Contemporary Considerations for Breast Core Needle Biopsy

Laura C. Collins, M.D.
Vice Chair of Anatomic Pathology
Director of Breast Pathology
Professor of Pathology
Beth Israel Deaconess Medical Center
and Harvard Medical School
Boston, MA

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center

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Outline

- Discuss how best to differentiate common and uncommonly encountered diagnostic challenges in breast tumor pathology, particularly as they pertain to breast CNB specimens
- Discuss how to anticipate and avoid diagnostic pitfalls
- Review morphologic clues and ancillary testing strategies that can support diagnostic interpretation, and help prevent errors
- Be aware that in contemporary practice, the risks are much greater

Potential Pitfalls

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- Benign epithelial proliferations vs. carcinomas
  - Radial scar/CSL/adenosis vs. invasive carcinoma
  - UDH vs. DCIS
  - Papillary lesions
  - DCIS vs. LCIS
- Triple negative breast tumors
  - Adenomyoepithelioma
  - Solid basaloid adenoid cystic carcinoma
  - Secretory carcinoma
  - Carcinomas arising in MGA
  - Acinic cell carcinoma
  - Tall cell carcinoma with reversed polarity
- Spindle cell lesions
  - Metaplastic carcinoma vs. benign spindle cell lesions
- Displaced epithelium
- Metastases

Radial scar/Complex sclerosing lesion/Sclerosing adenosis

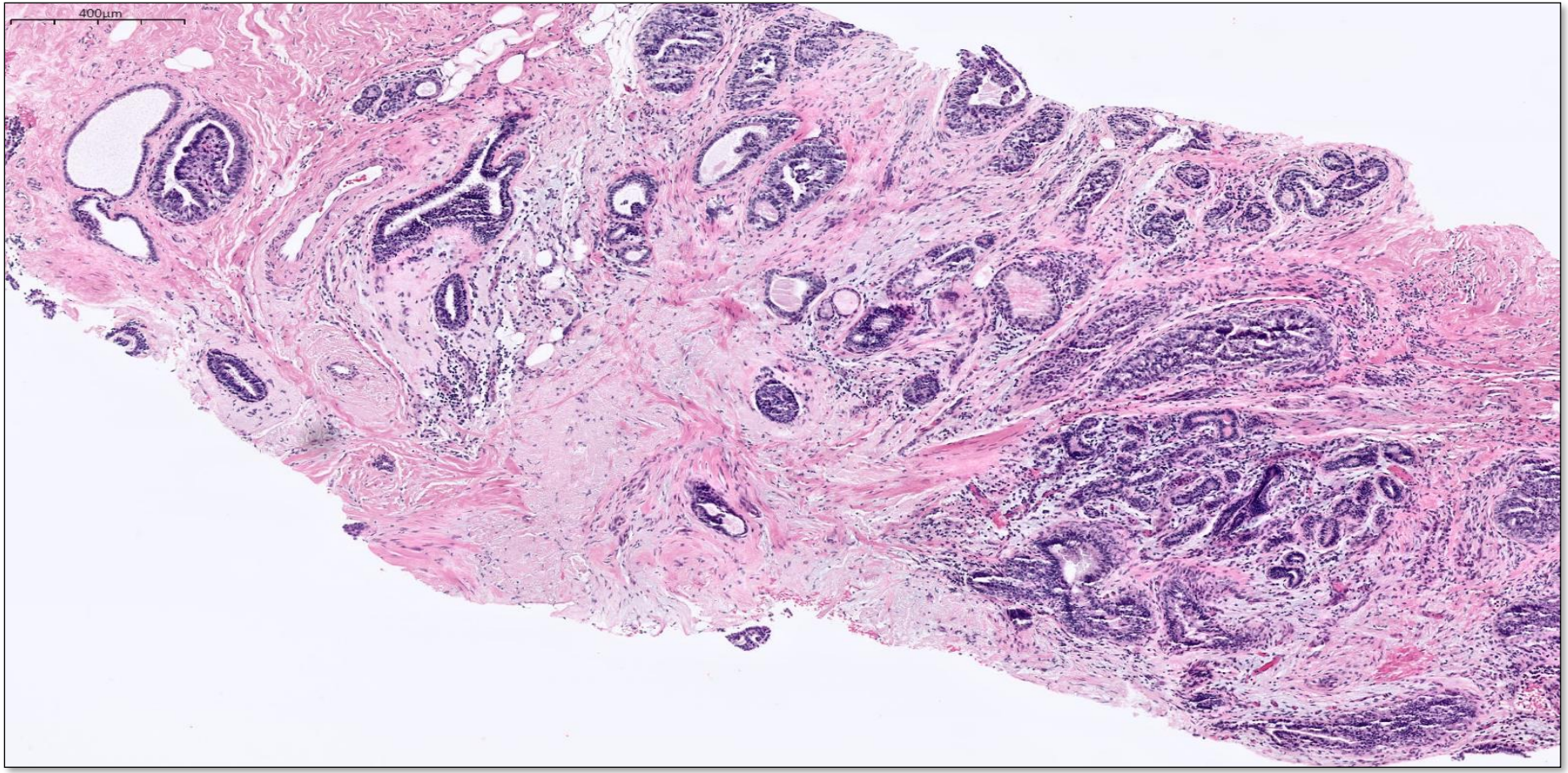
The challenge

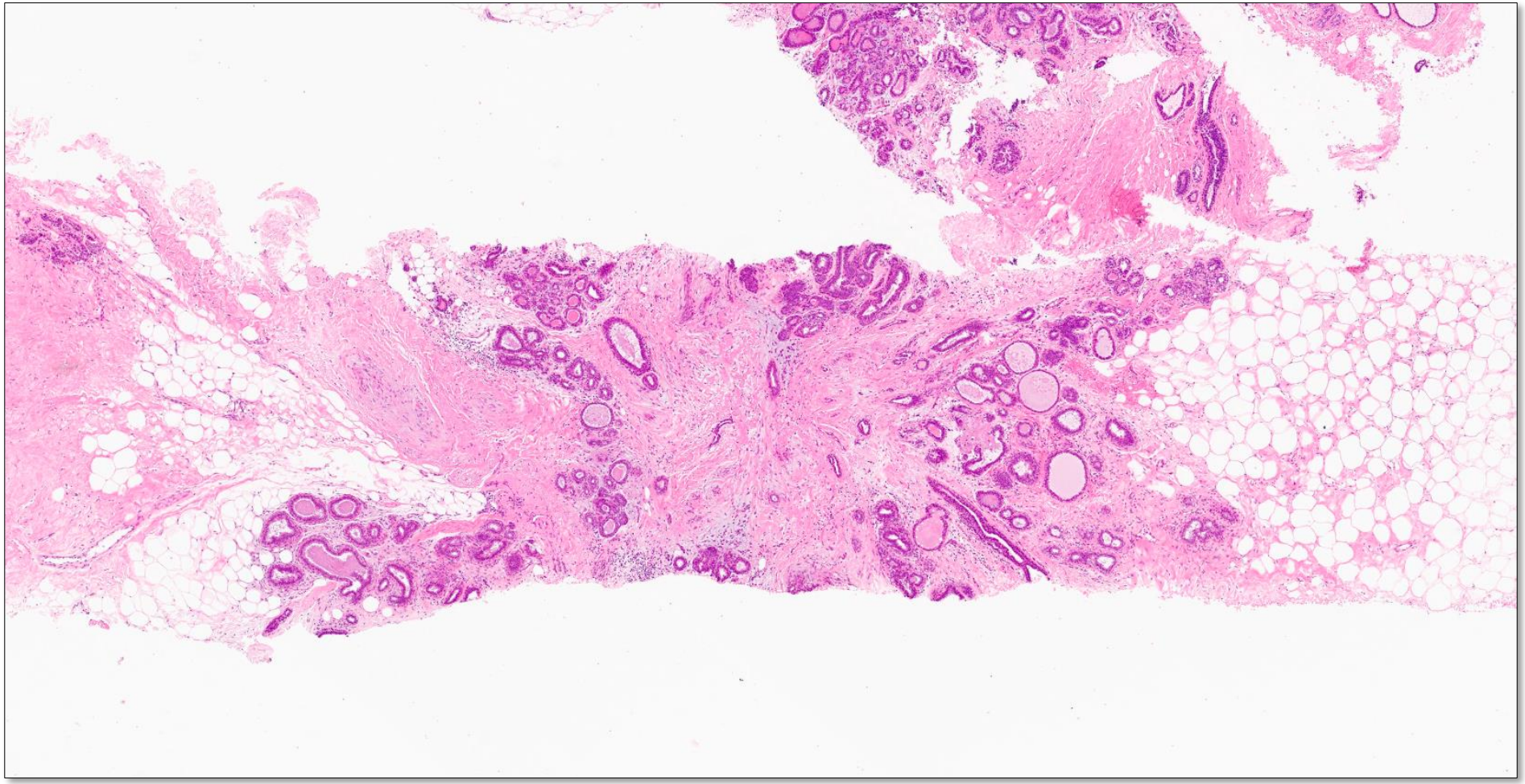
- RS/CSL can mimic carcinoma clinically, radiologically and pathologically
- Some imaging features favor RS, e.g. lucent center, greater extension of “stellate” features
- Pathologically, lobulocentric pattern and elastotic stroma favor a benign process; also dense fibrotic stroma favors benign over malignant
- Use of IHC to highlight myoepithelial cell layer helpful

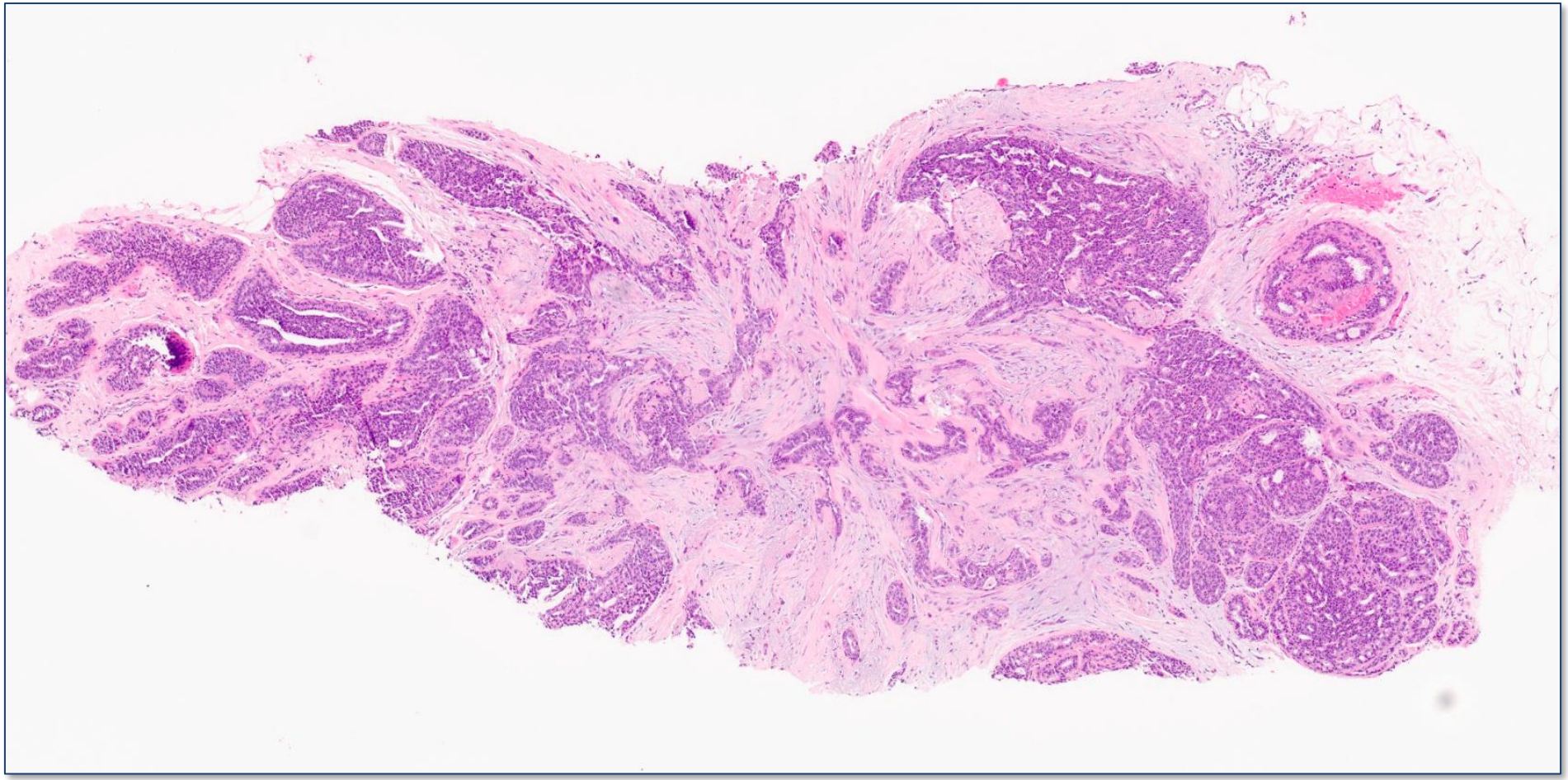
Benign Sclerosing Lesions vs. Invasive Carcinoma

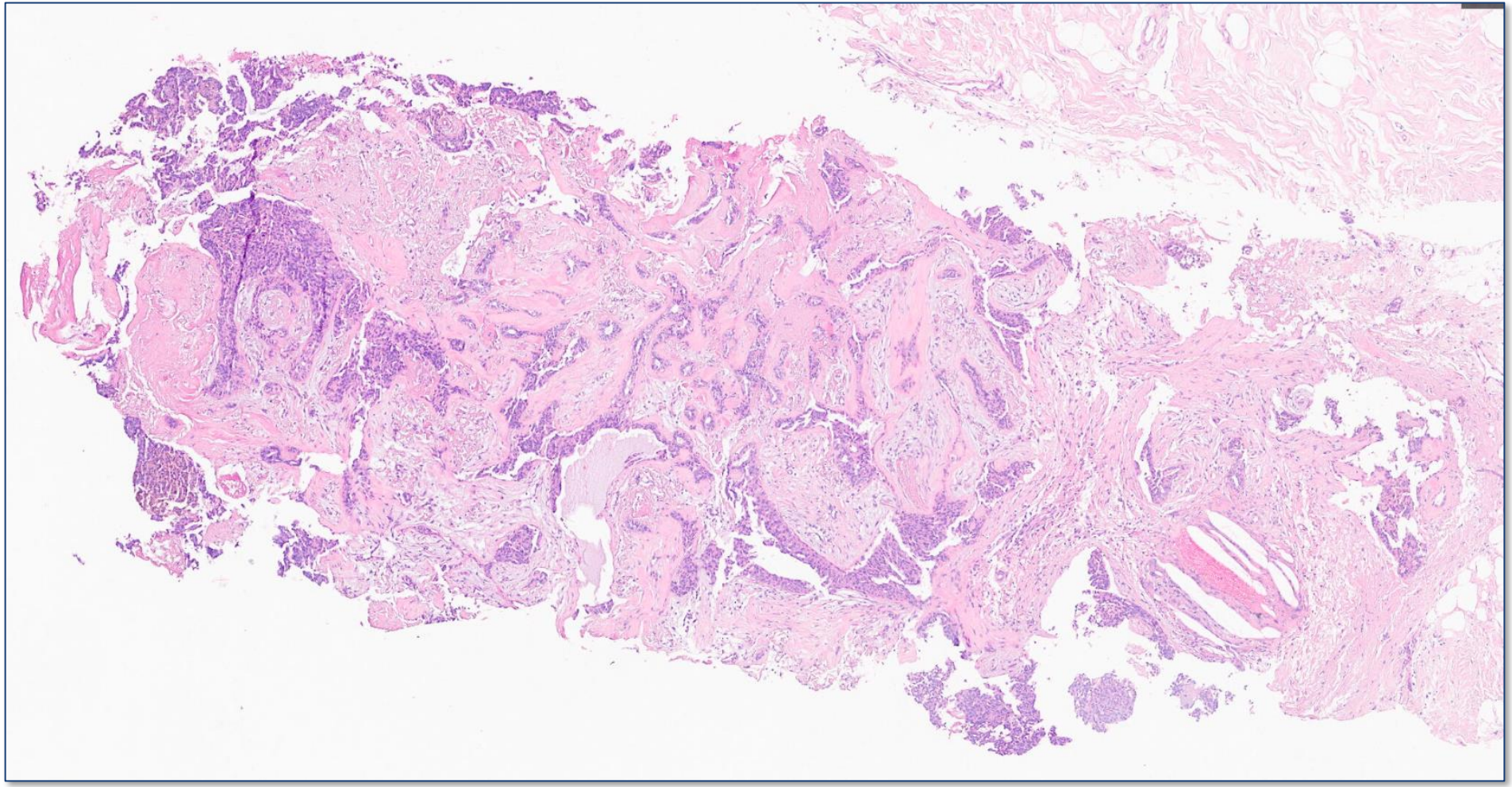
Two issues to consider:

- Invasive vs. not
- Atypical vs. not









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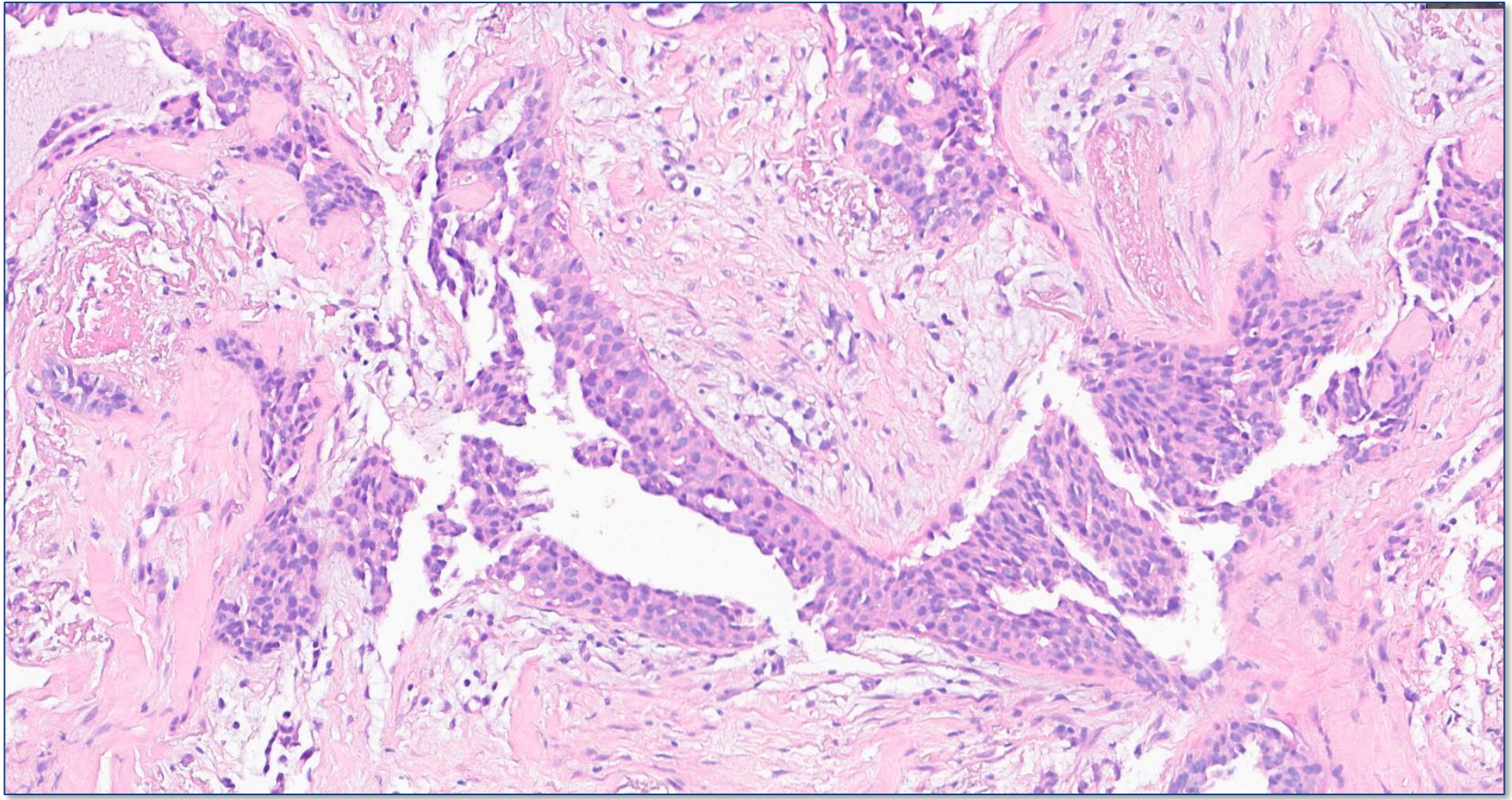
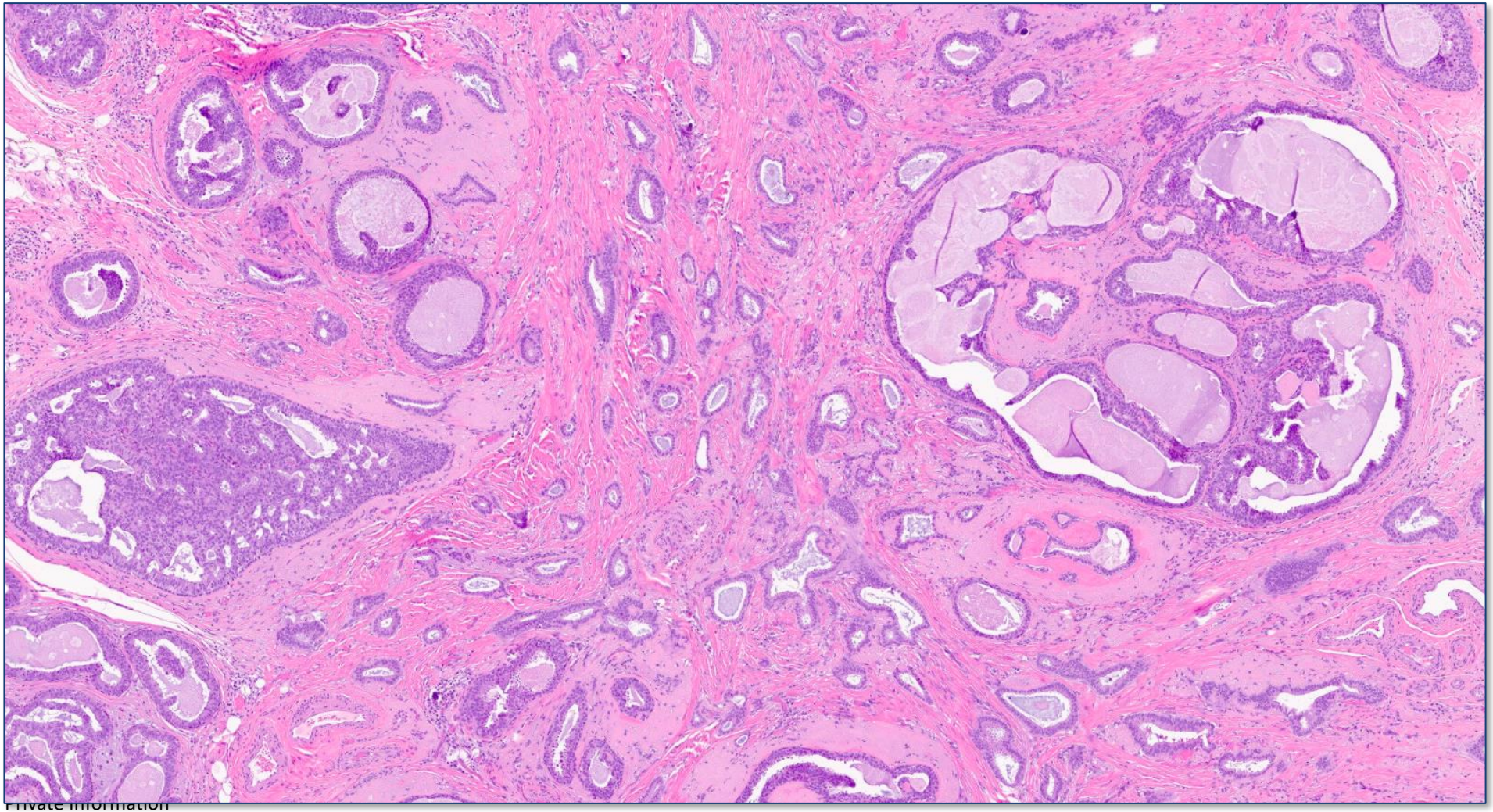
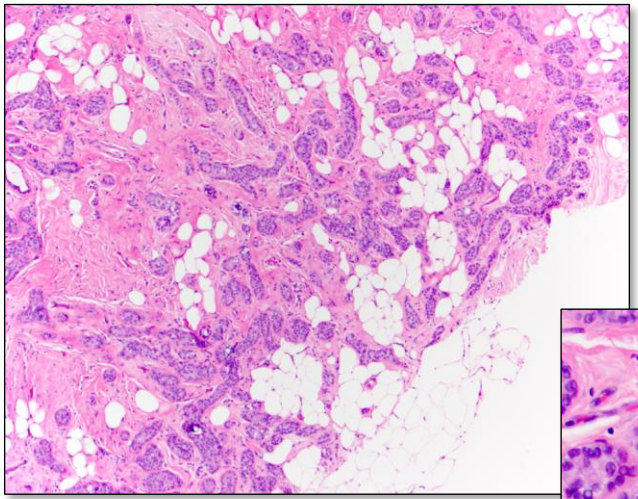
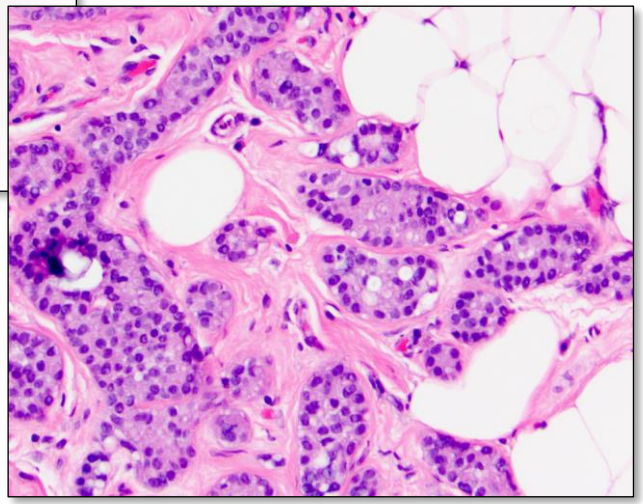
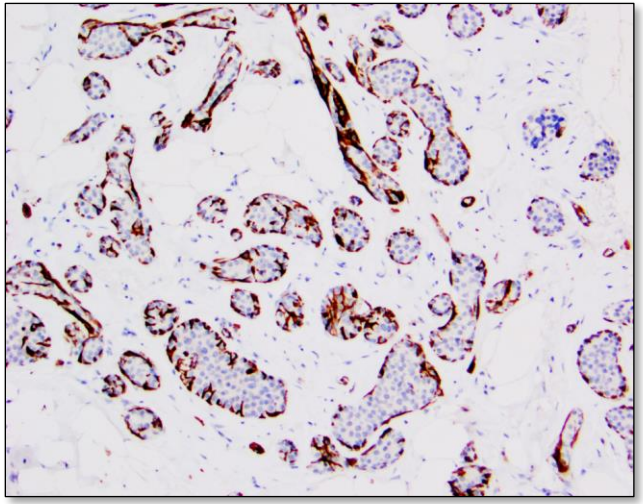




LCIS in adenosis



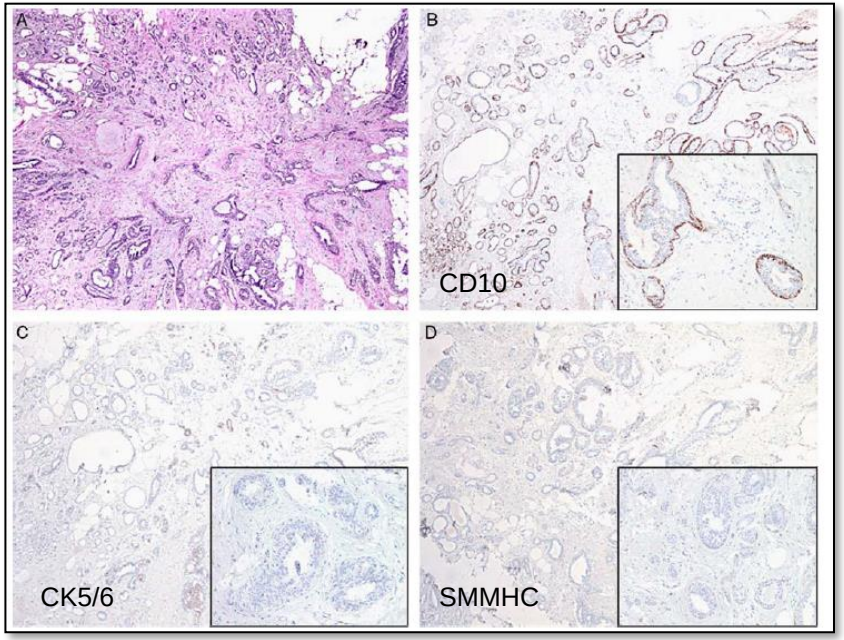




Phenotypic Alterations in Myoepithelial Cells Associated With Benign Sclerosing Lesions of the Breast

