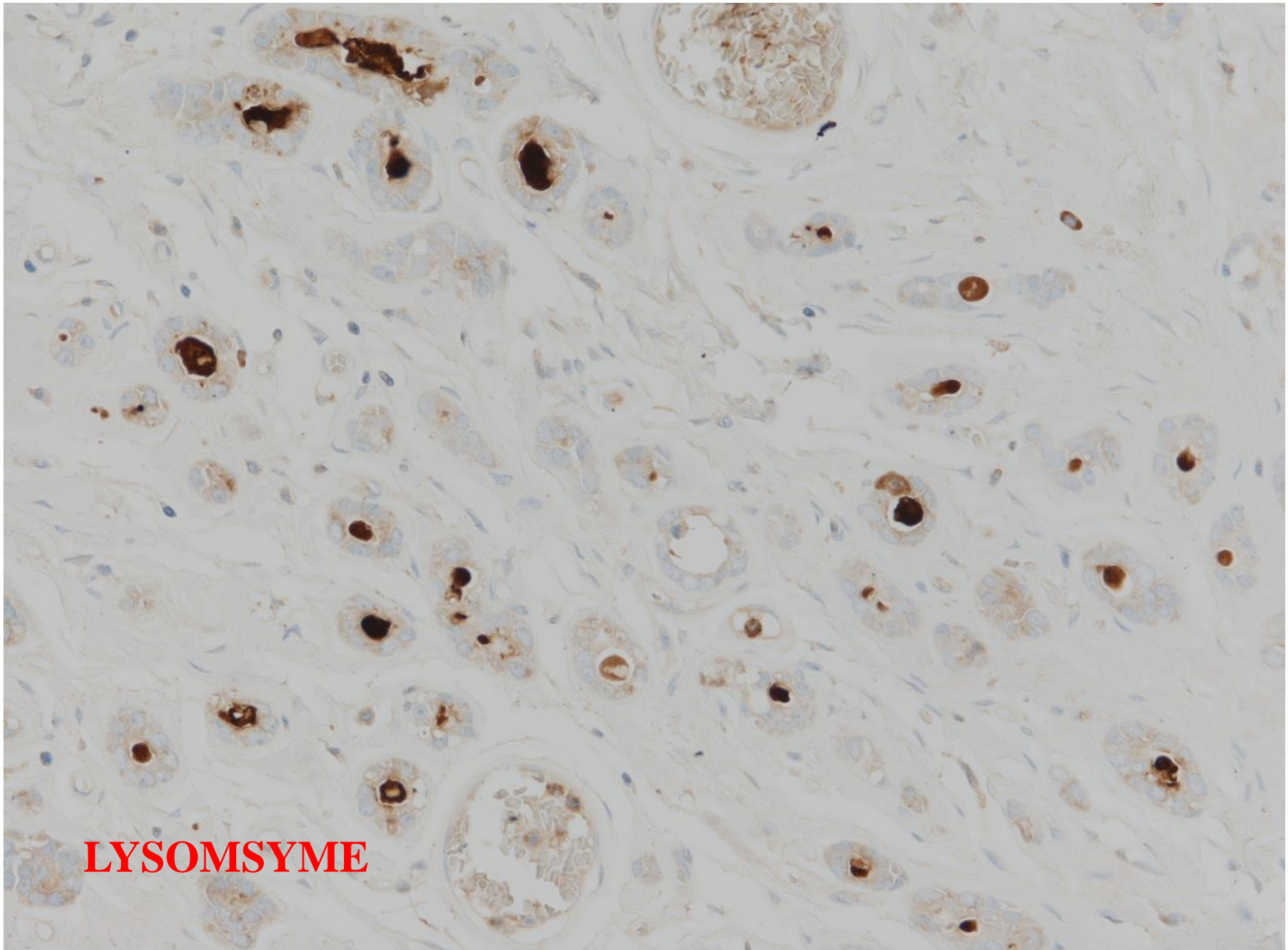


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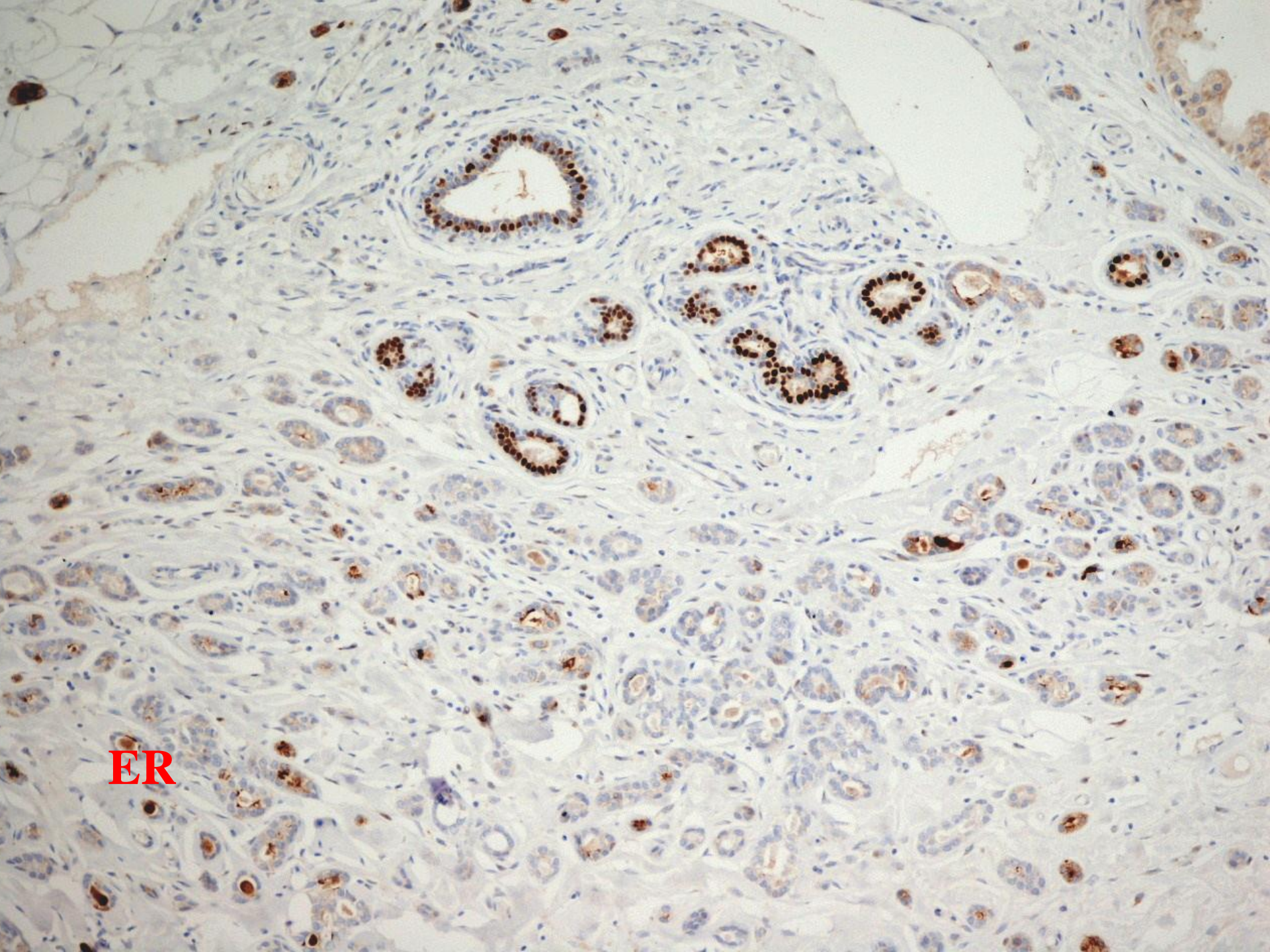




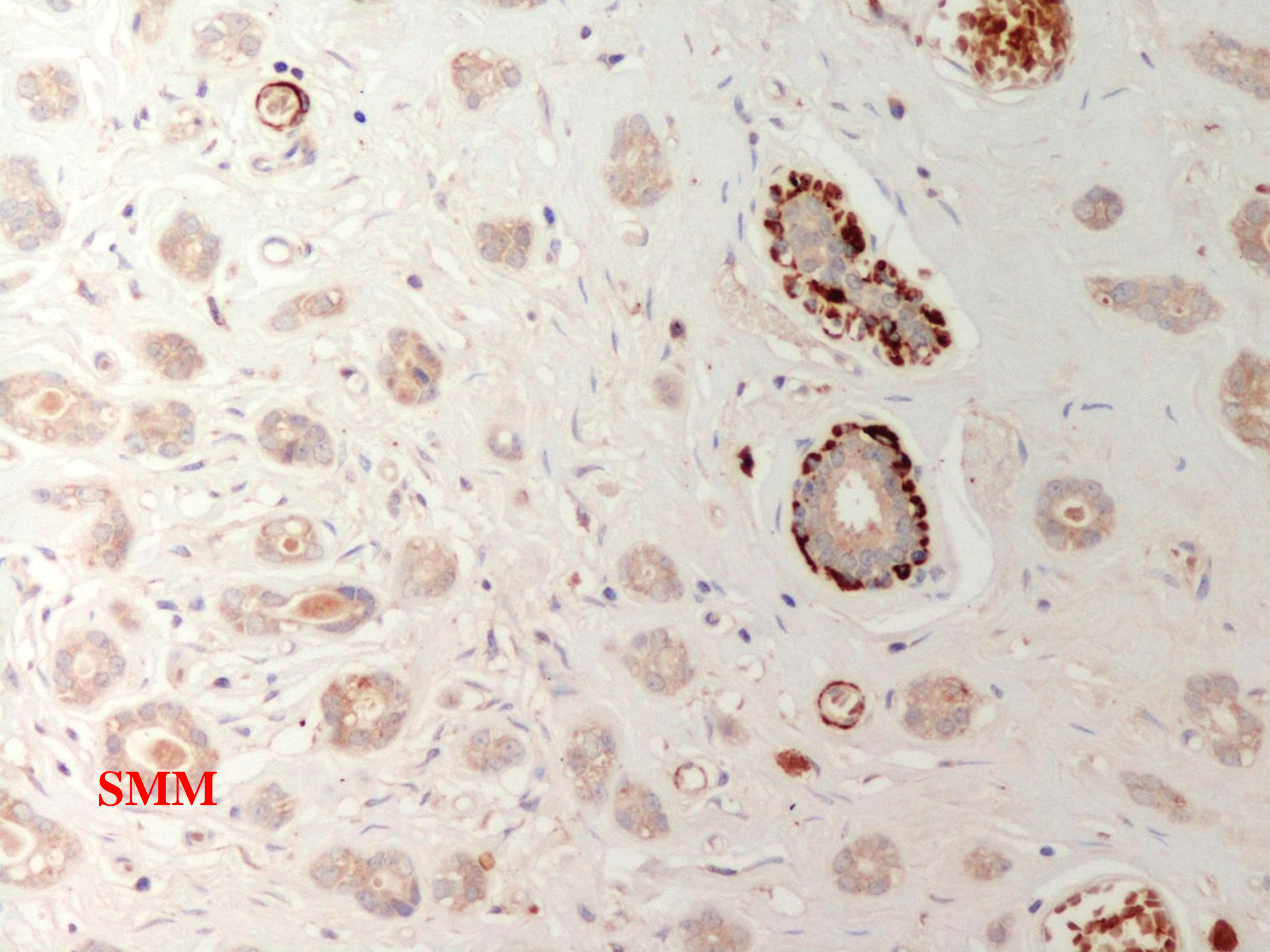
**S 100**



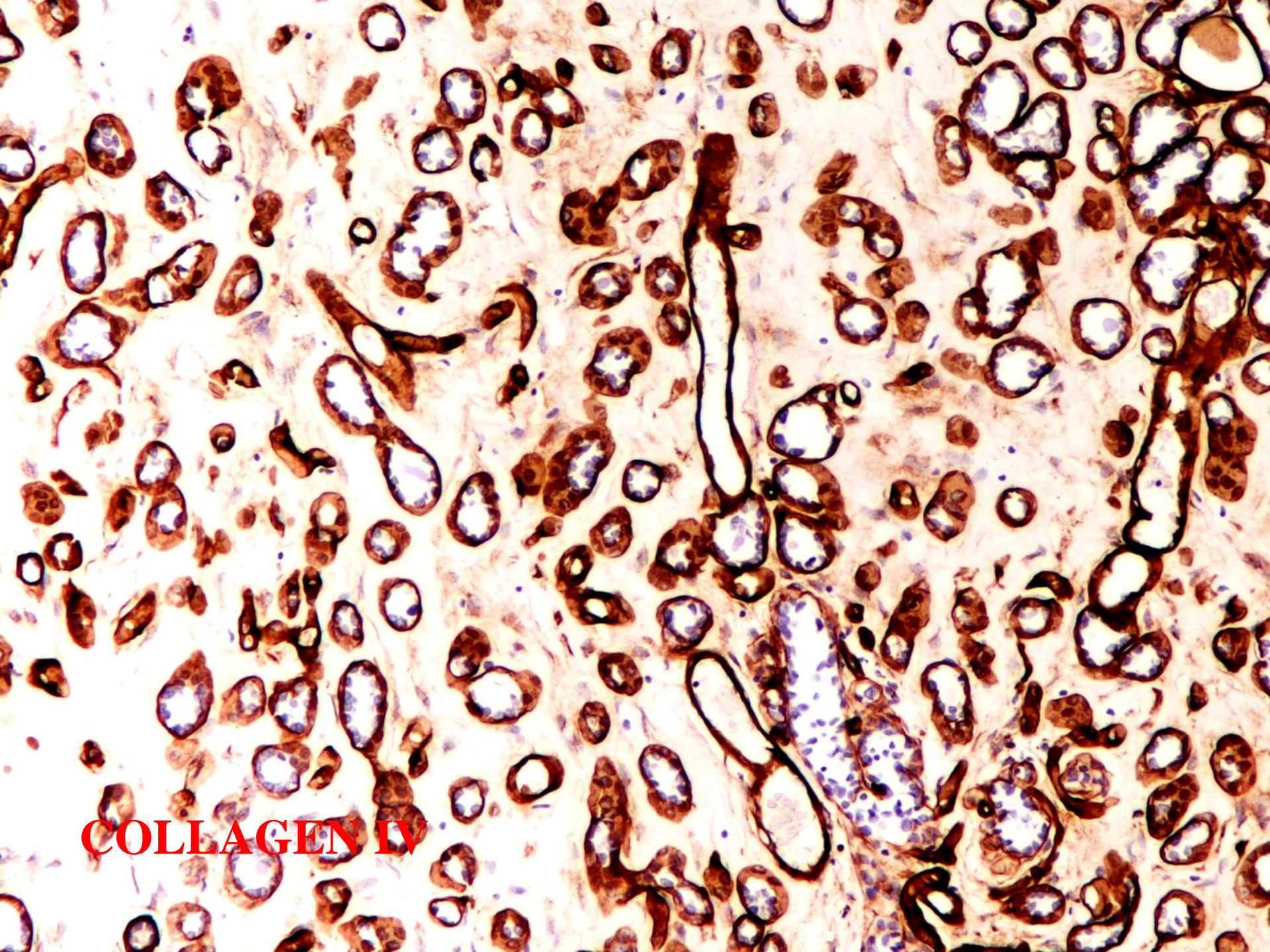
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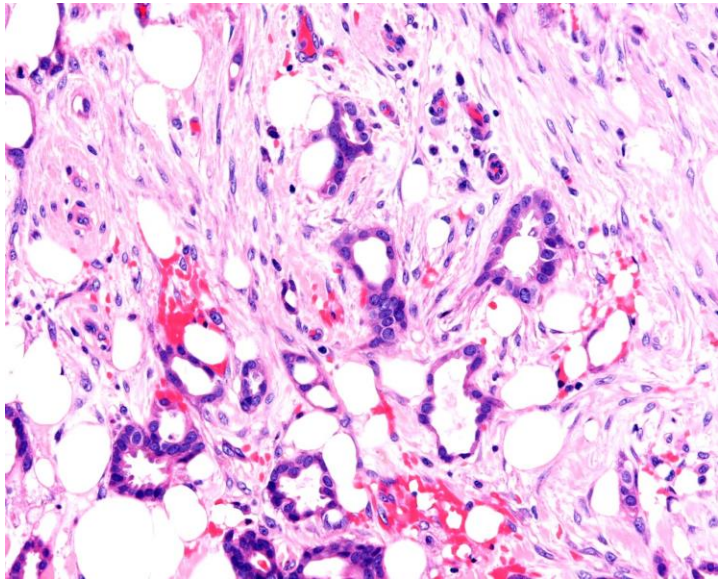
ER



**SMM**



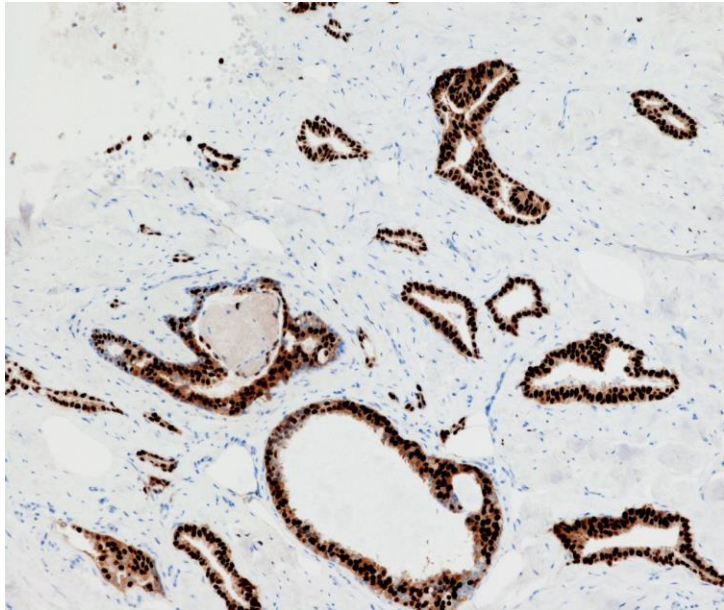
**COLLAGEN IV**



# Differential diagnosis

## TUBULAR CARCINOMA

- Angulated glands
- Apical snouts
- Desmoplastic stroma
- ER+



# MICROGLANDULAR ADENOSIS

## Clinicopathological features

- First description 1983. Two simultaneous series by Azzopardi(1) and Rosen(2)
- Rare lesion <100 reported all in female breast
- Age range: 28-82. Most frequent in postmenopausal women.
- Palpable mass or thickening

*(1)Microglandular adenosis of the breast-a lesion simulating tubular carcinoma. Histopathology 1983 7:169-180*

*(2)Microglandular adenosis , a benign lesion simulating invasive mammary carcinoma. Am J Surg Pathol 1983 7:137-144*

# Microglandular adenosis

## Morphology

- Infiltrative proliferation of uniform small glandular structure
- Set in fibrous focally adipocytic stroma
- PAS + intraluminal inspissated secretion
- Lack of myoepithelial layer but surrounded by BM
- Single layer of cuboidal cells without cytological atypia
- Clear or granular cytoplasm which lack apical blebbing
- Immunohistochemistry:
  - Luminal cytokeratin, S100 +
  - EMA, ER, PR, Her 2, GCDFP -



# Microglandular adenosis and breast carcinoma

- In Rosen's first article, microglandular adenosis was associated with in situ or invasive carcinoma in 4 (31%) out of 13 cases
- Rosen and his colleagues later reported more cases associated with carcinoma and suggested that microglandular adenosis may be a precancerous lesion
- This is supported by the presence of transition forms
- The immunohistochemical similarity of the 2 lesions when they co-exist
- And the presence of shared molecular changes
- Histological types of associated invasive carcinomas included ductal, lobular, adenoid cystic, metaplastic and acininc cell type

