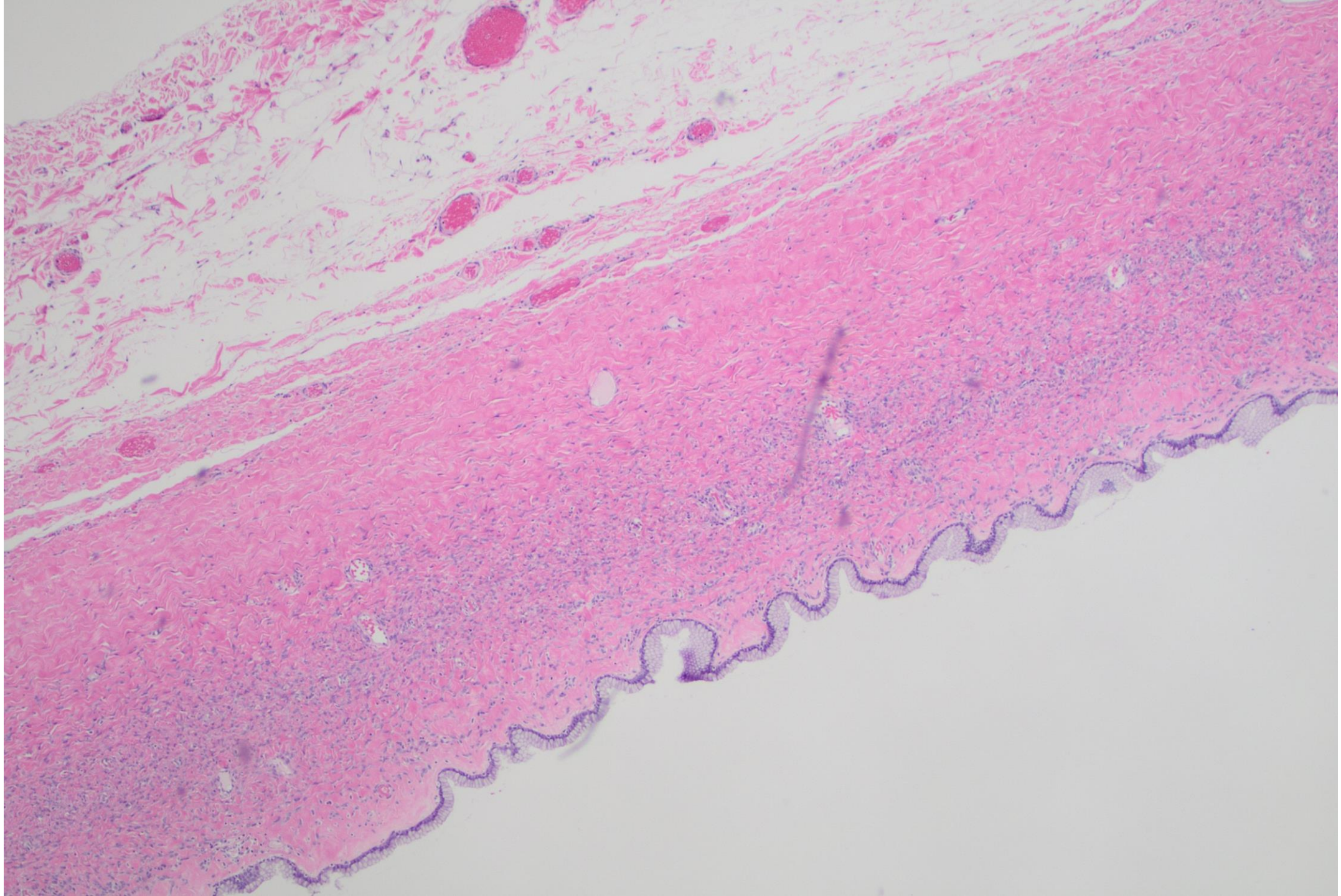
# July 2023 DIAGNOSIS LIST

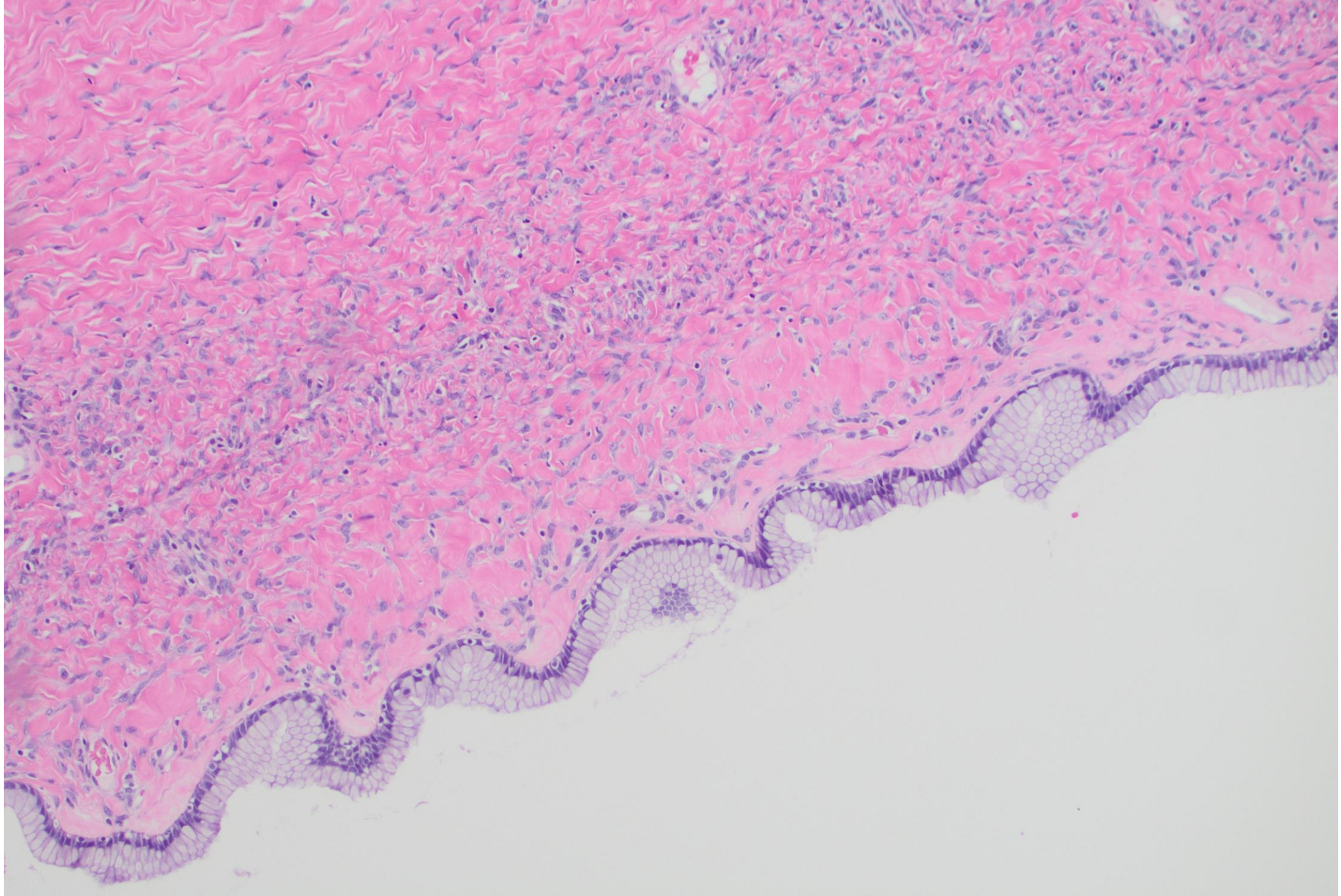
- 23-0701: Primary Retroperitoneal Mucinous Cystic Neoplasm -- Rumore
- 23-0702: Mixed Tumor of the Vagina --Rumore
- 23-0703:Neuroepithelial structures associated with the subepithelial nerve plexus of taste buds --Adebola Adeniyi/Hubert Lau
- 23-0704: Brain Toxoplasmosis --Harris Goodman
- 23-0705: Benign basaloid neoplasm arising from a nevus sebaceous --Monica Mikayakawa-Liu/KerriRieger
- 23-0706:*STK11* Adnexal Tumor -- Ying Liu/Brooke Howitt
- 23-0707: Renal medullary carcinoma --Emily Chan
- 23-0708: Metastatic papillary thyroid cancer to pancreas --Cindy Wang

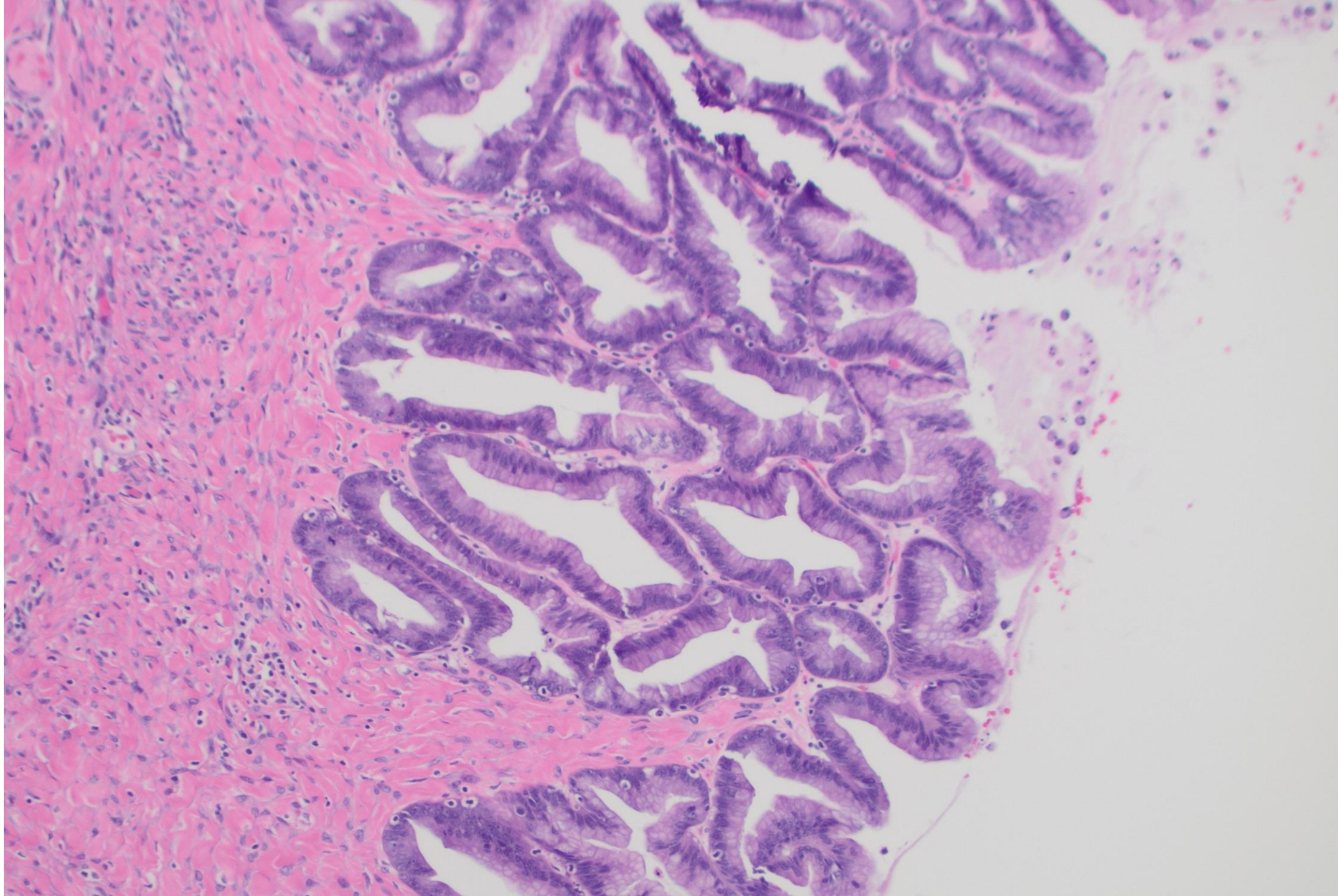
23-0701

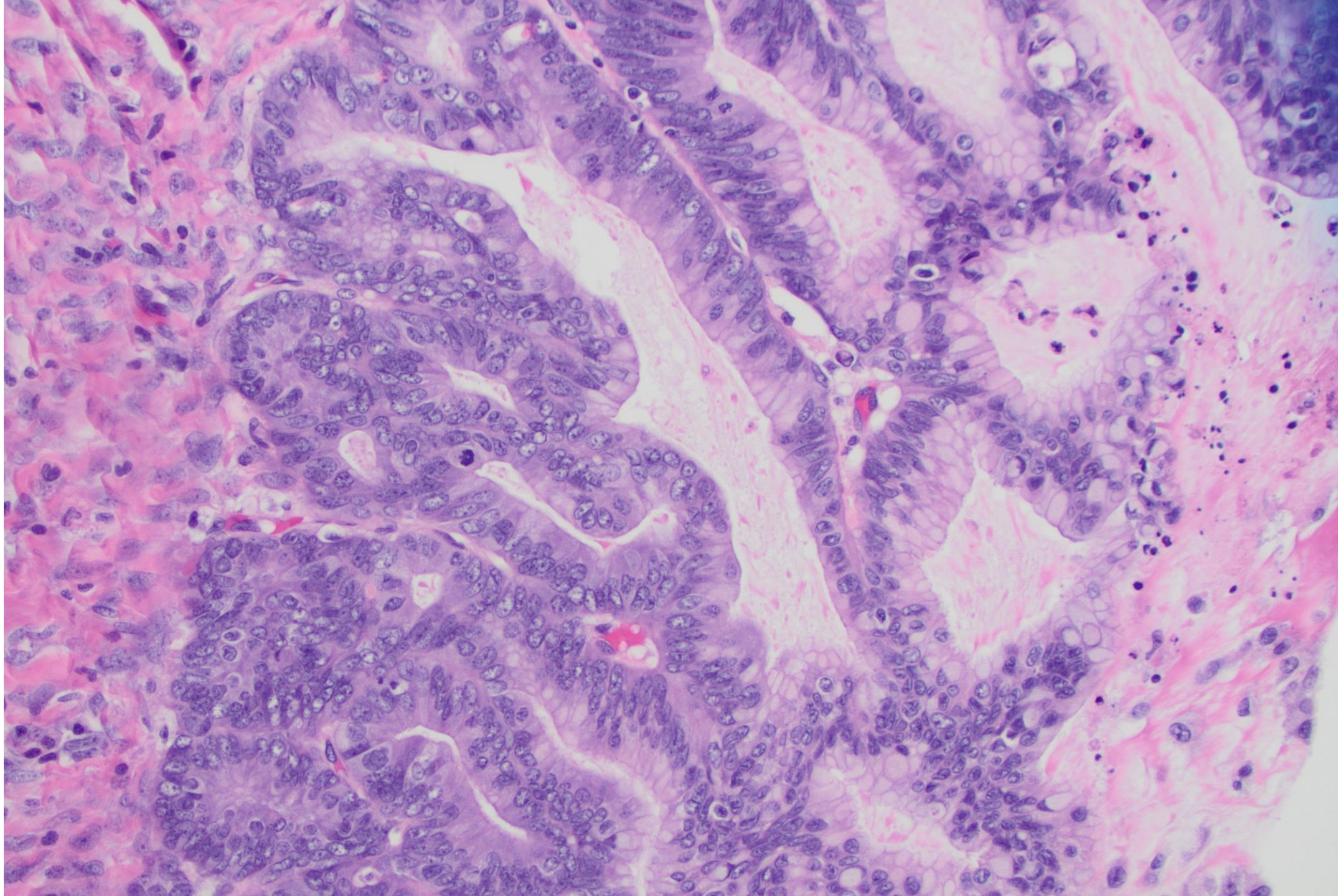
**Gregory Rumore; Kaiser Permanente**

20’s female with 9 cm retroperitoneal cystic mass displacing the descending colon. No attachments to colon or other structures.

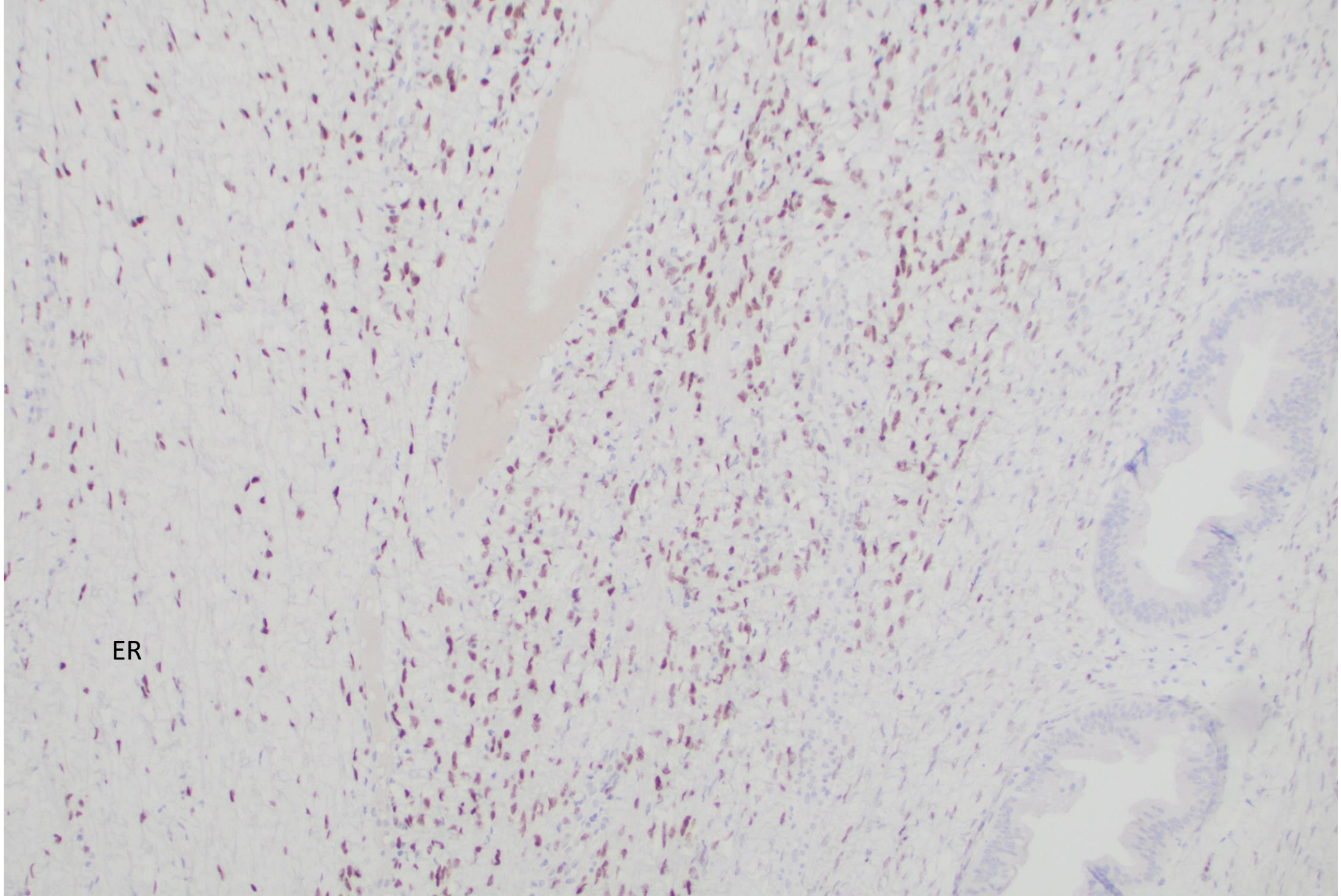








# DIAGNOSIS?


ER

# Primary Retroperitoneal Mucinous Cystic Neoplasm

- Females >9/1, typically young
- Non-specific symptoms related to pressure
- No pathognomonic imaging findings
- Similar to ovarian and pancreatic counterparts
- ER+ ovarian-like stroma
- 3 categories:
- Mucinous cystadenoma
- Mucinous LMP
- Mucinous Adenocarcinoma

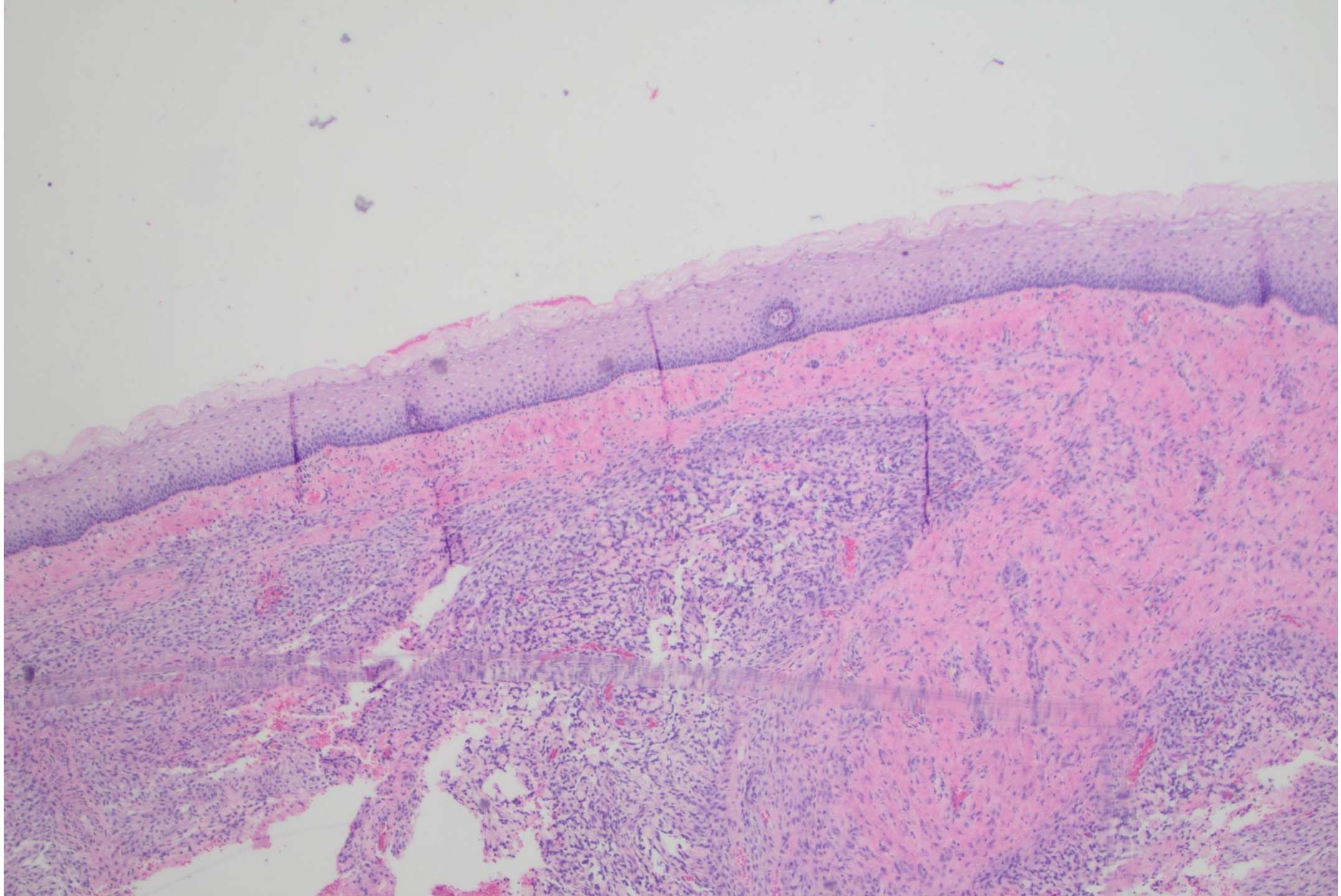
# Theories of Origin

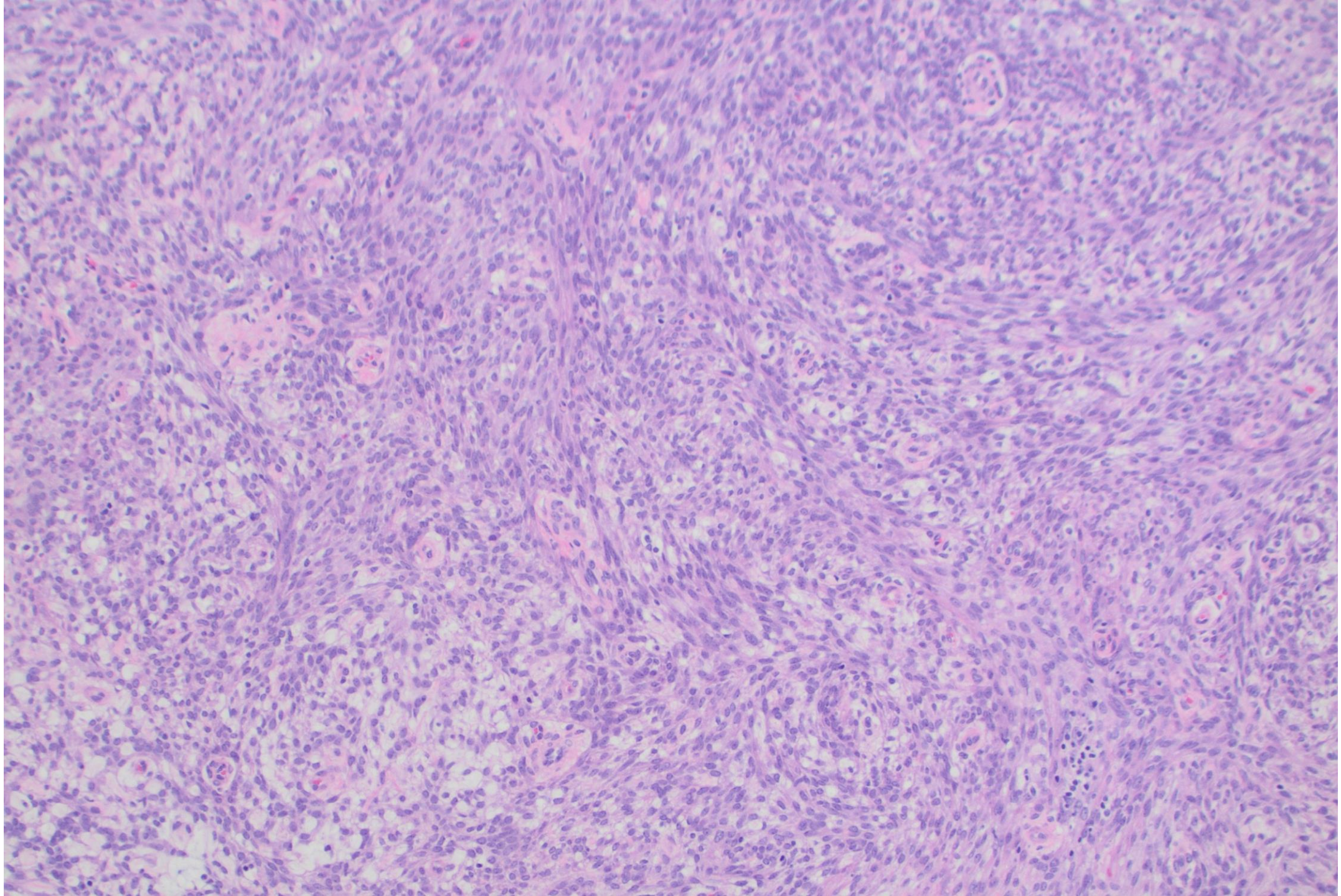
- Heterotopic ovarian tissue? (but rare cases reported in males)
- Invagination of multipotential mesothelium with mucinous metaplasia?

