Rare Breast Cancer Types
WHO 2019 position

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WHO 2019

Rare Breast and Salivary Cancers

- Acinic Cell
- Adenoid Cystic
- Secretory
- Mucoepidermoid
- Polymorphous adenocarcinoma
- Tall cell carcinoma with reversed polarity

Salivary gland like tumours of the breast

Benign

- Mixed tumour
- Adenomyoepithelioma
- Benign myoepithelioma

Malignant

- Acinic cell carcinoma
- Adenoid cystic carcinoma
- Low grade adenosquamous carcinoma
- Oncocytic carcinoma
- Mucoepidermoid carcinoma
- Malignant myoepithelioma

Low Grade TN BC

1. Salivary gland-like tumors of the breast

2. Low-grade TN breast neoplasia family

3. Rare additional subtypes of uncertain nature

Low Grade TN BC

1. Salivary gland-like tumors of the breast

- Adenoid cystic carcinoma (AdCC)
  - *MYB-NFIB fusion gene*
- Secretory
  - *ETV6-NTRK3* fusion-gene
- Vare rare subtypes:
  - Polymorphous carcinoma
  - Mucoepidermoid carcinoma
  - Adenomyoepithelioma

Low Grade TN BC

2. Low-grade TN breast neoplasia family

Microgladular adenosis (MGA)
Atypical MGA (AMGA) and
Acinic cell carcinoma (ACC)

Low Grade TN BC

3. Rare Additional Types of uncertain nature

- Low-grade variants of Metaplastic Breast Cancer, incl infiltrative epitheliosis

- Tall cell carcinoma with reversed polarity (Solid papillary carcinoma with reversed polarity (SPCRP)). *IDH2 p.Arg172 mutations*

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Rare Breast and Salivary Cancers

- Adenoid Cystic
- Secretory
- Mucoepidermoid
- Polymorphous adenocarcinoma
- Tall cell carcinoma with reversed polarity
- Acinic Cell

WHO 2019

Adenoid cystic carcinoma

- Adenoid cystic carcinoma (AdCC) is an invasive carcinoma composed of epithelial and myoepithelial neoplastic cells arranged in tubular, cribriform, and solid patterns associated with basophilic matrix and reduplicated basement membrane material
- Frequently associated with MYB-NFIB fusion (similar to salivary counterpart)

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Adenoid cystic carcinoma

Three subtypes have been defined, on the basis of architectural and cytological features:

- Classic AdCC
- Solid-basaloid AdCC (SB-AdCC)
- AdCC with high-grade transformation

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Adenoid cystic carcinoma

Classic AdCC:

- At low magnification, this subtype shows a central cribriform area surrounded by a peripheral area with predominant tubular architecture.
- Both areas show the same cellular composition, namely epithelial and myoepithelial cells.
- The glandular spaces in both areas are lined by epithelial-type

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Adenoid cystic carcinoma

Solid Basaloid-AdCC:

- Classic features of AdCC with solid nests composed of basaloid cells, with marked nuclear atypia, high mitotic count, and necrosis.
- Perineural invasion is a frequent finding in this subtype.
- SB-AdCC should be differentiated from carcinomas with basaloid morphology and small cell neuroendocrine carcinoma

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Adenoid cystic carcinoma

- **AdCC with high-grade transformation:**
- Well delineated in the salivary glands v rare in breast
- AdCC showing multiple areas of differentiation, small cell carcinoma, invasive ductal carcinoma, and malignant adenomyoepithelioma described

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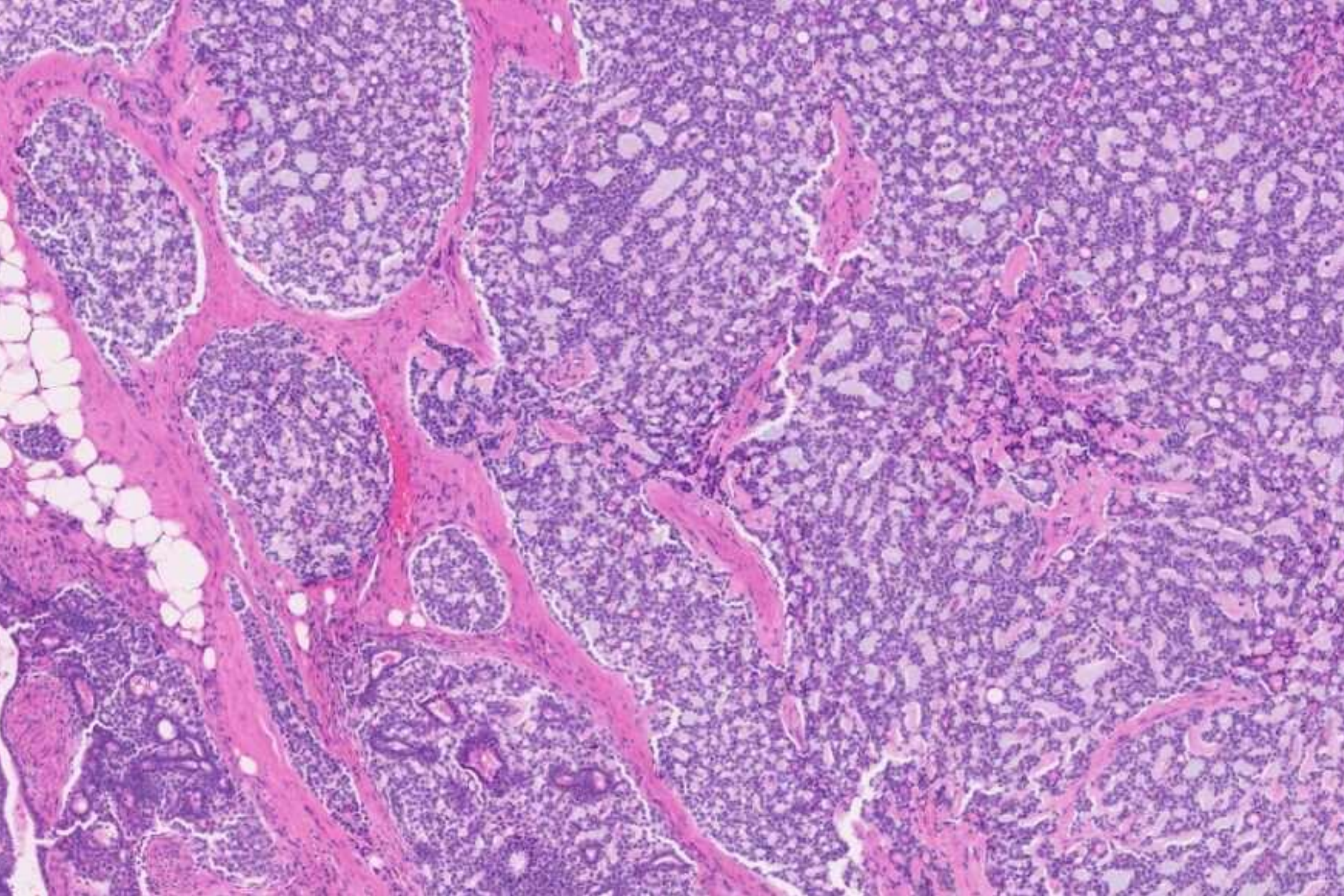
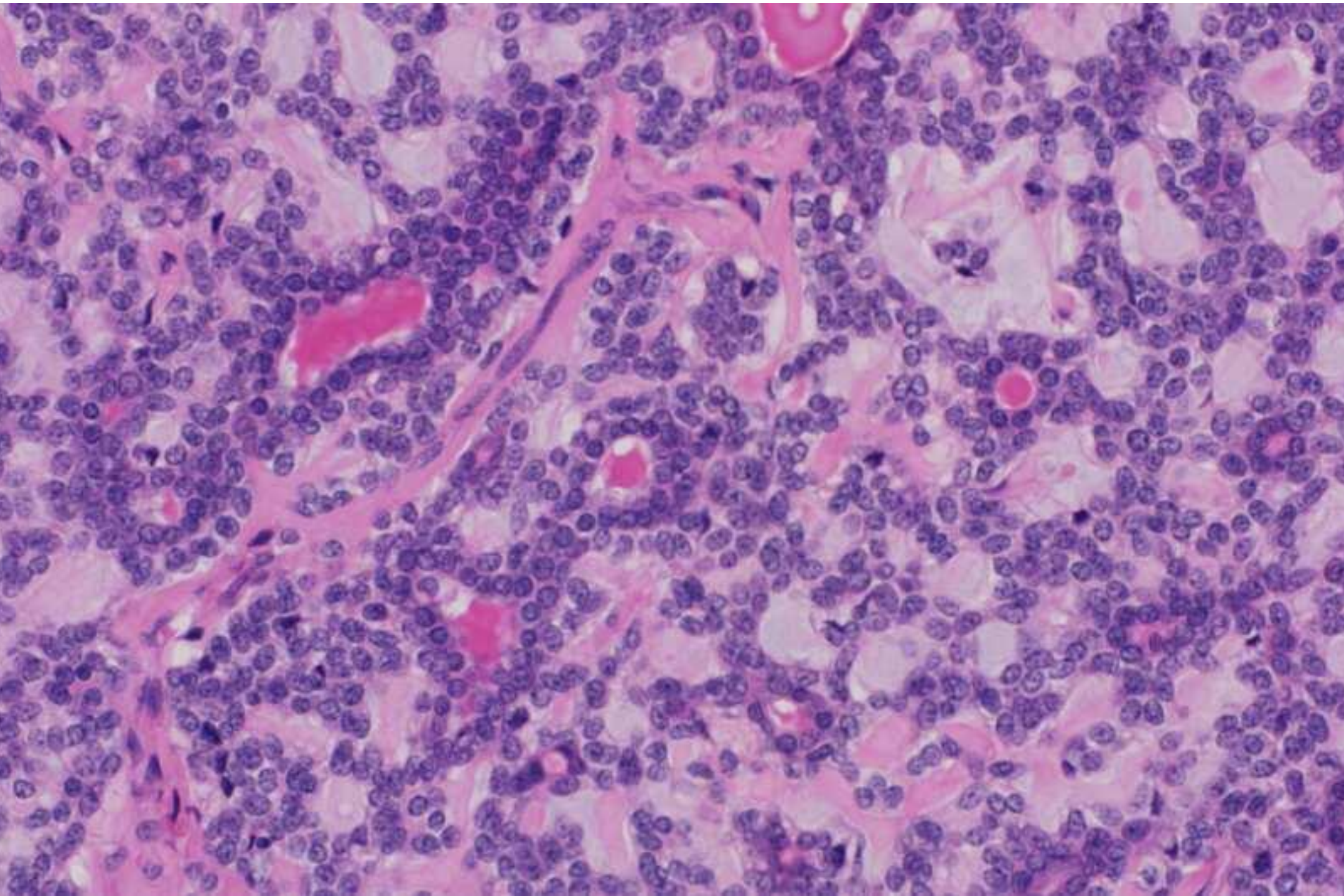
Adenoid cystic carcinoma

- **AdCC with high-grade transformation:**
- Case of AdCC described in association with an invasive ductal carcinoma, similar molecular alterations shared by the two components;
- mitochondrial DNA analysis demonstrated a clonal relationship between the two components
- Implys that AdCC neoplastic cells can acquire aggressive potential

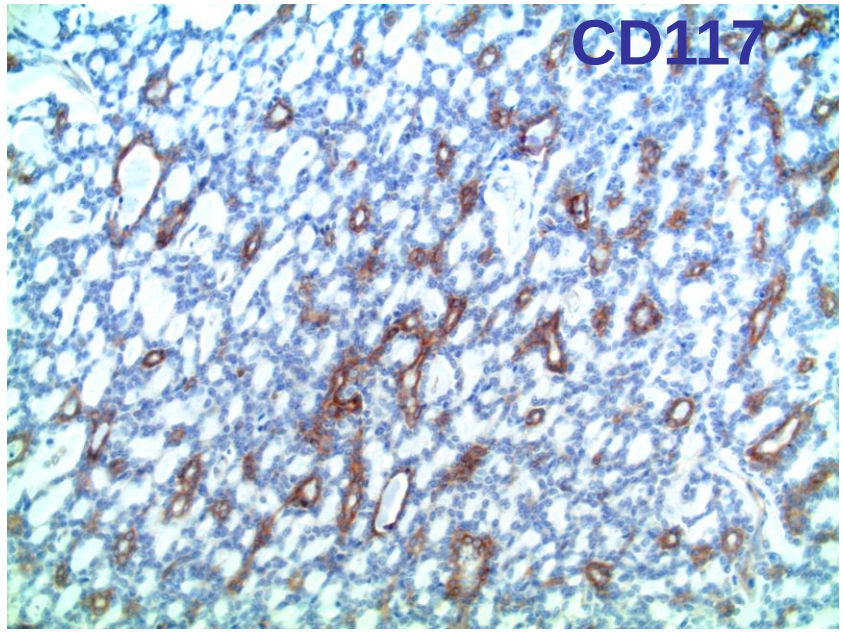
Adenoid cystic carcinoma

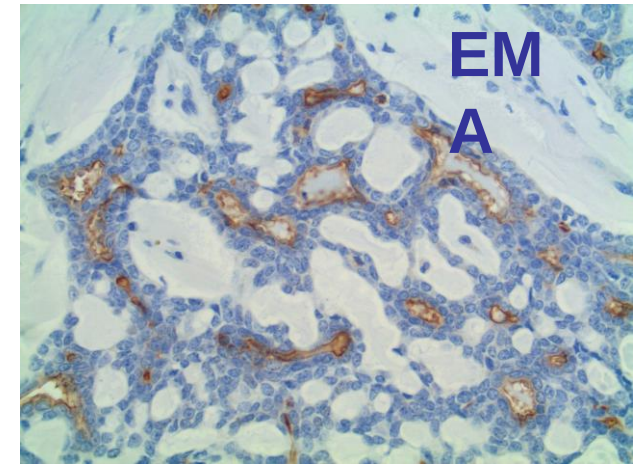
- 0.1 – 1% of breast cancers
- Wide age range
- Mass lesion, often periareolar, may be painful
- Well defined
- Excellent long term prognosis ->90-100% 10 year survival (cf salivary gland tumours)

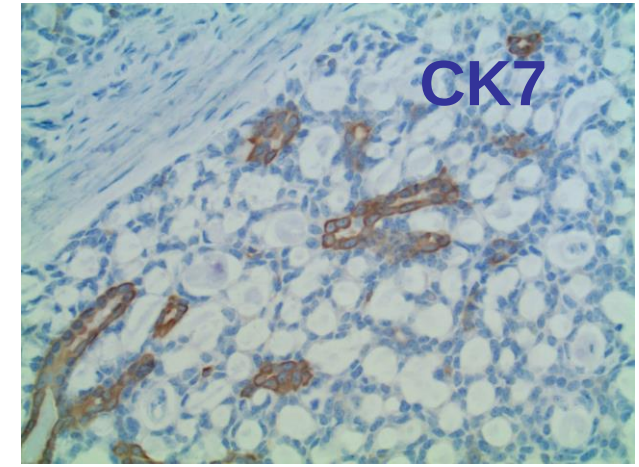




Epithelial cells

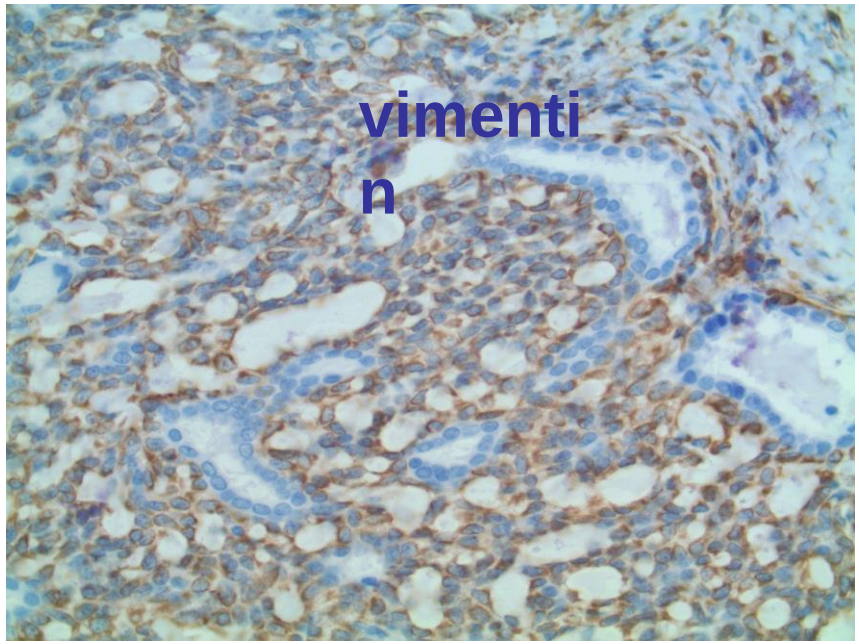


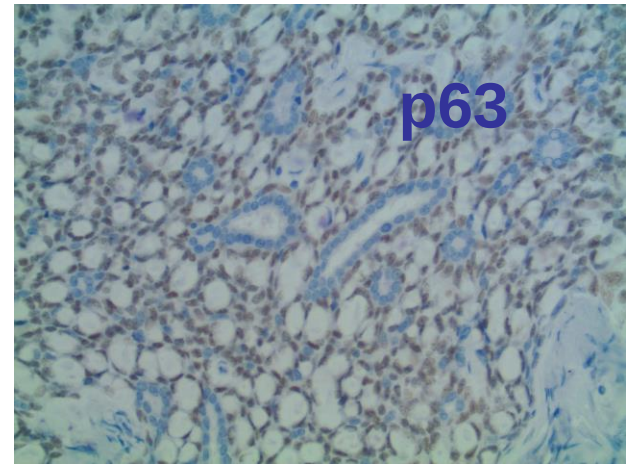


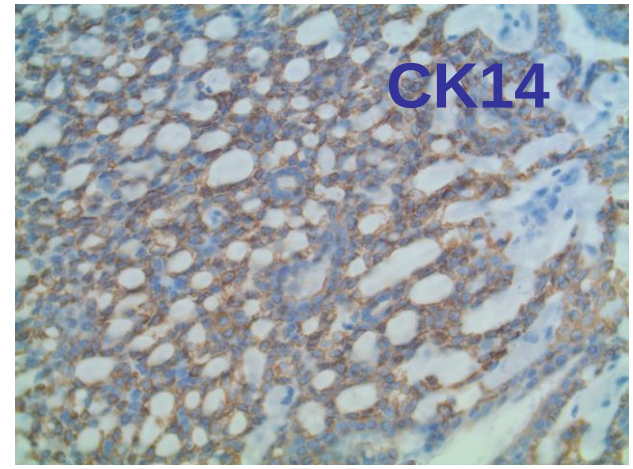


Basaloid cells

The University of Nottingham





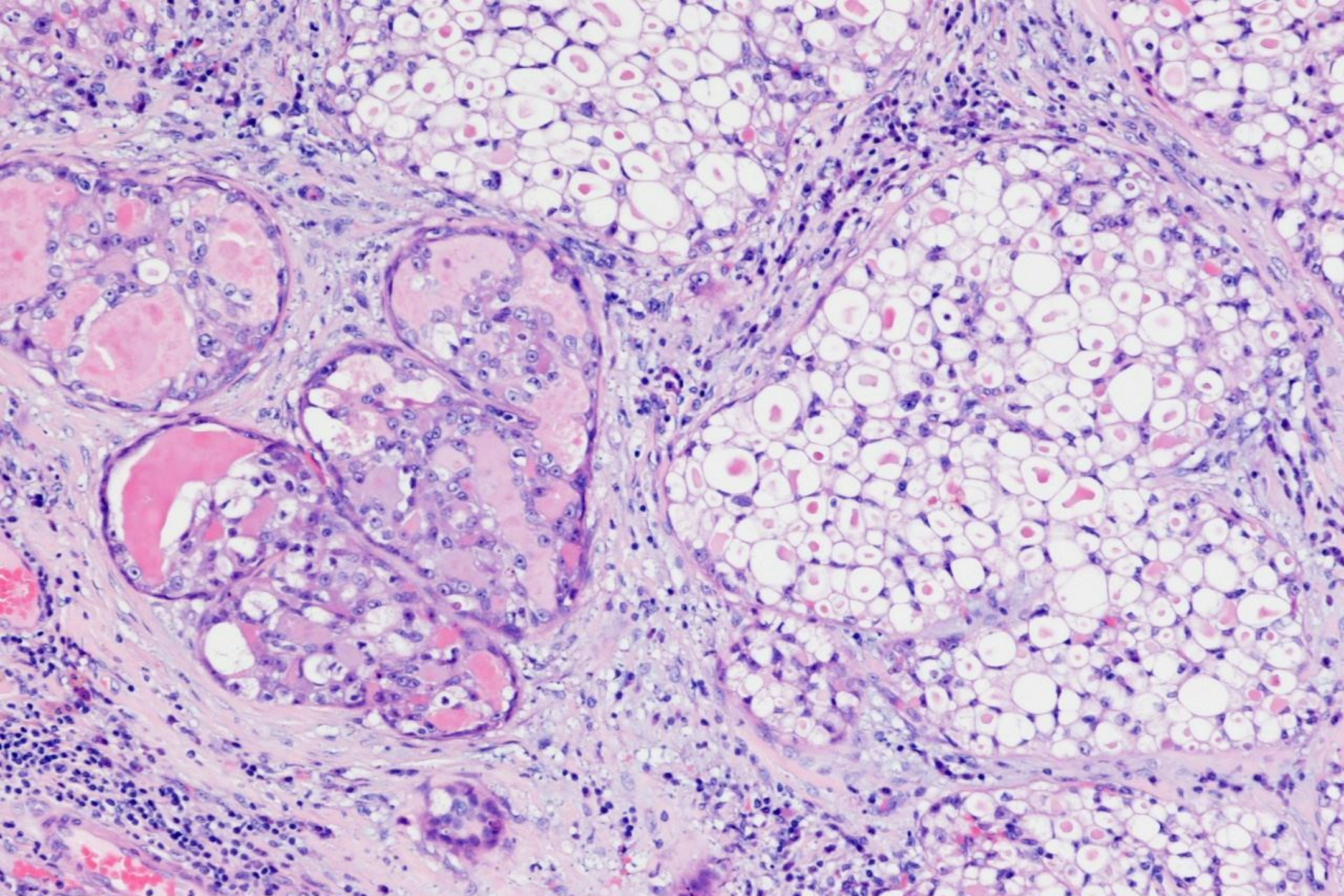


Adenoid cystic carcinoma

- Cribriform, solid, tubular, reticular, basaloid patterns
- Dual population: epithelial and basaloid cells
- Epithelial: CK7, CEA, EMA, CD117
- Basaloid: CK14, CD17, vimentin,S100, actin, calponin, p63
- May be associated with microglandular adenosis

Adenoid cystic carcinoma- molecular pathology

- Clusters with metaplastic and medullary carcinomas – triple negative
- Translocation t (6;9) (q22-23; p23-24) – similar to salivary and other adenoid cystic carcinomas



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Secretory carcinoma

- Secretory carcinoma is an invasive carcinoma composed of epithelial cells with intracytoplasmic secretory vacuoles and extracellular eosinophilic, bubbly secretions, arranged in a variable architecture
- frequently associated with ETV6-NTRK3 fusion.

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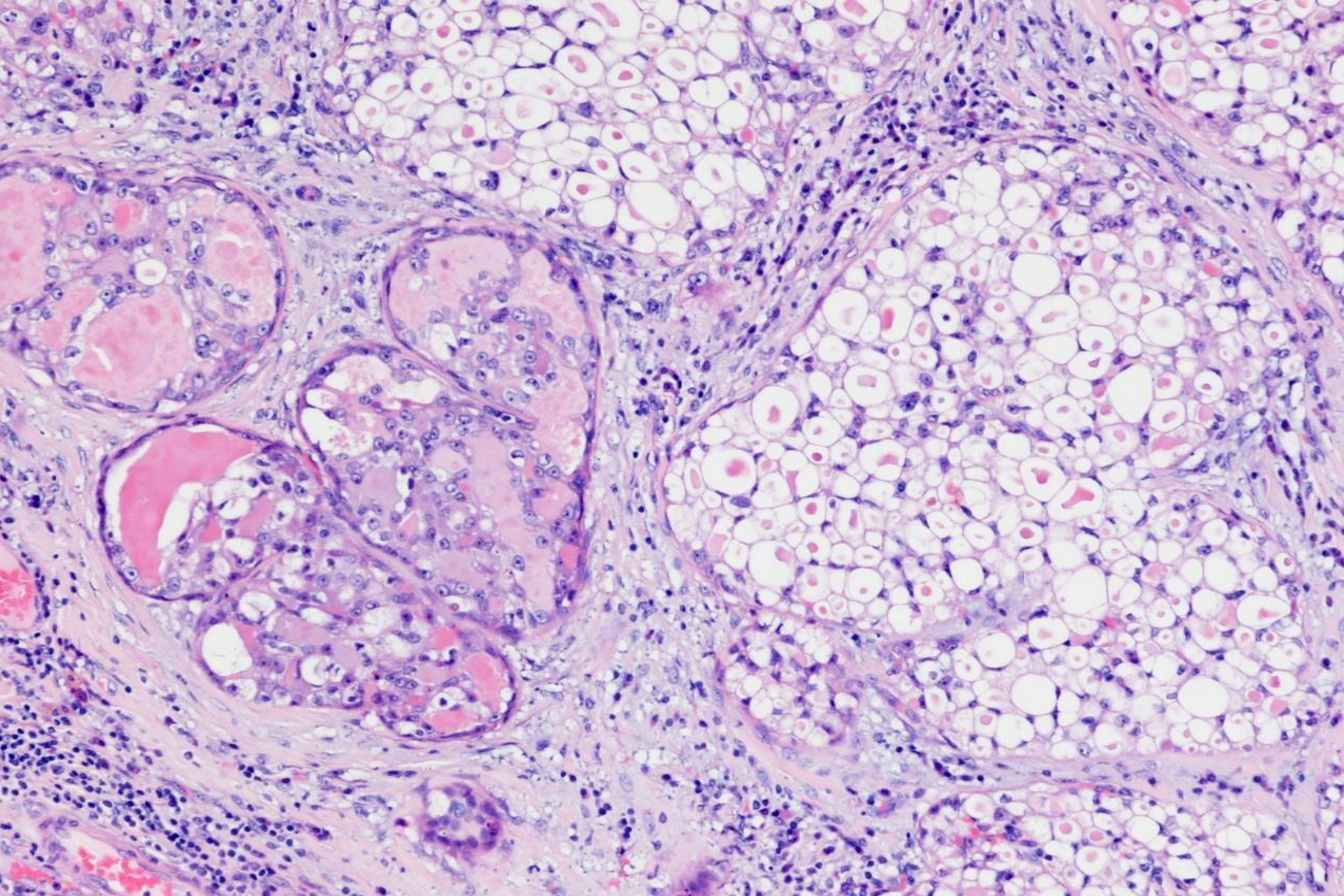
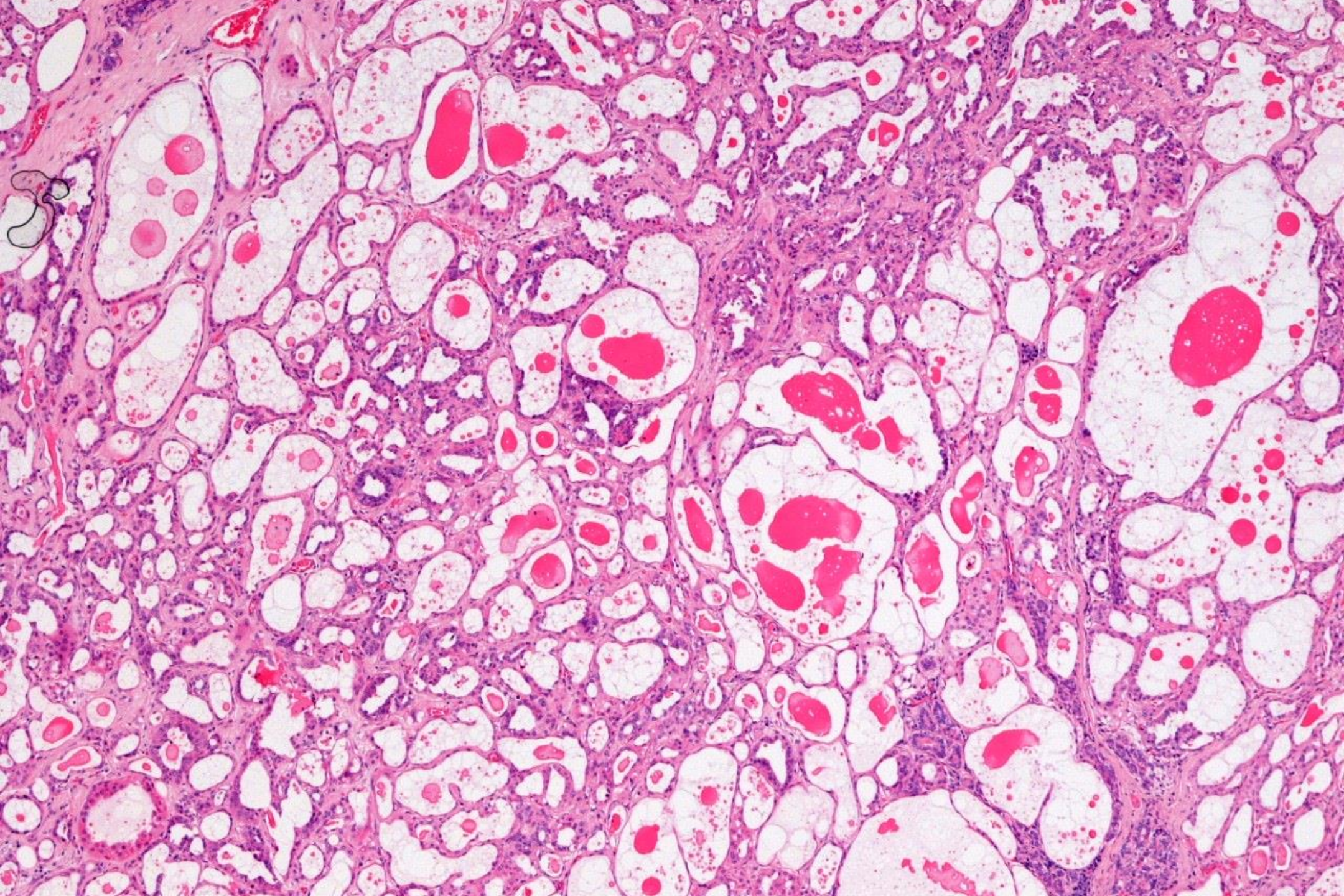
Secretory carcinoma

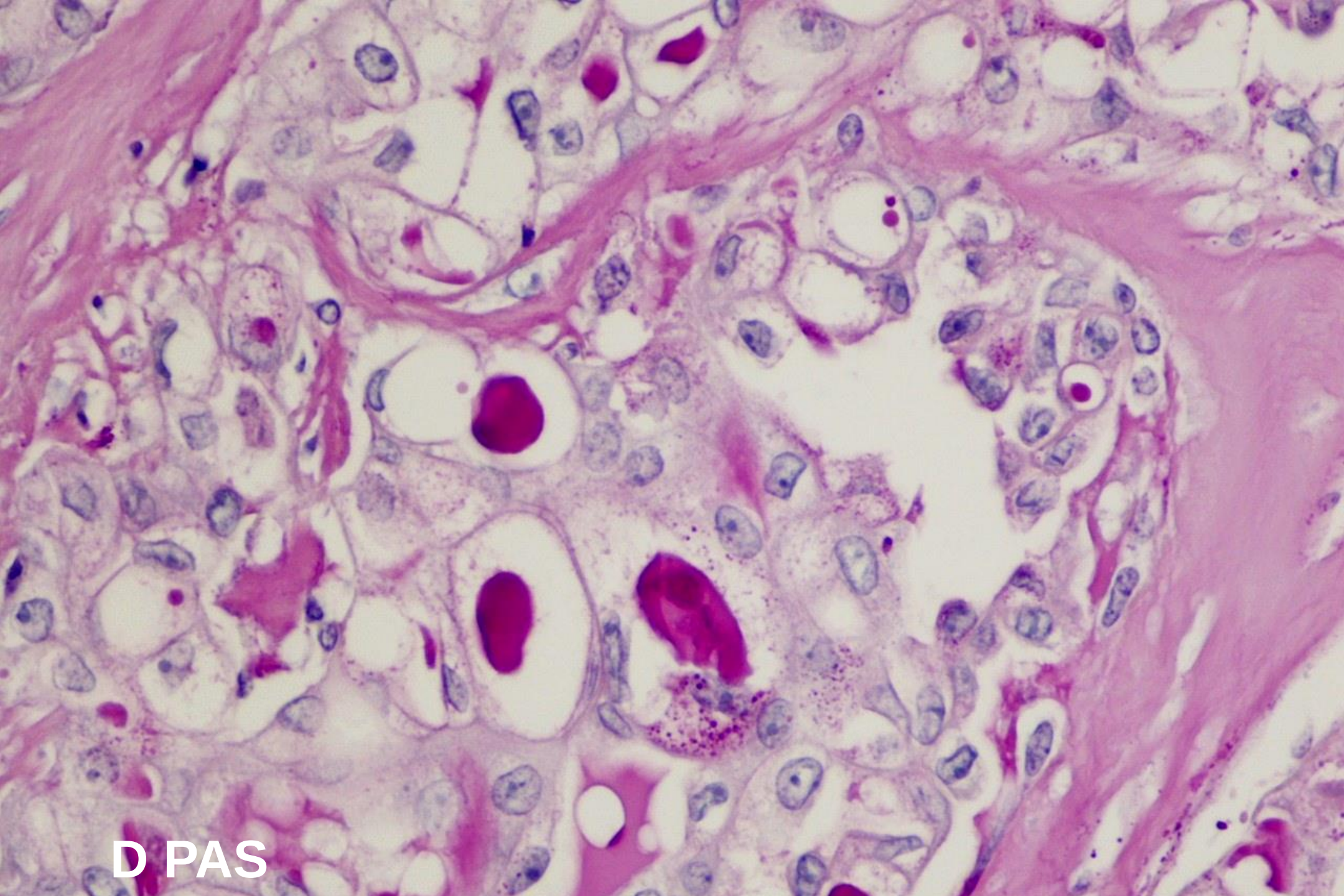
- ETV6-NTRK3 alteration in both invasive and in situ component i.e. an early event
- also identified in mammary analogue secretory carcinomas arising in other sites, such as the salivary glands, thyroid, and skin