# Microglandular adenosis

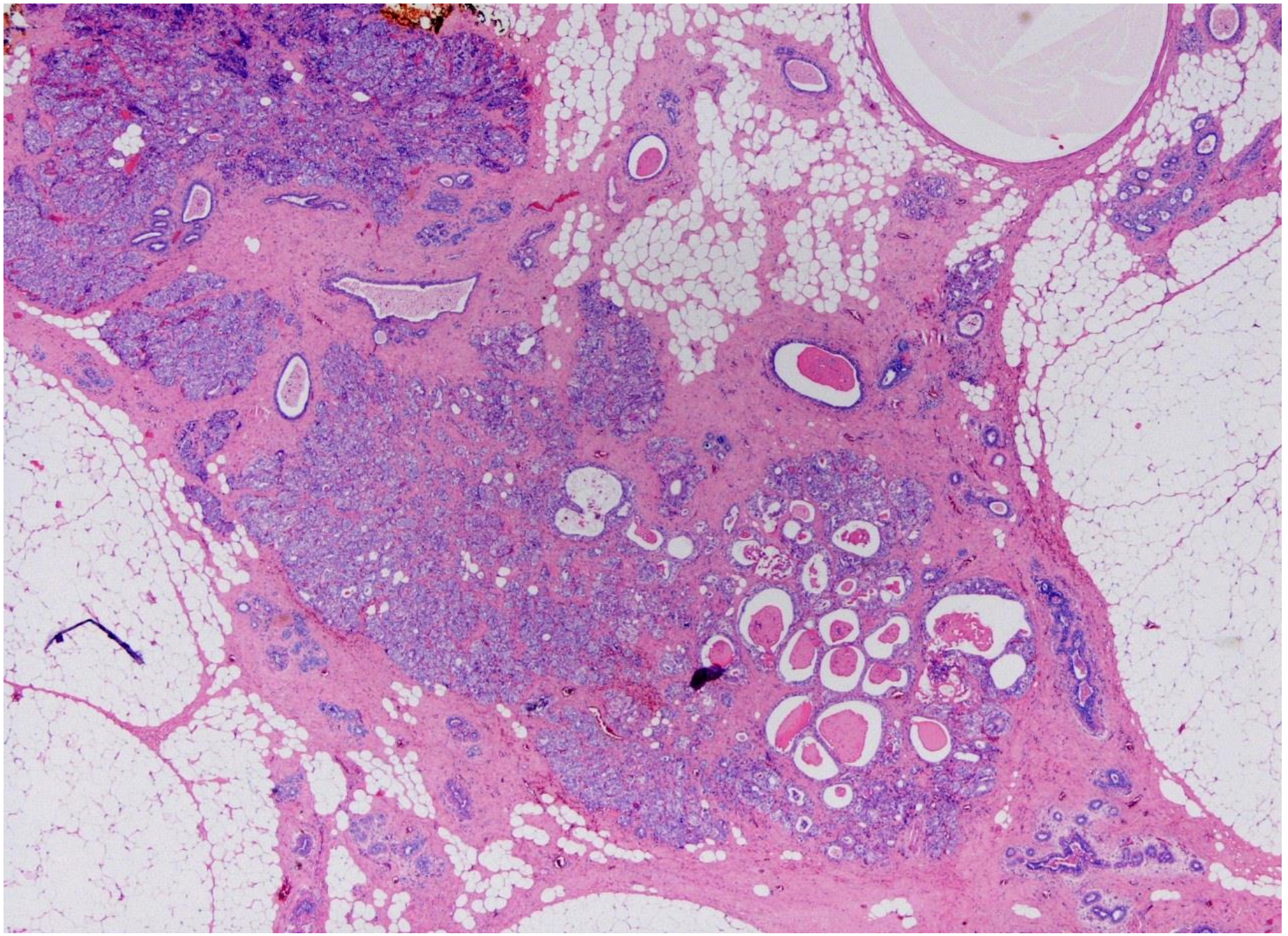
## Prognostic implications

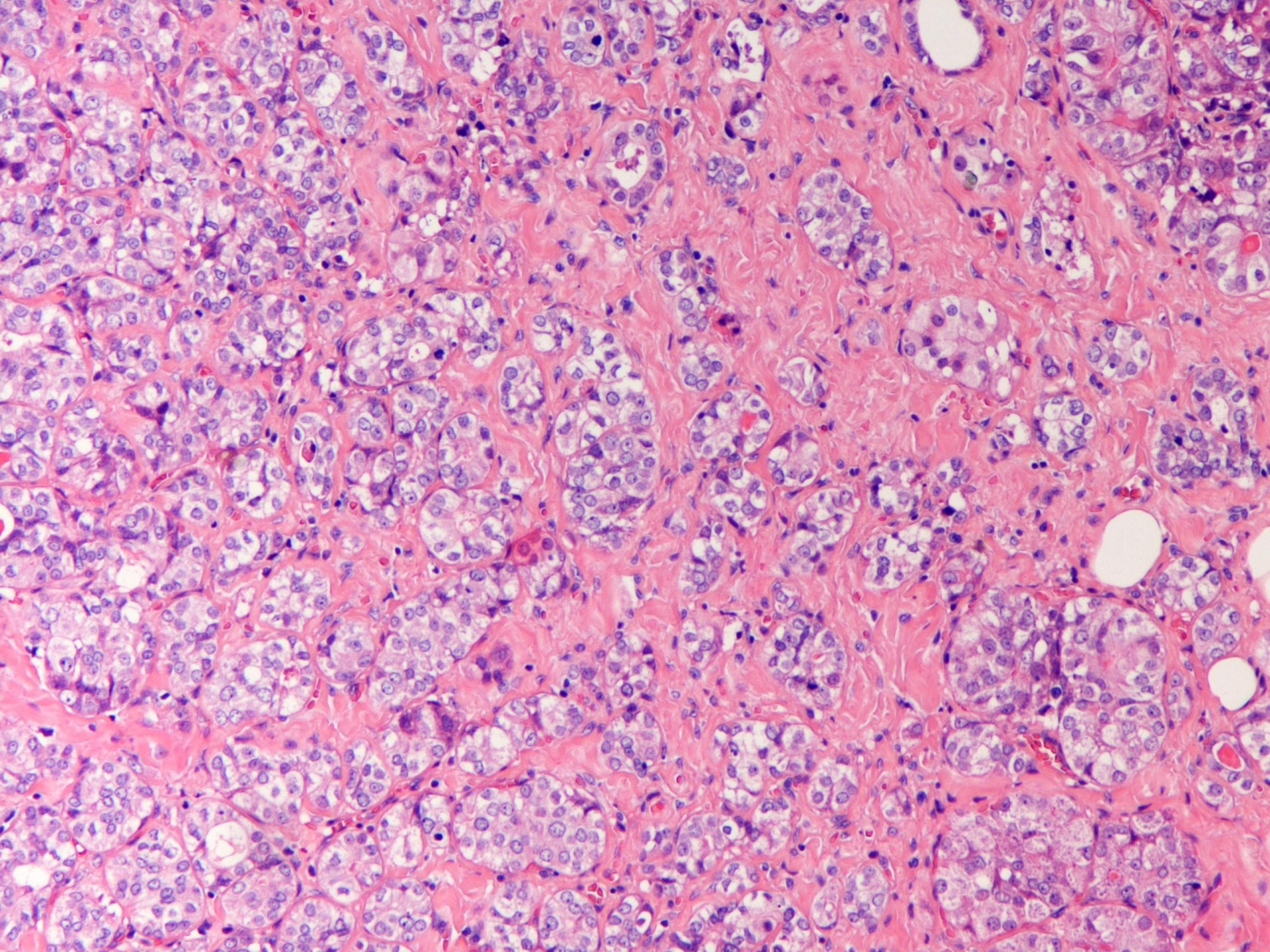
- Probably indolent in its uncomplicated form  
**BUT**
- Rosen(1) reported 14 carcinomas among 60 MGA
- Page(2) reported 17 cases of ACC associated with MGA
- Tavassoli(3) reported 20 cases of in situ and invasive carcinoma associated with MAG
- Atypical MGA

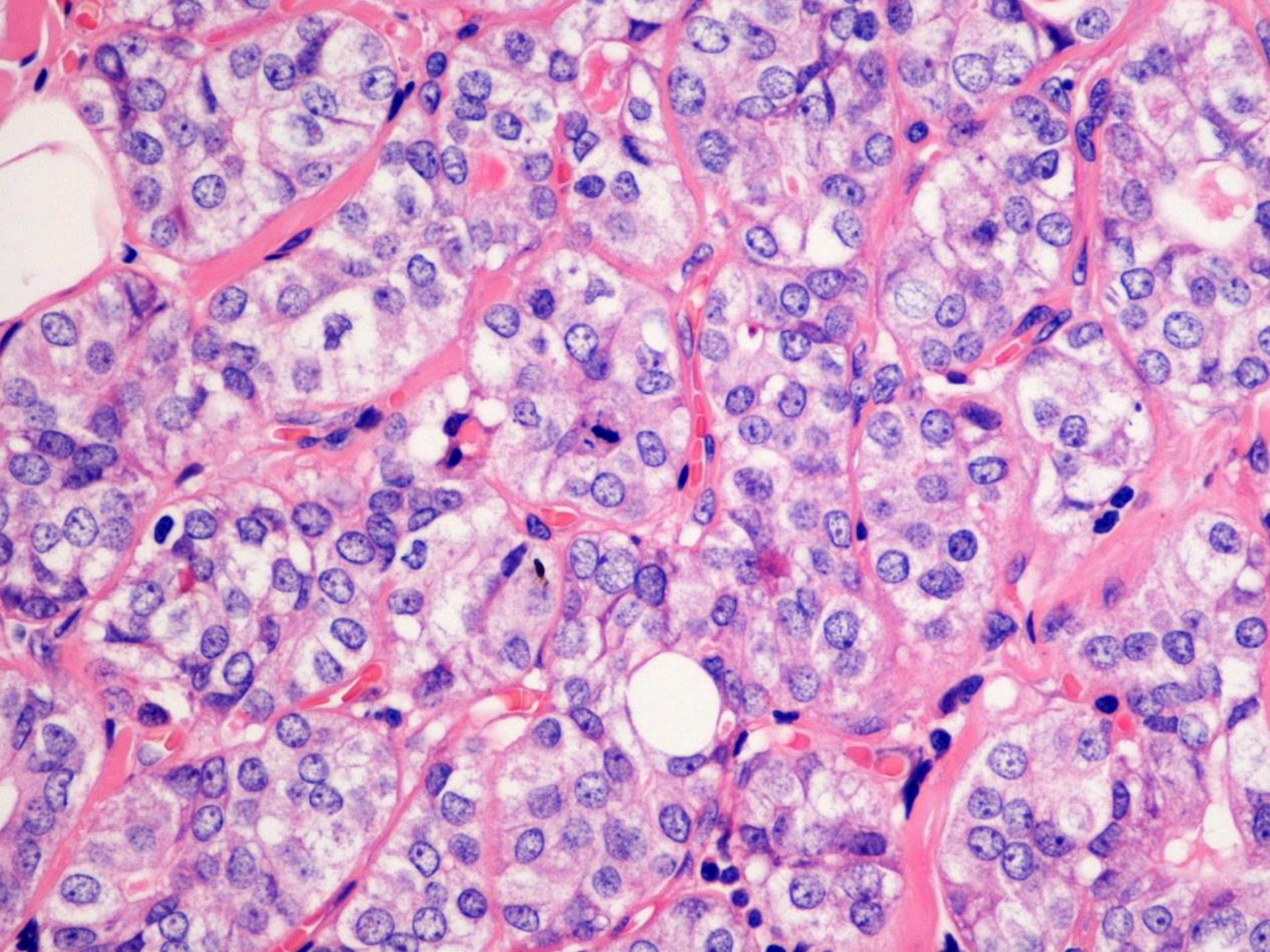
(1) *Carcinoma of the breast arising in Microglandular Adenosis.*  
*Am.J.Clin. Path. 1993; 100:507-13*

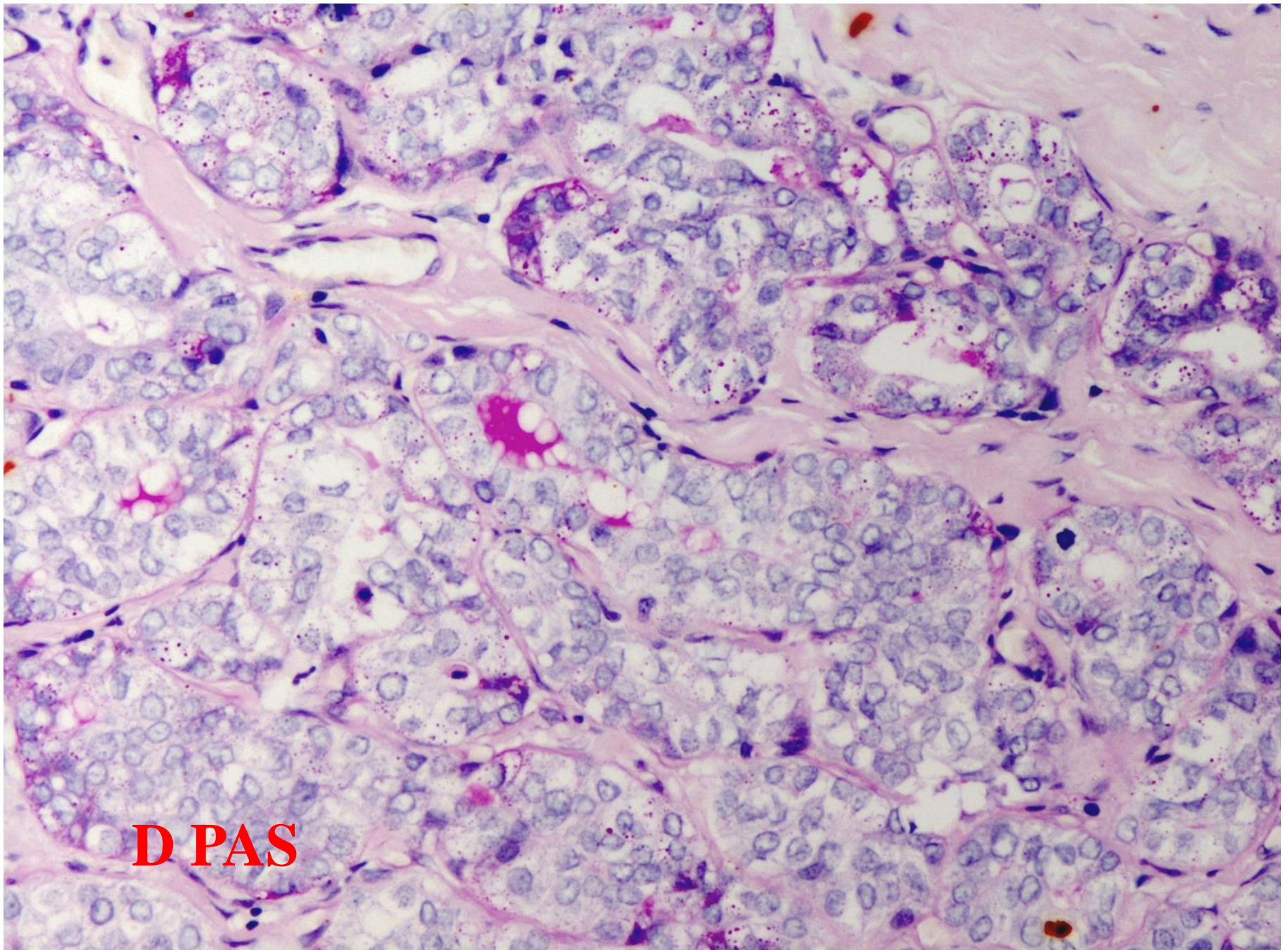
(2) *Microglandular Adenosis with transition into Adenoid Cystic Carcinoma of the breast.* *Am.J.Surg.Path. 27(8) 1052-60 2003*

(3) *Carcinoma arising in MGA* *Int.J.Surg.Path. 2000;8 303-15*

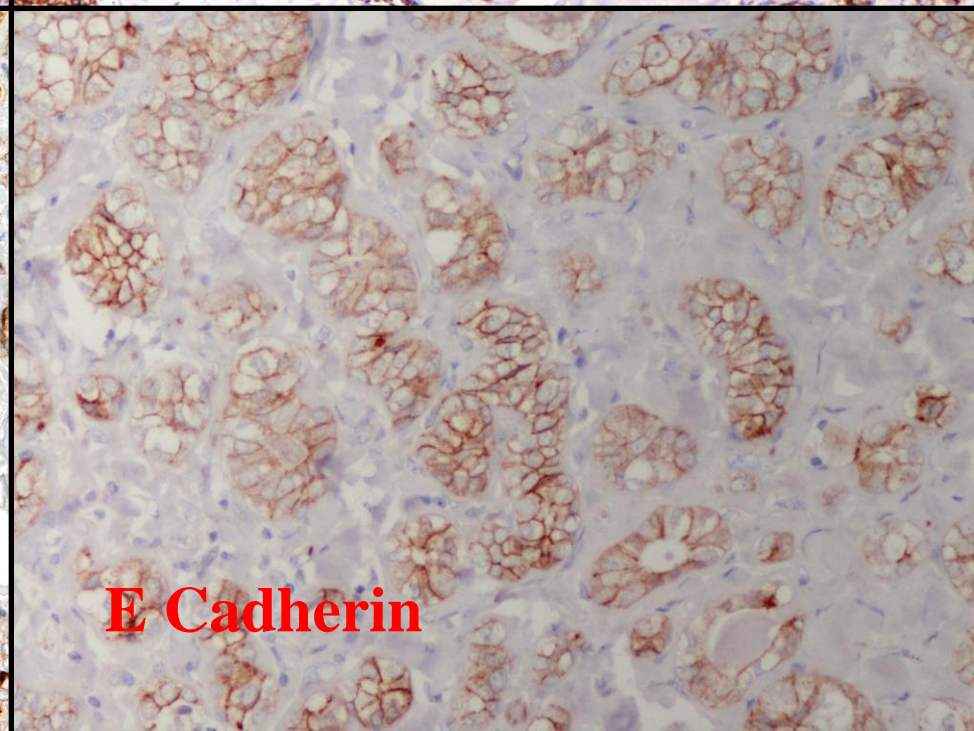
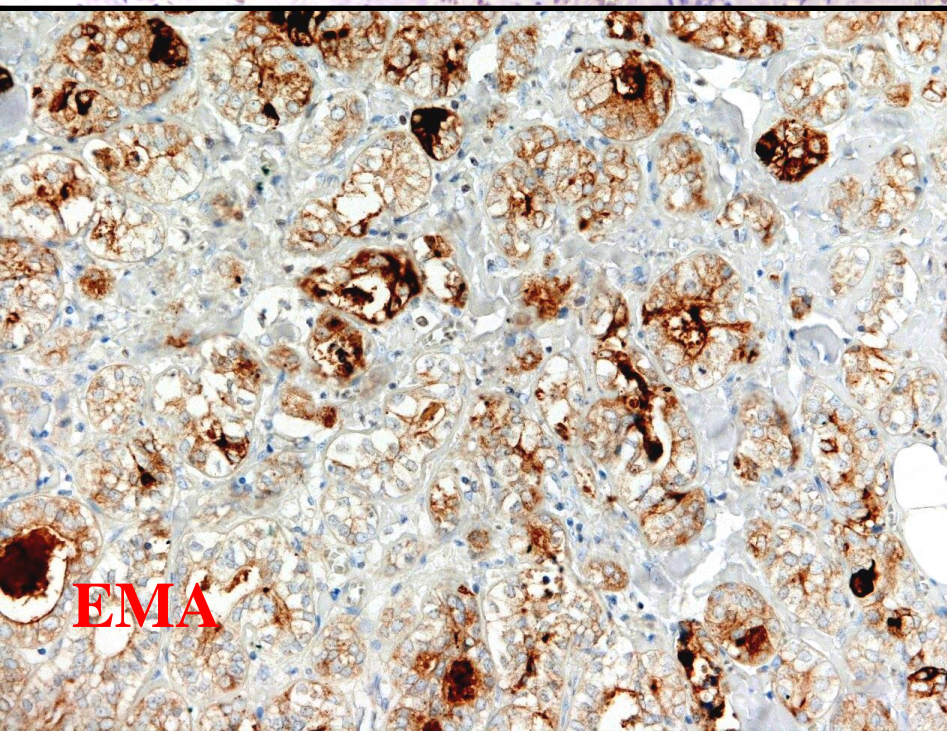
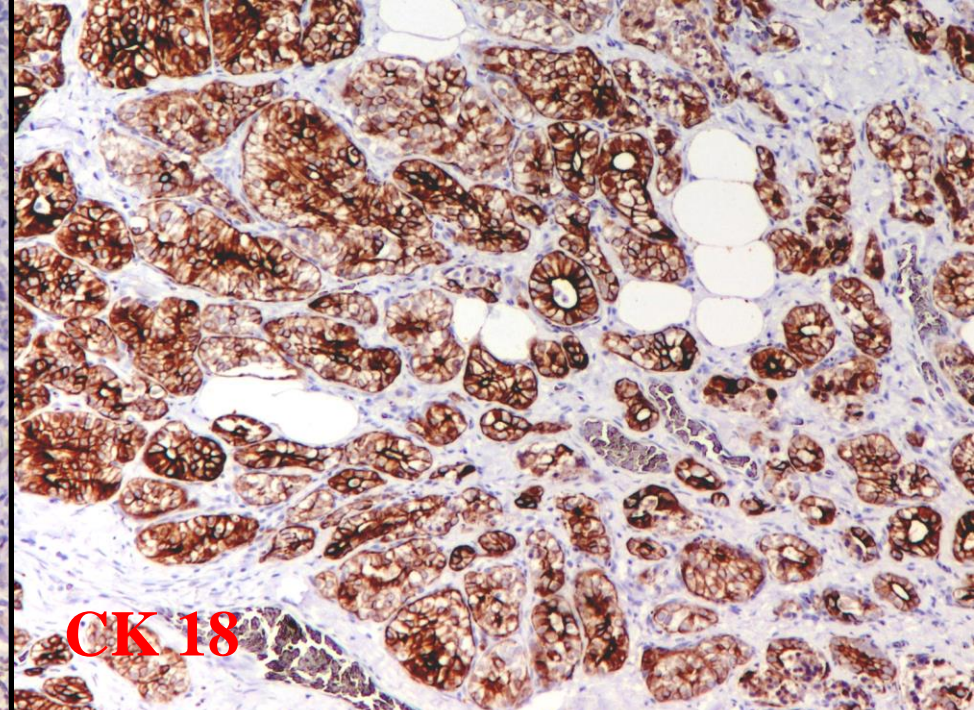
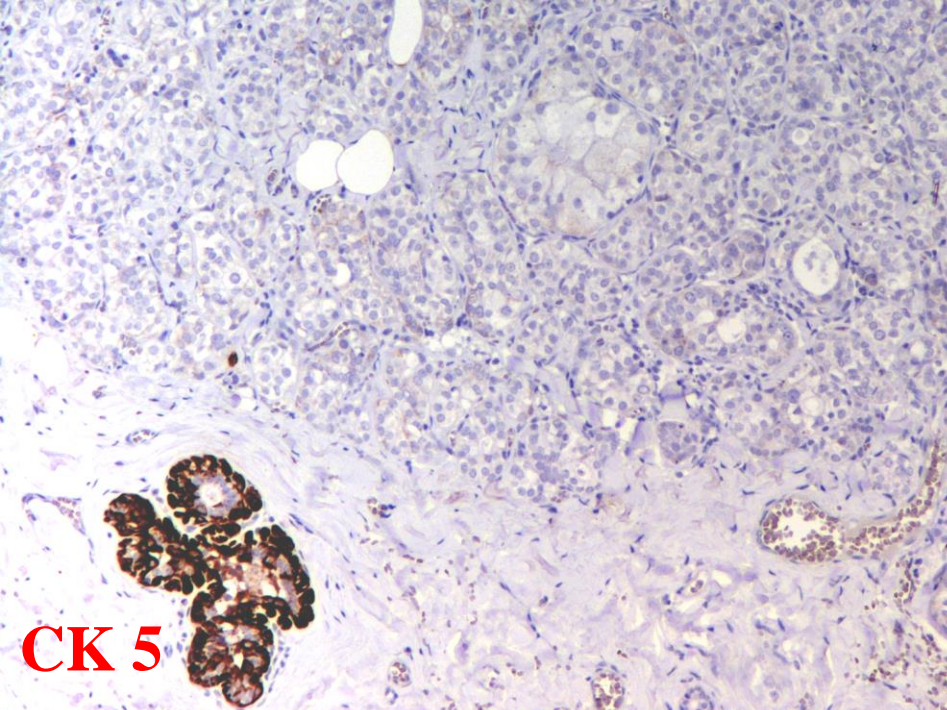