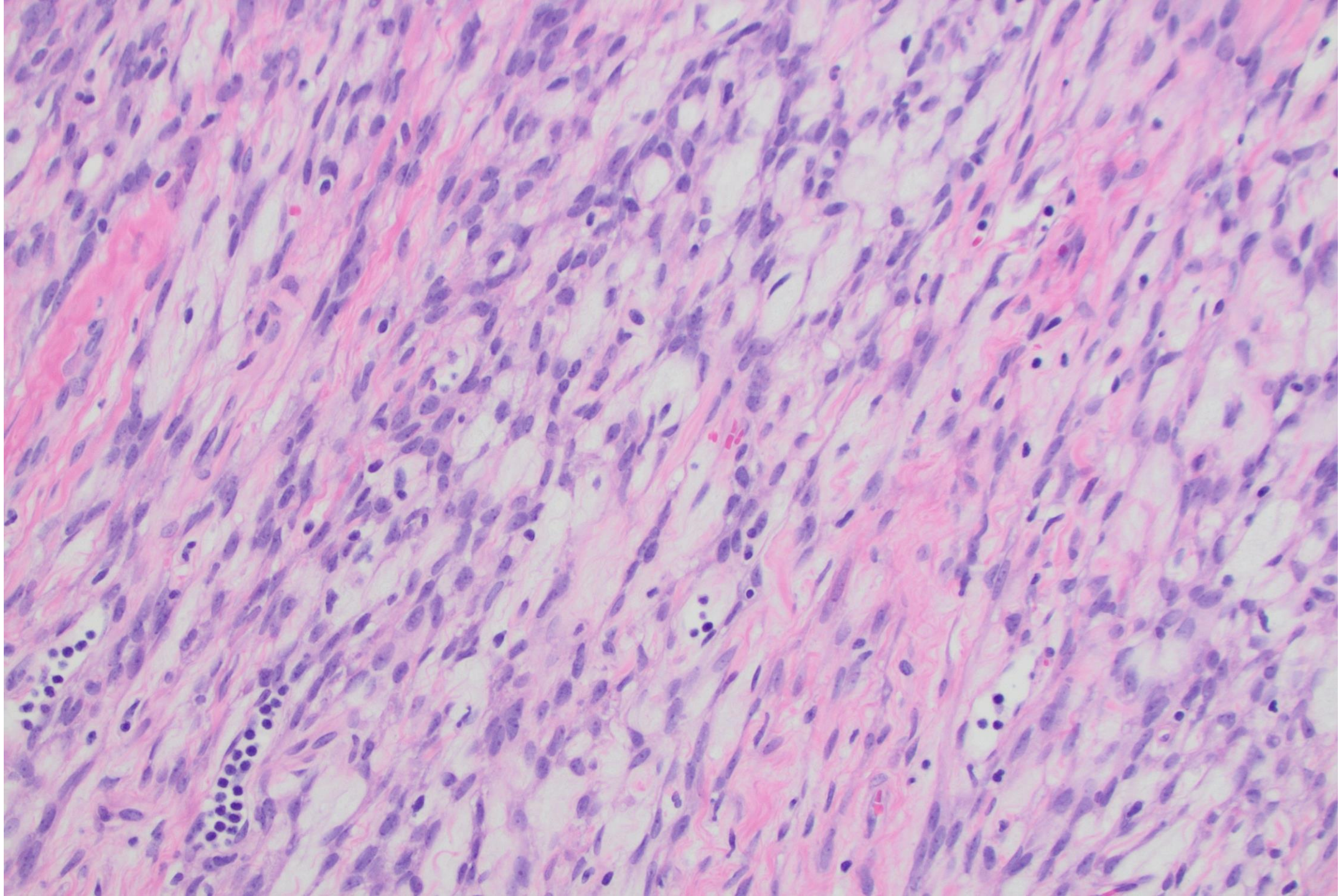
23-0702

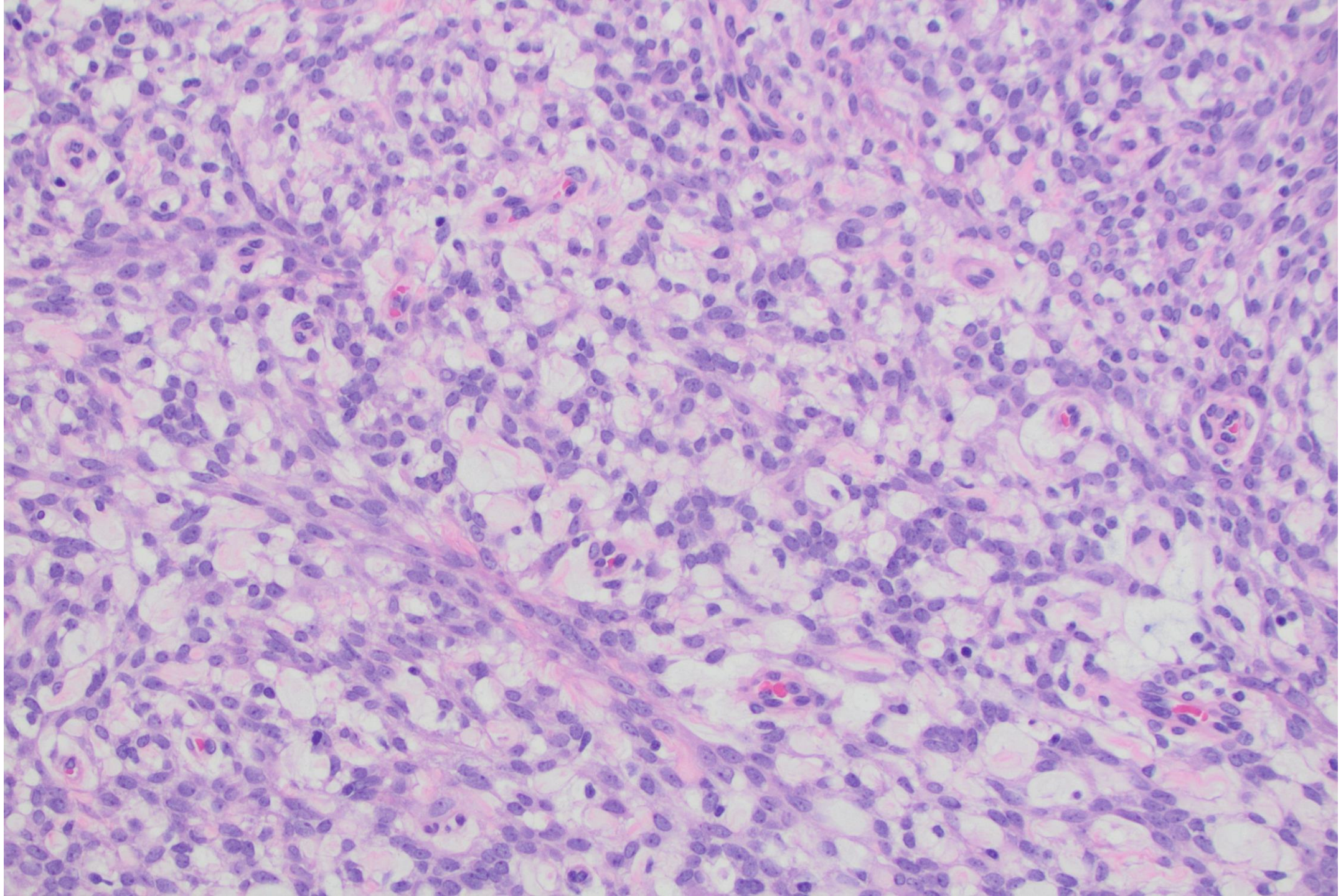
**Gregory Rumore; Kaiser Permanente**

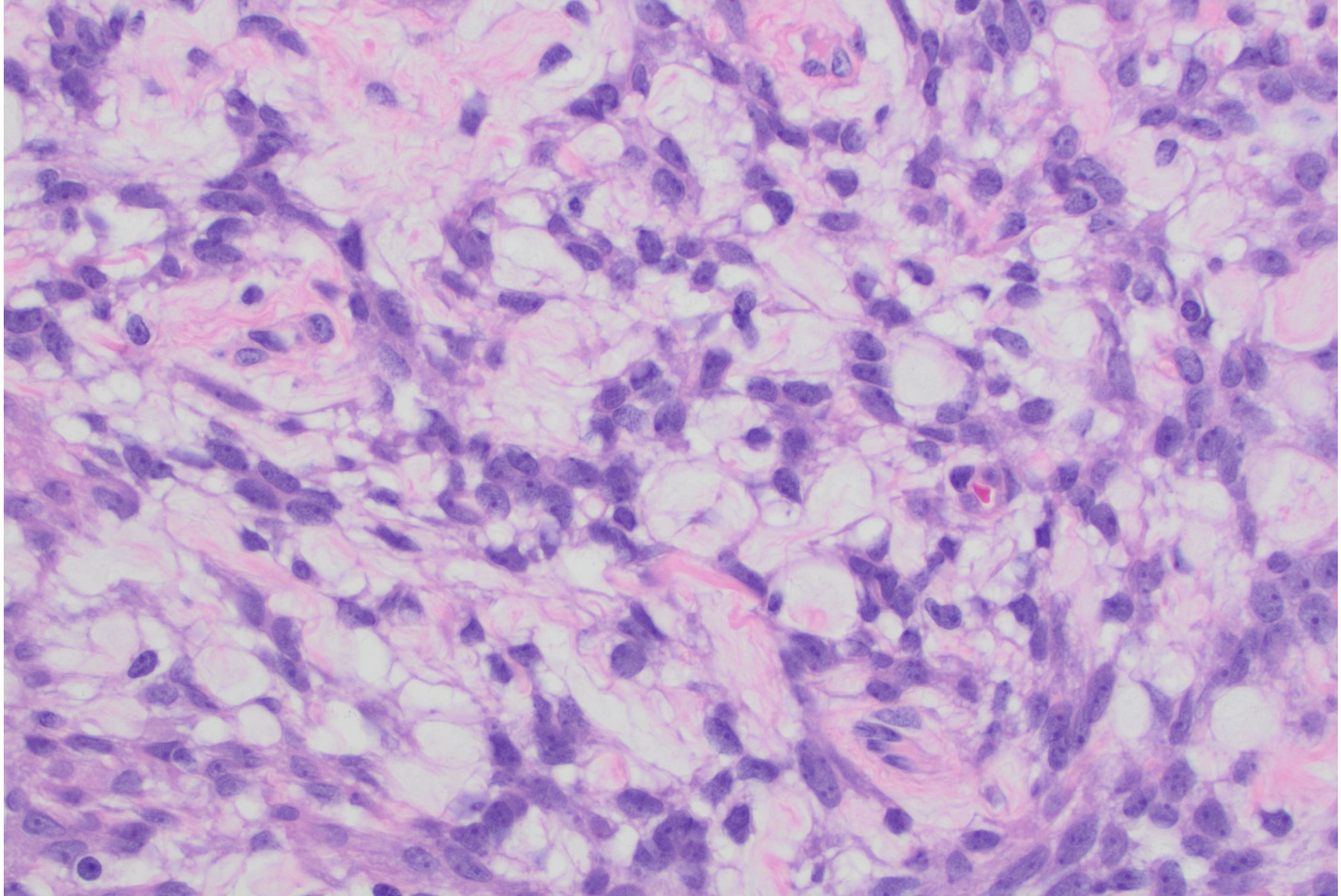
# 30’s female with vaginal discomfort and 2cm mass on broad stalk arising from L introitus