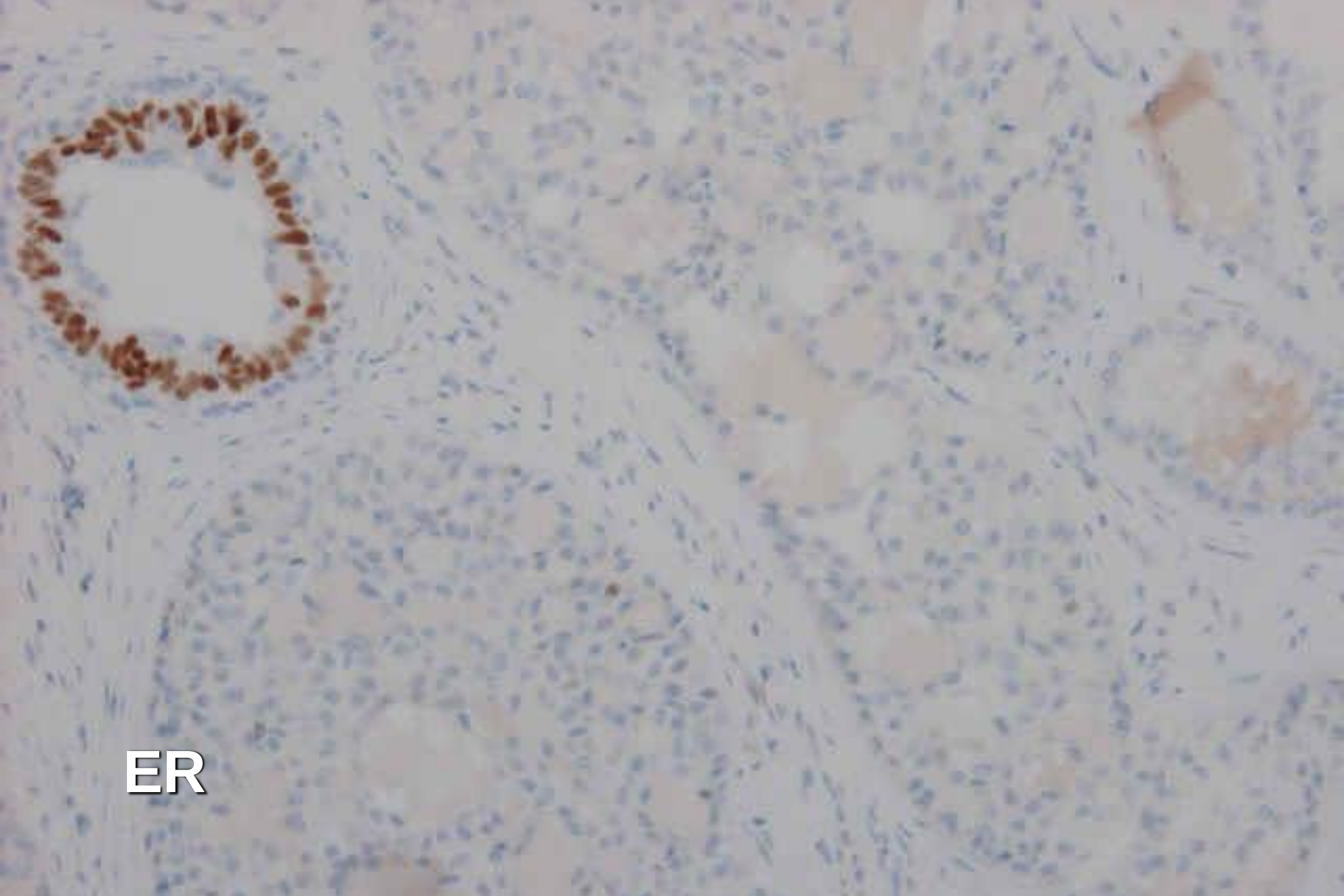
Secretory carcinoma

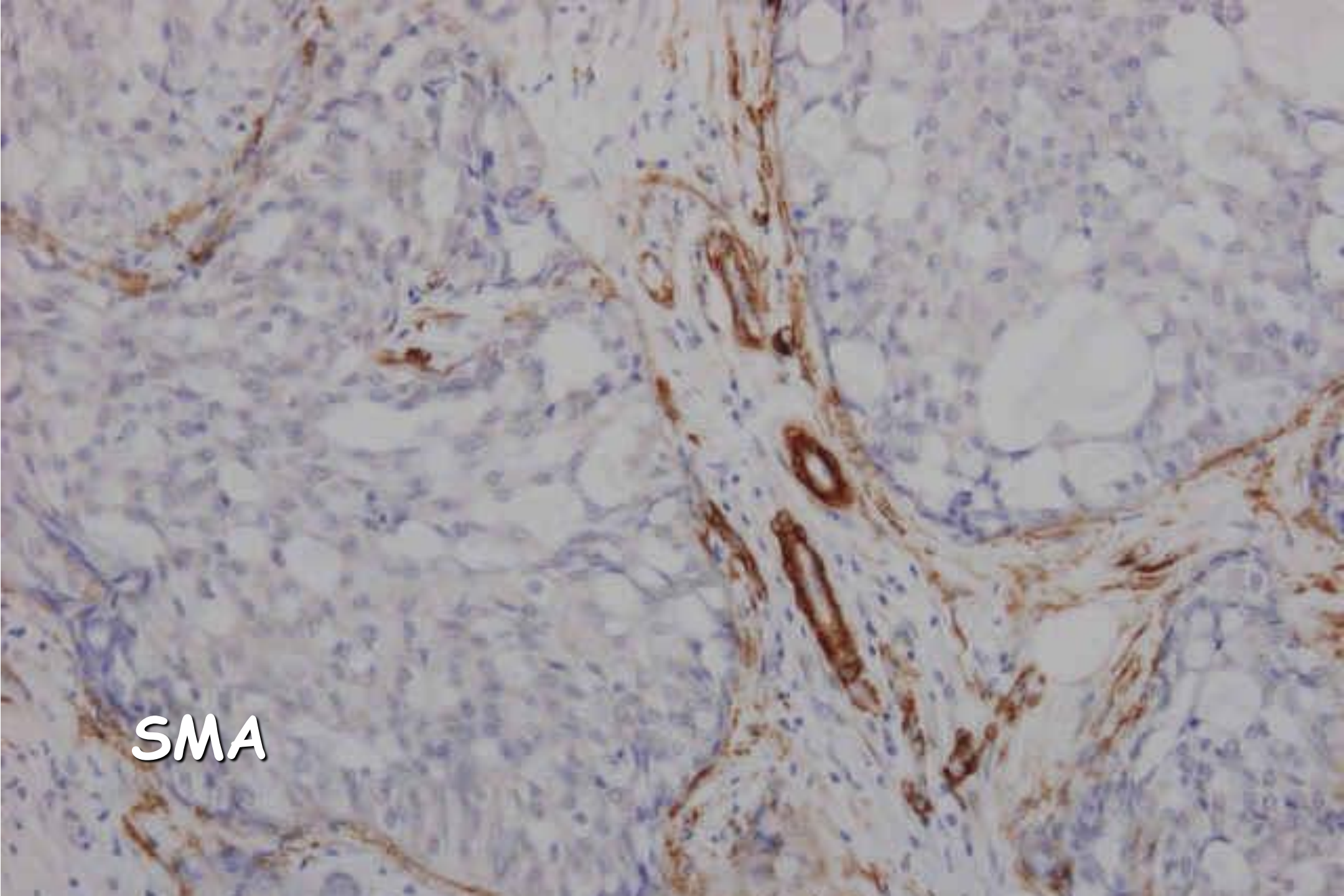
- First identified by McDivitt & Stewart in 1966 as a children's breast cancer but later recognised as also occuring in young, and a few adults. Male association
- Usually present as a well defined sub-areolar mass
- Prognosis is favourable and is thought to be better in children than in adults
- Local recurrences, if developed, are late
- Lymph node metastasis are uncommon
- Distant metastasis are exceedingly rare
- Death is unusual, but has been reported

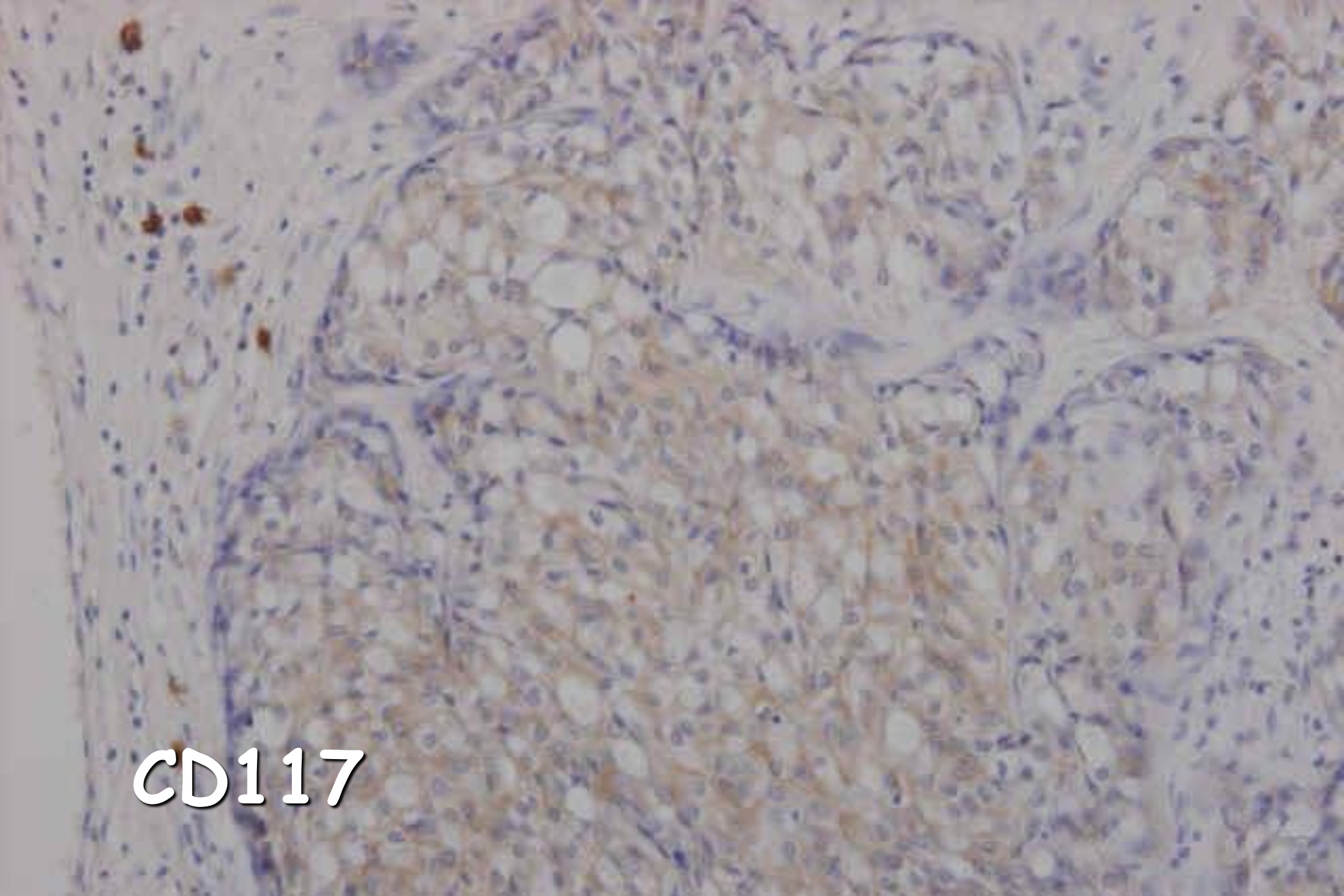


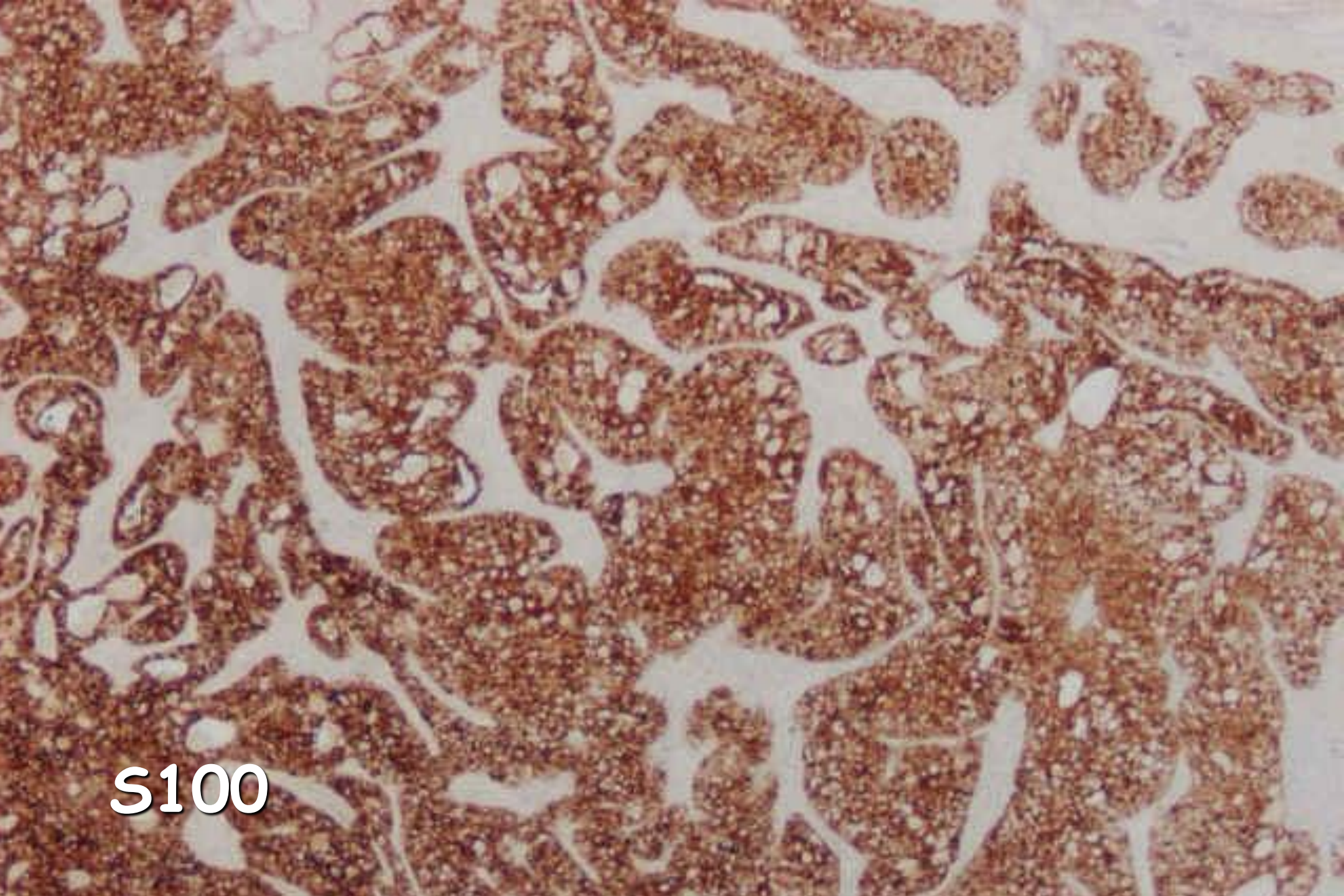



D PAS


ER


SMA


CD117


S100

Secretory carcinoma

- Low nuclear grade with vacuolated cytoplasm which may contain eosinophilic secretion arranged in cribriform patterns with the spaces containing eosinophilic secretions
- Typically, they show strong reactivity with S100
- They are mostly triple negative
- Express basal cytokeratins, and belong to the basal-like molecular group of breast cancers
- Genetically they are characterised by the presence of a chromosomal translocation t(12;15)(p13;q25) which results in the formation of ETV6-NTRK3 fusion gene

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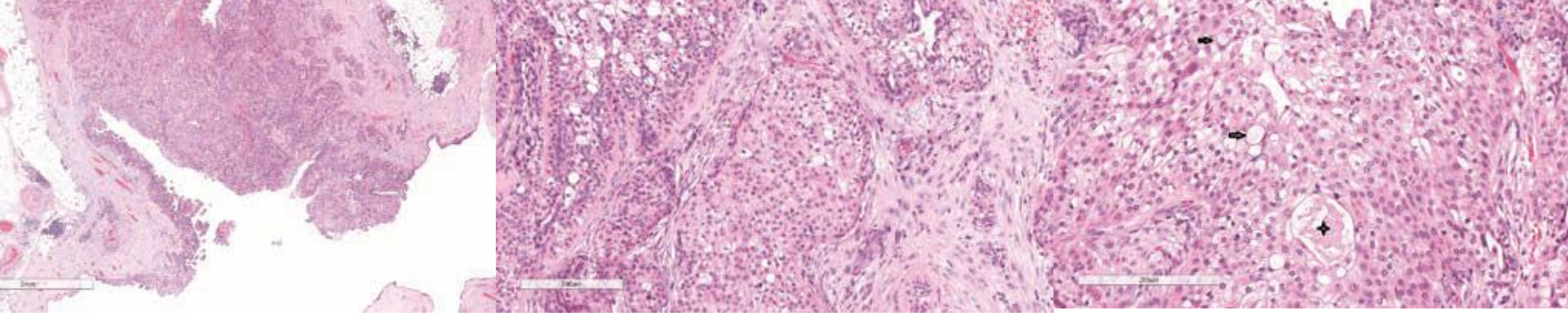
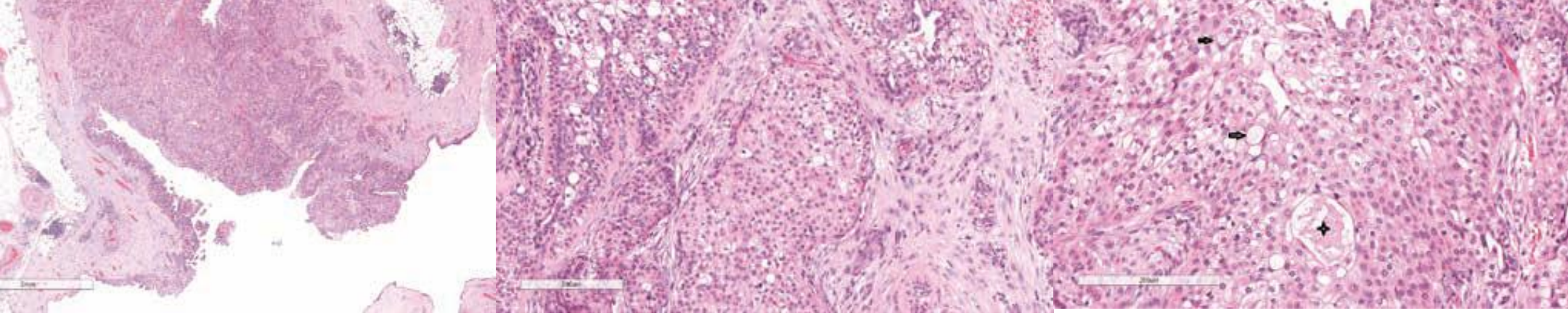
Mucoepidermoid carcinoma

- Mucoepidermoid carcinoma (MEC) is an invasive carcinoma composed of mixed mucinous, intermediate (transitional), and squamoid neoplastic cells arranged in solid and cystic patterns.
- < 40 cases reported to date
- wide range of histological features, spanning from low-grade to high-grade lesions
- Low and Int grade - very good prognosis
- High grade – poor prognosis



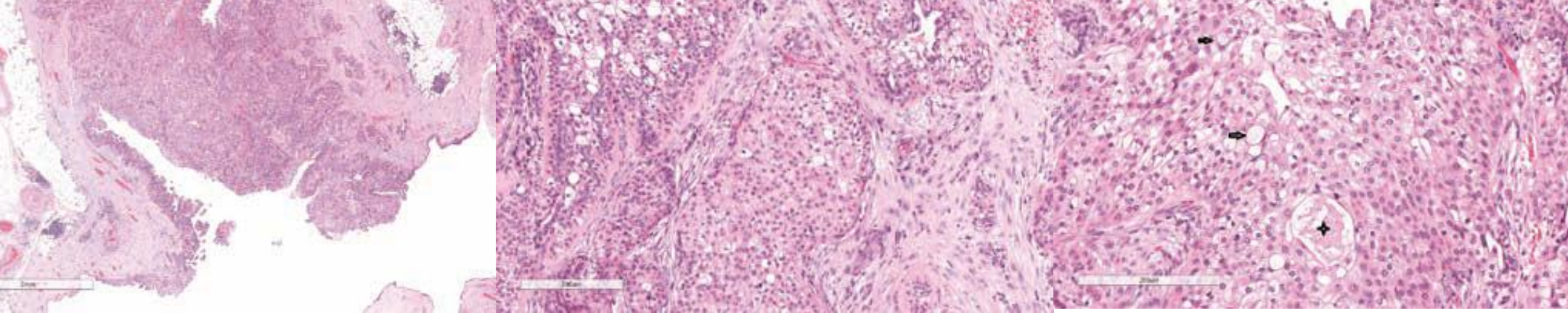
WHO 2019 - Mucoepidermoid

- Wide range of histological features, spanning from low-grade to high-grade lesions
- Grading by salivary gland or breast systems



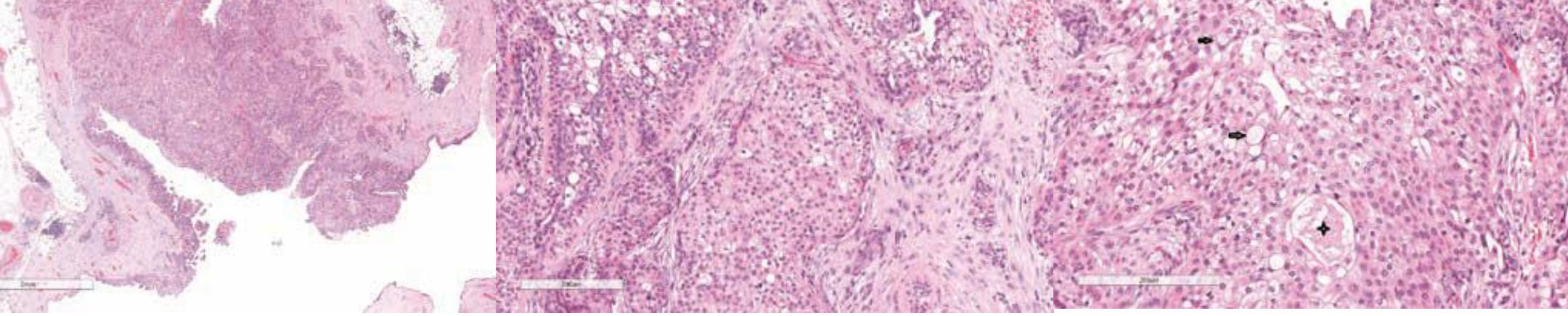
WHO 2019 - Mucoepidermoid

- **Low-grade MEC** more frequent cystic
- Cystic spaces are lined by mucous cells intermingled with eosinophilic cells
- Solid areas have peripheral layer of basaloid cells merging in groups of epidermoid cells and mucous cells.



WHO 2019 - Mucoepidermoid.

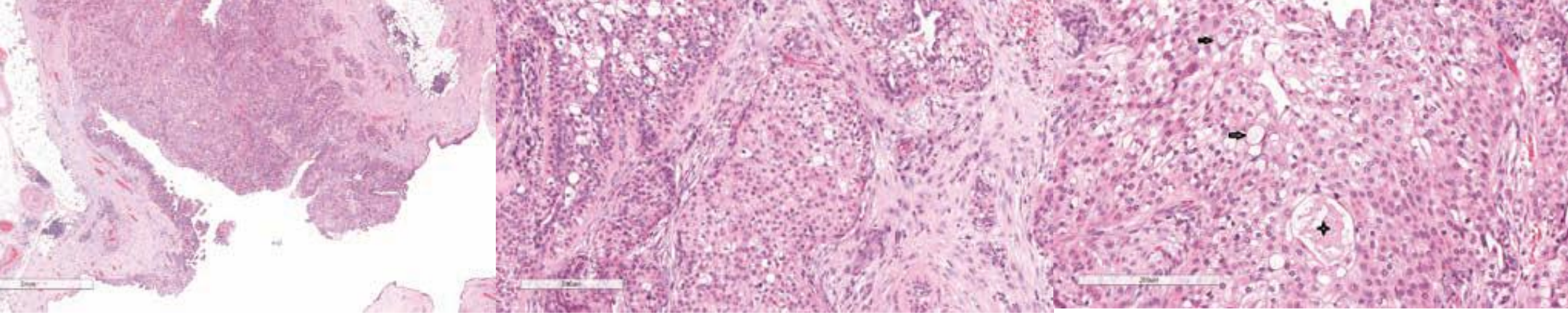
- **High-grade MEC** more frequently solid, and show same cell composition as low-grade
- Cytological atypia is present
- Mitotic figures numerous
- Necrosis can be present.



WHO 2019 - Mucoepidermoid.

- **Intermediate-grade** breast MEC has been occasionally reported.

- An intraductal component can be present.
- True keratinization with squamous pearls does not occur with any grade



WHO 2019 - Mucoepidermoid

IHC

- Triple negative ER PR HER2
- Basal epidermoid cells – High MW Ck & p63 +ve
- Mucoid cells – Low MW Ck +ve
- GATA 3 and Mammaglobin +ve

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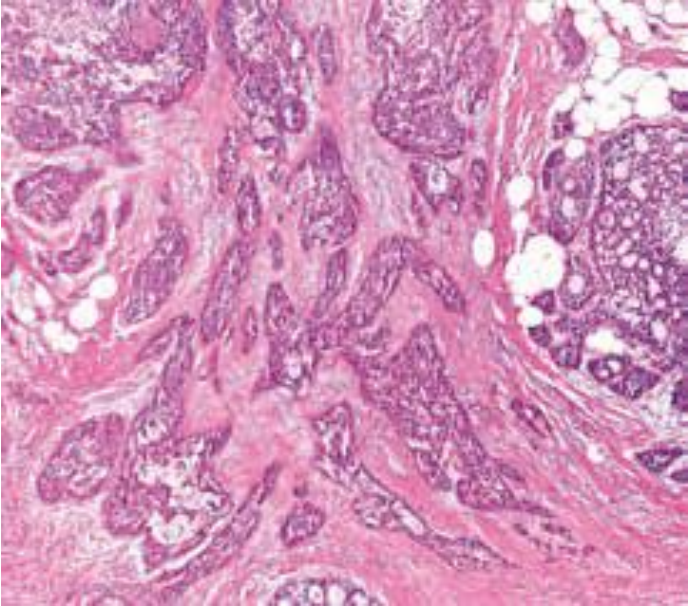
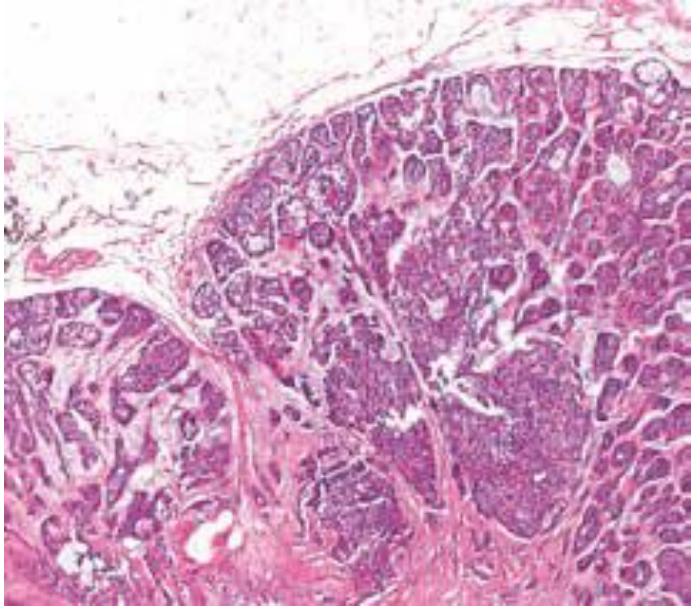
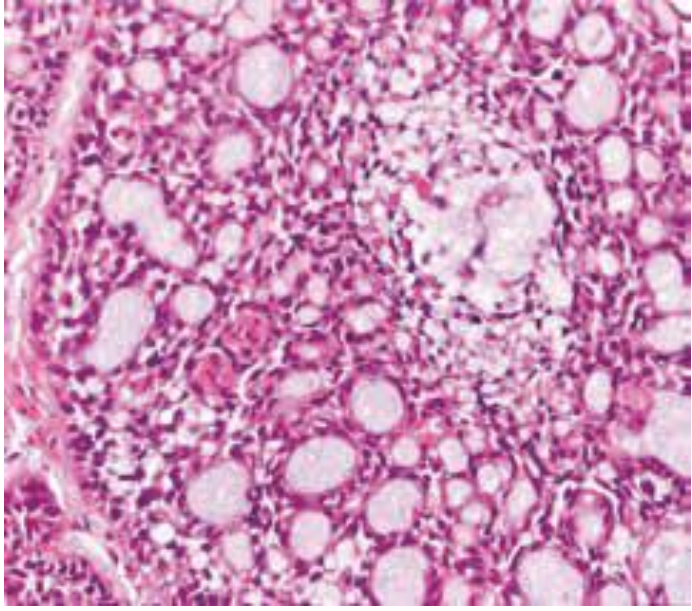
Polymorphous adenocarcinoma

- Polymorphous adenocarcinoma (PmA) invasive malignant tumour similar toPmA of the salivary glands
- monotonous neoplastic cells with architectural diversity, incl. large nests surrounded by cords and single files (single-cell infiltration).
- Only 3 breast cases reported to date
- 1 of the 3 cases reported had widespread metastases with death at 3 years
- The term “low-grade” should not be used for this breast tumour.