Justin B. Hilson, MD, Stuart J. Schnitt, MD, and Laura C. Collins, MD

Reduced expression of MEC markers is seen in some benign sclerosing lesions



Current Management of Radial Scar/CSL/adenosis

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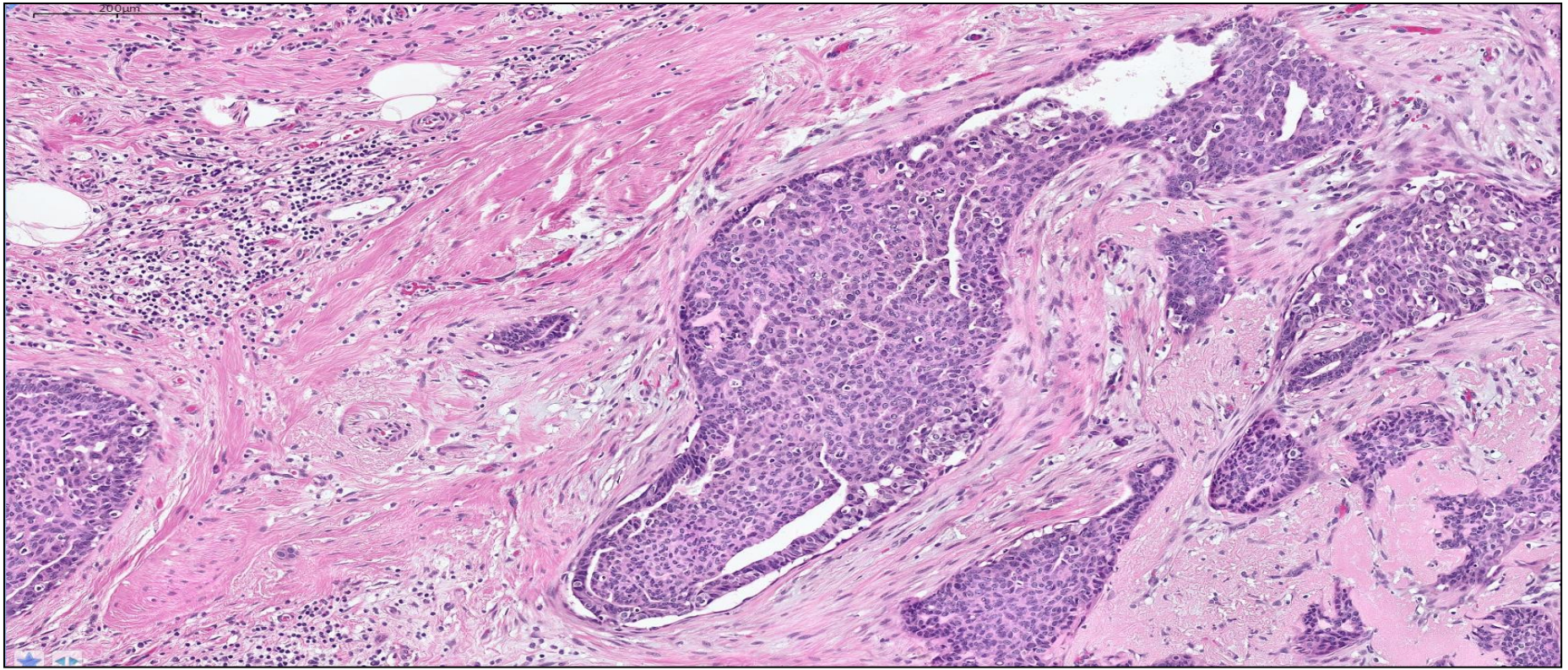
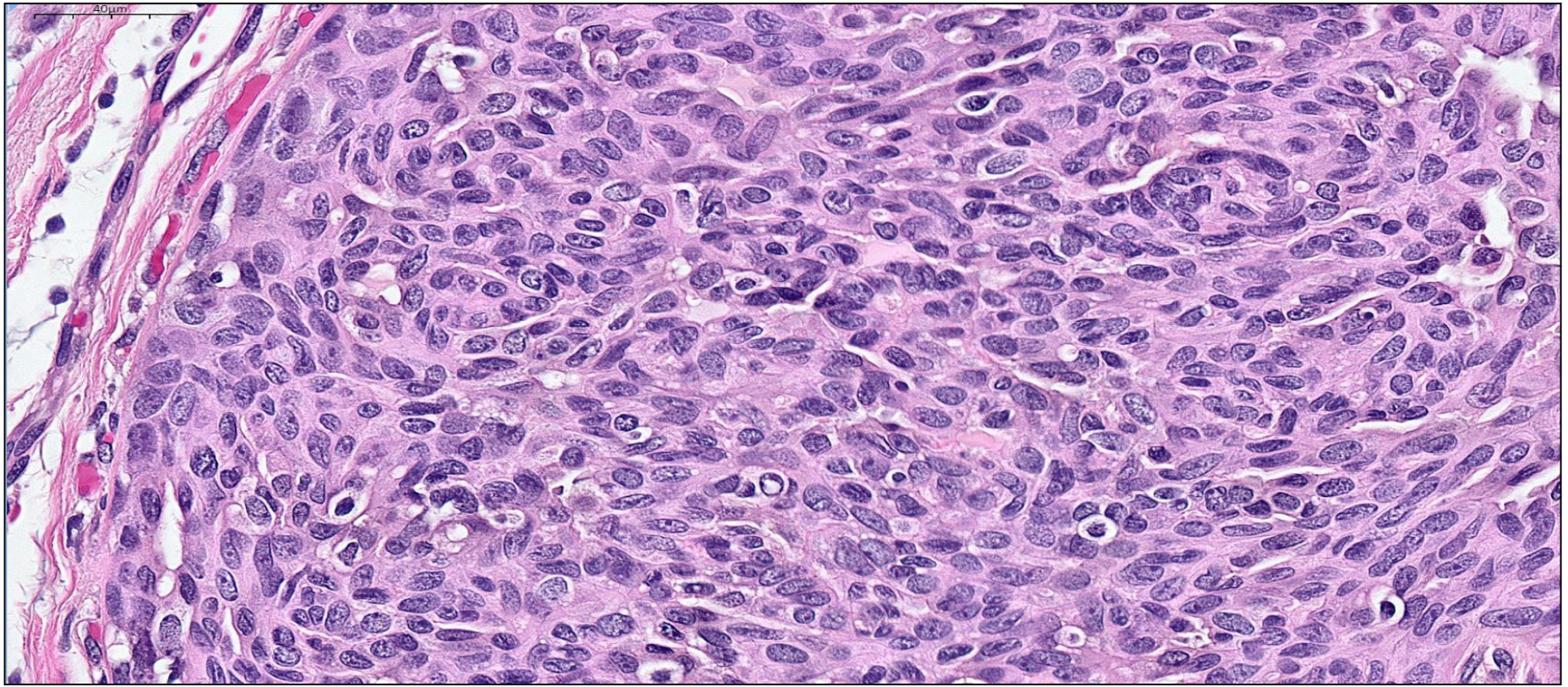
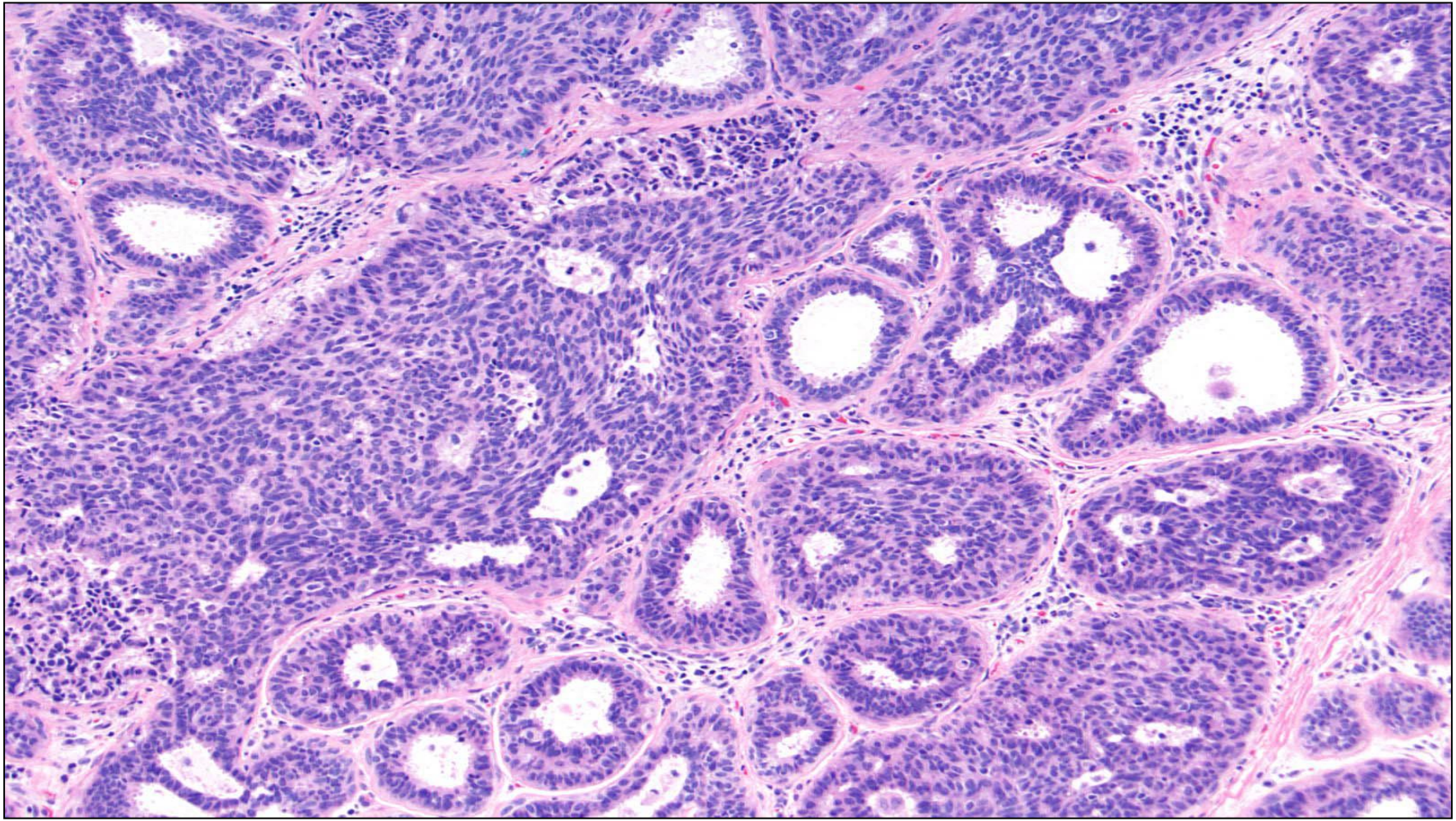
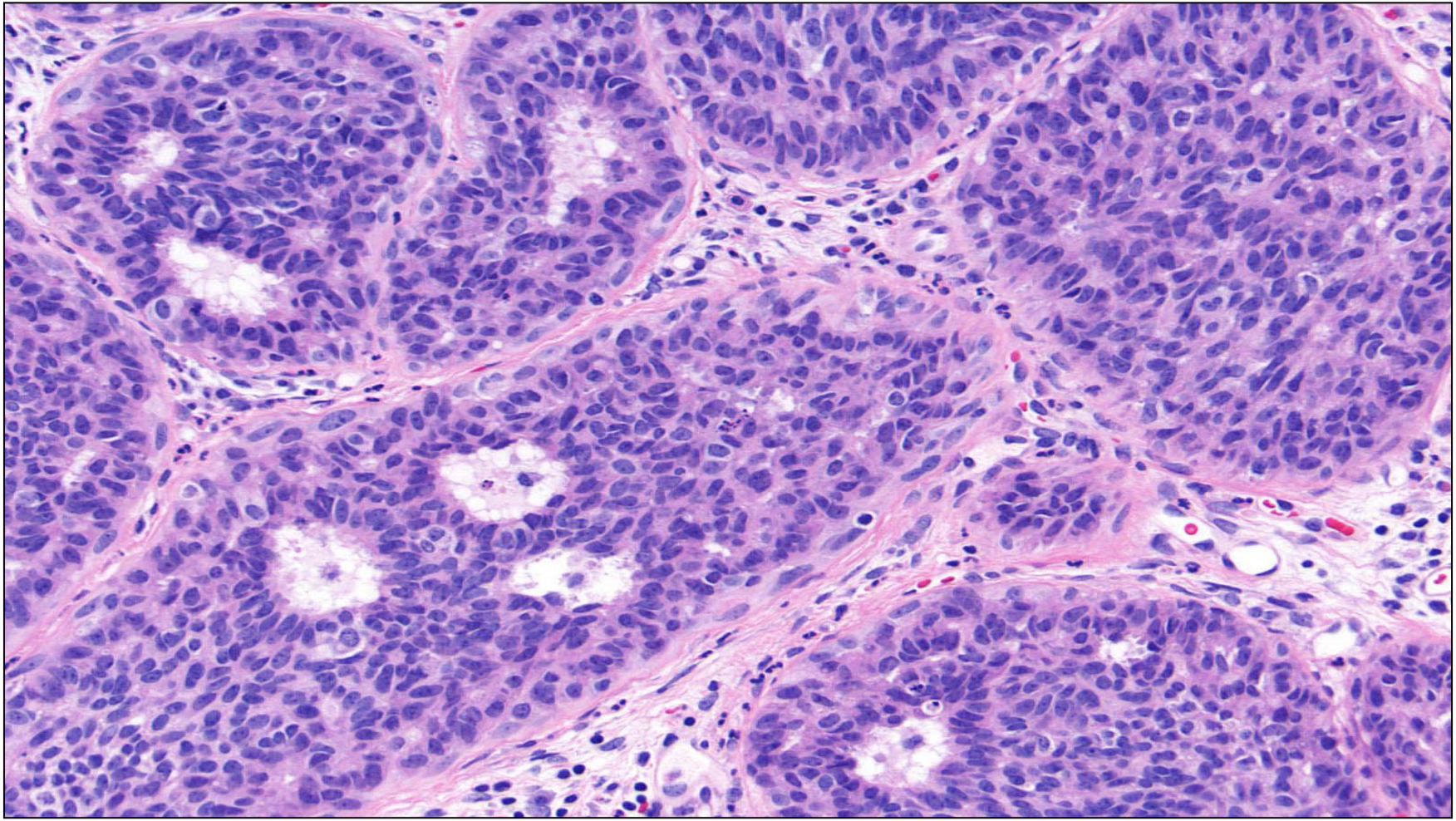
- Upgrade rates to DCIS or invasive carcinoma while lower than in the past, remain high enough (~5%) that excision is generally indicated for image detected lesions
- Radiologically-pathologically concordant sclerosing adenosis does not require excision
- Excision required if there is involvement by carcinoma in situ

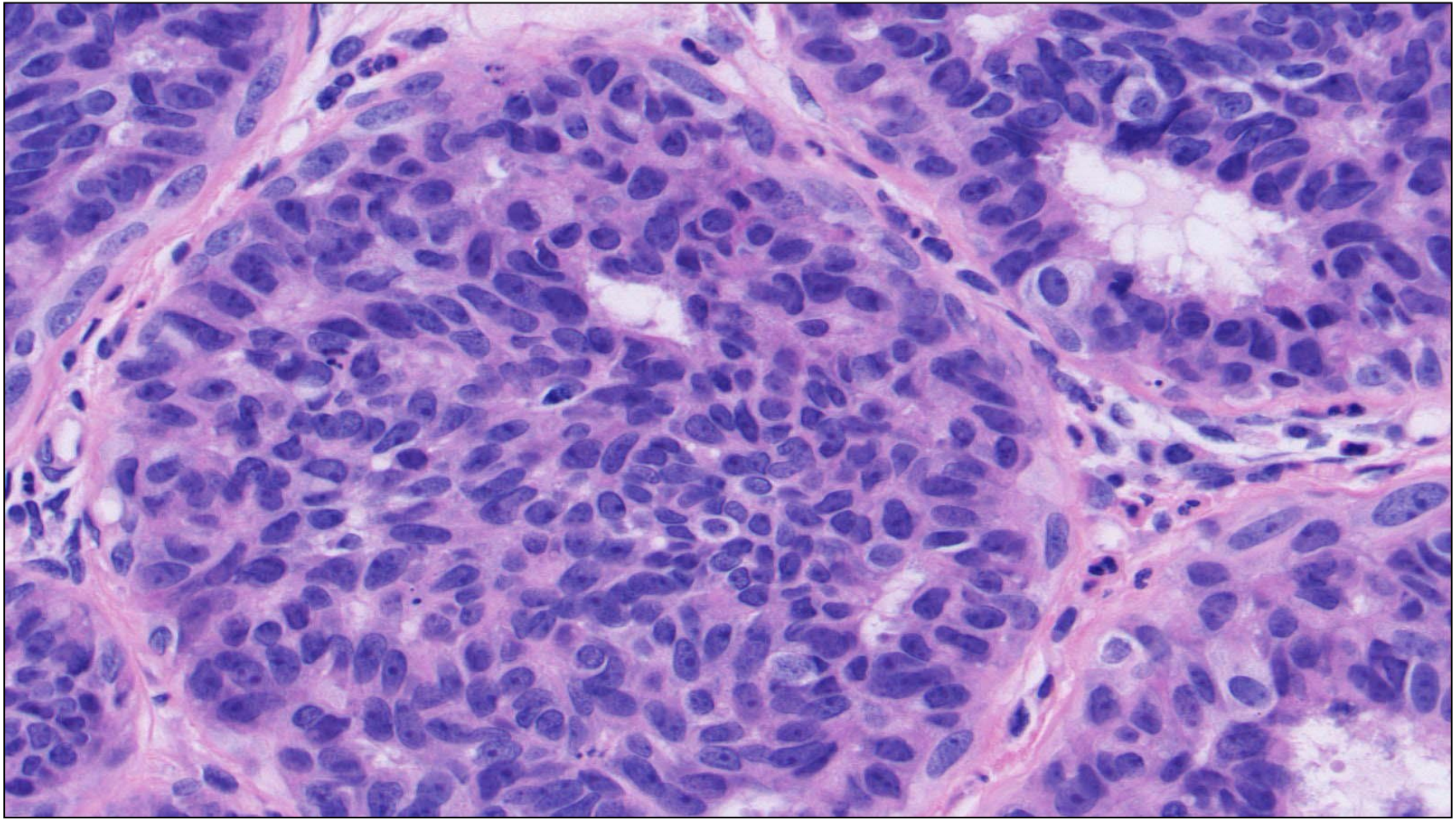
ASBS Consensus Guideline, 2016
Schiaffino, Radiol, 2020
NCCN, 2020

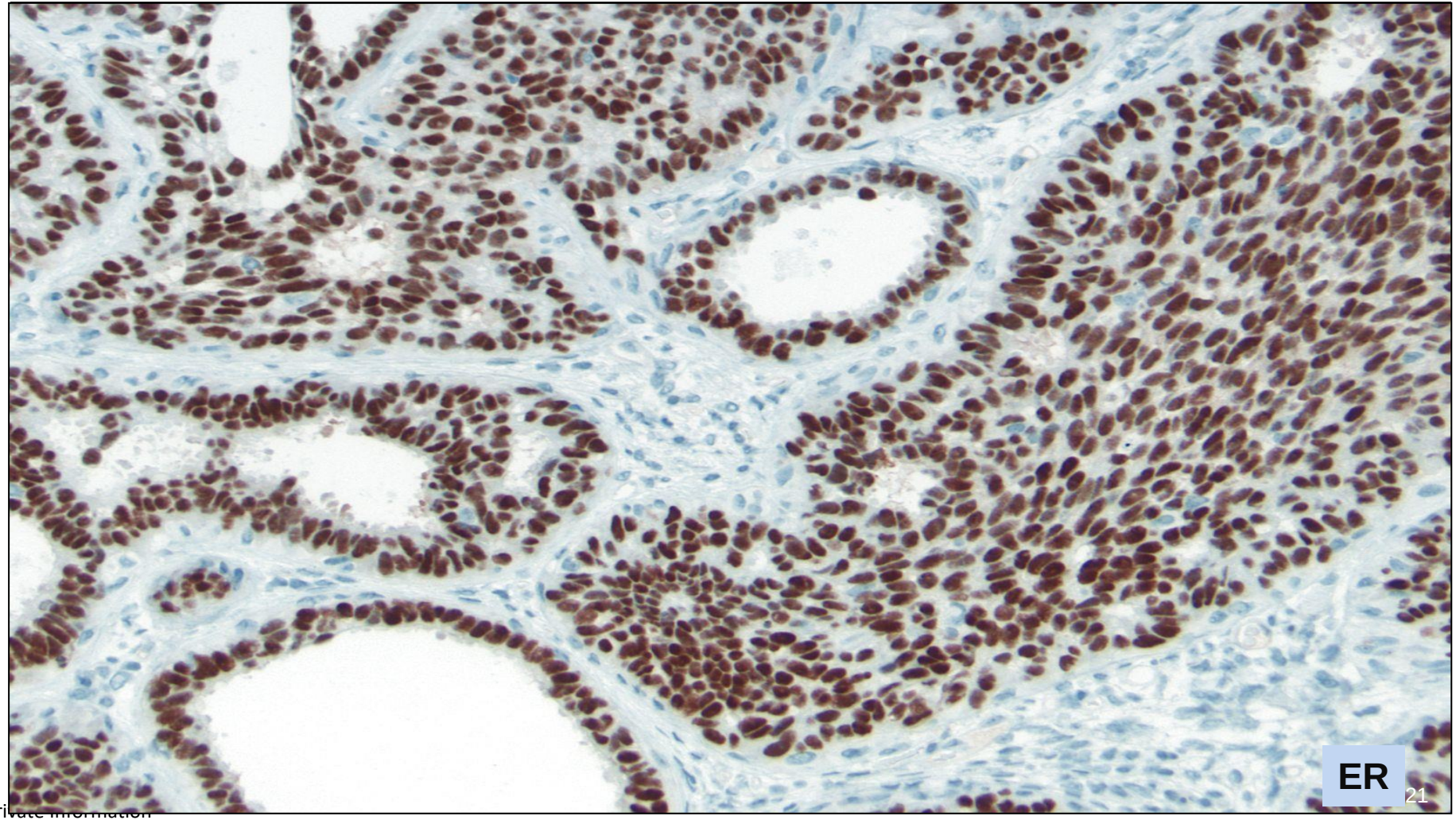












Adjunctive IHC

Invasive vs. benign/in situ

Myoepithelial cell markers

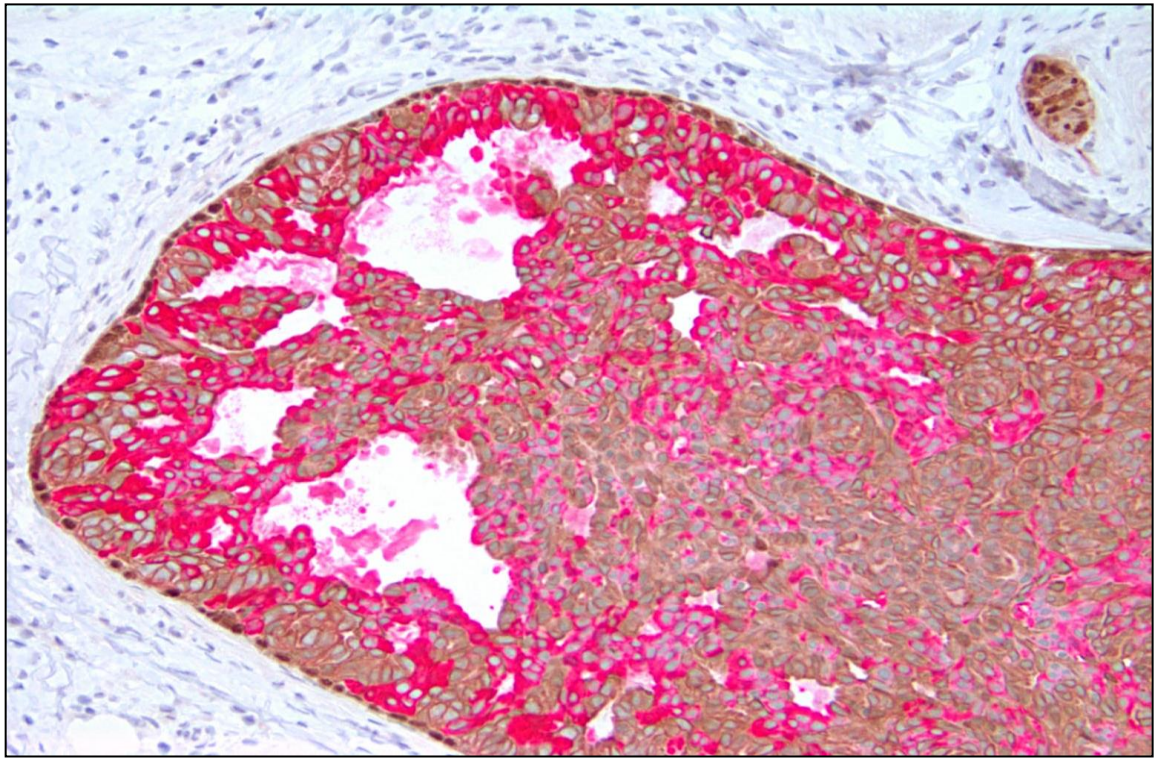
- P63
- SMMHC
- Calponin
- (CK 5/6)

Atypical vs. benign

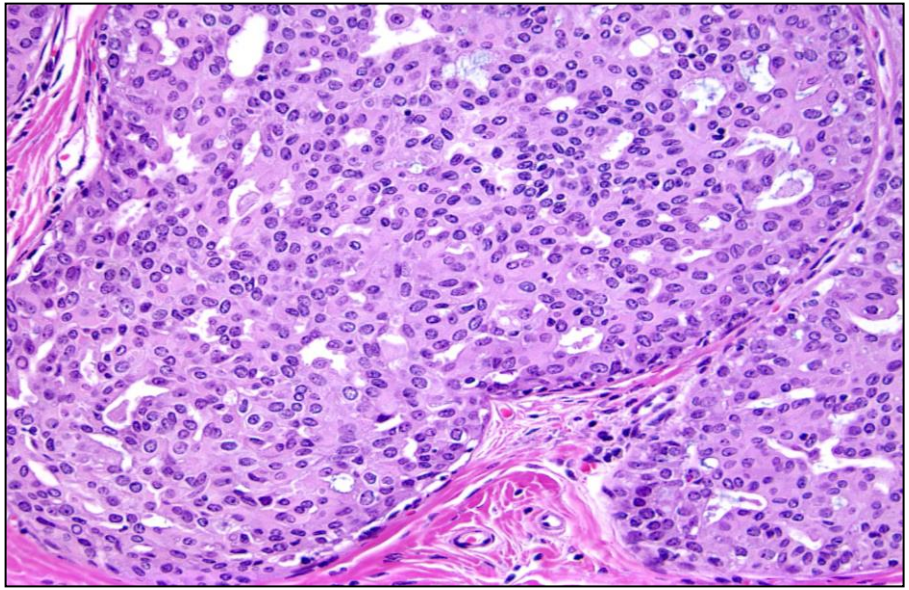
ER and CK 5/6 (or other cocktail)

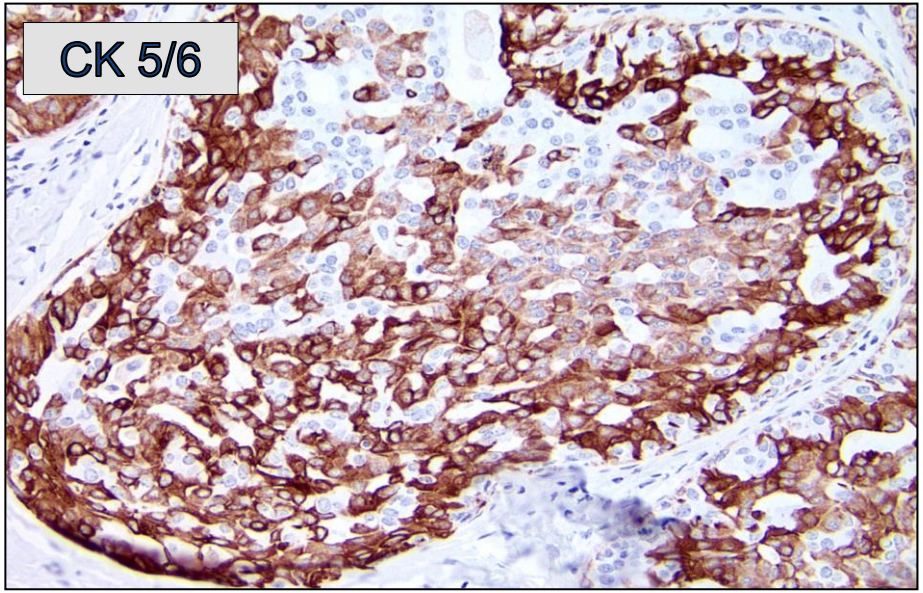
- Both heterogeneously positive in UDH
- Strongly and diffusely positive ER, and negative CK 5/6 in atypia/DCIS