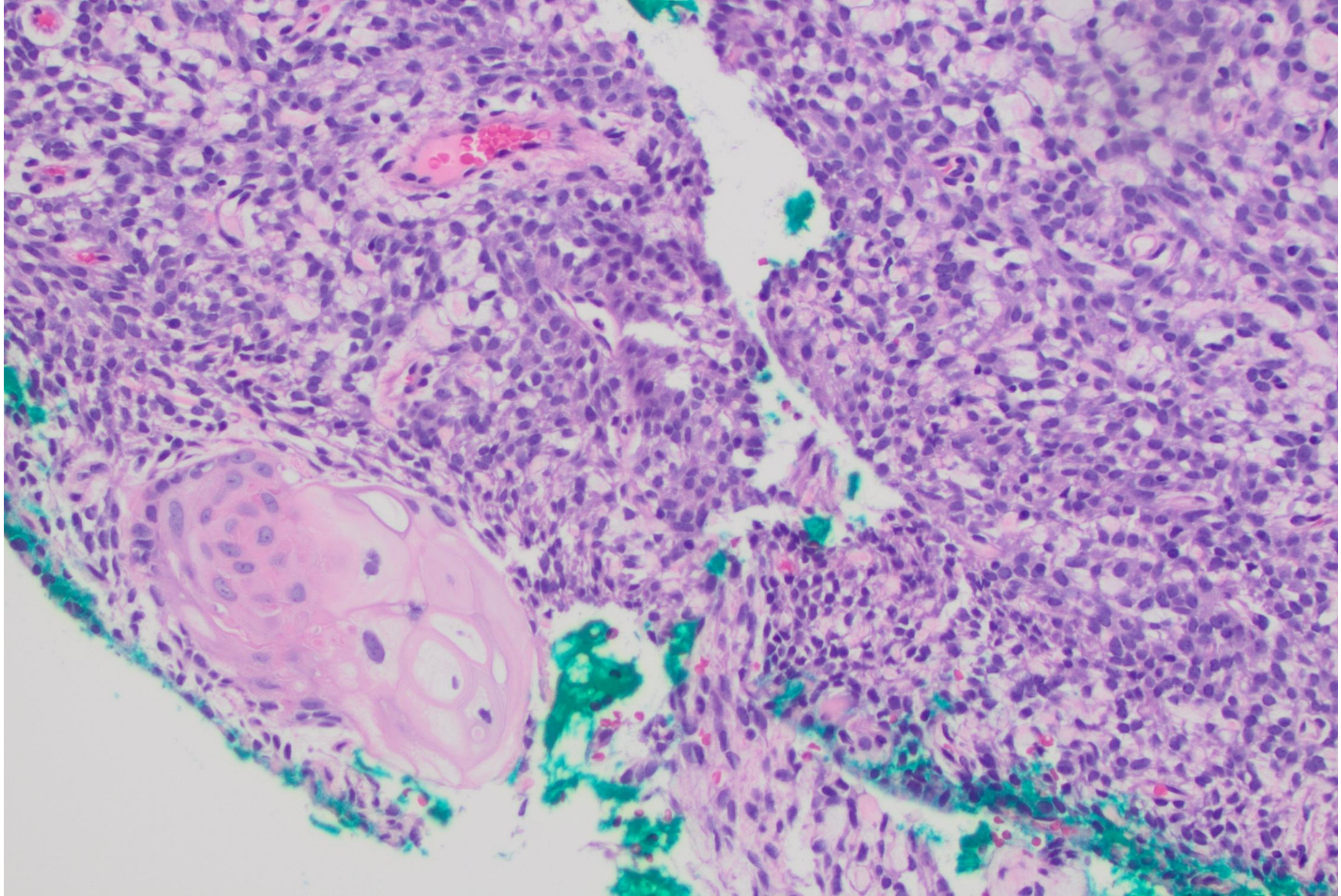


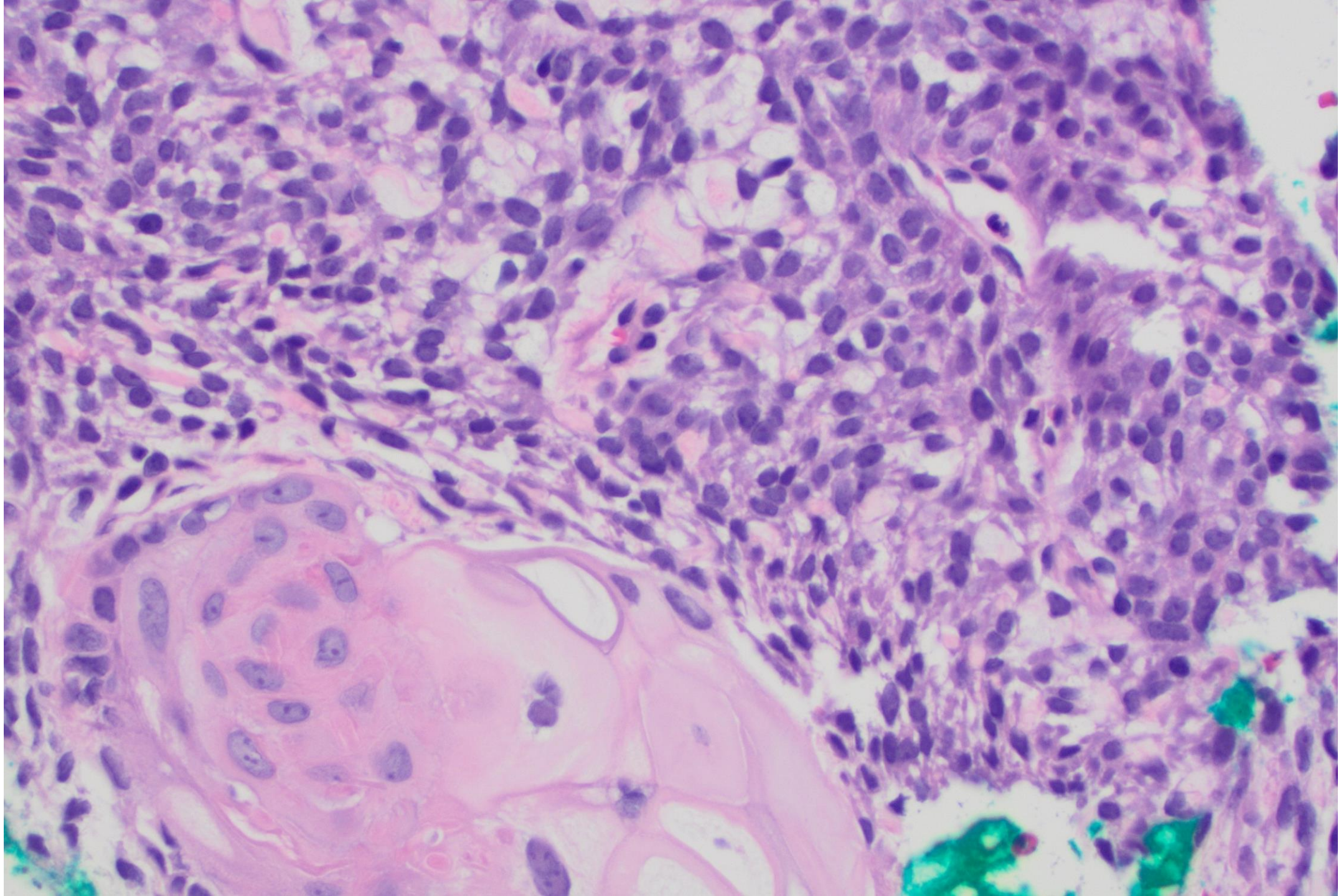




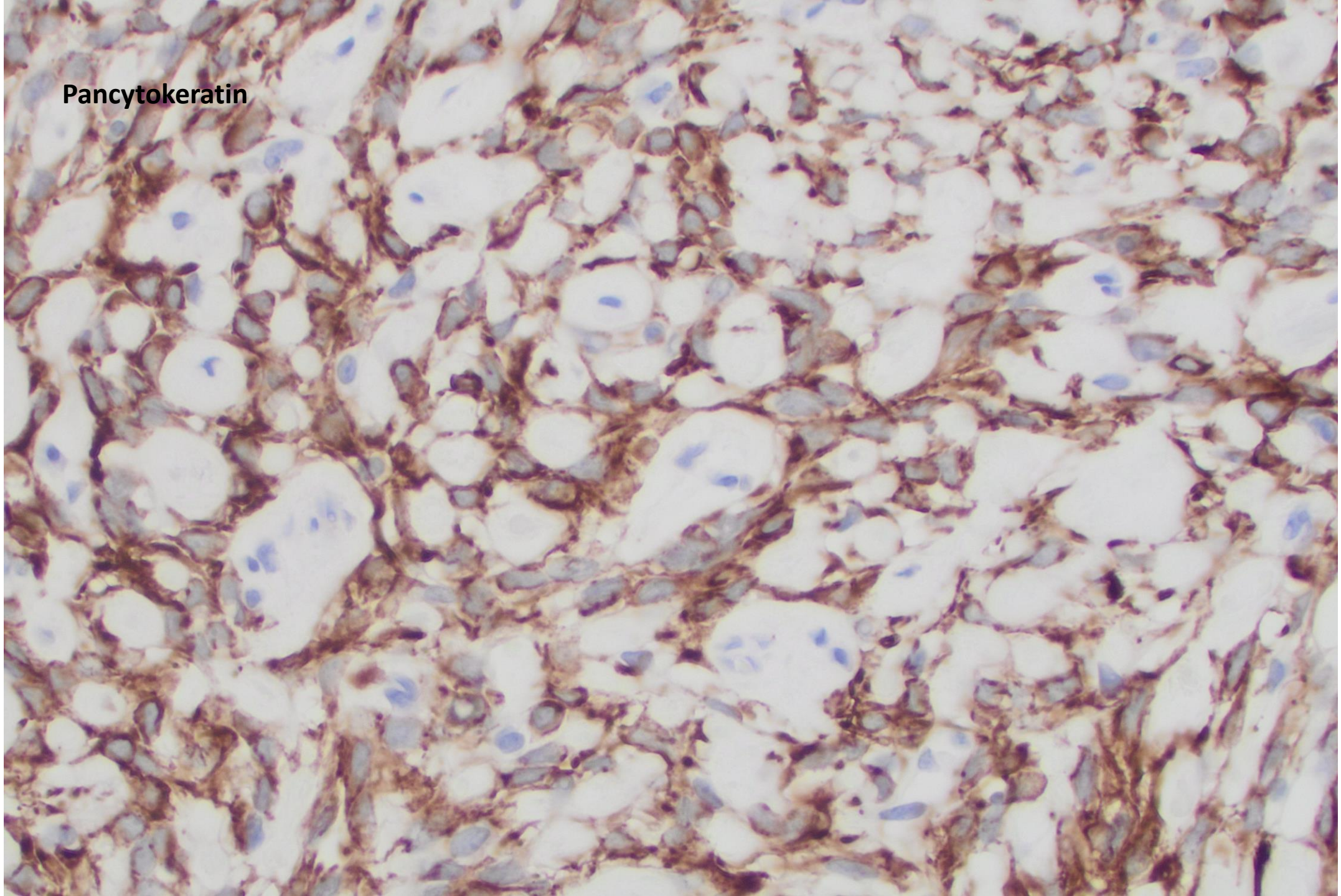


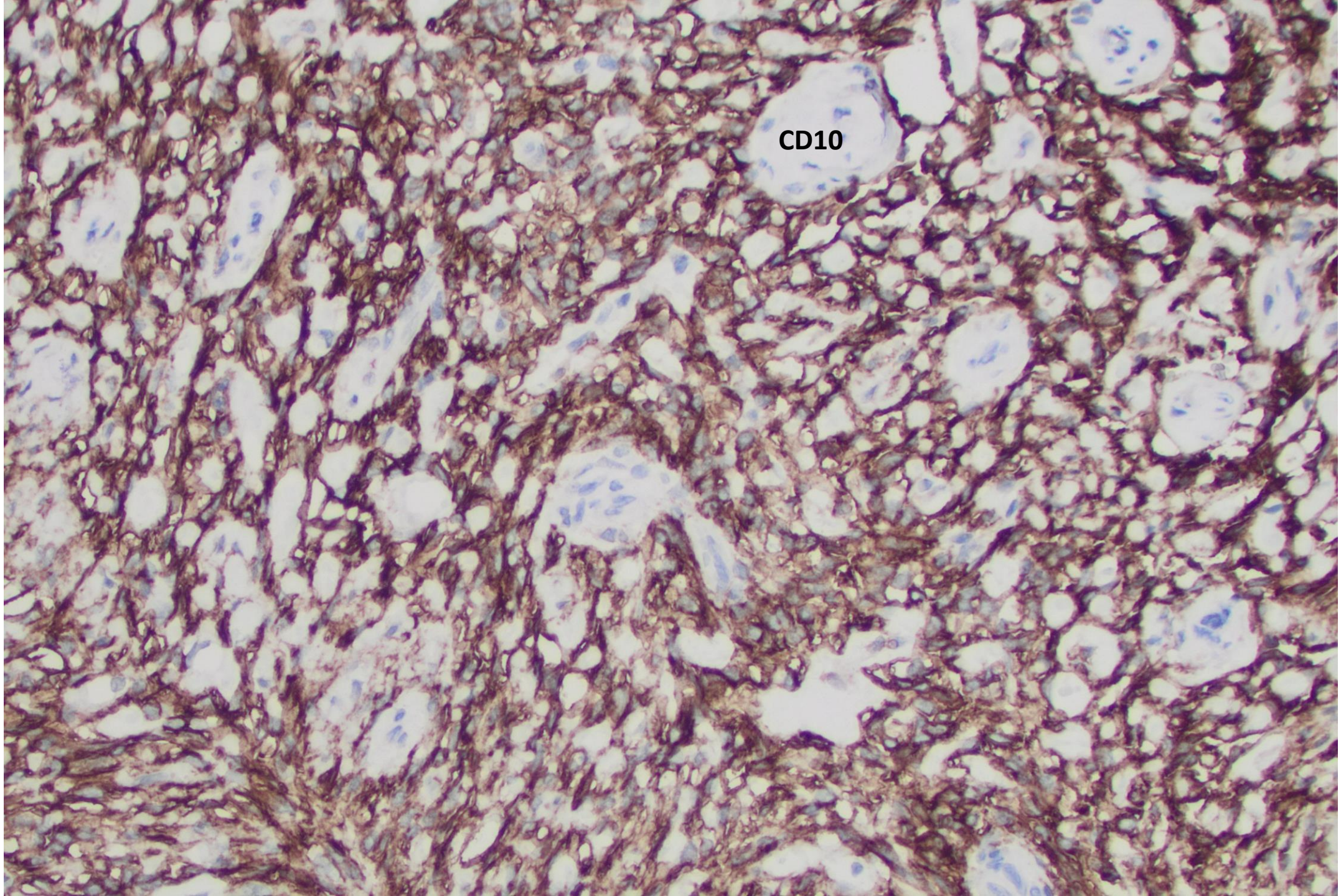


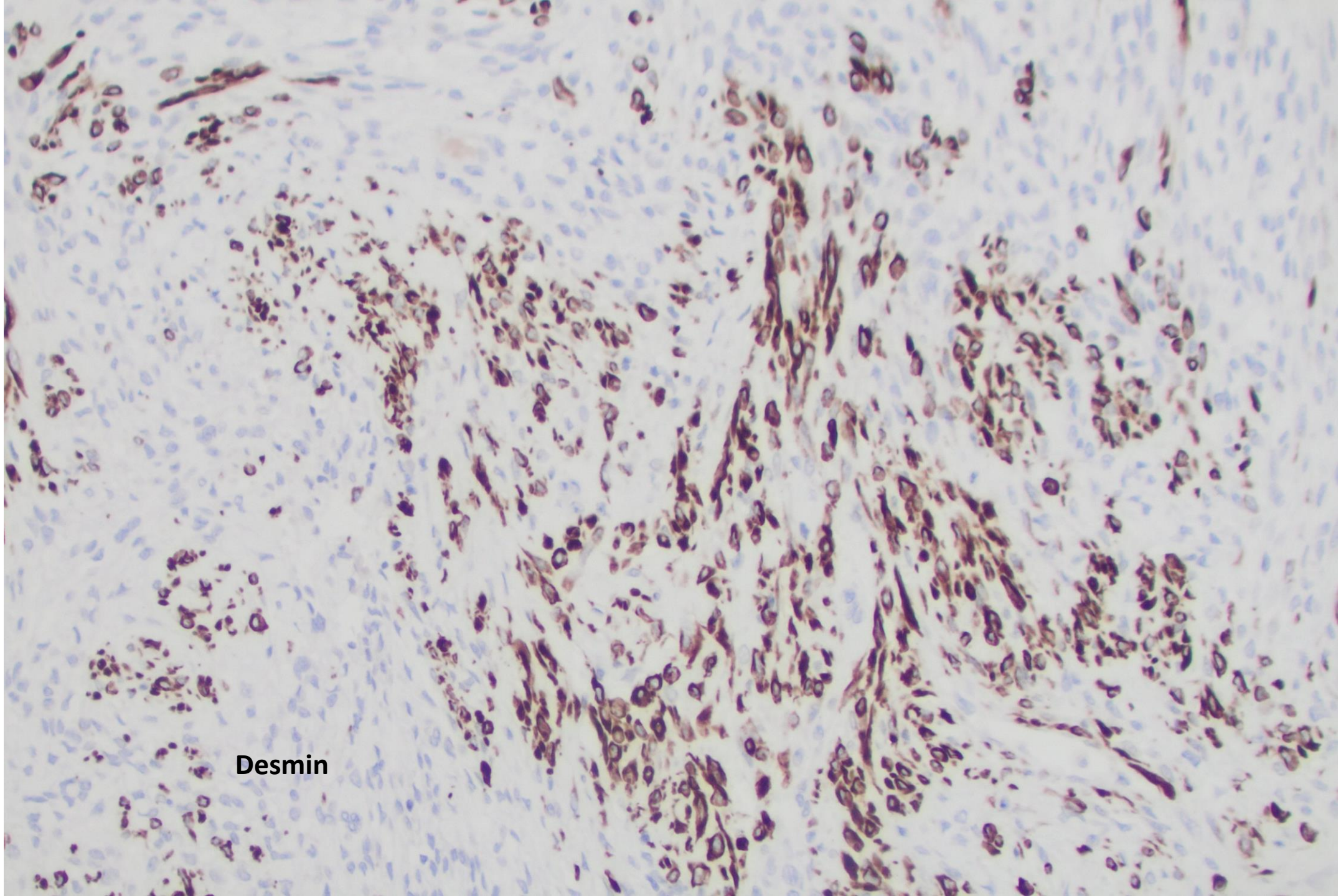


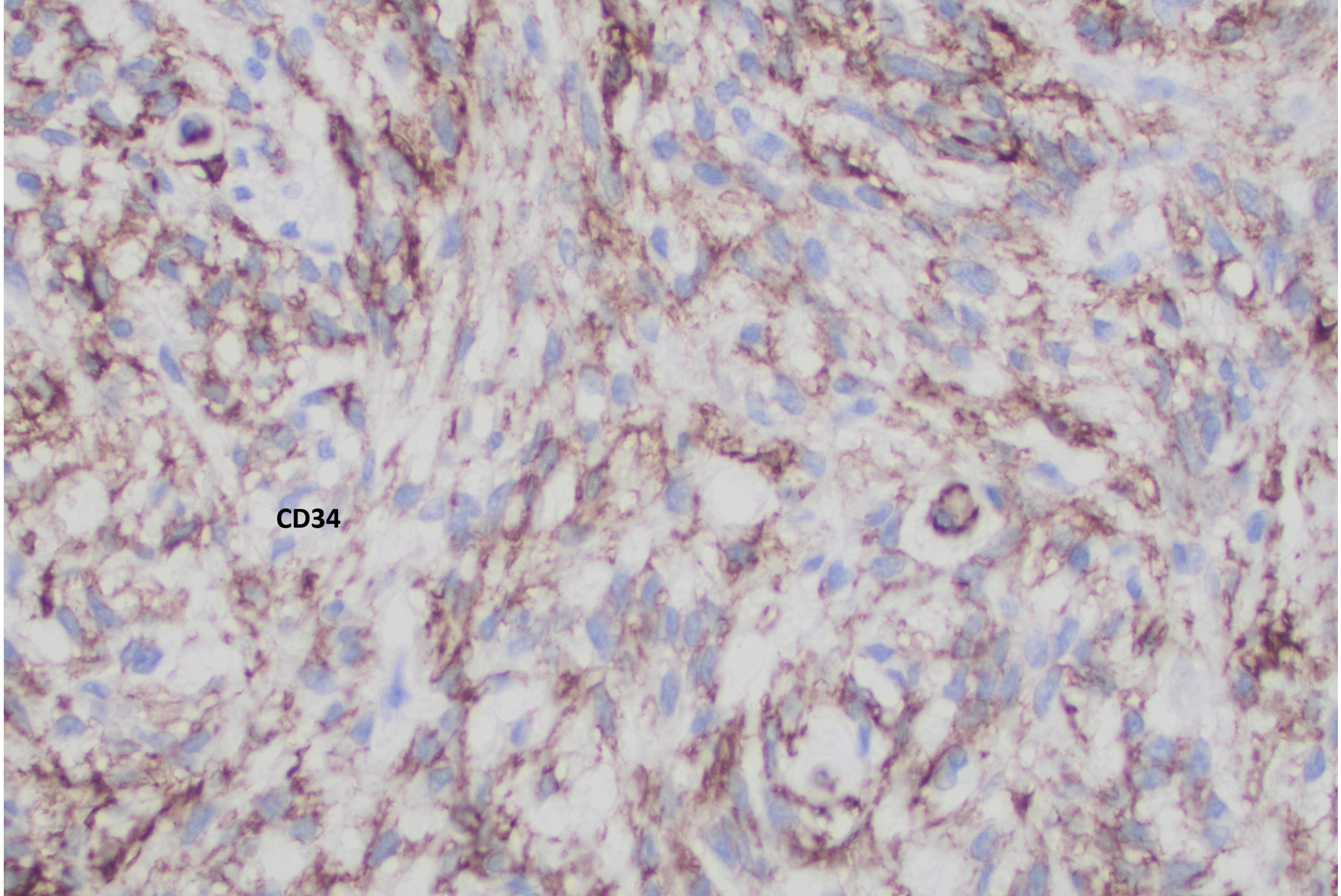


# DIAGNOSIS?


Pancytokeratin


CD10


Desmin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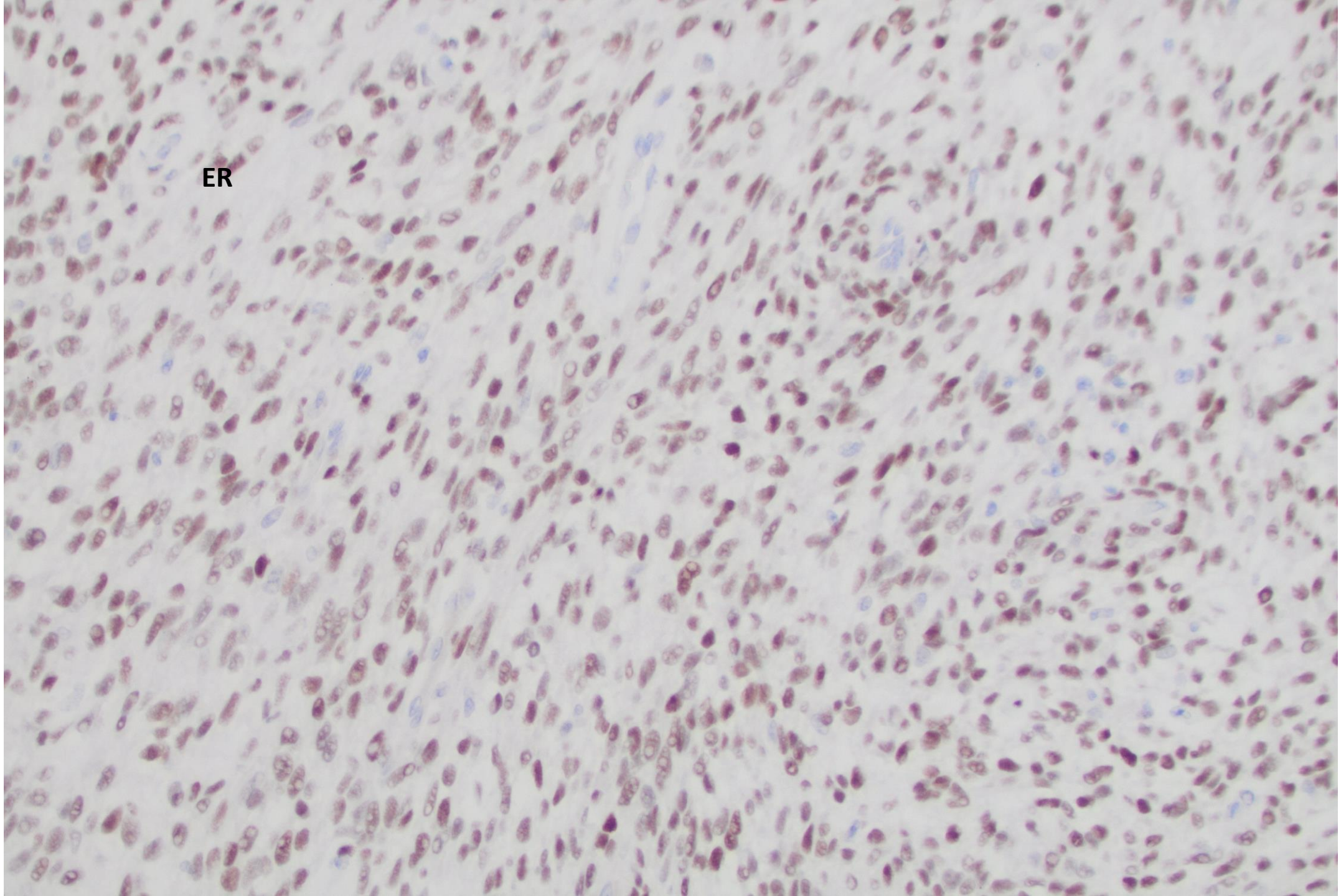
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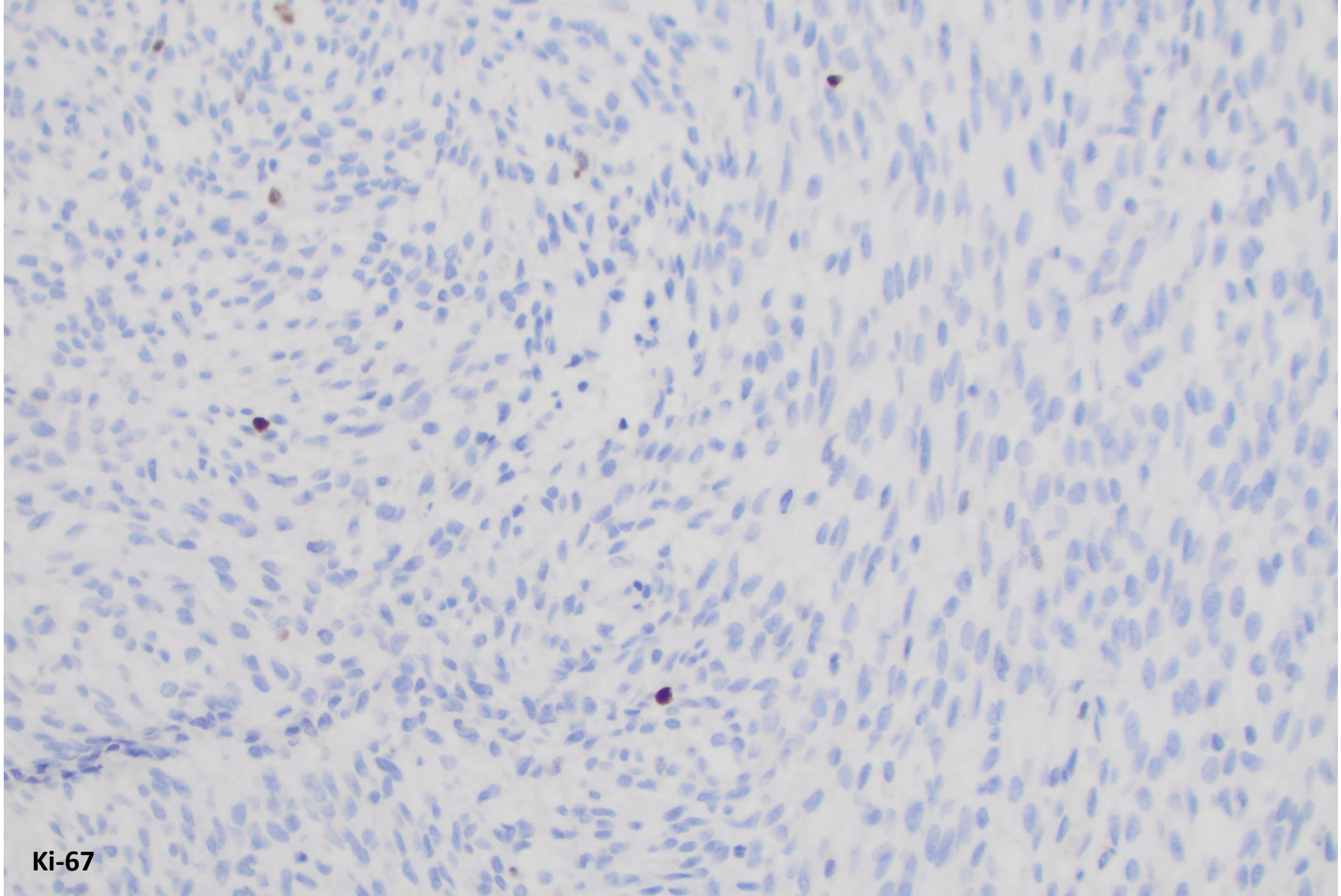

Ki-67

# Mixed Tumor of the Vagina

# Mixed Tumor

- Rare benign neoplasm with epithelial and stromal components
- Ages 20-69 (mean age=40)
- Slow growing and usually asymptomatic
- Introitus and posterior vagina most common
- Average size=3cm.

# Micro

- Submucosal, well circumscribed, non-encapsulated
- Variable cellularity
- Spindle cell component-fascicular, corded, nested, reticular
- Collagenous or myxoid matrix
- Minor epithelial component-small glands or squamous nests
- Low mitotic rate
- DDX=leiomyoma, leiomyosarcoma, angiomyofibroblastoma, myofibroblastoma, angiomyxoma, spindle cell SCCA

# IHC

- Positive-pancytokeratin, CK7, SMA, desmin, CD10, CD34, EMA, ER, PR
- Negative-CK20, S-100

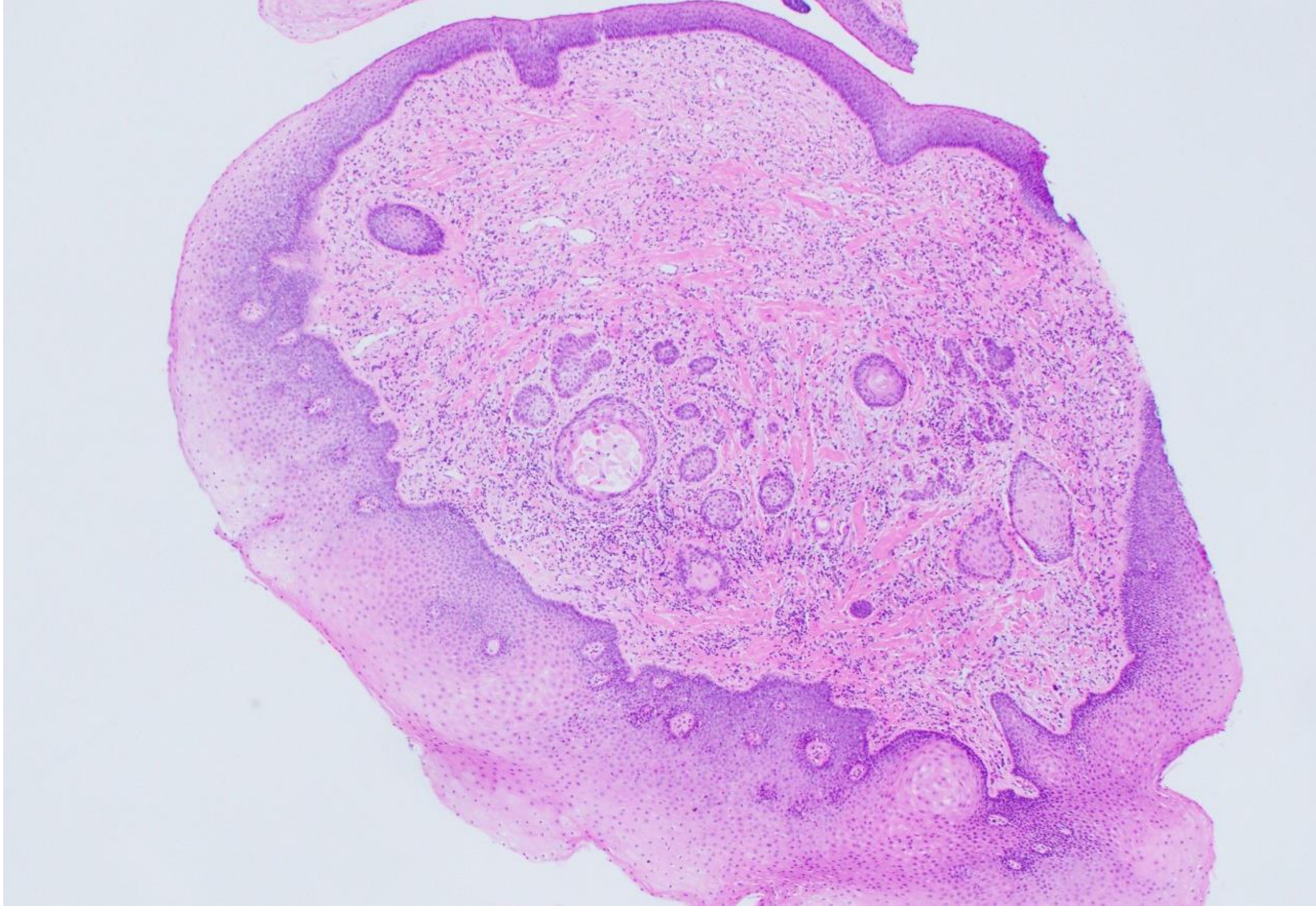
# Prognosis

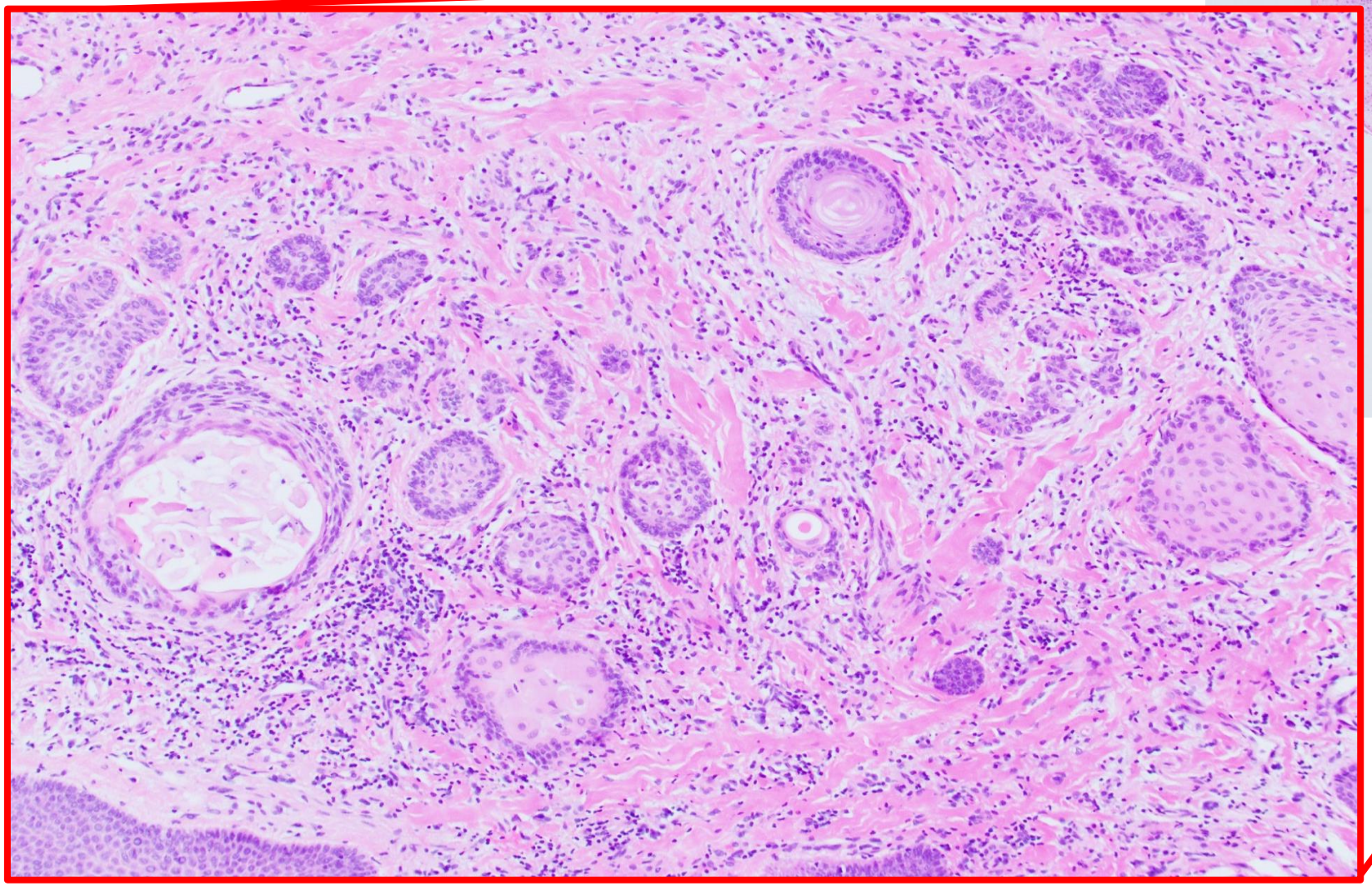
- Benign
- Complete excision and f/u recommended
- May recur locally-years later
- No distant spread