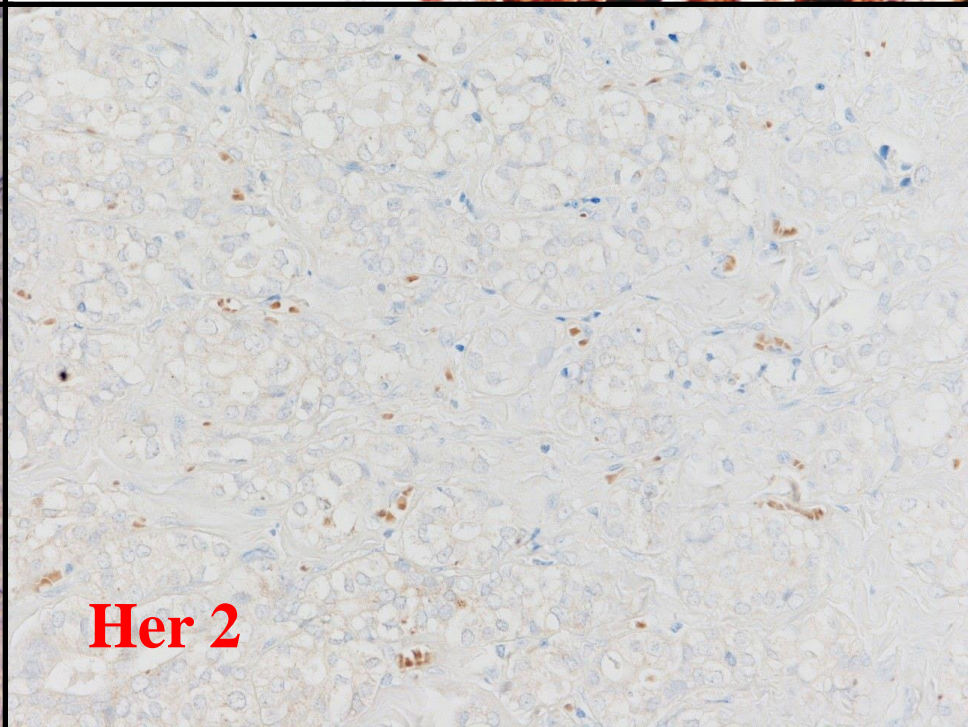
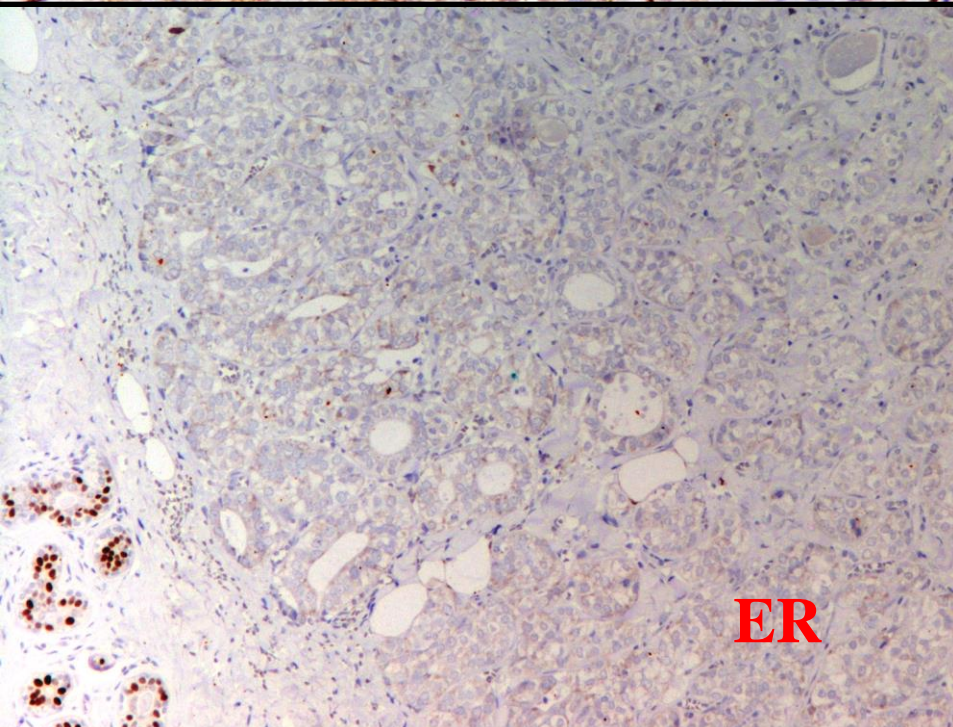
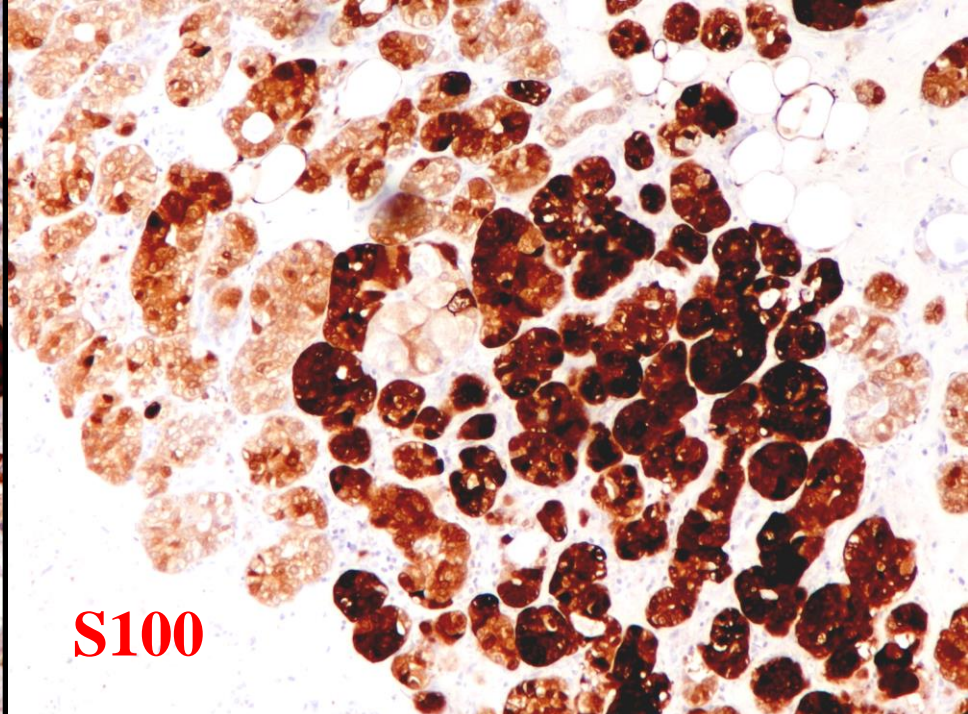
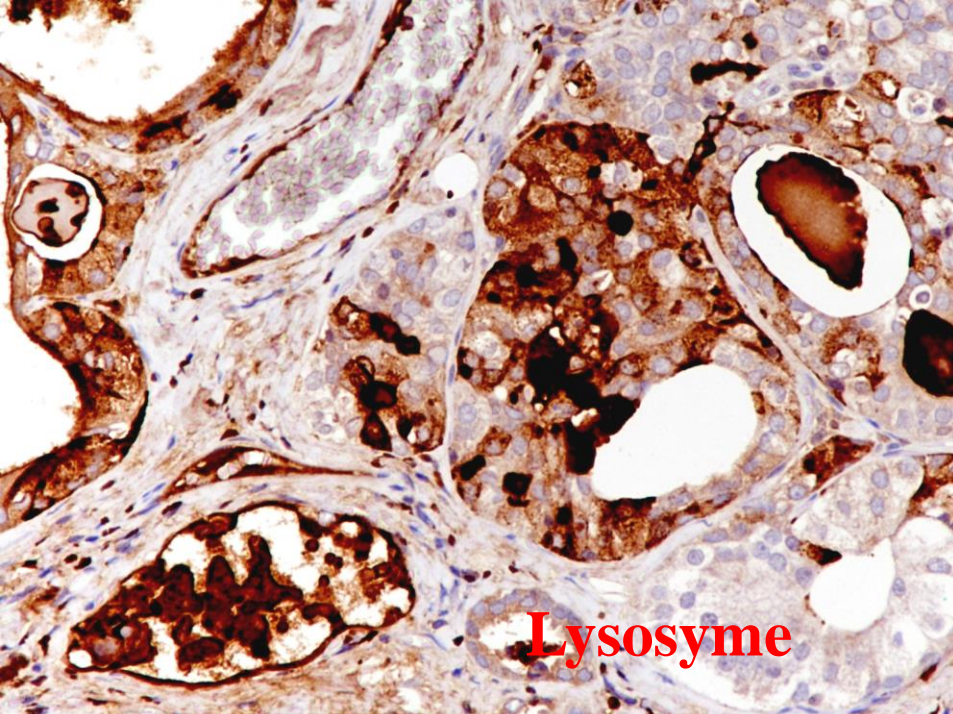




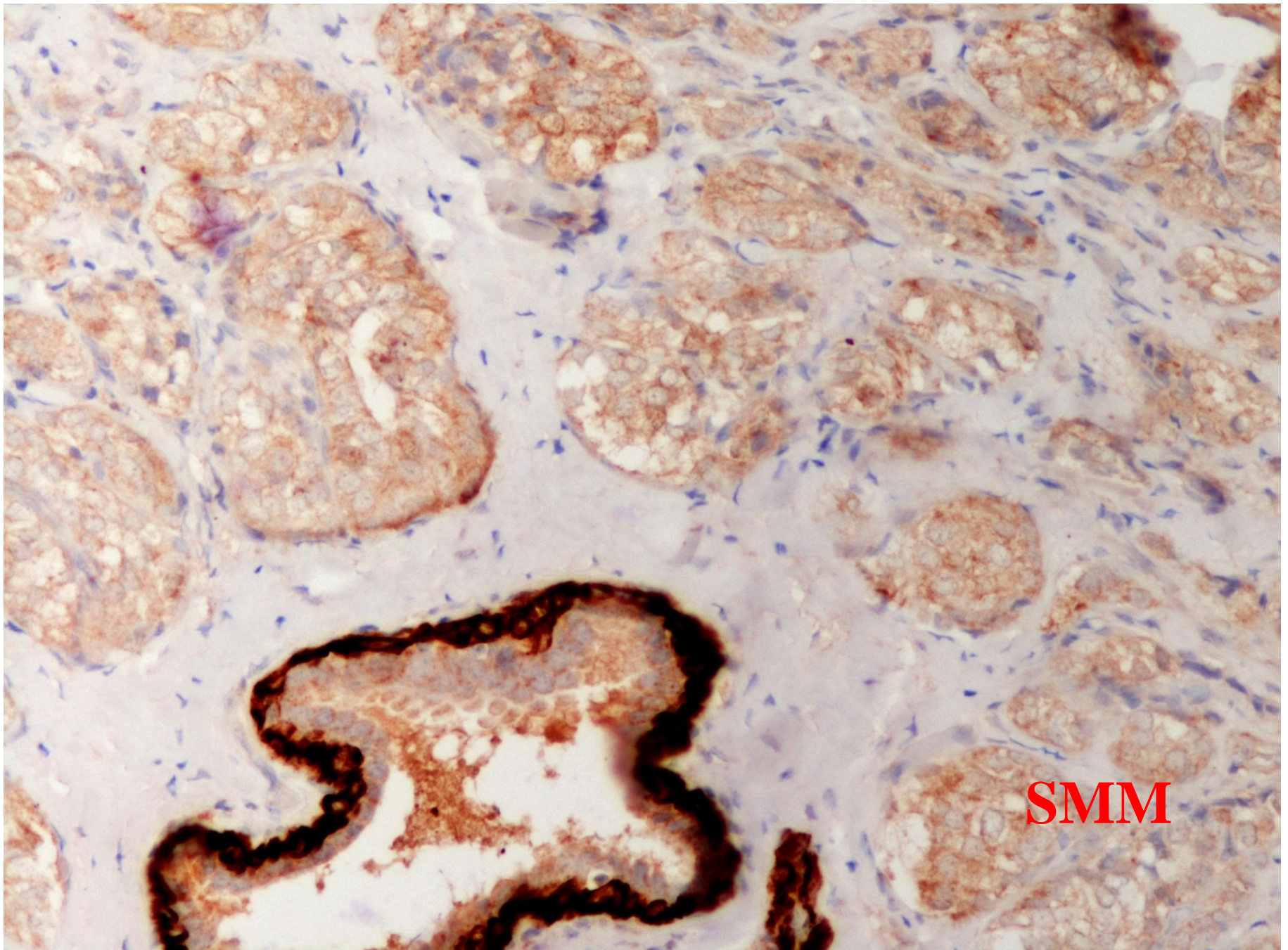


**D PAS**

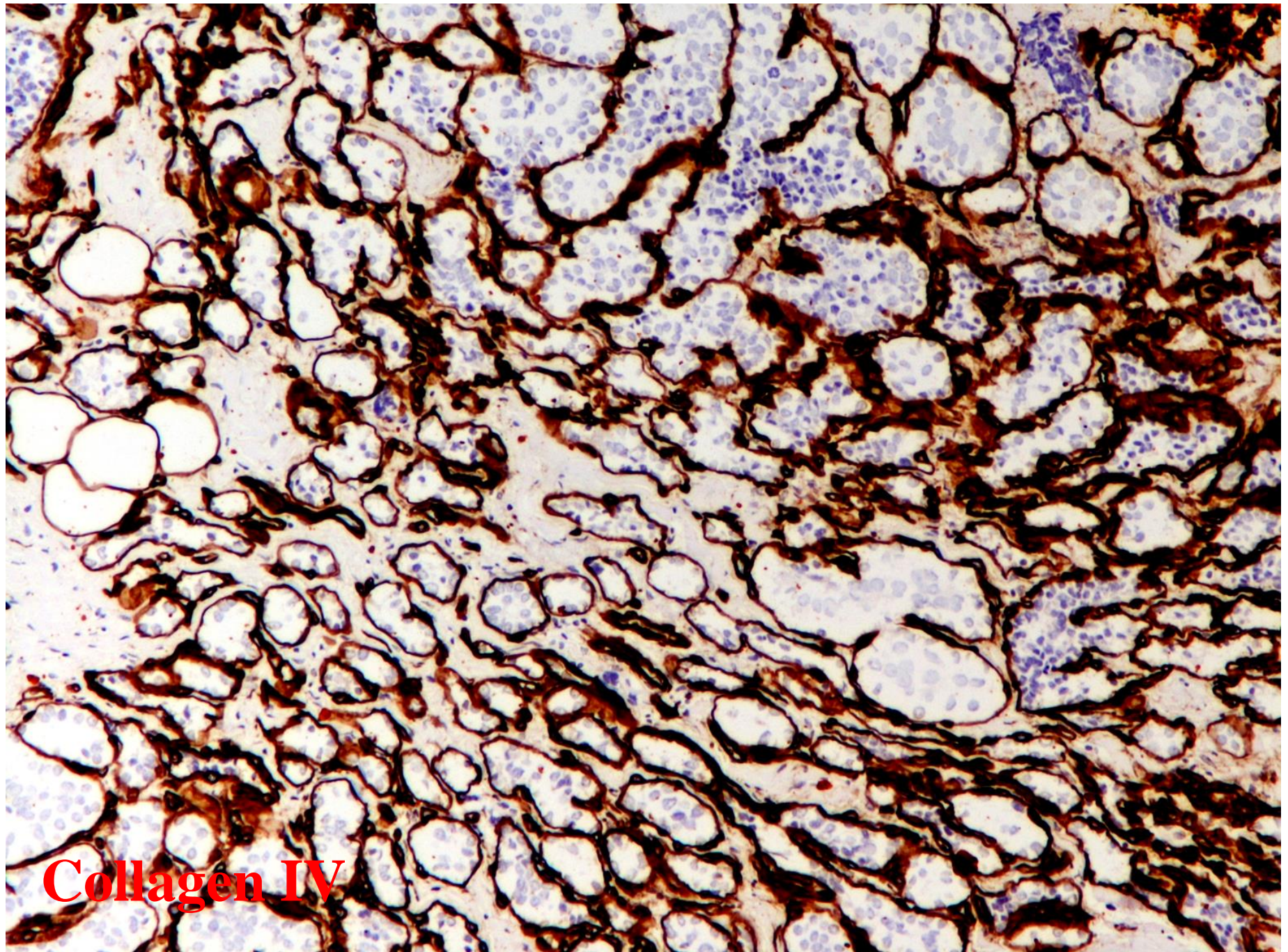








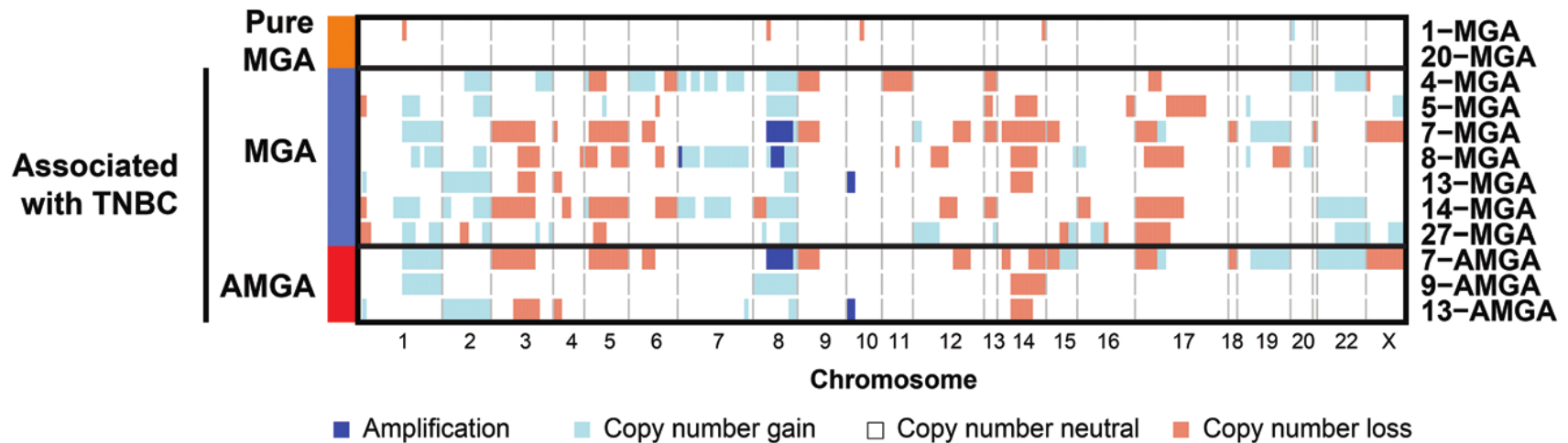
**SMM**



**Collagen IV**

# Microglandular adenosis associated with triple-negative breast cancer is a neoplastic lesion of triple-negative phenotype harbouring *TP53* somatic mutations