WHO 2019 - Polymorphous adenocarcinoma

- **Essential:** typical architectural pattern composed of a centrally
- located large solid area surrounded by thin strands of uniform and monotonous neoplastic cells.
- **Desirable:** focal and weak immunopositivity for CK7 and E-cadherin
- negative ER, PR, and HER2. *Note: bcl2 +ve*

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Tall cell carcinoma with reversed polarity

- New name, previous names:
  - solid papillary carcinoma resembling the tall cell variant of papillary thyroid carcinoma
  - solid papillary carcinoma with reverse polarity

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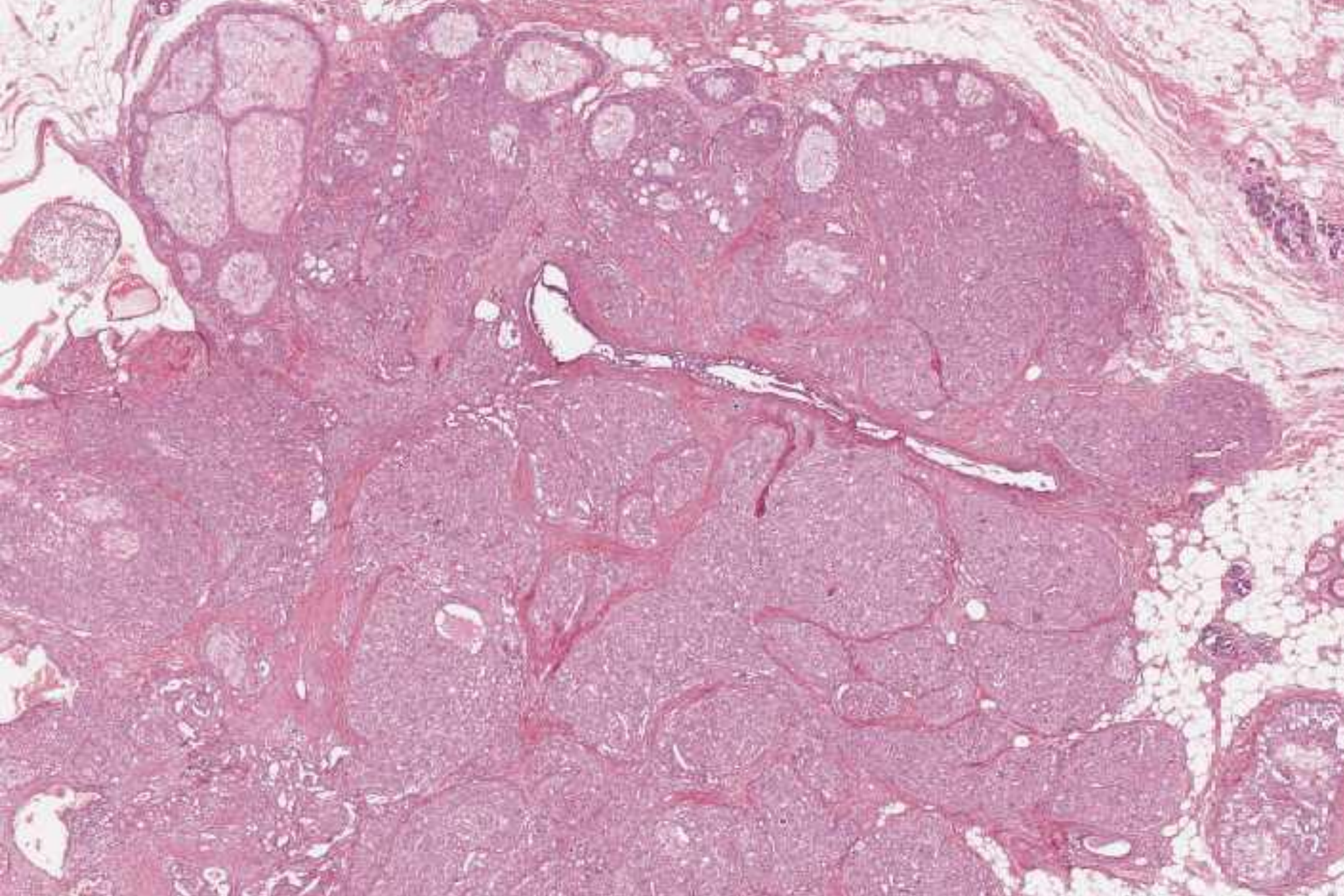
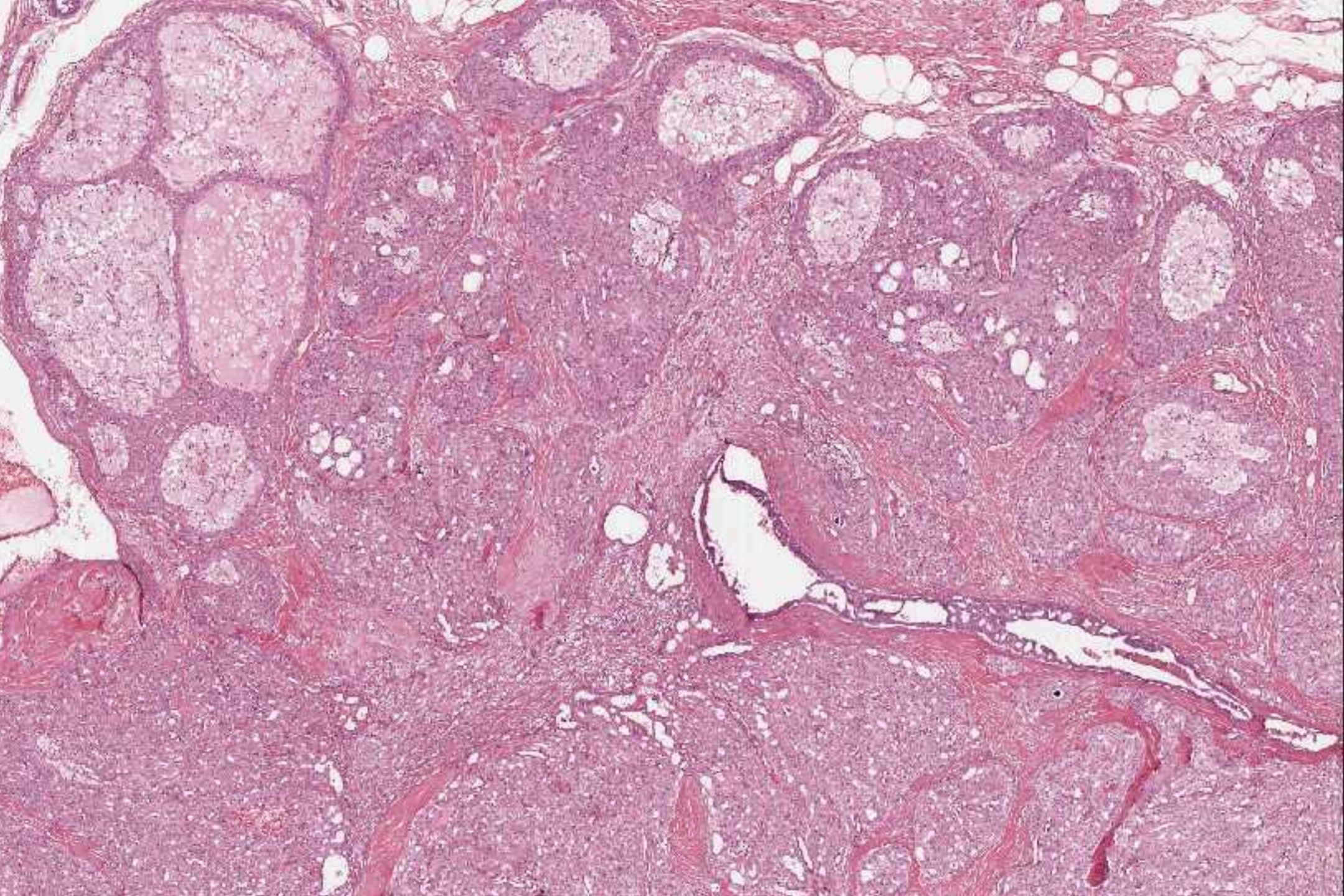
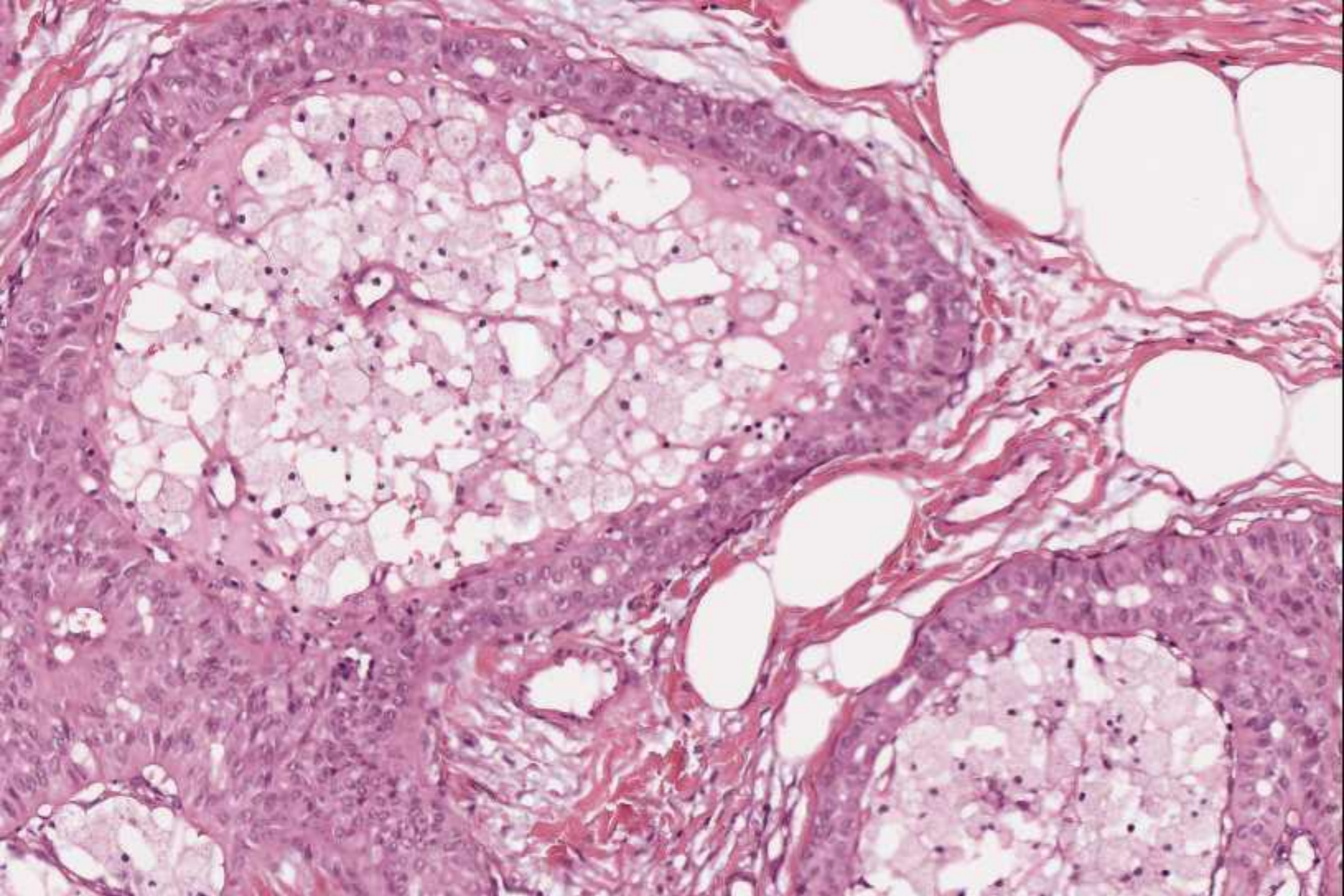
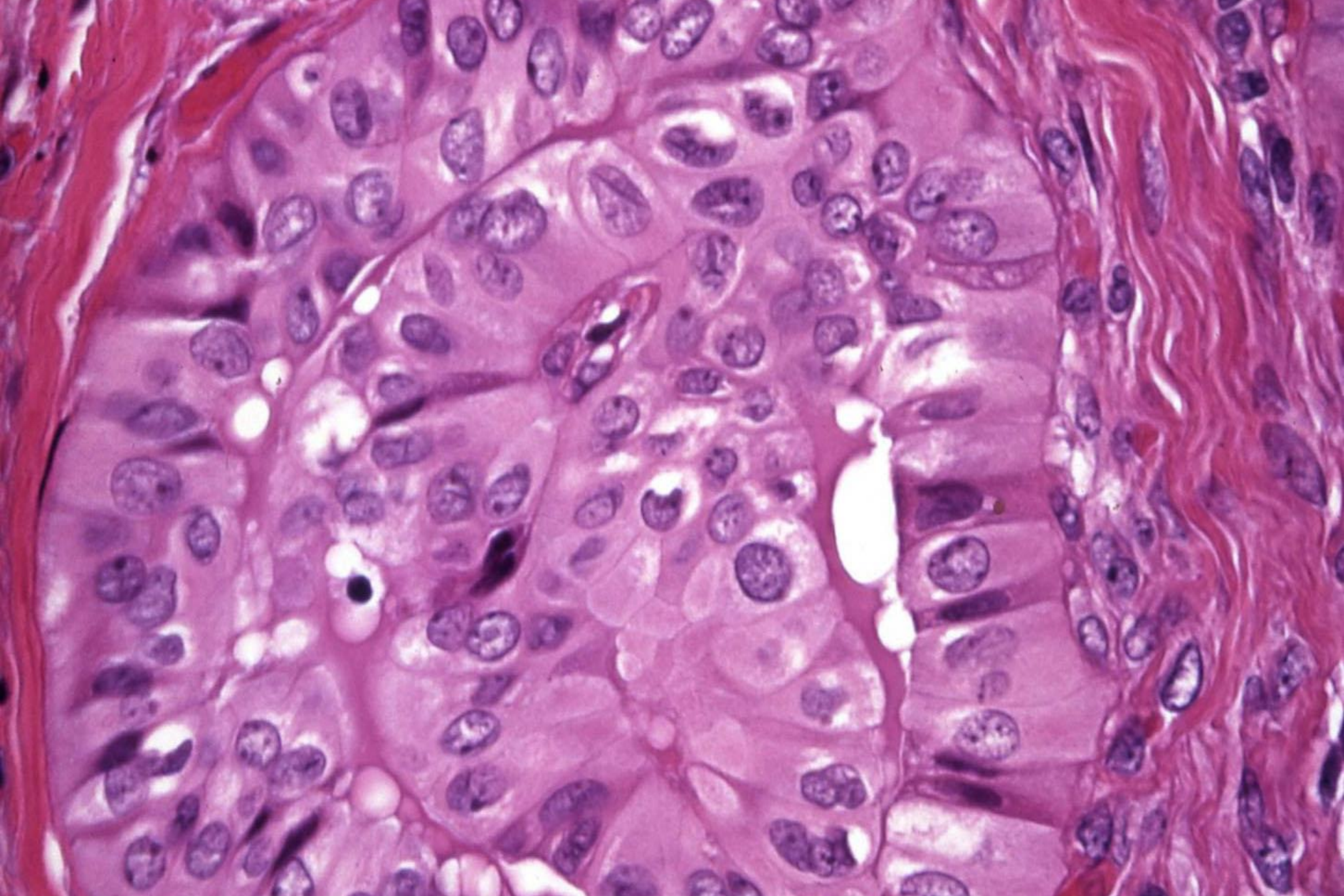
Tall cell carcinoma with reversed polarity

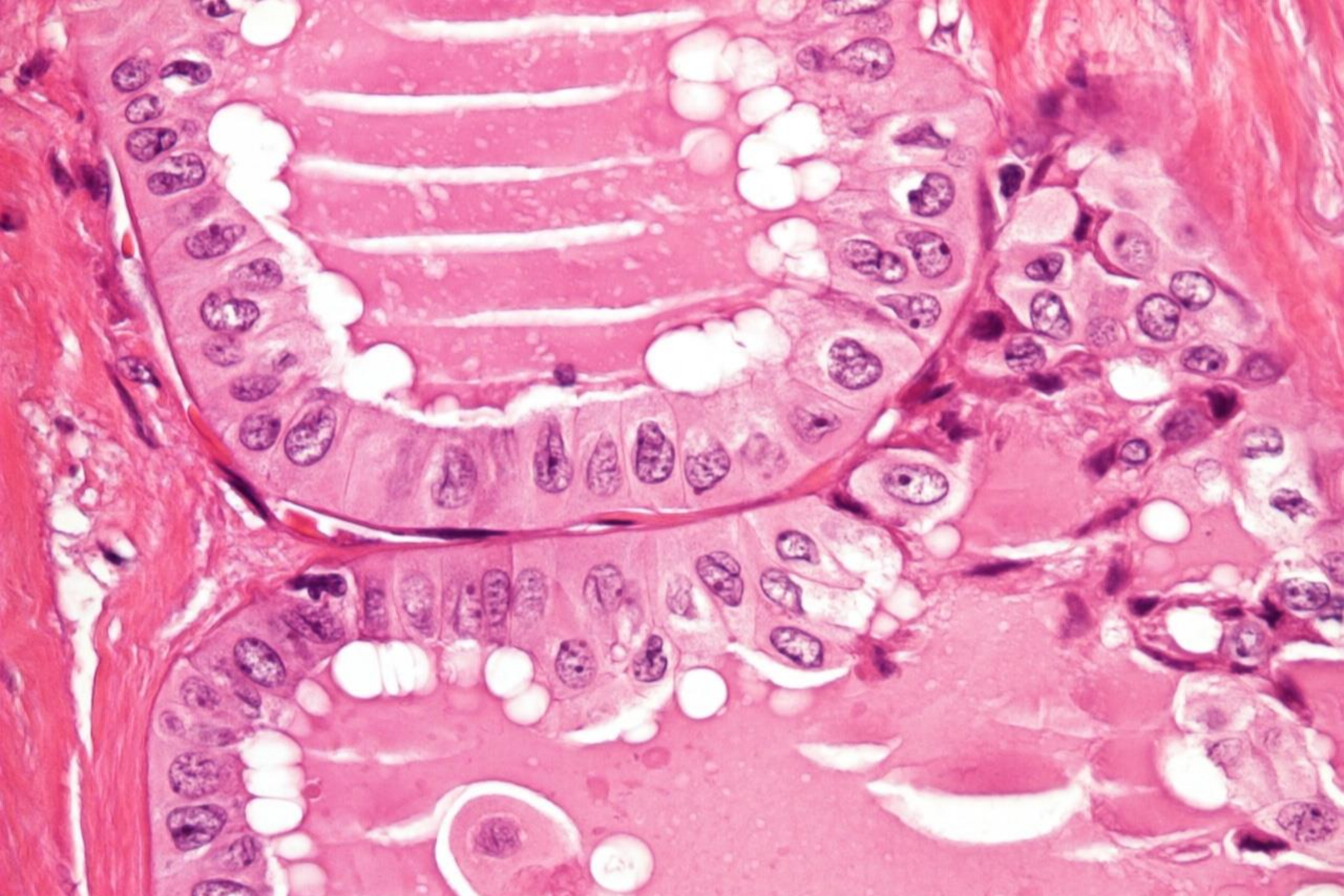
- rare subtype of invasive breast carcinoma characterized by tall columnar cells with reversed nuclear polarity, arranged in solid and solid papillary patterns
- most commonly associated with IDH2 p.Arg172 hotspot mutations.

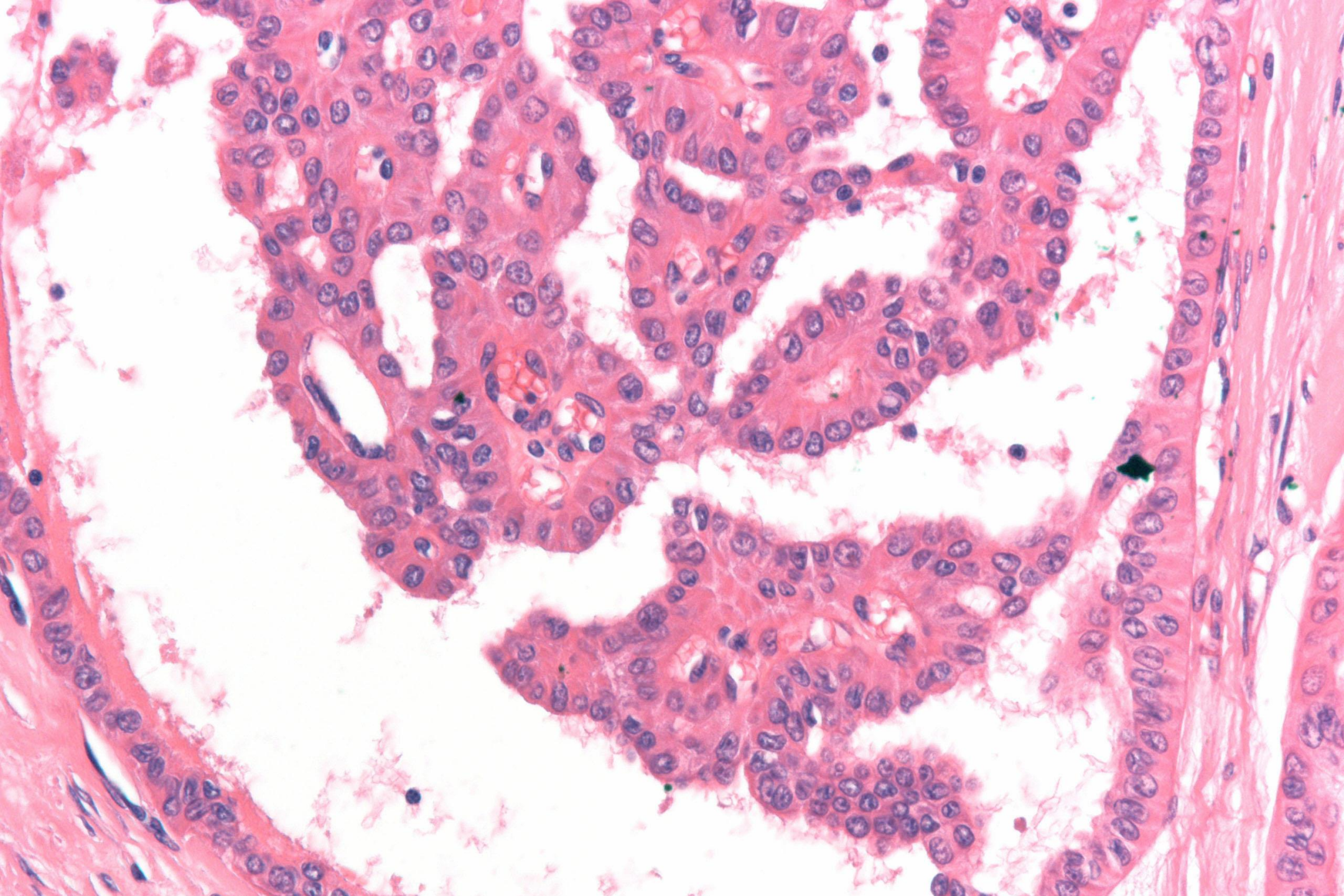


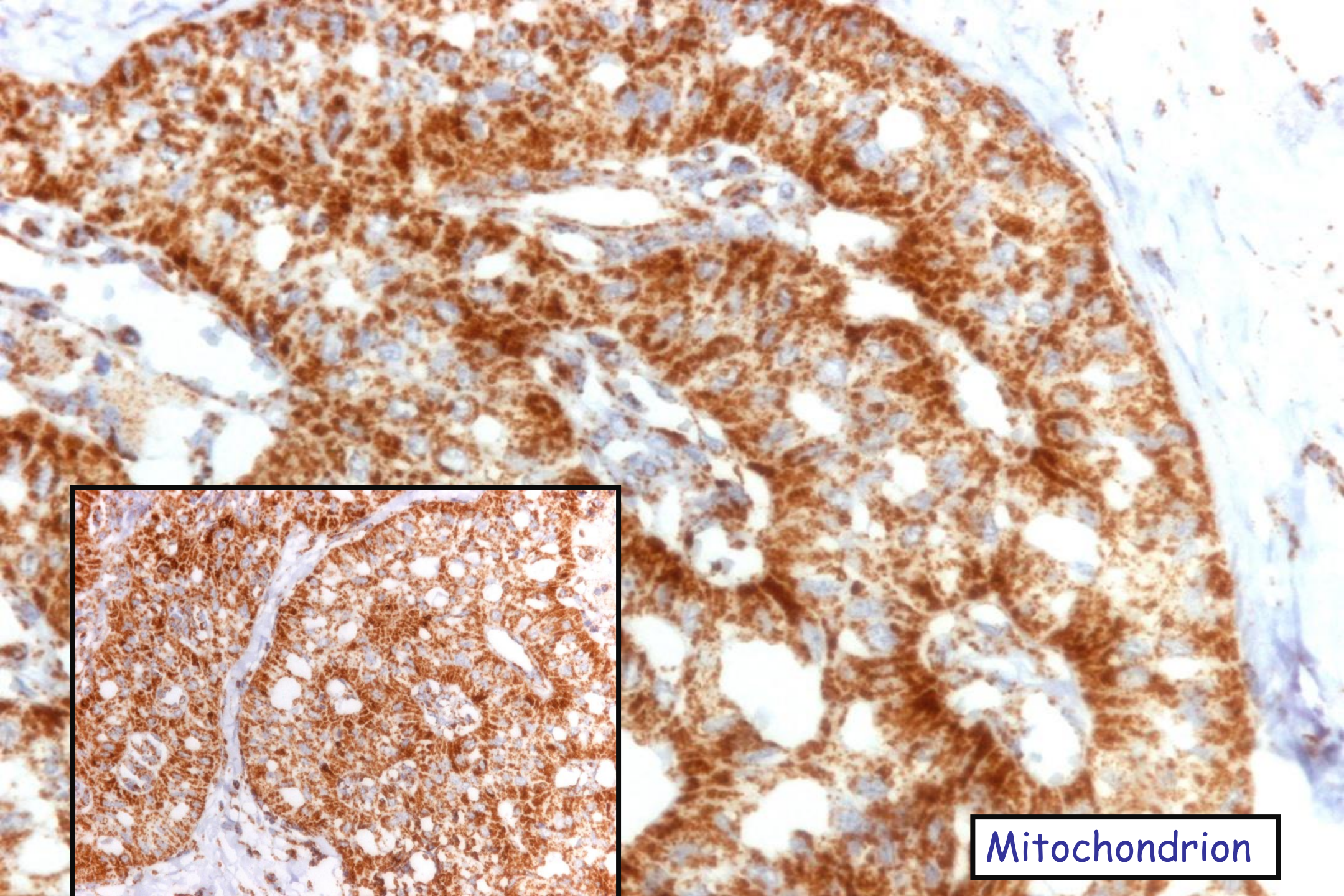











Mitochondrion

The American Journal of Surgical Pathology 27(8): 1114–1118, 2003

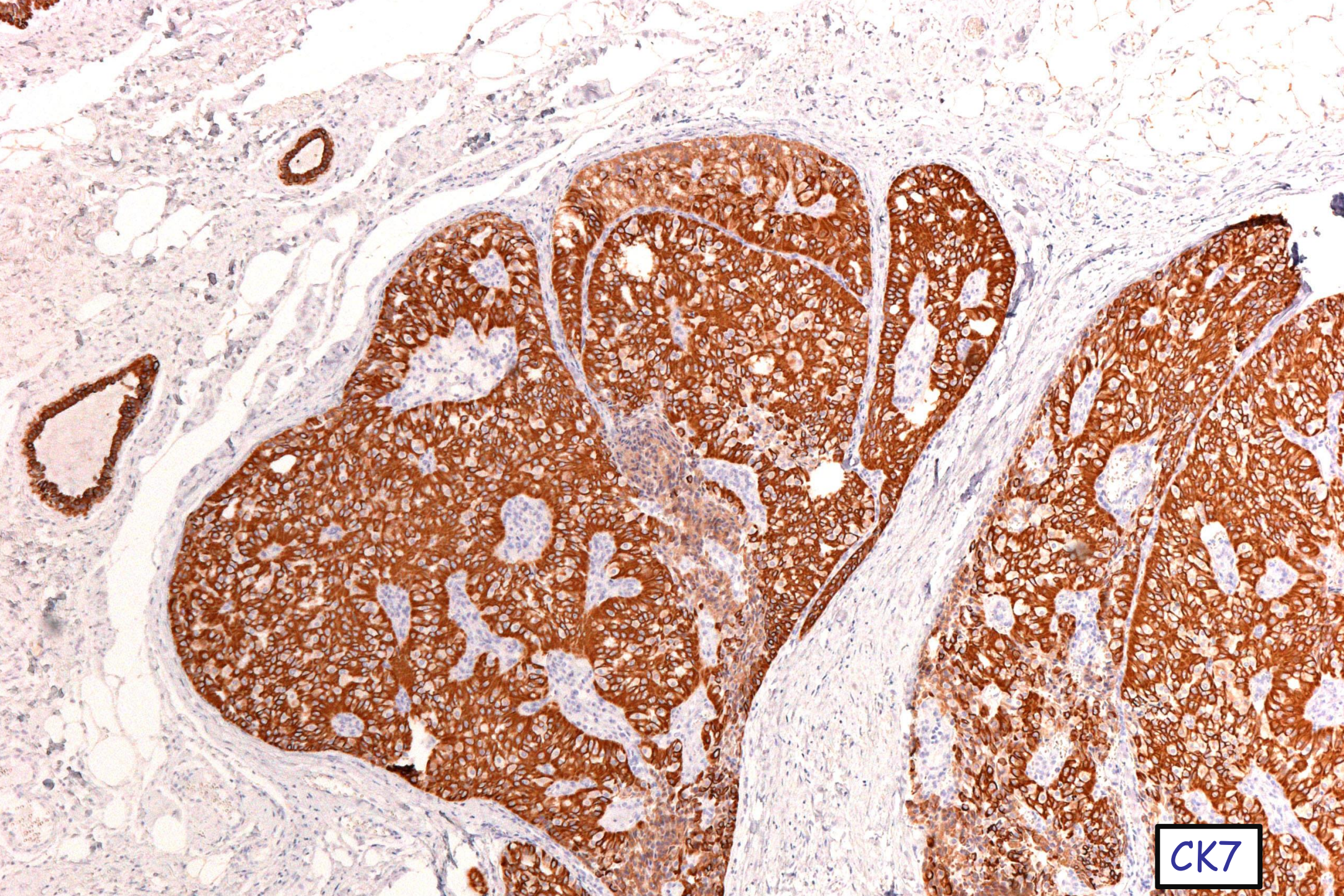
Breast Tumor Resembling the Tall Cell Variant of Papillary Thyroid Carcinoma

Report of 5 Cases

V. Eusebi, M.D., F.R.C.Path., S. Damiani, M.D., I. O. Ellis, M.D., F.R.C.Path., J. G. Azzopardi, M.D., F.R.C.Path., and J. Rosai, M.D., F.R.C.Path.