Triple Stain: LMK-red, HMK-brown, p63-brown nuclear

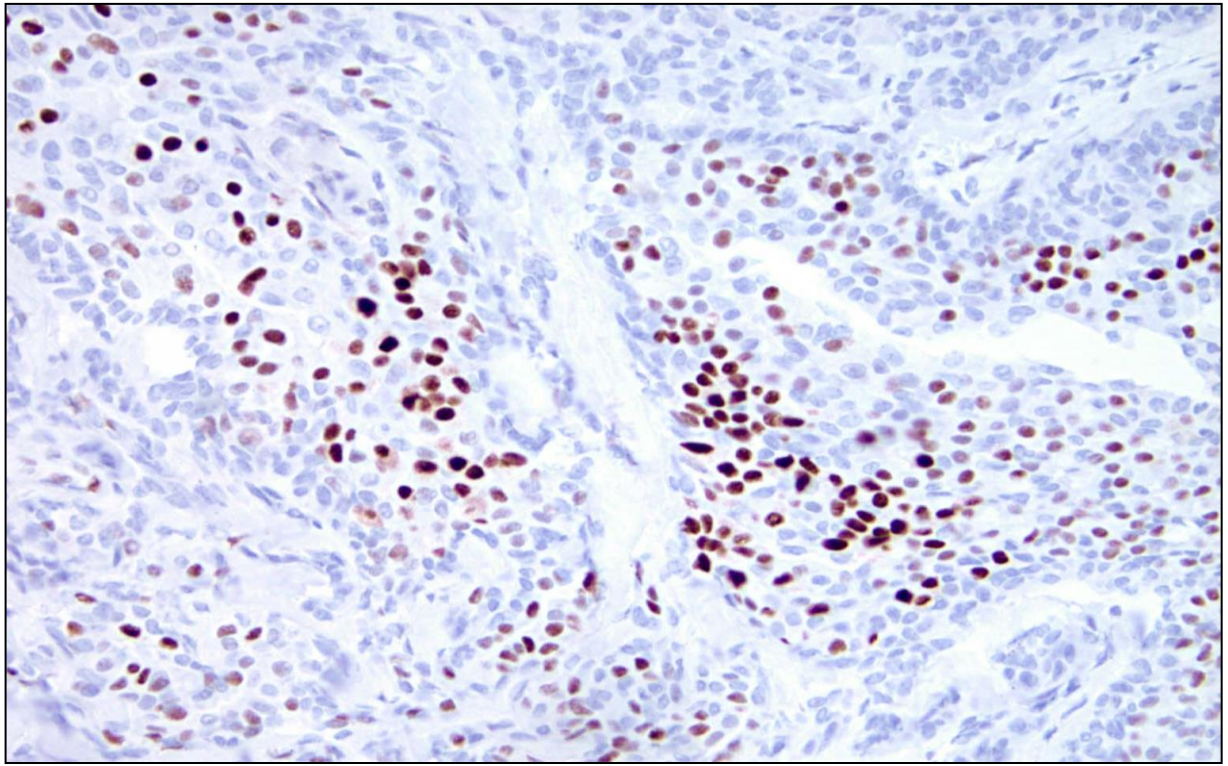


HMW-CK in UDH





Estrogen receptor staining in UDH

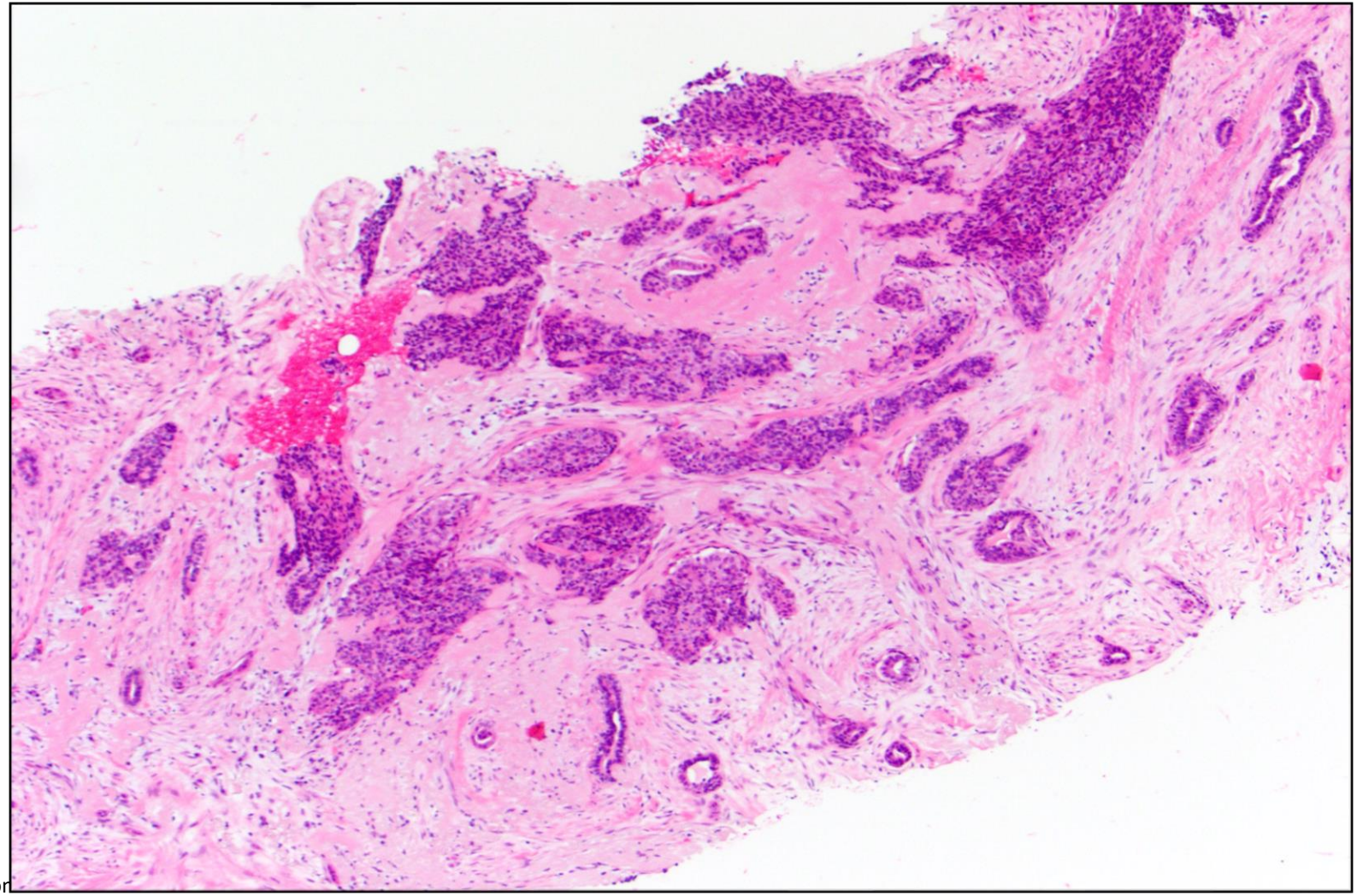


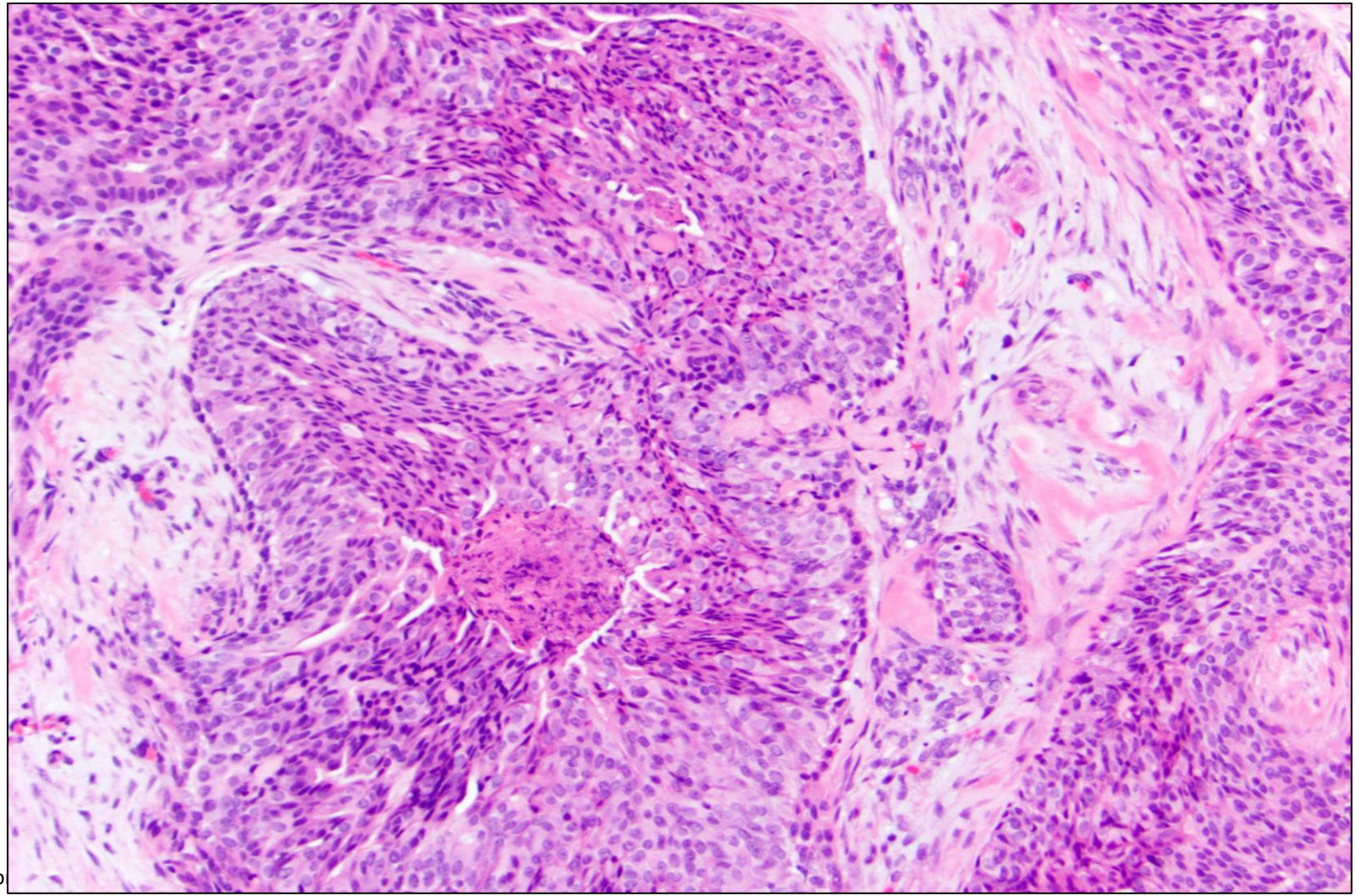
Potential pitfalls

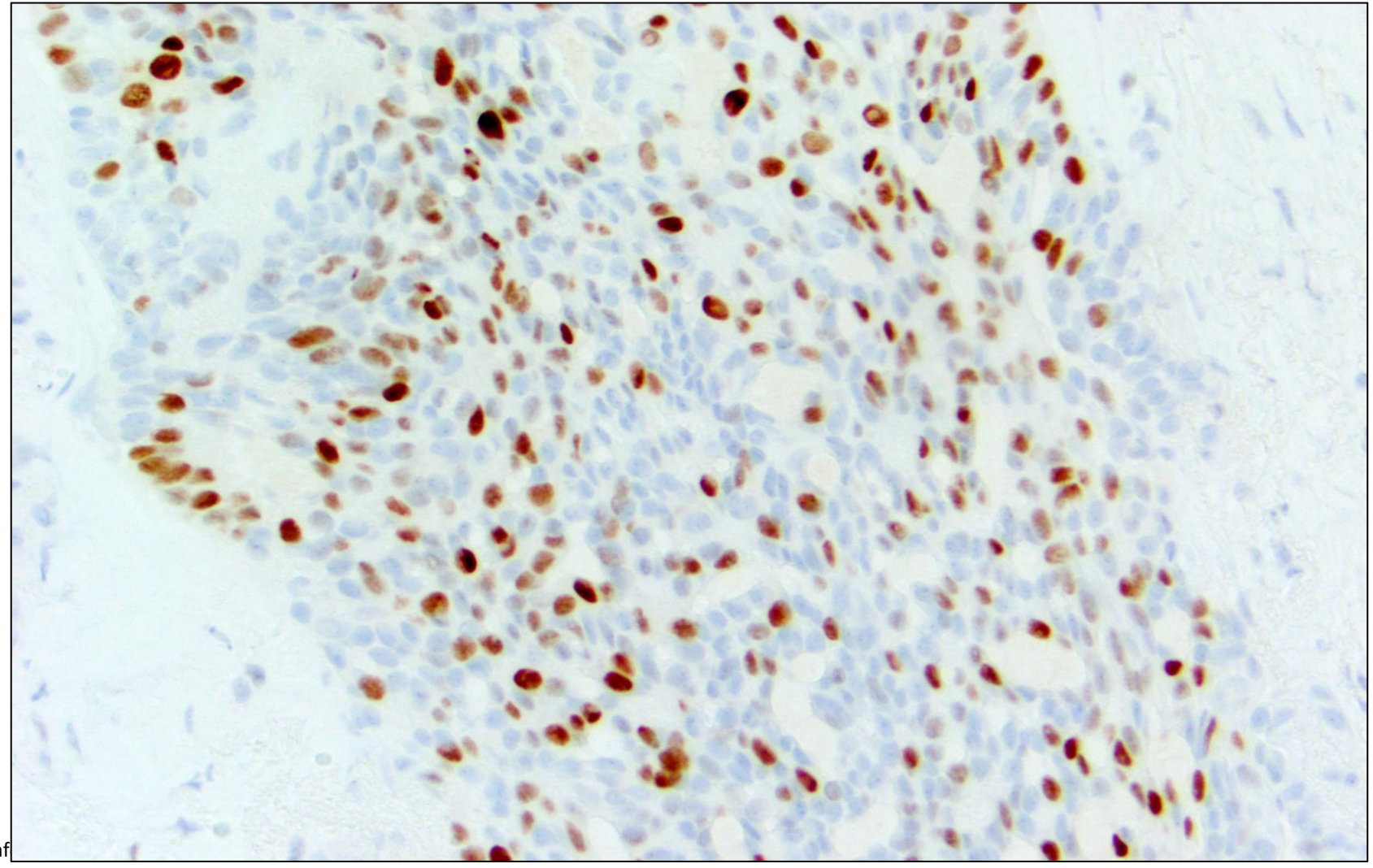
Presence of necrosis can lead to misinterpretation

- Imagine the proliferation without the necrosis
- Are the features those of UDH or DCIS?
- Use ER and CK 5/6 if necessary

- Is the stroma pink and fibrotic?
- Use MEC IHC if necessary, but interpret carefully



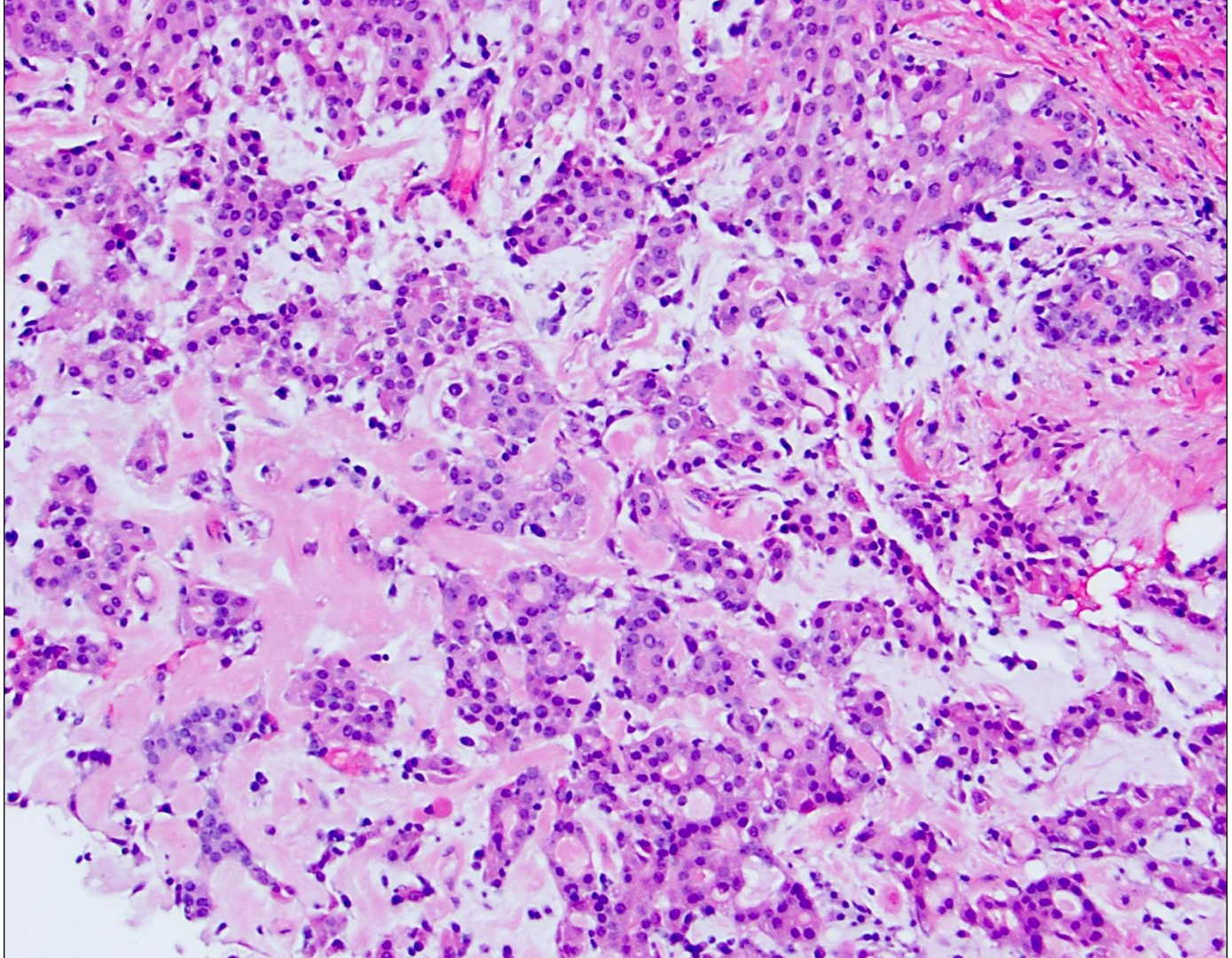


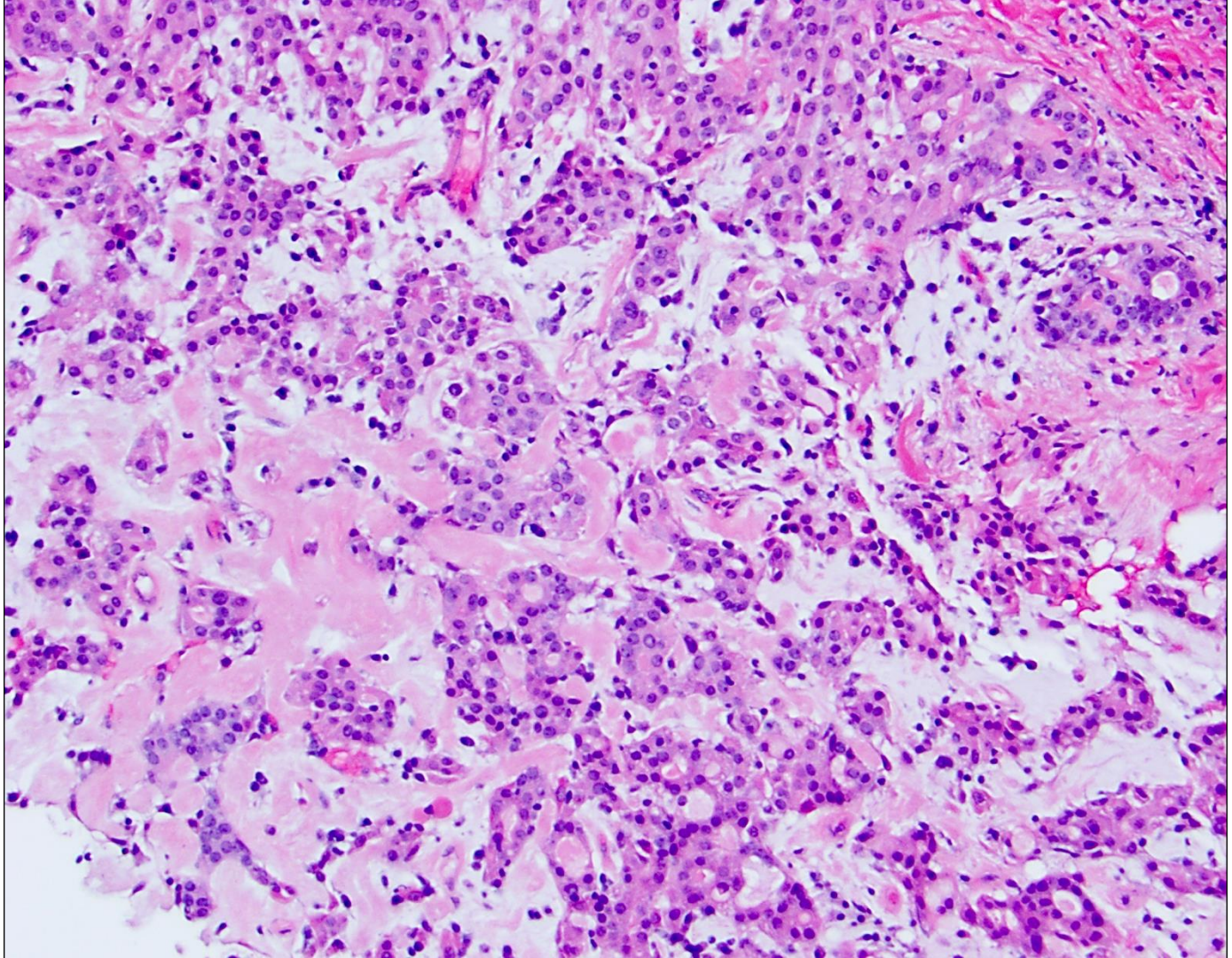


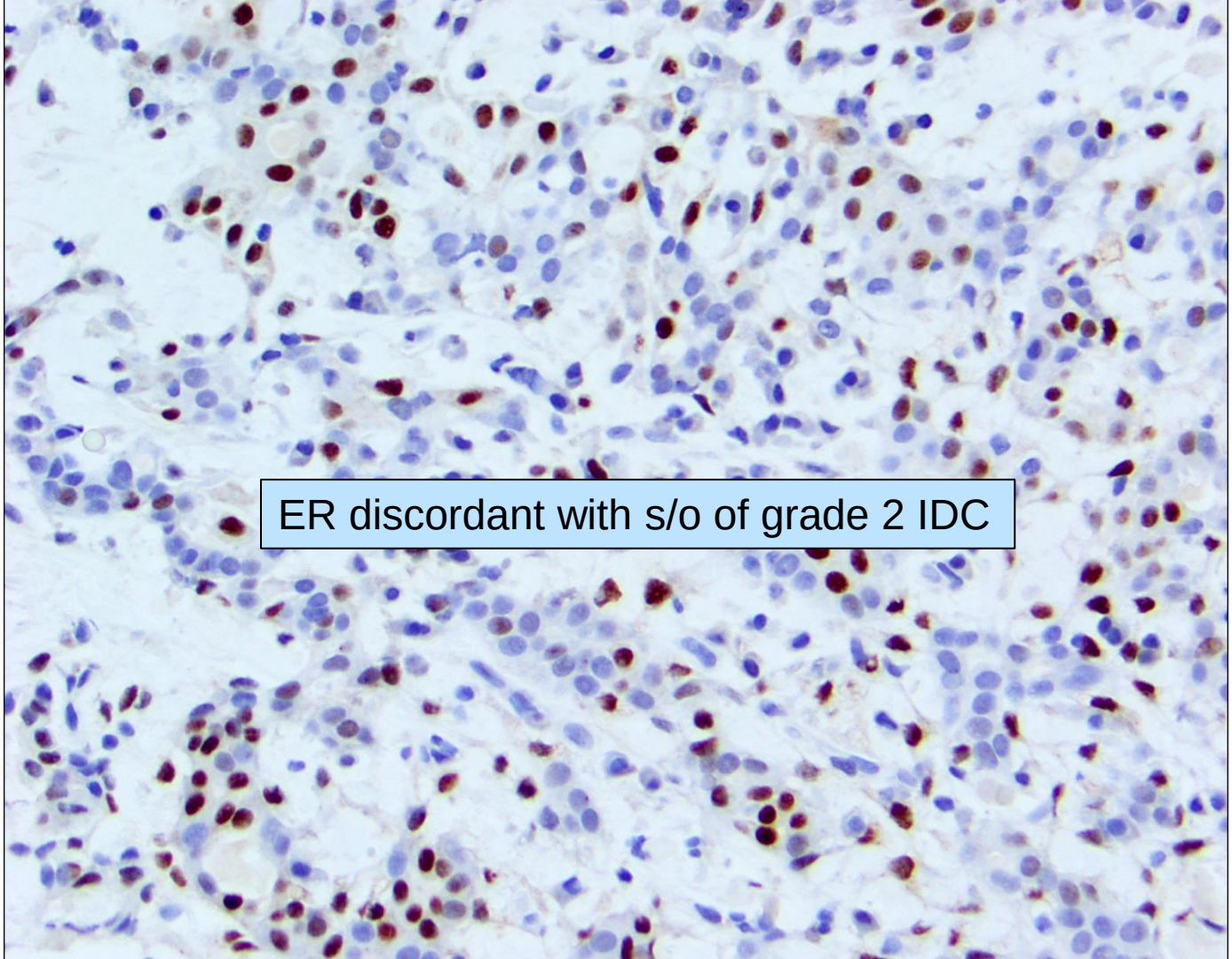
Heterogeneous expression of ER is a useful safety check

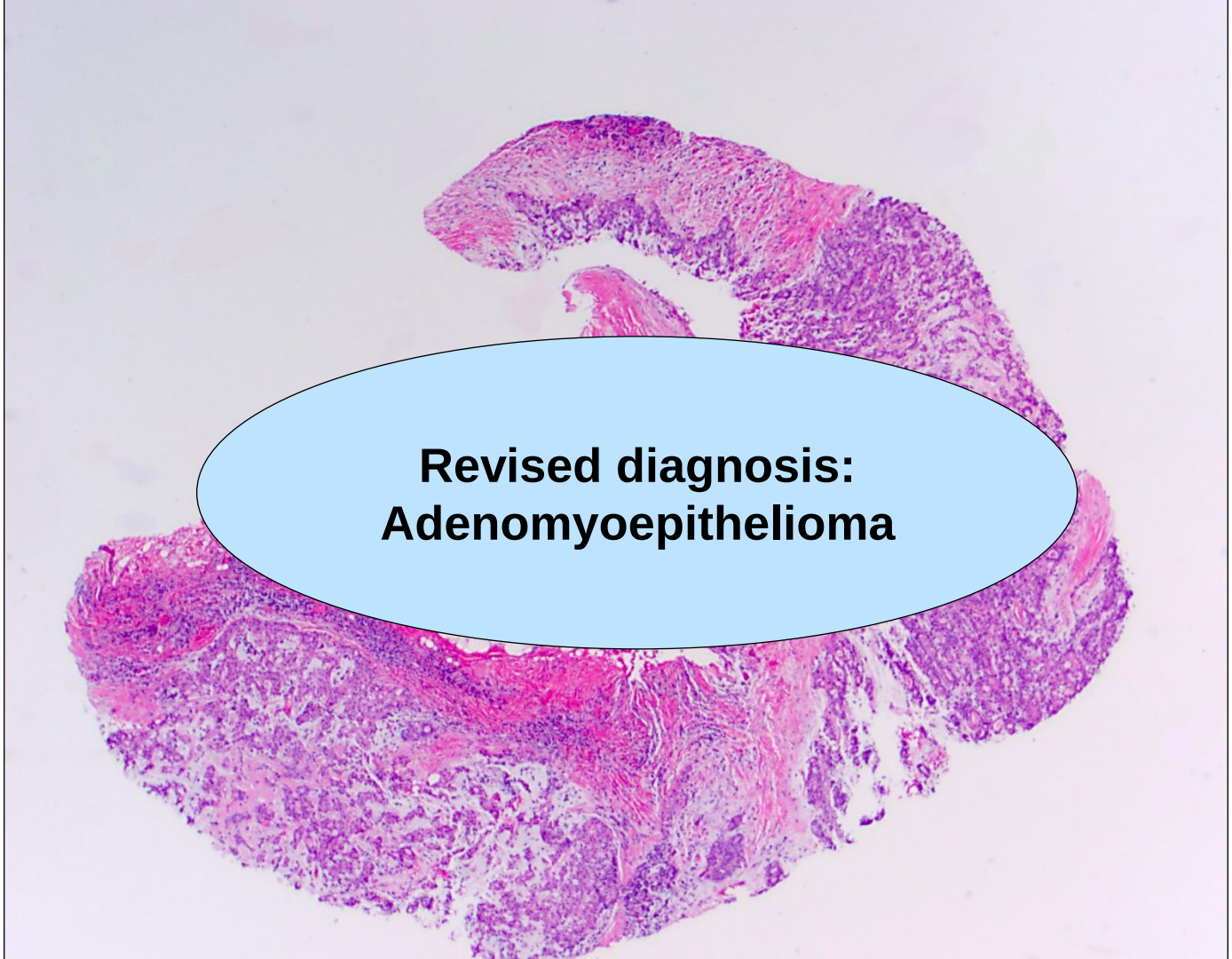
Triple negative tumors

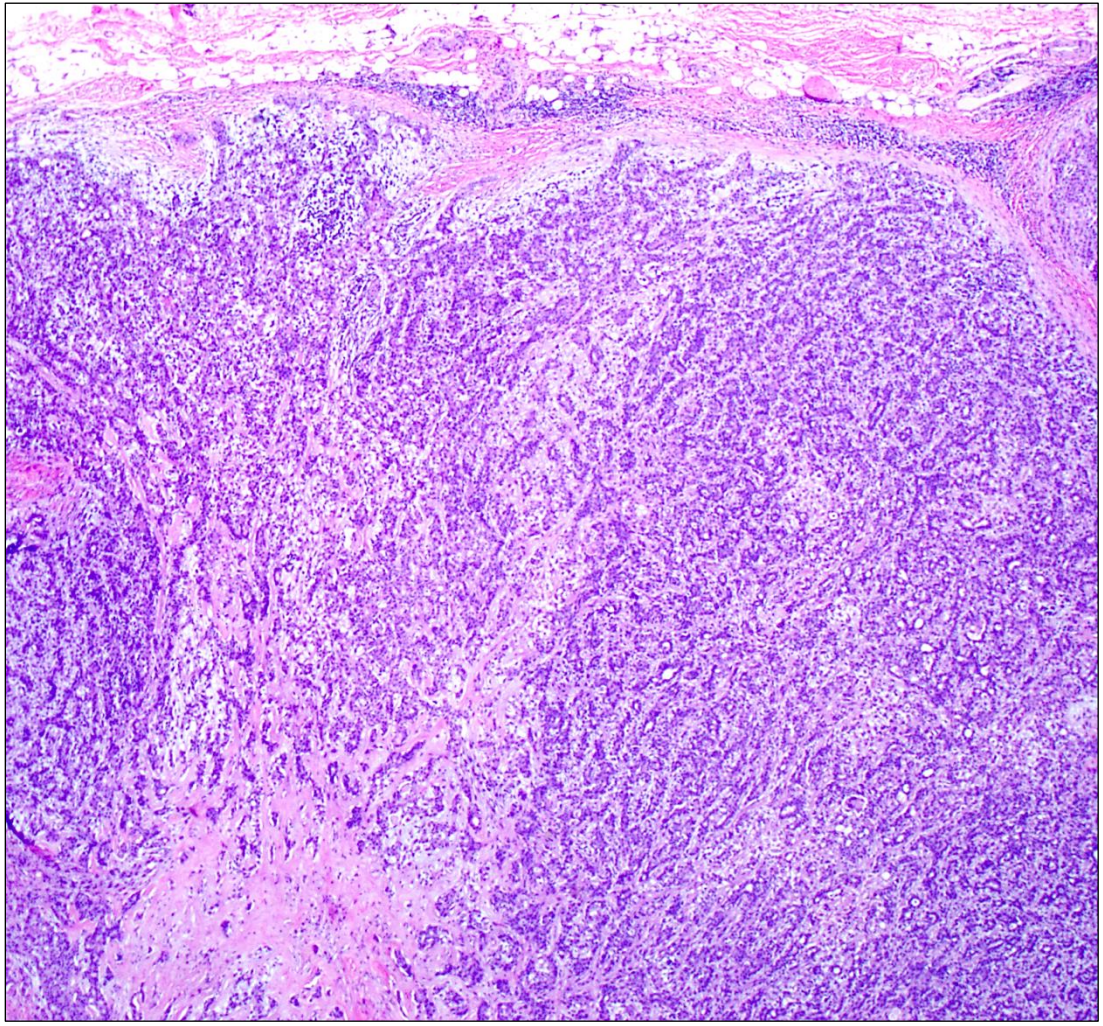
- Well-differentiated tumors
- Special histologic subtypes
- Poorly differentiated tumors