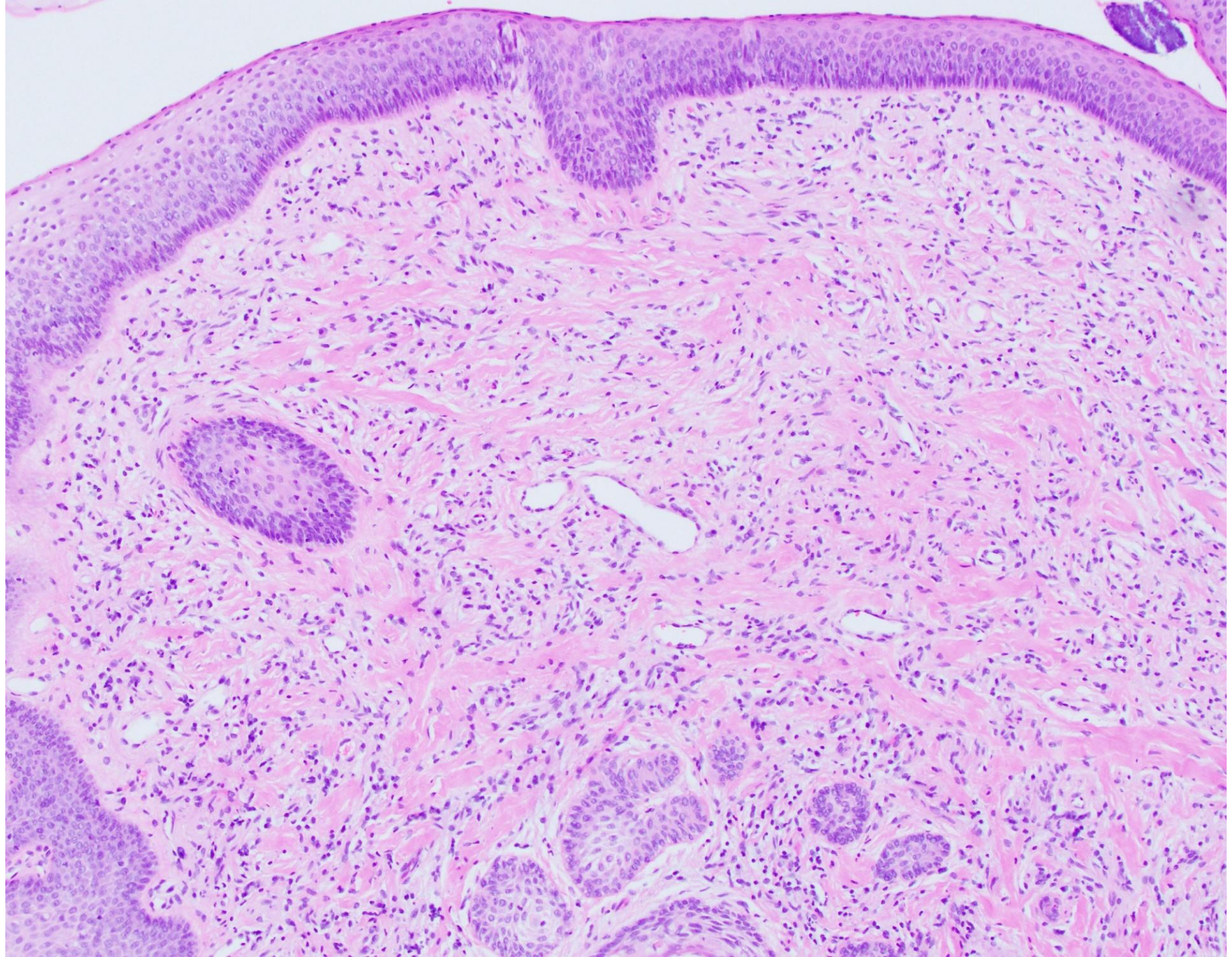
23-0703

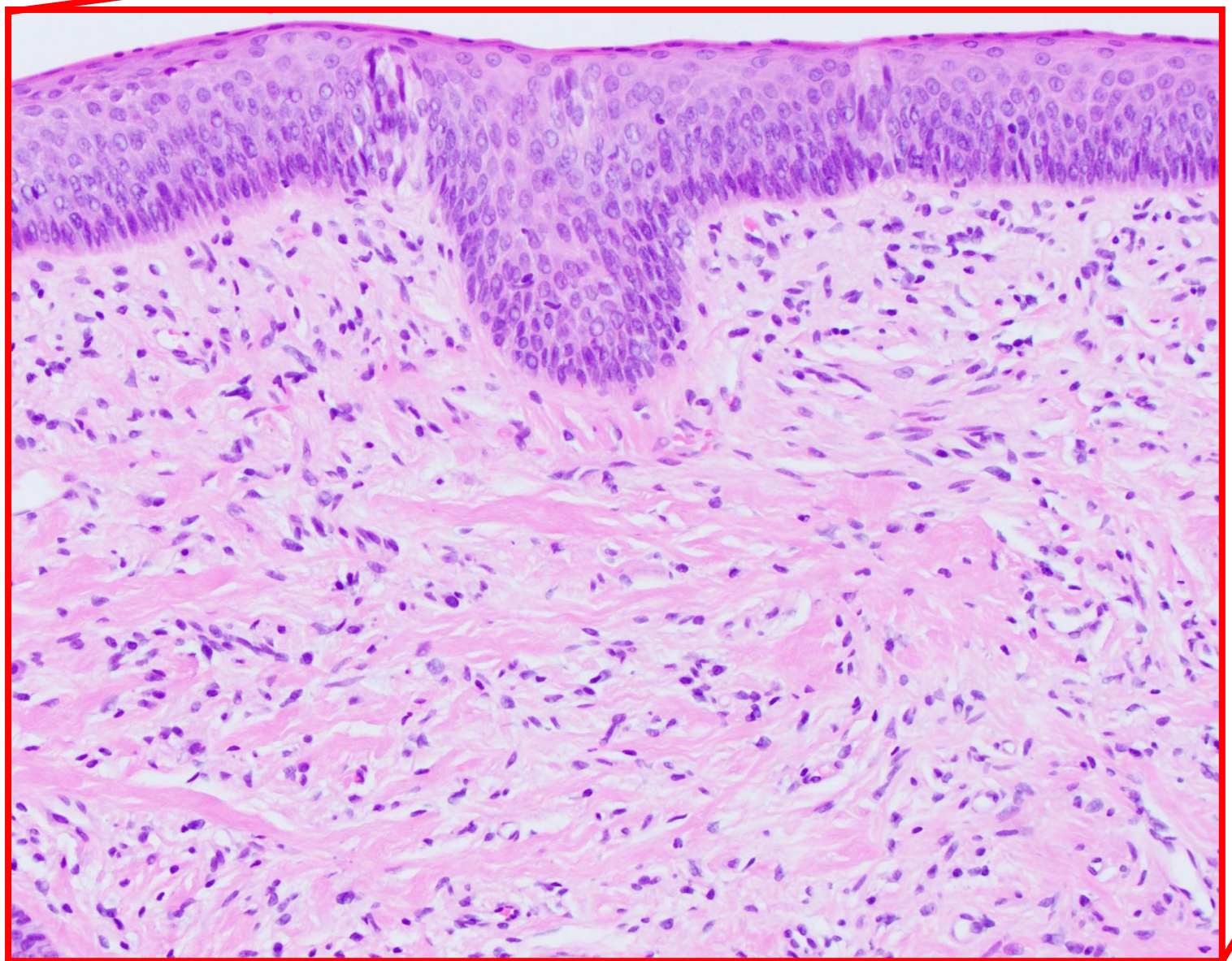
**Adebola Adeniyi/Hubert Lau; VA Palo Alto**

70 something-year-old man, base of tongue nodule biopsied during parotidectomy for metastatic squamous cell carcinoma

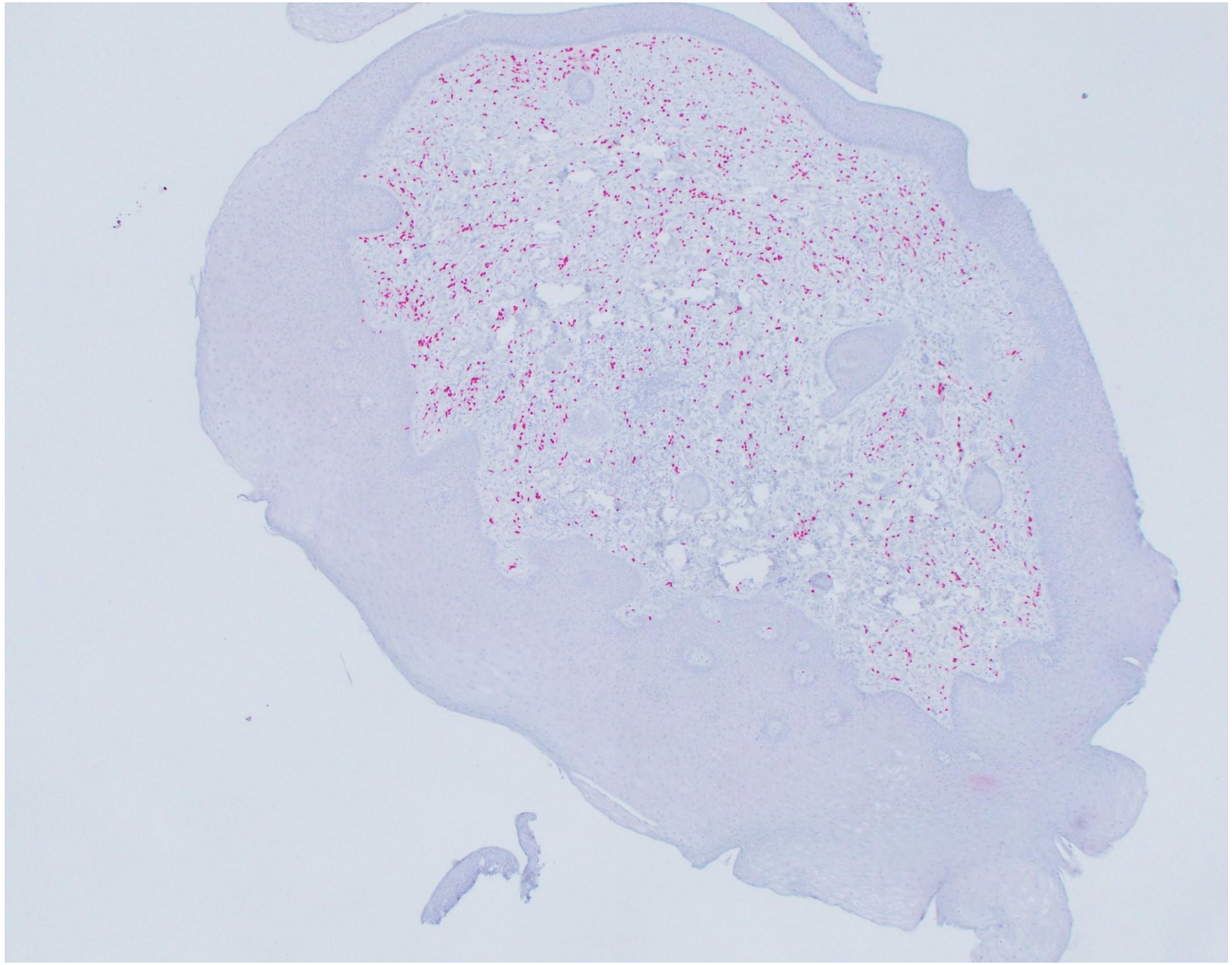








**Sox10**



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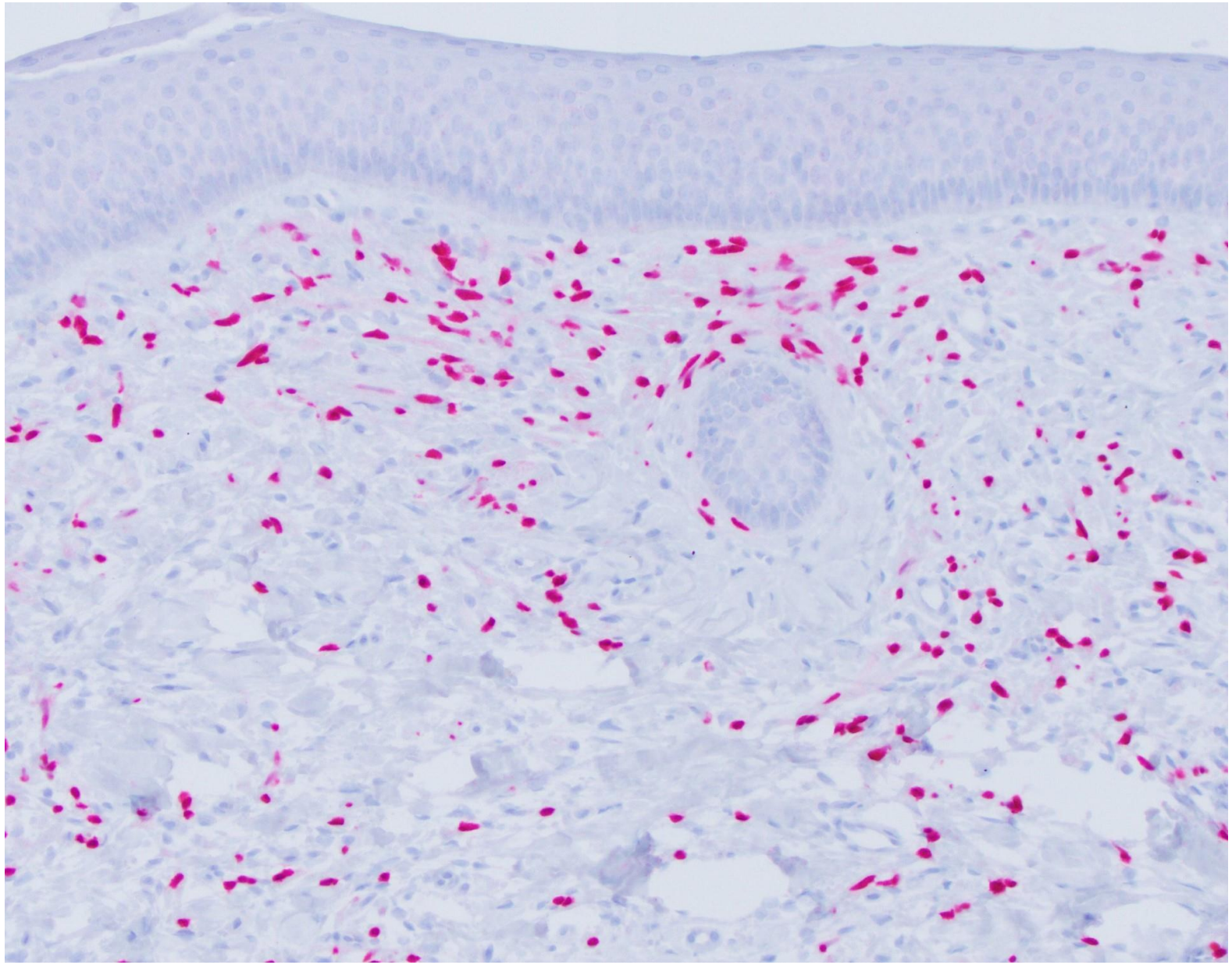


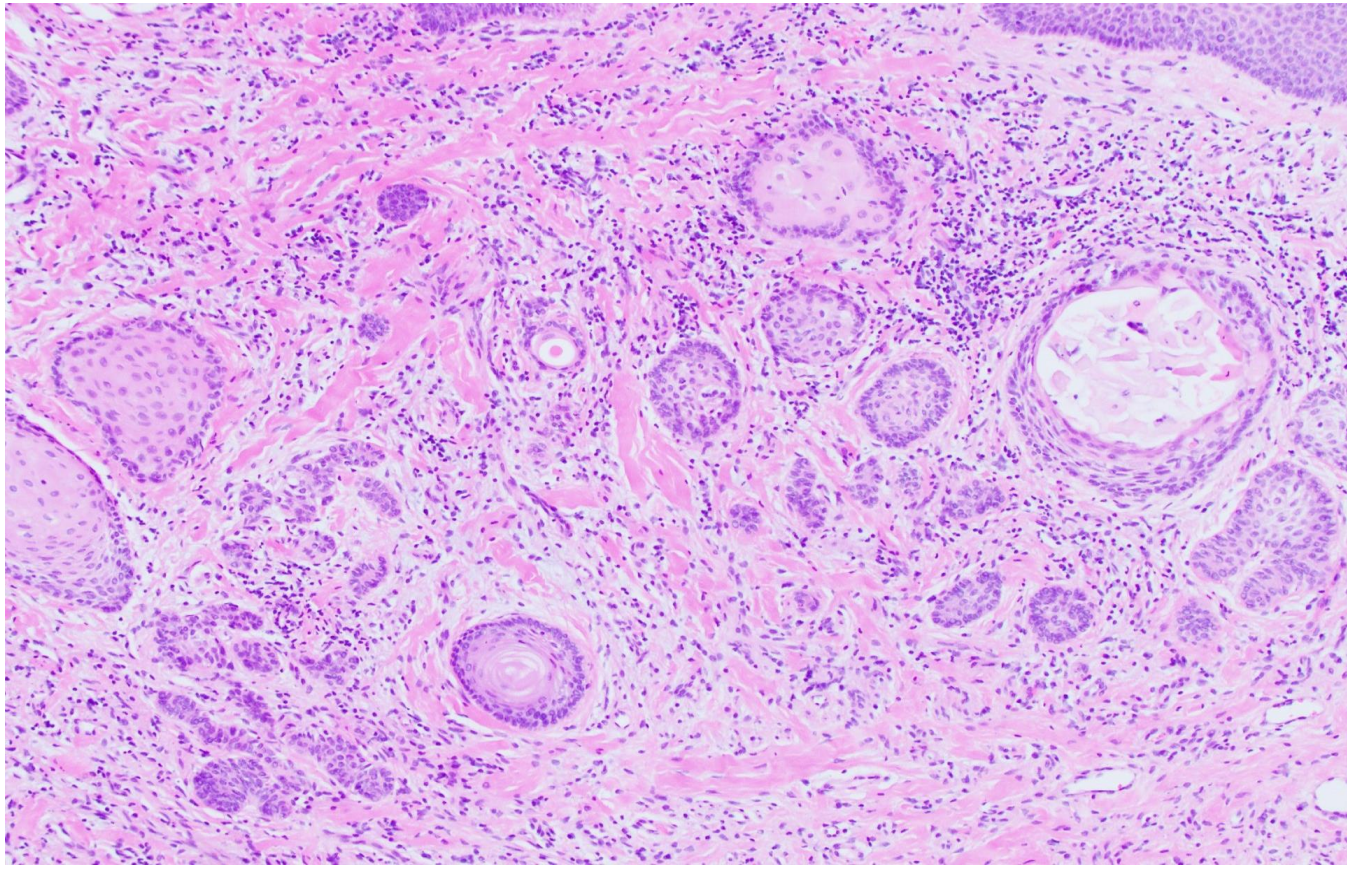
# DIAGNOSIS?

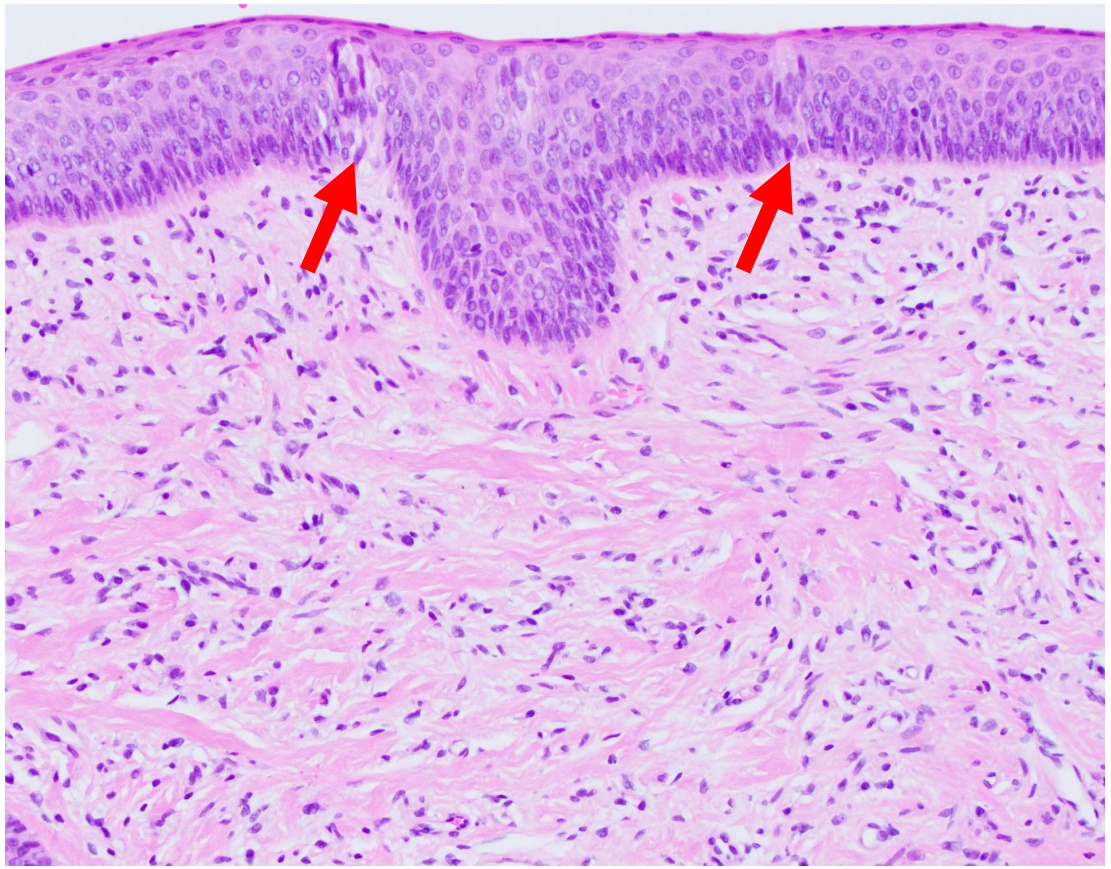
# Neuroepithelial structures associated with the subepithelial nerve plexus of taste buds

- Many embryologic epithelial remnants, such as juxtaoral organ of Chievitz (JOC), have been described in the oral region.
- When associated with peripheral nerves, they could be confused with perineural invasion by squamous cell carcinoma or other malignancy.
- Palazzolo et al. published a series of 4 cases showing neuroepithelial structures in the posterolateral tongue in close association with the subepithelial nerve plexus of taste buds.
- These structures resemble JOC but are located in the posterior tongue instead of deep soft tissue overlying the angle of the mandible and are associated with taste buds.