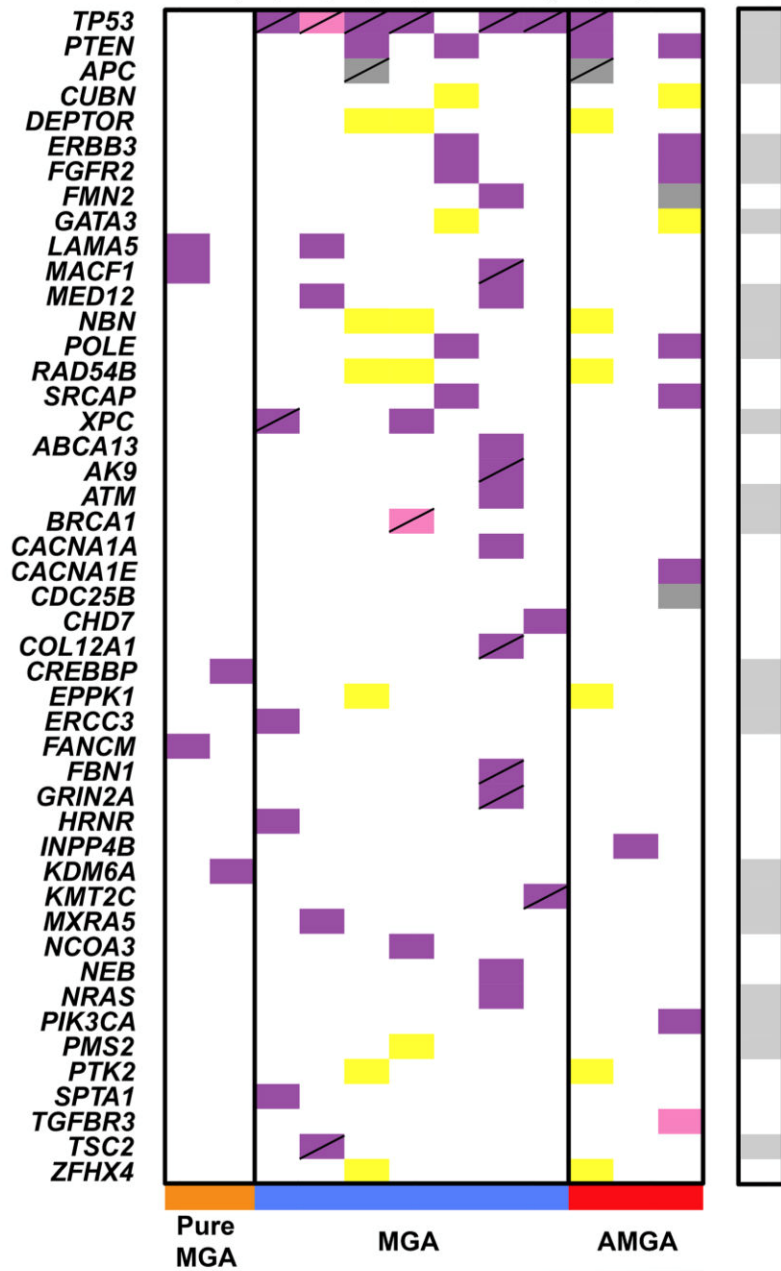
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1-MGA 20-MGA 4-MGA 5-MGA 7-MGA 8-MGA 13-MGA 14-MGA 27-MGA 7-AMGA 9-AMGA 13-AMGA Cancer gene



### Alteration type

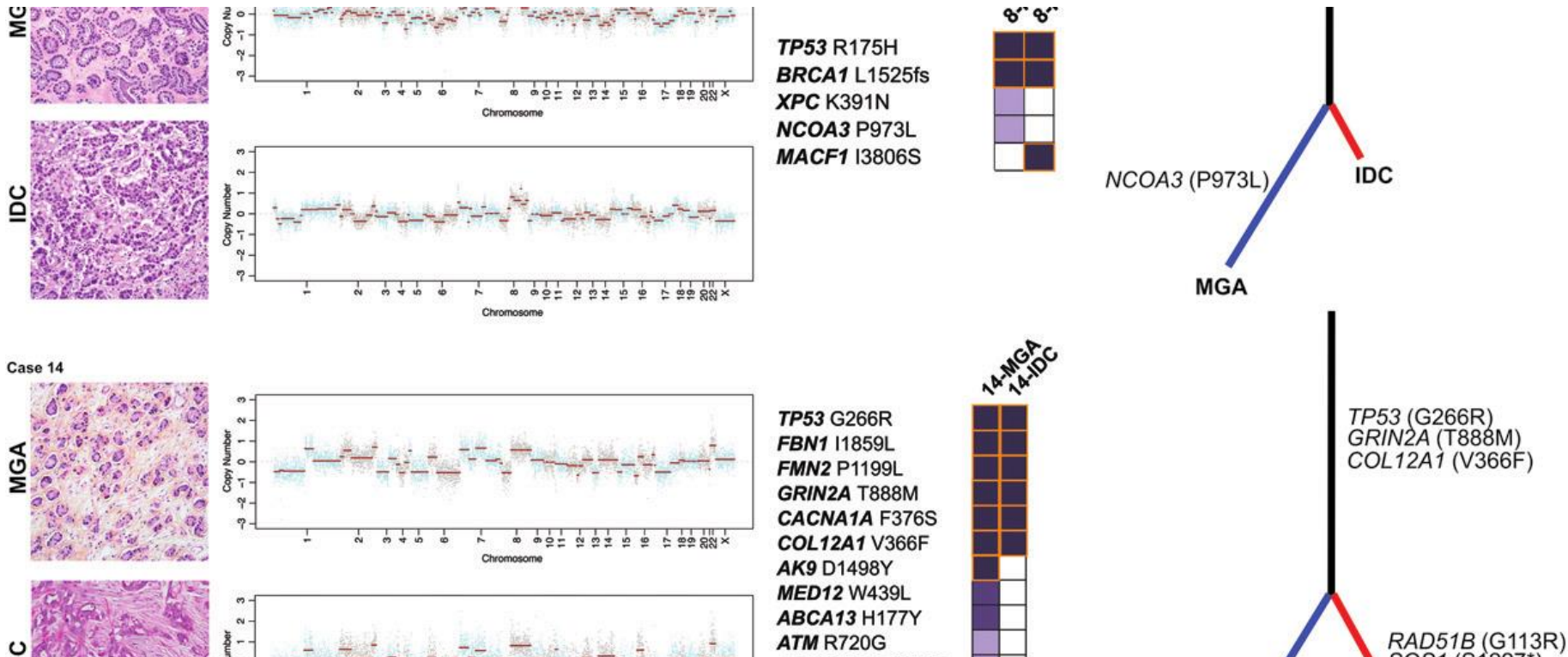
- Truncating SNV
- Missense SNV
- Frame-shift indel
- Loss of heterozygosity
- Amplification

Pure MGA MGA AMGA

Associated with TNBC

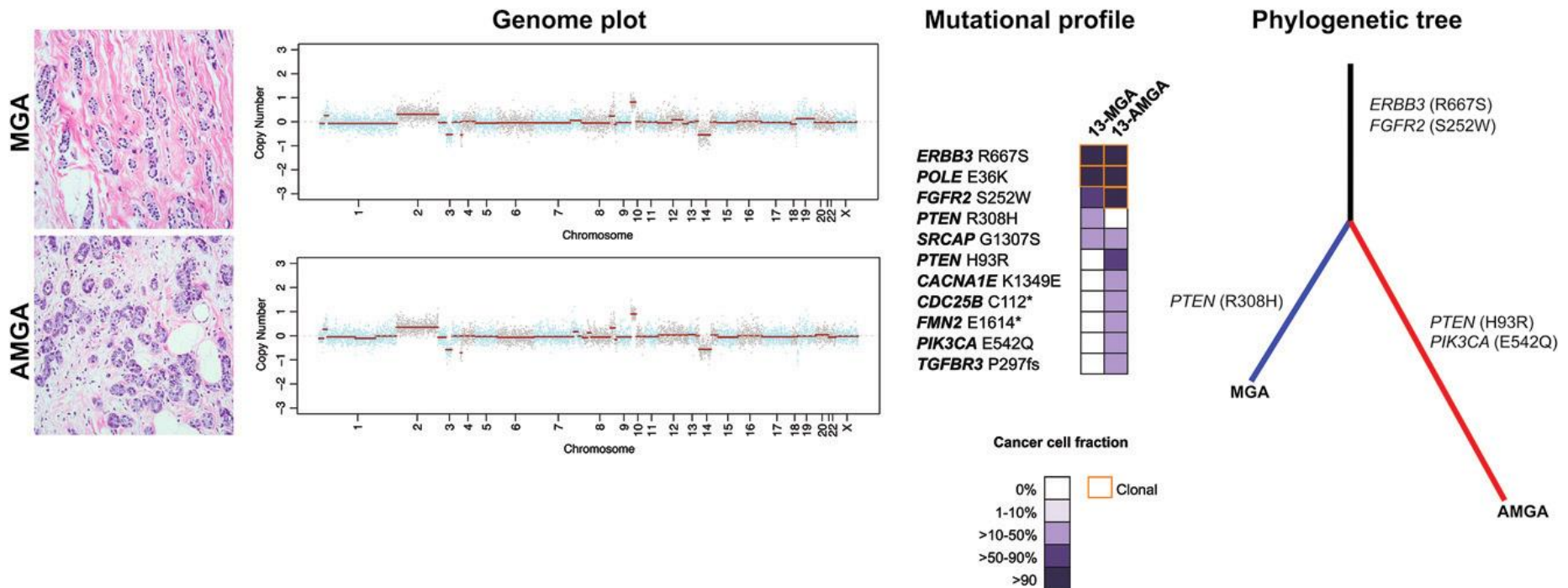
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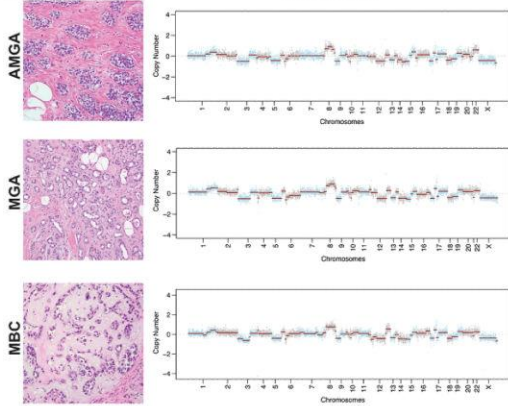
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Case 7

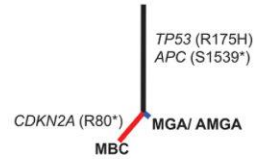
Genome plot



**TP53** R175H  
**APC** S1539\*  
**PTEN** M134I  
**CDKN2A** R80\*



Phylogenetic trees



Journal of Pathology

J Pathol 2016; 238: 677–688

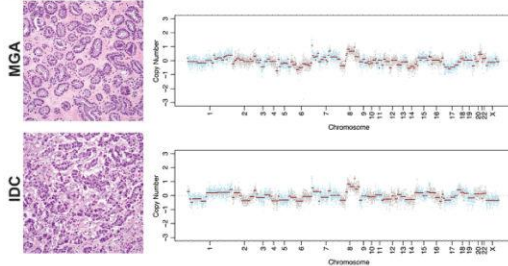
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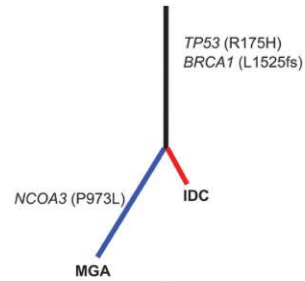
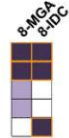
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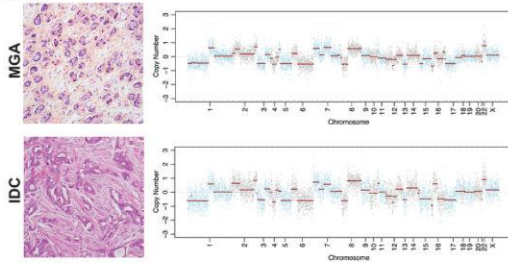
Case 8



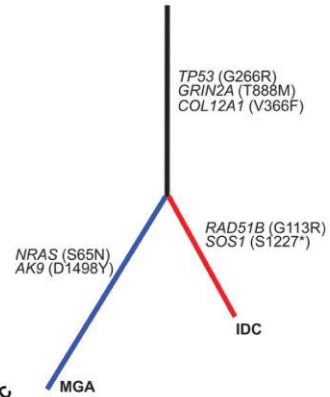
**TP53** R175H  
**BRCA1** L1525fs  
**XPC** K391N  
**NCOA3** P973L  
**MACF1** I3806S



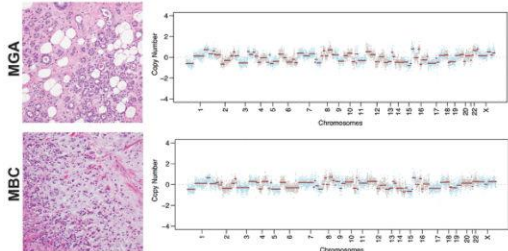
Case 14



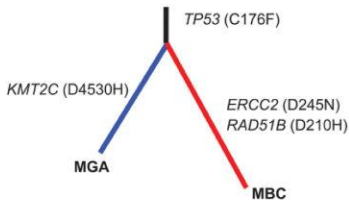
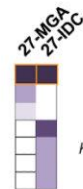
**TP53** G266R  
**FBN1** I1859L  
**FMN2** P1199L  
**GRIN2A** T888M  
**CACNA1A** F376S  
**COL12A1** V366F  
**AK9** D1498Y  
**MED12** W439L  
**ABCA13** H177Y  
**ATM** R720G  
**CACNA1A** T1344S  
**MACF1** G3580D  
**NRAS** S65N  
**NEB** K7431E  
**SOS1** S1227\*  
**RAD51B** G113R  
**BRCA2** A262V



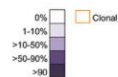
Case 27



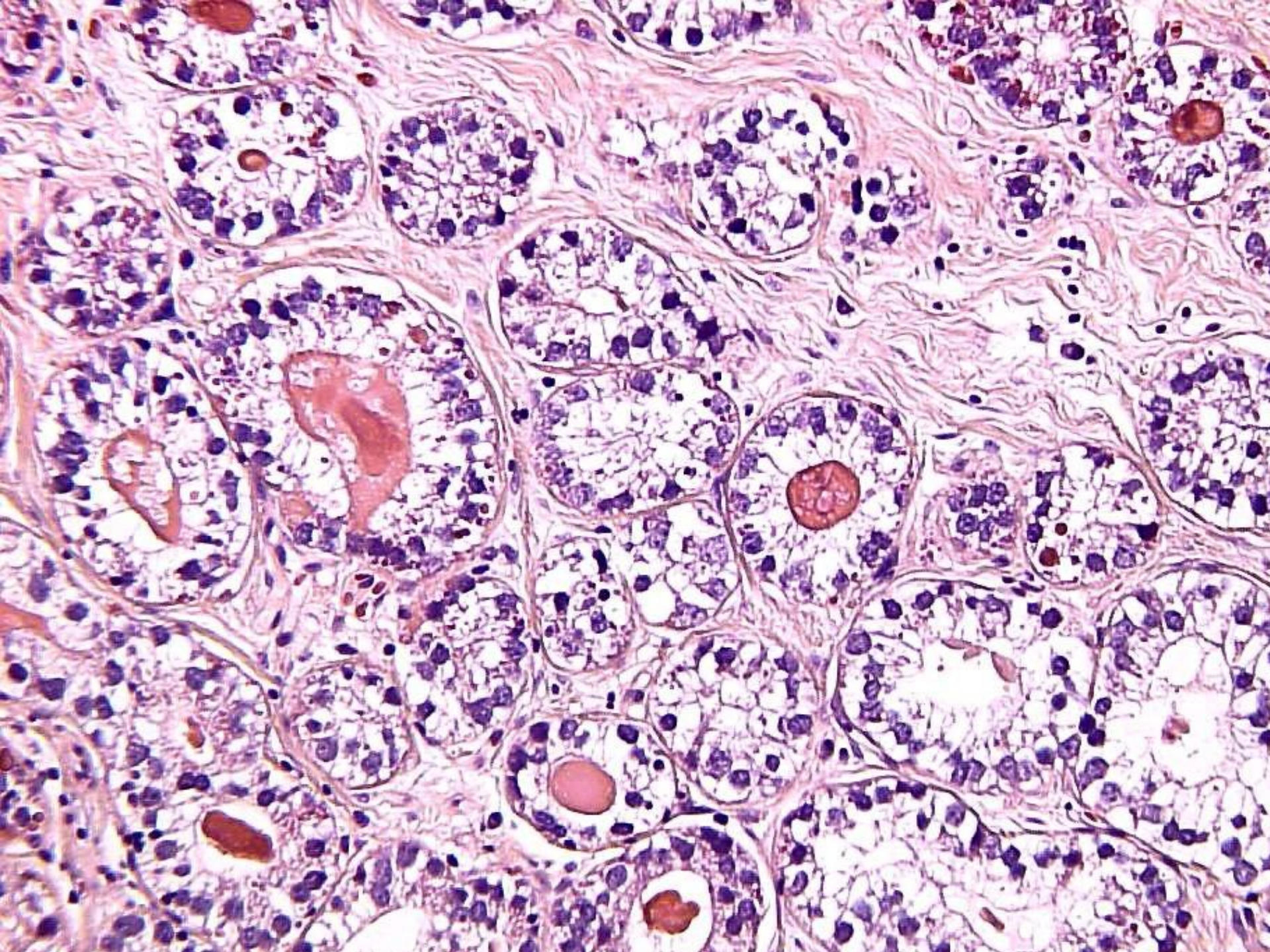
**TP53** C176F  
**CHD7** T335R  
**KMT2C** D4530H  
**ABCB1** R157G  
**ABCA13** R3784Q  
**ERCC2** D245N  
**RAD51B** D210H



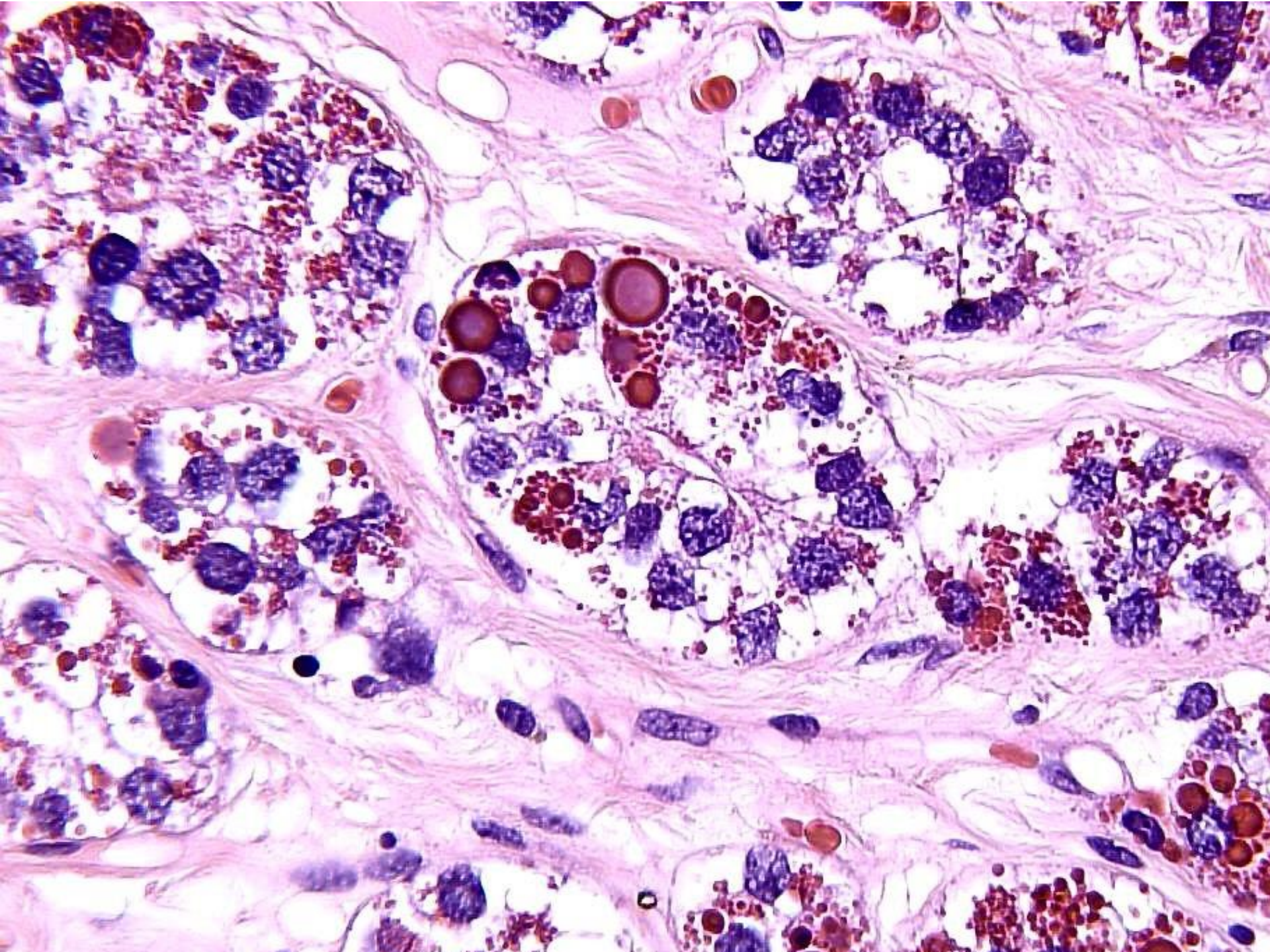
Cancer cell fraction



Clonal







# AcCC v MGA

- Overlapping architectural features-small glandular/acinar structure without myoepithelial layer
- IHC similarities- CK,S100,ER,Lysosyme, Her2,