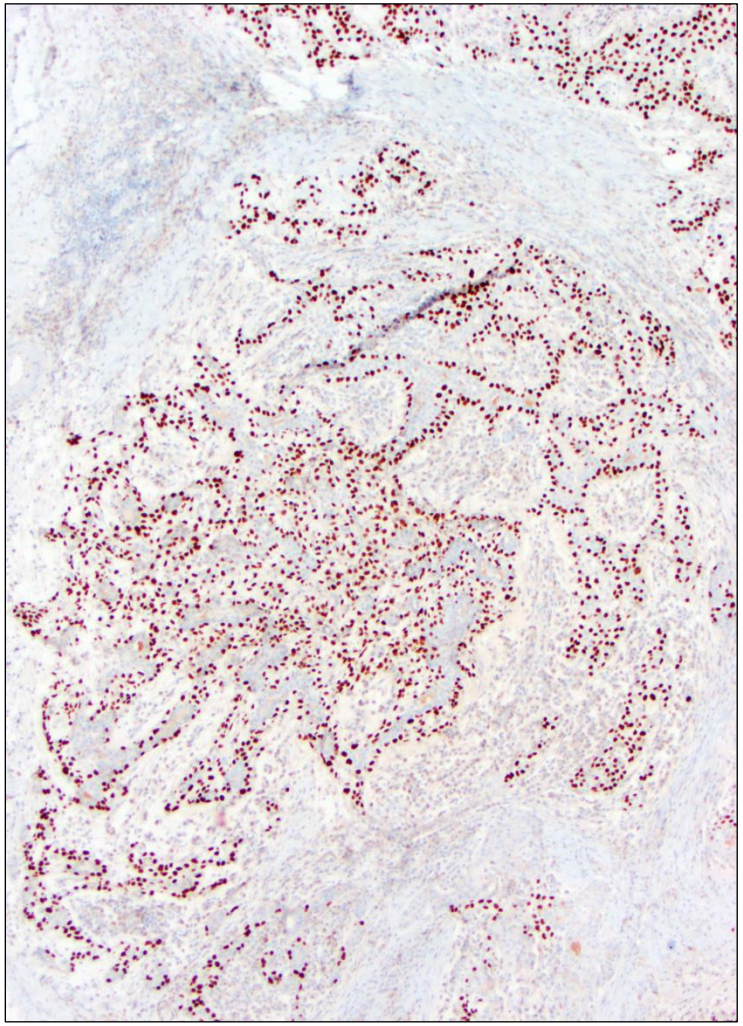








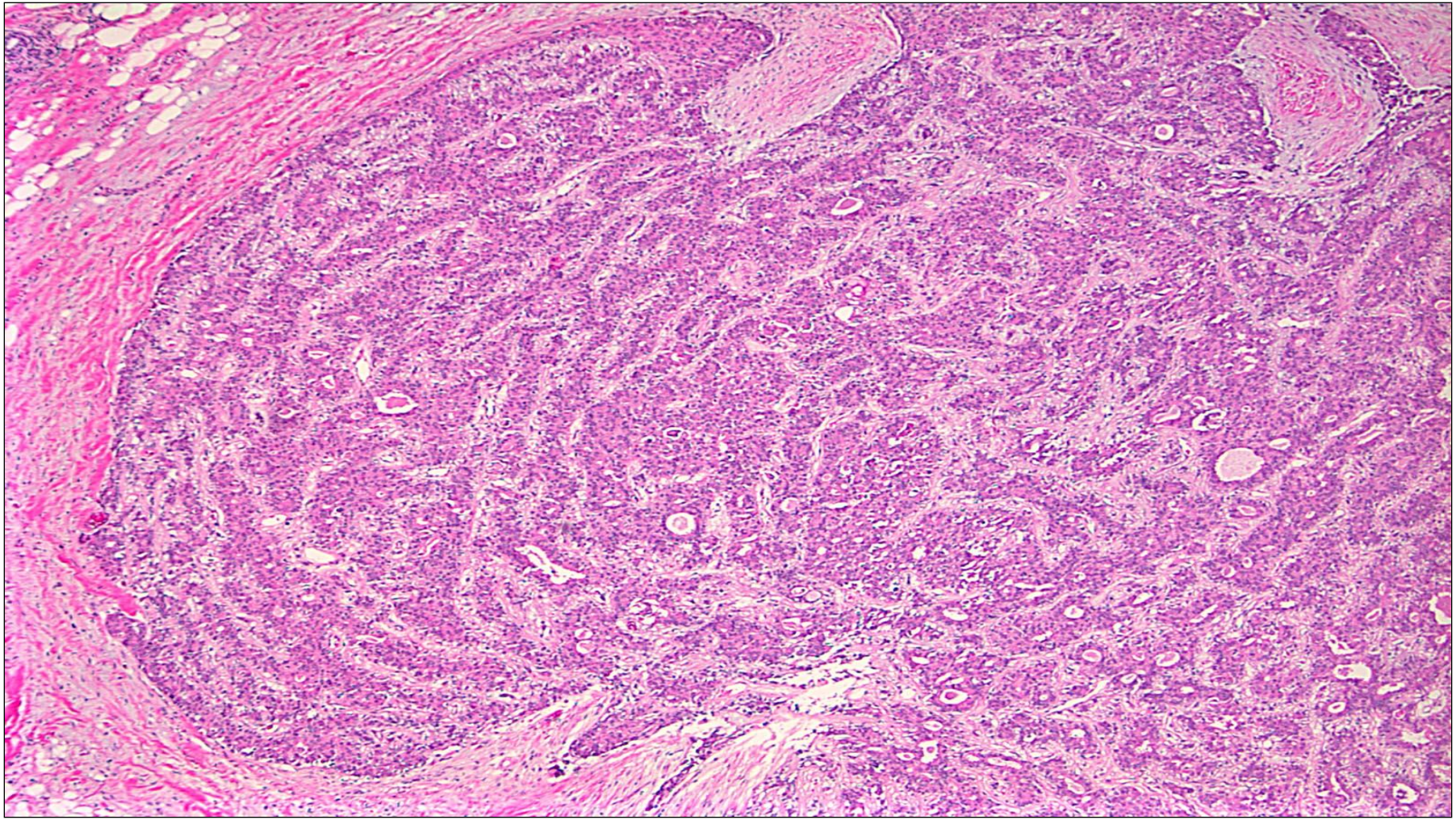


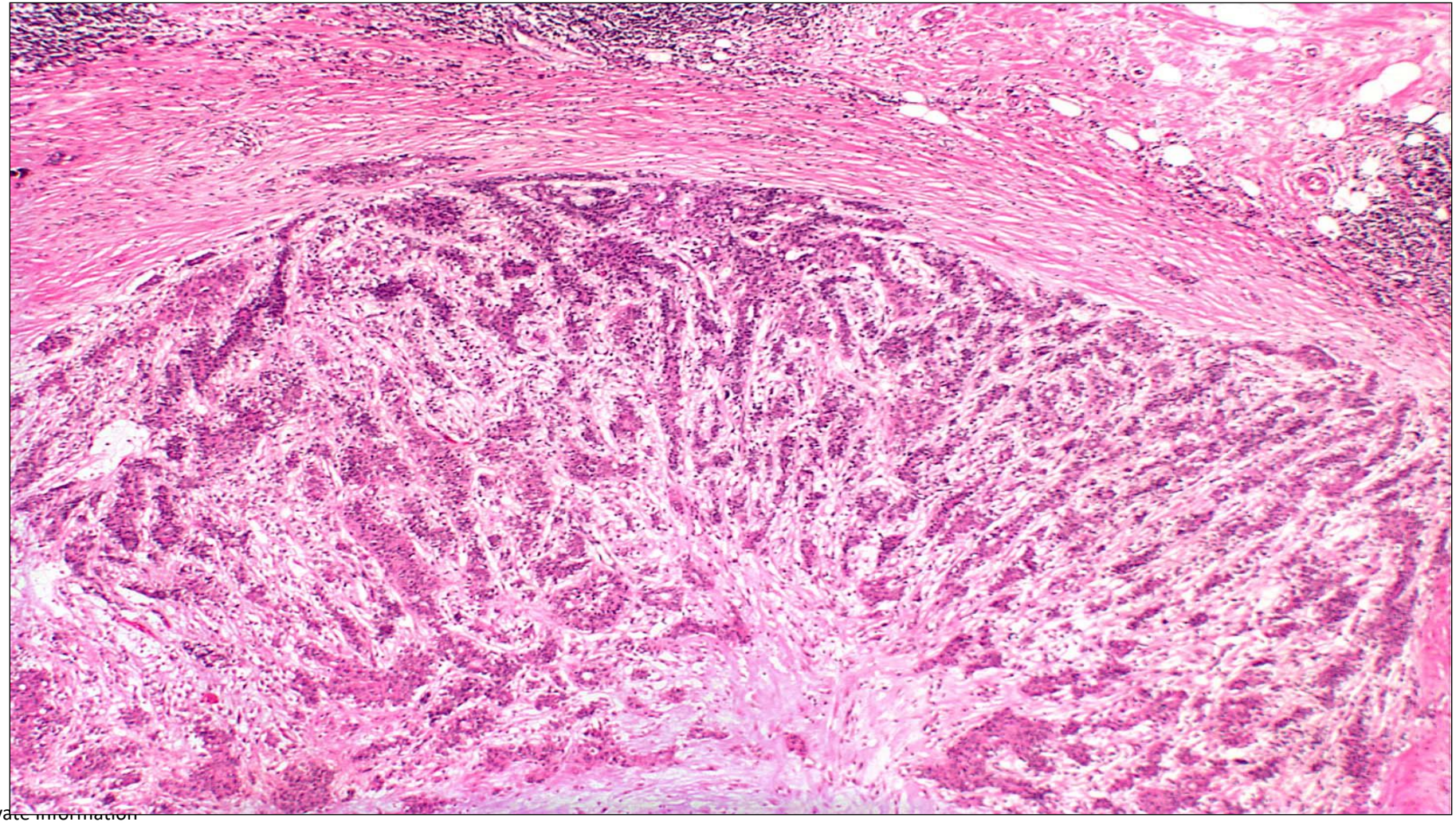


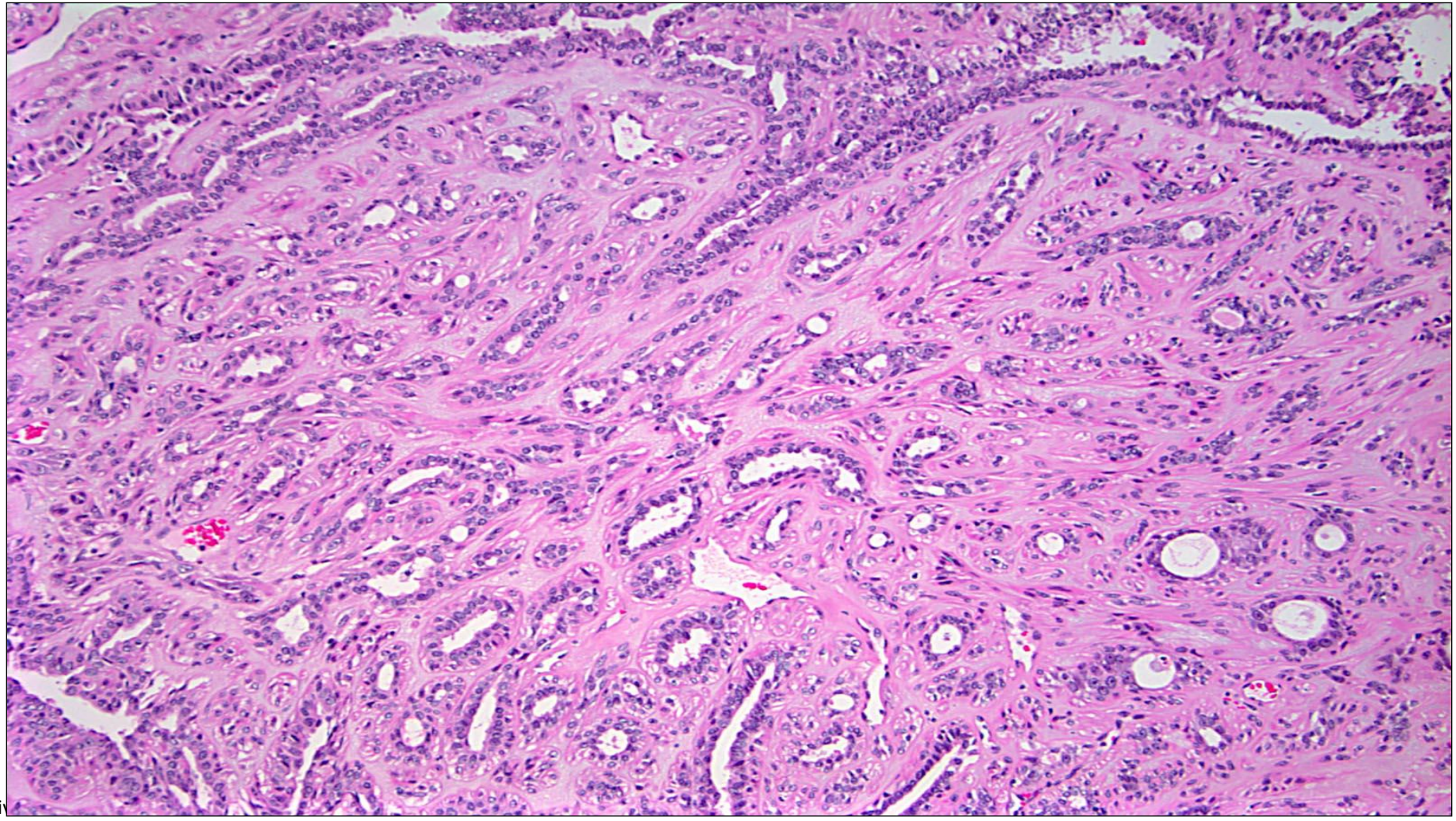
Adenomyoepithelioma

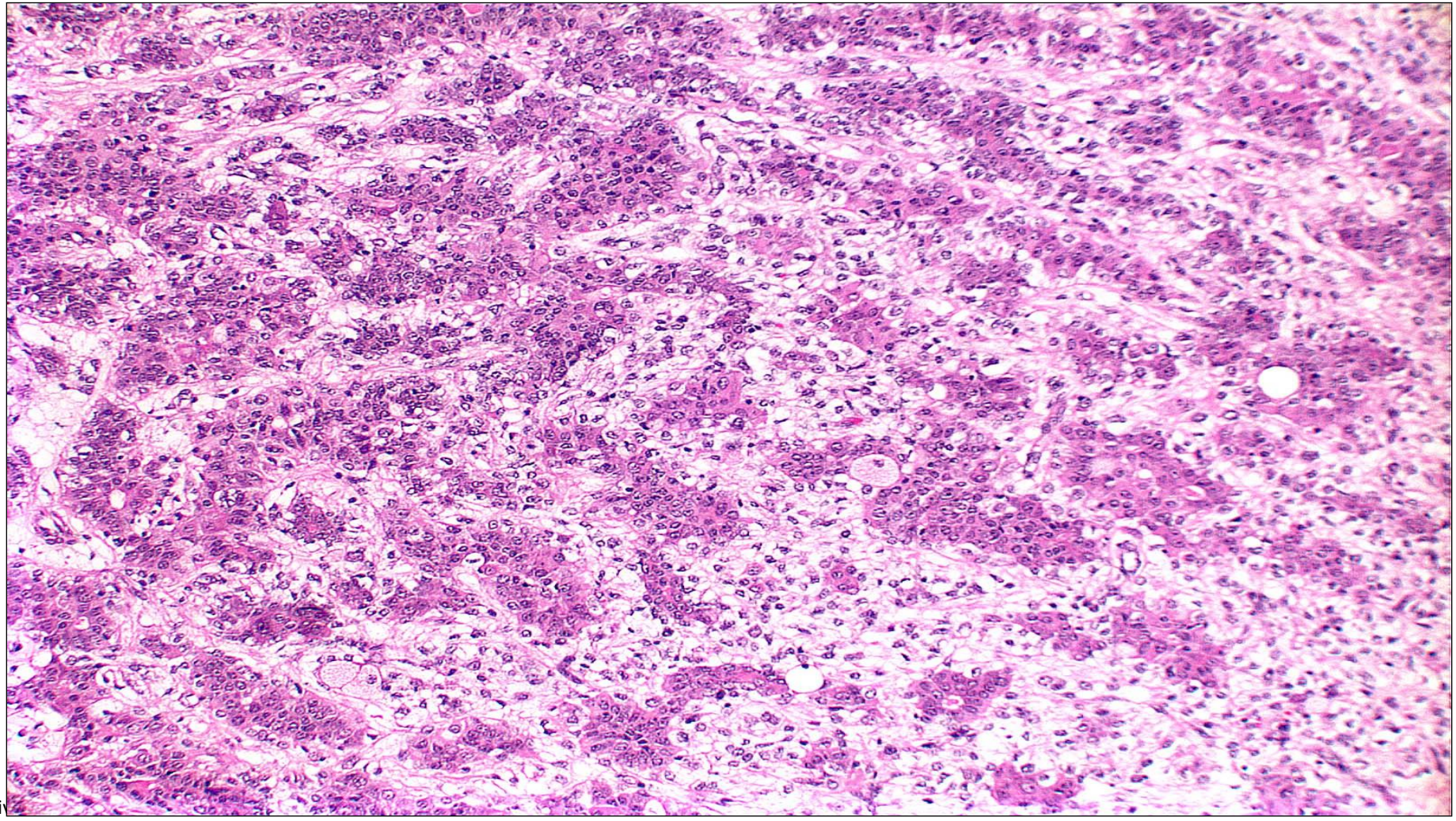
- Considered a variant of intraductal papilloma
- Often multinodular, lobulated masses
- Composed of epithelial and myoepithelial cells
- Myoepithelial cells prominent
- Many variants, including lobulated, spindle cell and tubular types
- May recur; WHO considers these tumors of low malignant potential
- Molecular analyses indicate *PIK3CA* hotspot mutations in >50% of cases; *AKT1* and *HRAS* mutations also reported
- Exclude metaplastic carcinoma

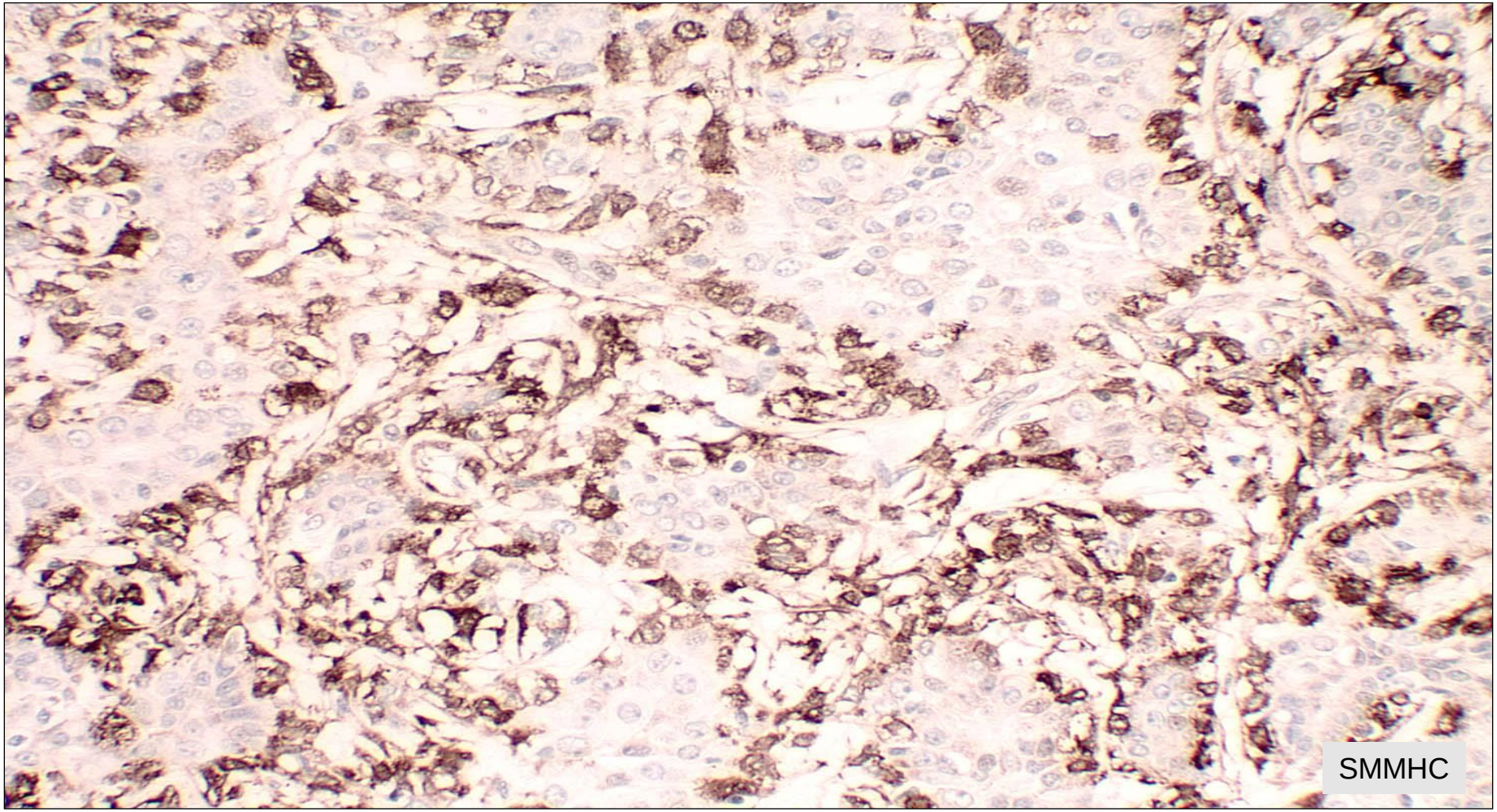
Hayes, 2011
Geyer, 2018
Ginter, 2020
WHO, 2019