Clinicopathologic Features 10 Cases	
Sex	All female
Age (years)	50-80 (mean 60.2)
Tumour location	2 cases R / 2 cases L / 6 cases unknown
Tumour size (cm)	0.6-2.5 (mean 1.51)
Presentation	Palpable nodule: 4 cases Mammography: 3 cases Unknown: 3 cases
FNA	C4 : 3 cases
Lymph node status [4 cases]	SLN negative : 3 cases Intramammary LN positive : 1 case
Follow-up	4 mos – 12,5 years (mean 5,72 years)
No tumour clinically evident in thyroid gland nor in cervical lymph nodes	

Imunohistochemical Findings (10 Cases)		
CK 7	Positive	10/10
Mitochondria	Positive	9/10
P 63	Negative	10/10
ER / PGR / AR / Herb2	Negative	10/10
TTF-1 / Thyroglobulin	Negative	10/10


CK7

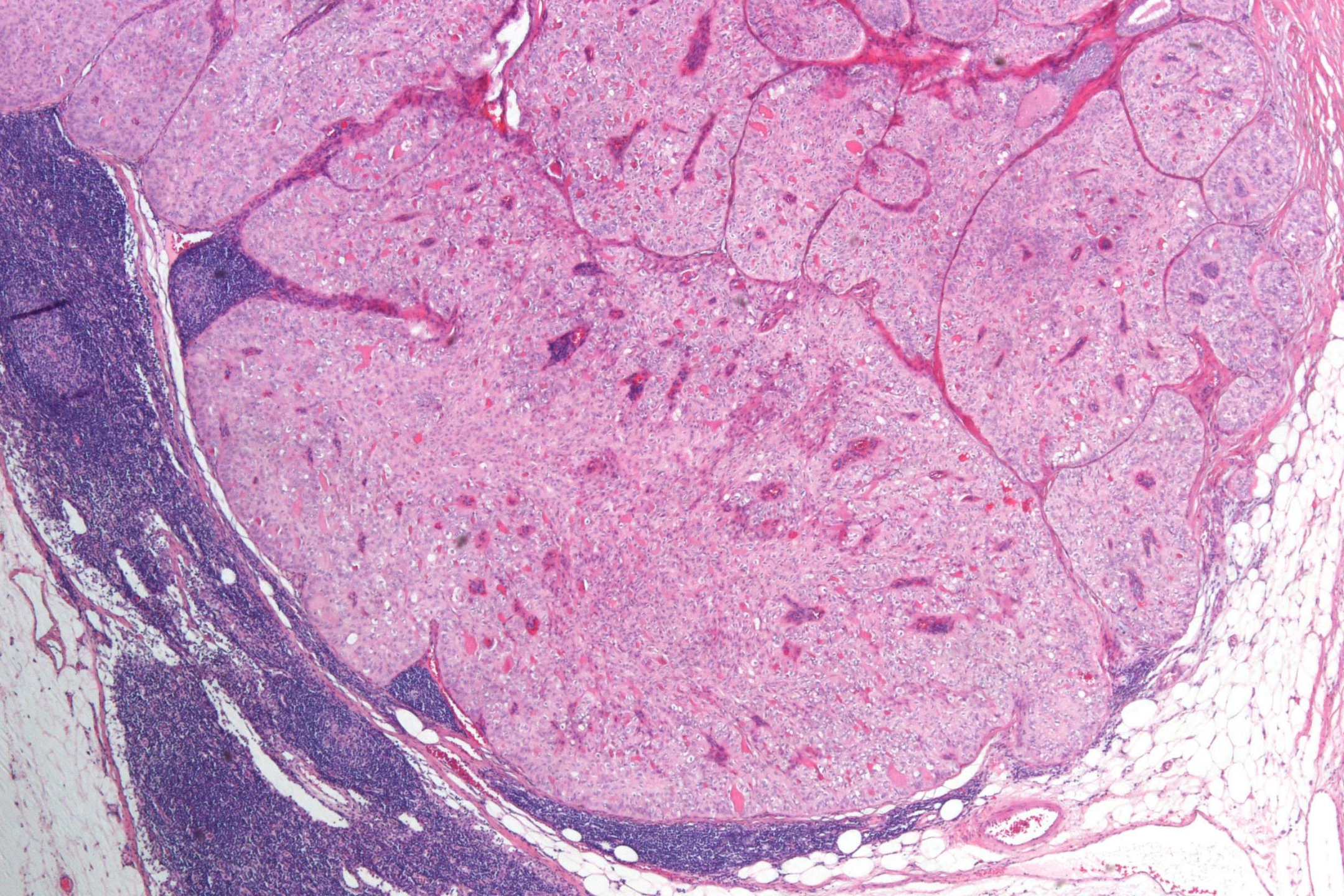
Stains	Number of positive cases
P 63	0/10
CK 14	1/10
CK 5/6	4/10
Laminin & Collagen IV	4/10

Follow-Up (FU)

(range 24 mos- 14.5 years)

(mean 7,72 years)

1 Patient	Lost FU
8 Patients	Alive and well (A&W)
1 Patient A&W (12,3 years)	9,4 years: local recurrence and 1 axillary lymph node metastasis



Molecular and Cellular Pathobiology

Cancer Research

IDH2 Mutations Define a Unique Subtype of Breast Cancer with Altered Nuclear Polarity

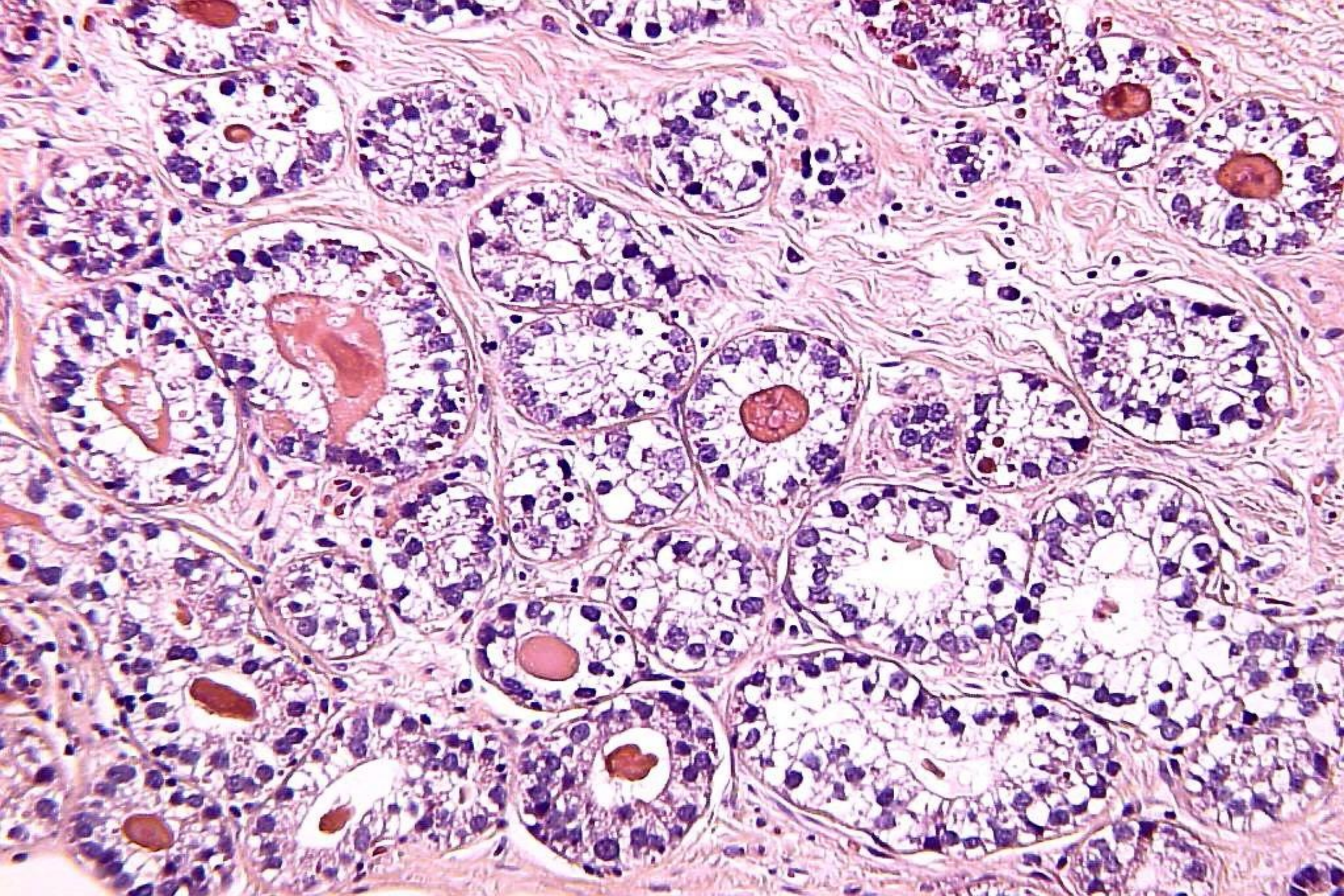
Sarah Chiang[1], Britta Weigelt[1], Huei-Chi Wen[1], Fresia Pareja[1], Ashwini Raghavendra[1], Luciano G. Martelotto[1], Kathleen A. Burke[1], Thais Basili[1], Anqi Li[1], Felipe C. Geyer[1], Salvatore Piscuoglio[1], Charlotte K.Y. Ng[1], Achim A. Jungbluth[1], Jörg Balss[2], Stefan Pusch[2], Gabrielle M. Baker[3], Kimberly S. Cole[4], Andreas von Deimling[2,5], Julie M. Batten[6], Jonathan D. Marotti[7], Hwei-Choo Soh[8], Benjamin L. McCalip[9], Jonathan Serrano[10], Raymond S. Lim[1], Kalliopi P. Siziopikou[11], Song Lu[12], Xiaolong Liu[13], Tarek Hammour[14], Edi Brogi[1], Matija Snuderl[10], A. John Iafrate[6,15], Jorge S. Reis-Filho[1], and Stuart J. Schnitt[15,16]

19 of 13 (77%) SPCRPs harbored hotspot mutations at R172 IDH2

Of which 8 of 10 displayed concurrent pathogenic mutations affecting PIK3CA or PIK3R1

First report of IDH2 hotspot mutations in breast cancer

Cancer Res; 76(24) December 15, 2016



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Acinic cell carcinoma

- Acinic cell carcinoma is a malignant epithelial neoplasm composed of clear and granular epithelial cells, some of which contain intracytoplasmic zymogen granules, arranged in microglandular and solid patterns.

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Acinic cell carcinoma

Essential diagnostic criteria:

- neoplastic cells with eosinophilic and basophilic granular cytoplasm and PASD-positive intracytoplasmic granules
- immunohistochemical positivity for EMA and markers of serous acinar differentiation.

Acinic Cells Carcinoma(AcCC)
Clinicopathological features

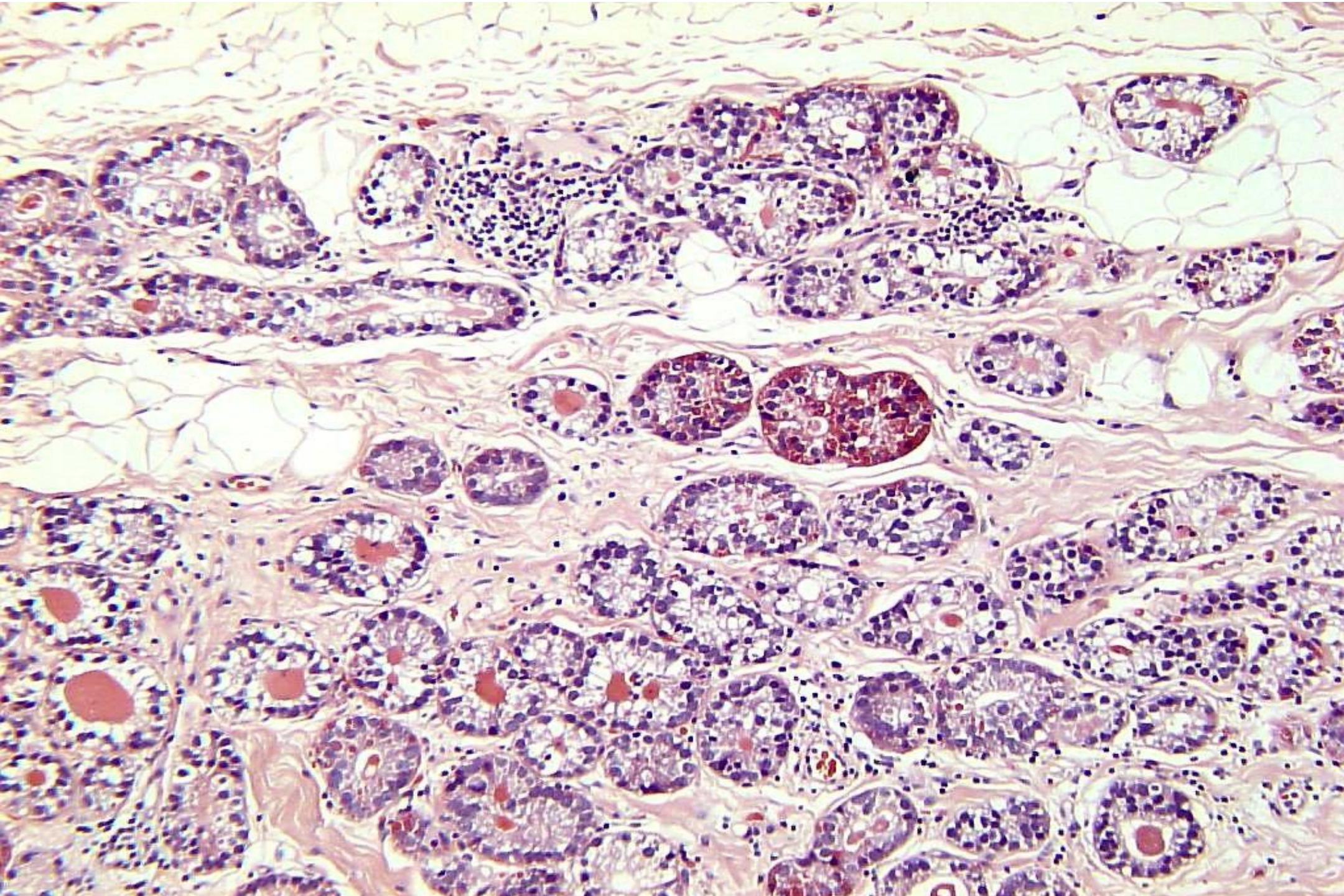
- First report by Roncaroli 1996

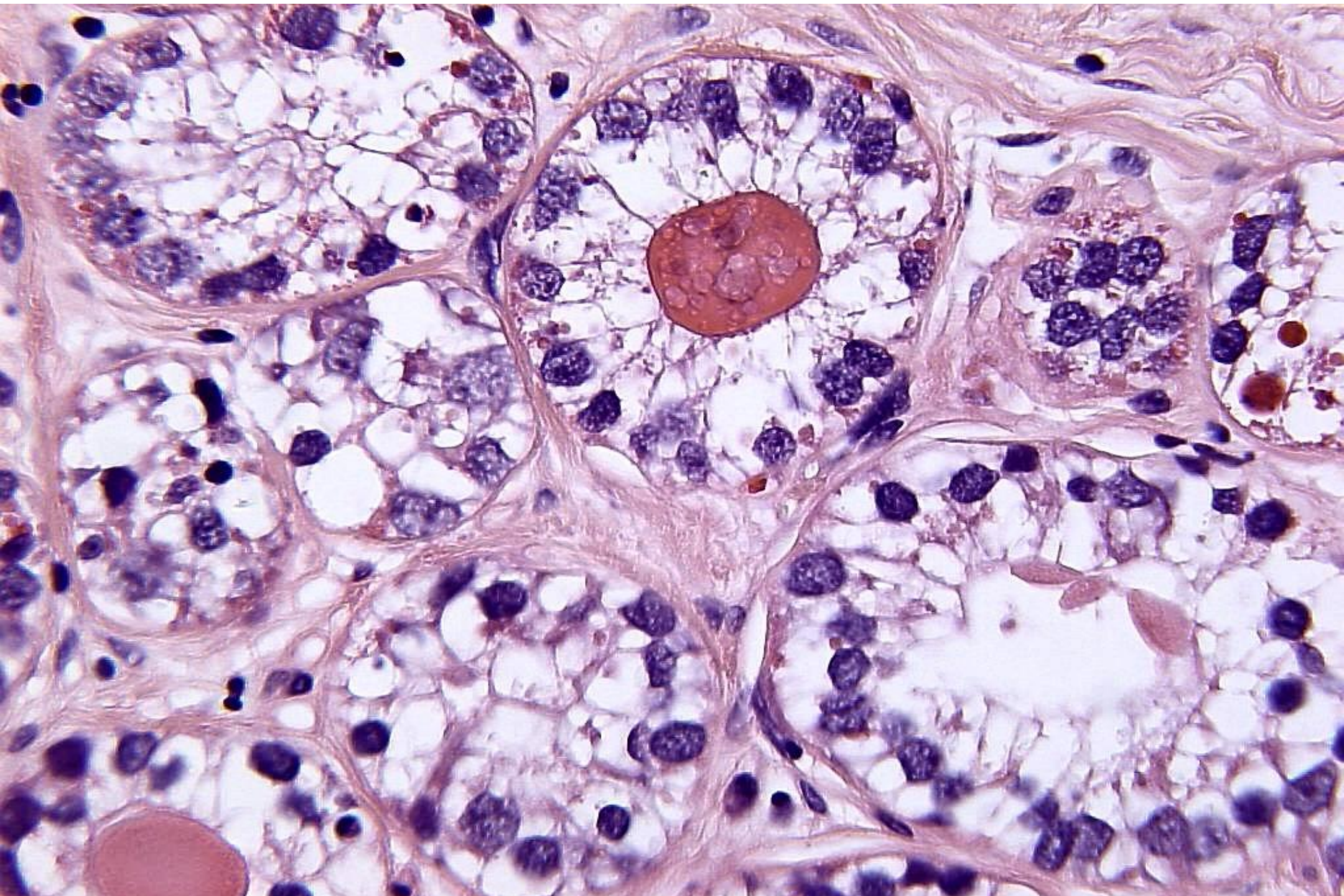
Acinic cell-like carcinoma of the breast. Virchows Arc 1996;429:69-74

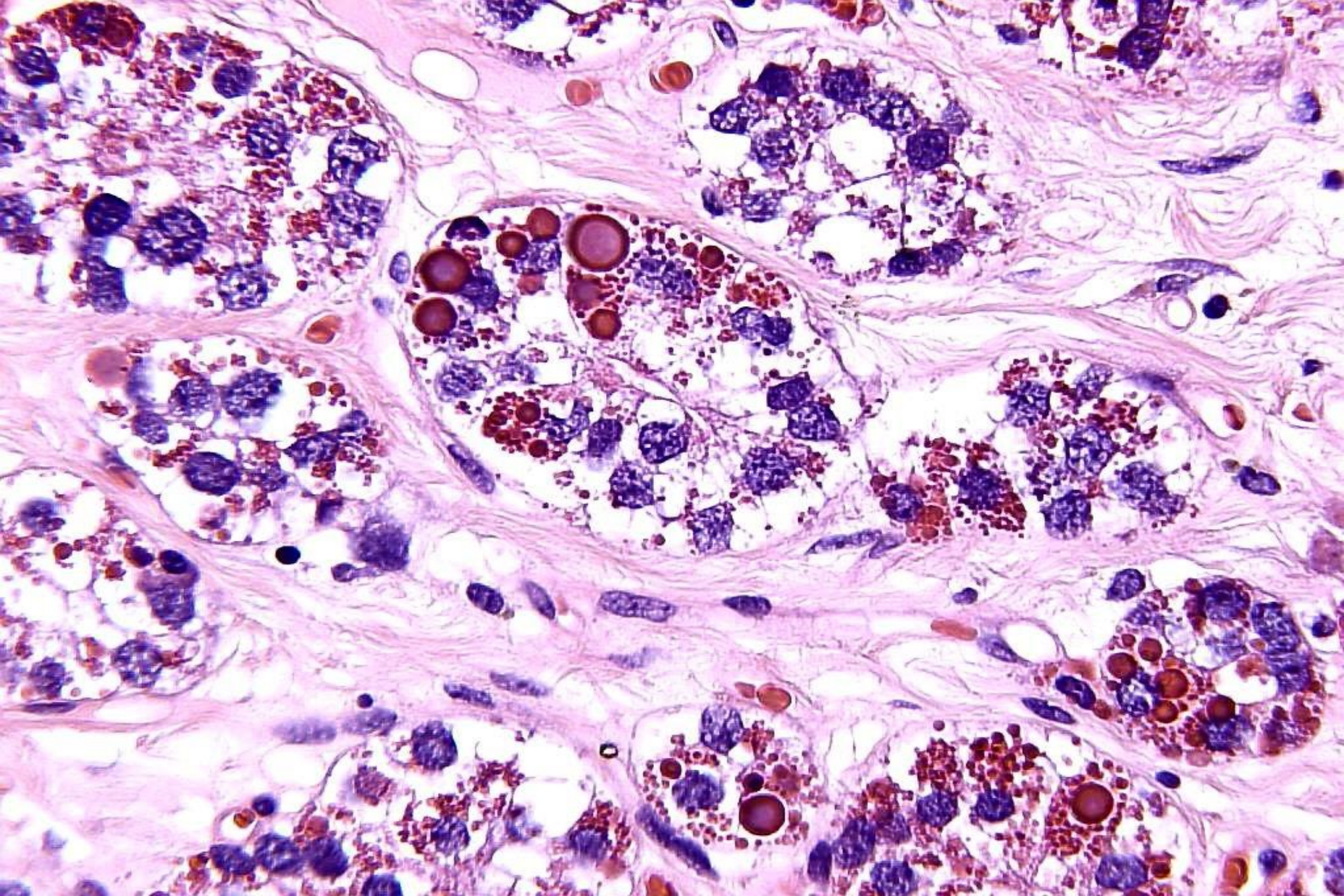
- Defined by serous differentiation
- Infiltrative margin
- Microglandular areas merging with solid aggrageates
- Intraluminal inspisssated secretion
- Stroma can be fibro-fatty without desmoplasia

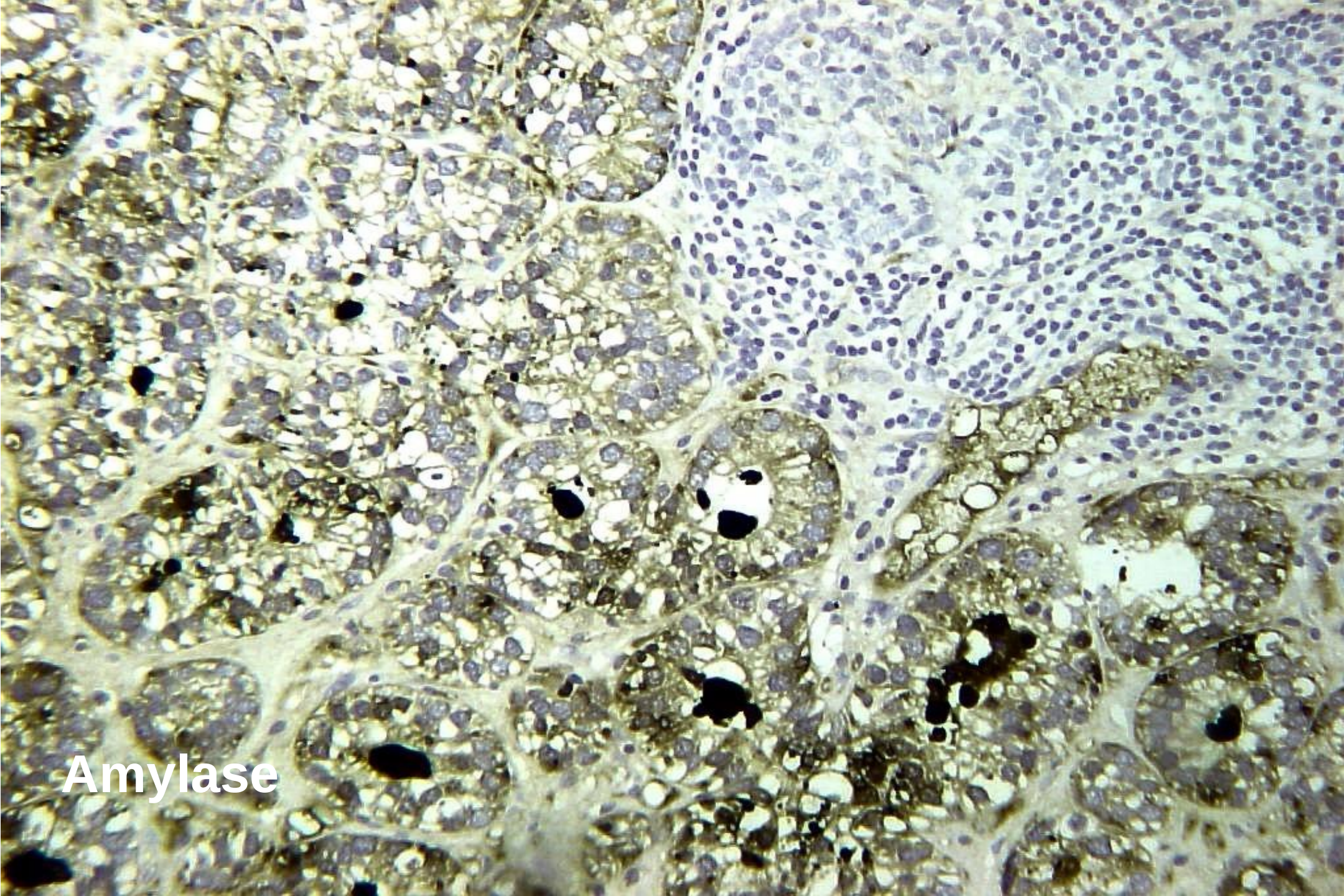
AcCC of the breast
Morphology II

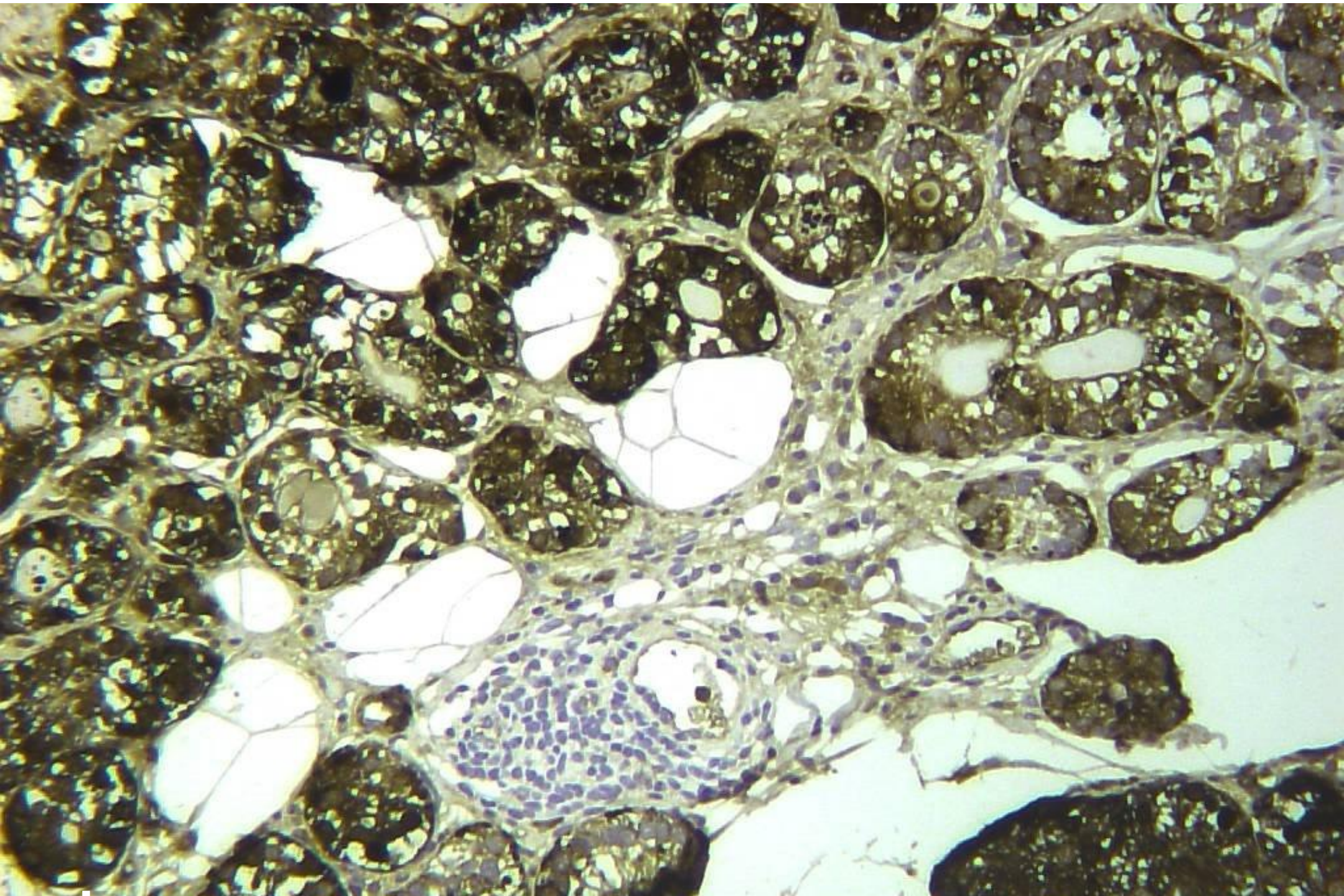
- Abundant eosinophilic or amphophilic granular cytoplasm
- Variable mitotic count
- Immunohistochemistry:
  - \+ Luminal cytokeratins, S100, Lysosyme, alfa 1-antitrypsin, alfa-amylase(focal, scanty), IgA, E Cadherin
  - \- Basal cytokeratins, ER, PR, HER 2, GCDFP
- EM: membrane bound zymogen granules 0.08-0.9um