## **But**

- AcCC usually with solid areas
- Lack of BM
- IHC differences-EMA, ?Amylase
- Zymogen granules on EM

# Acinic cell carcinoma

**Journal of Pathology**

*J Pathol* 2015; **237**: 166–178

Published online 29 July 2015 in Wiley Online Library

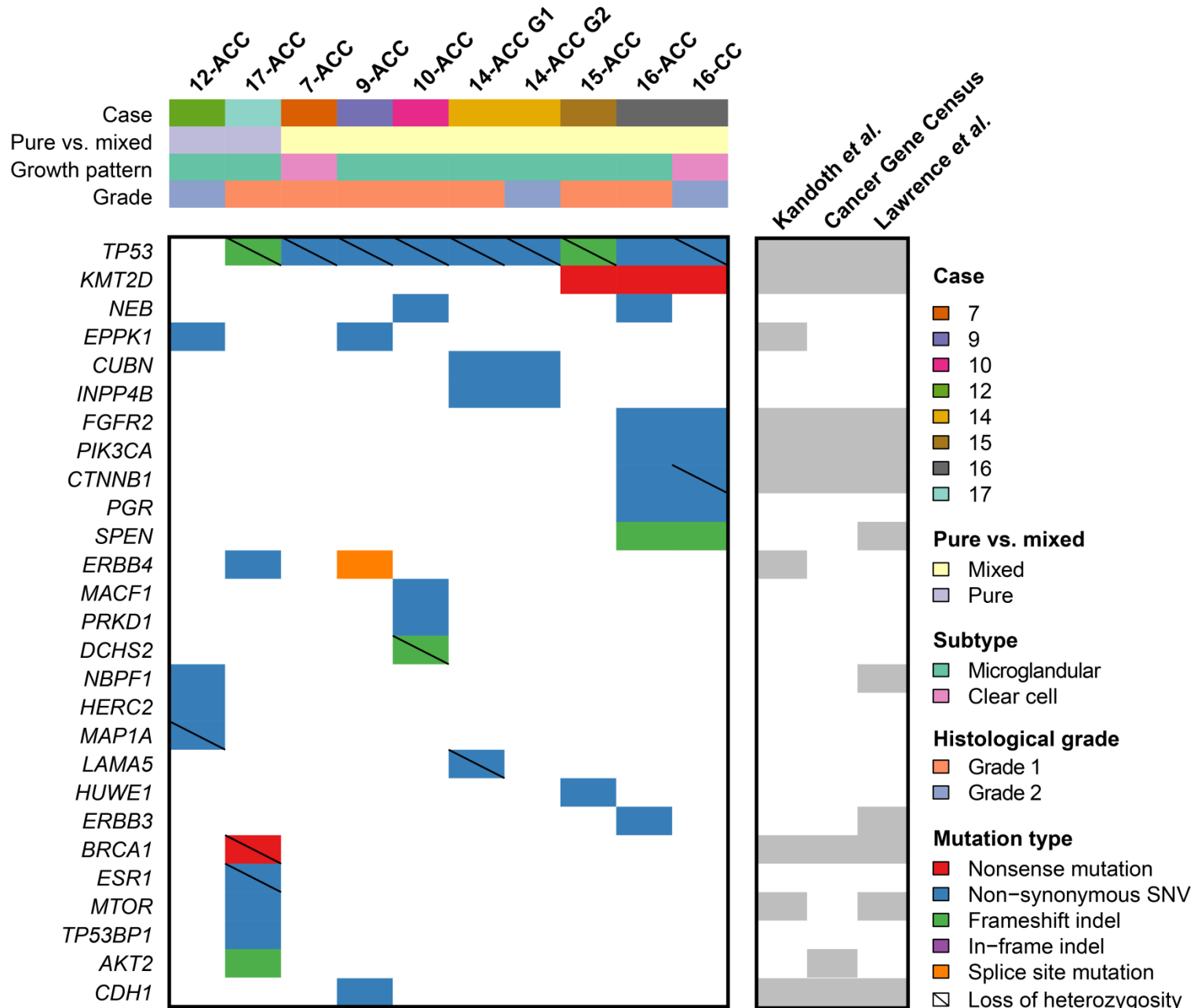
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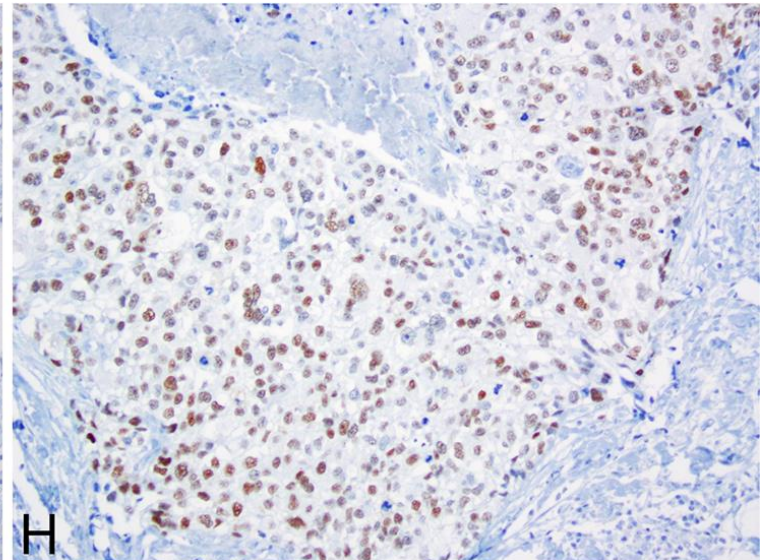
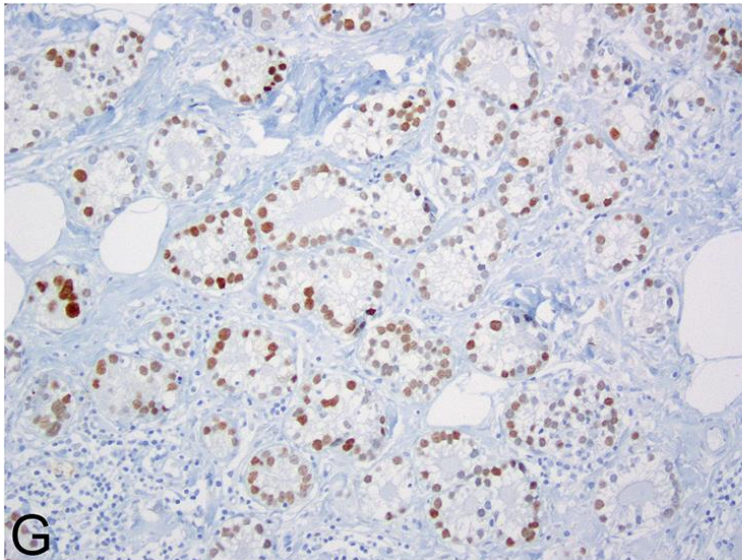
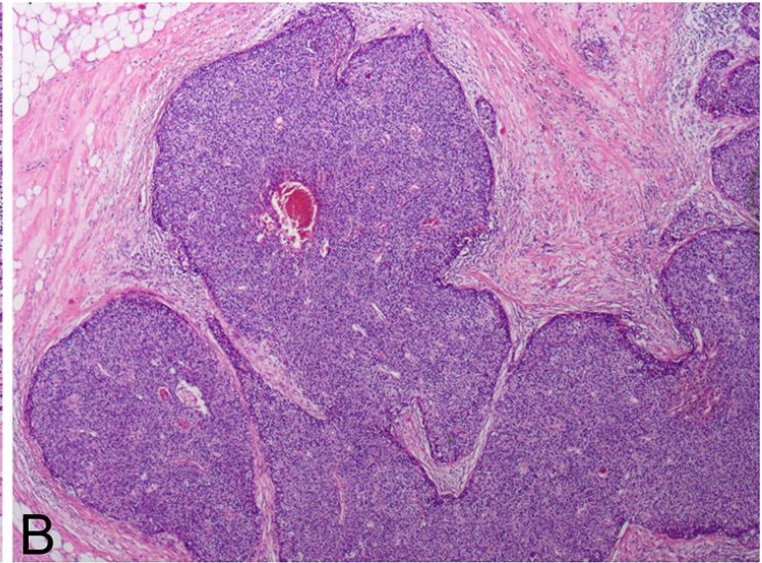
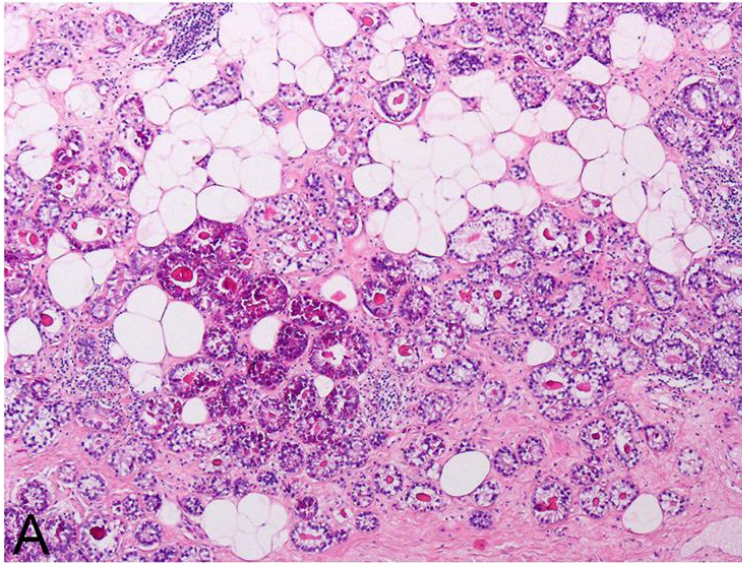
## The repertoire of somatic genetic alterations of acinic cell carcinomas of the breast: an exploratory, hypothesis-generating study

Elena Guerini-Rocco,<sup>1,2†</sup> Zsolt Hodi,<sup>3†</sup> Salvatore Piscuoglio,<sup>1†</sup> Charlotte KY Ng,<sup>1†</sup> Emad A Rakha,<sup>3</sup> Anne M Schultheis,<sup>1</sup> Caterina Marchiò,<sup>1,4</sup> Arnaud da Cruz Paula,<sup>1</sup> Maria R De Filippo,<sup>1</sup> Luciano G Martelotto,<sup>1</sup> Leticia De Mattos-Arruda,<sup>1,5</sup> Marcia Edelweiss,<sup>1</sup> Achim A Jungbluth,<sup>1</sup> Nicola Fusco,<sup>1,2</sup> Larry Norton,<sup>6</sup> Britta Weigelt,<sup>1\*</sup> Ian O Ellis<sup>3\*</sup> and Jorge S Reis-Filho<sup>1\*</sup>

# Landscape of somatic genetic alterations

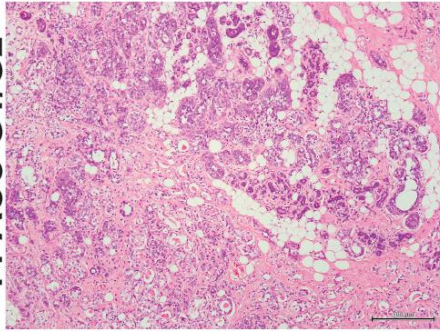


# ACCs and high grade TNBCs share identical *TP53* mutations and p53 expression

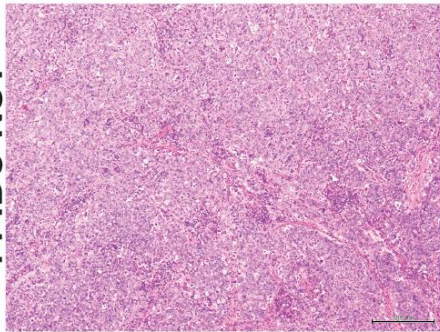


# Mixed ACC and IDC-NST sharing founder genetic alterations

H&E

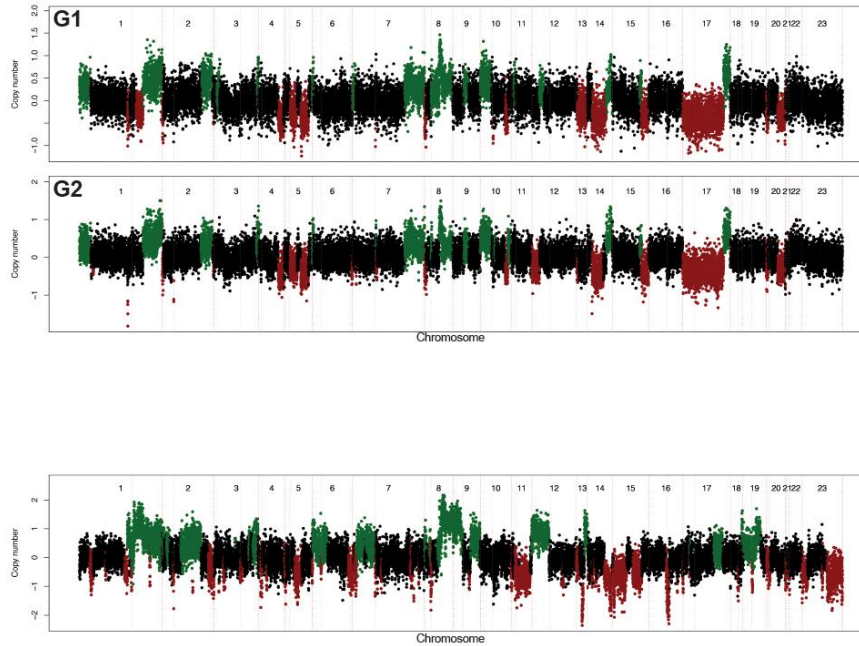


14-ACC G1/G2



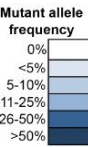
14-IDC-NST

Genome plot

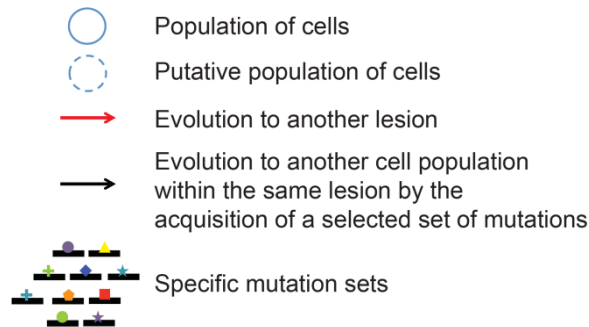
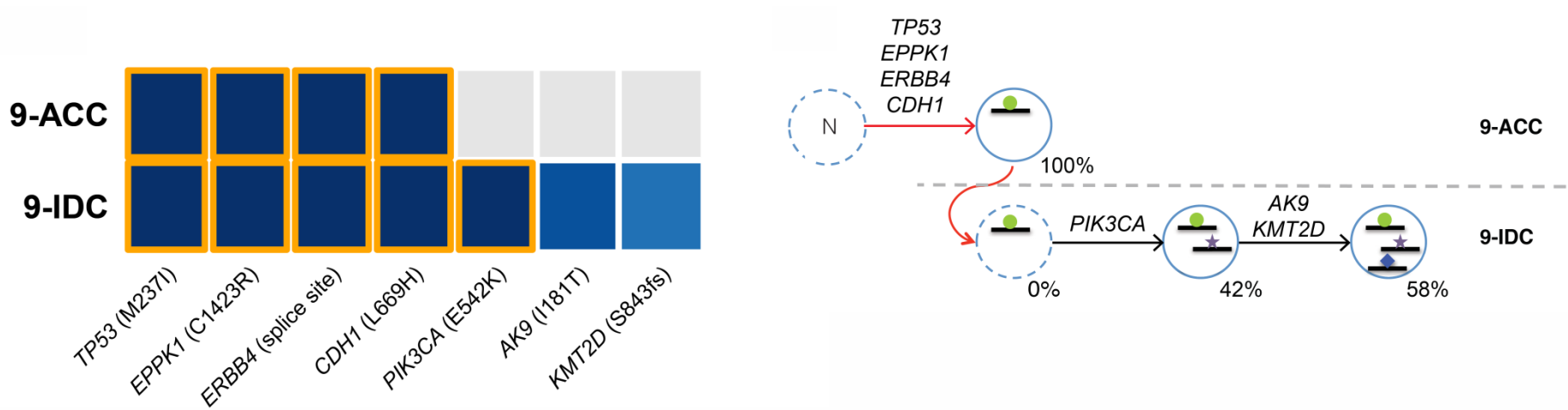


Mutational profile

Mutation	14-ACC G1	14-ACC G2	14-IDC-NST
TP53	Dark Blue	Dark Blue	White
R273C	Dark Blue	Dark Blue	White
INPP4B	Dark Blue	Dark Blue	White
Q306K	Dark Blue	Dark Blue	White
CUBN	Light Blue	Light Blue	White
L2280F	Light Blue	Light Blue	White
LAMA5	Light Blue	Light Blue	White
A907T	Light Blue	Light Blue	White
AHNAK2E4	Light Blue	Light Blue	White
550Q	Light Blue	Light Blue	White
CUBN	Light Blue	Light Blue	White
I3556T	Light Blue	Light Blue	White
AHNAK2	Light Blue	Light Blue	White
L4561I	Light Blue	Light Blue	White
PRKCD	Light Blue	Light Blue	White
T609S	Light Blue	Light Blue	White
RAD50	Light Blue	Light Blue	Dark Blue
S560R	Light Blue	Light Blue	Dark Blue
BRCA2	Light Blue	Light Blue	Dark Blue
R2991C	Light Blue	Light Blue	Dark Blue
ARID1A	Light Blue	Light Blue	Dark Blue
M1022V	Light Blue	Light Blue	Dark Blue
COL12A1	Light Blue	Light Blue	Dark Blue
P2308fs	Light Blue	Light Blue	Dark Blue
PLECR	Light Blue	Light Blue	Dark Blue
4551H	Light Blue	Light Blue	Dark Blue
KMT2D	Light Blue	Light Blue	Dark Blue
S940	Light Blue	Light Blue	Dark Blue
HUWE1	Light Blue	Light Blue	Dark Blue
T3640P	Light Blue	Light Blue	Dark Blue
KMT2D	Light Blue	Light Blue	Dark Blue
K1686fs	Light Blue	Light Blue	Dark Blue
CACNA1C	Light Blue	Light Blue	Dark Blue
K82fs	Light Blue	Light Blue	Dark Blue
MDN1	Light Blue	Light Blue	Dark Blue
S4730L	Light Blue	Light Blue	Dark Blue
PLEC	Light Blue	Light Blue	Dark Blue
R417C	Light Blue	Light Blue	Dark Blue
MDN1	Light Blue	Light Blue	Dark Blue
A391S	Light Blue	Light Blue	Dark Blue



# Progression from ACC to high-grade TNBC



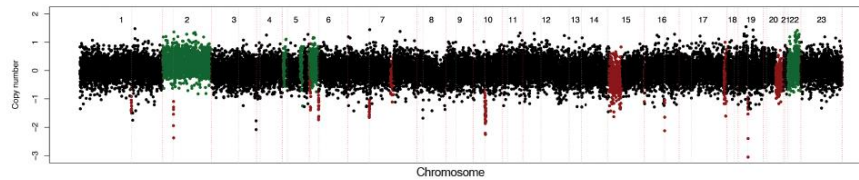
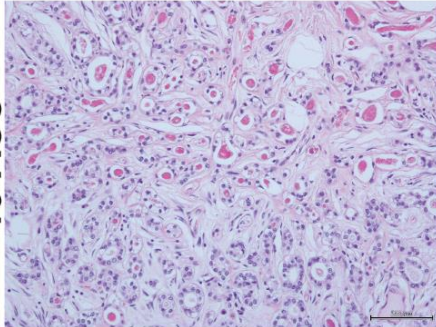
# Classic and clear cell ACC and metaplastic breast cancer: parallel progression and convergent phenotypes

H&E

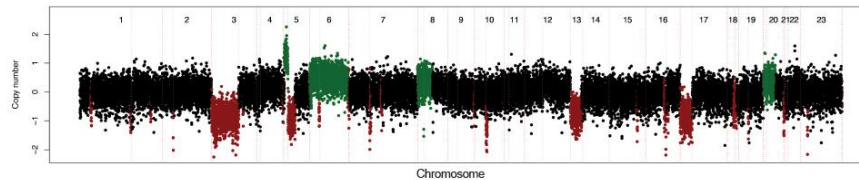
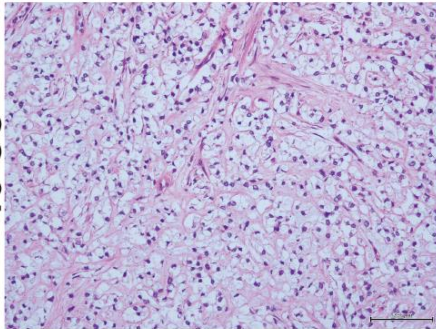
Genome plot