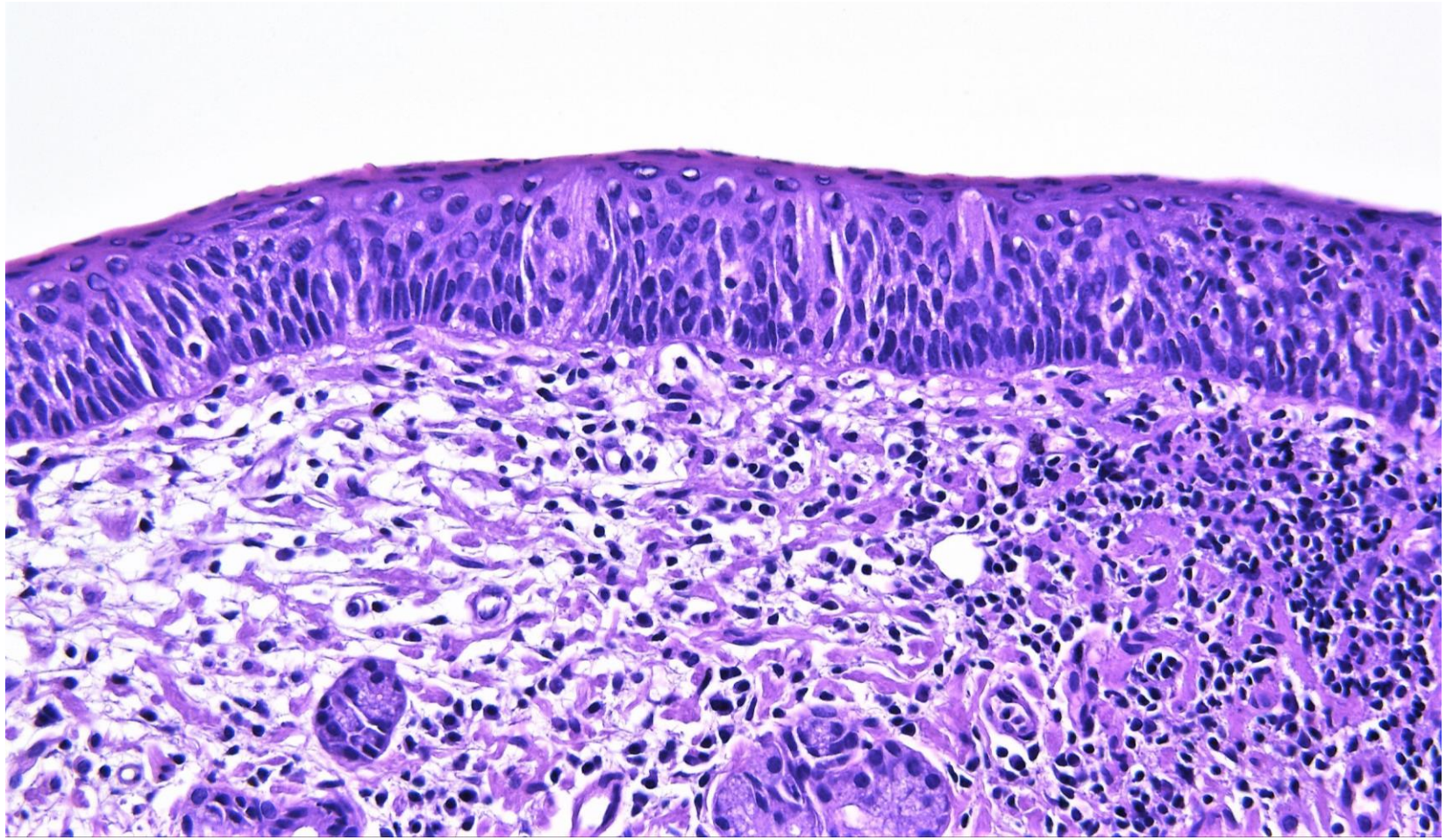
Palazzolo MJ, Fowler CB, Magliocca KR, Gnepp DR. Neuroepithelial structures associated with the subepithelial nerve plexus of taste buds: a fortuitous finding resembling the juxtaoral organ of Chievitz. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014 Apr;117(4):497-501.

# Neuroepithelial structures associated with the subepithelial nerve plexus of taste buds: histomorphology



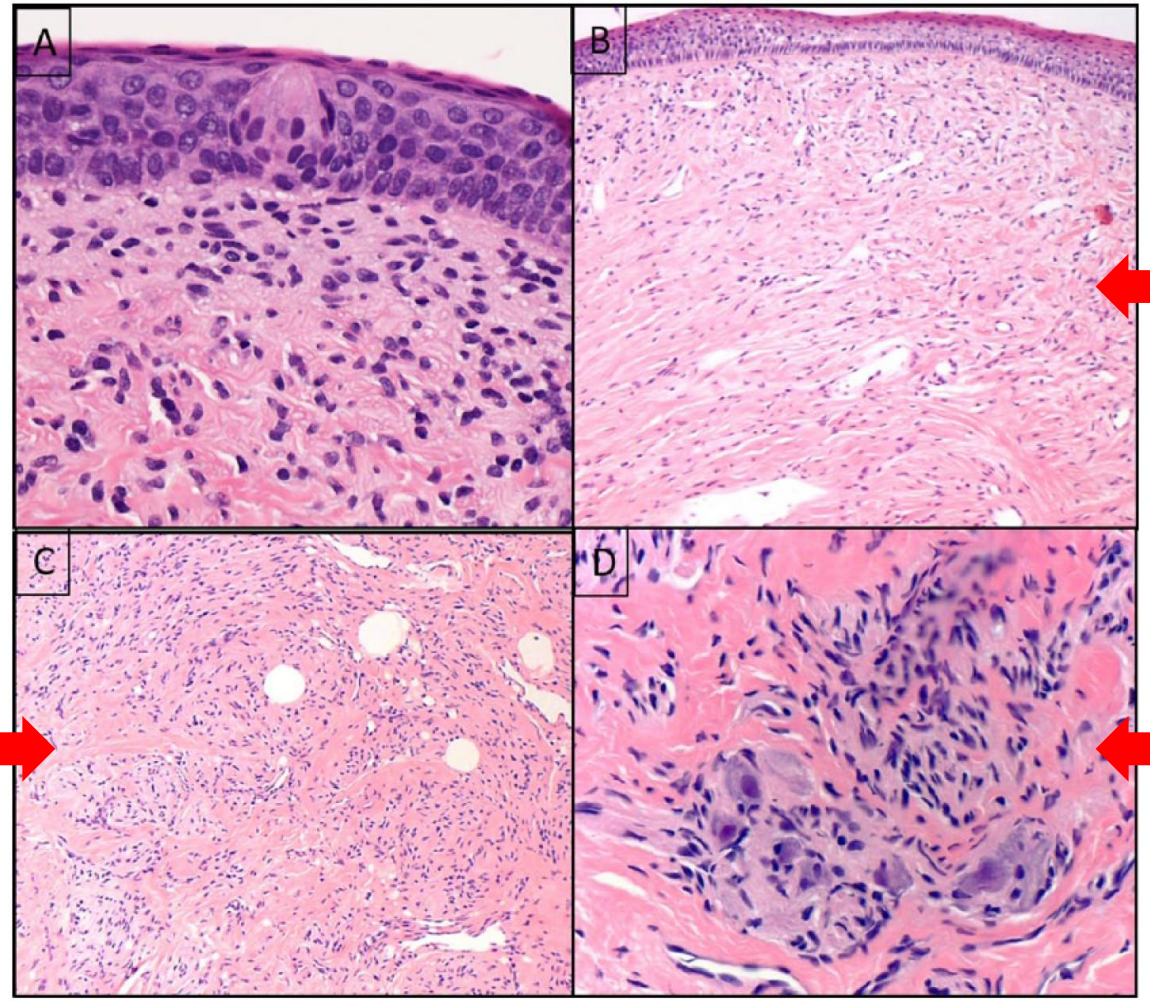


Taste buds appear as lightly-staining ovoid bodies that extend perpendicularly from the basement membrane. The adjacent epithelium can show basal stratification and potentially mimic dysplasia, especially on frozen section.



https://twitter.com/Patholwalker/status/1170928271069831168/photo/1

# Subepithelial nerve plexus of taste buds (aka subgemmal neurogenous plaque): histomorphology




Superficial zone: ovoid to spindled cells within collagenous stroma (neurofibroma-like pattern)

Deeper zone: small nerve fascicles (neuroma-like pattern)

Occasional ganglion cells can be seen, potentially mimicking ganglioneuroma

Alnajar H, O'Toole TR, Lin DM, Al-Khudari S, Gattuso P. Subgemmal Neurogenous Plaque: A Clinical and Pathologic Review With Comparison to Common Head and Neck Neural Tumors. *Clinical Pathology*. 2019;12.

# Subepithelial nerve plexus of taste buds (aka subgemmal neurogenous plaque, SNP)

- Alnajar et al. looked at all peripheral nerve lesions from the oral cavity, oropharynx, or larynx diagnosed at a single tertiary care center over a 17-year period.
- 26 cases were identified: original diagnoses were neuroma (n=9), neurofibroma (n=9), proliferation of peripheral nerve or subepithelial nerve bundle (n=6), and ganglioneuroma (n=2).
- After re-examination, 20 cases were reclassified as or confirmed to be SNP (3 neuromas and 3 neurofibromas were confirmed).
- Conclusion: SNP is easily misdiagnosed as a neural neoplasm, and true neural neoplasms in head and neck mucosal sites are rare.

Alnajar H, O'Toole TR, Lin DM, Al-Khudari S, Gattuso P. Subgemmal Neurogenous Plaque: A Clinical and Pathologic Review With Comparison to Common Head and Neck Neural Tumors. *Clinical Pathology*. 2019;12.

# Take-home points

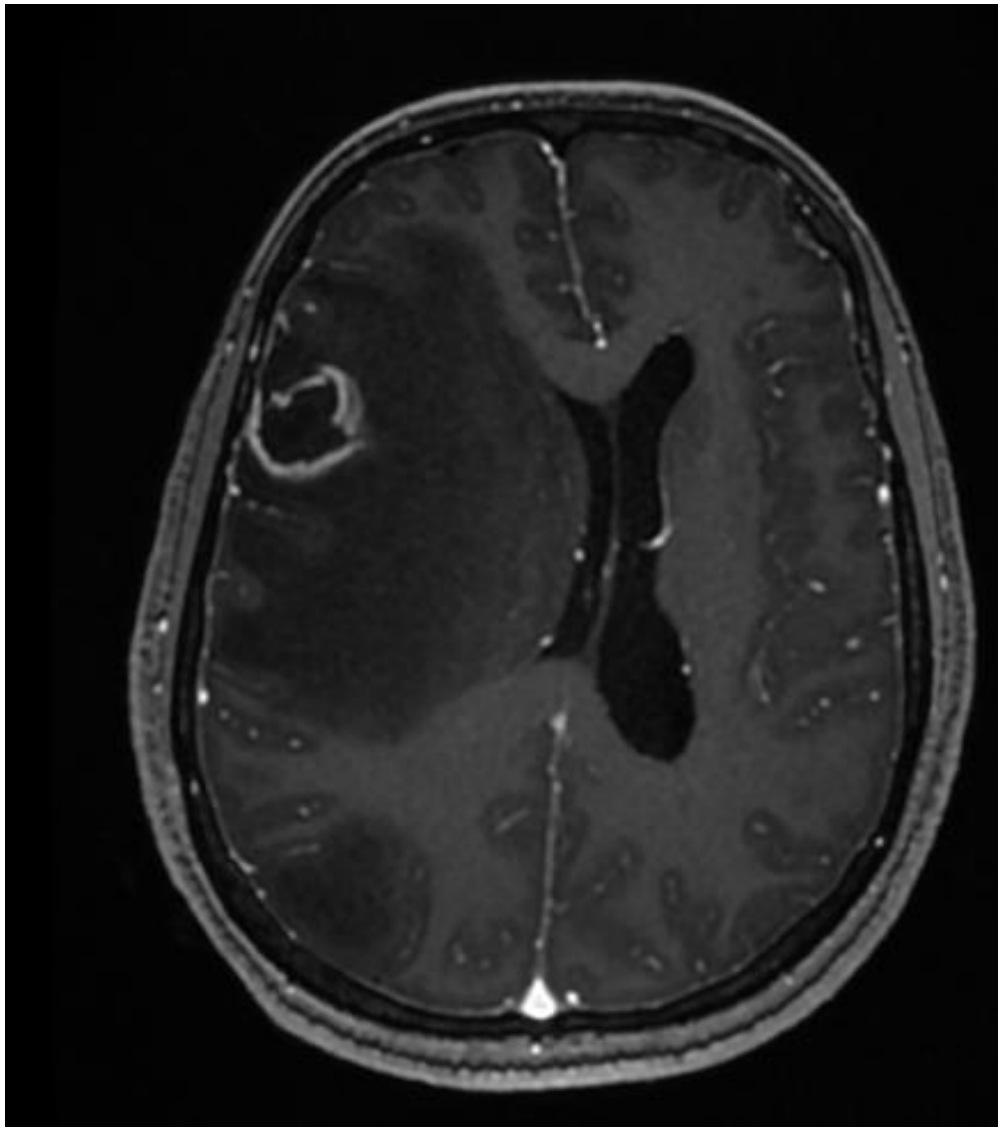
- Benign neuroepithelial structures analogous to JOC are present in the posterolateral tongue.
- Recognition of these structures can help avoid misdiagnosing the squamous islands as invasive carcinoma or the subepithelial nerve plexus as a neoplastic neural proliferation.
- The epithelium adjacent to taste buds can show basal stratification and potentially mimic dysplasia, especially on frozen section.

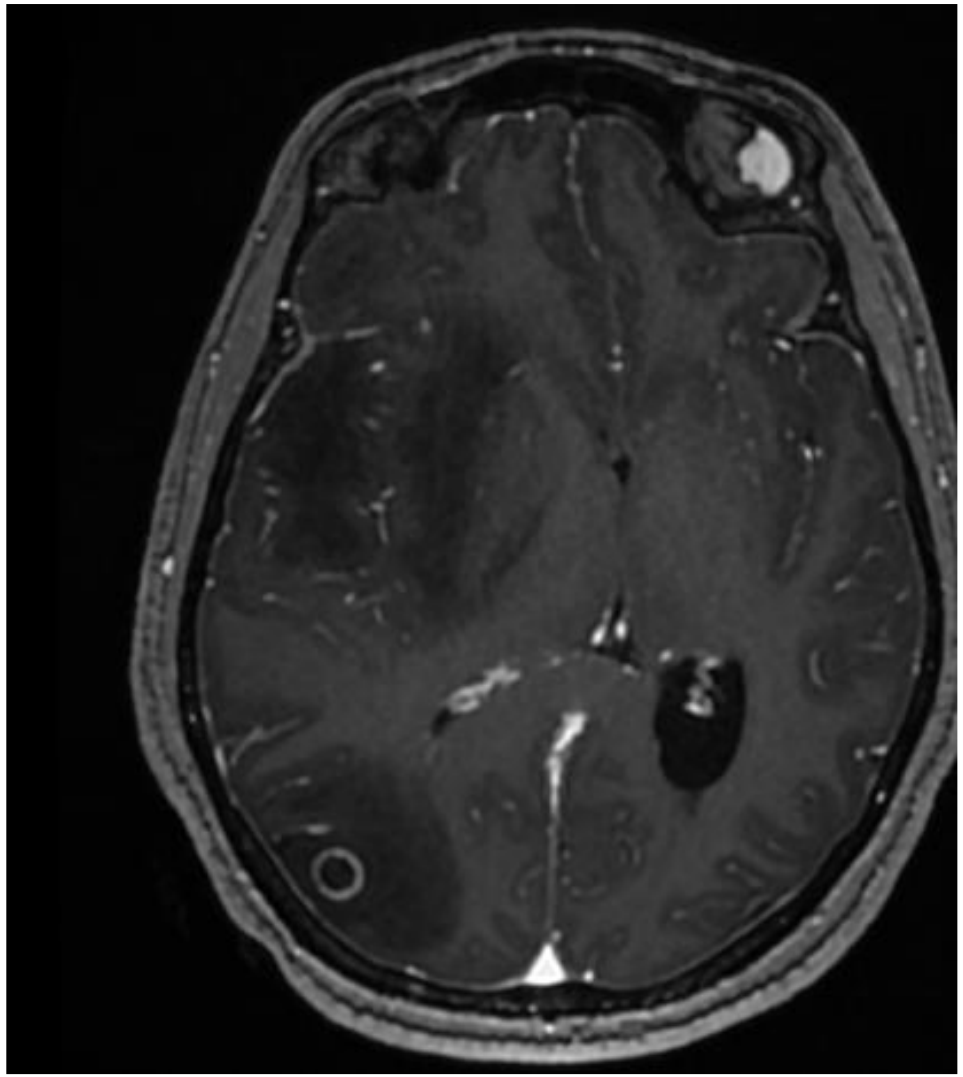
23-0704

**Harris Goodman**

40ish year old Ethiopian woman, with a recent history of new molluscum contagiosum, who presents with headache.  She states she has been healthy her whole life.

- MRI showed 2.3 x 2.2 cm peripherally enhancing lesion in the right frontal lobe and 1.0 x 0.9 cm enhancing lesion in the right parieto-occipital region, with adjacent vasogenic edema and mass effect.



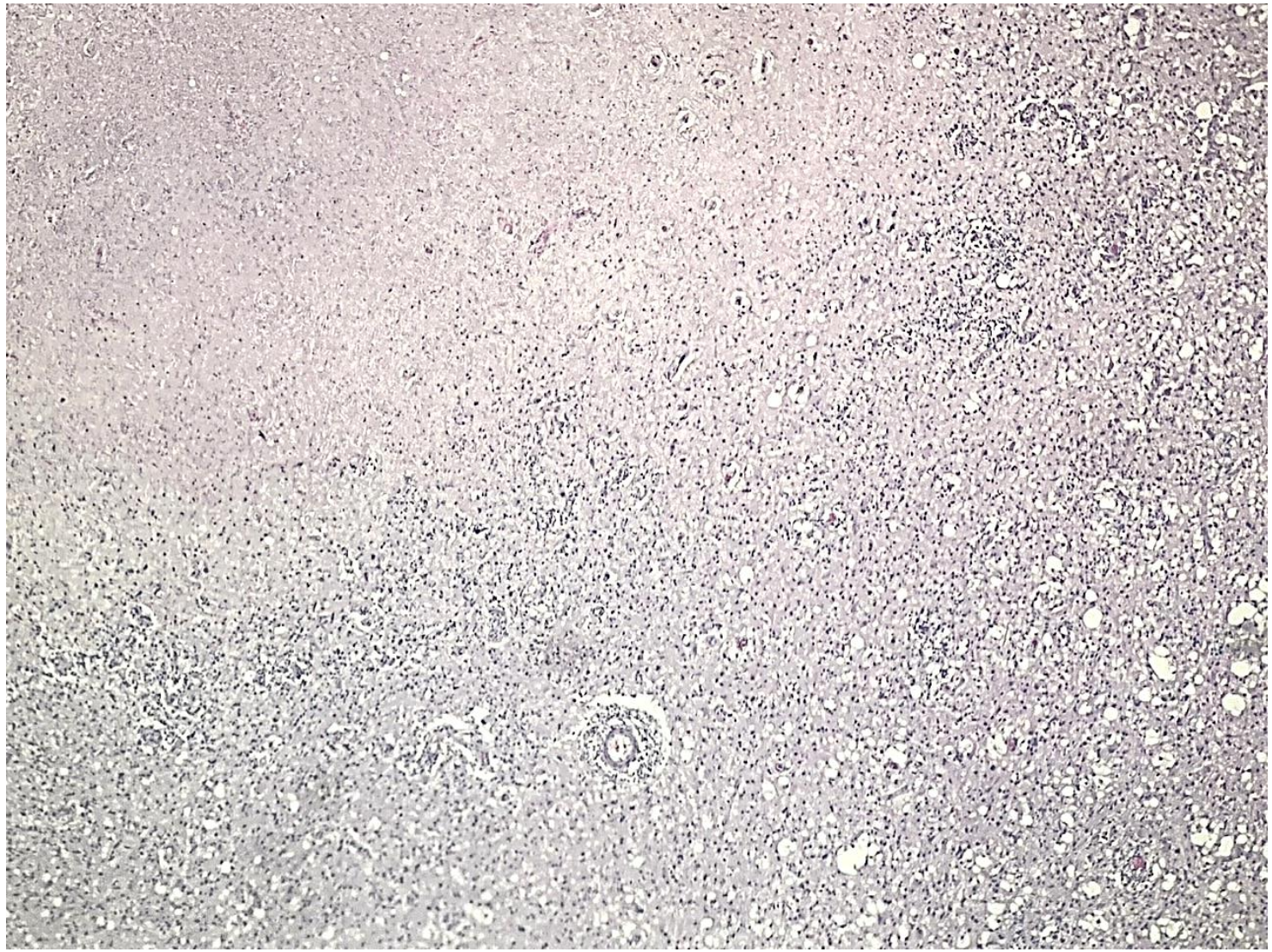


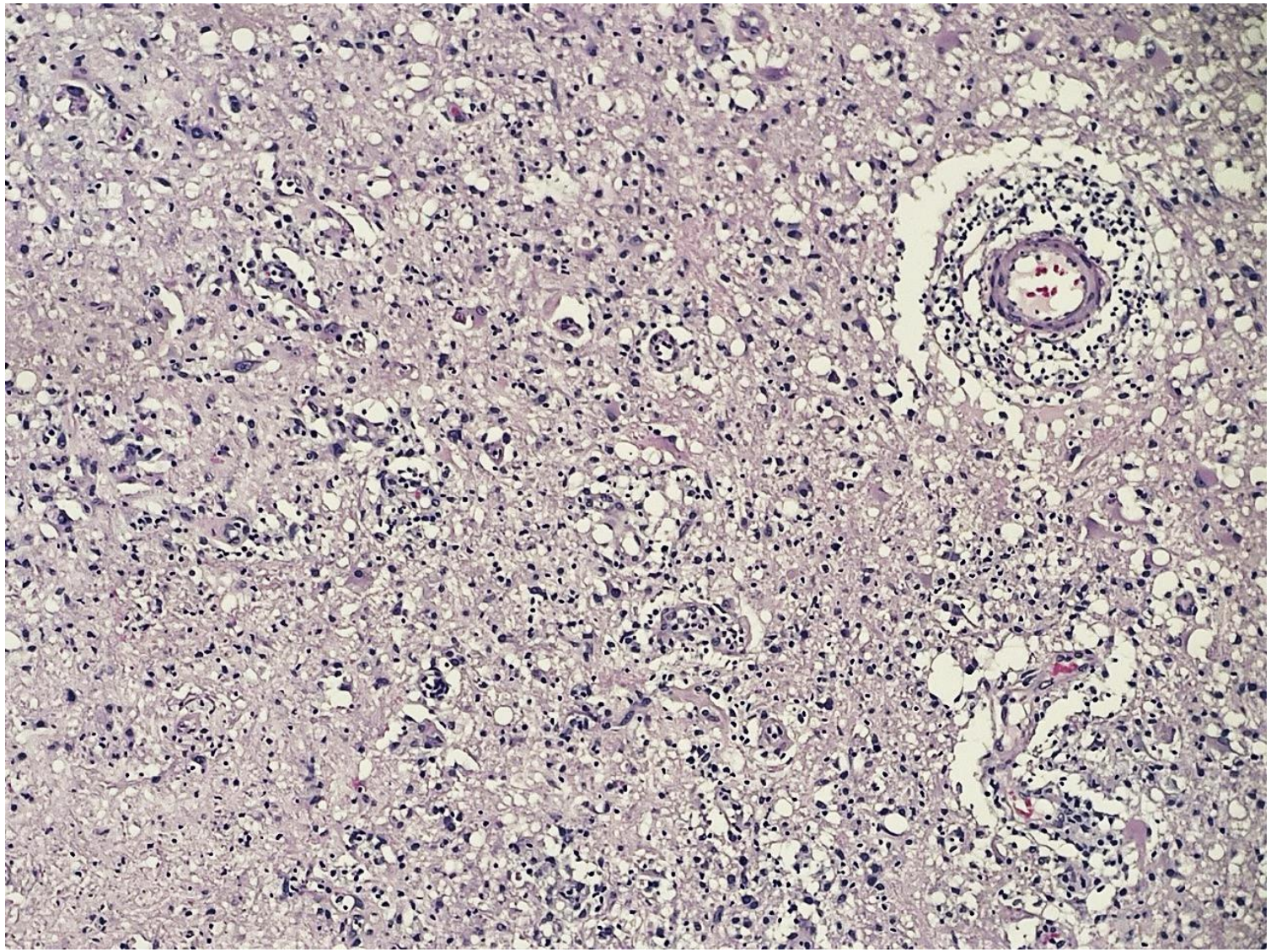
- Neurosurgery consulted.  “Findings concerning for malignant metastatic disease.“  Decadron 4 mg Q 6 hours started.

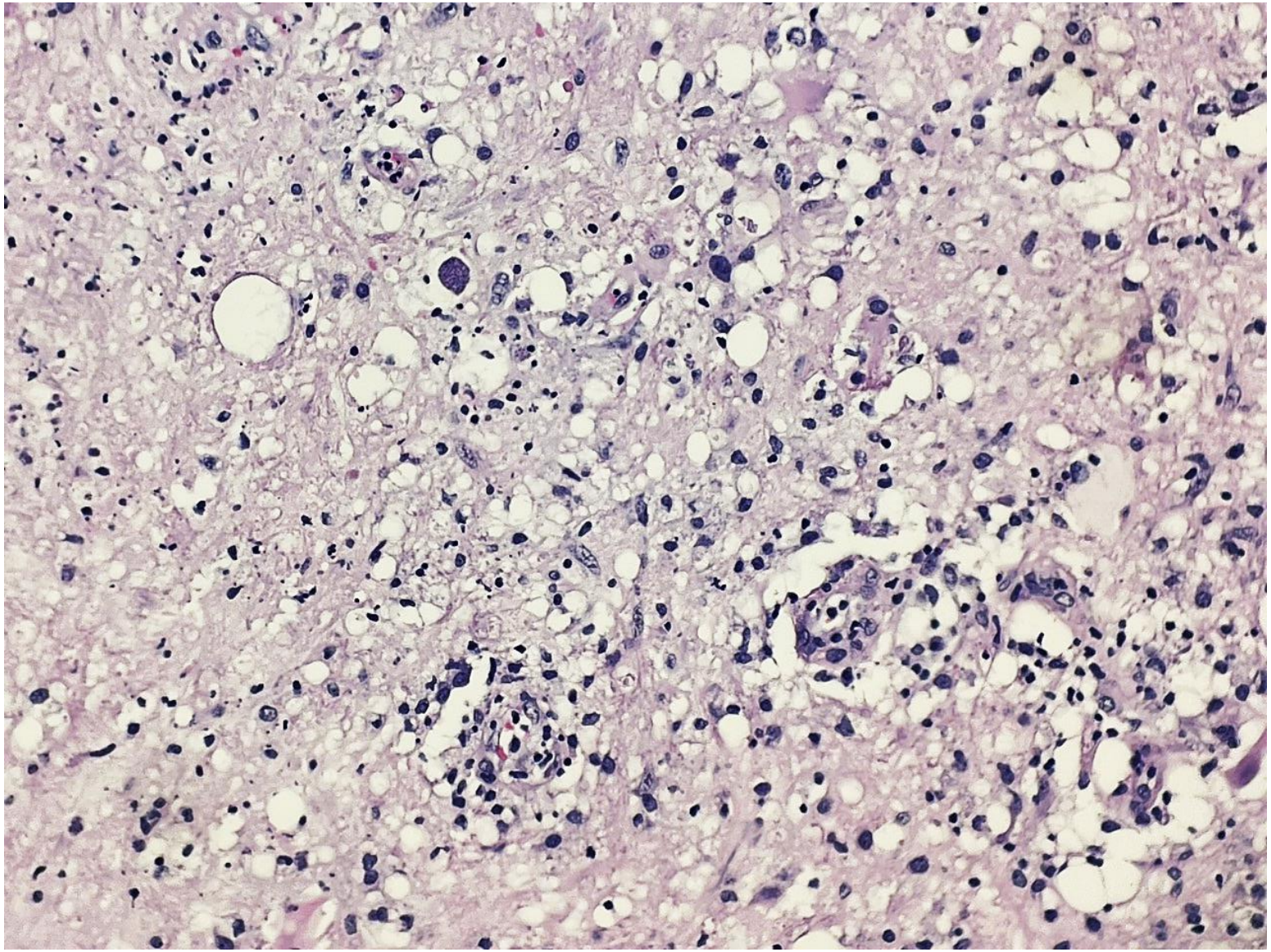
- (HPA-axis suppression likely in any adult receiving >3 mg/day fo > 2 weeks.)