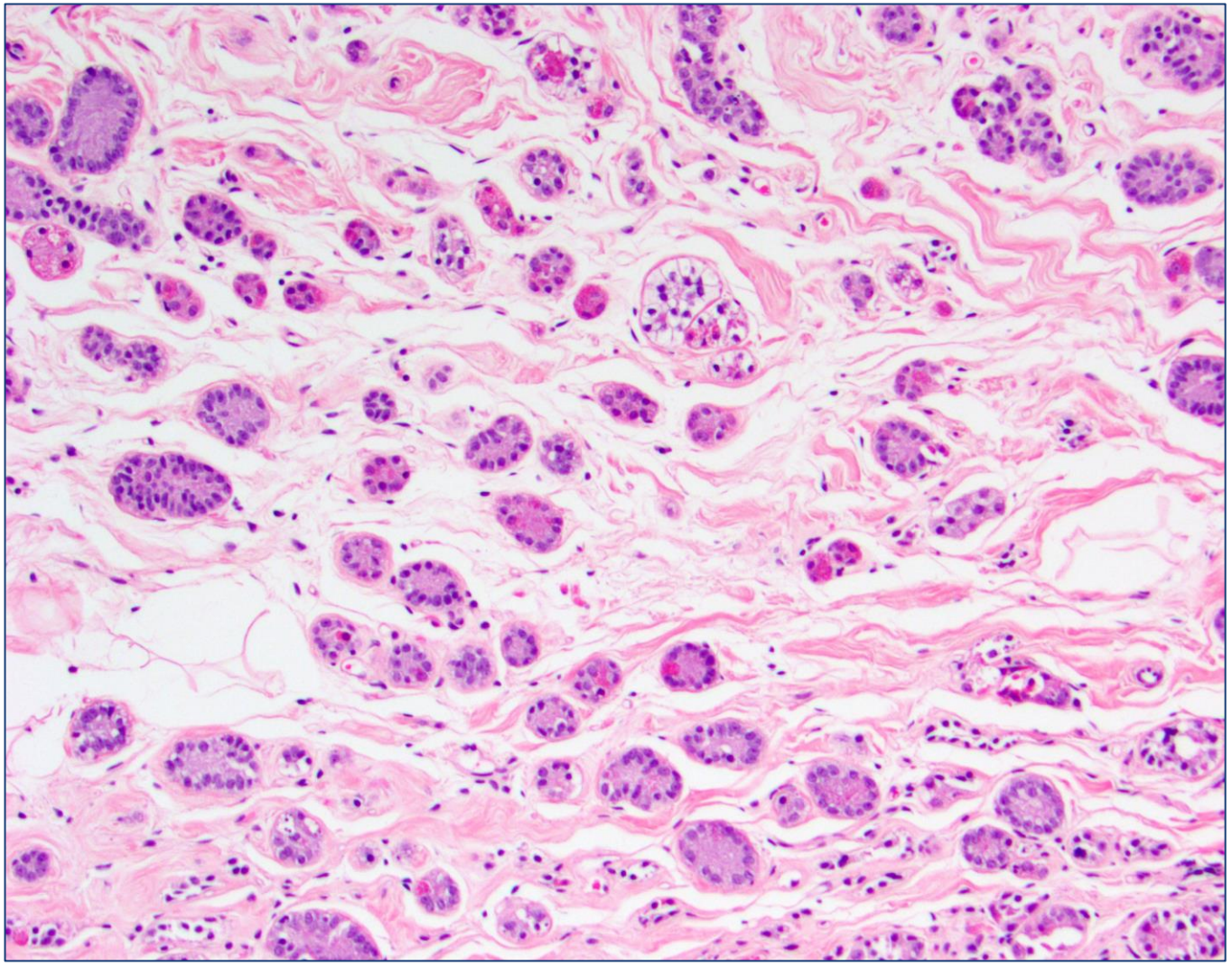


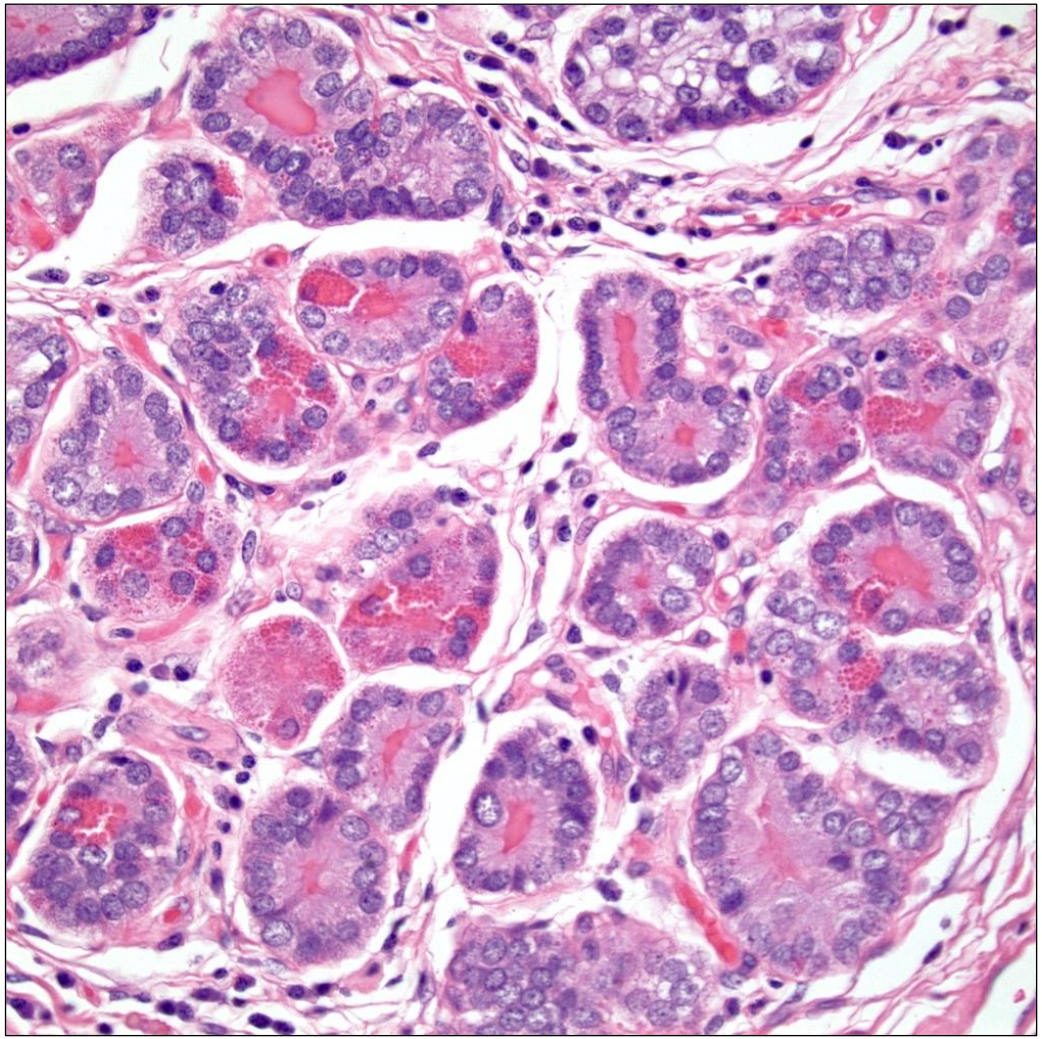


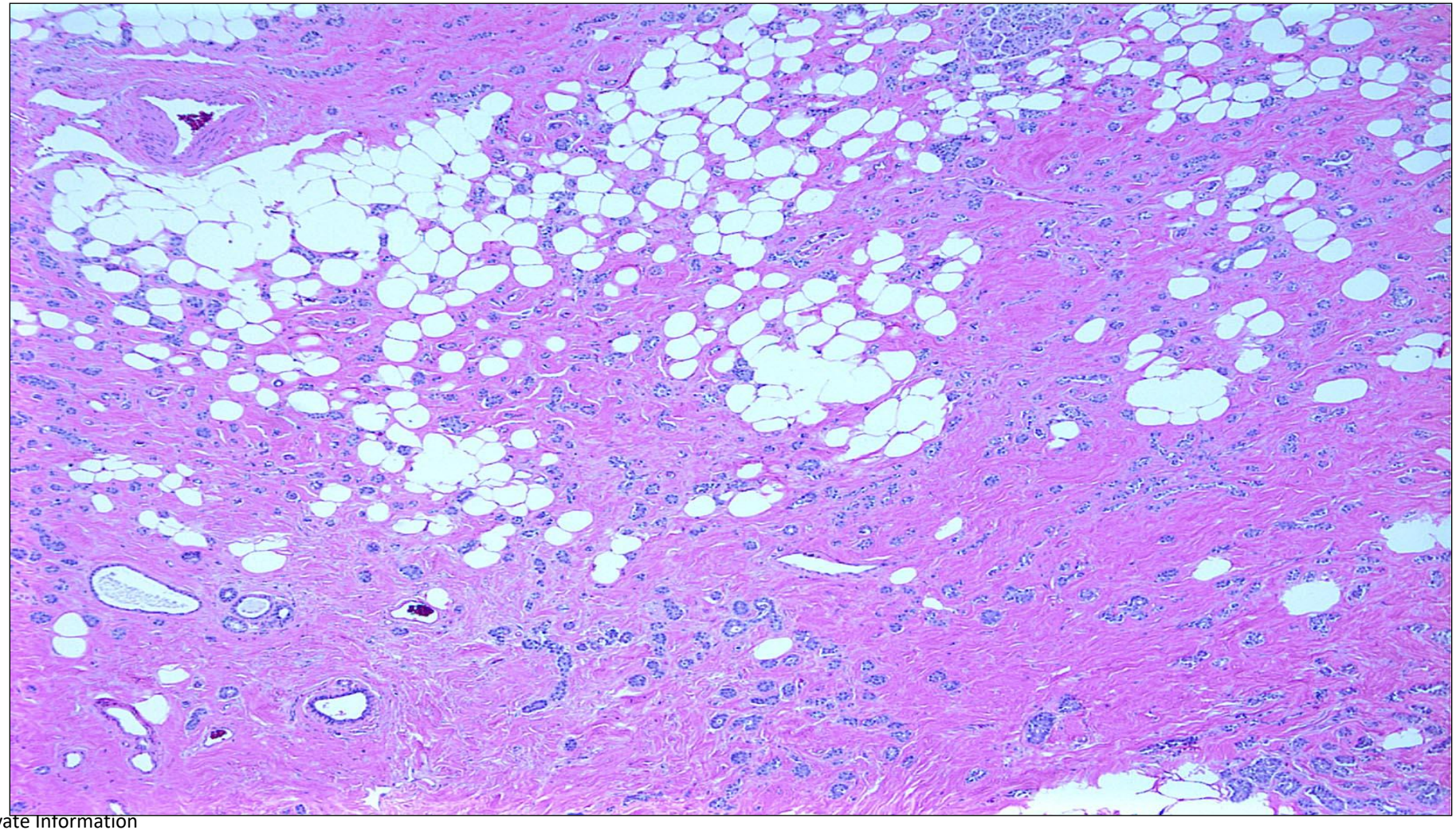


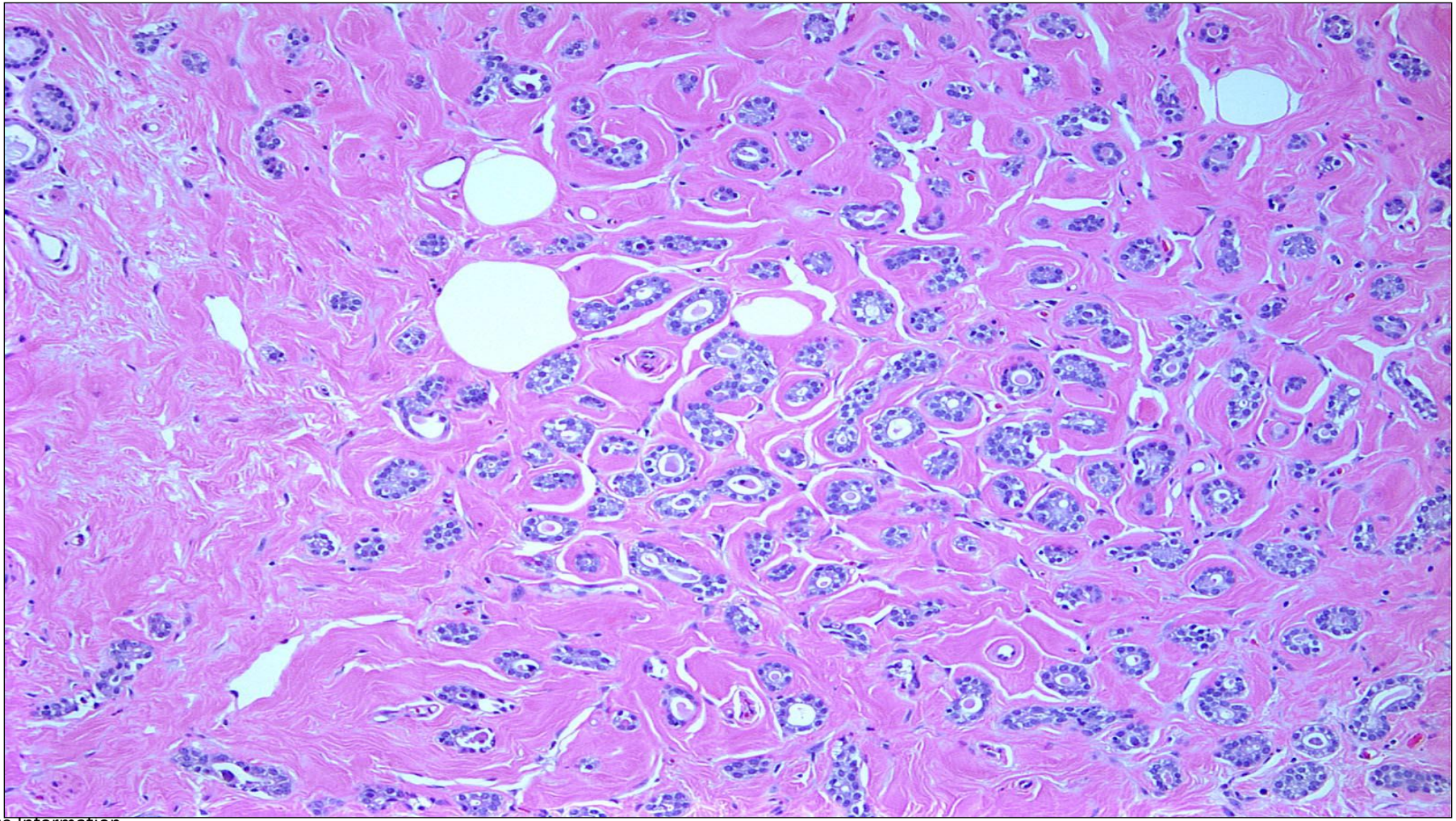


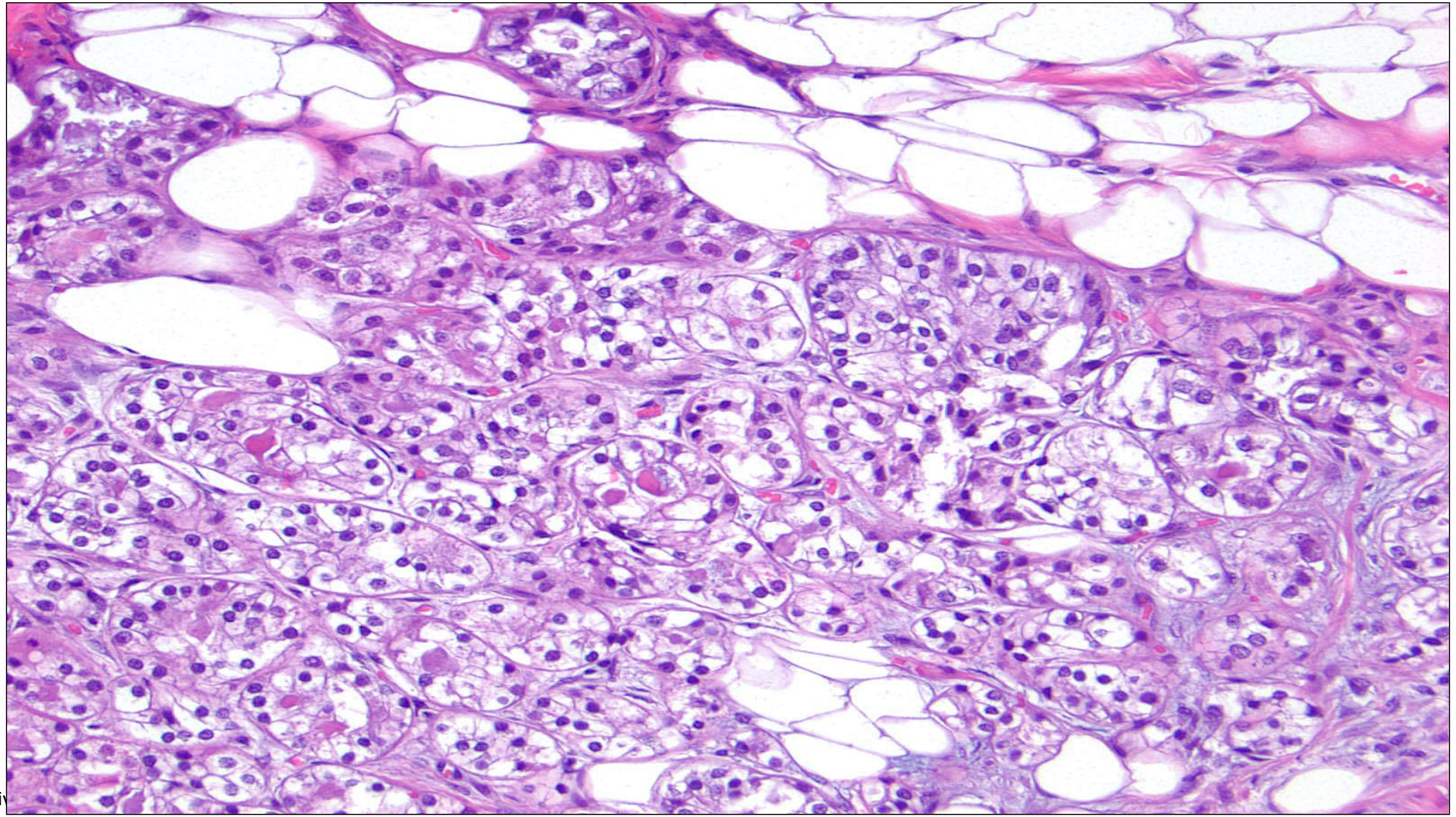
ACINIC CELL CARCINOMA
MICROGLANDULAR ADENOSIS

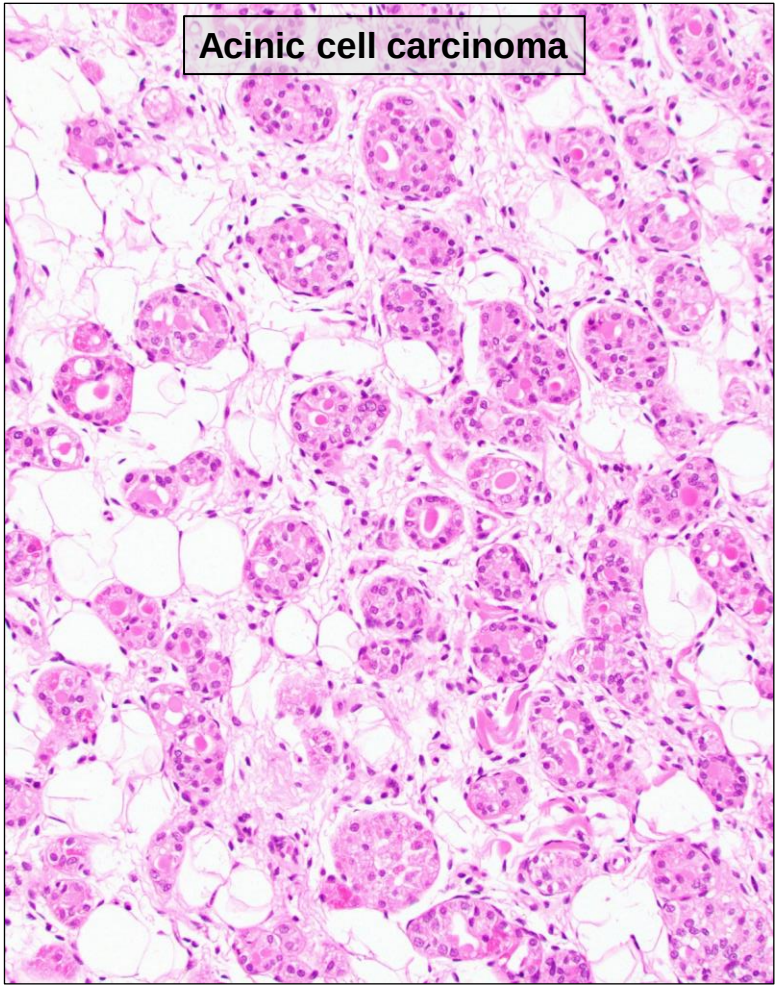


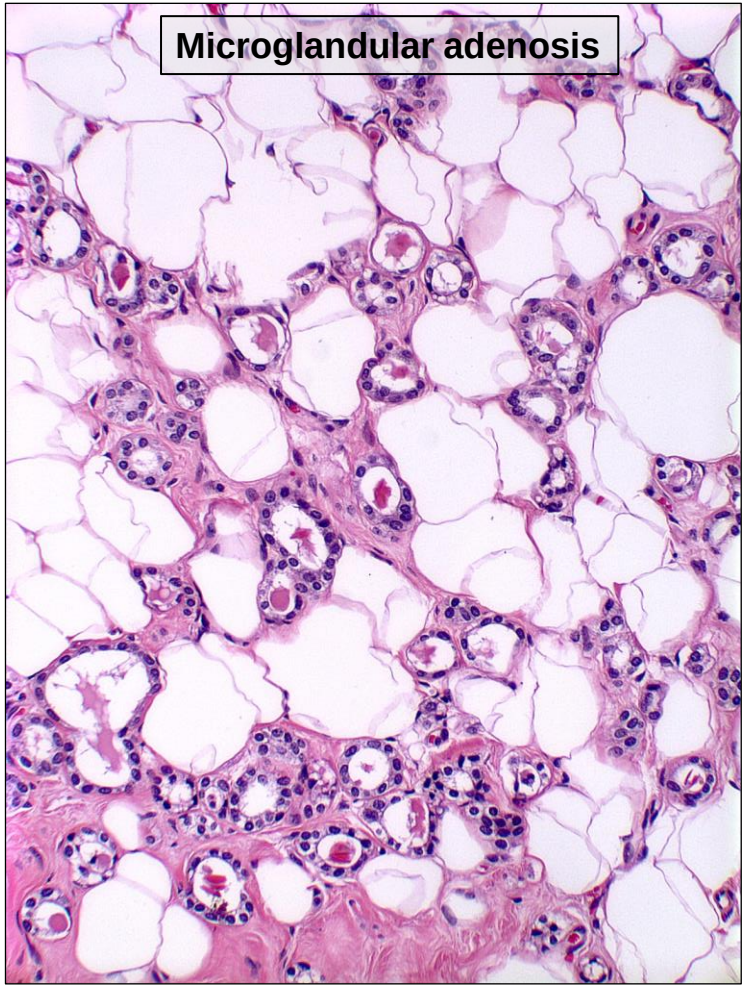








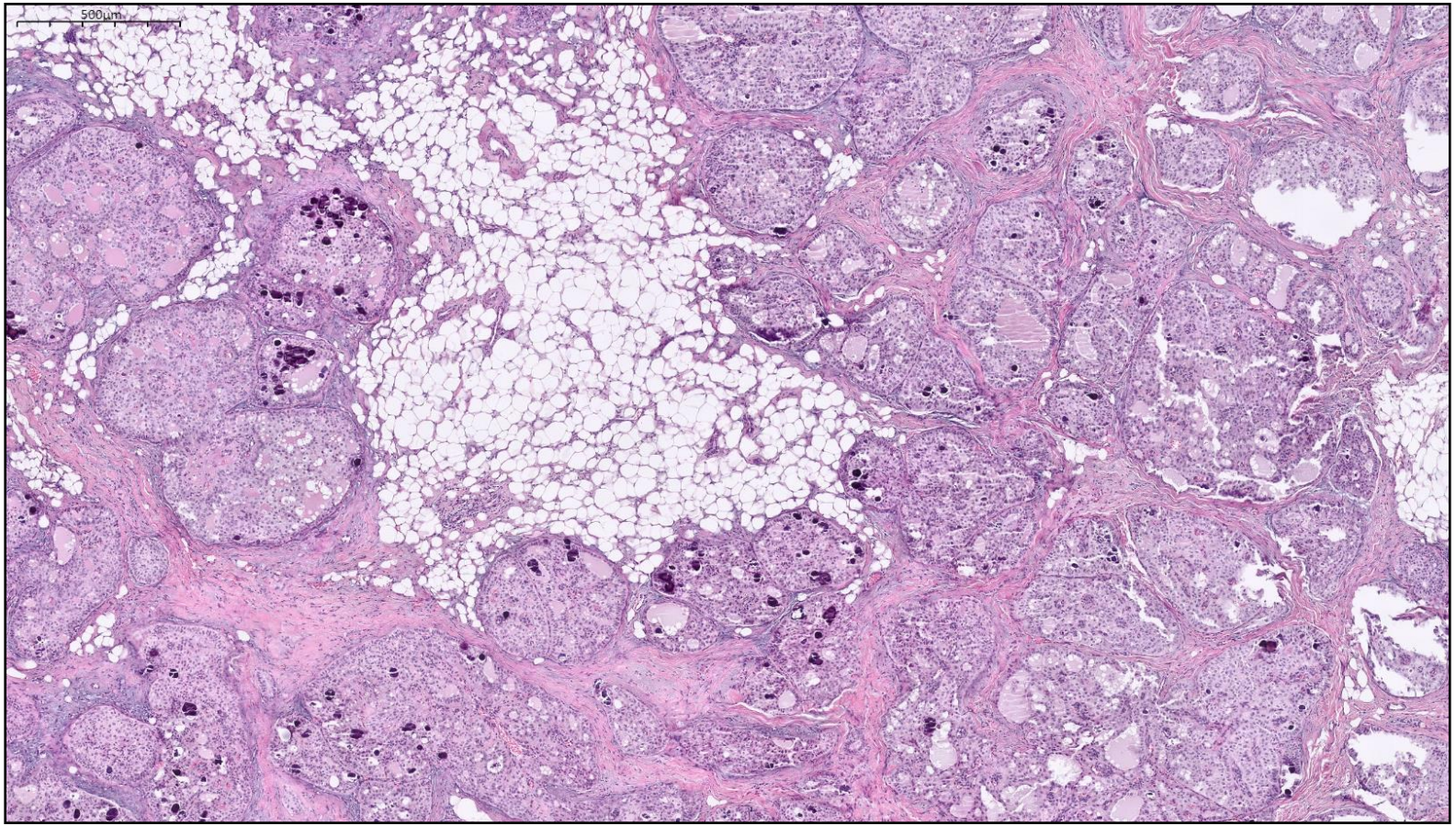


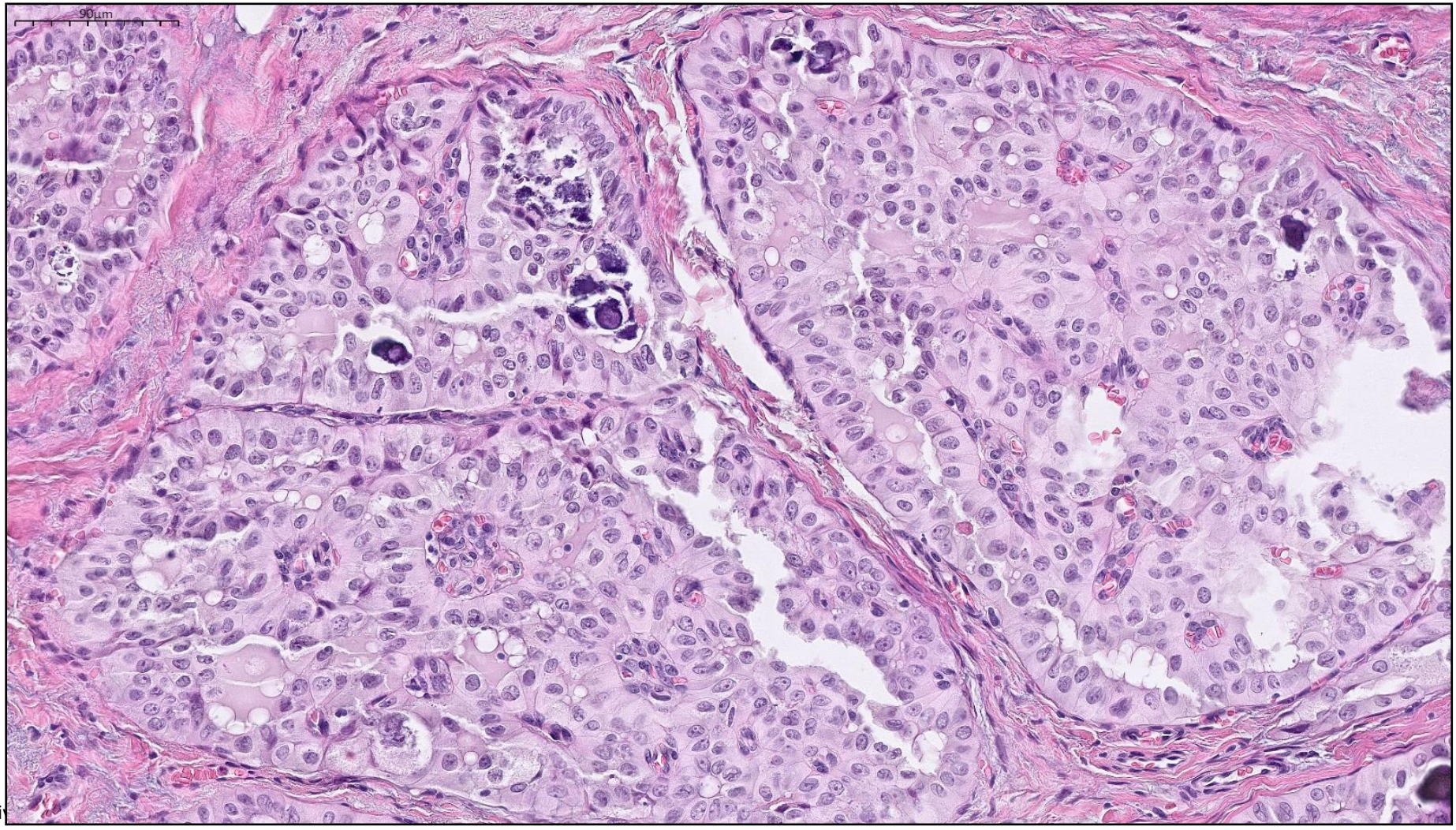


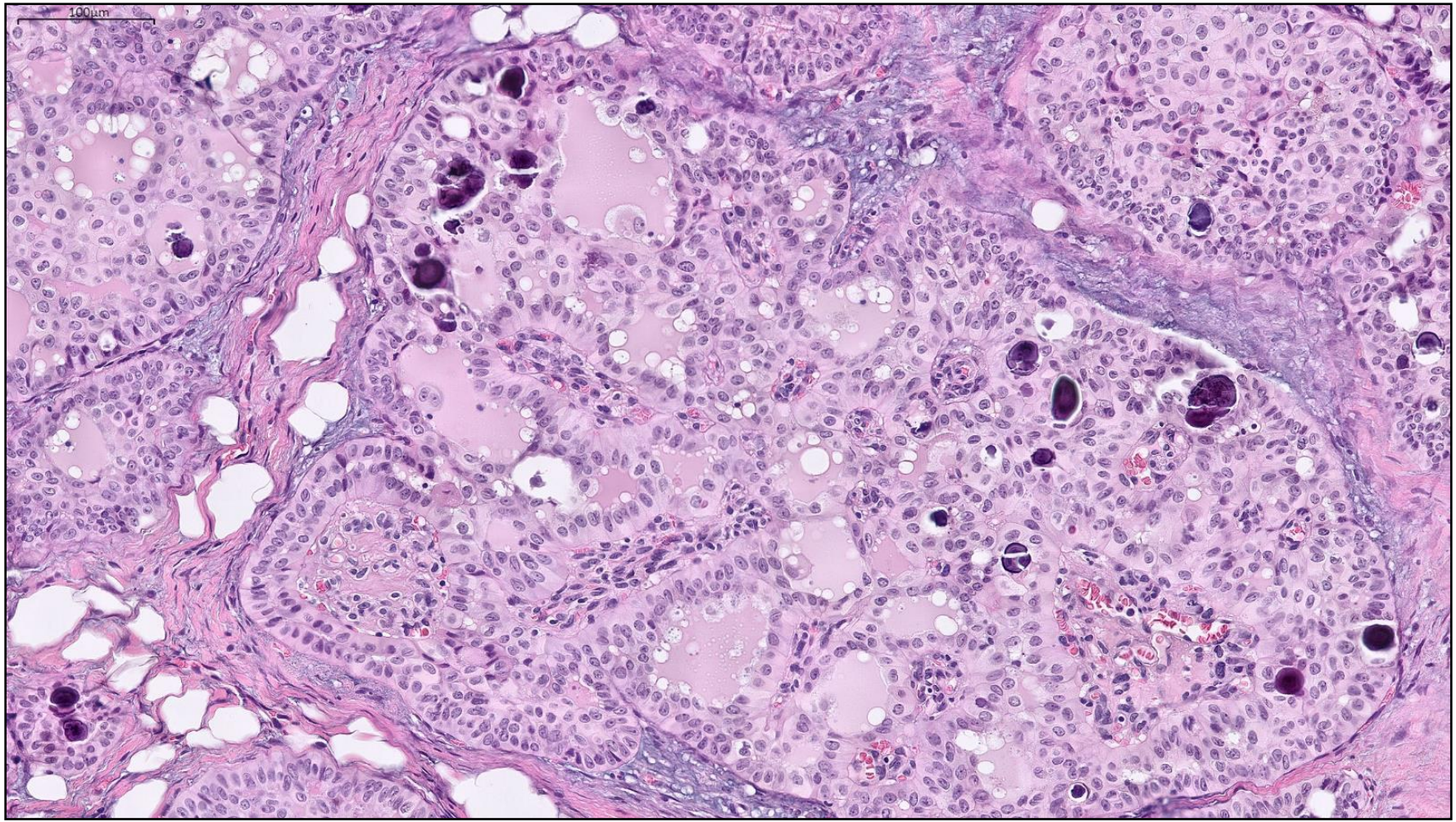
ER AS A SAFETY CHECK

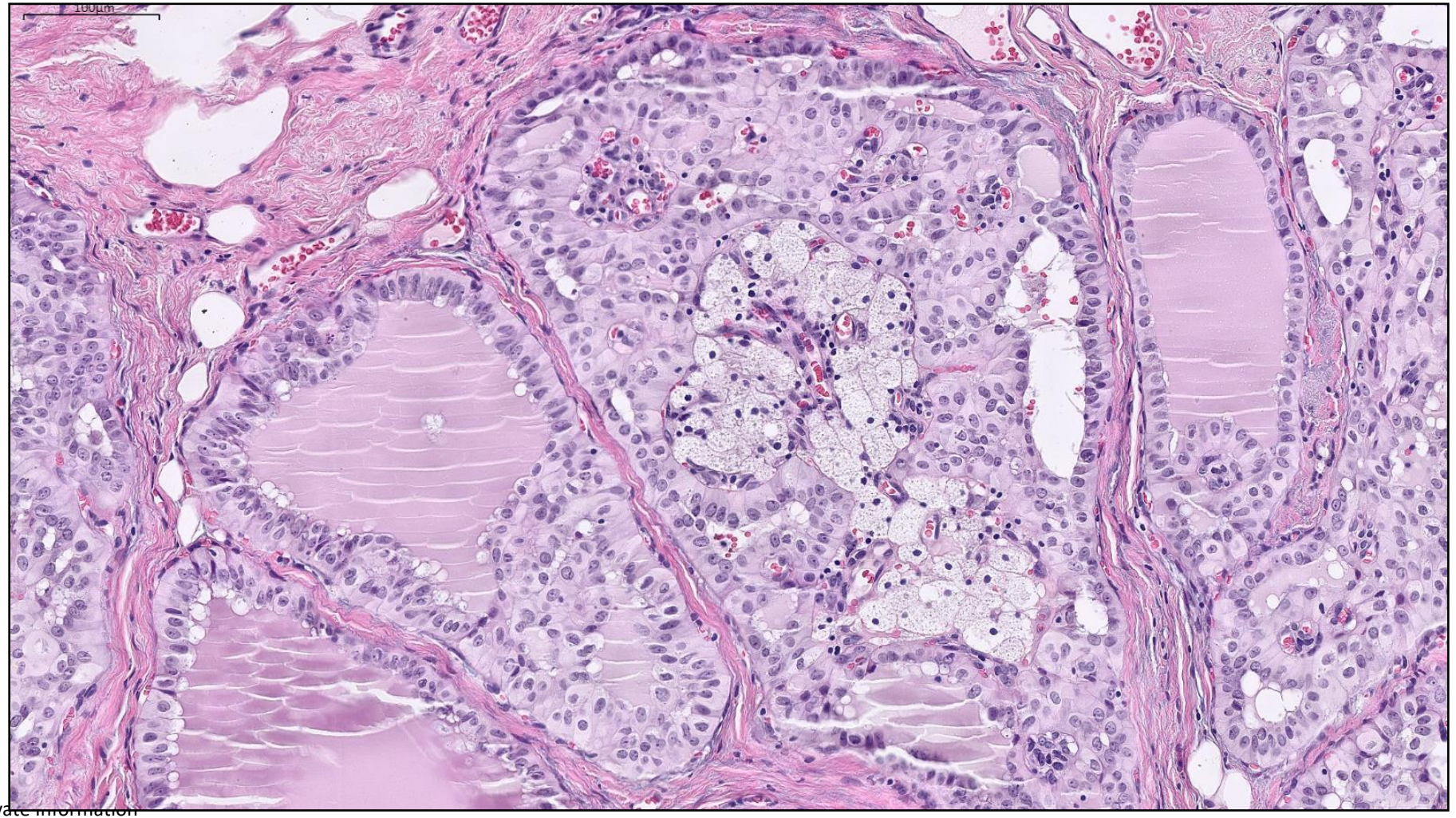
Heterogeneous expression of ER

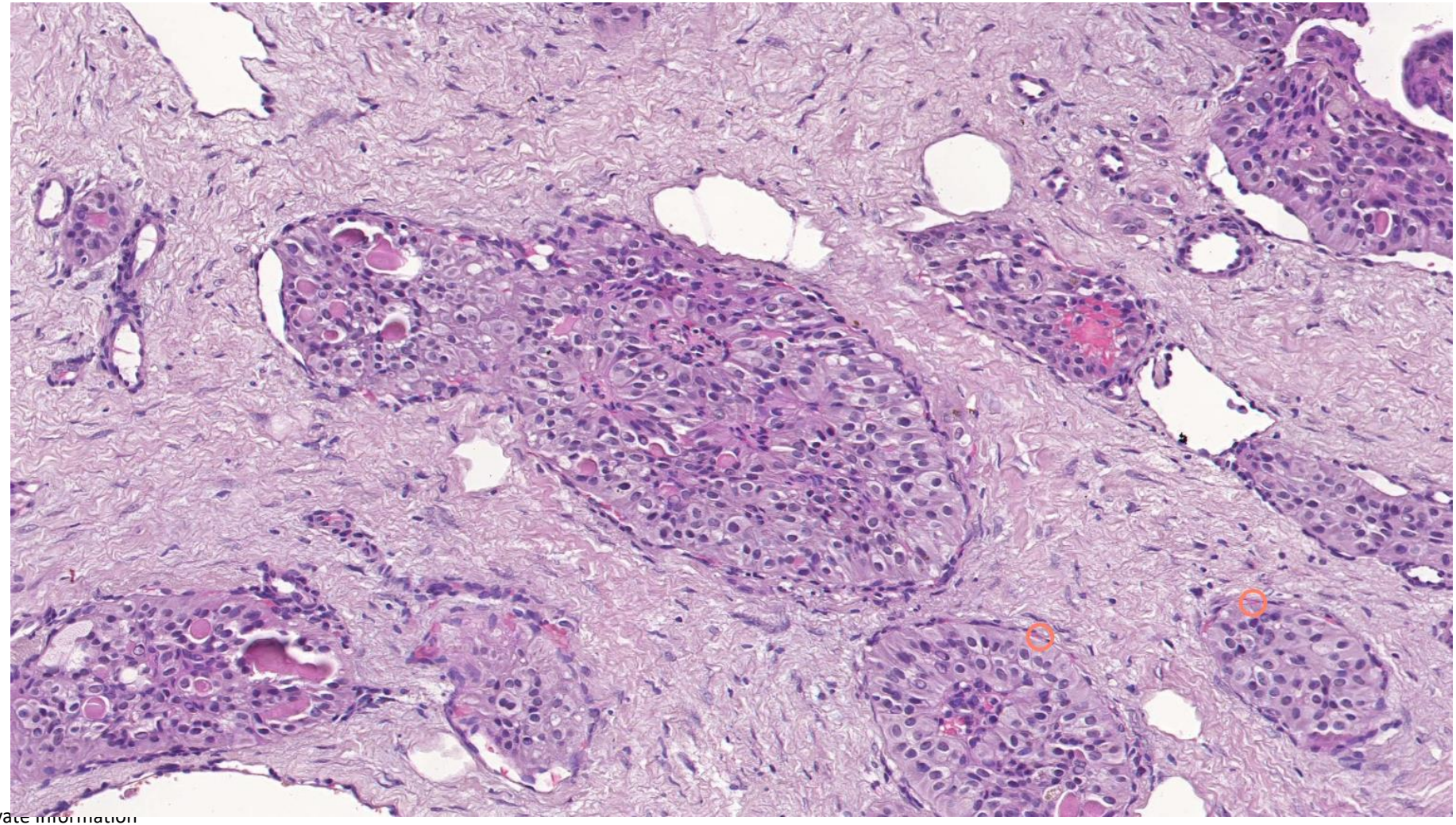
Absence of ER expression in a well-differentiated tumor

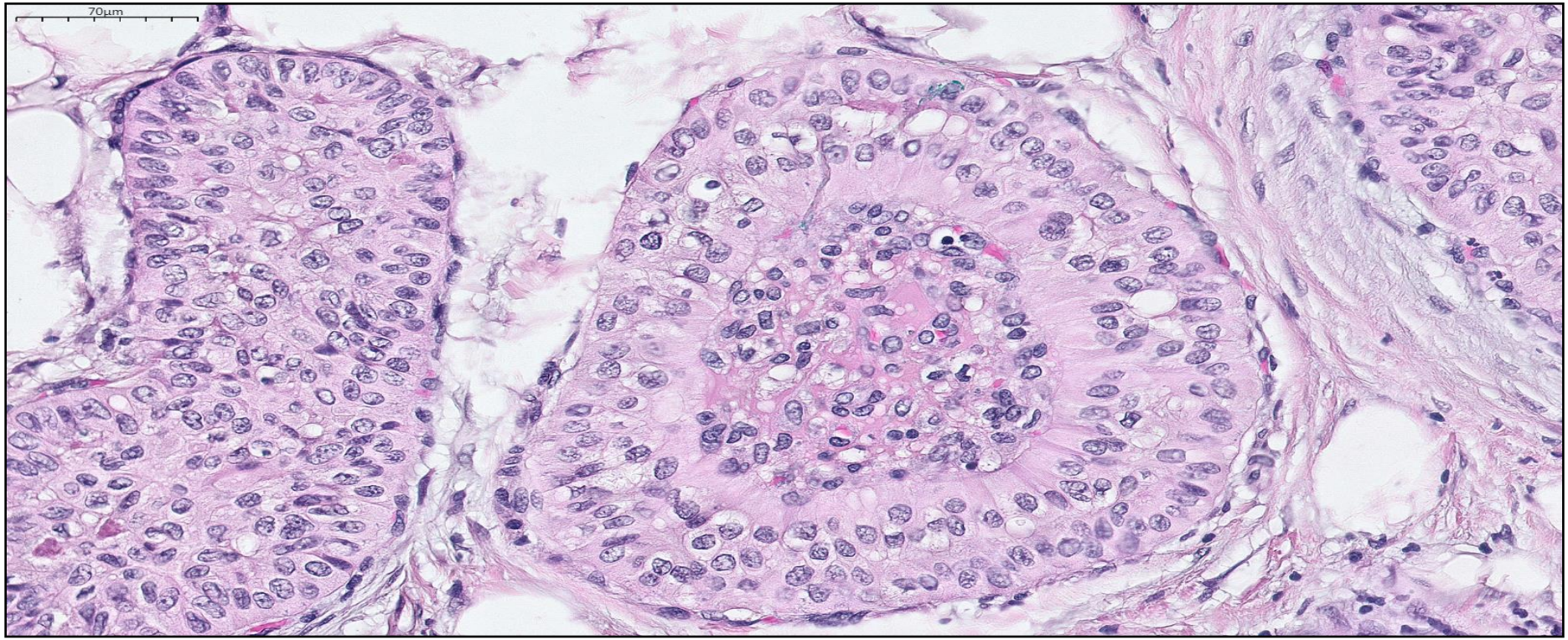



90µm





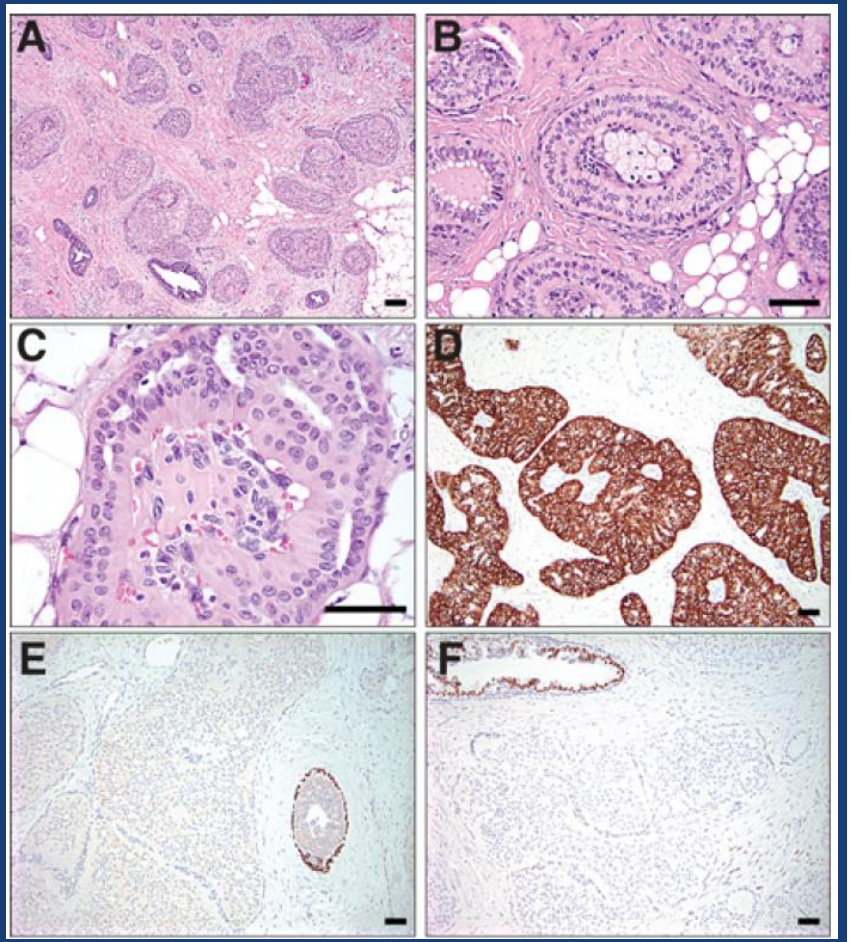




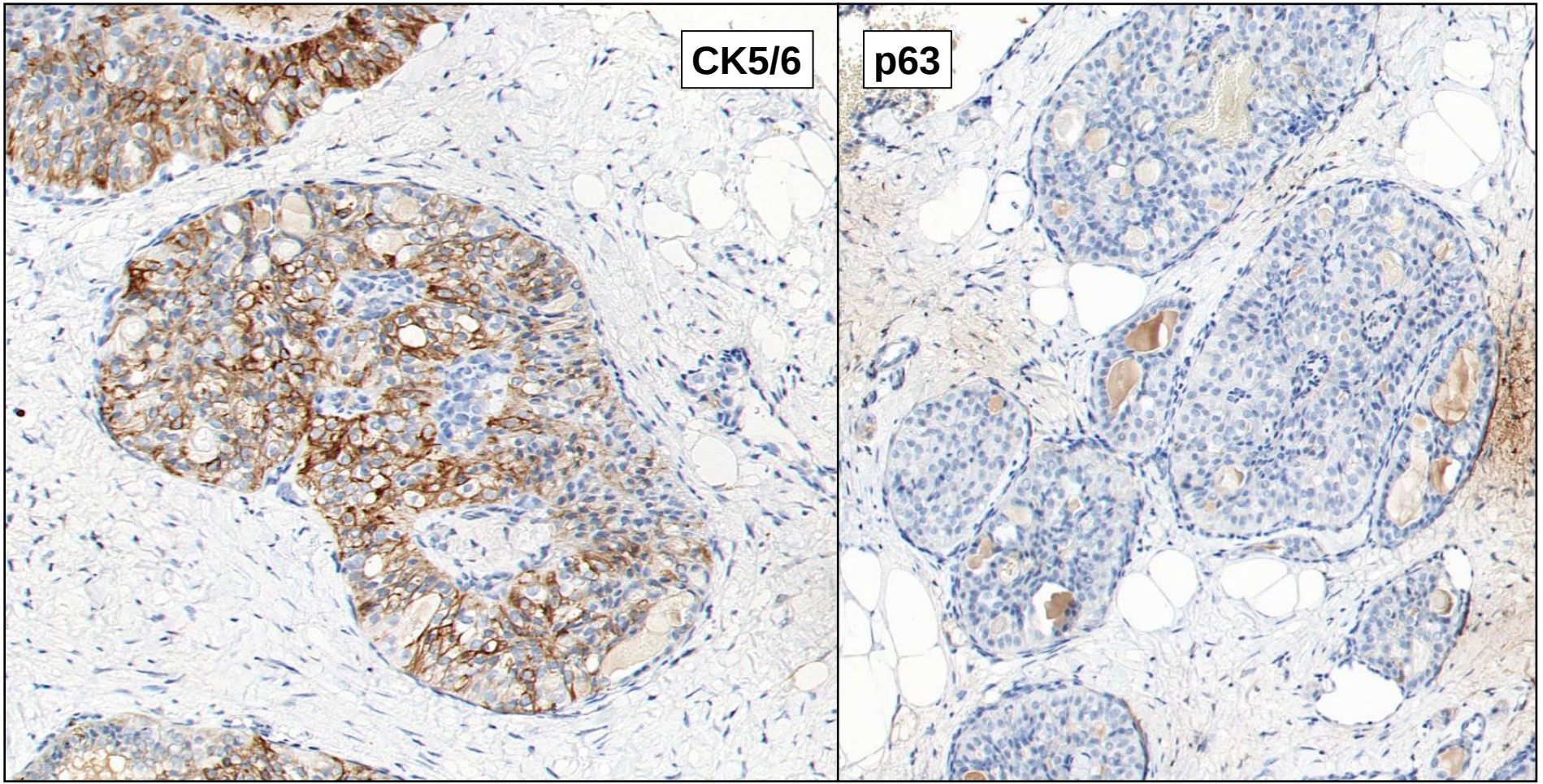
TALL CELL CARCINOMA WITH REVERSED POLARITY

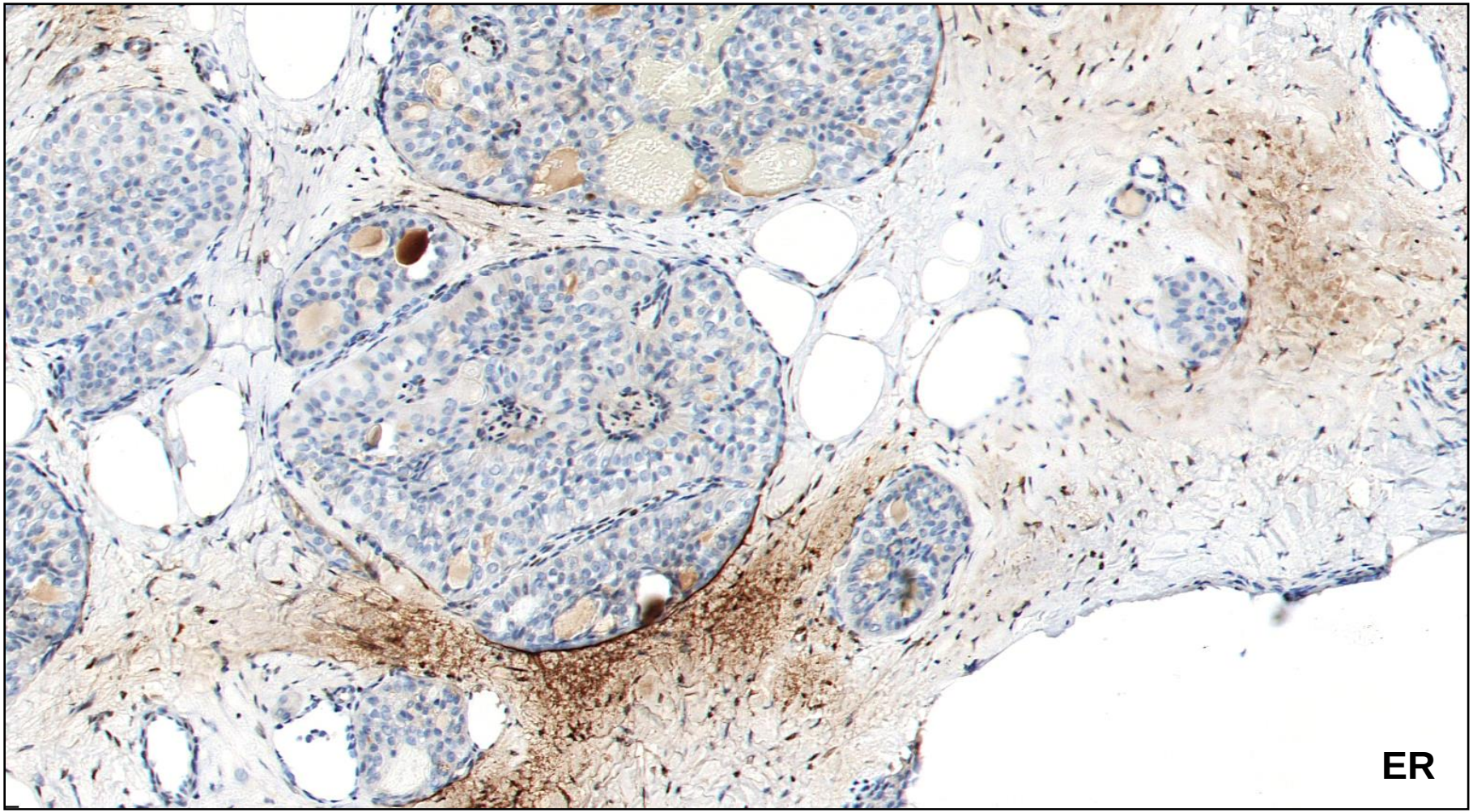
IHC Markers

- CK7+, CK20-, CK5/6+
- MEC marker negative
- S100+
- ER/PR/HER2 negative
- TTF-1 negative
- Thyroglobulin negative
- IDH2 positive