Mutational profile

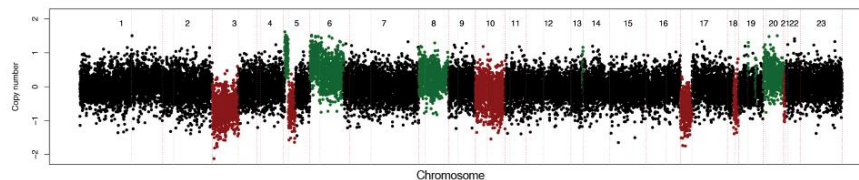
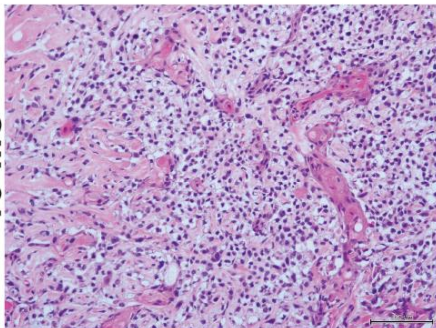
16-ACC



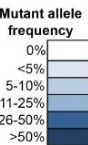
16-CC



16-MC

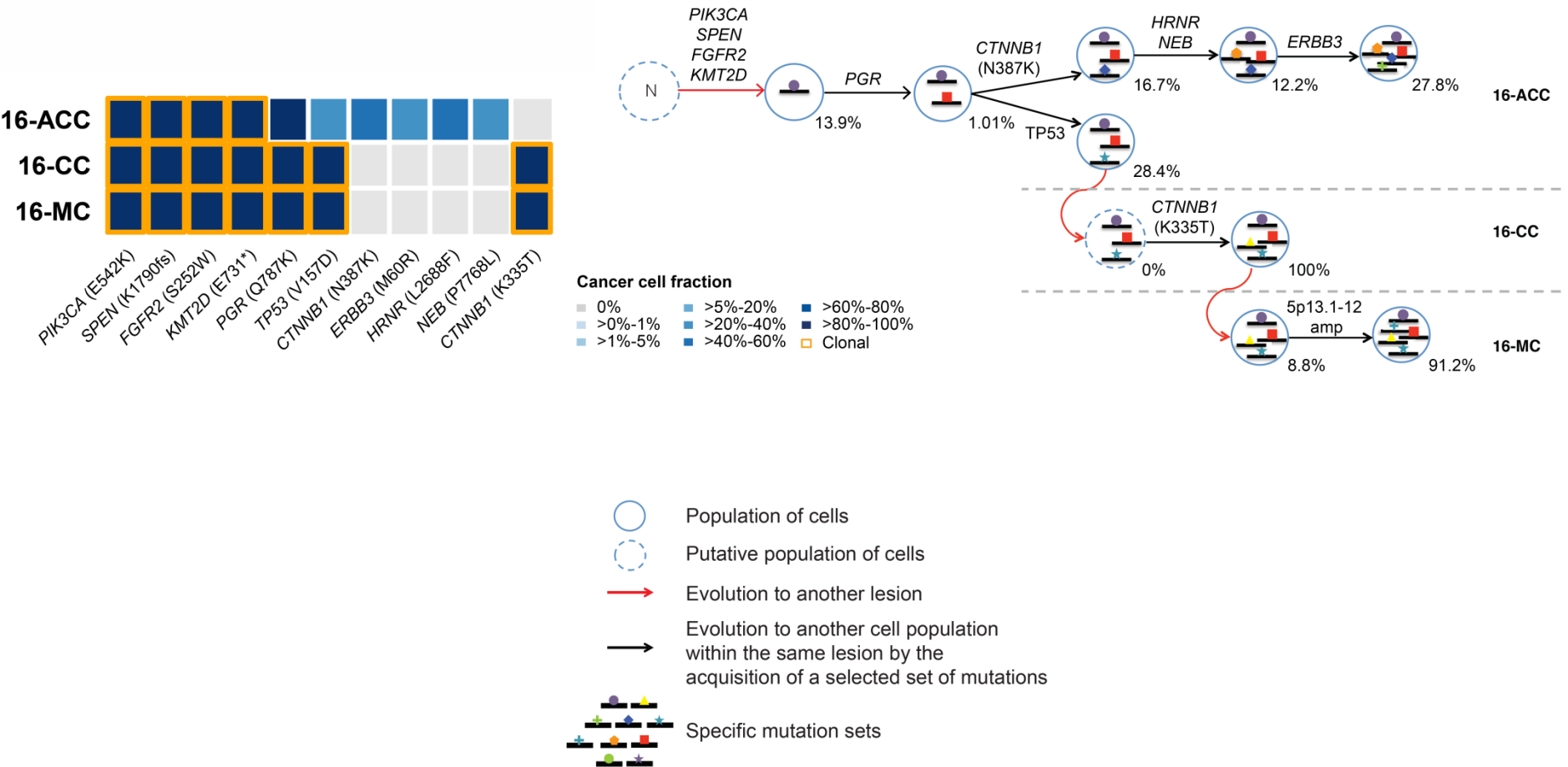


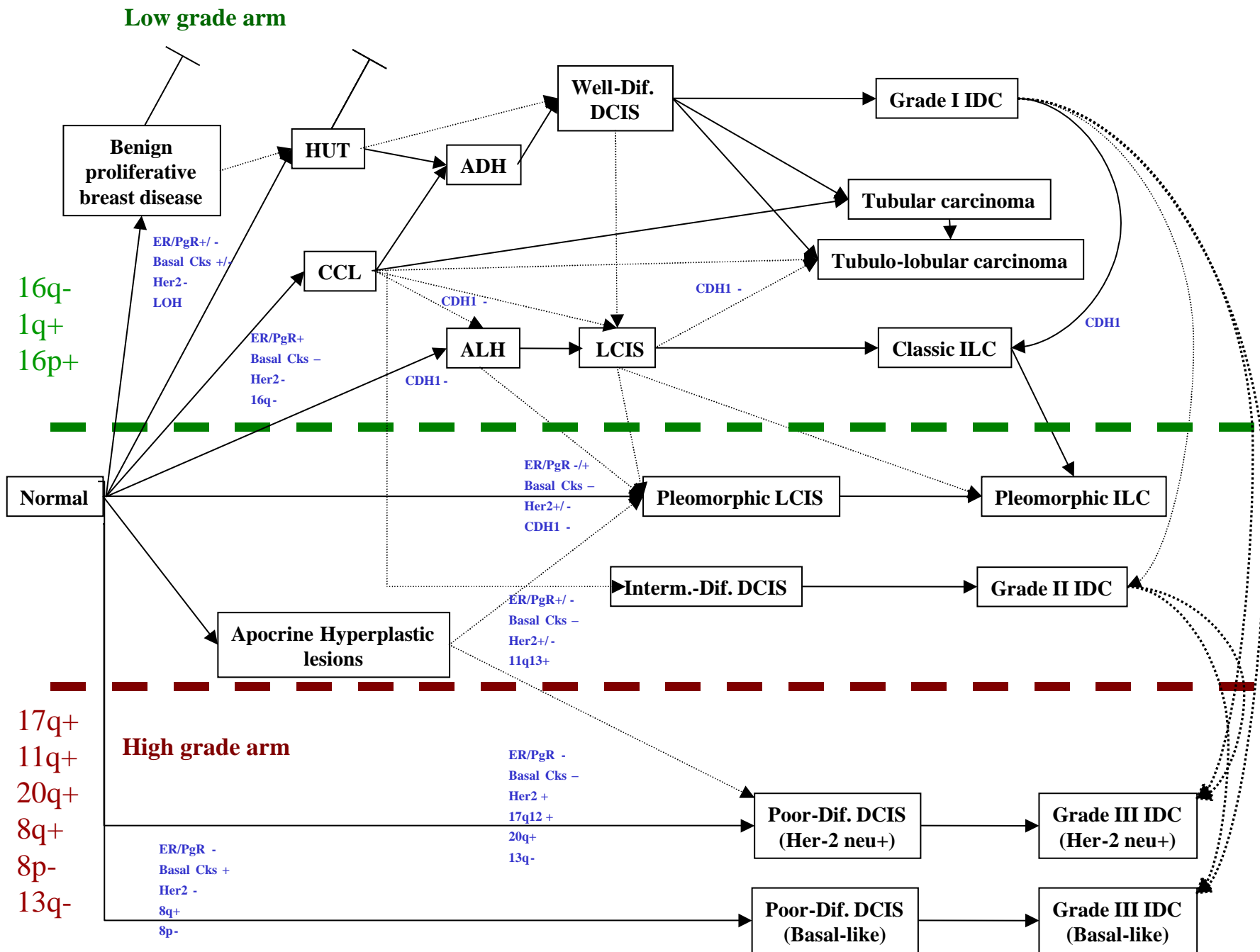
Mutation	16-ACC	16-CC	16-MC
<i>SPEN</i>	Dark Blue	Dark Blue	Dark Blue
K1790fs	Dark Blue	Dark Blue	Dark Blue
<i>FGFR2</i>	Light Blue	Dark Blue	Dark Blue
S252W	Light Blue	Dark Blue	Dark Blue
<i>KMT2D</i>	Light Blue	Dark Blue	Dark Blue
E731*	Light Blue	Dark Blue	Dark Blue
<i>PIK3CA</i>	Light Blue	Dark Blue	Dark Blue
E542K	Light Blue	Dark Blue	Dark Blue
<i>PGR</i>	Light Blue	Dark Blue	Dark Blue
Q787K	Light Blue	Dark Blue	Dark Blue
TP53	Light Blue	Dark Blue	Dark Blue
V157D	Light Blue	Dark Blue	Dark Blue
<i>CTNNB1</i>	Light Blue	Dark Blue	Dark Blue
N387K	Light Blue	Dark Blue	Dark Blue
<i>HRNR</i>	Light Blue	Dark Blue	Dark Blue
L2688F	Light Blue	Dark Blue	Dark Blue
<i>NEB</i>	Light Blue	Dark Blue	Dark Blue
P7768L	Light Blue	Dark Blue	Dark Blue
<i>ERBB3</i>	Light Blue	Dark Blue	Dark Blue
M60R	Light Blue	Dark Blue	Dark Blue
<i>CTNNB1</i>	Light Blue	Dark Blue	Dark Blue
K335T	Light Blue	Dark Blue	Dark Blue





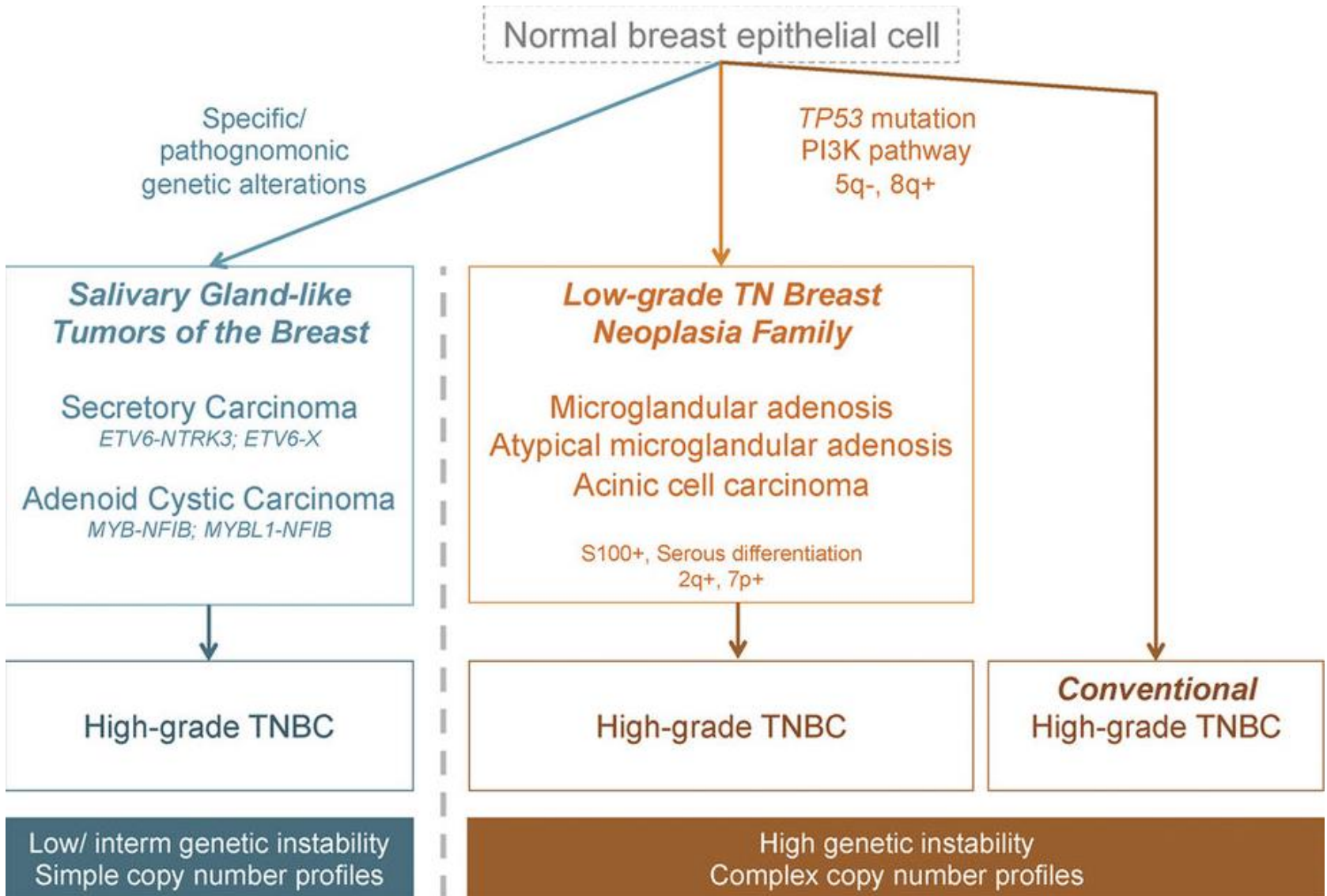
# Classic and clear cell ACC and metaplastic breast cancer: parallel progression and convergent phenotypes

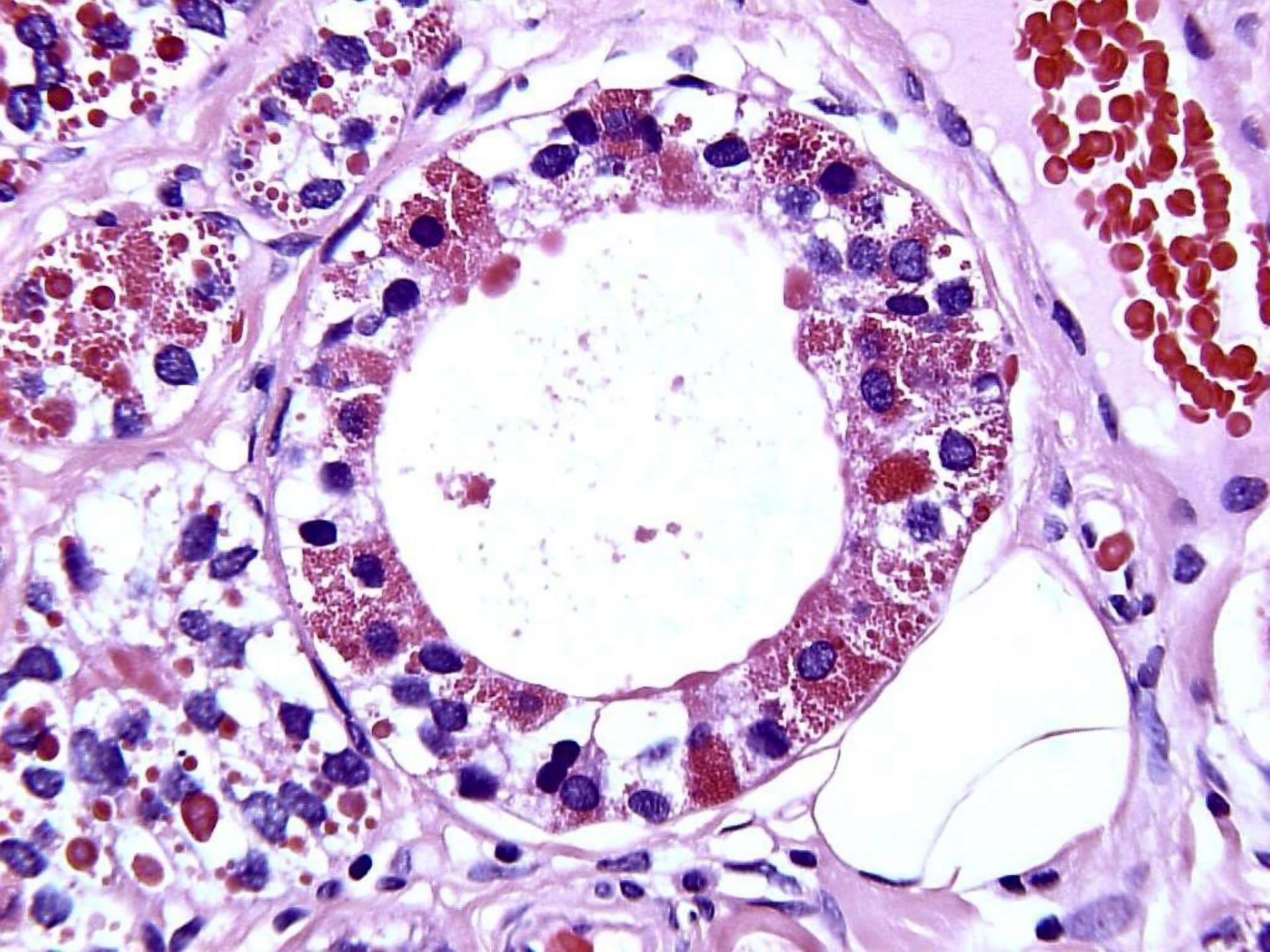


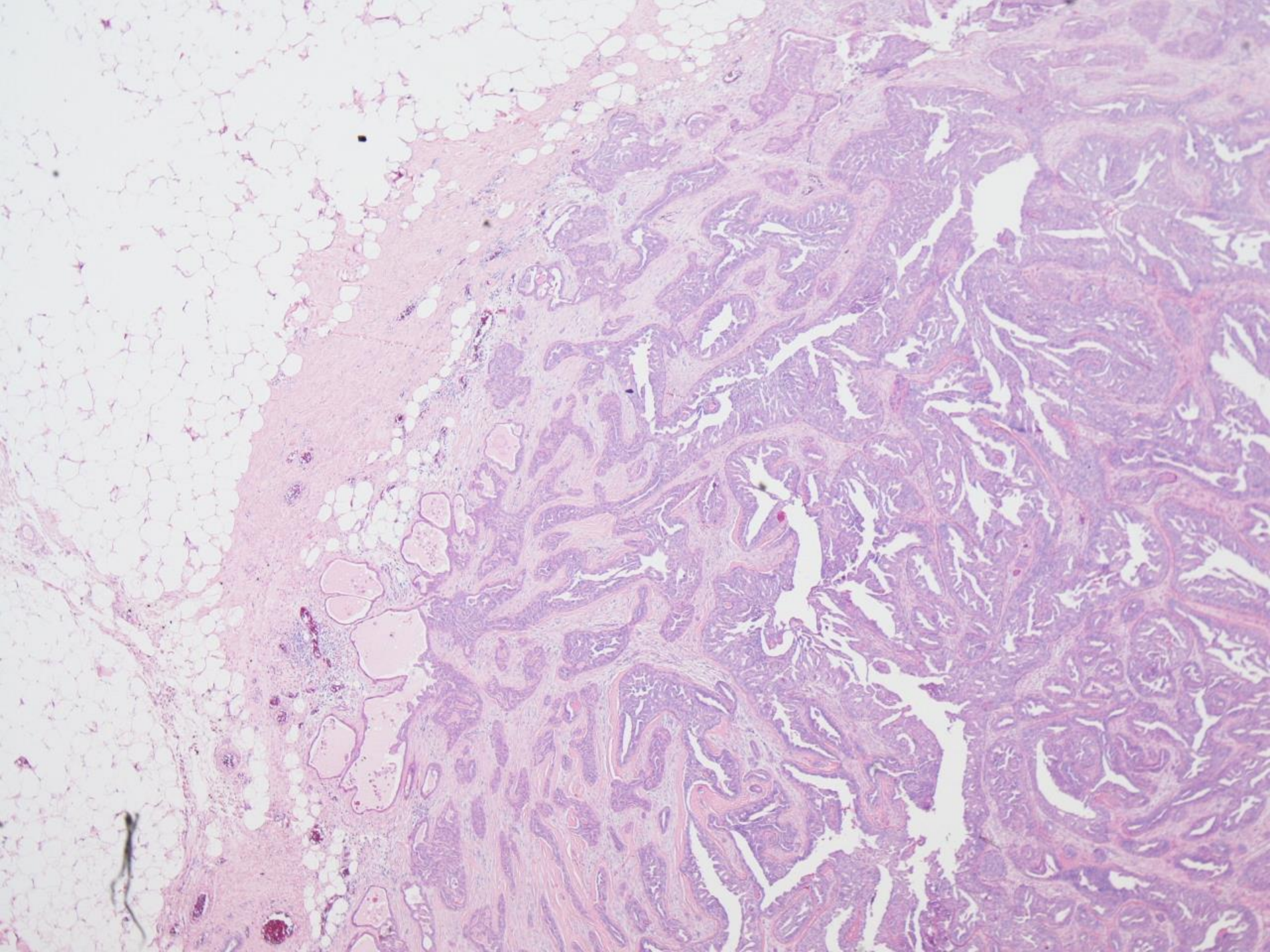


Simpson P, Reis-Filho JS, Gale T et al. J Pathol. 2005 Jan;205(2):248-54.