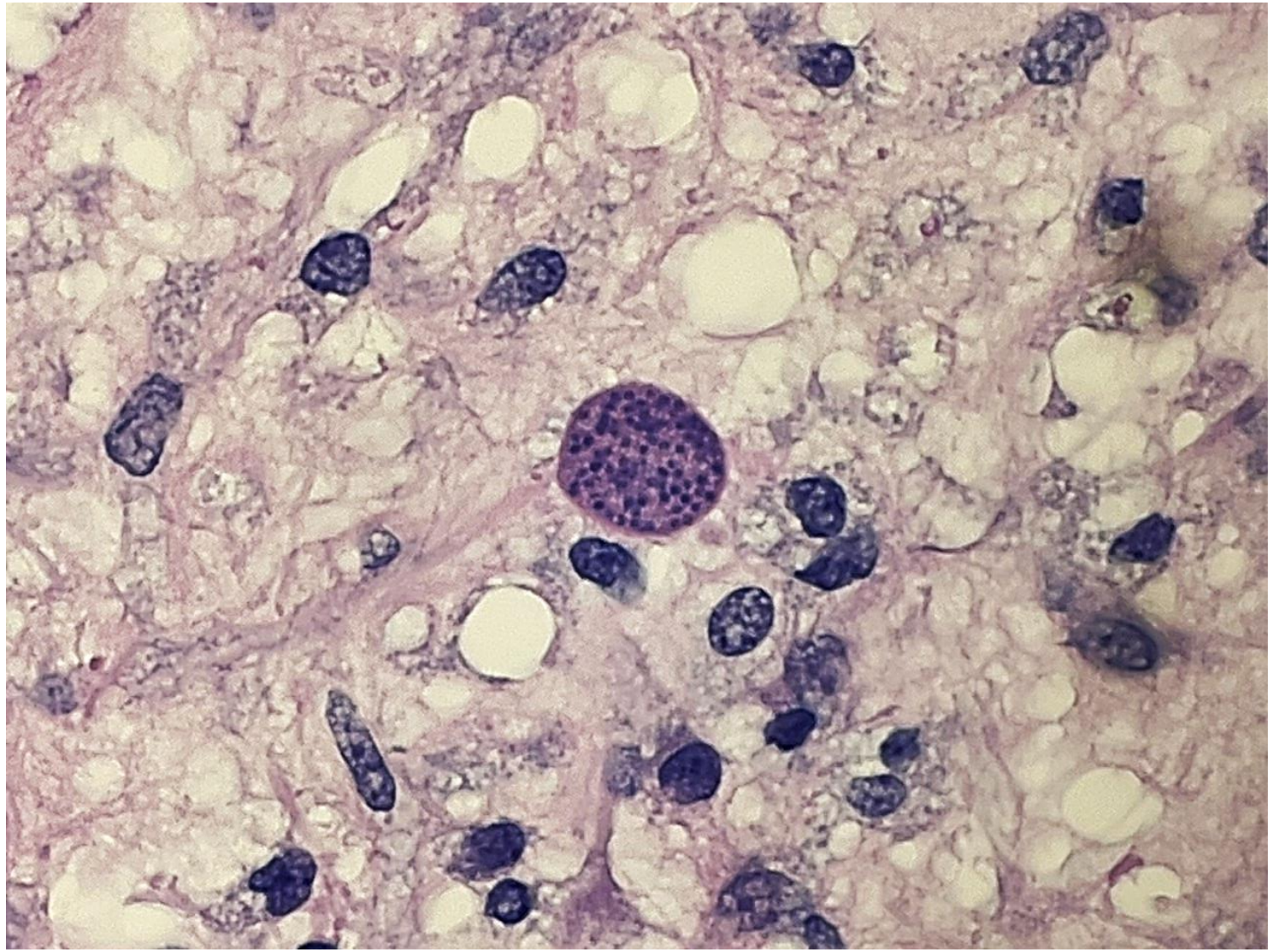
- Oncology and Palliative Medicine consulted as well.

- Patient is extremely sad, scared, and at first unwilling to undergo surgery.  Eventually consents.
- 3 cm and 1.5 cm portions of frontal lobe excised.









# DIAGNOSIS?

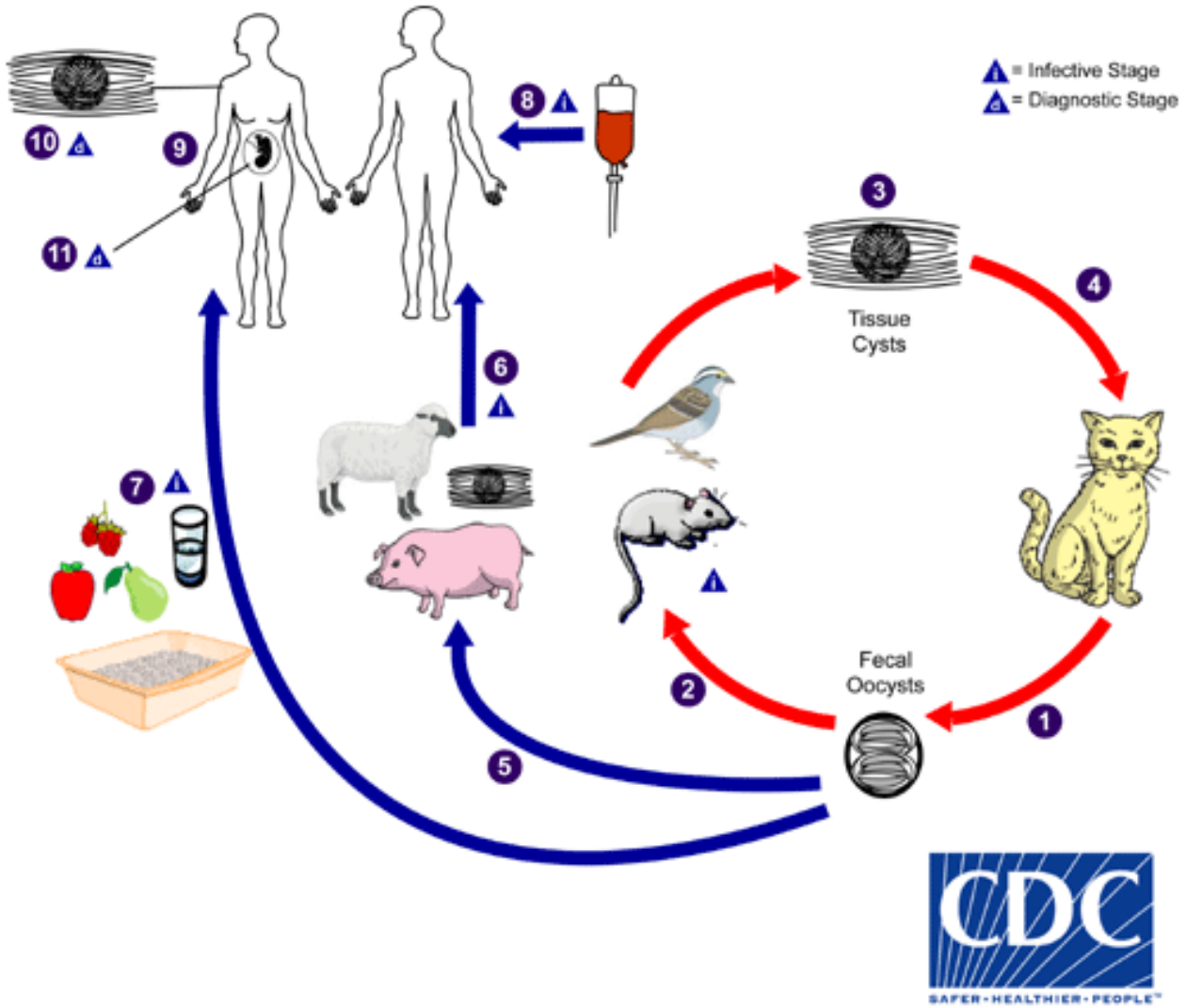
# SBPS 23-

- Cerebral toxoplasmosis
- HIV  (combo antibody/antigen) test positive.

# SBPS 23-

- Toxoplasma gondii
  - Protozoan, with cats the only definitive host for the sexual stage of reproduction.
  - Trophozoites multiple in the cat intestines and produce oocytes.
  - Unsporulated oocytes shed in cat feces.
  - Intermediate hosts (e.g. birds, rodents and humans) injest oocytes, which transform into tachyzoites.
  - Tachyzoites localize in tissue and become cyst bradyzoites.

# SBPS 23-


= Infective Stage
= Diagnostic Stage
Tissue Cysts
Fecal Oocysts
1
2
3
4
5
6
7
8
9
10
11
CDC
SAFER·HEALTHIER·PEOPLE™

# SBPS 23-

Humans can become infected by any of several routes:

- Eating undercooked meat of animals harboring tissue cysts.
- Consuming food or water contaminated with cat feces or by contaminated environmental samples (such as fecal-contaminated soil or changing the litter box of a pet cat).
- Blood transfusion or organ transplantation.
- Transplacentally from mother to fetus.

# SBPS 23-

Diagnosis of toxoplasmosis:

- Serology
- Demonstration of tissue cysts
- PCR

Treatment of toxoplasmosis:

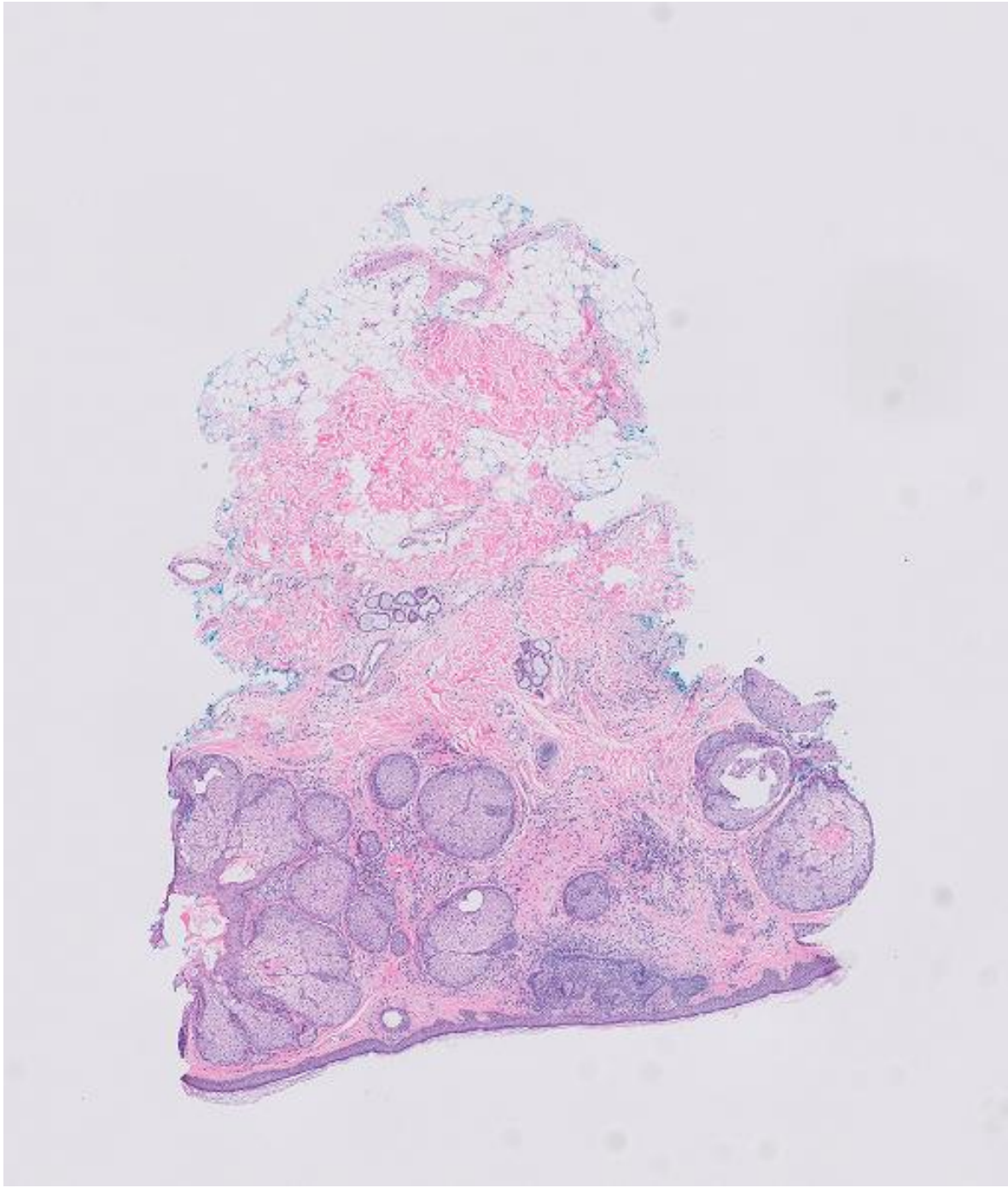
Pyrimethamine (with folinic acid) and sulfadiazine or clindamycin

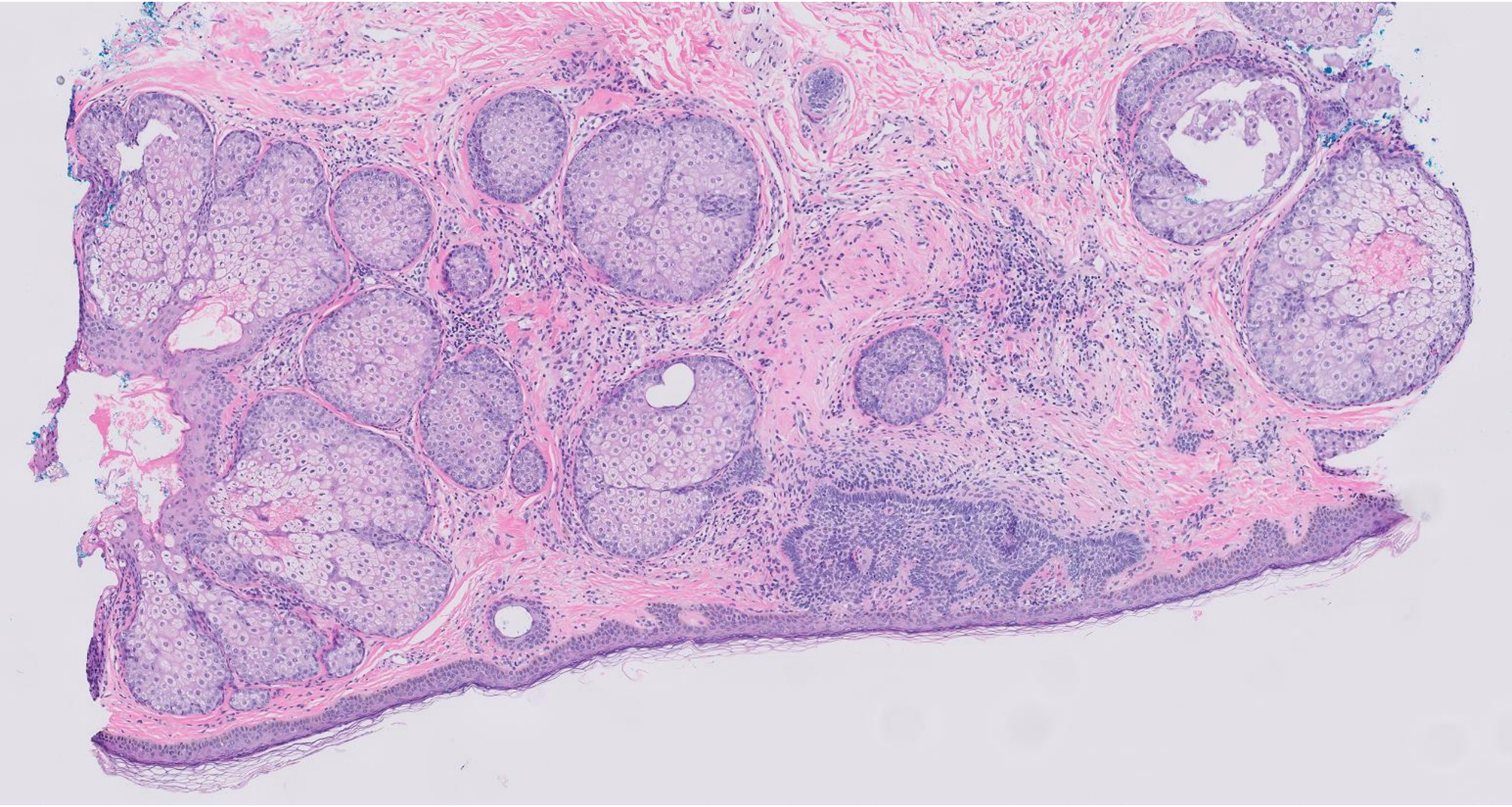
23-0705

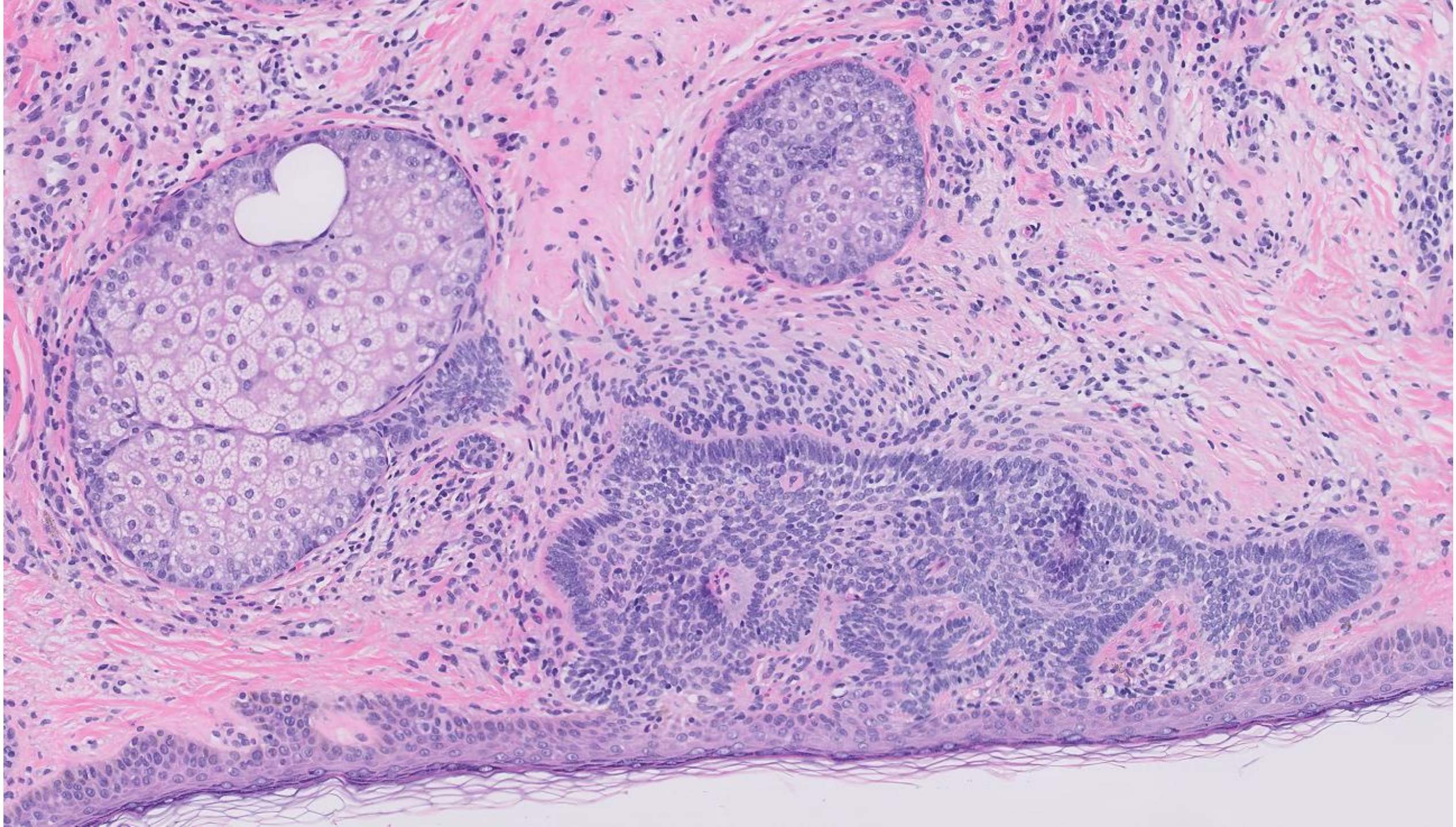
**Monica Mikayakawa-Liu/Kerri Rieger; Stanford**

15 y/o F presents with a 2mm pink atrophic plaque on left cheek, present since birth. The lesion has grown with her as she's grown, and there are no changes of texture or elevation. There was an instance of bleeding for several months and has not been associated with pain.