Chiang, Cancer Res, 2016





Tall Cell Carcinoma with Reversed Polarity

- Few cases described in the literature (~40 cases)
- Post menopausal women
- Median tumor size 1.1 cm
- Limited data indicate indolent behavior
- *IDH2* mutations in 65-100% of cases; 30-90% with concurrent mutations of *PIK3CA* or *PIK3R1*
- IDH2 R172 protein expression by IHC (among 14/15 cases, 93%); highly sensitive and specific

Chiang, Cancer Res, 2016
Bhargava, 2017
Lozada, 2018
Alsadoun, 2018
Zhong, 2018
Pareja, Mod Pathol, 2020

	Chiang 2016	Bhargava 2017	Lozada 2018	Alsadoun 2018	Zhong 2018	Pareja 2020
Number of cases	13	3	5	9	9	14
IDH2 mutation	77%	67%	100%	78%	100%	100%
PIK3CA mutation	62%	33%	67%	N/A	86%	50%

Differential Diagnostic Considerations for TCCRP

- Usual ductal hyperplasia
- Papillomatosis
- Low grade invasive carcinoma, NST
- Metastasis

Breast Tumor Resembling the Tall Cell Variant of Papillary Thyroid Carcinoma

Report of 5 Cases

AJSP, 2003

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.

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]

Breast Tumor Resembling Tall Cell Variant of Papillary Thyroid Carcinoma

AJCP, 2017

A Solid Papillary Neoplasm With Characteristic Immunohistochemical Profile and Few Recurrent Mutations

Rohit Bhargava, MD,[1] Anca V. Florea, MD,[2] Manuela Pelmus, MD,[2] Miroslawa W. Jones, MD,[1] Marguerite Bonaventura, MD,[1] Abigail Wald, PhD,[3] and Marina Nikiforova, MD[3]

Solid Papillary Breast Carcinomas Resembling the Tall Cell Variant of Papillary Thyroid Neoplasms

AJSP, 2017

A Unique Invasive Tumor With Indolent Behavior

Maria P. Foschini, MD, Sofia Asioli, MD,* Susan Foreid, MD,† Gabor Cserni, MD,‡ Ian O. Ellis, MD, FRCPath,§ Vincenzo Eusebi, MD, FRCPath,* and Juan Rosai, MD, FRCPath‖*

Nomenclature

WHO expert panel proposes:

Tall Cell Carcinoma with Reversed Polarity

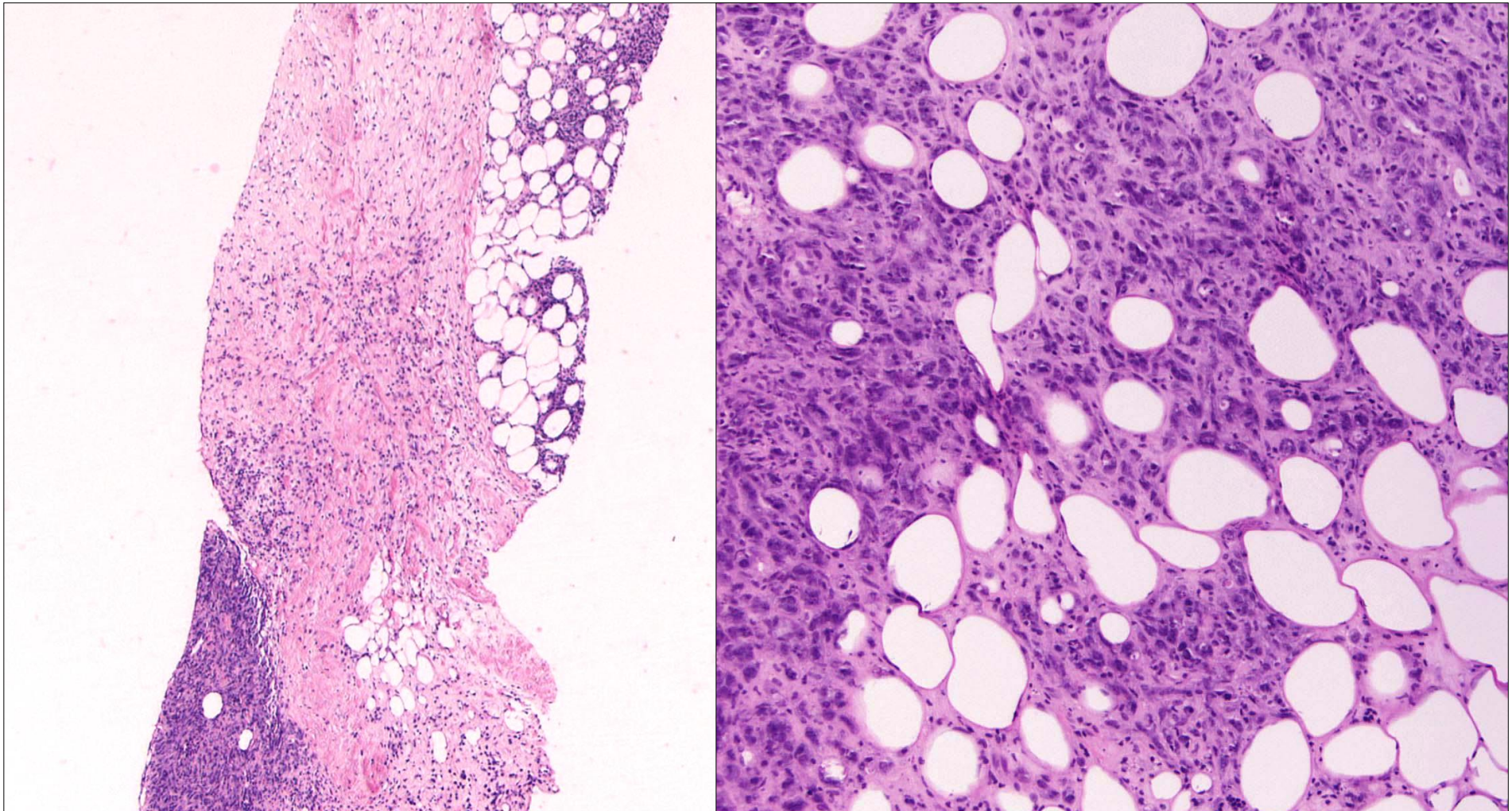
High grade triple negative cancers

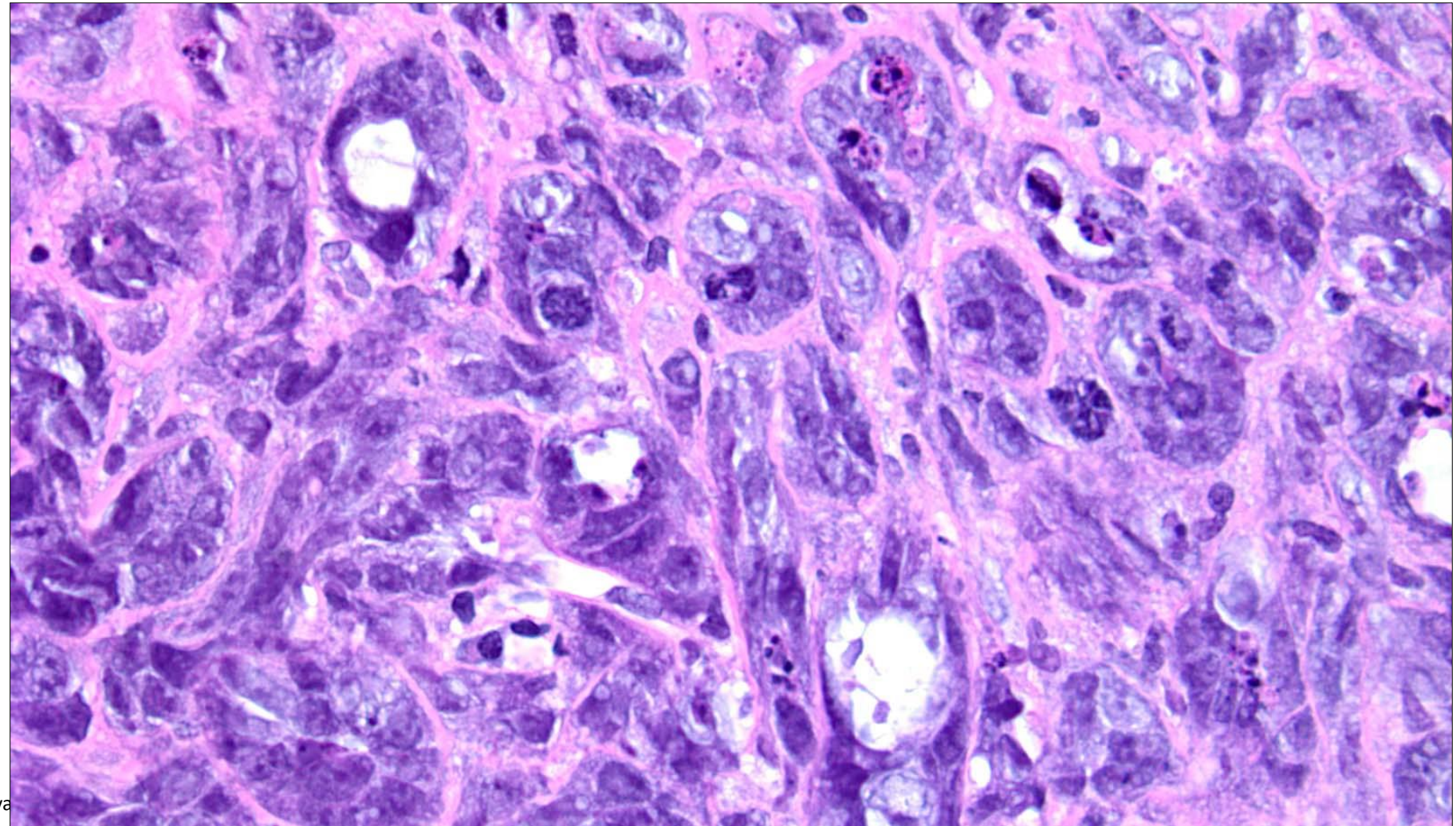
Case History

- Case of an 80 year old female with a history of breast cancer
- Radiologic DDX:

  "Tumor vs. fat necrosis"

- Case seen among routine, heavy case-load





Priva

Invasive ductal carcinoma, grade 3 with necrosis

Biomarkers ordered

ER, PR, HER2 negative
“Triple Negative”

- **Case reviewed for presentation at radiology/pathology correlation conference**
- **Among just 10 cases for presentation**

- **Unusual features for IDC NOS**
- **Nuclei somewhat spindly**
- **Presence of necrosis**
- **Triple negative**
- **No in situ component**

Conceivable this is a “basal-like carcinoma” which is characterized by these features

Next steps

Show case around

- **Breast pathologists away!**

Obtain more history (?type and grade of original breast cancer)

- **Prior surgery not at our institution**

Confirmatory immunostains

- **Won’t be ready in time for conference**

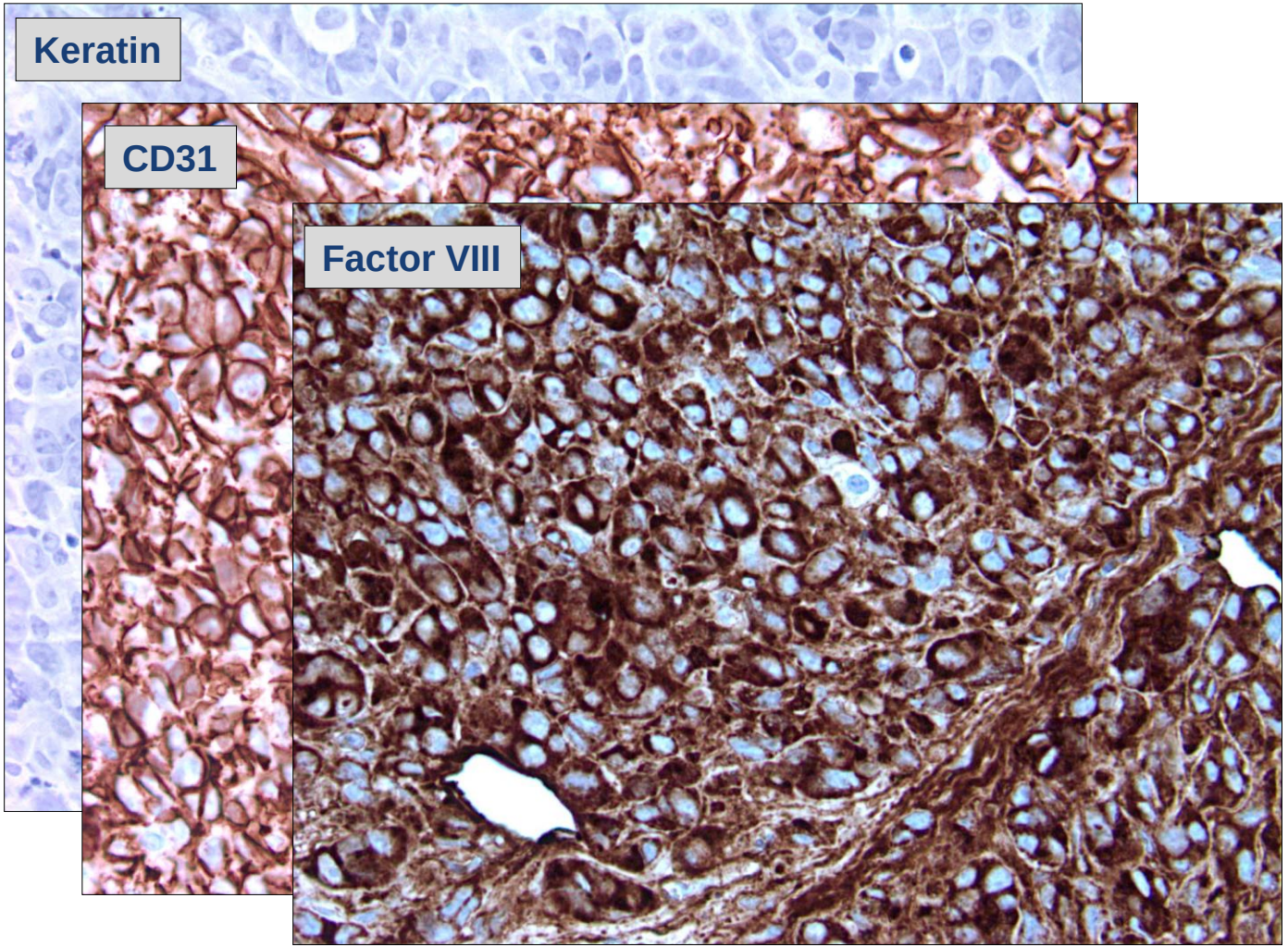
At Conference

- Additional history provided
- Prior cancer was grade 1, IDC
- Purplish red lesions extensively involving the breast
- ?Angiosarcoma

Further work up

Additional immunostains ordered:

- Vascular markers (CD34, CD31)
- Keratin cocktail



IHC in Vascular Tumors

- Aberrant keratin staining has been reported (especially in the epithelioid variant)
- p63 recently reported in malignant vascular tumors
- Always use a panel of markers

Spindle cell lesions

Spindle Cell Lesions of the Breast

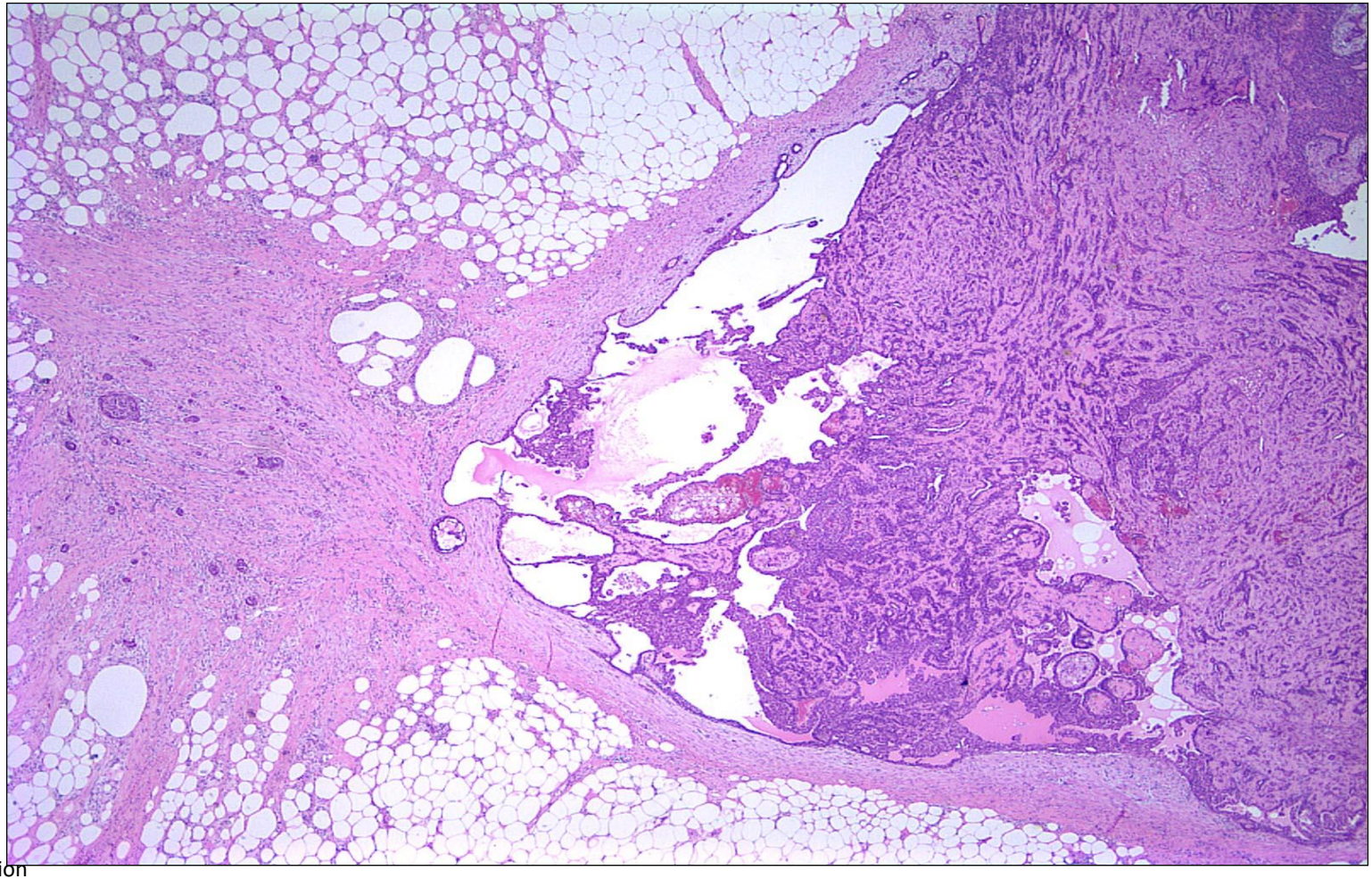
Bland spindle cells

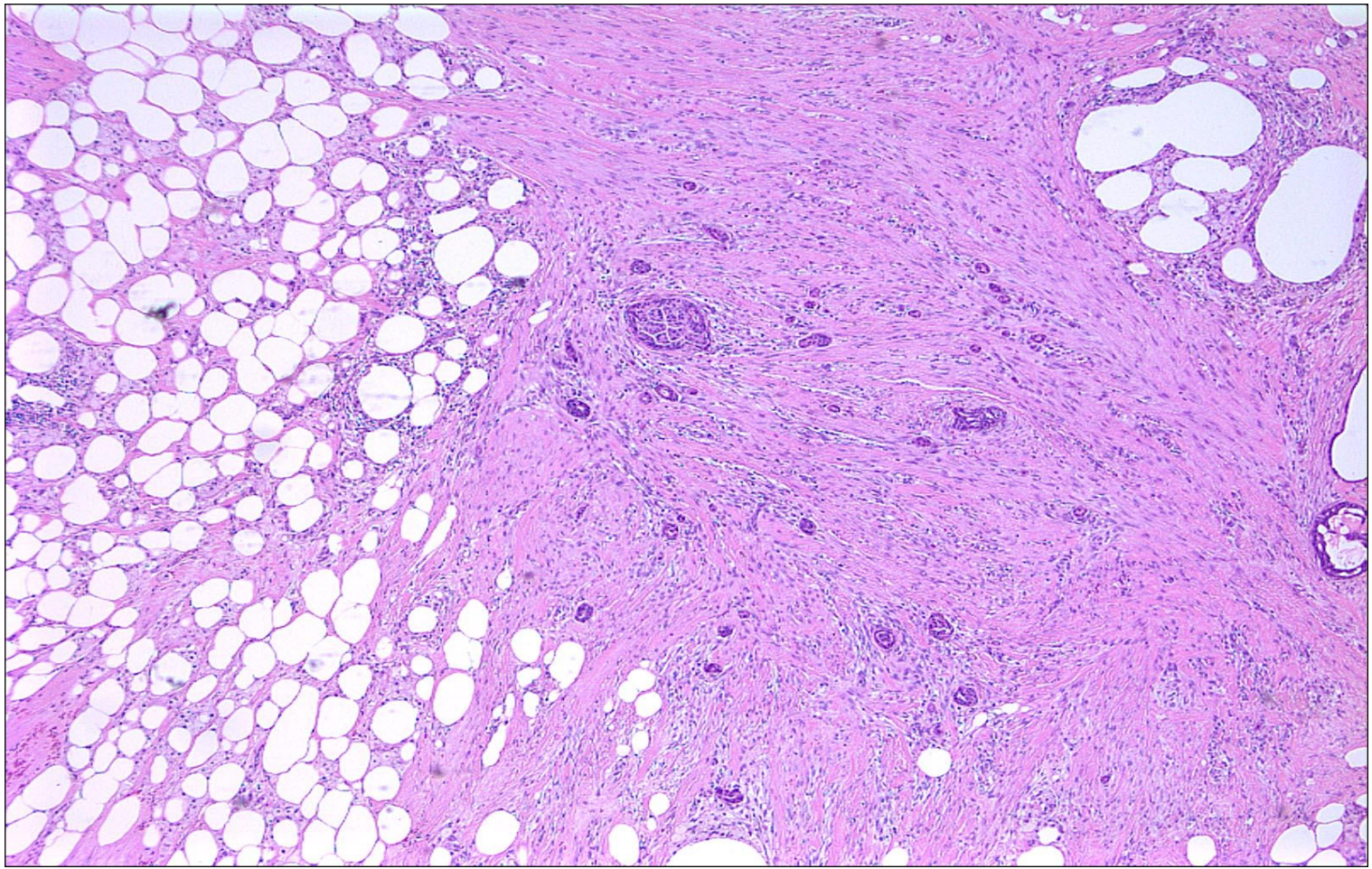
- Scar
- Desmoid Fibromatosis
- Myofibroblastoma
- PASH (fascicular type)
- Adenomyoepithelioma
- Spindle cell carcinoma
- Fibromatosis-like metaplastic carcinoma

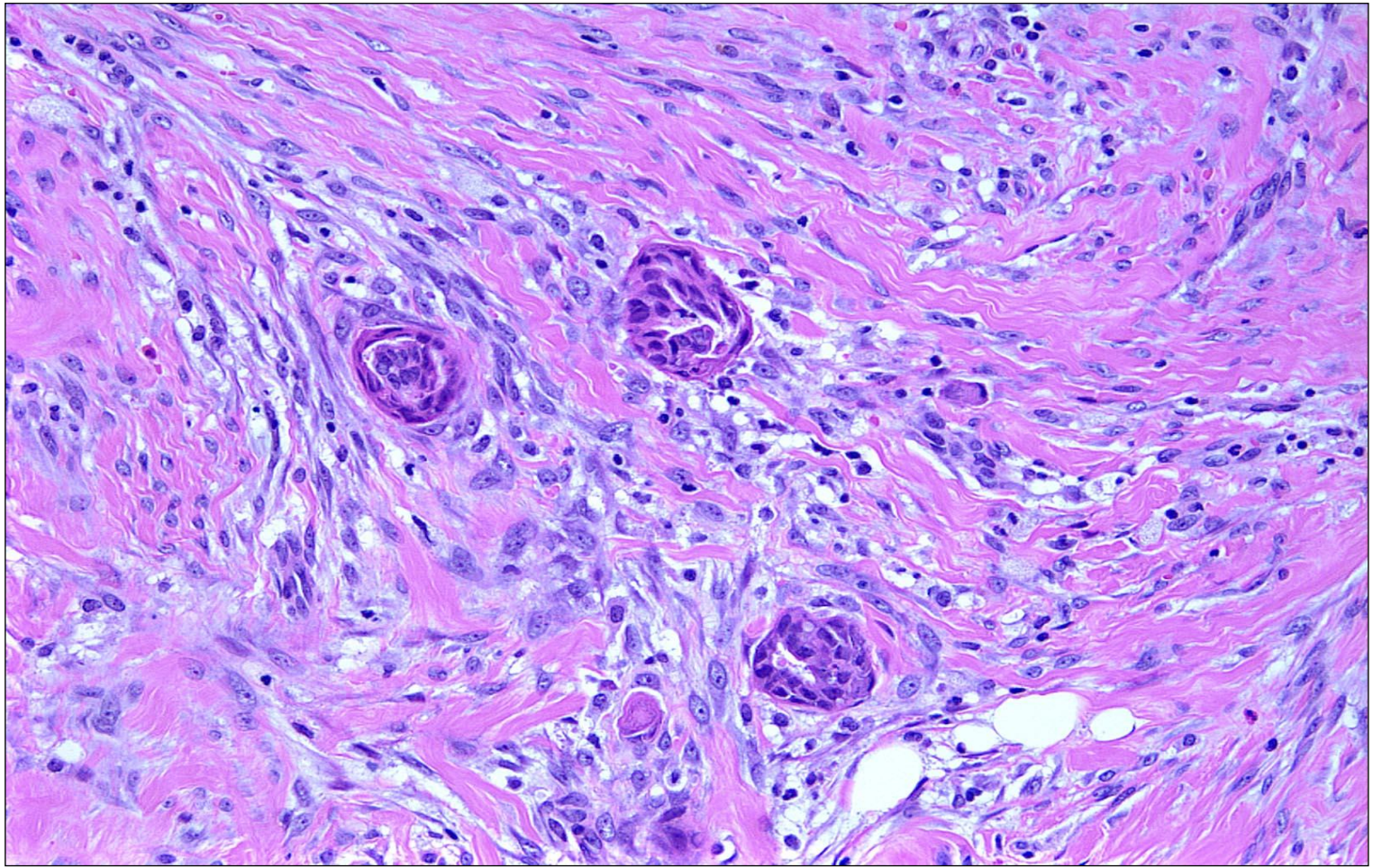
Atypical spindle cells

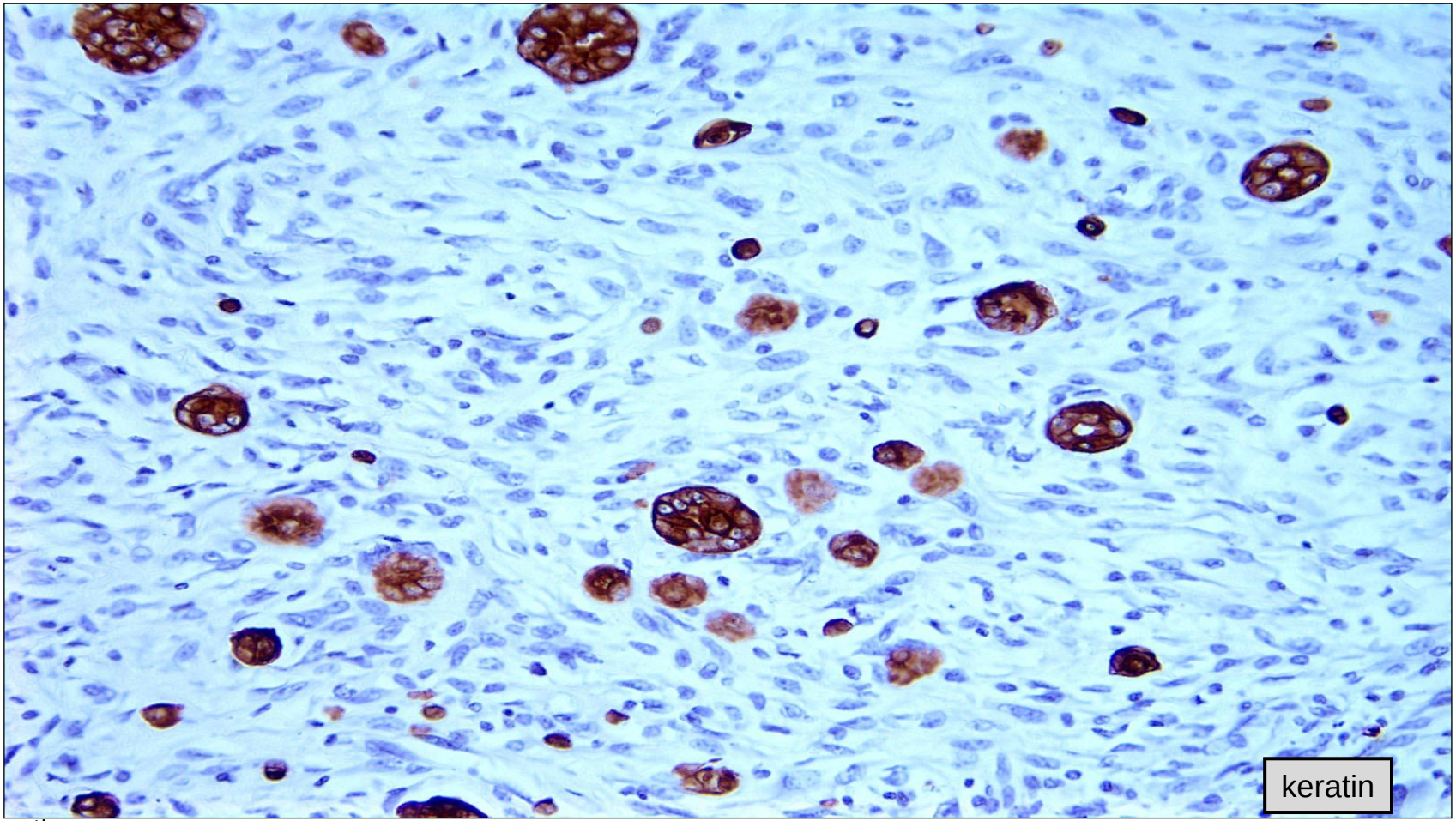
- Spindle cell carcinoma
- Phyllodes tumor
- Angiosarcoma
- Nodular fasciitis
- Solitary fibrous tumor
- Sarcoma (primary or metastatic)
- Metastatic spindle cell carcinoma
- Metastatic melanoma