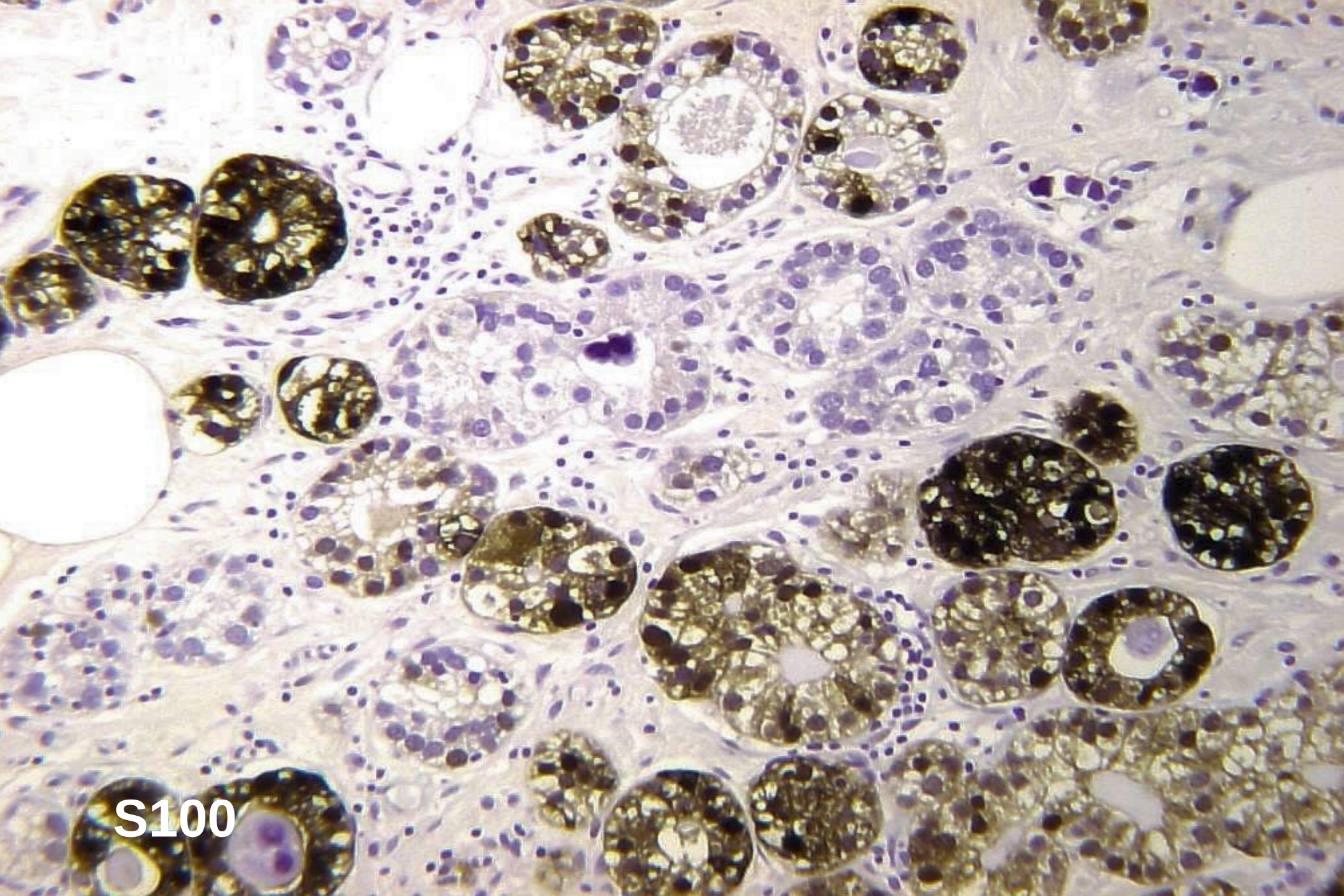


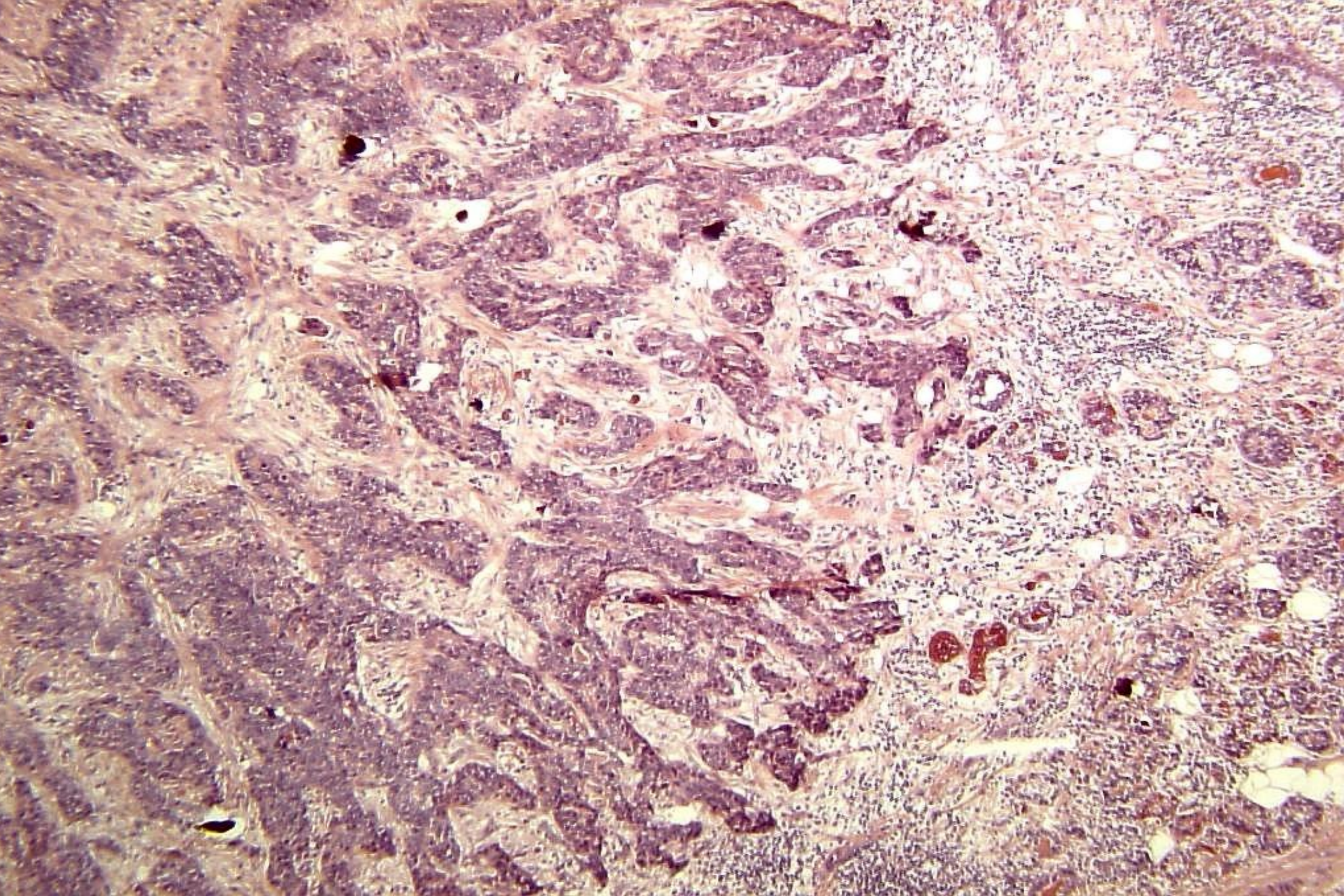


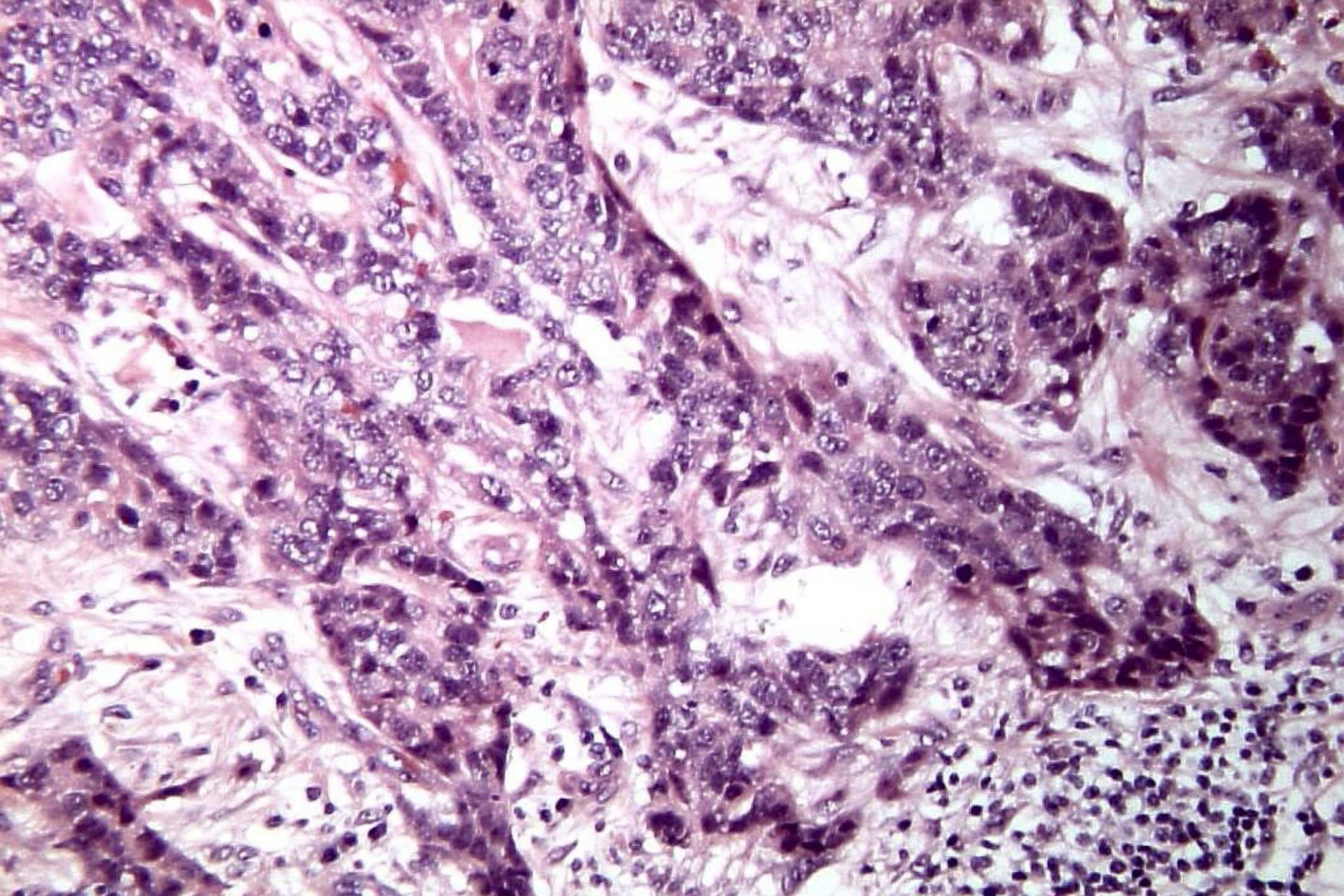



Amylase




S100





Differential diagnosis

Tumours with granular cytoplasm

- Neuroendocrine carcinoma – ICH
- Oncocytic tumours – mitochondria
- Apocrine carcinoma – GCDFP 15

Tumours with architectural similarities

- Microglandular adenosis
- Secretory carcinoma

AcCC v MGA

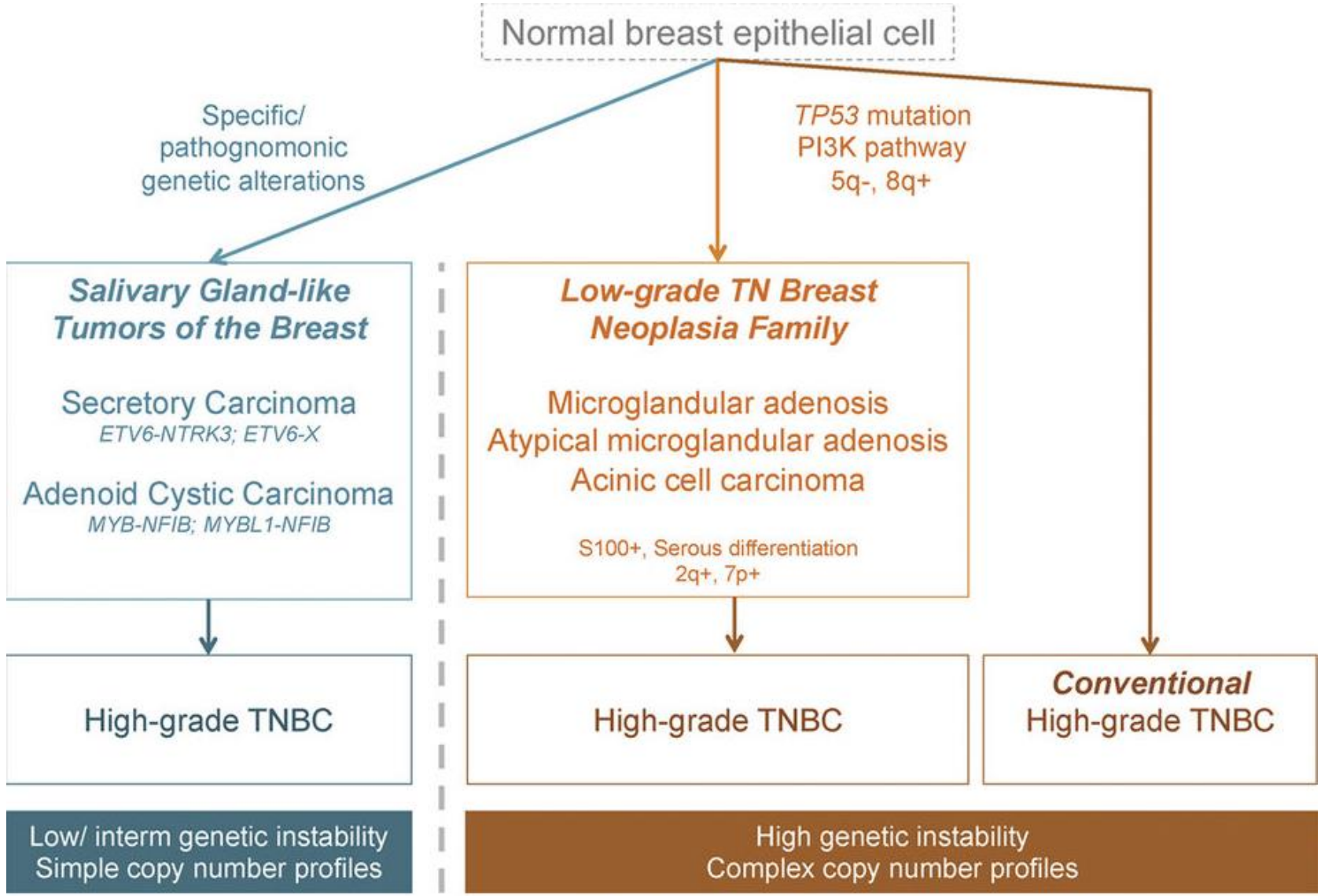
- Overlapping architectural features-small glandular/acinar structure without myoepthelial layer
- IHC similarities- CK,S100,Lysosyme, ER, Her2
- Morphological similarities between MGA and AcCC
- Transitional forms do exist
- Reported carcinomas associated with MGA retain the acinar architecture
- High rate of invasive carcinoma also reported with MGA

AcCC v MGA

But

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

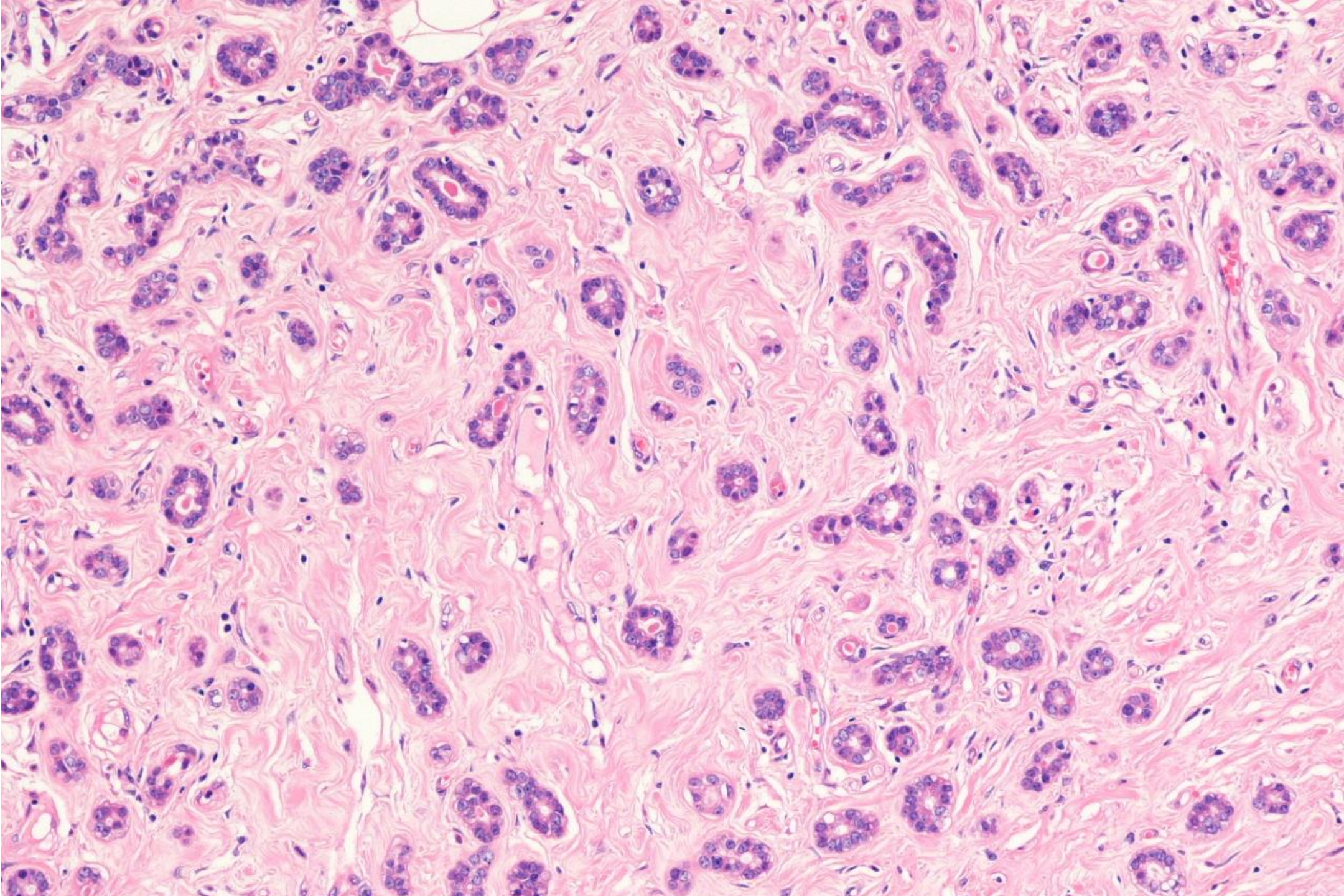
Triple Negative Breast Cancer

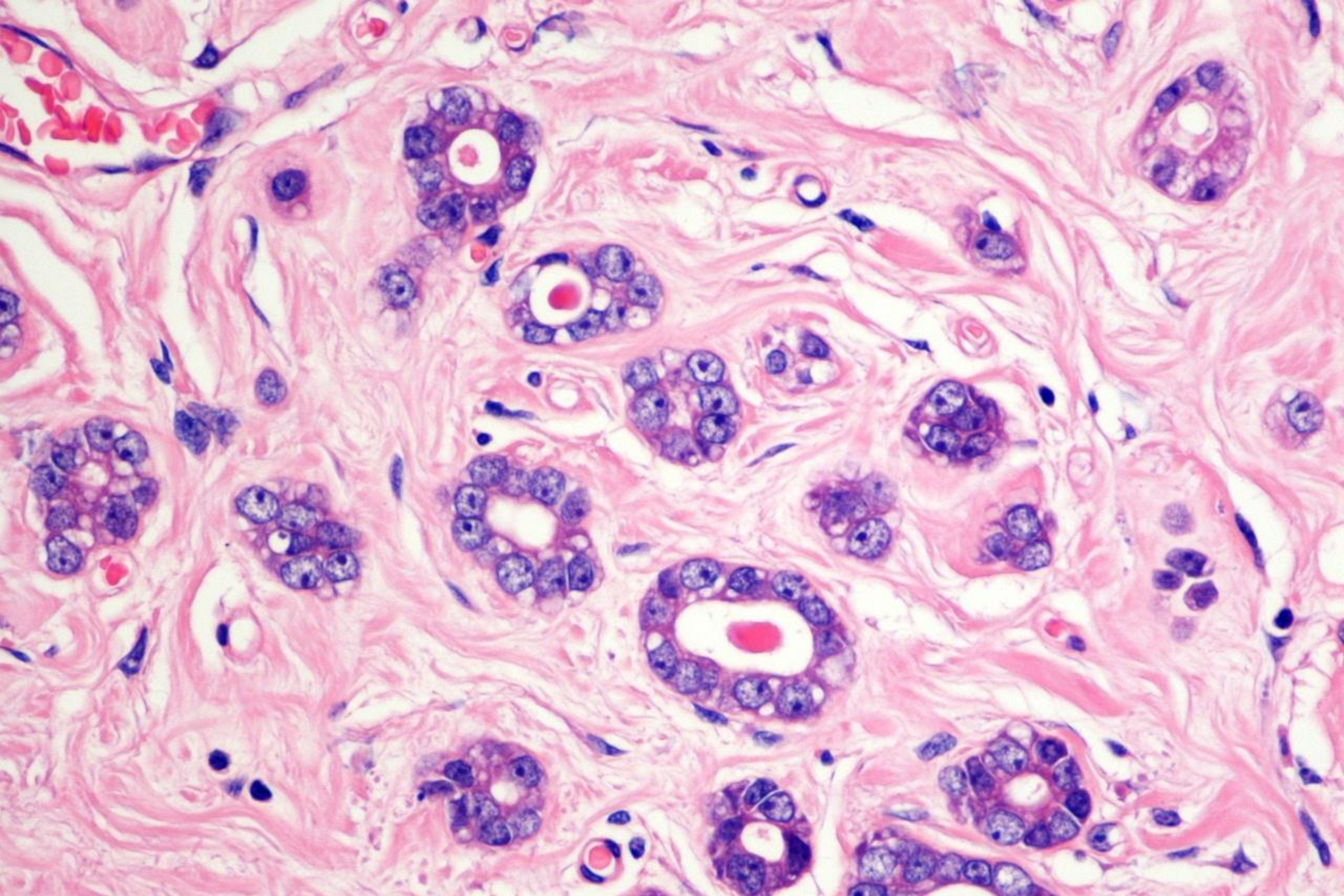


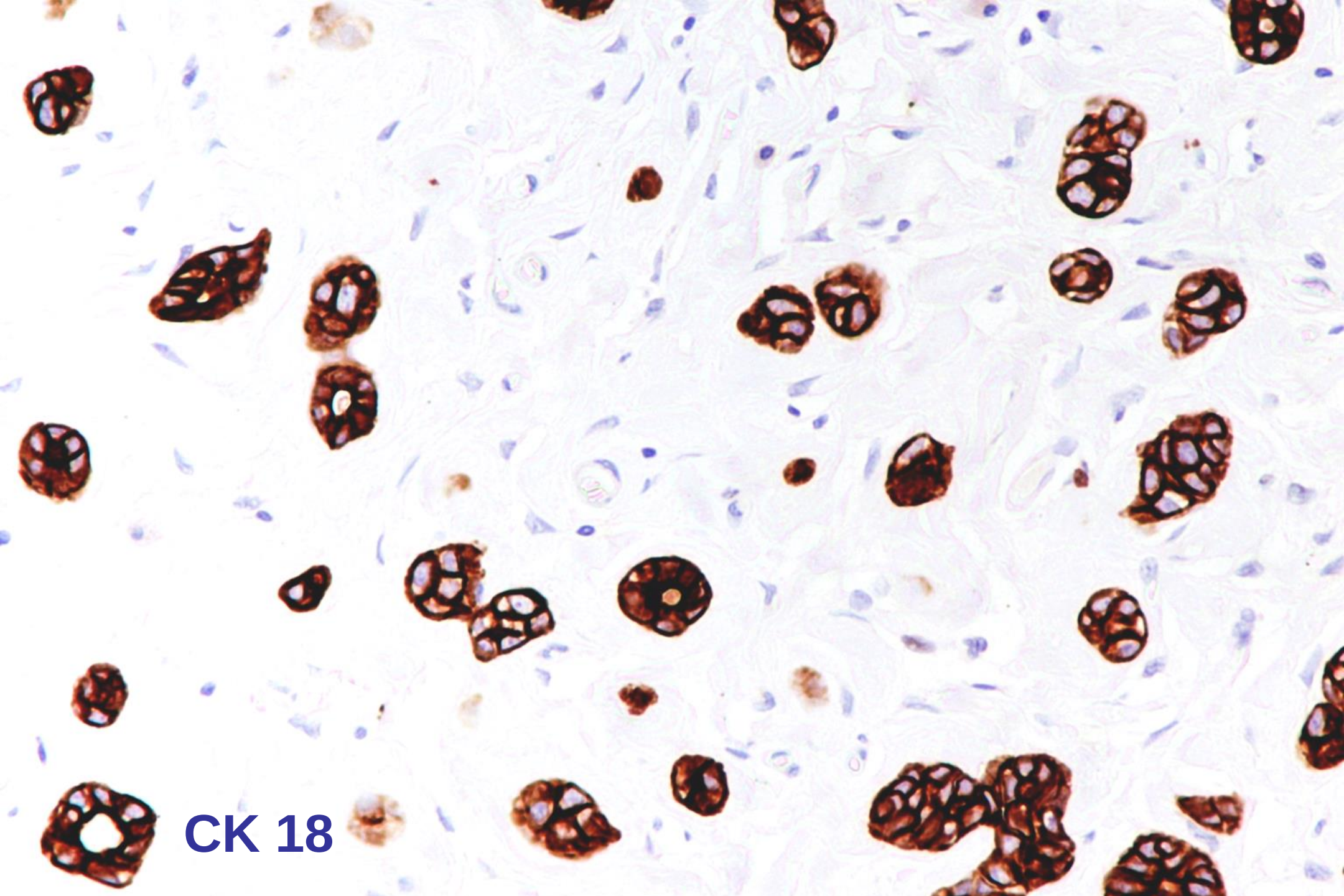
Low Grade TN BC

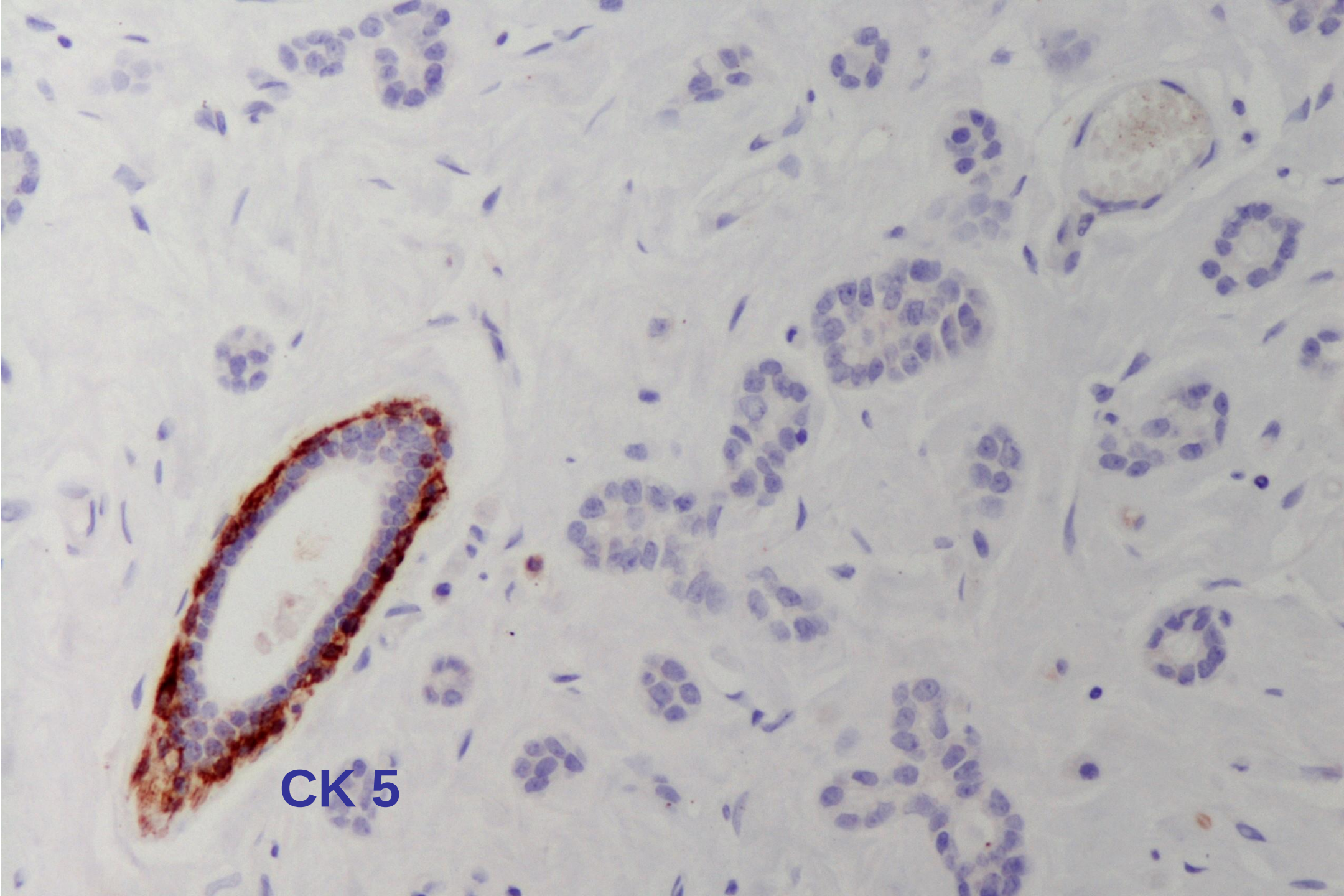
Low-grade TN breast neoplasia family

- Microglandular adenosis (MGA)
- Atypical MGA (AMGA)
- Acinic cell like carcinoma (ACC)