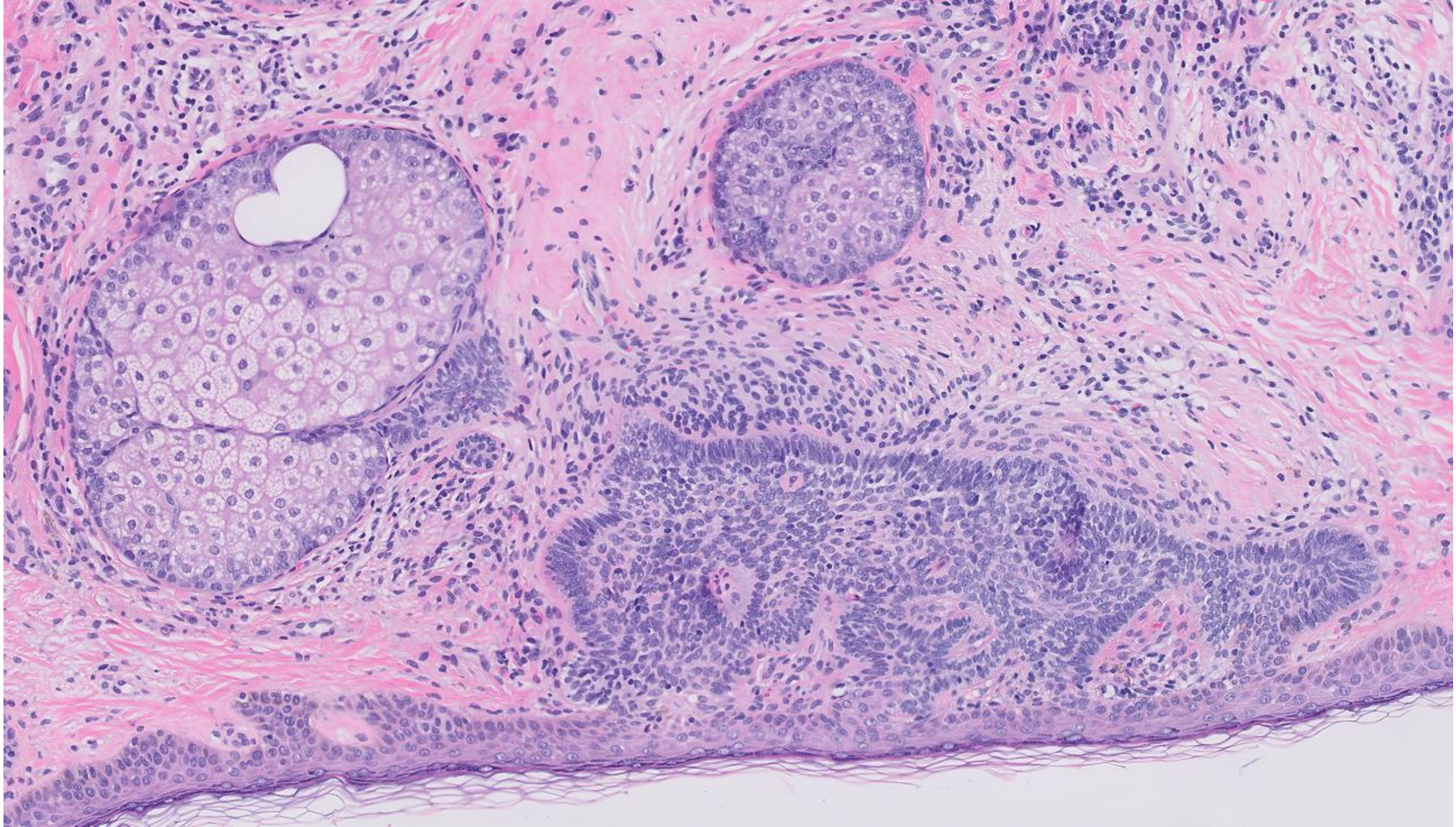
# H&E





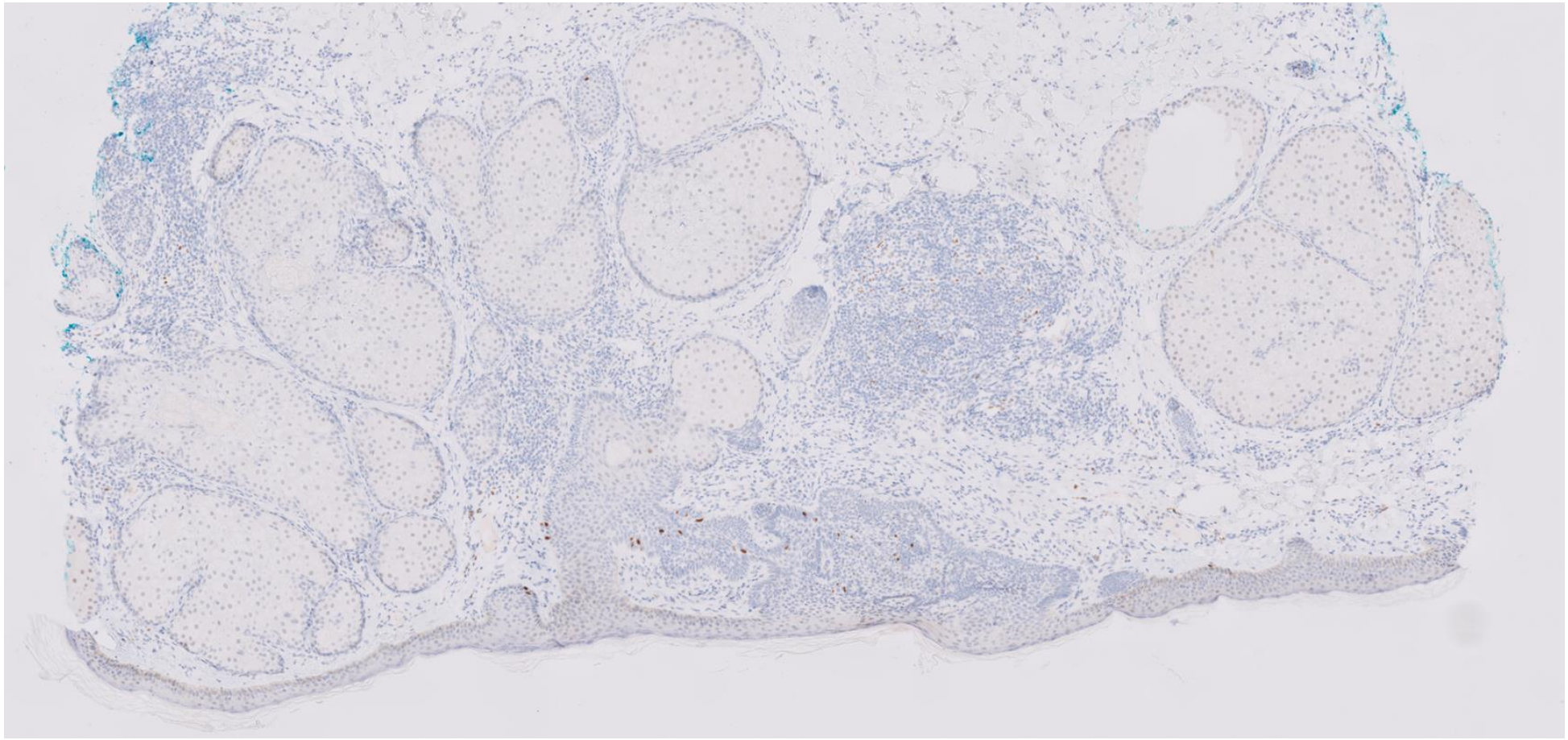


# DIAGNOSIS?



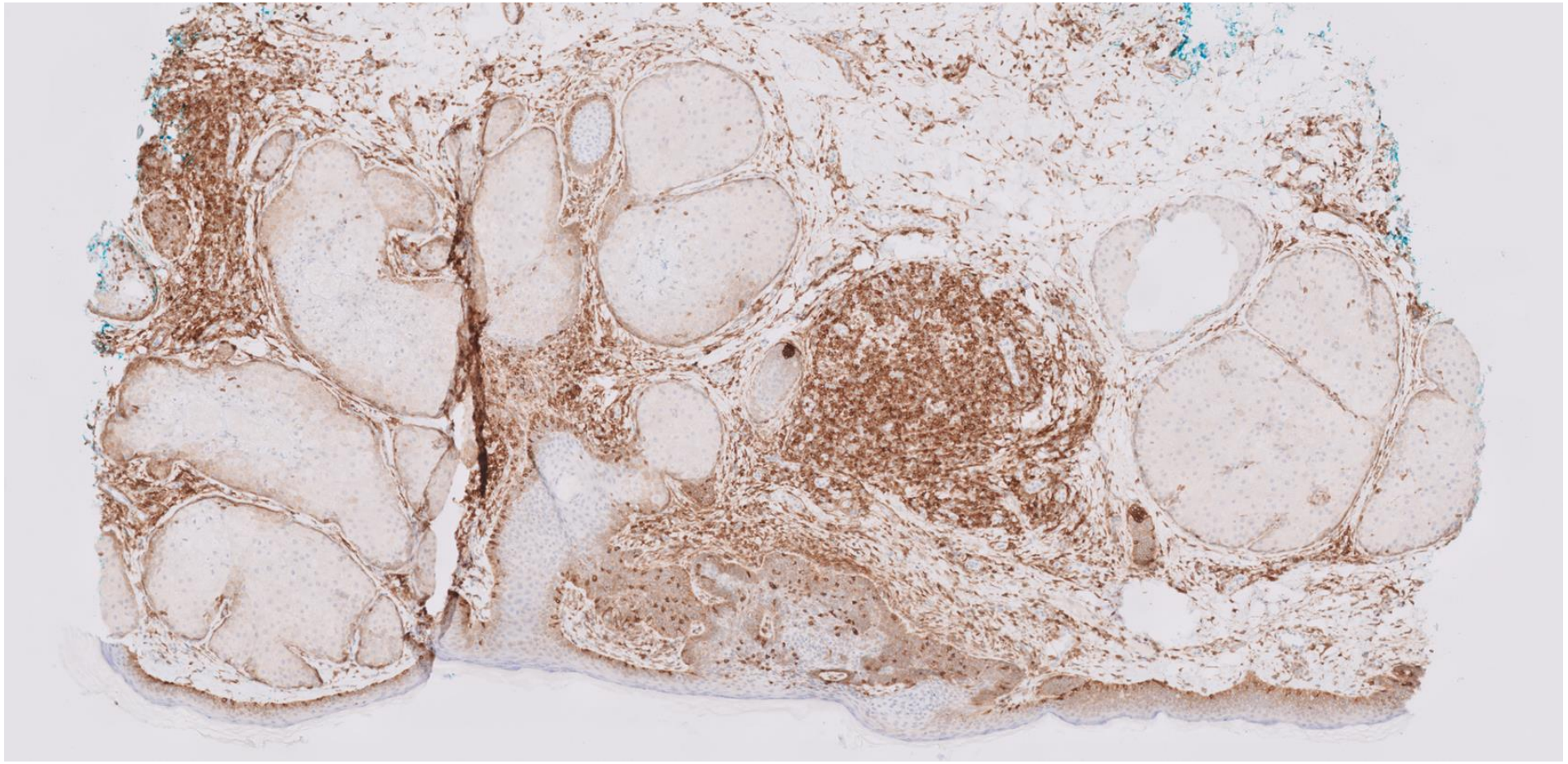
- Positive palisading
- Negative for retraction/mucin/necrosis

# INSM1



- INSM1 highlights Merkel cells, which are present in the basaloid proliferation, suggesting it’s benign

# BCL2



- BCL2 should highlight everything in BCC, but only highlights the rim adnexal structures
- This basaloid proliferation has a rim-like staining pattern

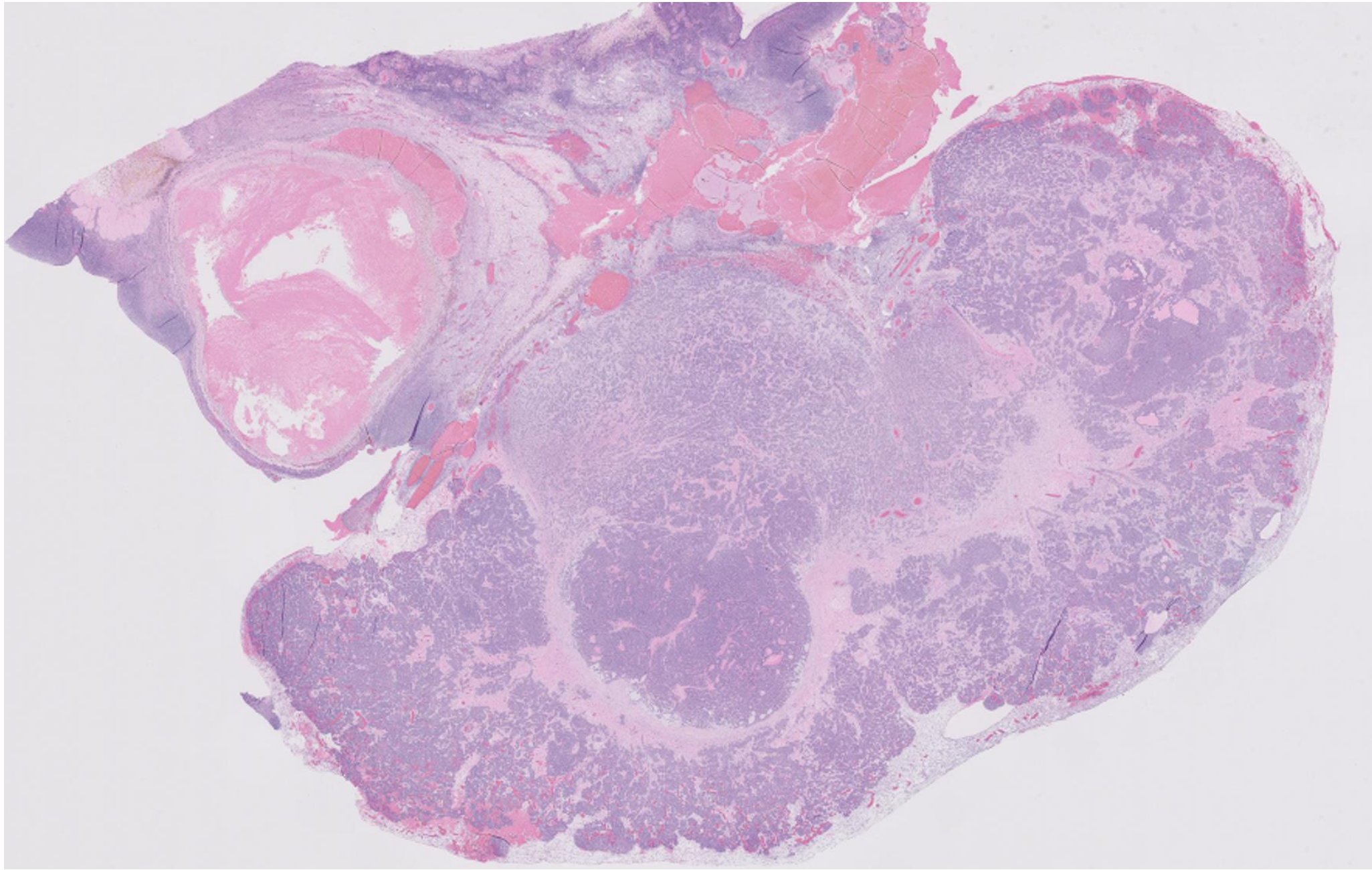
# Benign basaloid neoplasm arising from a nevus sebaceous

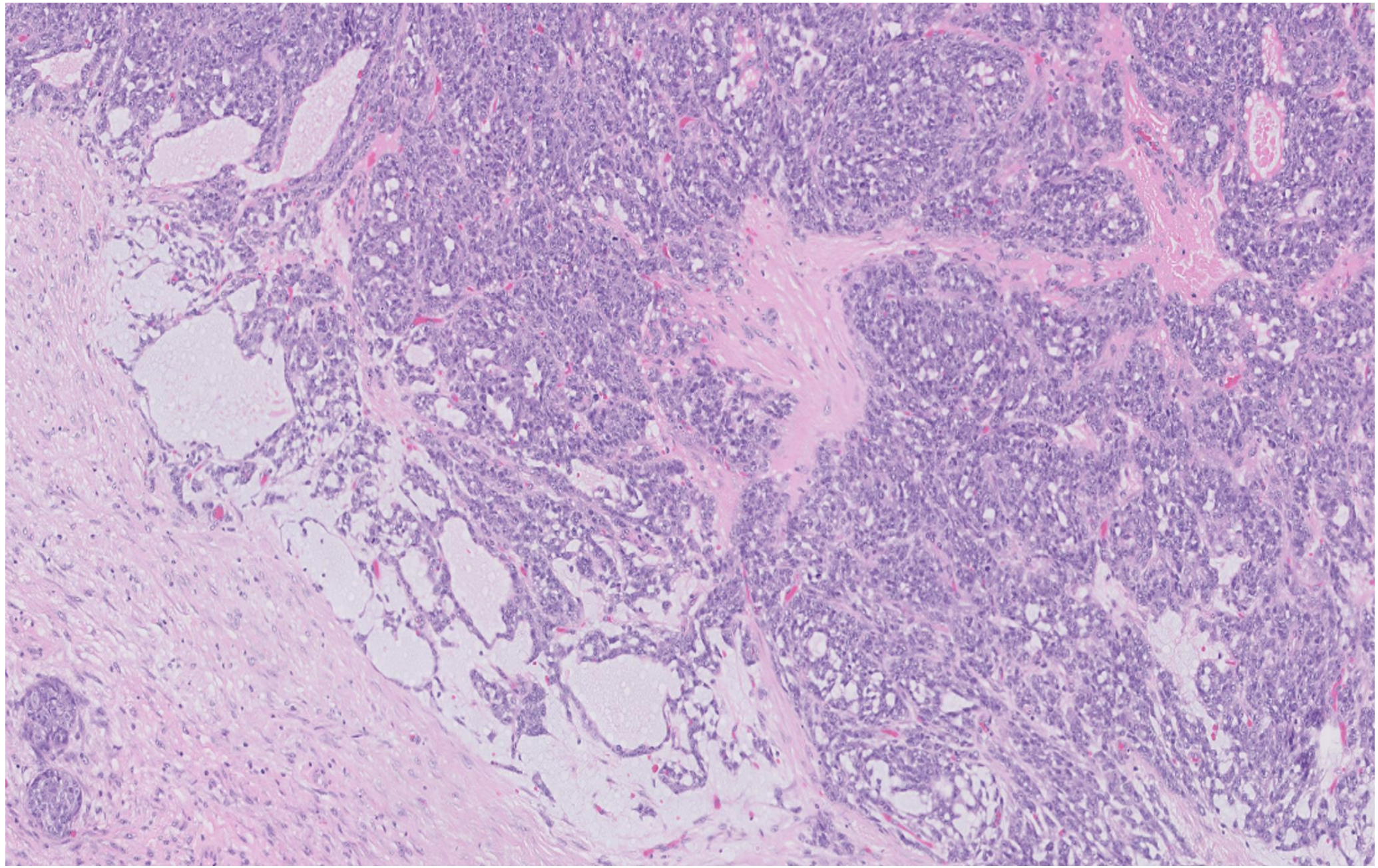
- Important because treatment is different.
- Nevus sebaceous is associating with RAS mutations and opens up possibility of MEC-inhibitors
- BCC treatment is excision

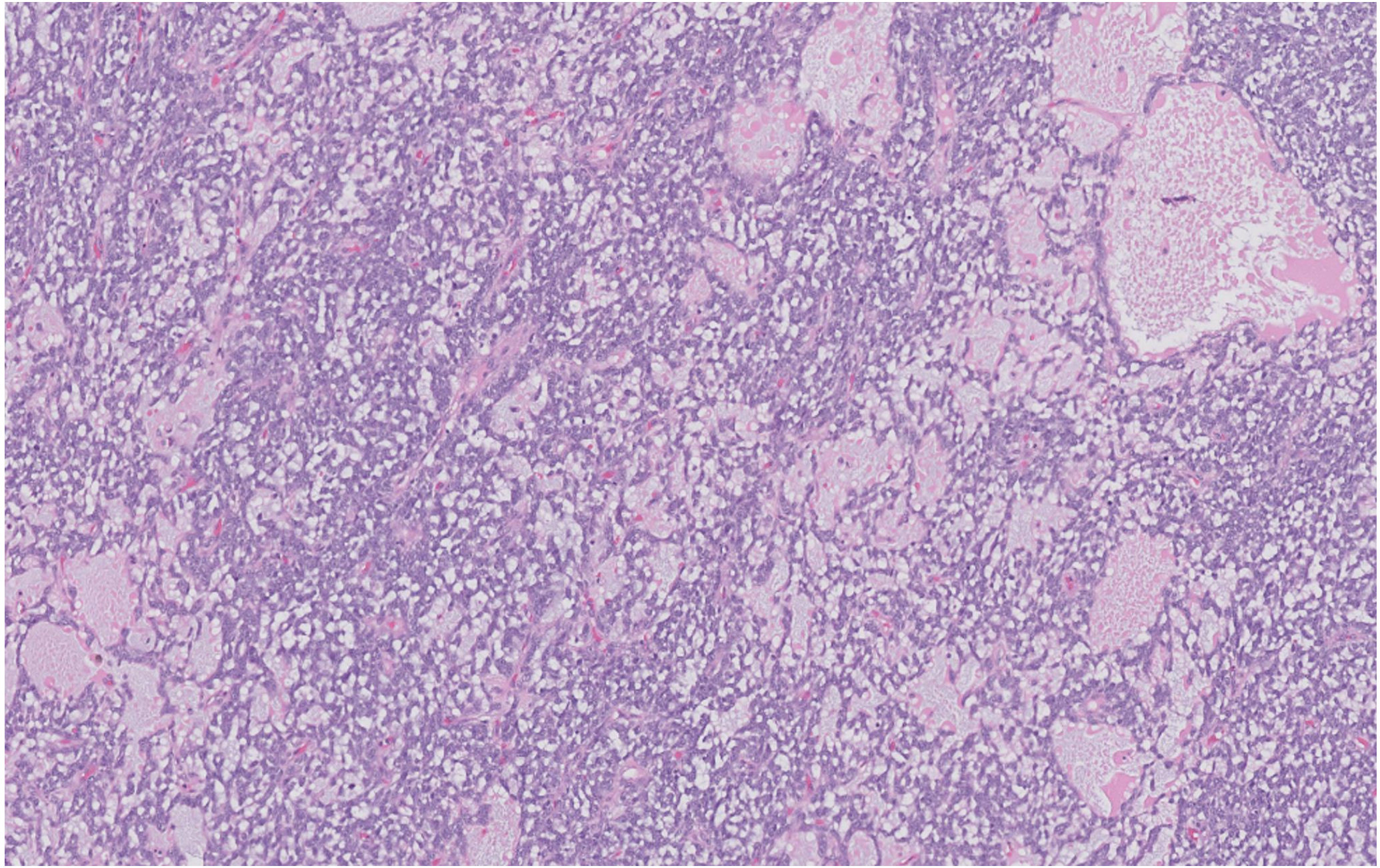
23-0706

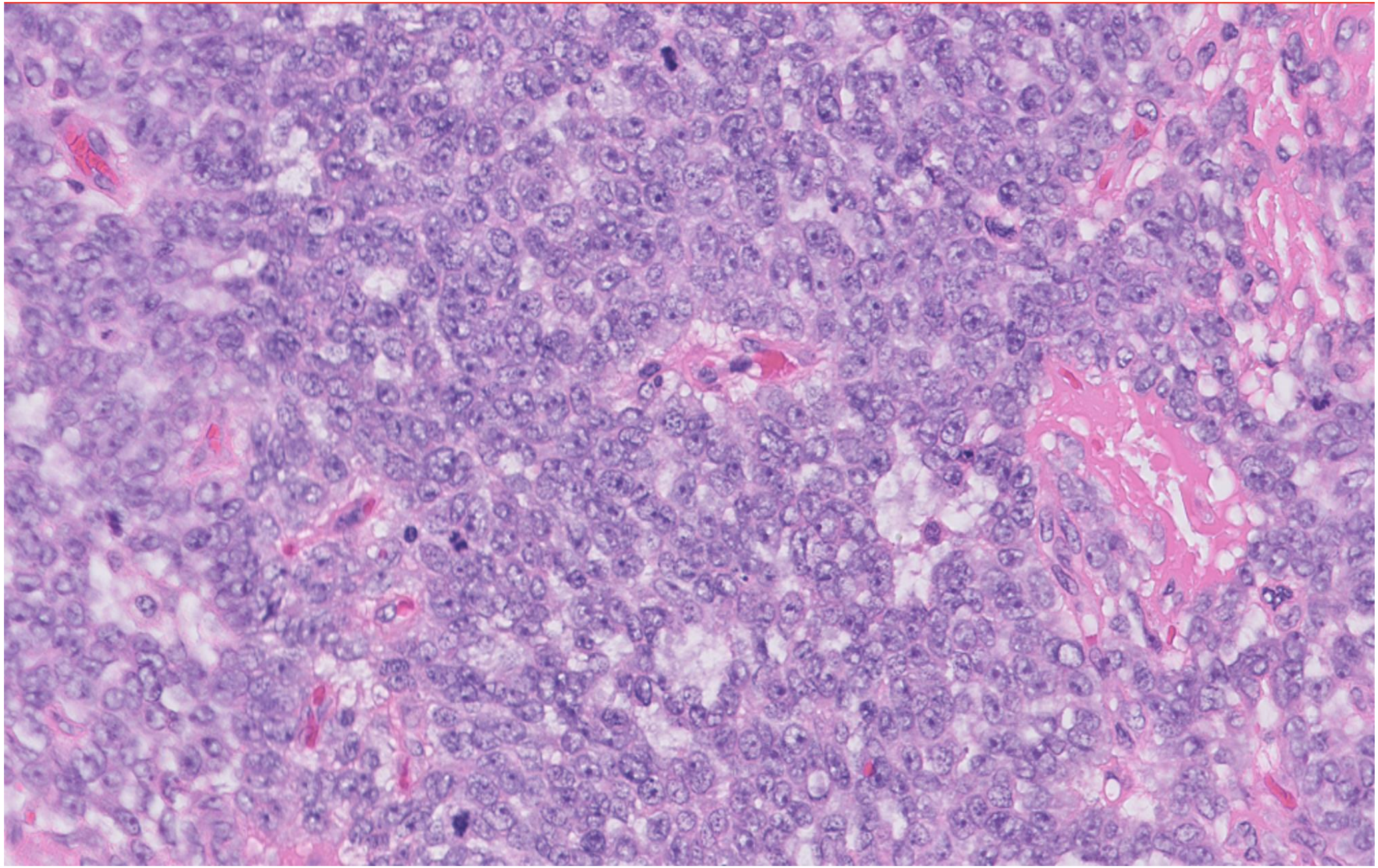
**Ying Liu/Brooke Howitt; Stanford**

40-year-old female with pelvic masses underwent TAHBSO, right hemicolectomy, resection for pelvic masses









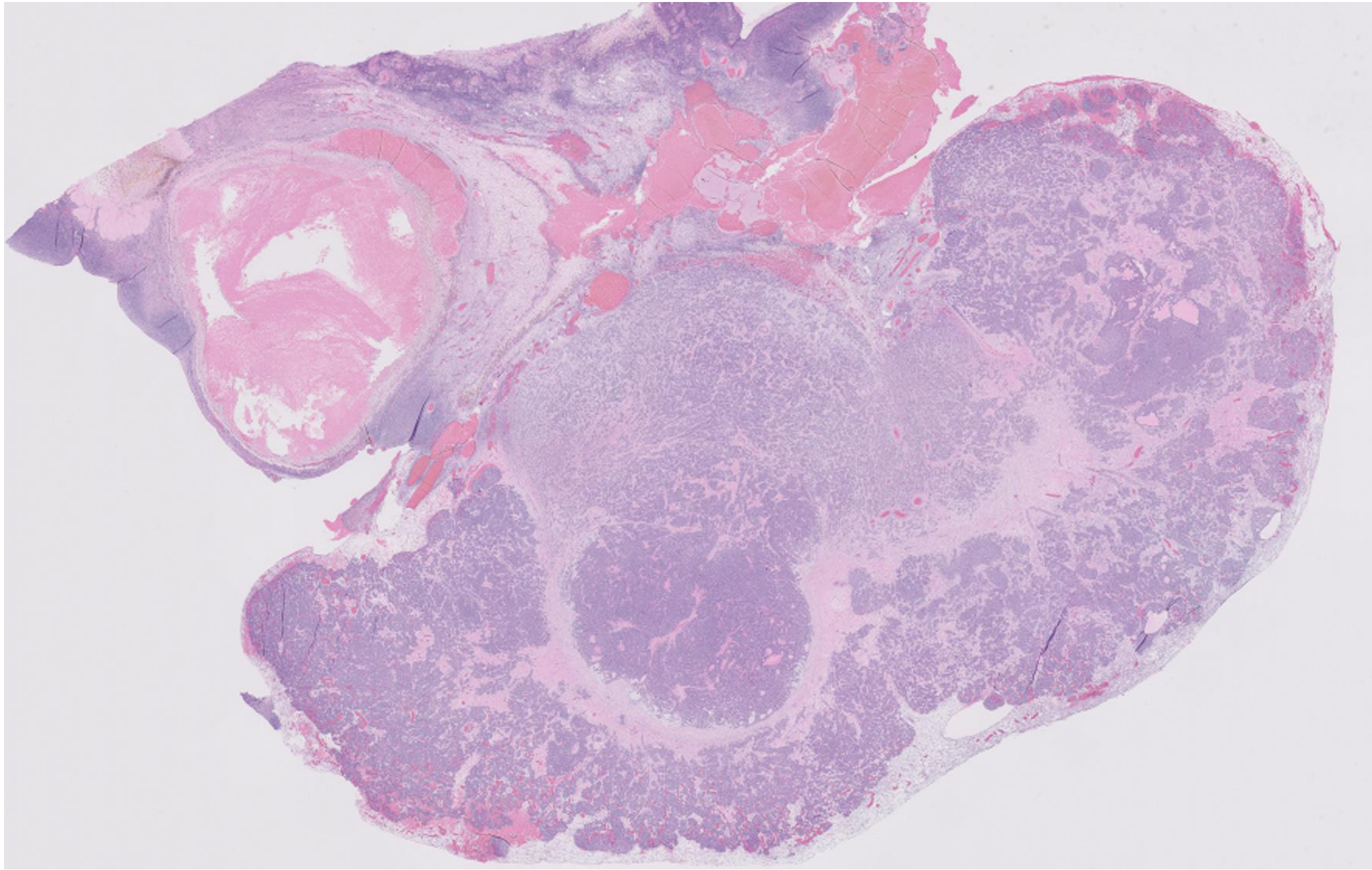
# DIAGNOSIS?