# Triple Negative Breast Cancer







Seminars in Diagnostic Pathology (2010) 27, 5-12



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Pathology**

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# **Epitheliosis, infiltrating epitheliosis, and radial scar**

**Vincenzo Eusebi, MD, FRCPath, Rosemary R. Millis, MB, BS, FRCPath, DSc(Med)**

*From the Department of Pathology "M. Malpighi," Bellaria Hospital, University of Bologna, Bologna, Italy.*

**WHO 2003**

**Epitheliosis synonym of  
Usual Ductal Hyperplasia**

# Epitheliosis & DCIS g1 cribriform

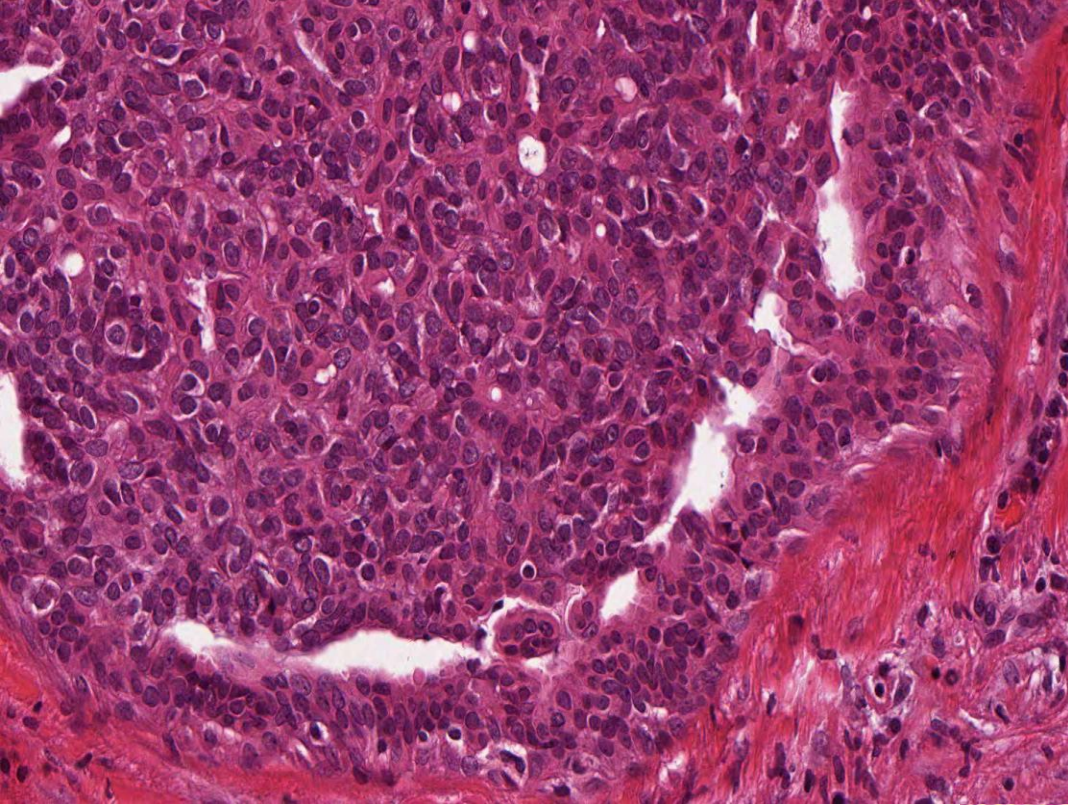
## UDH (Epitheliosis)

- Irregular spaces
- Spaces at periphery
- Cells overlapping
- Cells different sizes & shapes
- Nuclei different sizes & shapes

## Low Grade DCIS

- Regular spaces
- No zoning of spaces
- Evenly spaced
- Cells one type
- Monotonous nuclei

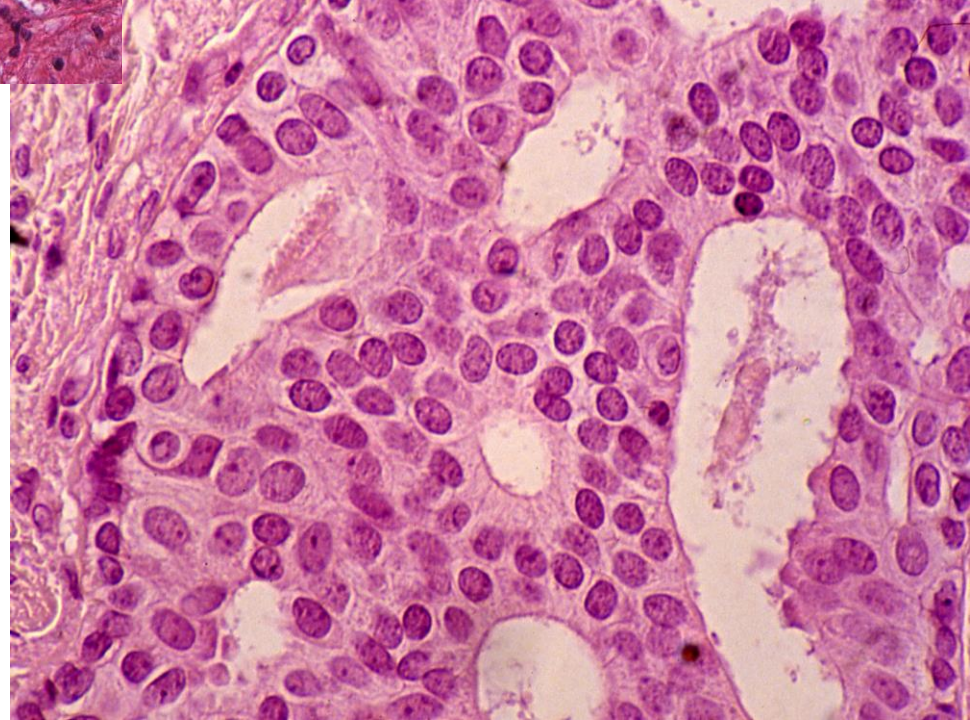




## UDH (Epitheliosis)

Peripheral spaces  
cells overlapping

**DCIS low Grade**



# IHC Profiles

## UDH (Epitheliosis) v LG DCIS

### UDH (Epitheliosis)

- Keratins 5/6 & 14 & 17
- P63 positive
- ER & PR generally negative
- Actin may be diffuse
- EMA generally negative

### LG DCIS

- Only low weight keratins
- P63 periphery
- ER & PR positive
- Actin at basal layer
- EMA positive

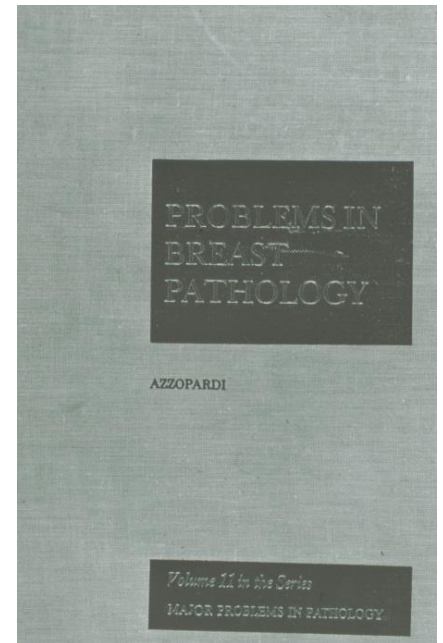
# Azzopardi, J.G. “Problems in breast Pathology” (1979, page 176)

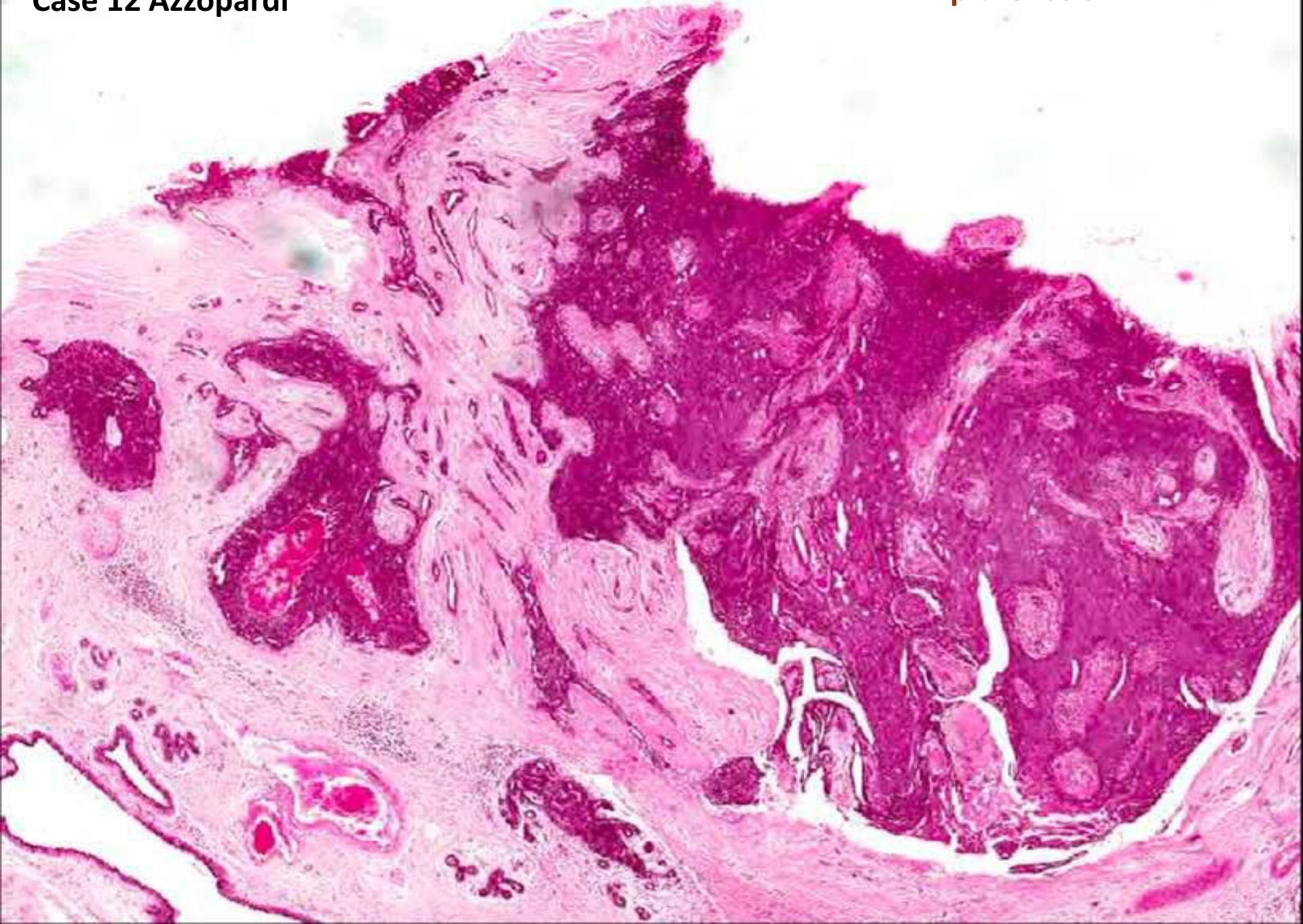
## Infiltrating Epitheliosis

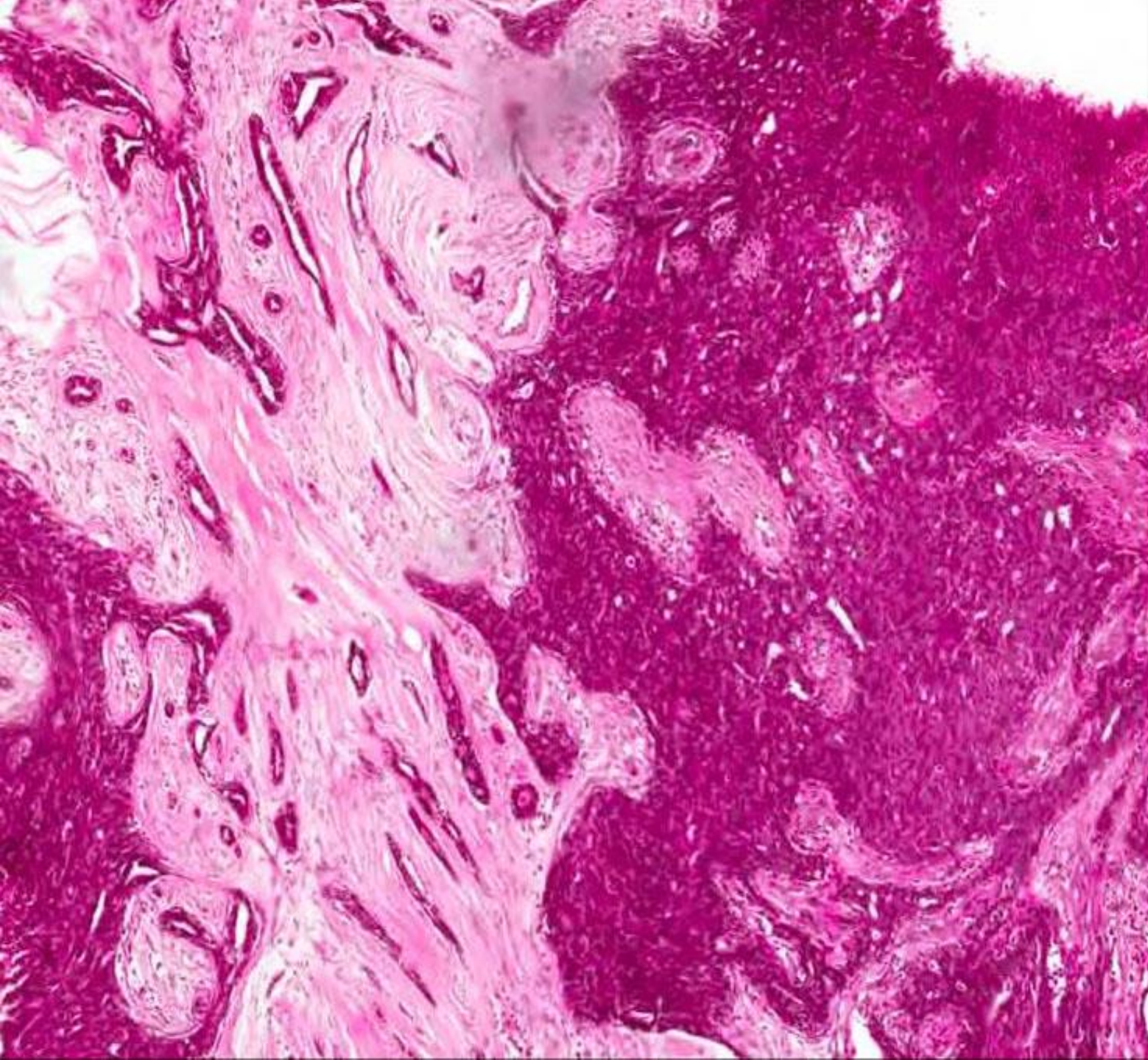
1- Foci of classical epitheliosis

2- Foci of epitheliosis with irregular , triangular or pointed edges.

3- The proliferating epithelium appears to “flow out” into the adjacent stroma.







**Case 12  
Azzopardi**

**Epitheliosis  
with  
irregular  
triangular  
pointed  
edges**

**Epithelium  
flows  
out into  
the adjacent  
stroma**

# **Azzopardi, J.G. “Problems in breast Pathology” (1979, page 182)**

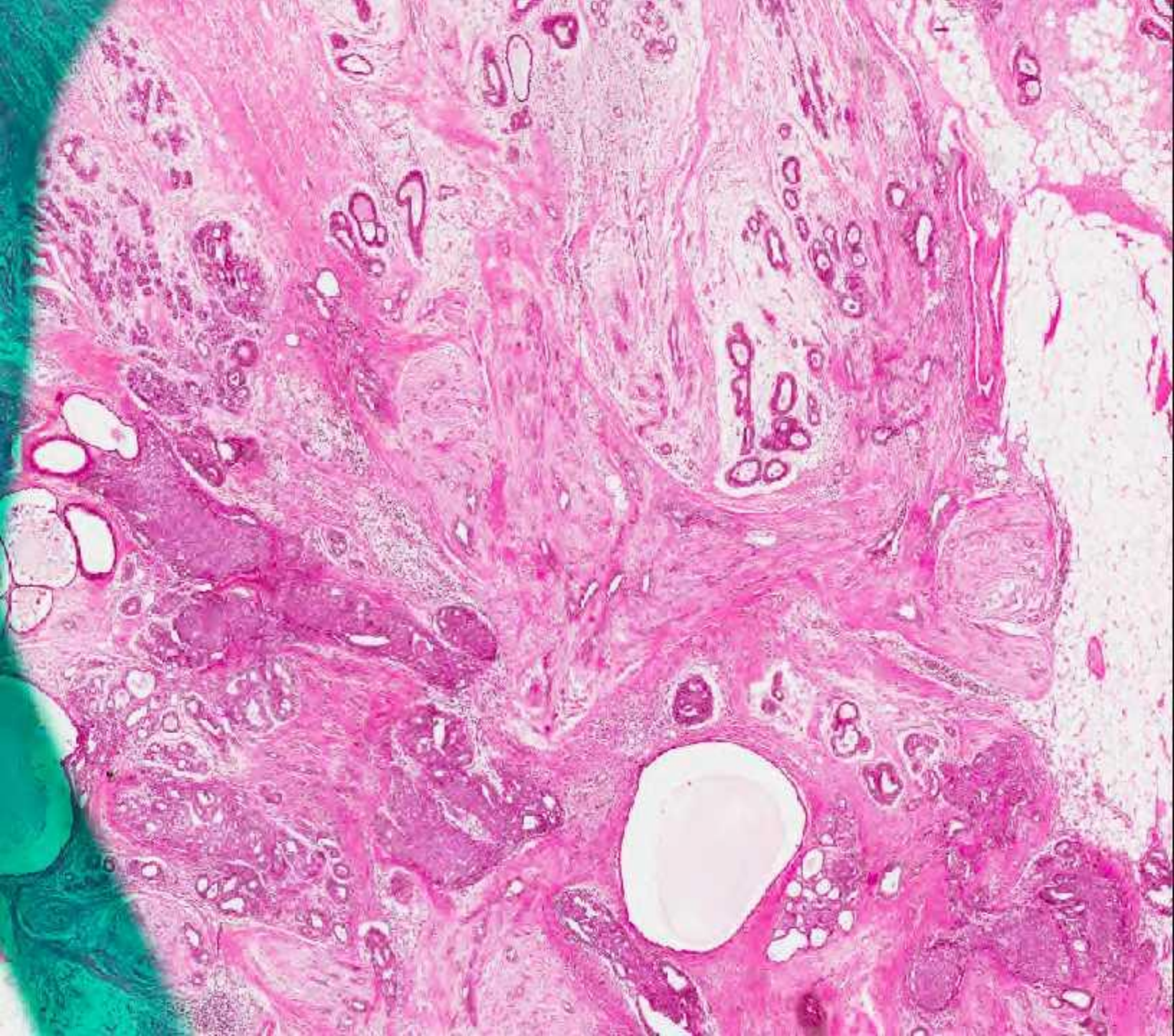
## **Infiltrating Epitheliosis**

### **Stroma**

- 1- Reactive fibroblastic proliferation with loose myxoid stroma.
- 2- Dense sclerotic and hyaline collagenous tissue ...not unlike the appearances seen in a keloid.
- 3- Irregular elastosis