CK 18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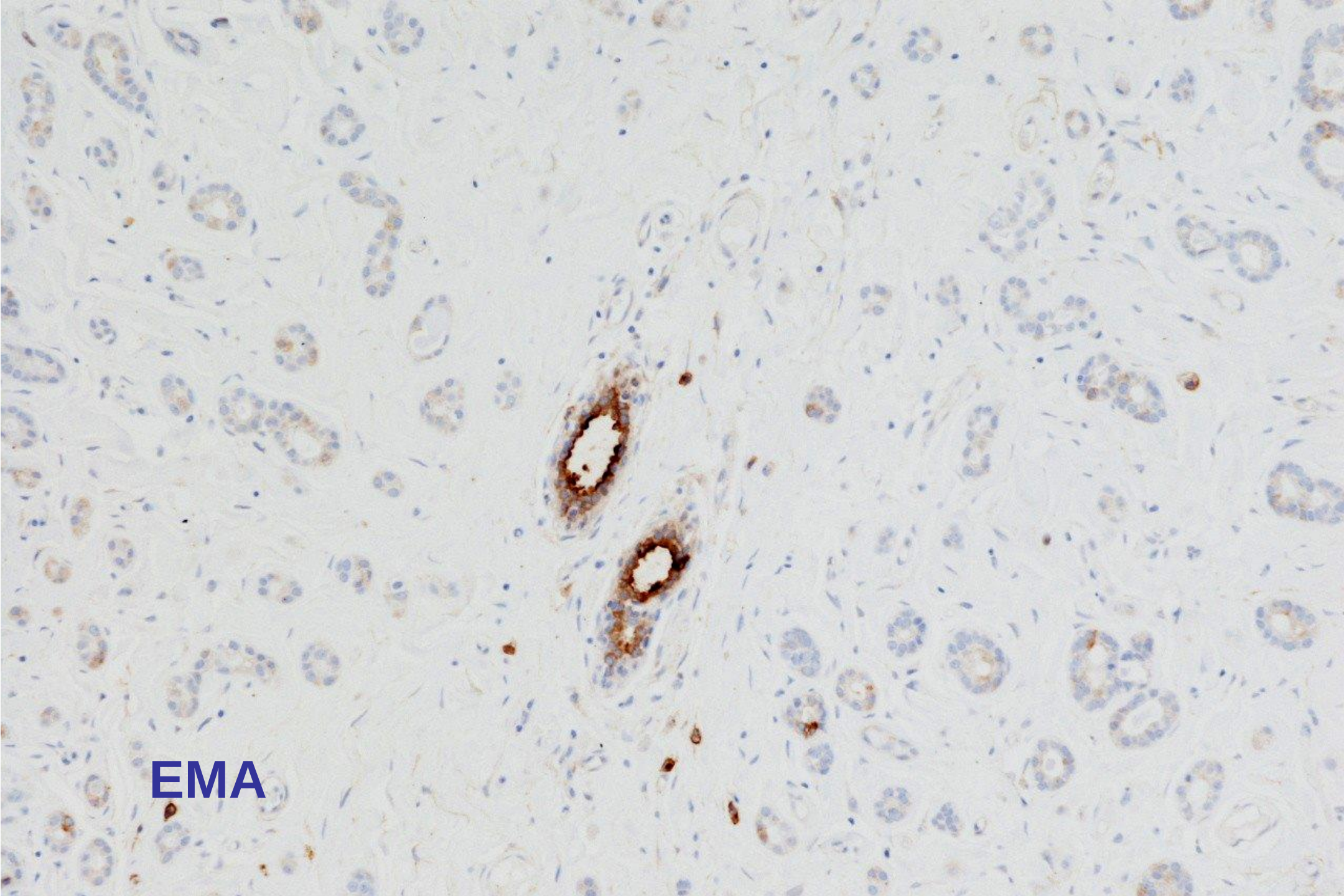
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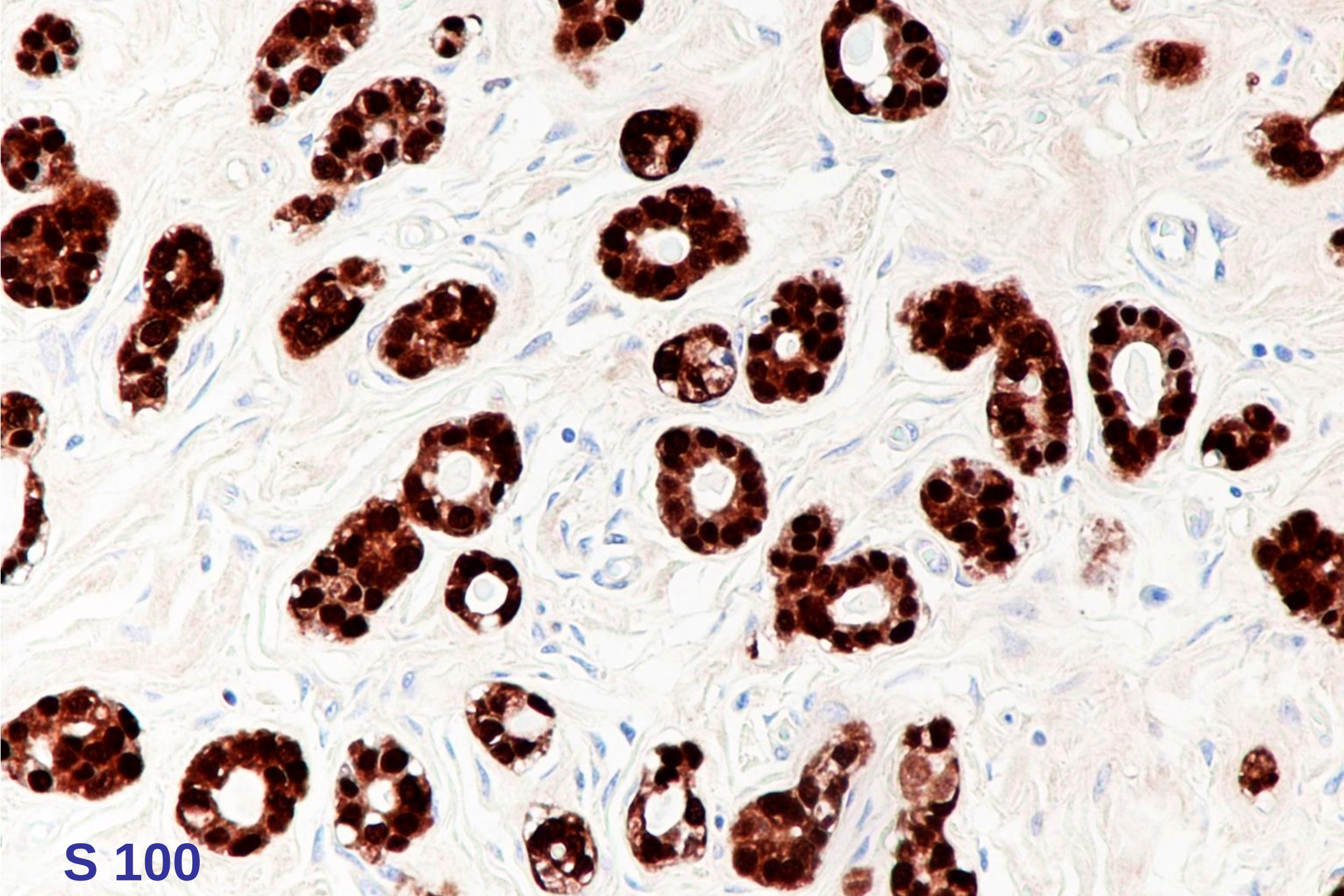
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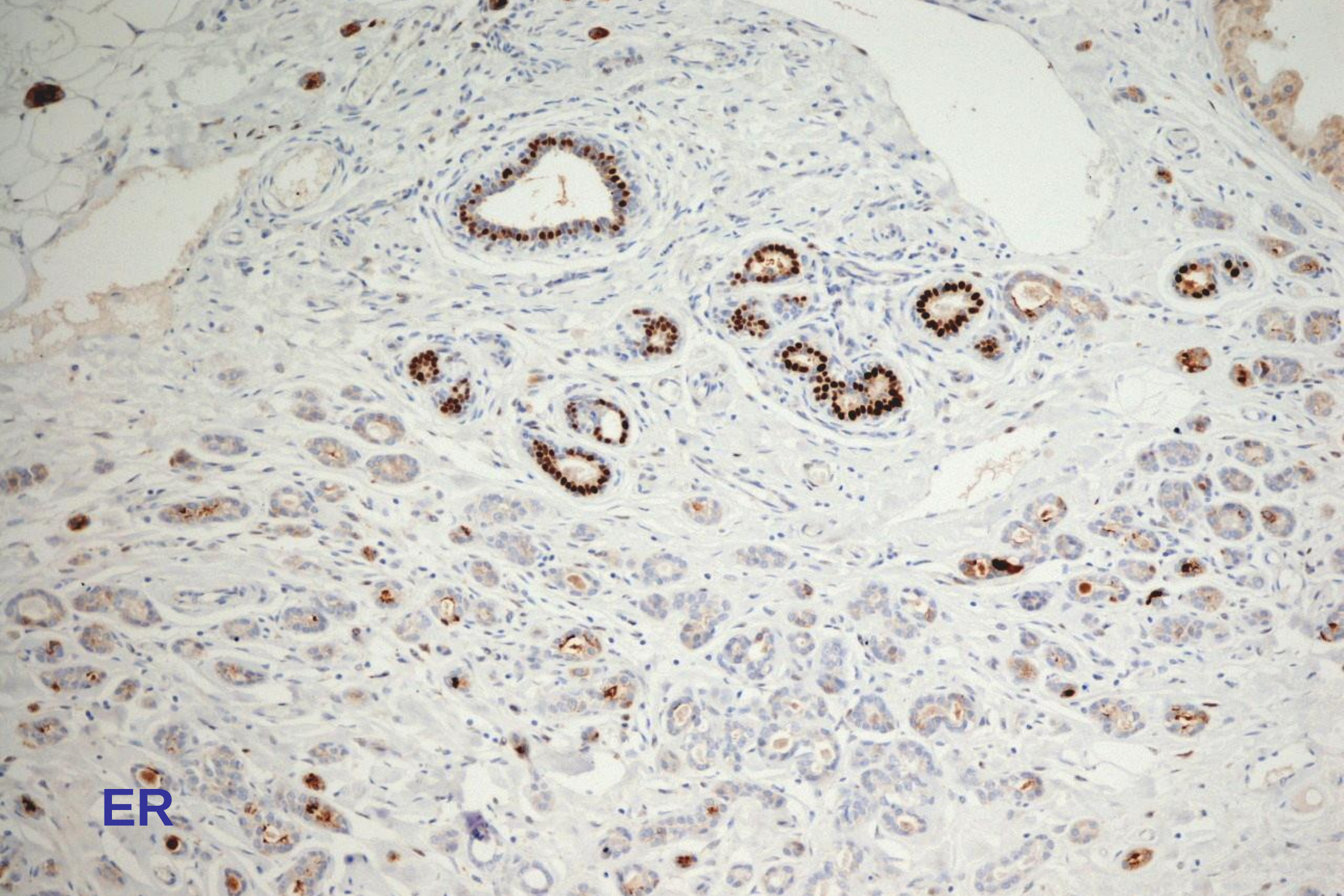
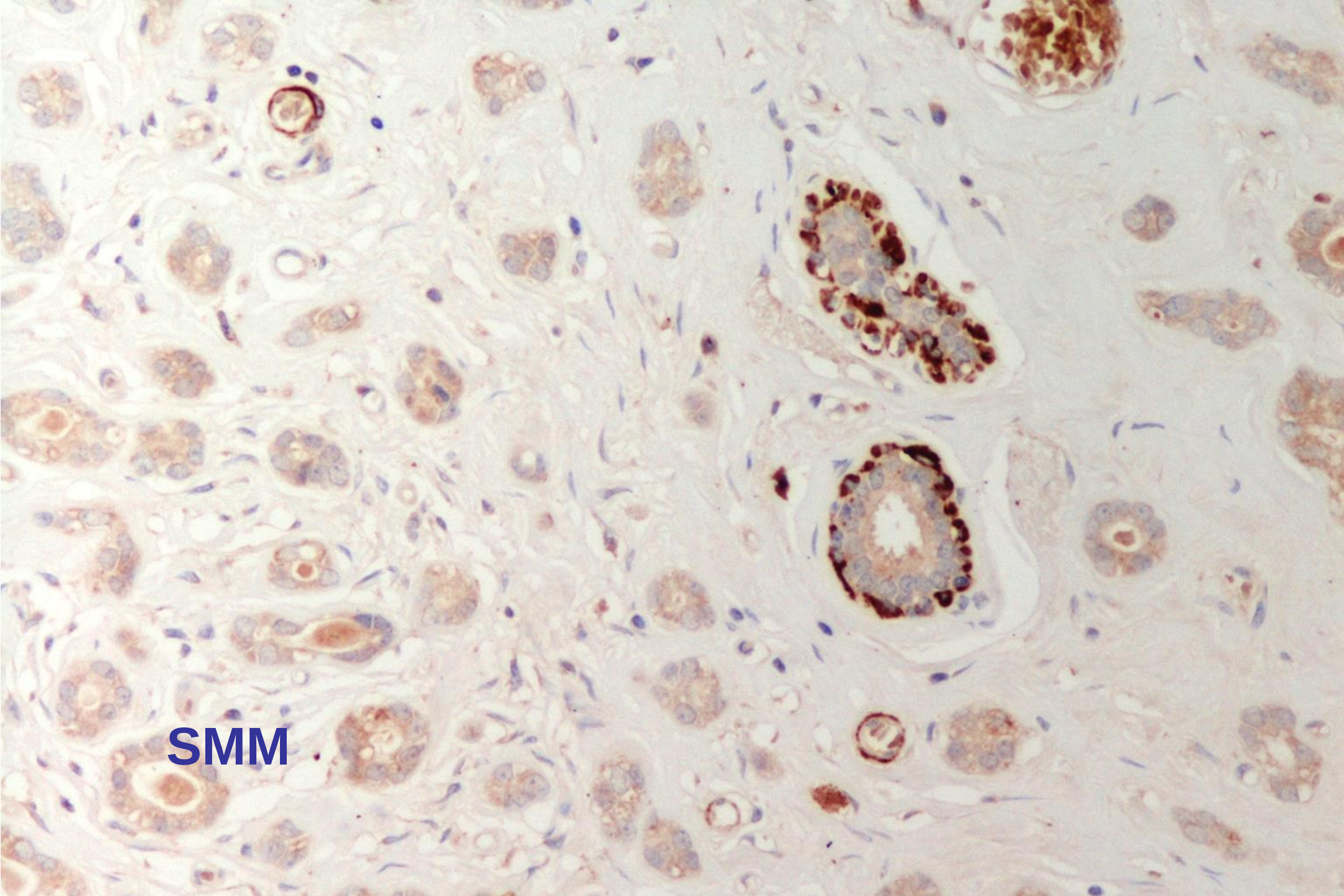
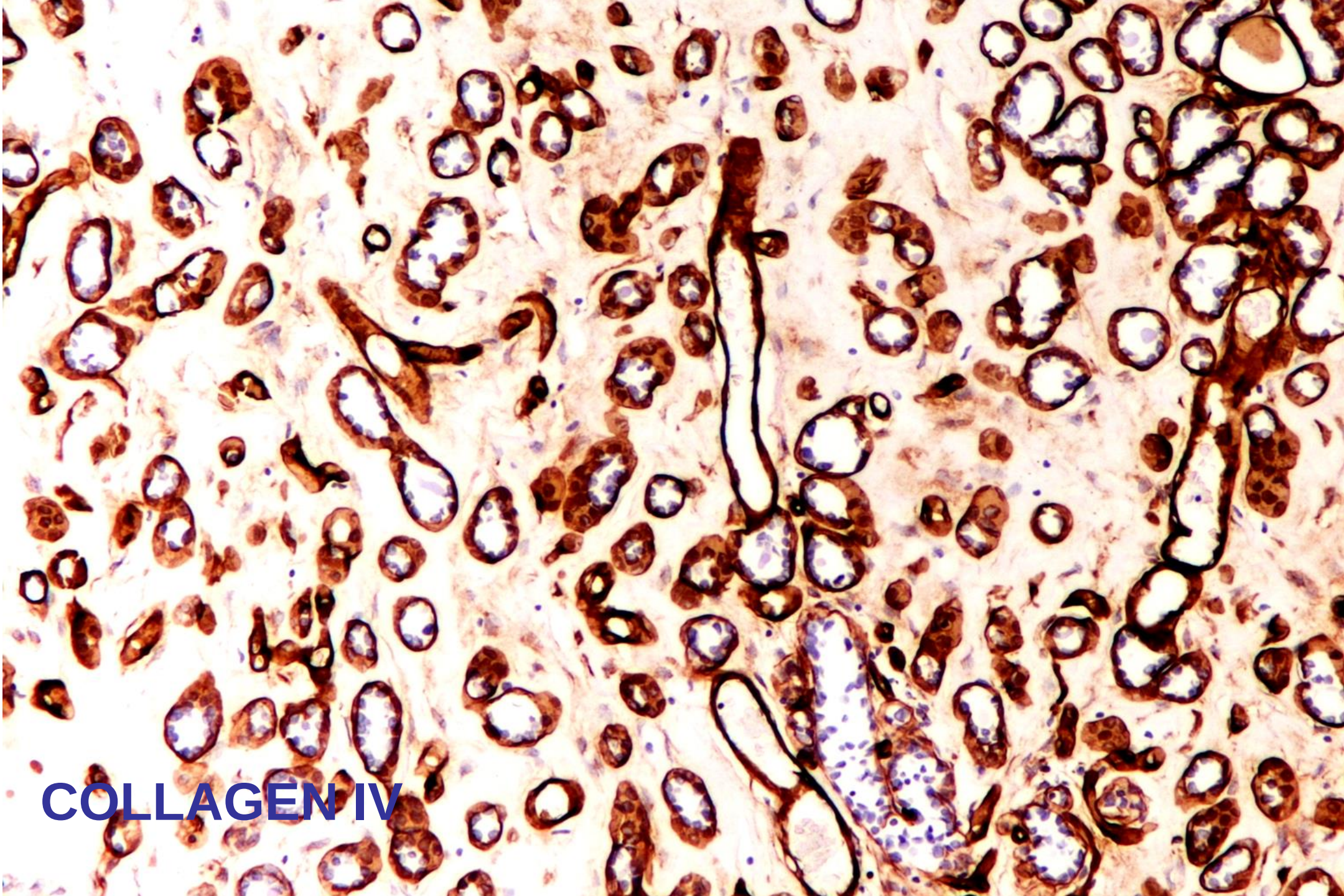

ER


SMM


COLLAGEN IV

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 CK, S100

    - EMA, ER, PR, Her 2, GCDFP

Microglandular adenosis

Prognostic implications

- Probably indolent in its uncomplicated form

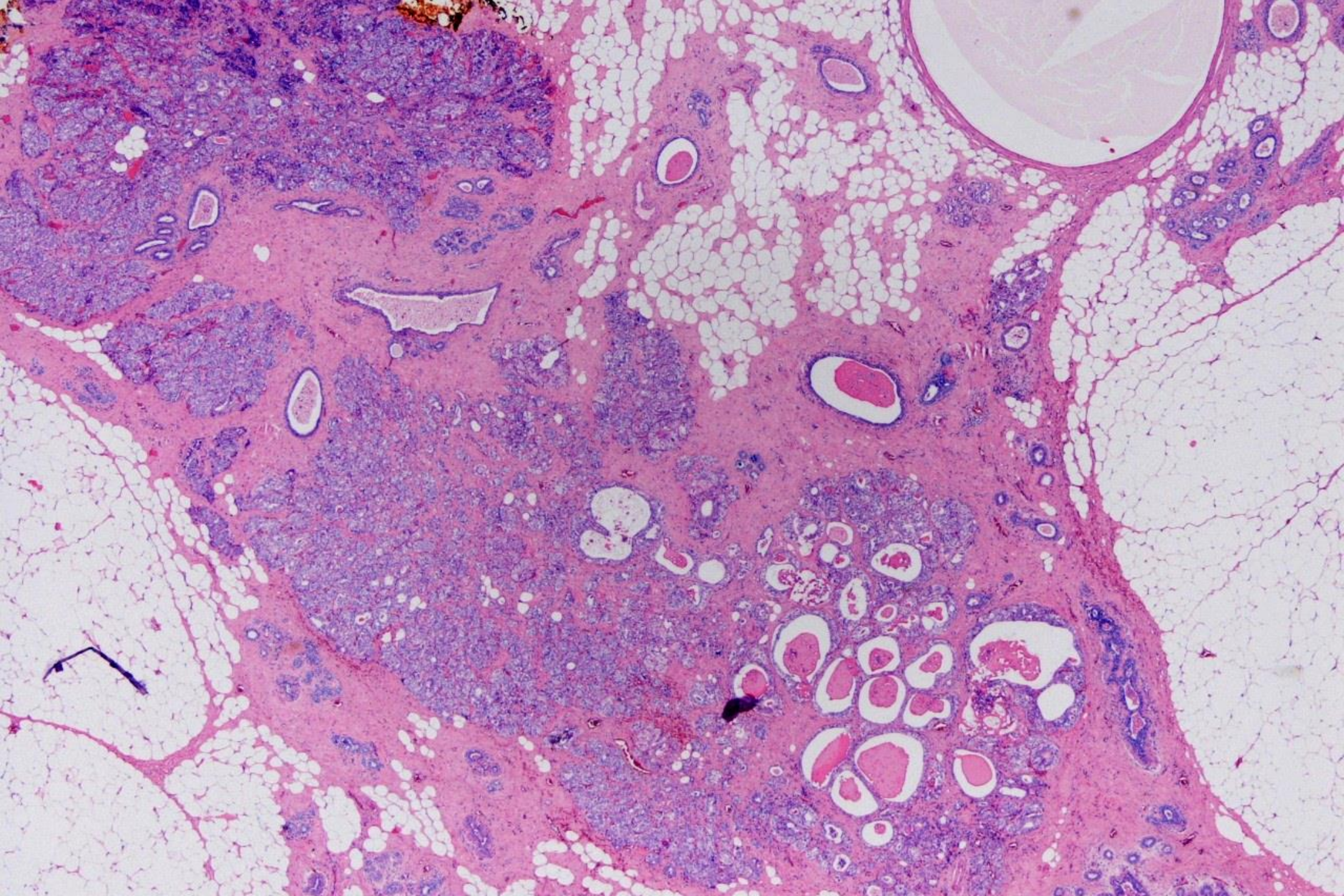
BUT:

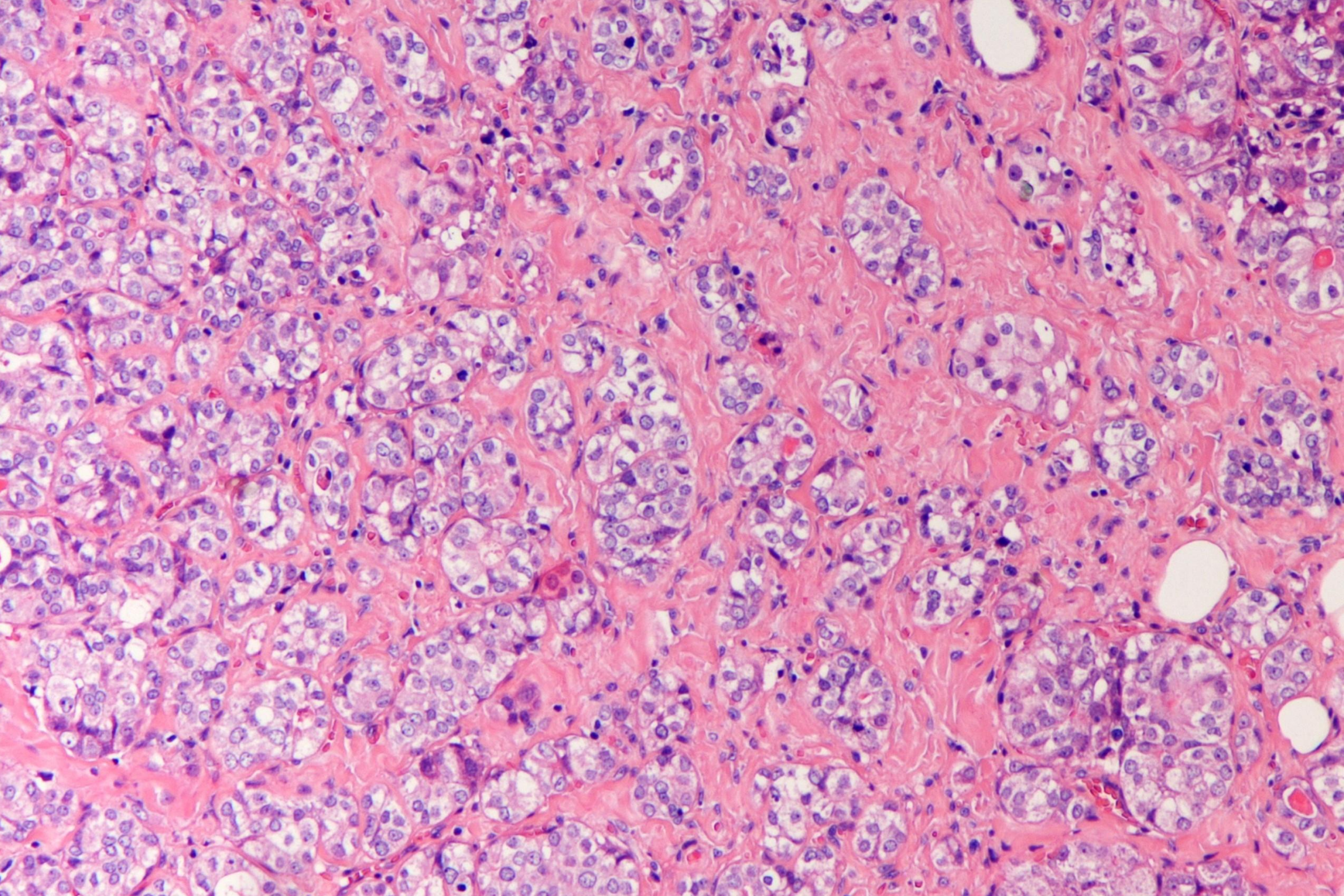
- Rosen (1) reported 14 carcinomas among 60 MGA
- Page (2) reported 17 cases of ACC associated with MGA
- Tavassoli (3) reported 20 cases of in situ and invasive carcinoma associated with MGA
- Atypical MGA

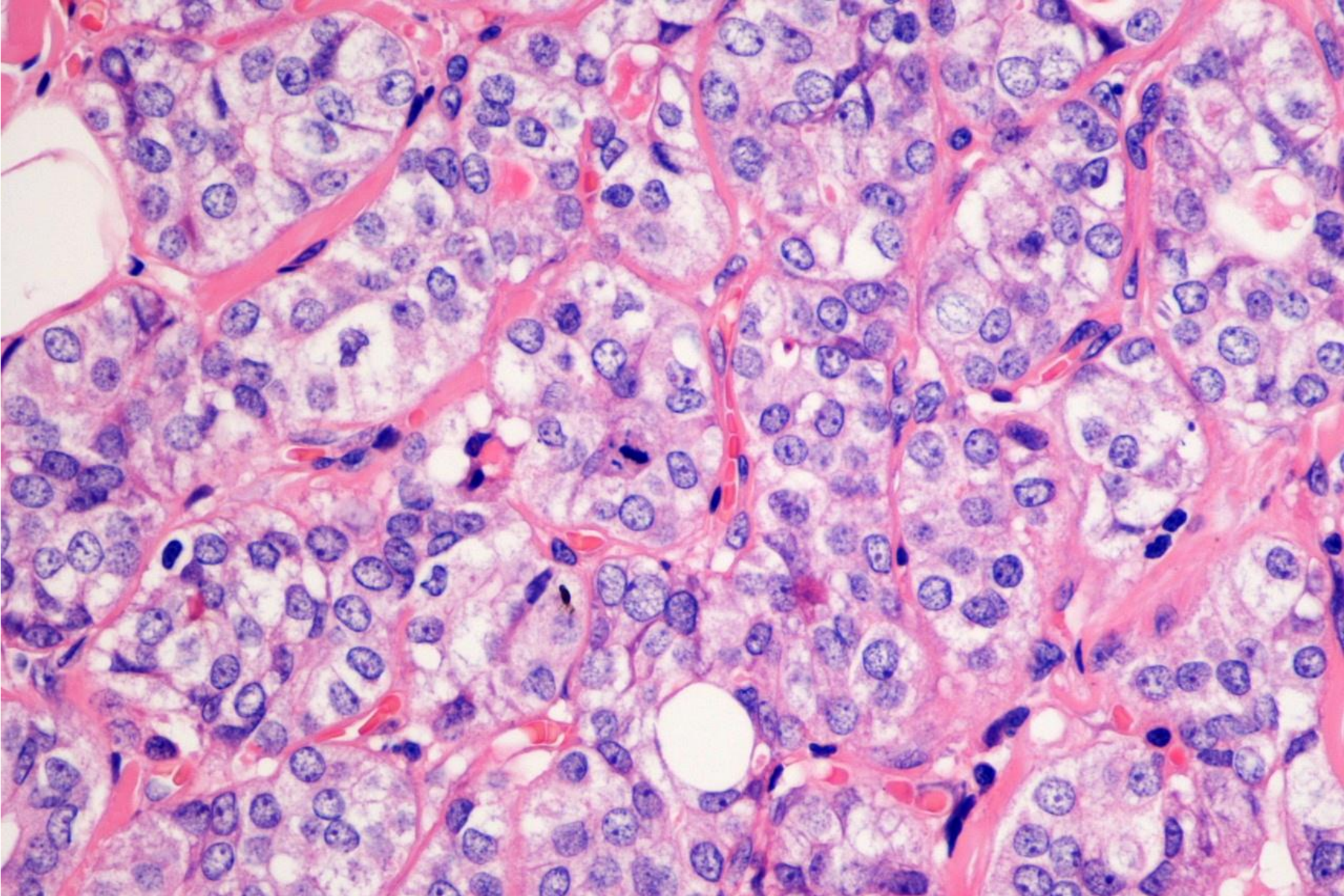
(1) Carcinoma of the breast arising in Microglandular Adenosis. Am.J.Clin. Path. 1993; 100:507-13

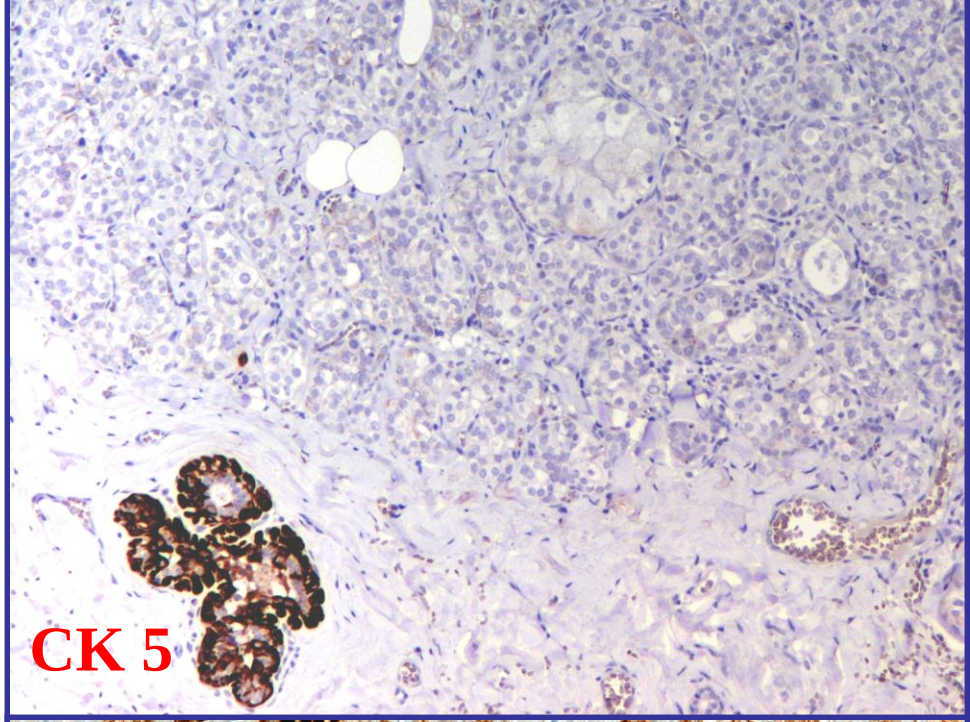
(2) Microglandular Adenosis with transition into Adenoid Cystic Carcinoma of the breast. Am.J.Surg.Path. 27(8) 1052-60 2003

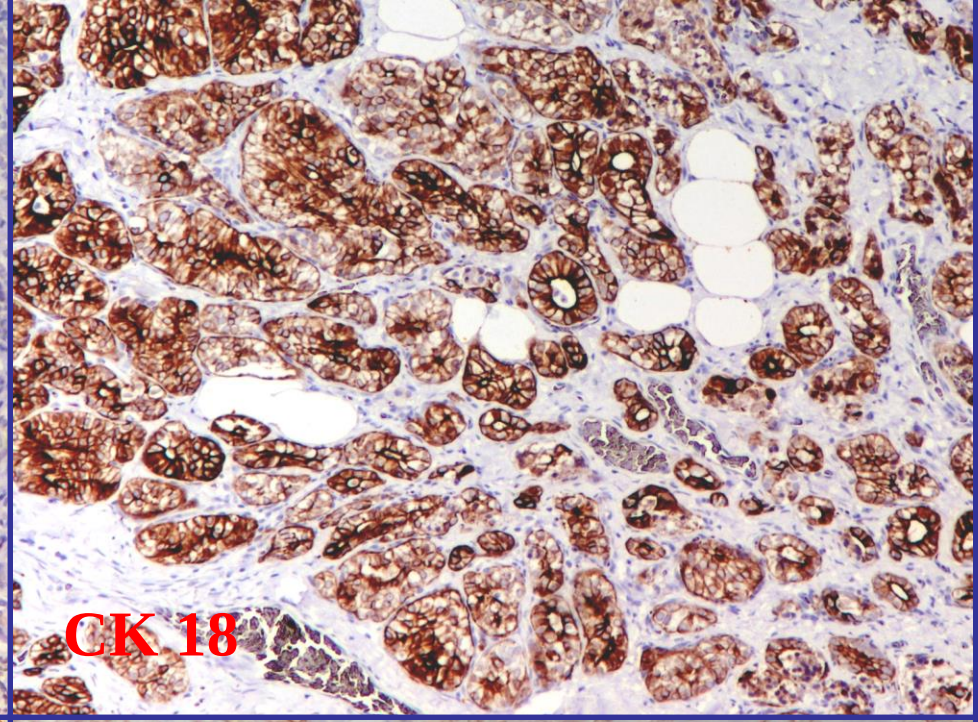
(3) Carcinoma arising in MGA Int.J.Surg.Path. 2000;8 303-15








CK 5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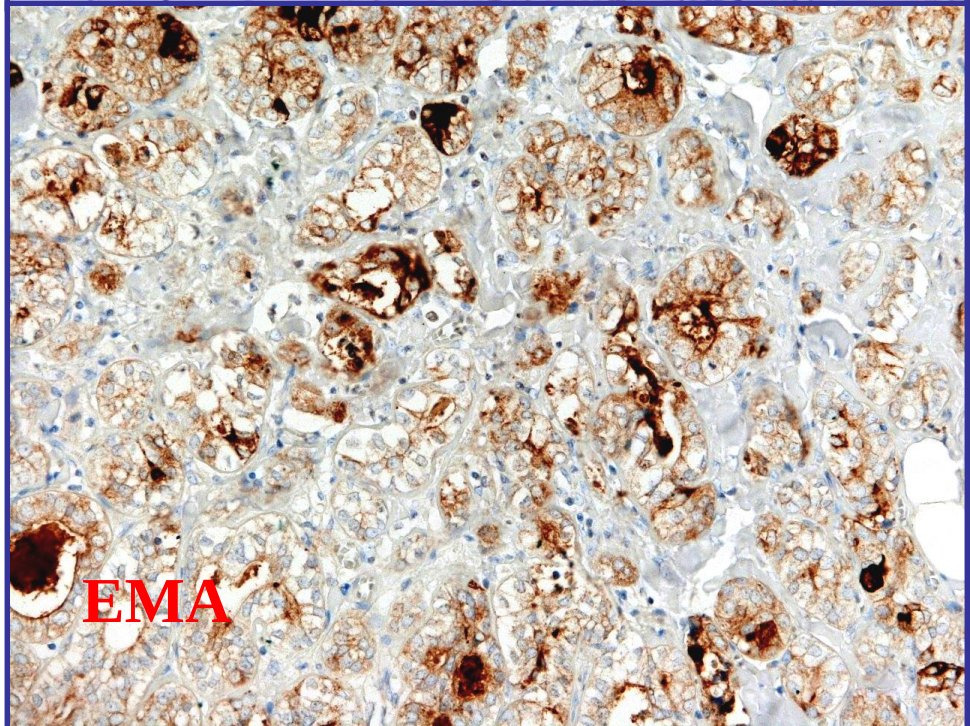
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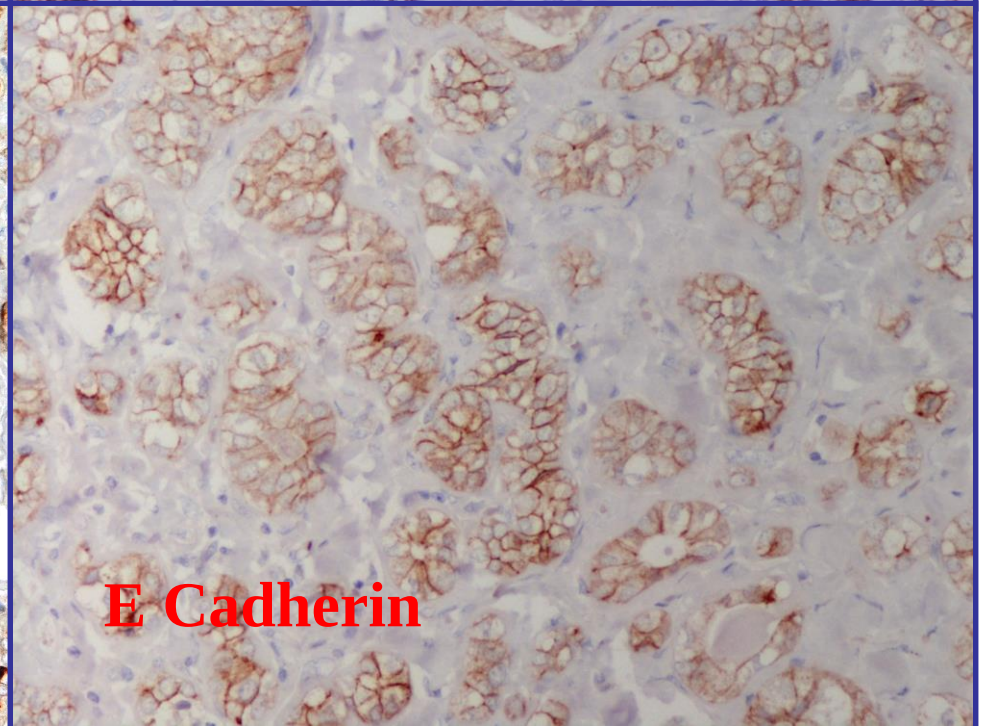
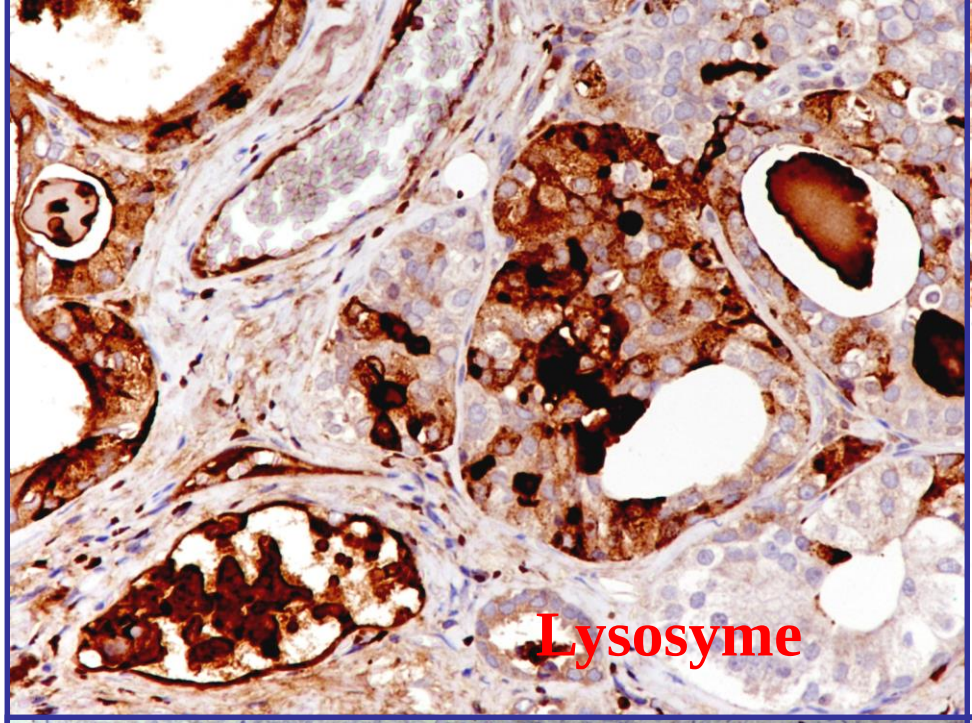