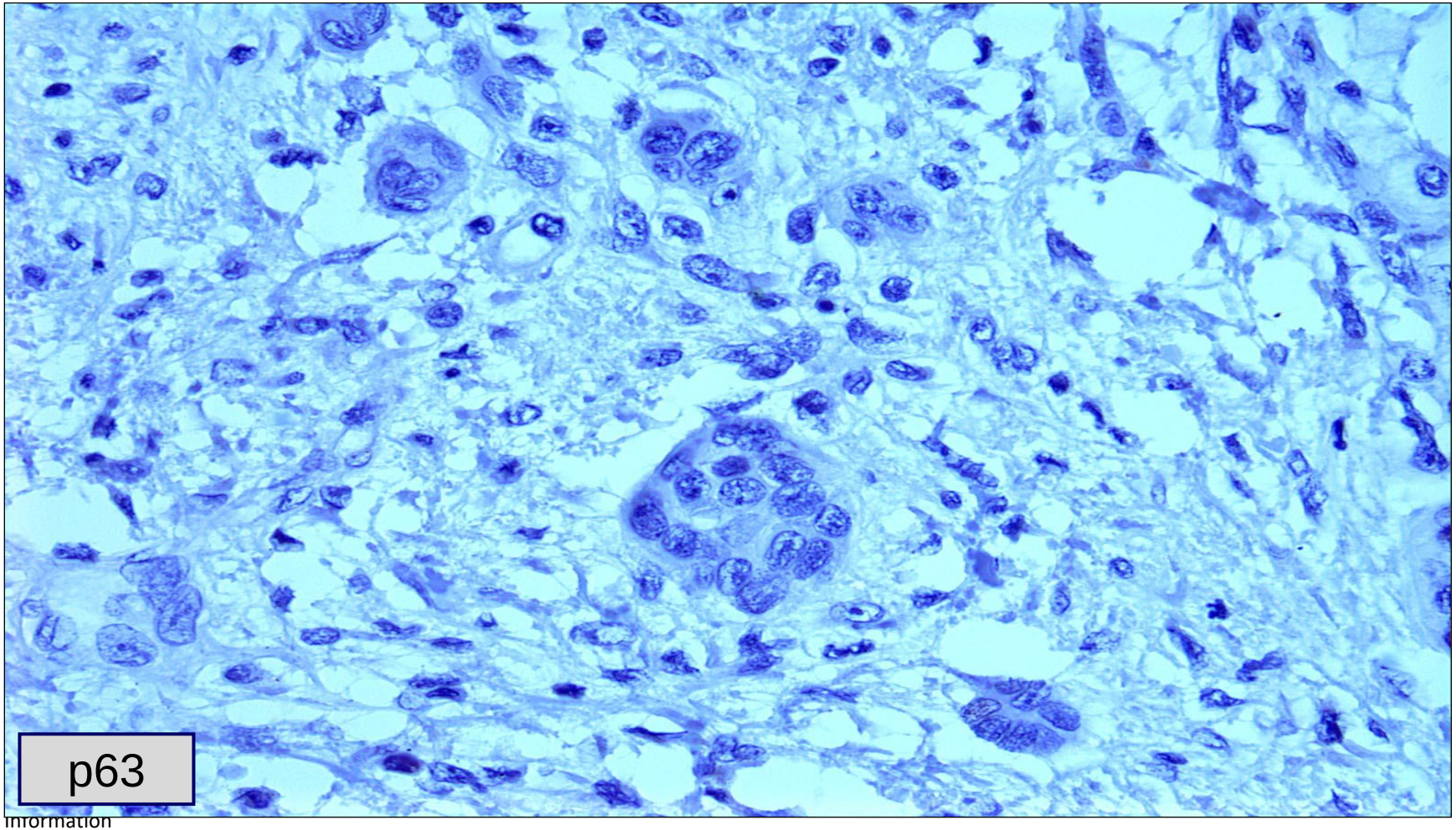
Displaced epithelium

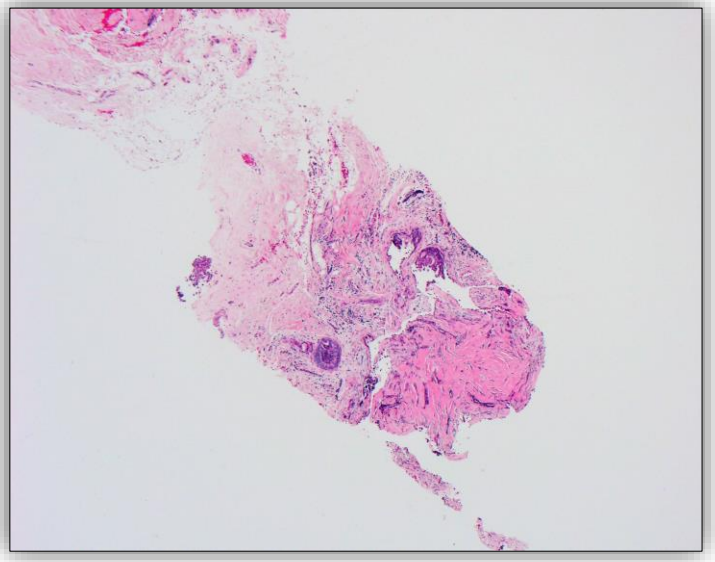


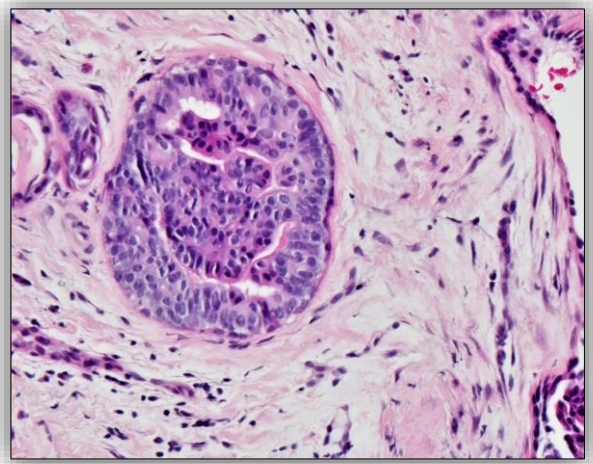


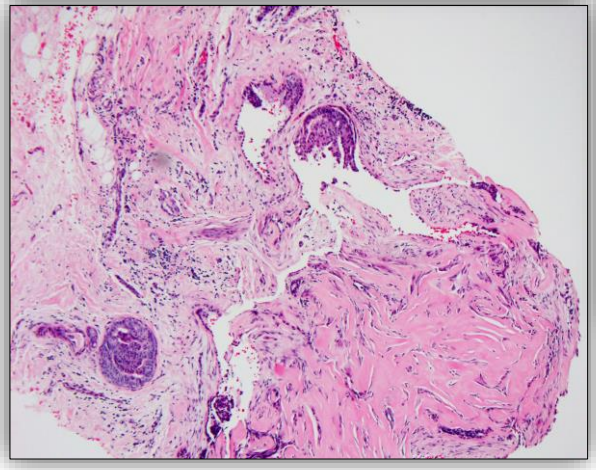


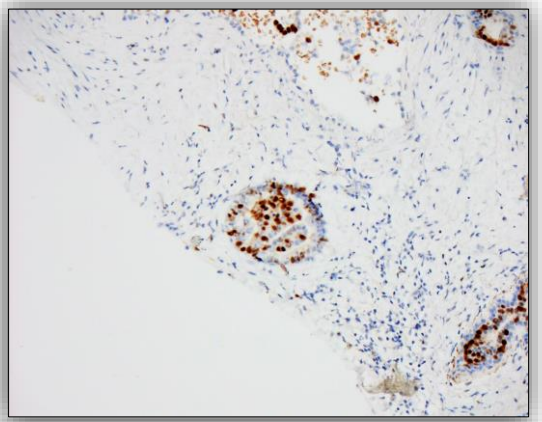


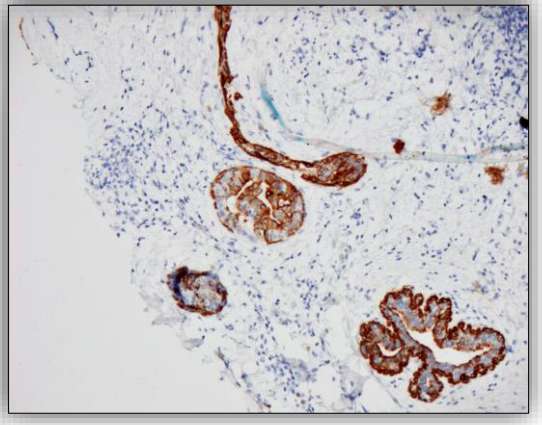


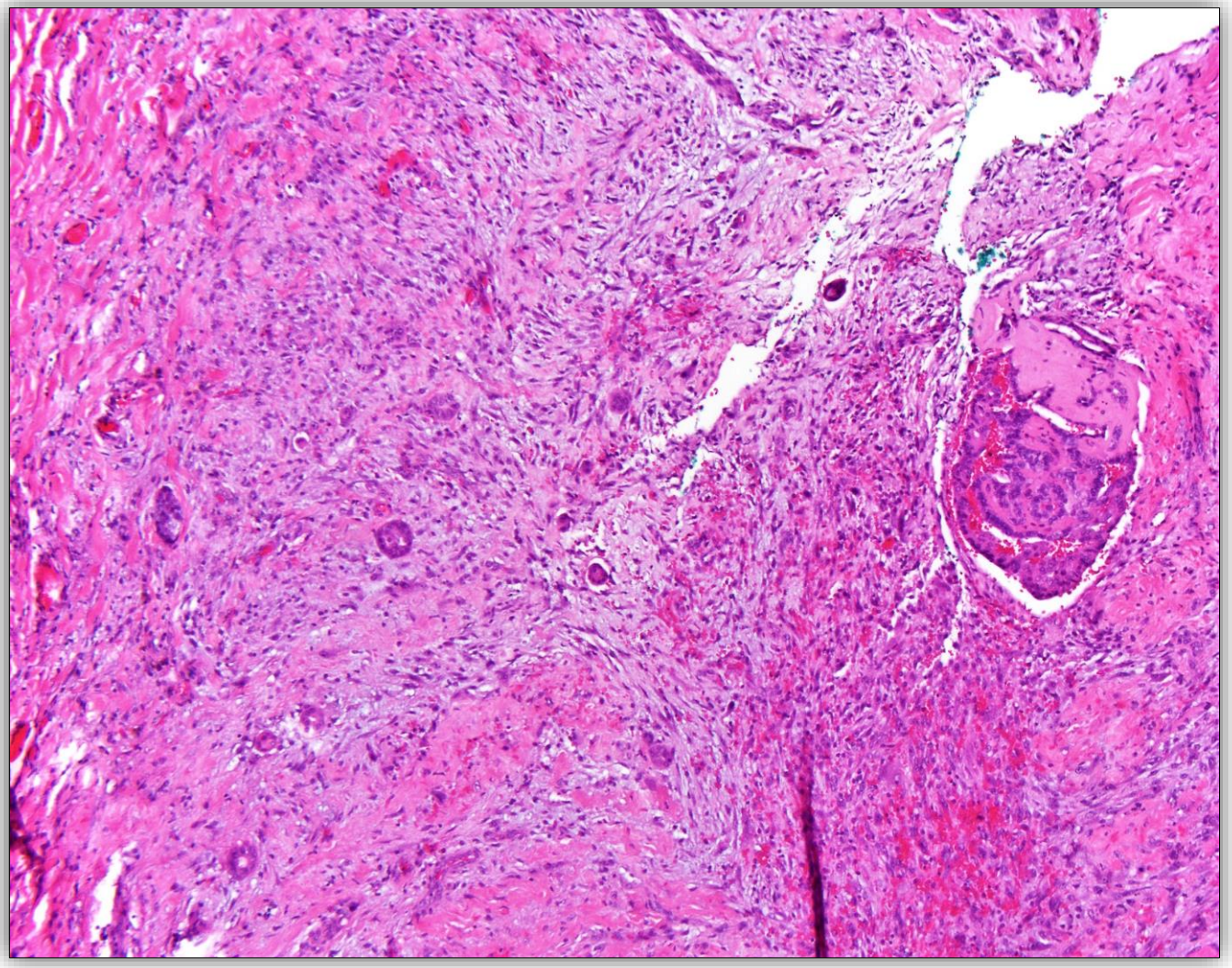


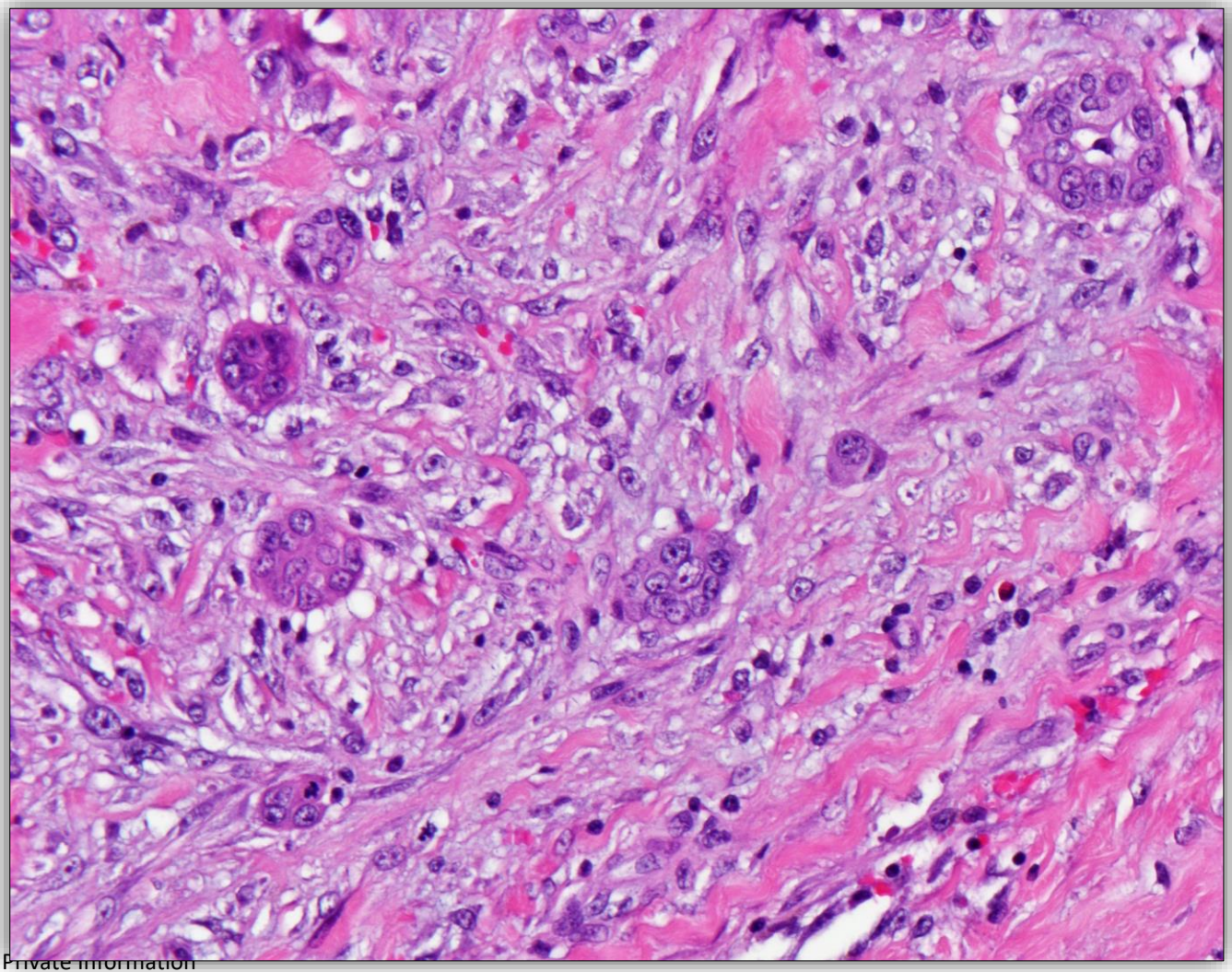


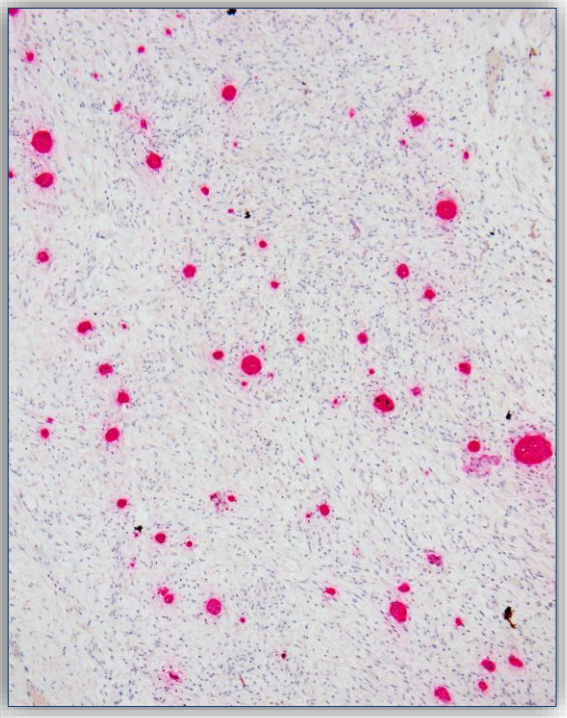












CKAE1/3 and p63

To Avoid Overdiagnosis

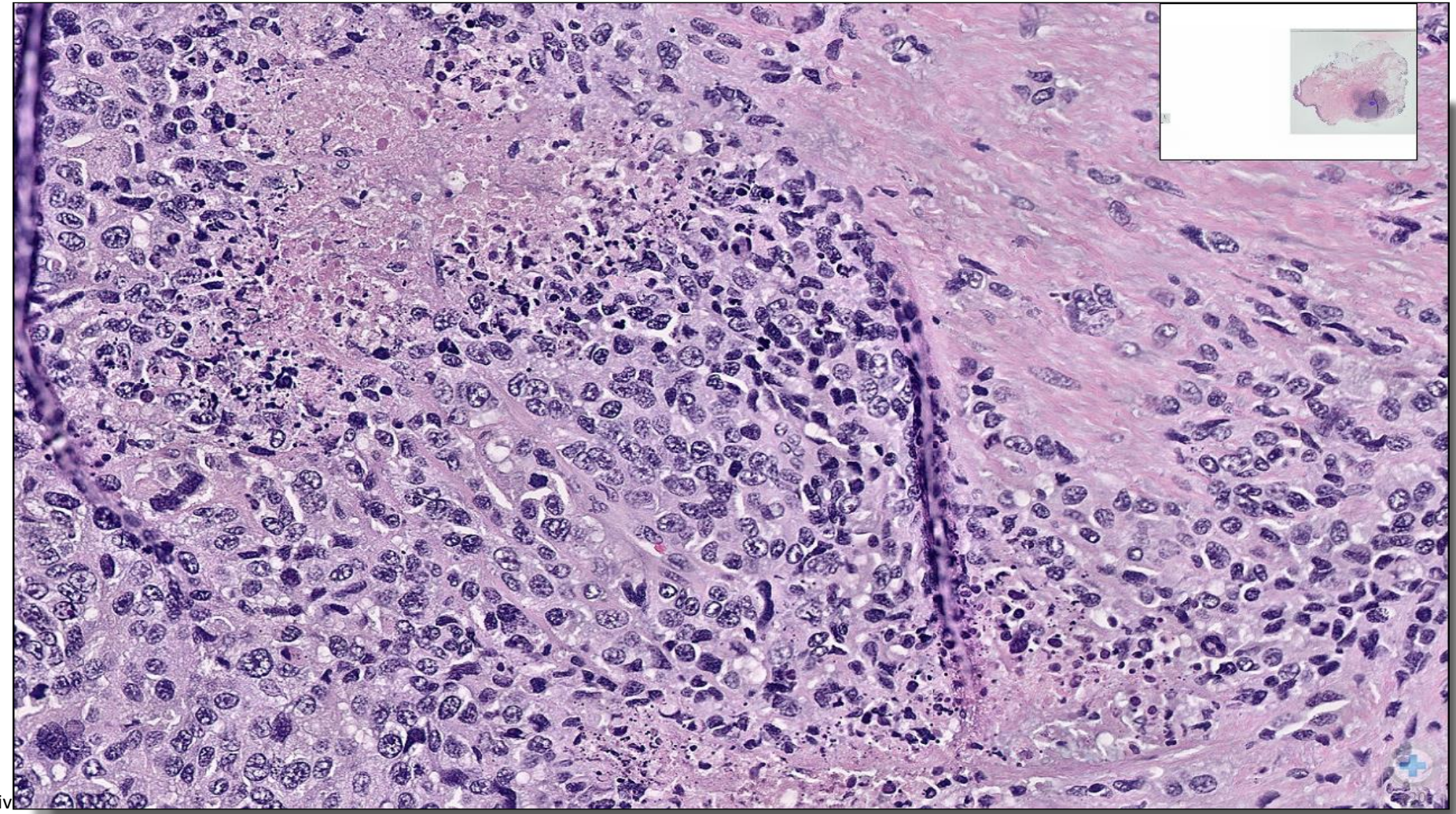
- Think of the possibility
- Look for invasion away from biopsy site
- Look for recognized type of invasive cancer
- For LVI, be extremely conservative if there is only DCIS or a benign lesion
- Look for vascular involvement away from biopsy site

OTHER HIGH RISK SITUATIONS

Era of Neoadjuvant Systemic Therapy

In an era of NAST, it is particularly prudent to review the H&E slide at the time of receptor s/o especially for TNC

- Confirm that morphology is c/w breast carcinoma
- Ensure there is no prior history of another cancer
- Consider further IHC work up, if findings are atypical and/or in the setting of h/o cancer



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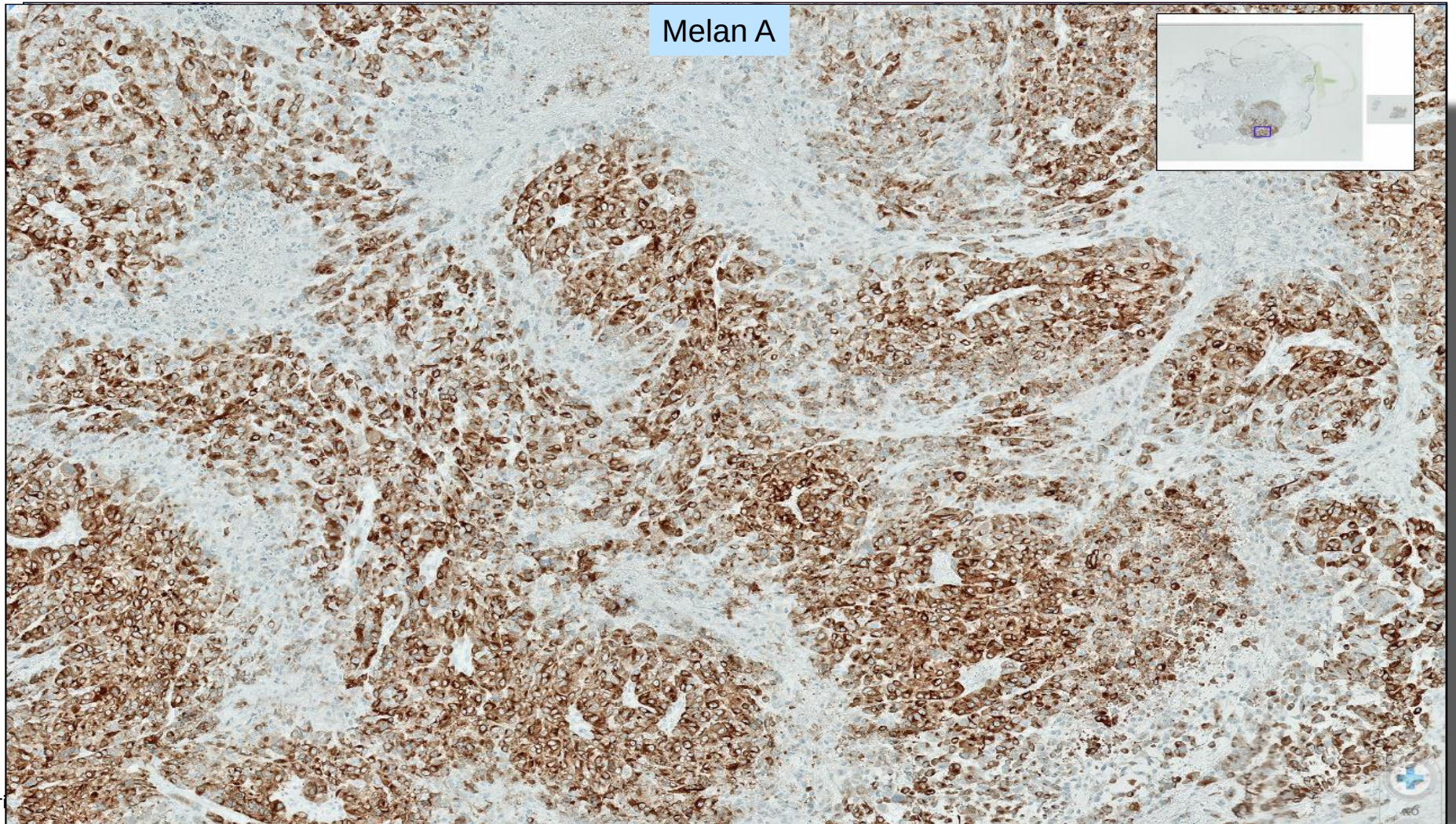

Melan A

Lesions Metastatic to the Breast

- Don’t forget that not all cancers in the breast are breast cancer
- Consider this when morphology is atypical
- Absent in situ component-with caveats
- History of other cancer
- Triple negative cancers

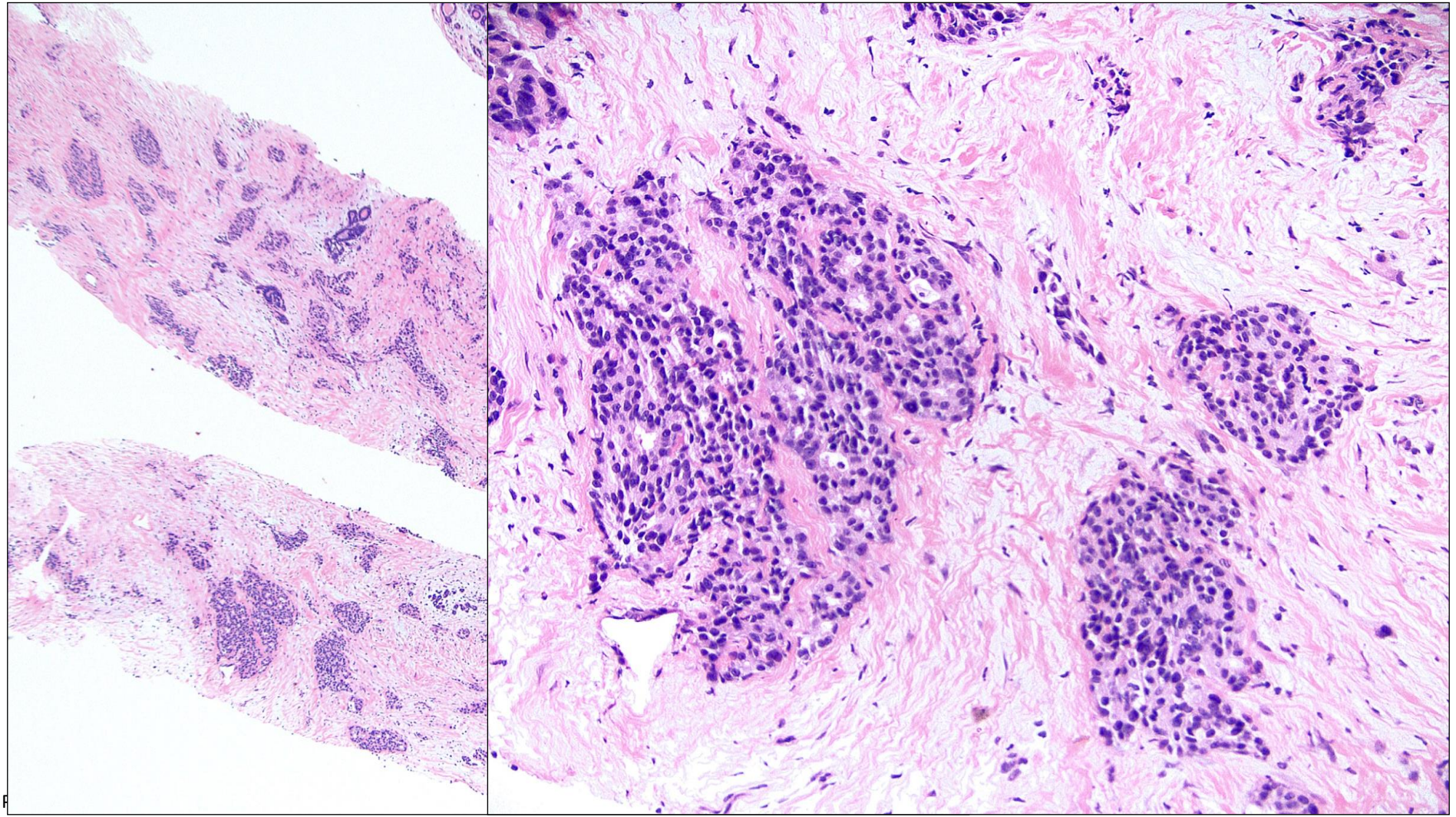
Lesions Metastatic to the Breast

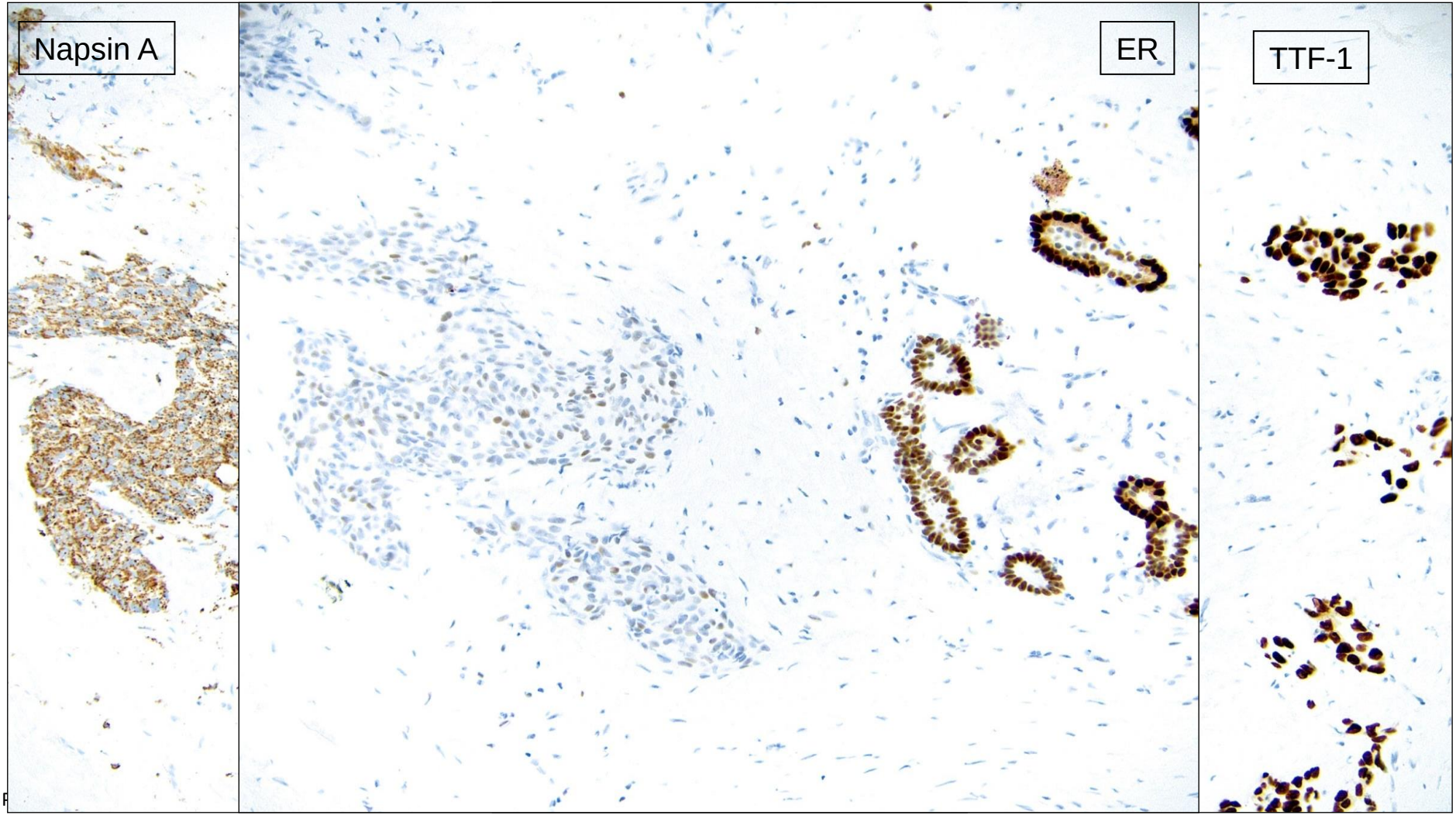
Malignancies metastatic to the breast are rare (0.2-2%)