**Azzopardi  
Case 27**

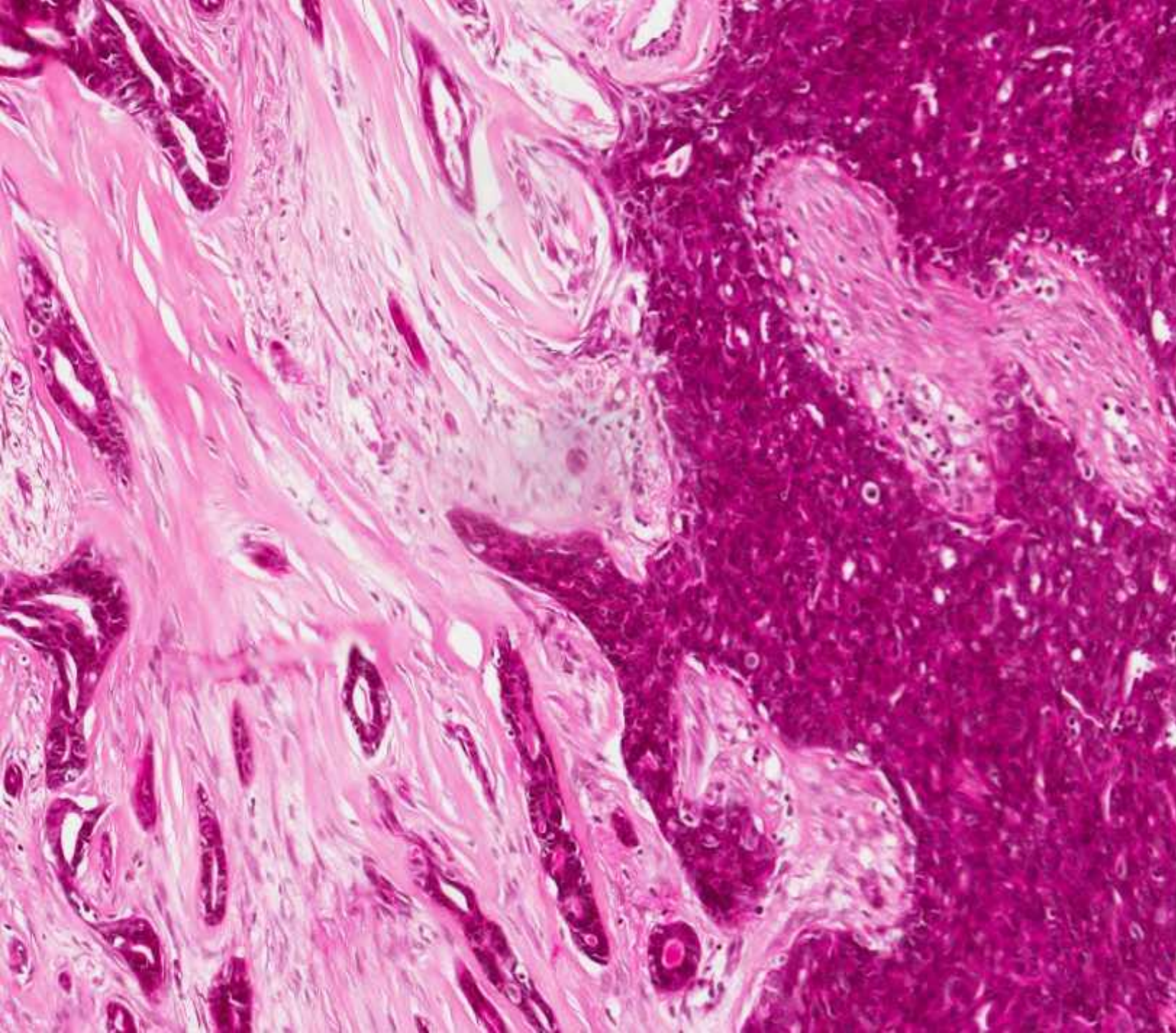
**Loose  
myxoid  
stroma**



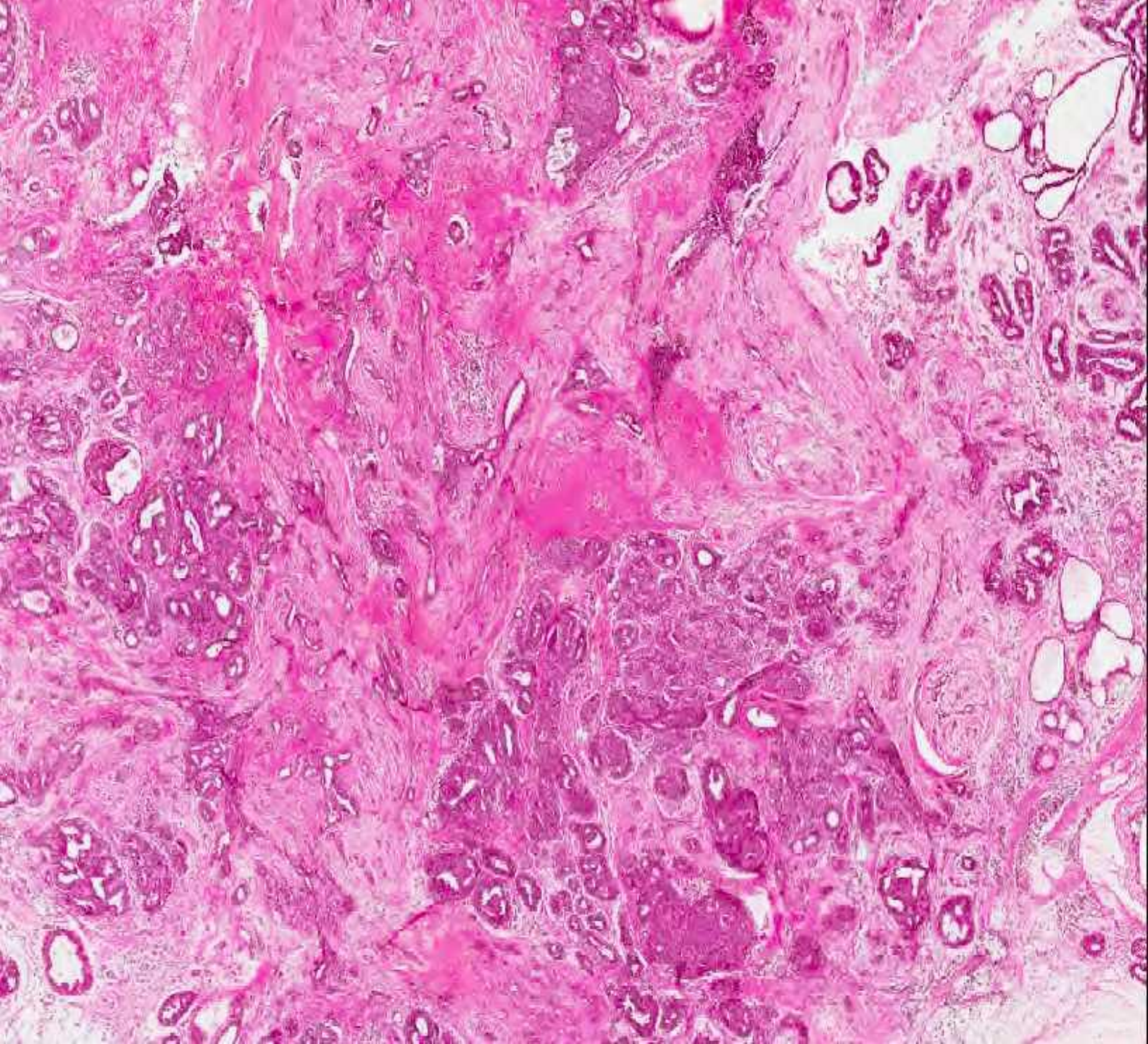
**Azzopardi  
Case 12**

**Keloid-  
like  
fibers**

**CD 34-**



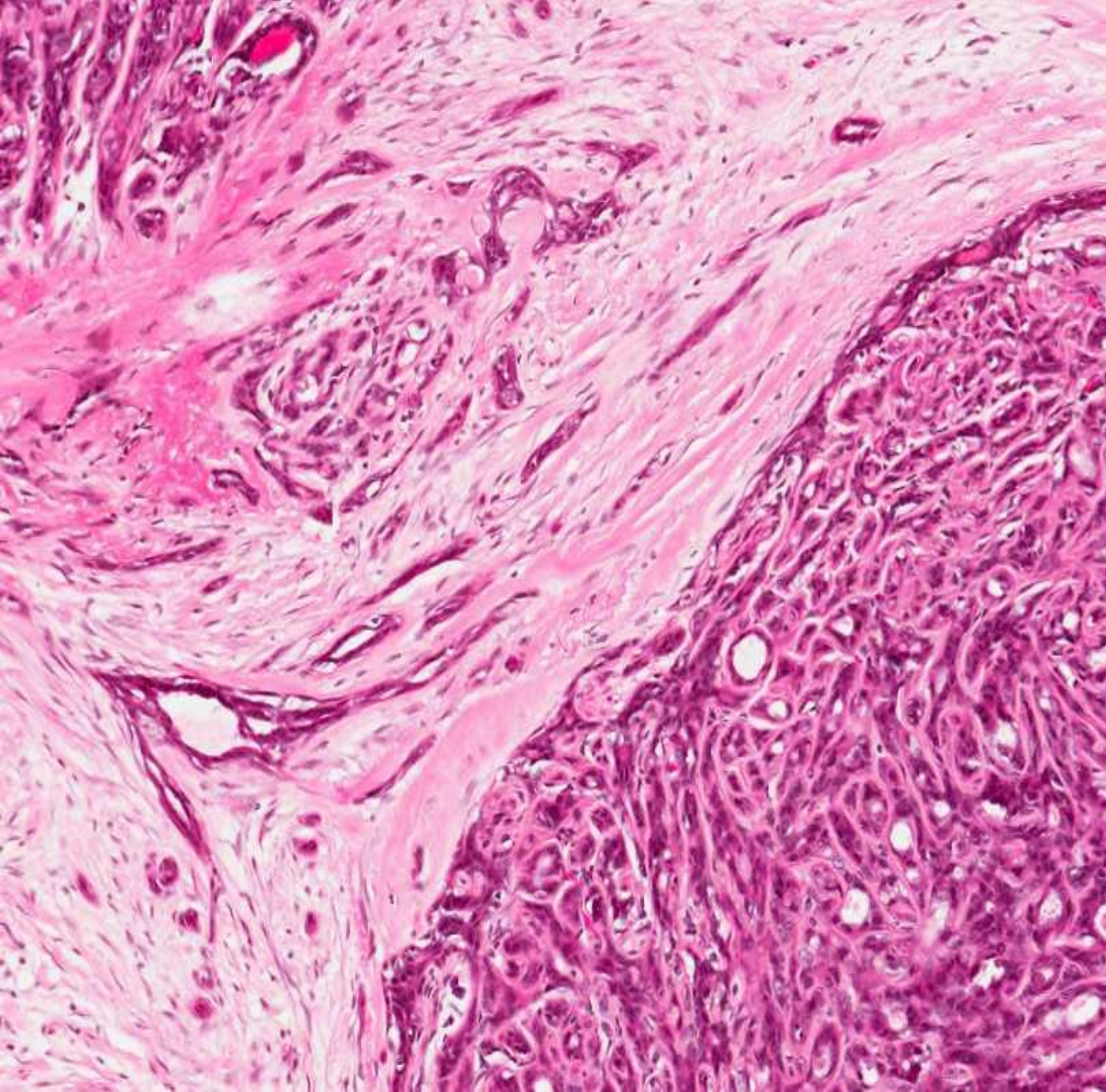




**Azzopardi  
Case 28**

**Irregular  
Elastosis**

**CD 34-**



**Azzopardi Case  
10**

**Tubular adenoma**

**Infiltrating  
epitheliosis**

**Keloid like fibers**

**CD 34 -**

Azzopardi, J.G. “Problems in breast Pathology” (1979, page 187)

... these lesions represent two pathogenetically distinct entities; one with infiltrating epitheliosis as the primary lesion with secondary stromal alterations  
the other with a primary scleroelastotic scar based on obliterative duct disease.

Seminars in Diagnostic Pathology (2010) 27, 5-12



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Pathology**

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# **Epitheliosis, infiltrating epitheliosis, and radial scar**

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*From the Department of Pathology "M. Malpighi," Bellaria Hospital, University of Bologna, Bologna, Italy.*

**SCLEROELASTOTIC LESION A BENIGN  
(INVOLUTIVE) LESION**

**INFILTRATIVE EPITHELIOSIS POSSIBLE  
PRECURSOR OF LAGSC**

**Denley H, Pinder SE, Tan PH, Sim CS, Brown R,  
Barker T, Gearty J, Elston CW, Ellis IO**

Metaplastic carcinoma of the breast arising  
within complex sclerosing lesion: a report of  
five cases.

Histopathology 36: 203-209, 2000.

**The Journal of Pathology: Clinical Research**

*J Path: Clin Res* April 2017; **3**: 115–122

Published online 28 February 2017 in Wiley Online Library

(wileyonlinelibrary.com). DOI: 10.1002/cjp.2.68

**Original Article**

# Next generation sequencing of the nidus of early (adenosquamous proliferation rich) radial sclerosing lesions of the breast reveals evidence for a neoplastic precursor lesion

Mark J Wilsher,<sup>1\*</sup> Thomas W Owens<sup>2</sup> and Richard JN Allcock<sup>3,4</sup>

<sup>1</sup> *Douglass Harly Moir Pathology, Macquarie Park, New South Wales 2113, Australia*

<sup>2</sup> *Discipline of Physiology, School of Medical Sciences & Bosch Institute, The University of Sydney, Camperdown, New South Wales, Australia*

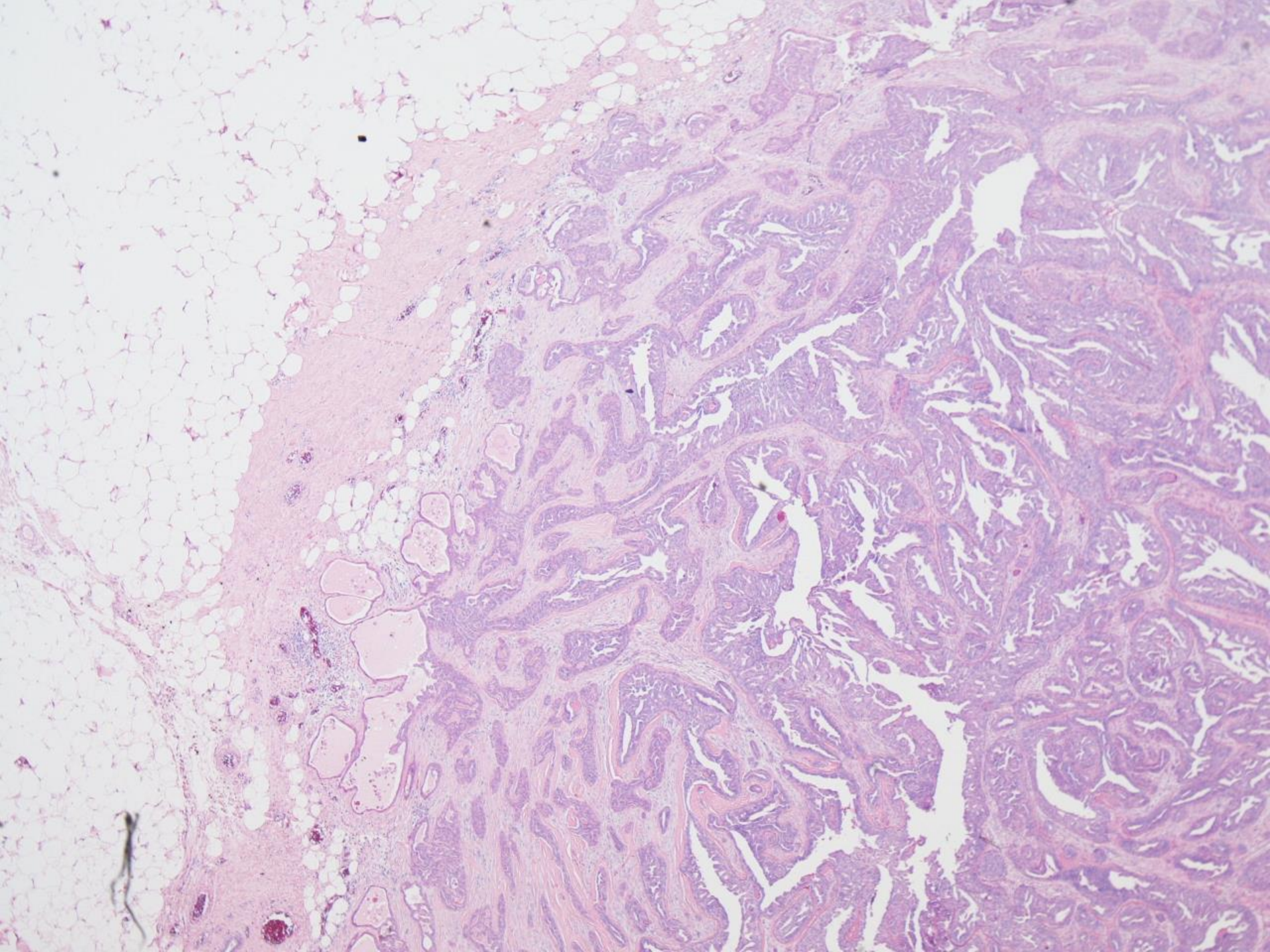
<sup>3</sup> *School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia 6009, Australia*

<sup>4</sup> *Pathwest Laboratory Medicine WA, QEII Medical Centre, Nedlands, Western Australia 6009, Australia*

## PIK3CA mutation









# Breast Lesions of Uncertain Malignant Potential

Lesions with uncertain malignant nature with show some features characteristic of malignancy such as infiltrative margins and absence of peripheral myoepithelial cells, but lack other features such as cytonuclear atypia, lymphovascular invasion or evidence of metastasis.

- Microglandular Adenosis and Atypical MA
- Infiltrative Epitheliosis
- Skin adnexa-like and salivary gland-like tumours
  - non-cutaneous mammary pleomorphic adenoma and cylindroma

# Skin Adnexal Tumours

- Show to your dermatopathology friend
- If they recognize the entity as a specific form of skin adnexal tumour ask them to report it
- If they don't then share with your breast pathology friends and come to a consensus diagnosis

# Mammary Pleomorphic Adenoma

## Key Features:

- Rare
- Frequently occurs in the retroareolar region.
- Circumscribed

Characterised by a mixture of cells featuring epithelial and myoepithelial phenotypes embedded in an abundant stroma with myxoid, chondroid, or osseous metaplasia.

## D.D.

matrix-producing metaplastic carcinoma, adenomyoepithelioma and papilloma with cartilaginous metaplasia.

# Mammary Pleomorphic Adenoma

## Behaviour:

Reported indolent clinical behaviour of breast supports their benign nature

## However:

- Local recurrences of breast PA have been reported
- Cytologically malignant features characteristic of conventional mammary-type carcinomas have been demonstrated and categorised as “carcinoma ex pleomorphic adenoma”
- Lymphovascular invasion and distant metastasis have been reported in histologically benign salivary gland PA
- Absence of peripheral myoepithelial cells is a feature

# Mammary Pleomorphic Adenoma

## Nature:

? the lack of cytological atypia, mitotic activity and focal preservation of peripheral myoepithelial cells may represent features of indolence as seen in other low-grade malignant tumours akin to low-grade adenoid cystic carcinoma and low-grade matrix-producing MBC, rather than features defining benign biological nature of a breast tumour

# Mammary Pleomorphic Adenoma

## **Nature:**

? the lack of cytological atypia, mitotic activity and focal preservation of peripheral myoepithelial cells may represent features of indolence as seen in other low-grade malignant tumours akin to low-grade adenoid cystic carcinoma and low-grade matrix-producing MBC, rather than features defining benign biological nature of a breast tumour

Histological features that favour PA over matrix producing metaplastic carcinoma include small size, underlying benign papillary structure, absence of significant cytonuclear atypia, scant myxoid stroma and presence of bone.

# Mammary Pleomorphic Adenoma

## Nature:

Breast PA is often associated with a papillary lesion or ductal adenoma similar to other low-grade metaplastic carcinomas and adenomyoepithelioma.

These tumours may represent a form of low-grade indolent breast tumour that resides at the lower end of a spectrum of matrix-producing metaplastic carcinoma featuring prominent stromal metaplastic differentiation and low-grade cytological features.



# Mammary Pleomorphic Adenoma

## Pitfalls:

The diagnosis of breast PA can be difficult on core biopsy.

Cases have been reported breast as matrix-producing metaplastic carcinoma on preoperative core biopsy that was followed by a benign diagnosis following surgical excision. To avoid such inconsistency and in view of the above as well as the lack of molecular evidence to help characterise these lesions as benign or malignant, we propose to consider them as lesions of uncertain malignant potential.

# Mammary Cylindroma

## Background

Low grade adenoid cystic carcinomas of the breast is considered as malignant tumour akin to their salivary gland counterpart,

However a tumour showing prominent cylindromatous differentiation in the breast is considered as a benign tumour.

# Mammary Cylindroma

## Background

Historically breast adenoid cystic carcinomas exhibiting prominent basaloid features and producing a characteristic cylindromatous pattern have been recognized in the breast and the terms adenoid cystic carcinoma and cylindroma have been used interchangeably.

More recent publications considered that such lesions were similar to the benign skin counterpart, hence the use of the term '**dermal analogue tumour**'

# Mammary Cylindroma

## Background

Areas of normal lactiferous duct can be observed transitioning into cylindroma which has been postulated to imply a site of origin of the tumour from within the breast.

‘pseudo-infiltration’ of the surrounding tissue has been reported

# Mammary Cylindroma

## Issues

Basaloid, solid variants of adenoid cystic carcinoma of the breast can mimic breast cylindroma including nodular and trabecular growth patterns and the presence of basement membrane like material.

Both adenoid cystic carcinoma and breast cylindroma share the same immunoprofile with triple negative phenotype, p63 and strong c-kit expression.

? shared c-kit positivity may indicate origin from a shared common progenitor cell

# Skin Adnexal Tumours

## Practical advice:

- Show to your dermatopathology friend
- If they recognize the entity as a specific form of skin adnexal tumour ask them to report it
- If they don't then share with your breast pathology friends and come to a consensus diagnosis



The University of  
**Nottingham**