E Cadherin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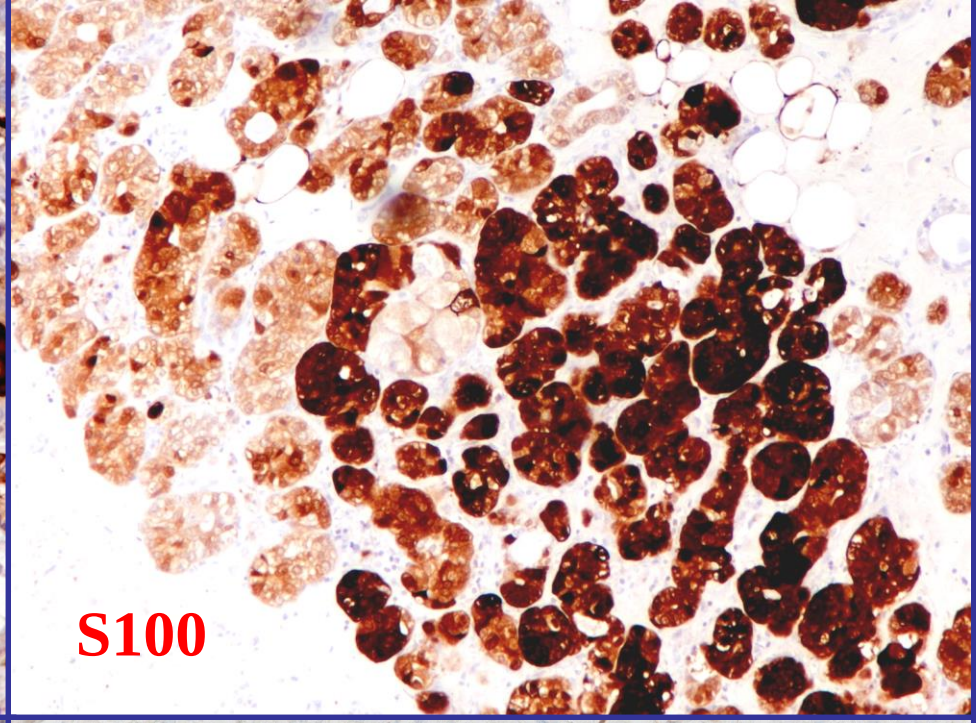
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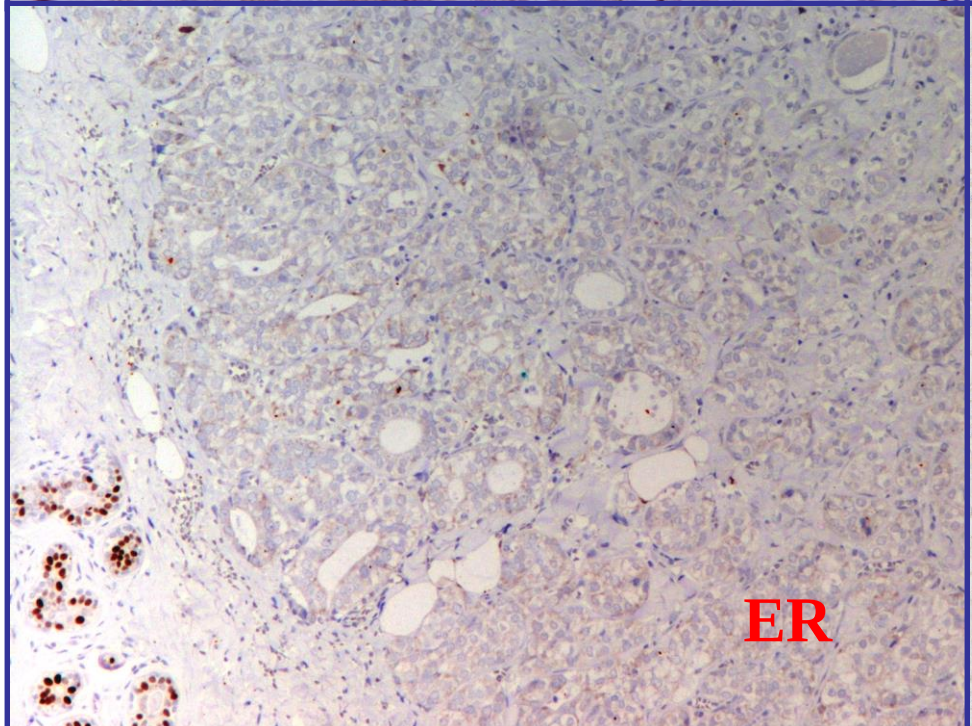
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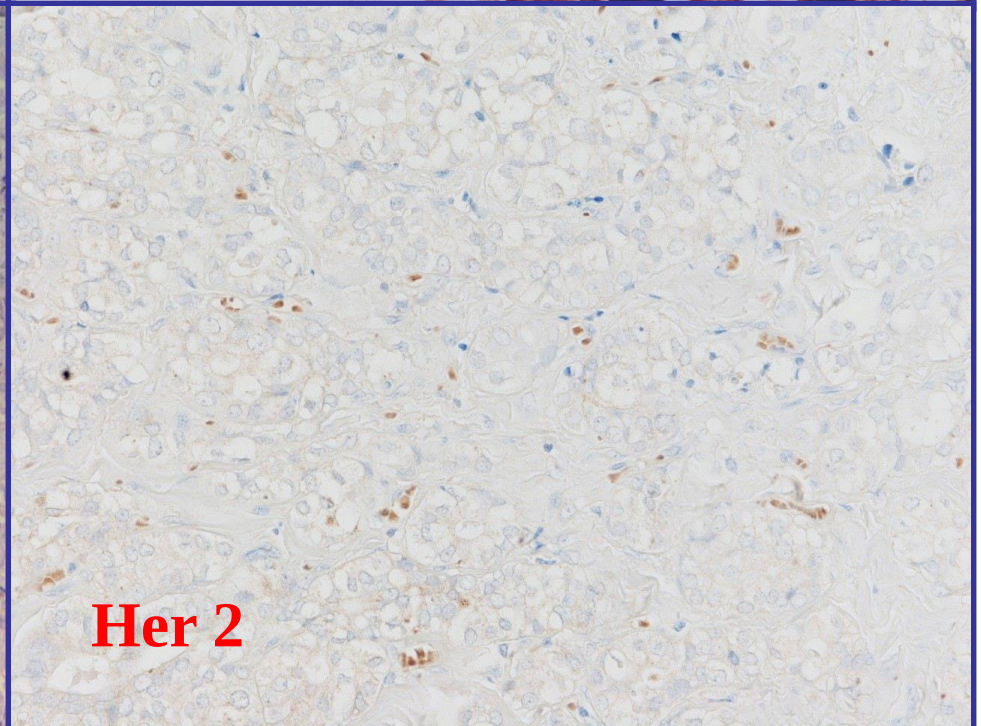
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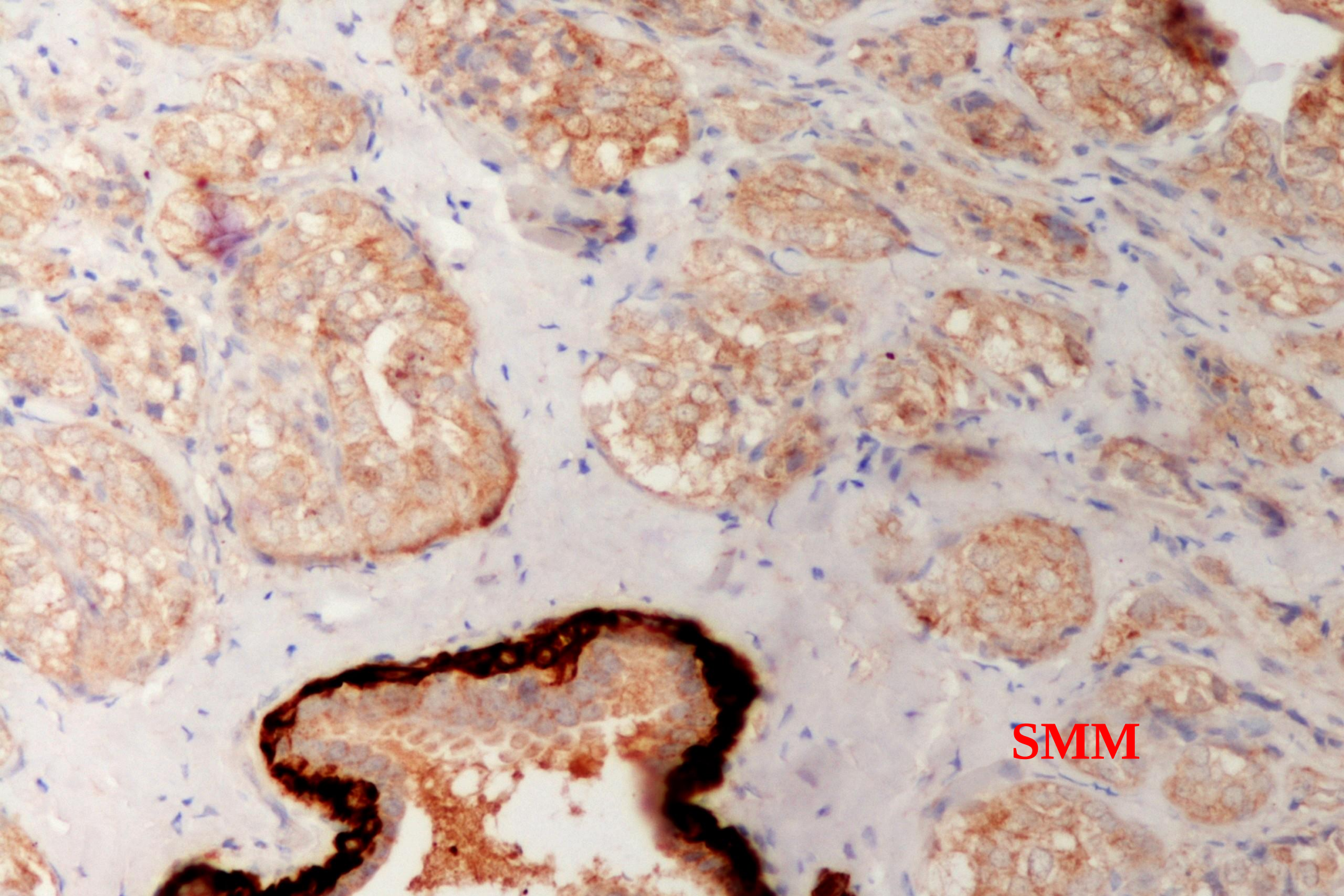
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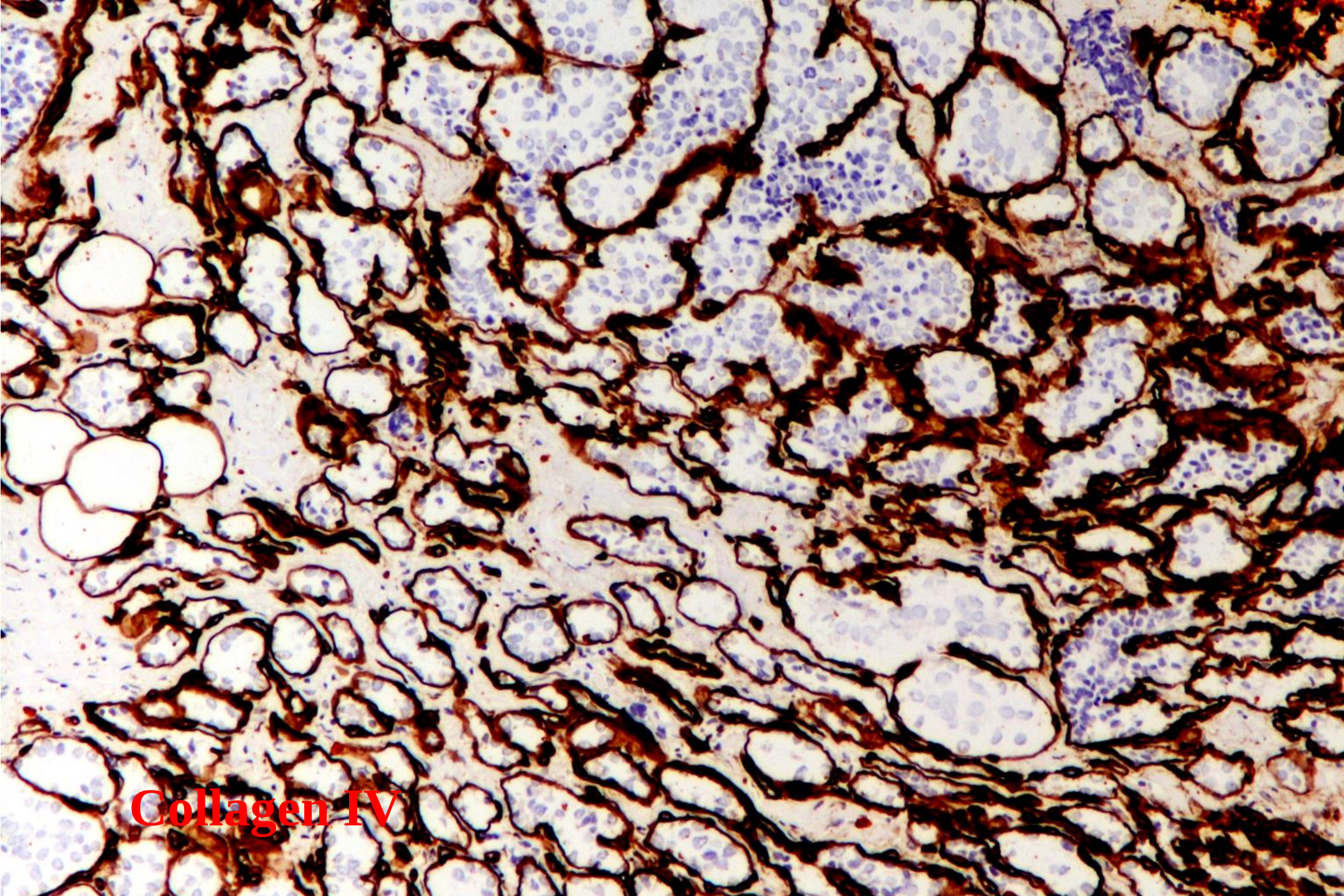
Collagen IV

Journal of Pathology
J Pathol 2016; **238:** 677–688
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4691

ORIGINAL PAPER

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

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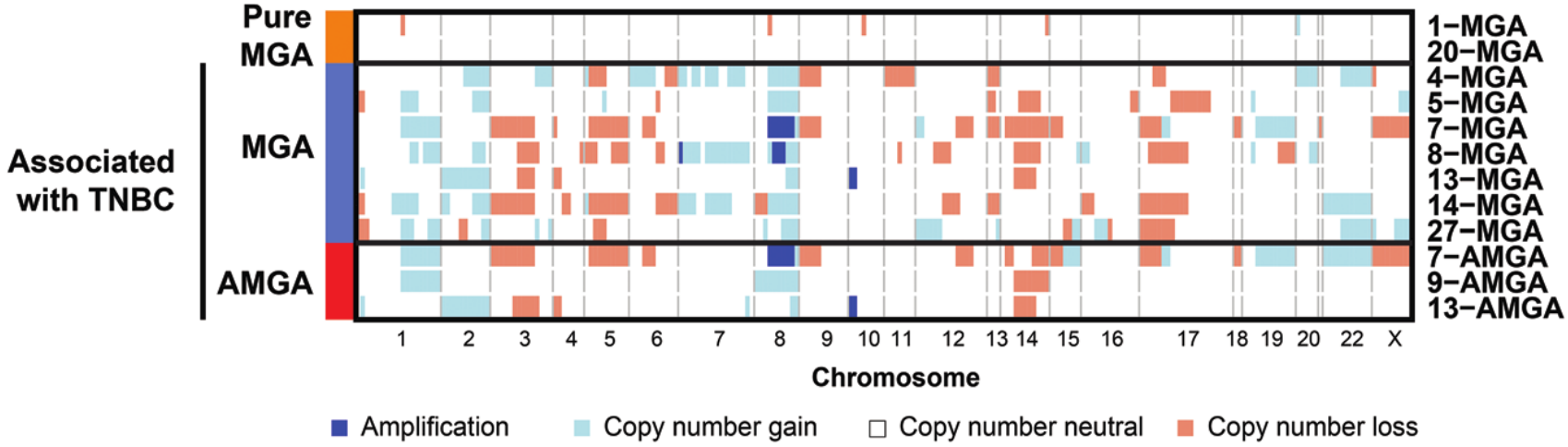

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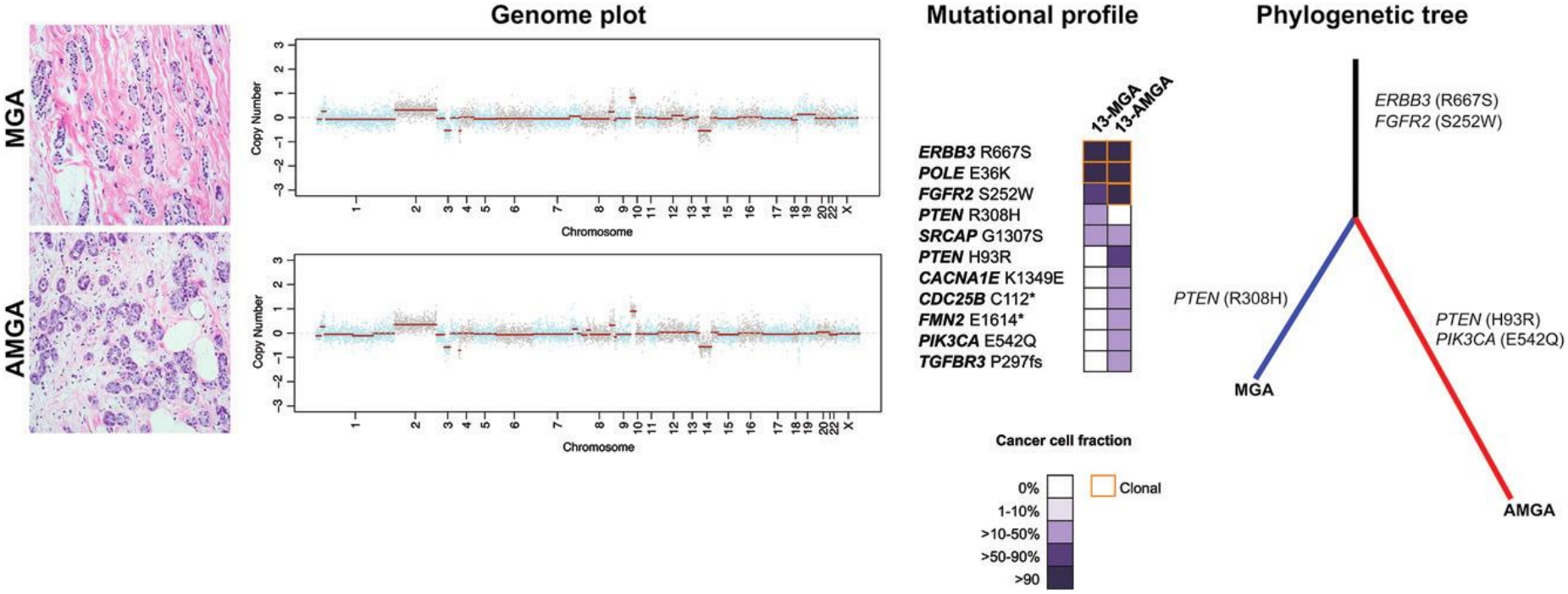

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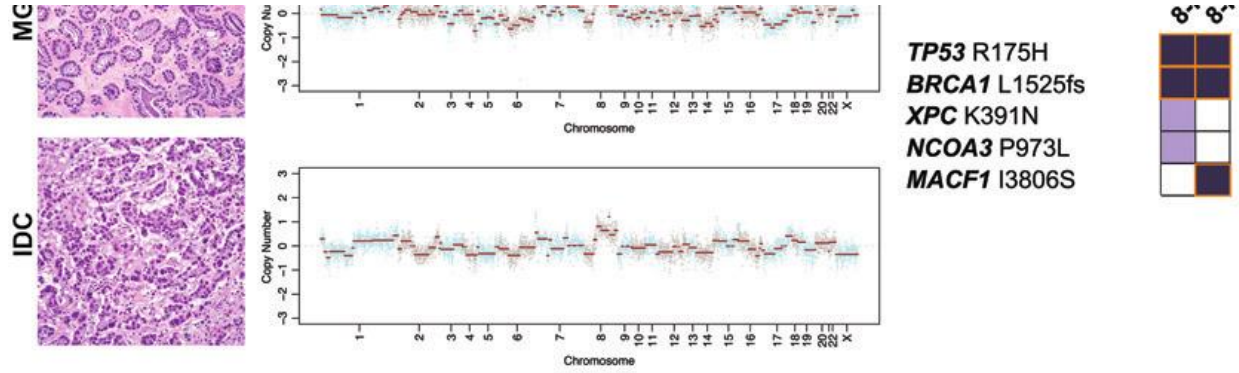

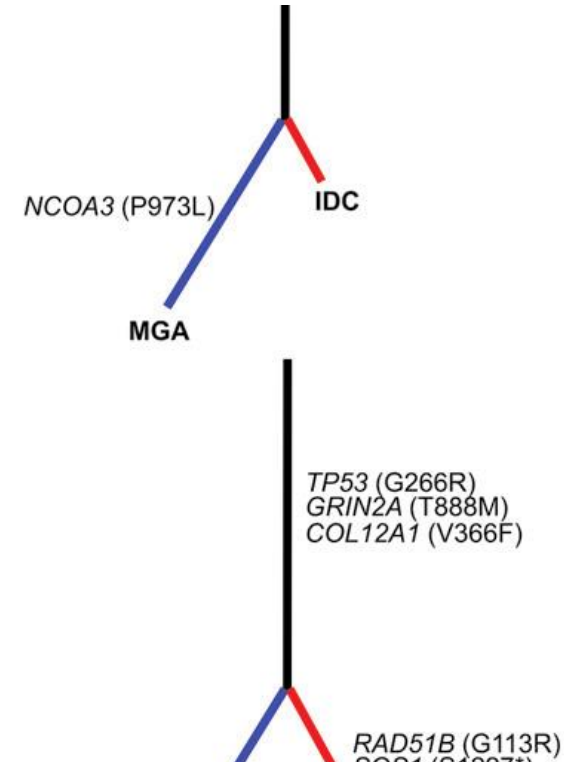

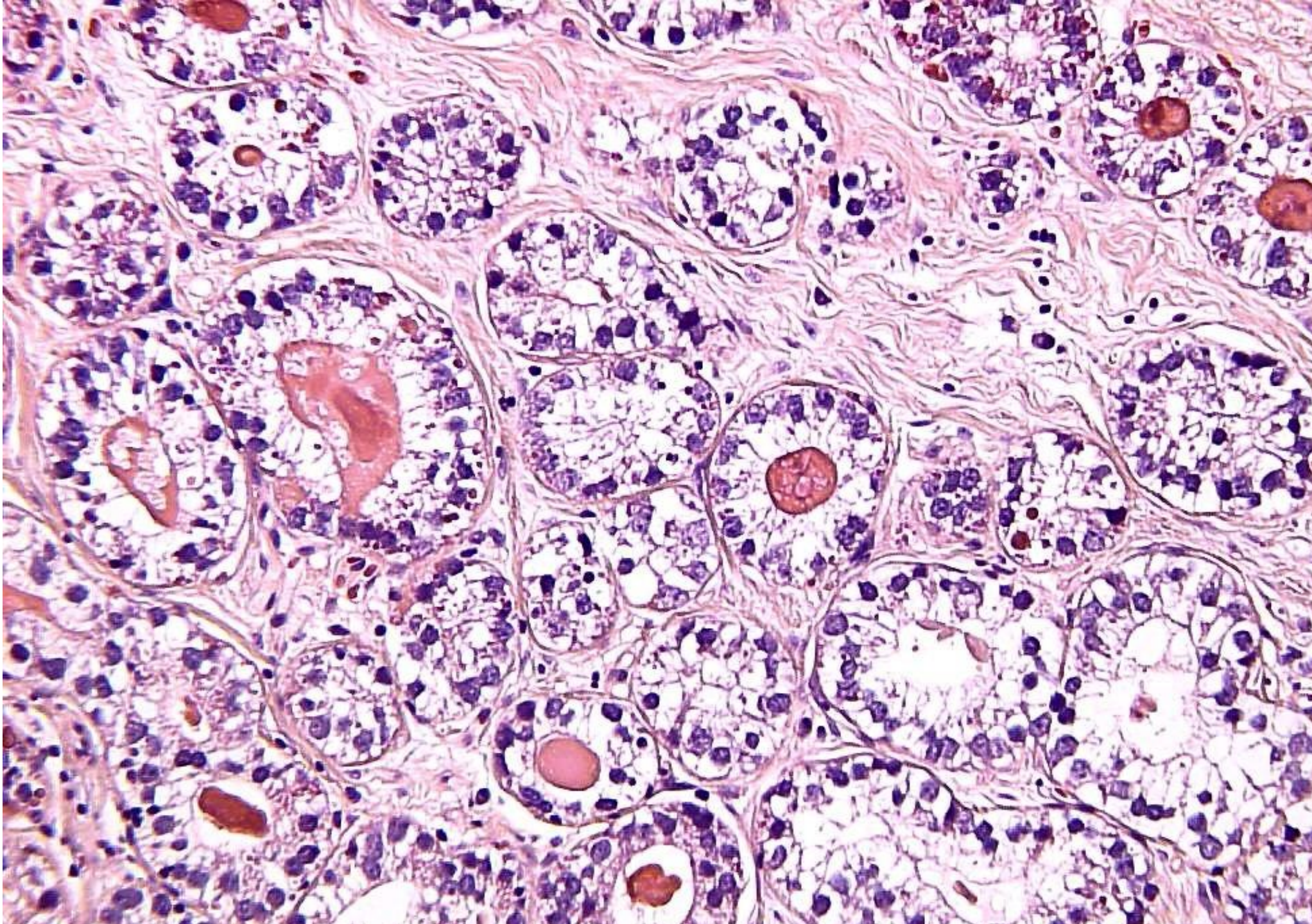

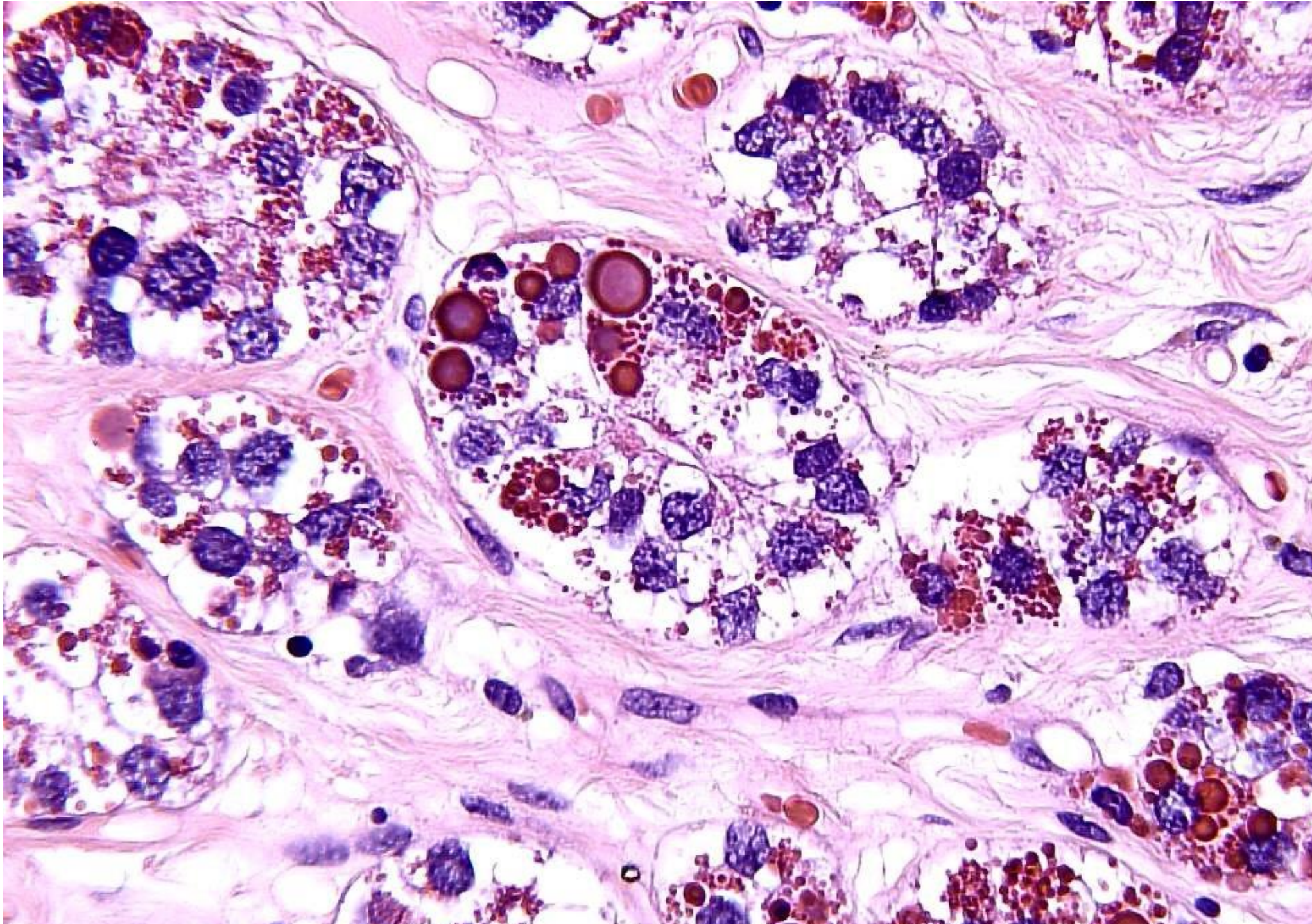

AcCC v MGA

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- IHC similarities- CK,S100,ER,Lysosyme, Her2,

But

- AcCC usually with solid areas
- Lack of BM
- IHC differencies-EMA, ?Amylase
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Acinic cell carcinoma