Common primary tumors:

- Melanoma
- Ovarian carcinoma
- Lung carcinoma
- Lymphoma

Klingnen, Tumor Biol, 2009
DeLair, Mod Pathol, 2013
Yang, Arch Pathol Lab Med, 2017




Napsin A
ER
TTF-1

IHC in metastatic lesions-LUNG

Some lung cancers (~10%) show focal ER expression (frequency appears to be antibody clone-related)

Some lung cancers (~5%) are focally GCDFP positive, and these are usually also TTF-1 negative

Some breast cancers (~2%) are TTF-1 positive

Use caution when interpreting small biopsies

Wang, Appl Immuno Mol Morph, 2009
Robens, Am J Surg Pathol, 2010
Abd El-Maqsoud, Tum Biol, 2016

IHC in Metastatic Lesions-Breast markers

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ER, PR, HER2

GATA3, GCDFP-15, mammaglobin, SOX10, TRPS1

Combination improves sensitivity

Caveats:

- ER, also seen in lung, thyroid, NE and gyn tract
- HER2 may be seen in lung and gastric cancers
- GATA3, also seen in skin and urothelial cancers
- GCDFP-15, also seen in skin, salivary gland and prostate
- Mammaglobin, also seen in endometrial, ovarian and melanomas
- Absence does not exclude breast origin

IHC in Metastatic Lesions, SOX10

- Mediates differentiation of neural crest-derived cells
- Expressed in ~40% of TNBC and metaplastic carcinomas, rarely seen in ER+ or HER2+ tumors
- Useful in the differential with lung adenocarcinoma, even TTF1 negative tumors
- Consider in the differential with S100+ epithelioid malignant neoplasm

Cimino-Mathews, Human Pathol, 2013
Nelson, Hum Pathol, 2017
Laurent, Am J Surg Pathol, 2019

IHC in Metastatic Lesions

TRPS1

Trichorhinophalangeal syndrome type 1 (TRPS1)

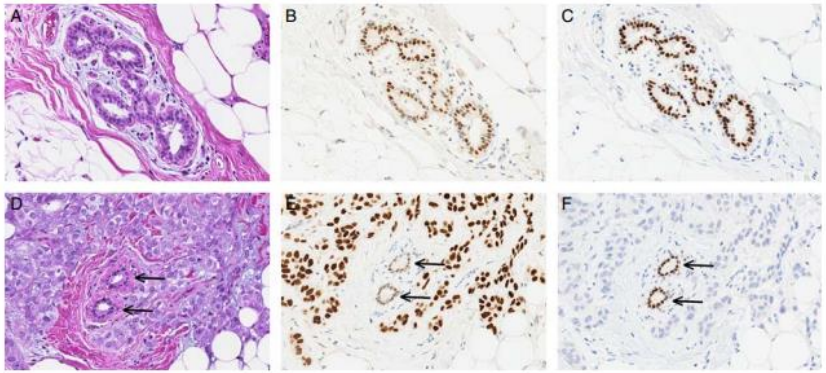
High sensitivity and specificity for breast, especially useful in TNBC

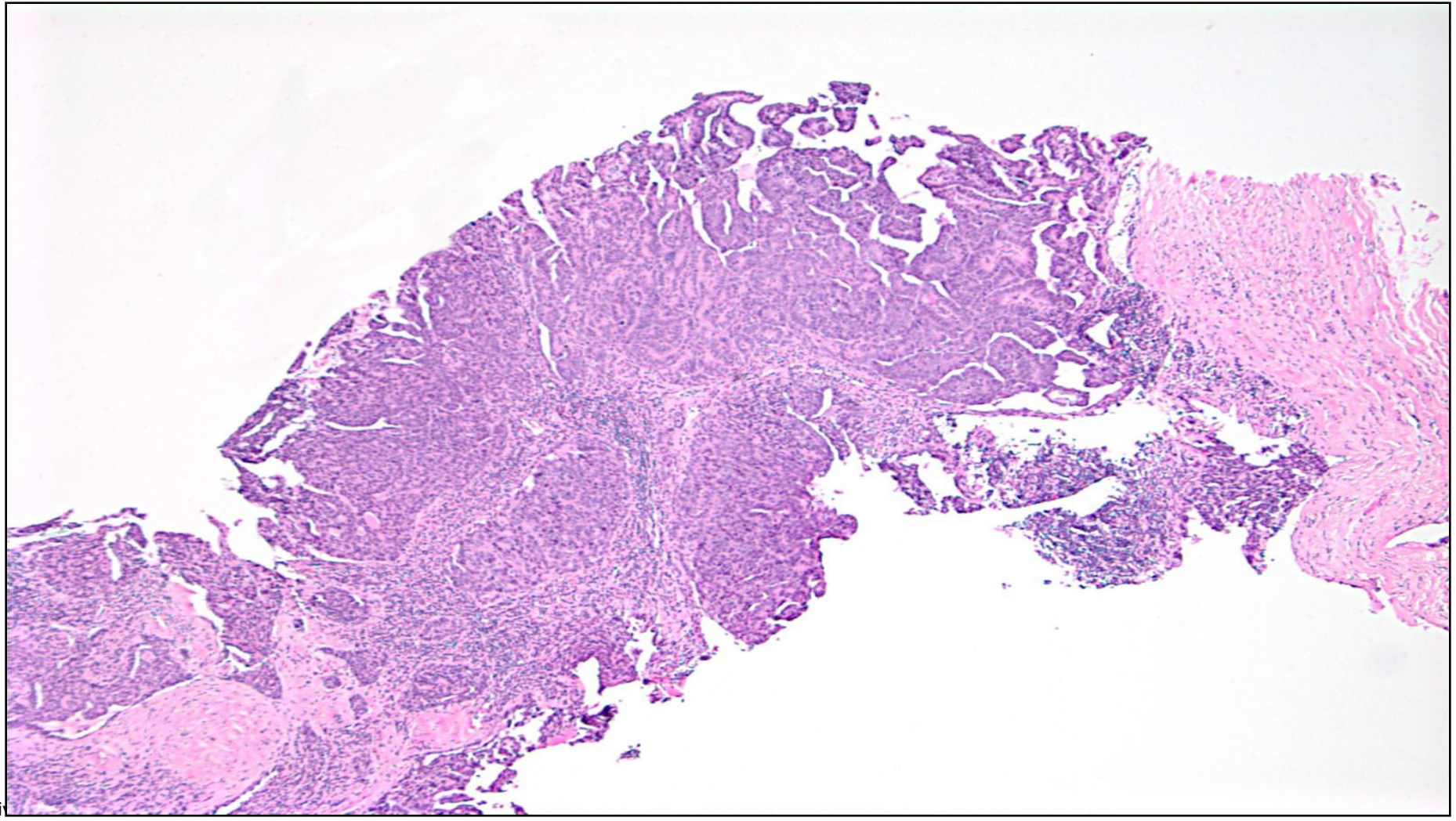
Caveats:

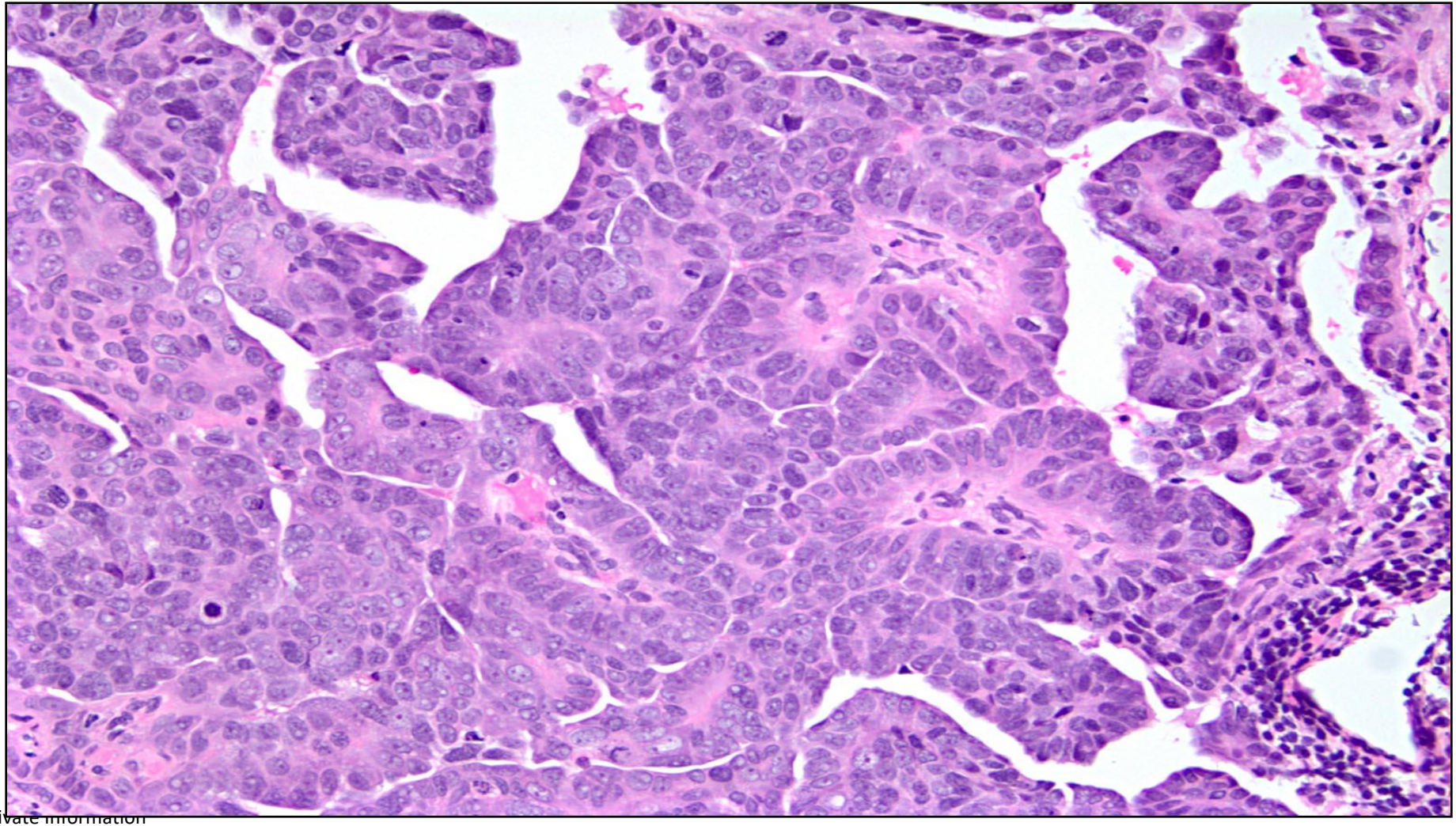
- May be seen in other tumors e.g. lung, bladder, but expression usually low/weak
- Serous carcinoma may express TRPS1, therefore combination with PAX8 recommended
- Salivary gland carcinoma most problematic with ~15% of cases demonstrating strong expression with TRPS1

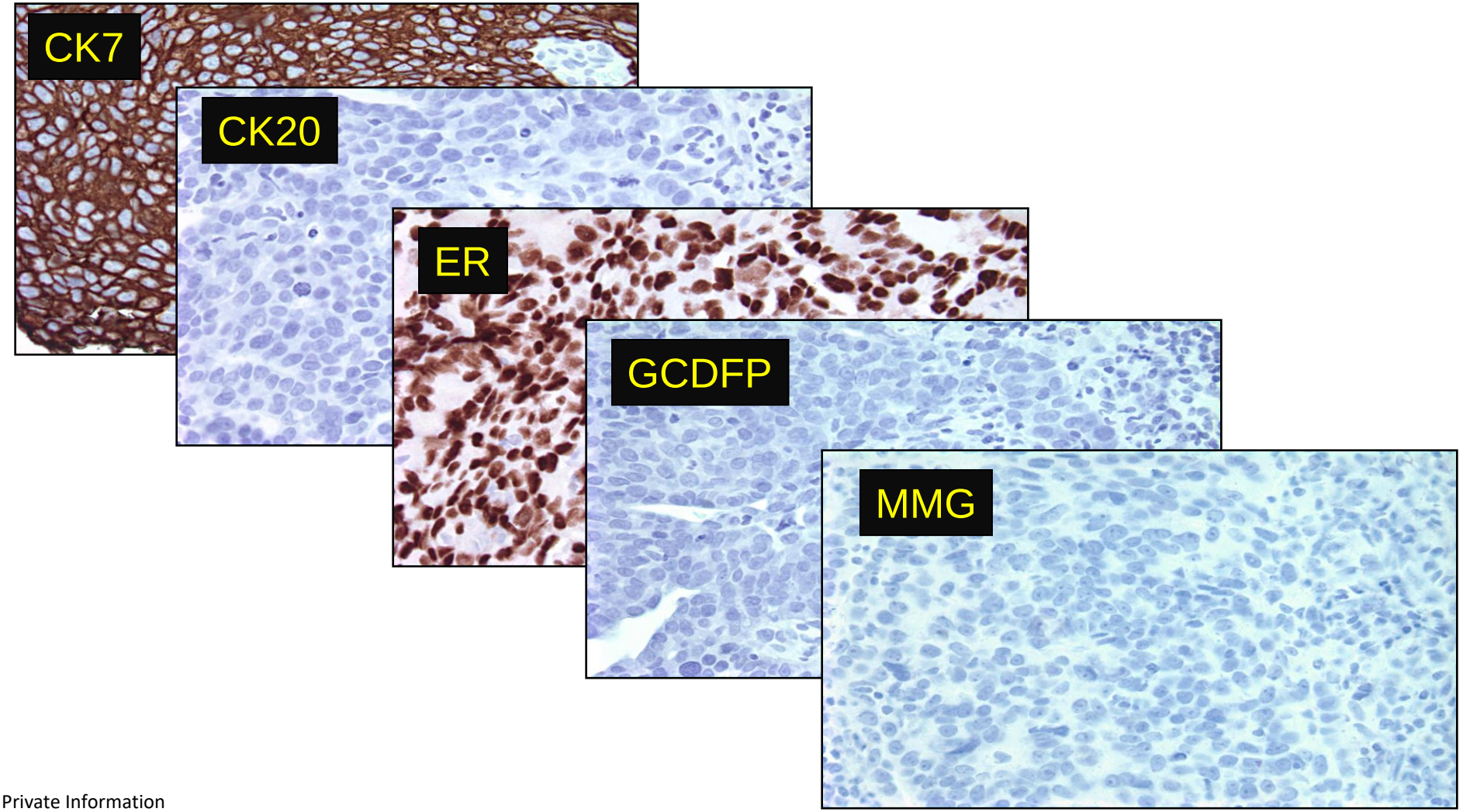
Ai, Mod Pathol, 2021
Parkinson, AJSP, 2022

Breast carcinoma		Negative	Positive			Total
			Low	Intermediate	High	
TRPS1						
ER/PR+		3 (2%)	5 (3%)	22 (12%)	146 (83%)	176
HER2+		9 (13%)	5 (8%)	14 (21%)	39 (58%)	67
TNBC	Metaplastic	7 (14%)	3 (5%)	12 (23%)	30 (58%)	52
	Nonmetaplastic	26 (14%)	8 (5%)	41 (22%)	109 (59%)	184
GATA3						
ER/PR+		8 (5%)	7 (4%)	27 (15%)	131 (76%)	173
HER2+		8 (12%)	8 (12%)	22 (33%)	29 (43%)	67
TNBC	Metaplastic	41 (79%)	7 (13%)	3 (6%)	1 (2%)	52
	Nonmetaplastic	90 (49%)	20 (11%)	48 (26%)	26 (14%)	184

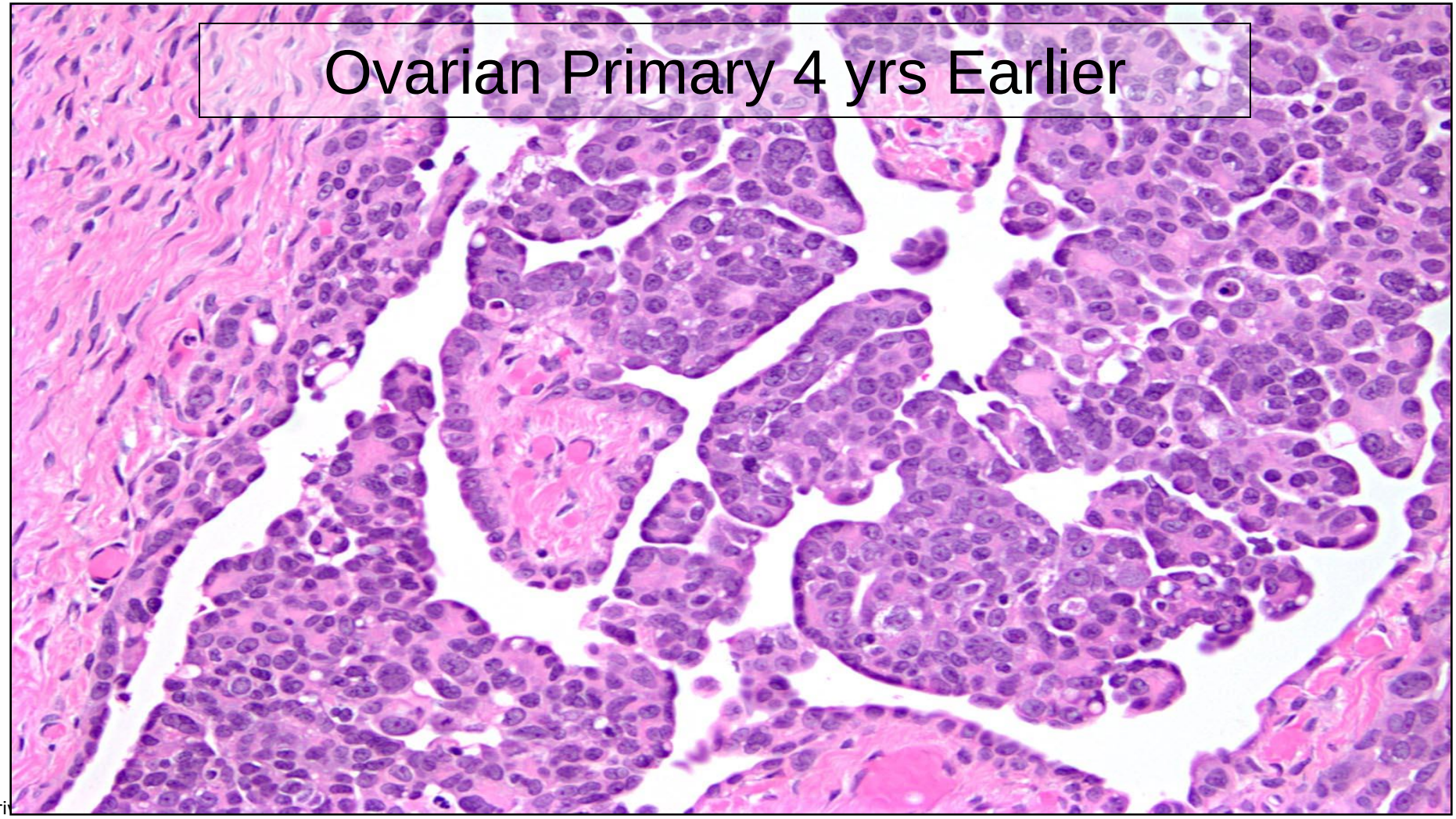




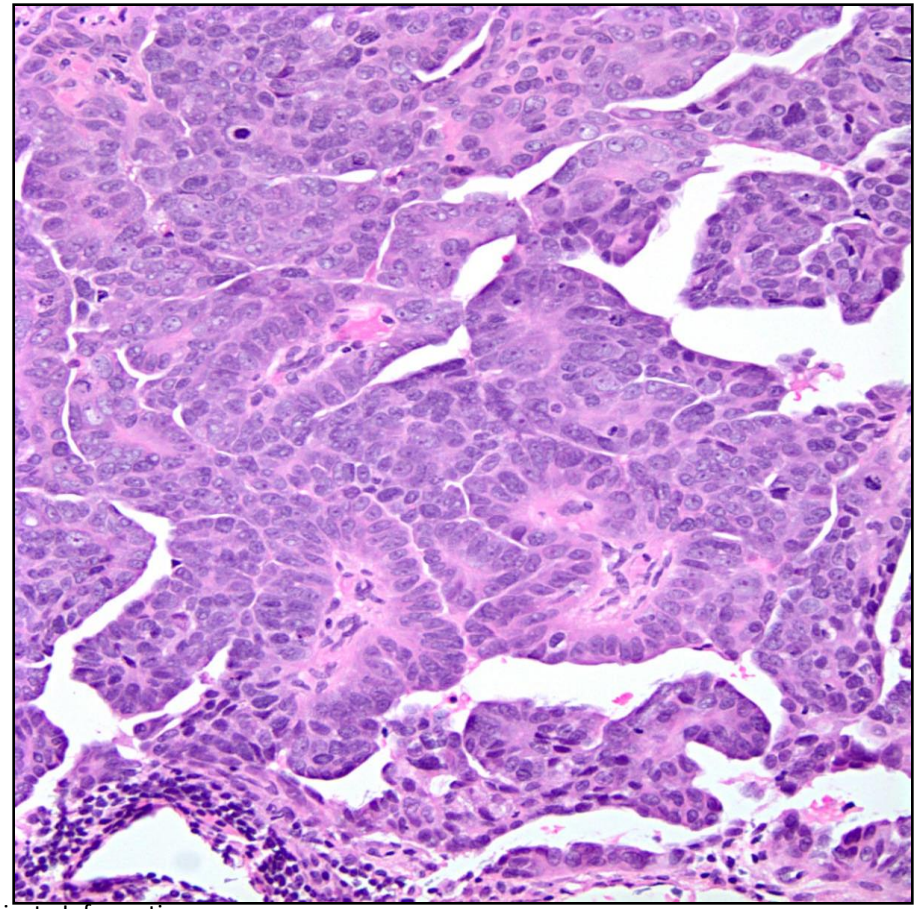




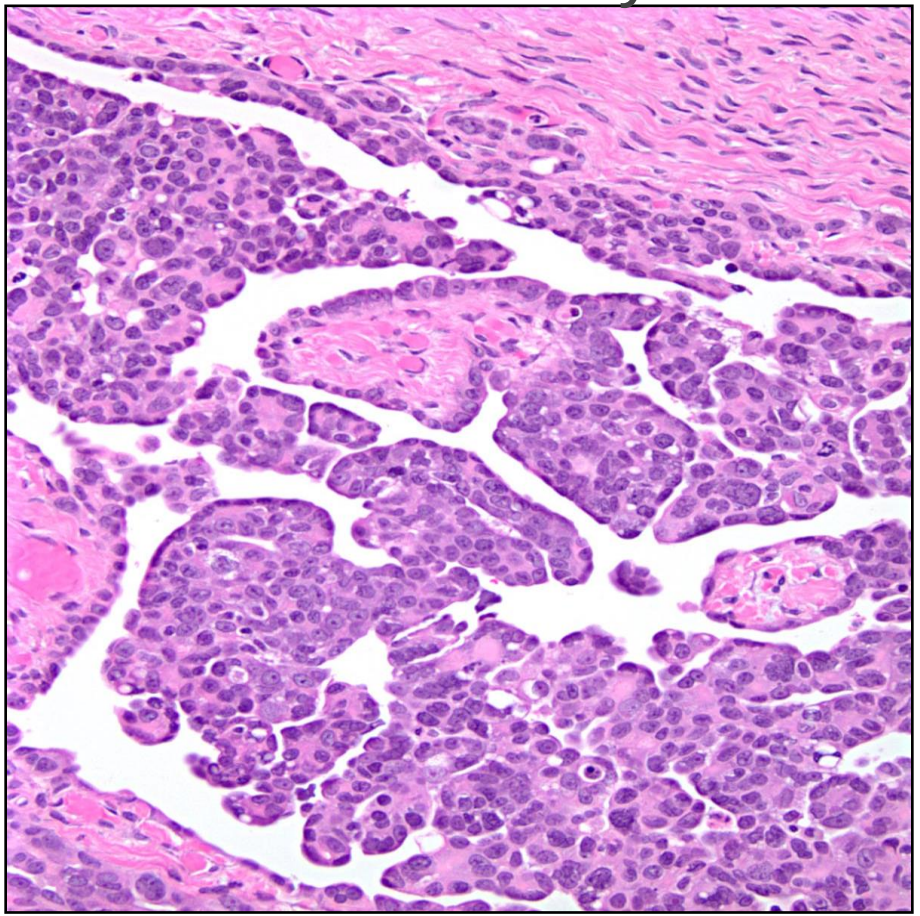
Ovarian Primary 4 yrs Earlier

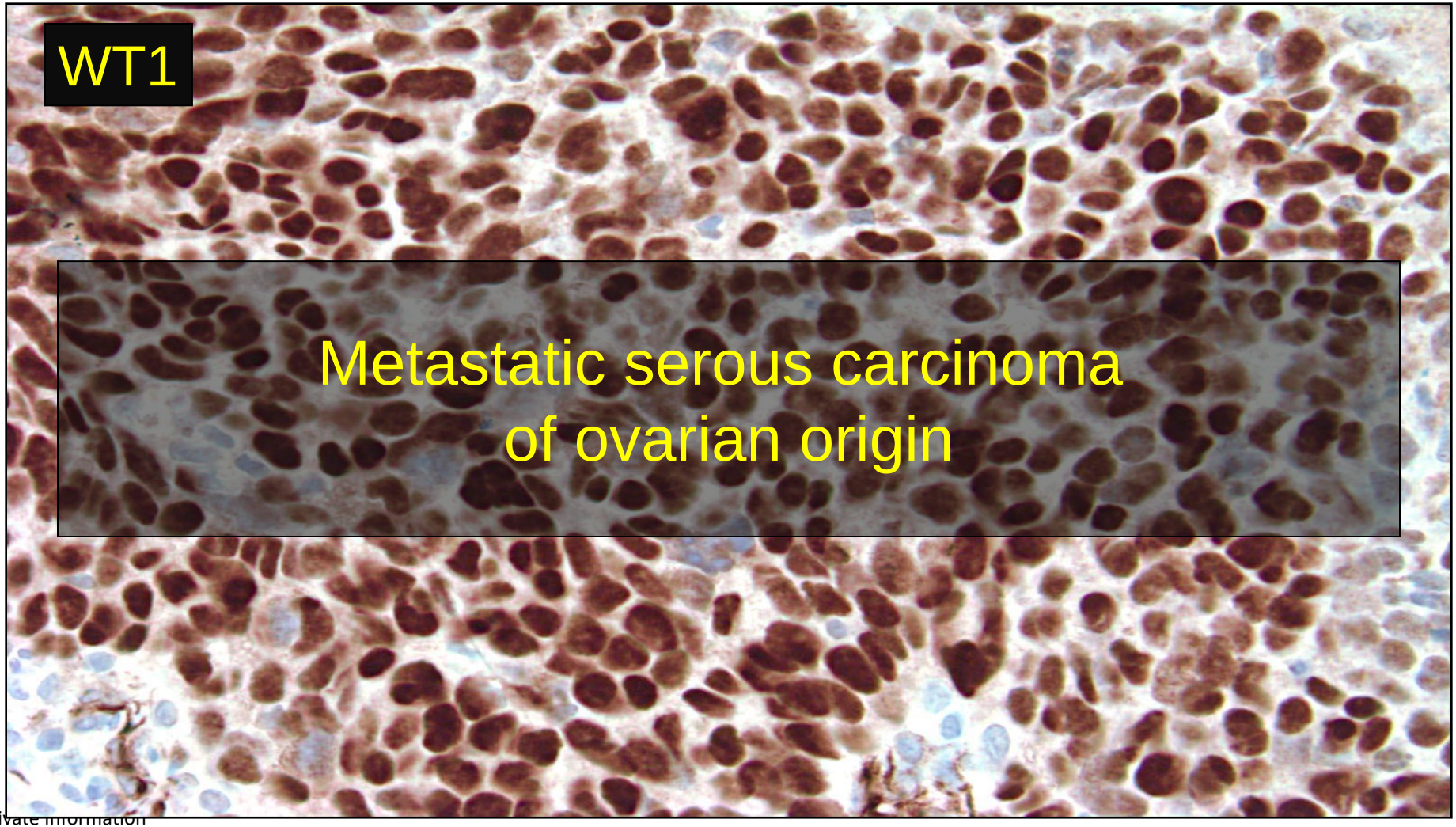


Breast CNB



Ovarian Primary





IHC in Metastatic Lesions, Ovary

Most commonly misdiagnosed

Often ER/PR positive

PAX8 and WT1 most useful

PAX8+ in 87% of ovarian (96% if mucinous excluded) and ~3% breast

WT1+ in 85% of ovarian and 2% of breast

EMA useful if micropapillary breast carcinoma in the DDX

Beware!

- Mucinous breast carcinomas can be WT1+
- Up to 64%, though weak and focal

Nonaka, AJSP, 2008
Domfeh, Mod Pathol, 2008
DeLair, Mod Pathol, 2013
Singh, Mod Pathol A, 2019

Ensure Receptor Status is Concordant with H&E Findings

ER low positive tumors, usually high grade

- Be accurate with % positivity
- Otherwise may exclude patients from triple negative therapies/trials
- Ensure low grade tumors are strongly and diffusely positive

Ensure Receptor Status is Concordant with H&E Findings

Be careful about HER2 2+ vs. 3+ (and 0 vs. 1+)

- FISH not mandated for IHC 3+ tumors
- Patients with palpable HER2 overexpressing tumors are often candidates for chemotherapy; whereas ER+, HER2 negative patients may not be
- Ensure morphology is compatible with HER2 positivity (apocrine histology; abundant eosinophilic cytoplasm; high grade tumors)

Re-review and Consider Further IHC Work Up

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- If findings are unusual
- Receptor status is discordant
- In the setting of h/o cancer

Summary

- Discussed how to differentiate common and uncommonly encountered diagnostic challenges in breast tumor pathology
- Discussed how to anticipate and avoid diagnostic pitfalls
- Reviewed morphologic clues and ancillary testing strategies that can support diagnostic interpretation, and help prevent errors
- Emphasized that risks are much greater for CNB