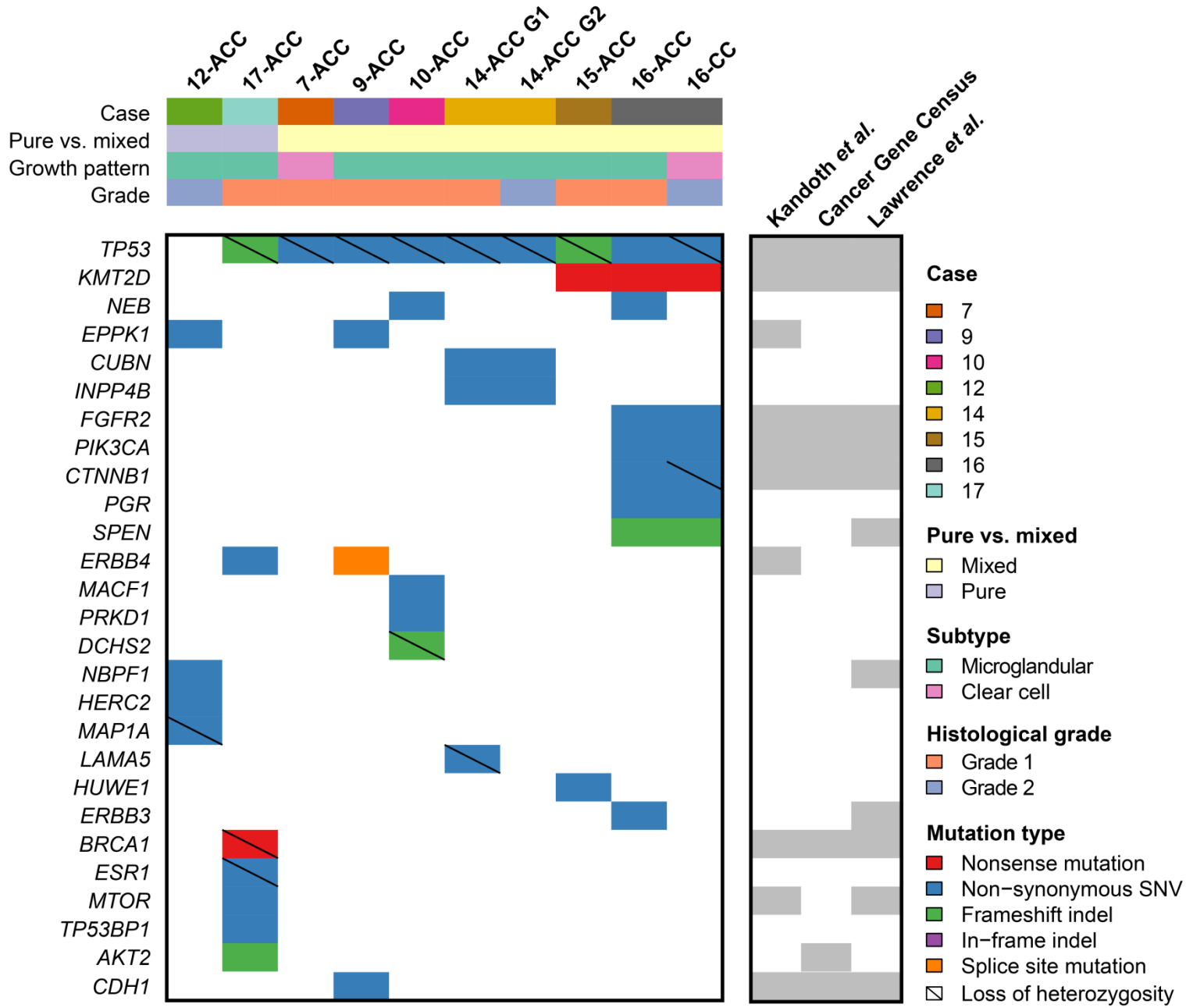
Journal of Pathology
J Pathol 2015; **237:** 166–178
Published online 29 July 2015 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4566

ORIGINAL PAPER

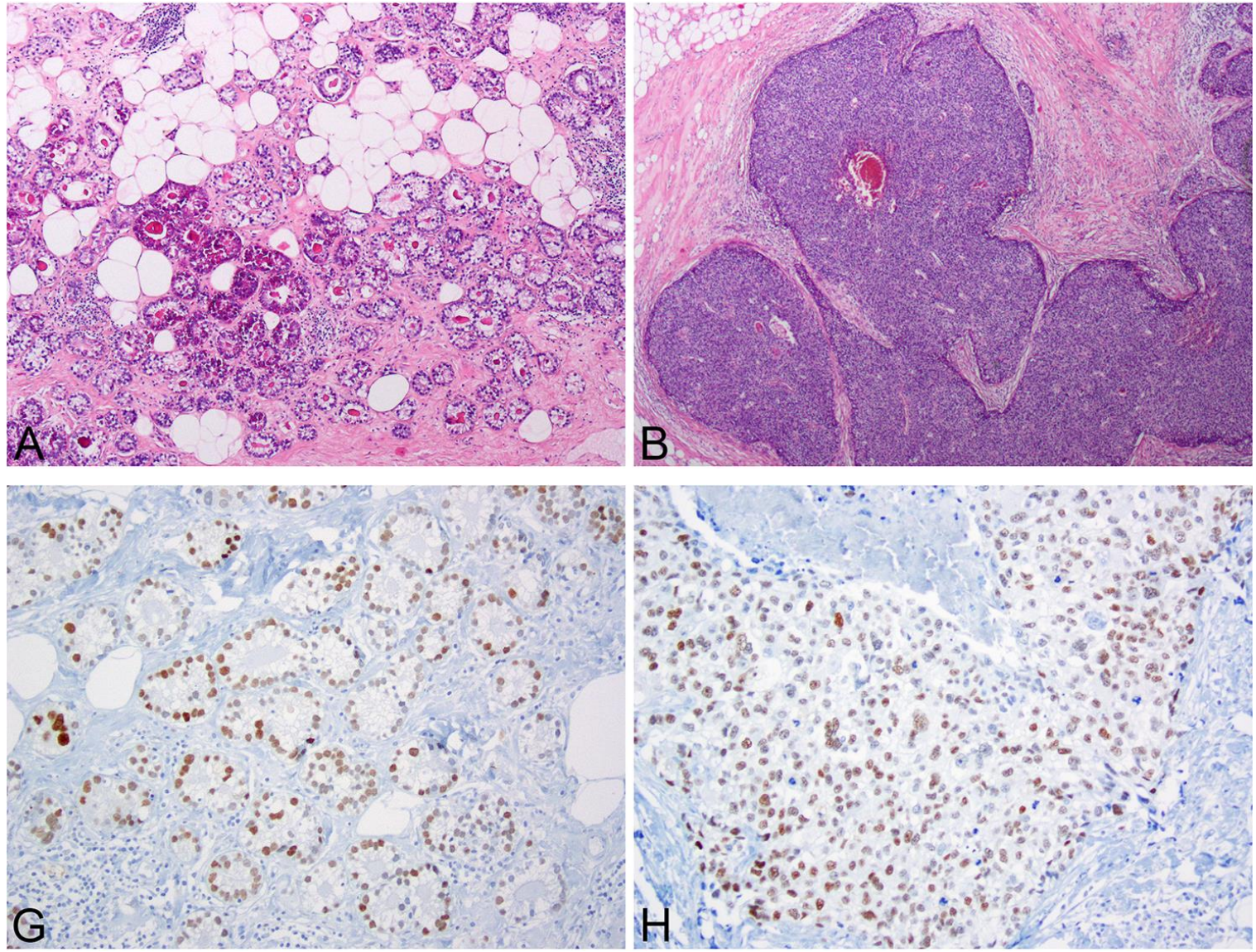
The repertoire of somatic genetic alterations of acinic cell carcinomas of the breast: an exploratory, hypothesis-generating study

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

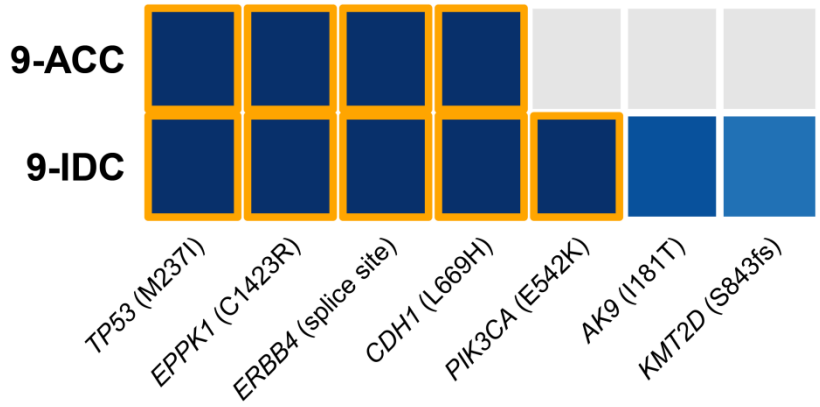
Landscape of somatic genetic alterations

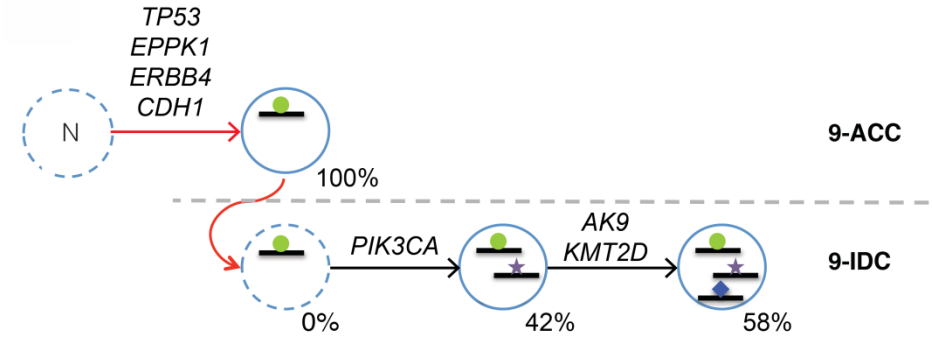


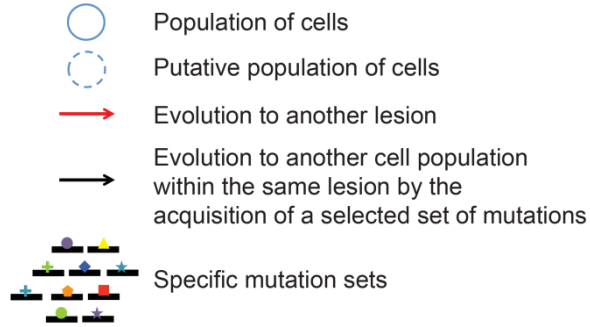
ACCs and high grade TNBCs share identifcal *TP53* mutations and p53 expression



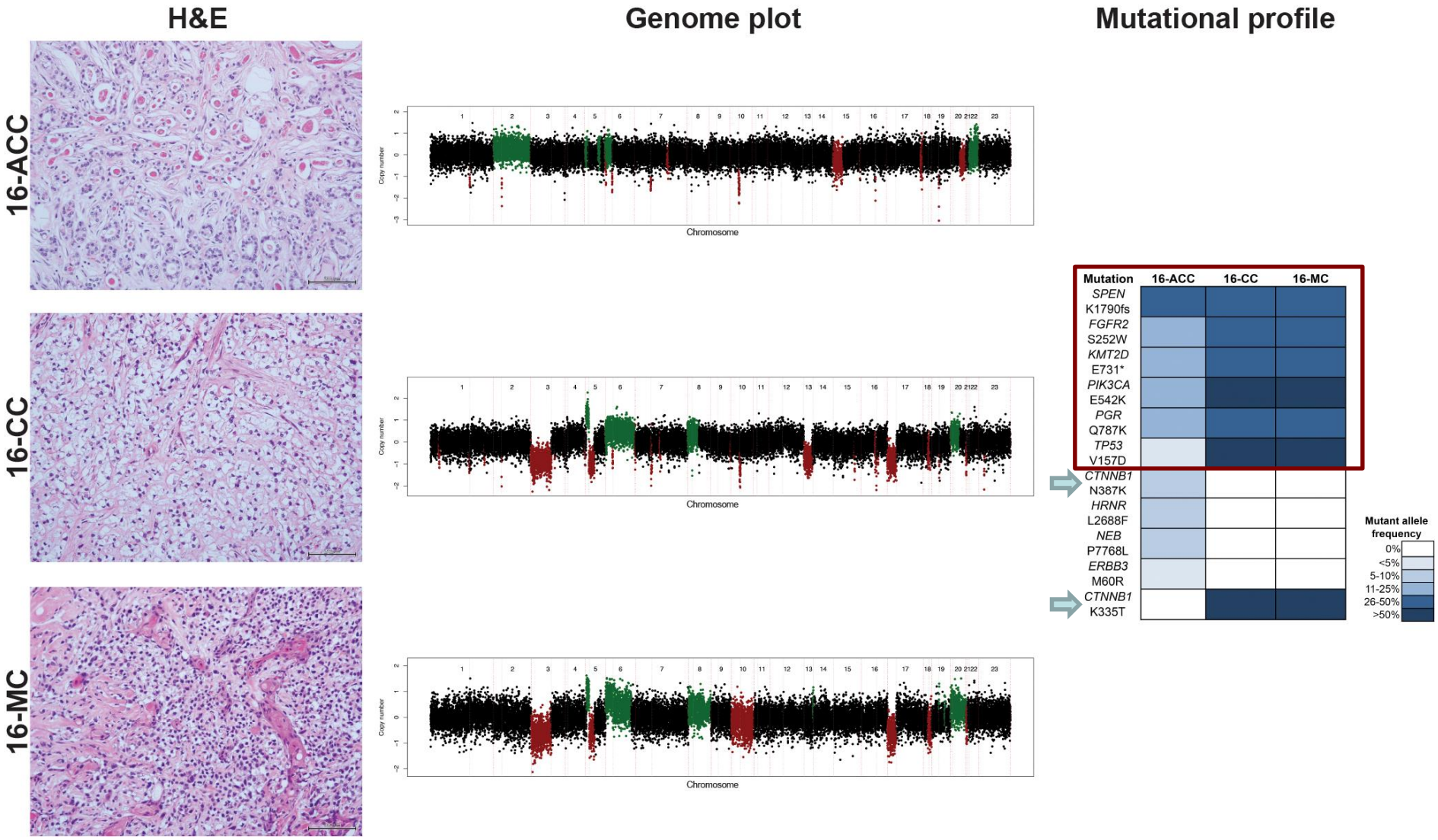
Progression from ACC to high-grade TNBC







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



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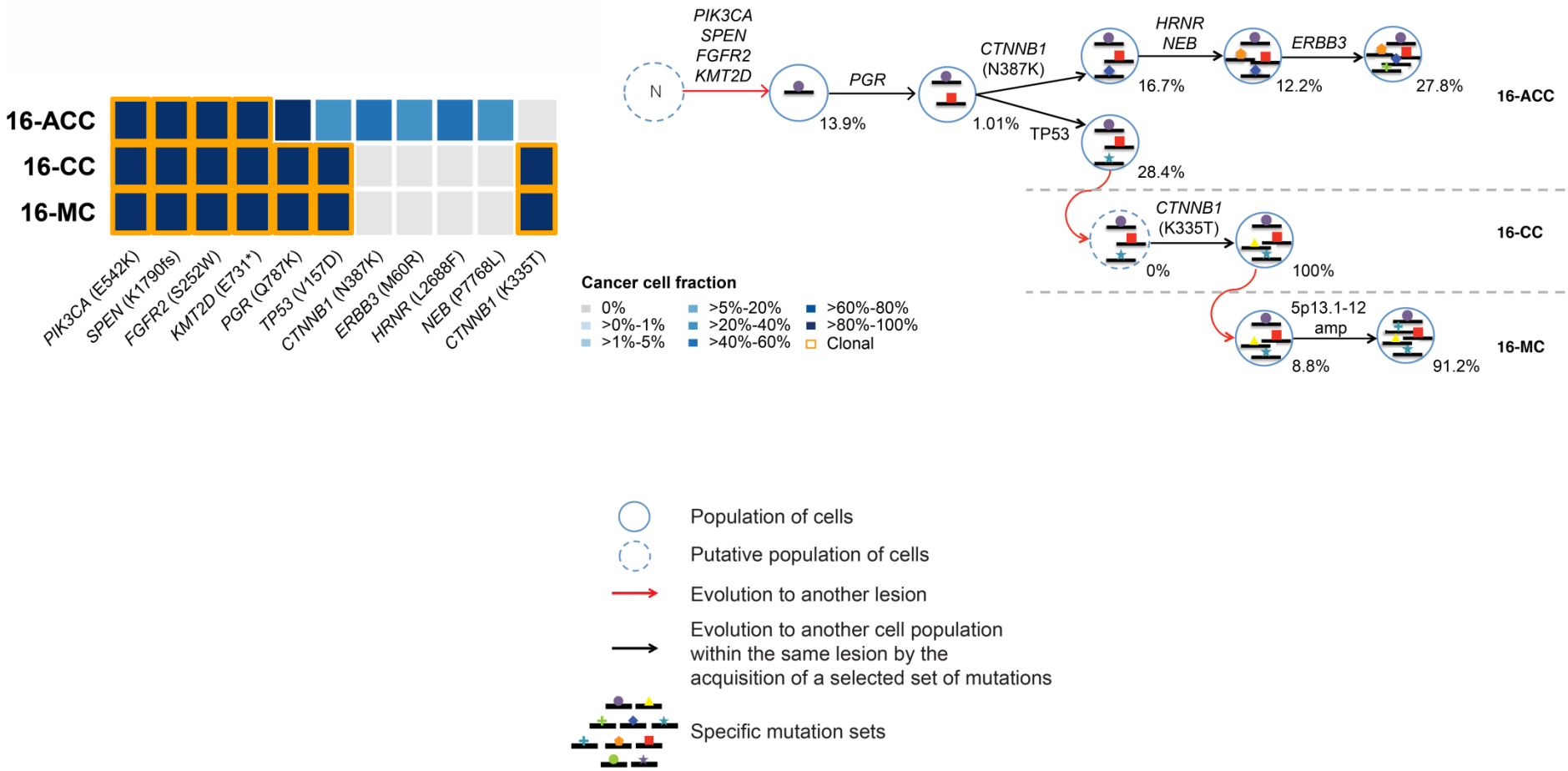
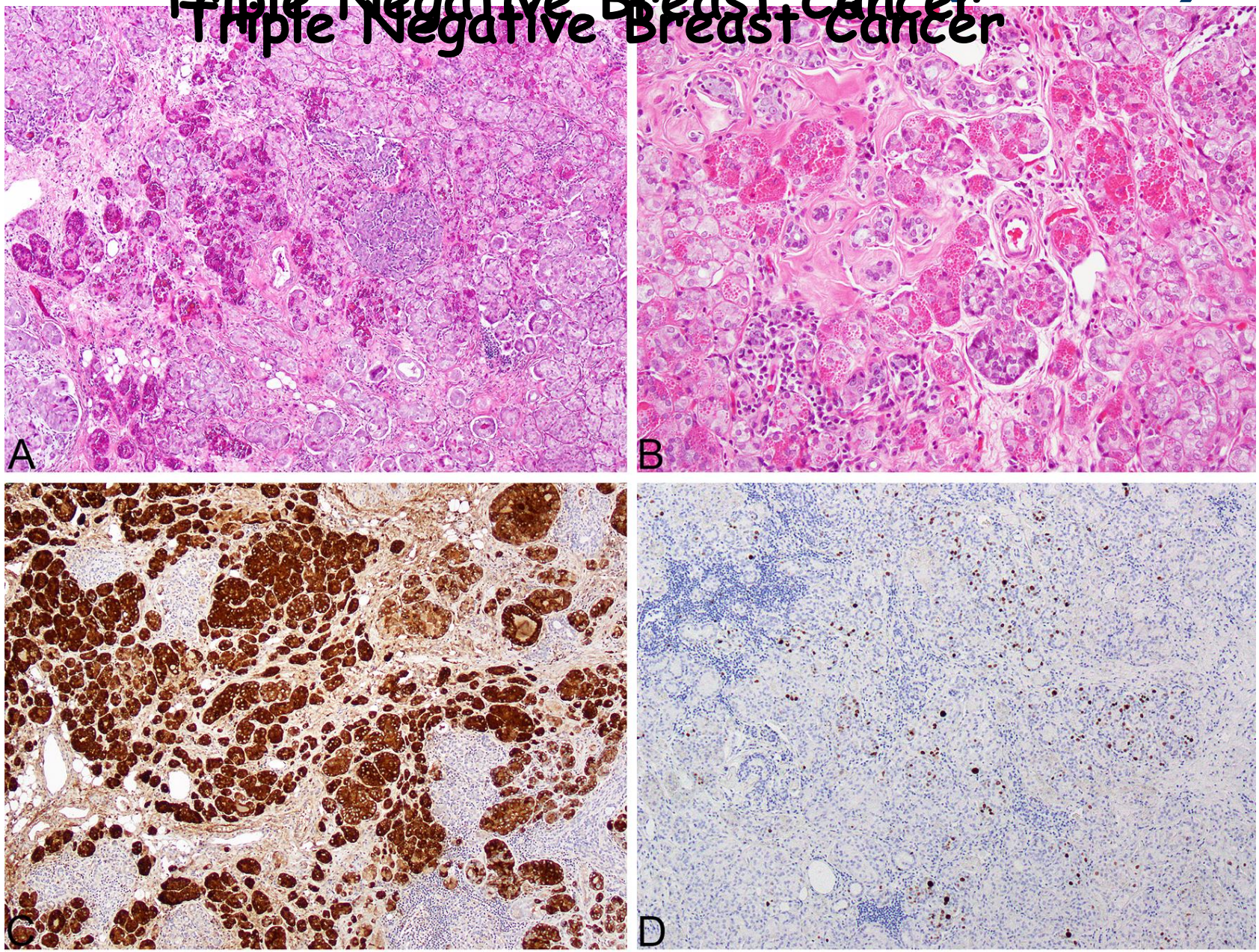
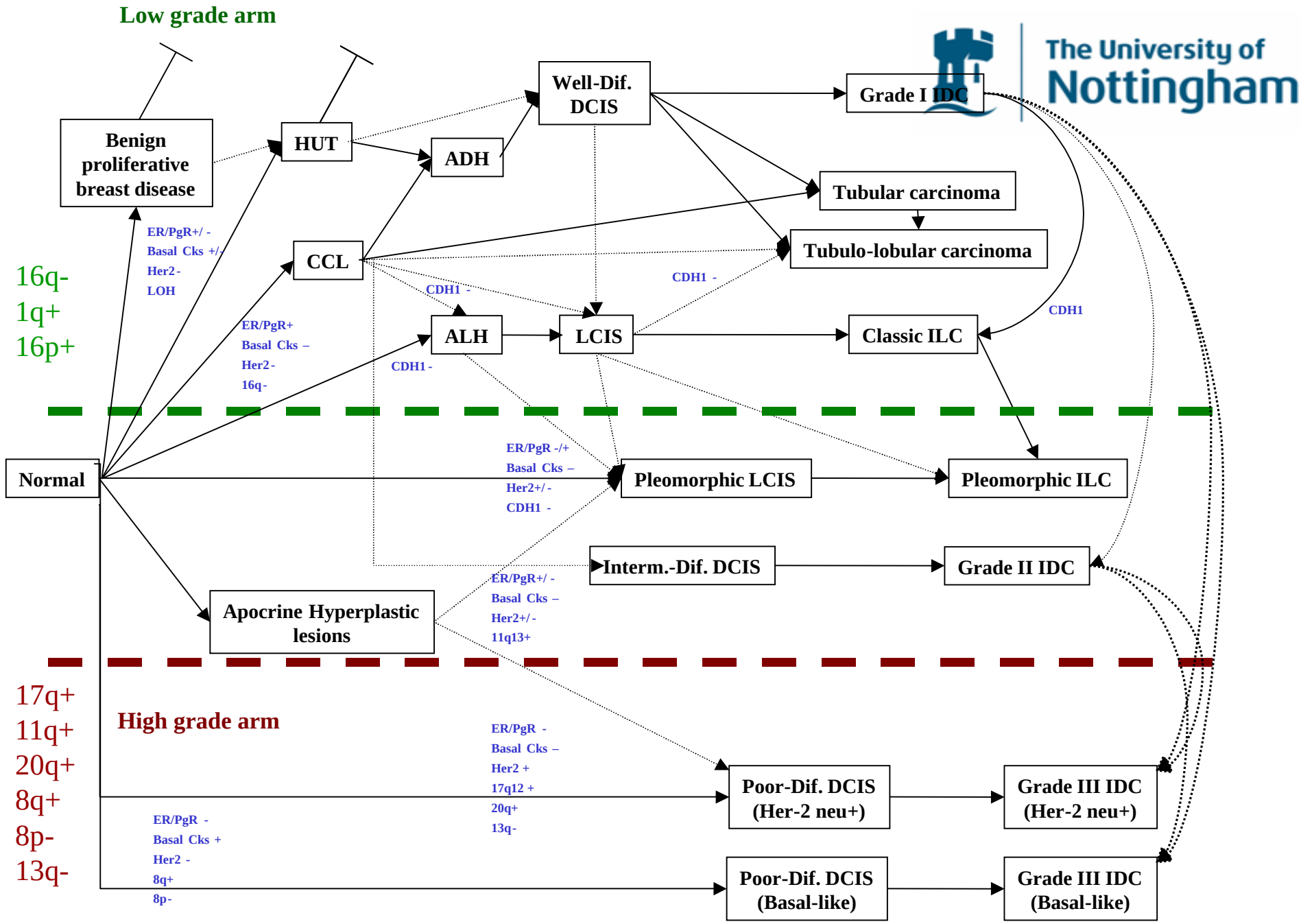


Acinic cell carcinomas (ACCs)

Triple Negative Breast Cancer

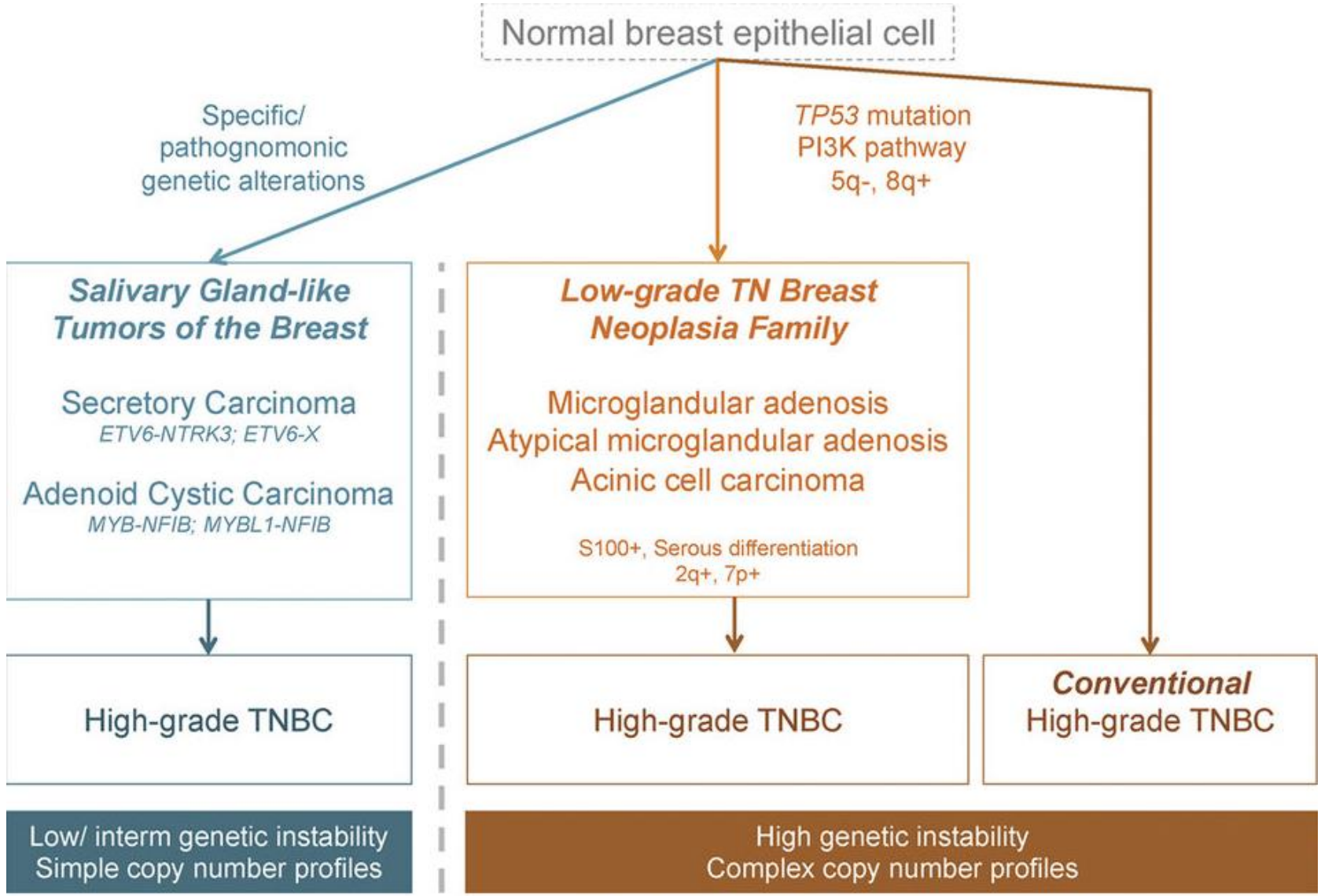
Triple Negative Breast Cancer





Simpson P, et al. J Pathol. 2005 Jan;205(2):248-54.

Triple Negative Breast Cancer

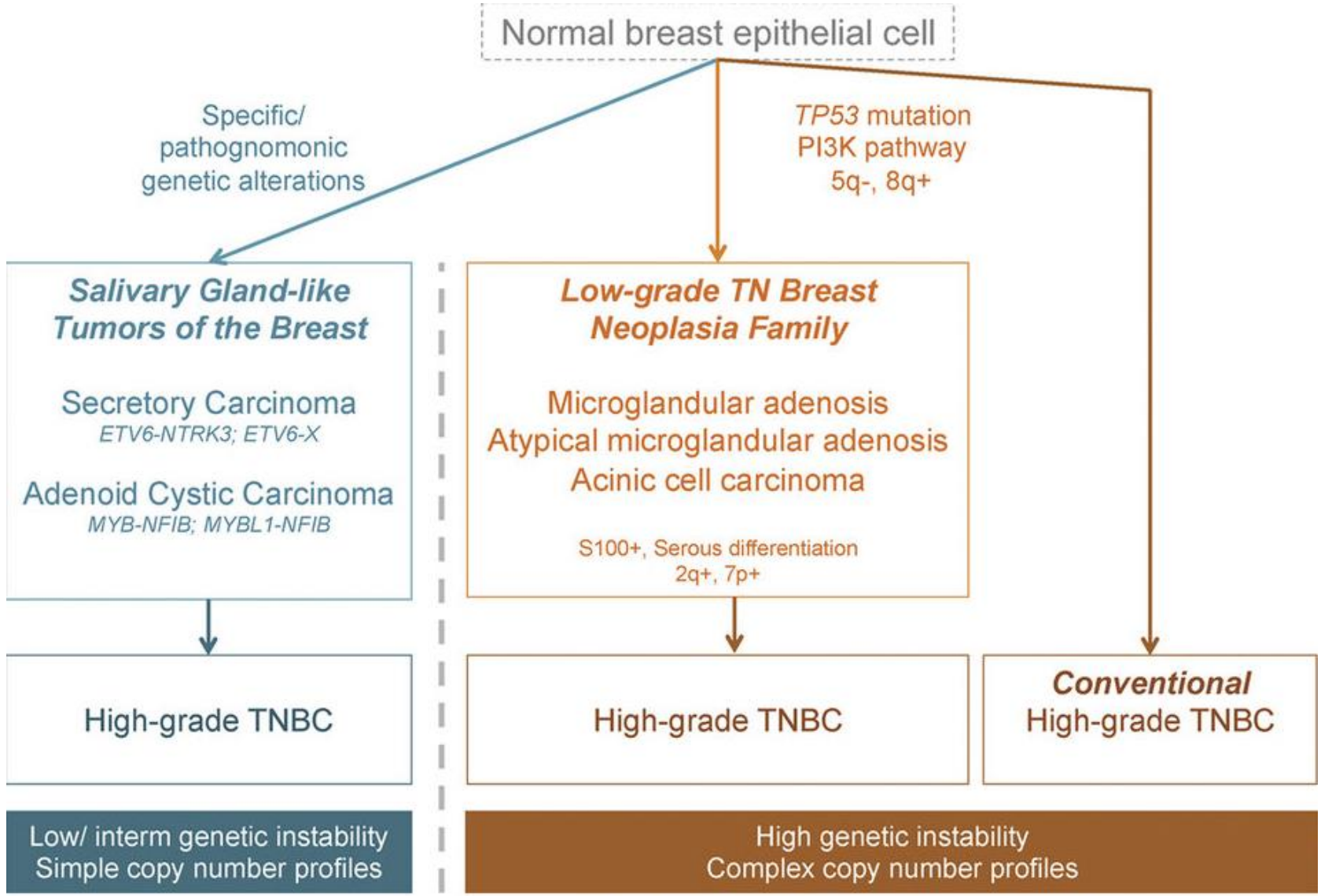


WHO 2019

Rare Breast and Salivary Cancers

- Acinic Cell
- Adenoid Cystic
- Secretory
- Mucoepidermoid
- Polymorphous adenocarcinoma
- Tall cell carcinoma with reversed polarity

Triple Negative Breast Cancer

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