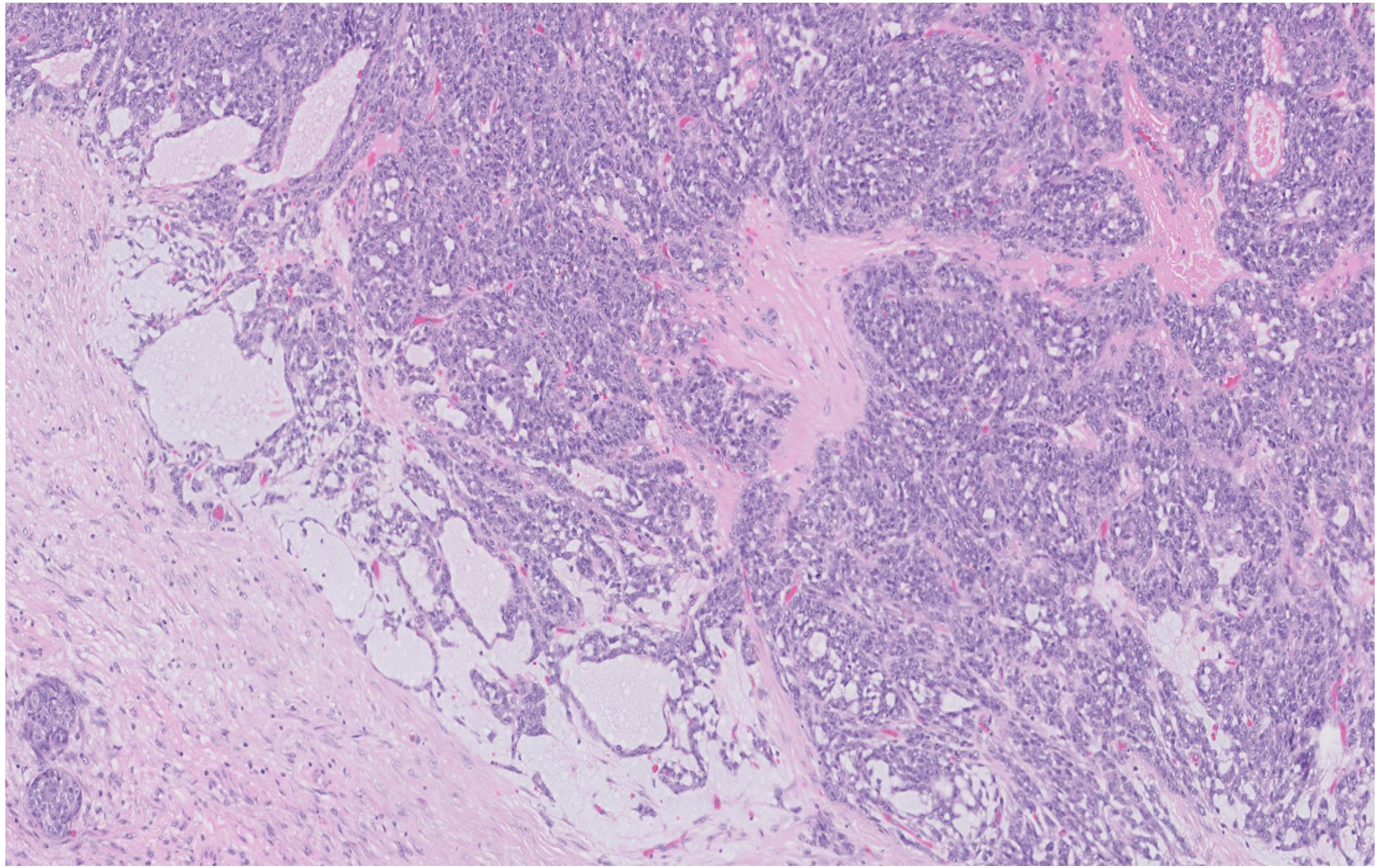
# South Bay 2023 Meeting

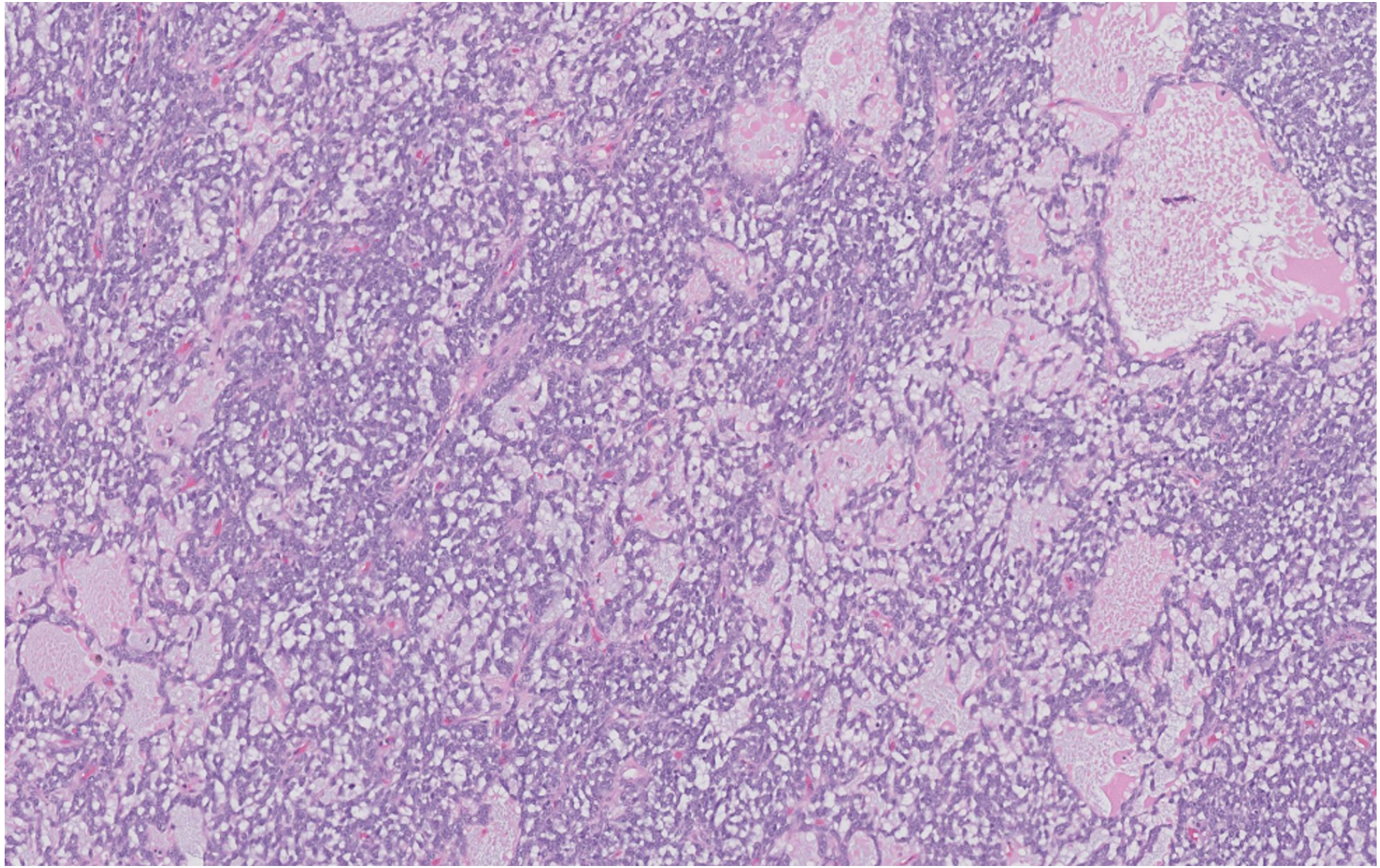
Ying Liu/Brooke Howitt; Stanford

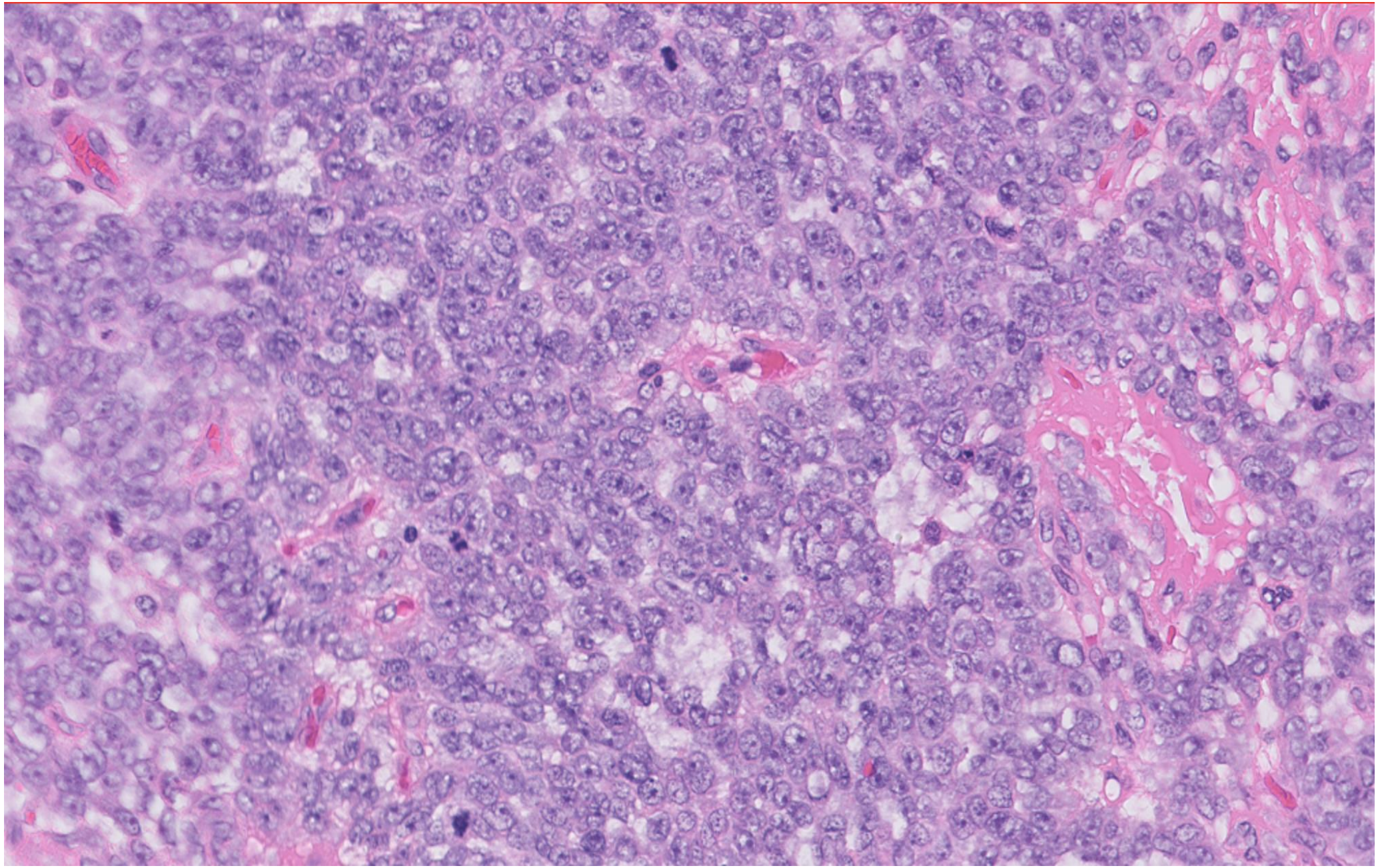
40-year-old female with pelvic masses underwent TAHBSO, right hemicolectomy, resection for pelvic masses

(consult case provided courtesy of Dr. Nathan Shumaker, Mission Health in Asheville, NC)





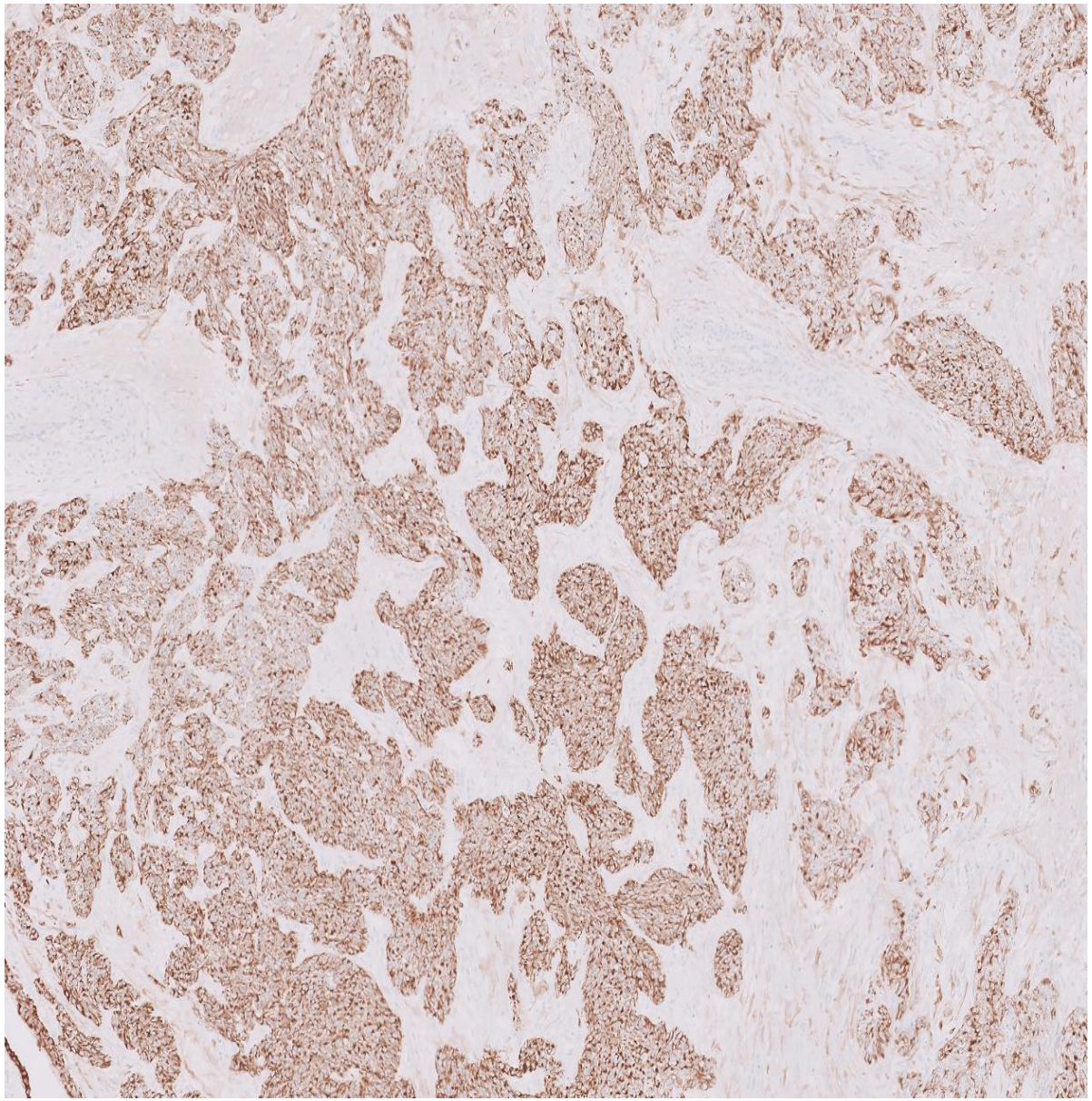




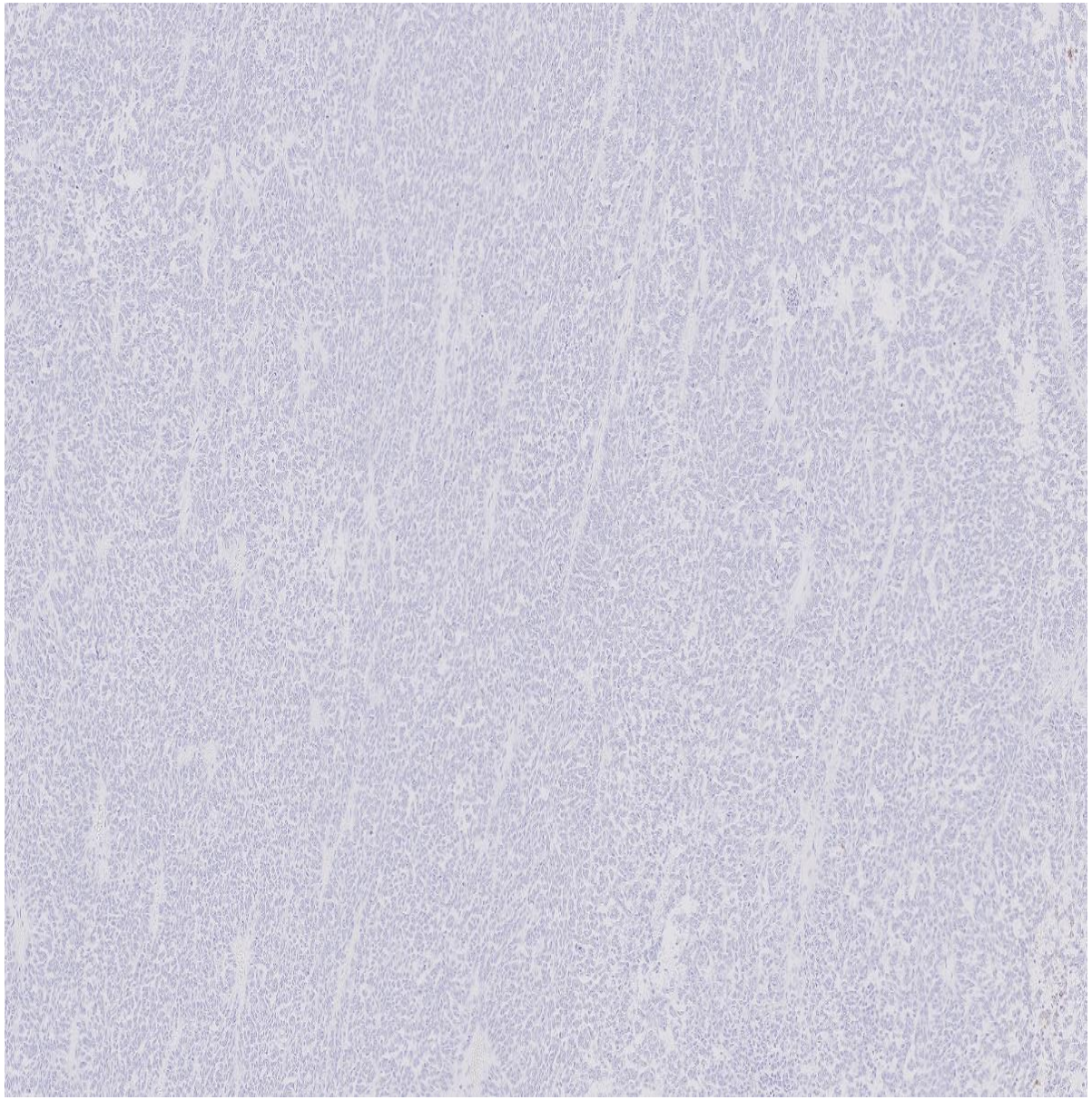
# Differential Diagnosis

- Adult granulosa cell tumor
- Juvenile granulosa cell tumor
- Sertoli-Leydig cell tumor
- Malignant mesothelioma
- Mullerian adenocarcinoma
- Mesonephric-like carcinoma
- ……

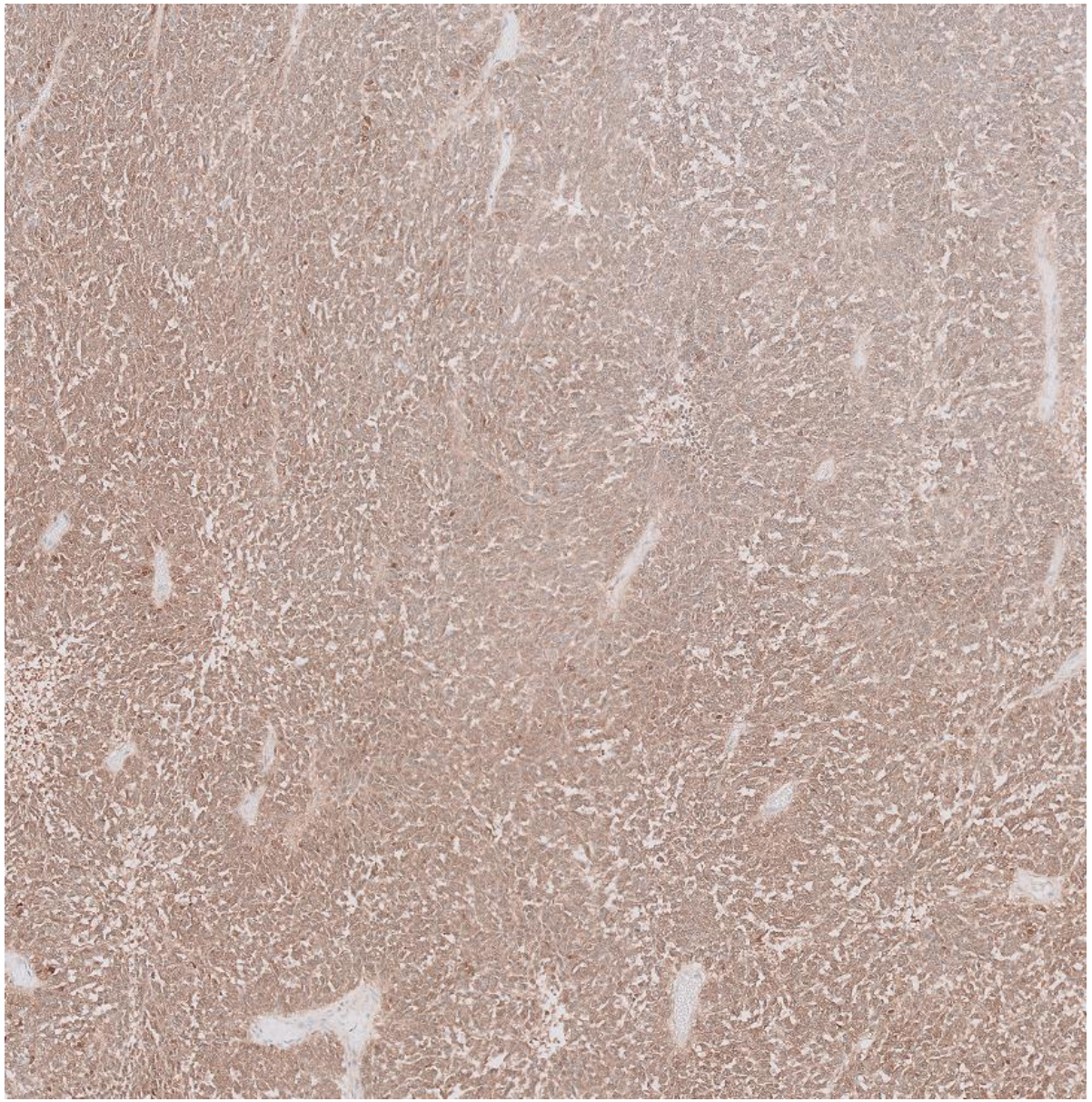
Pankeratin



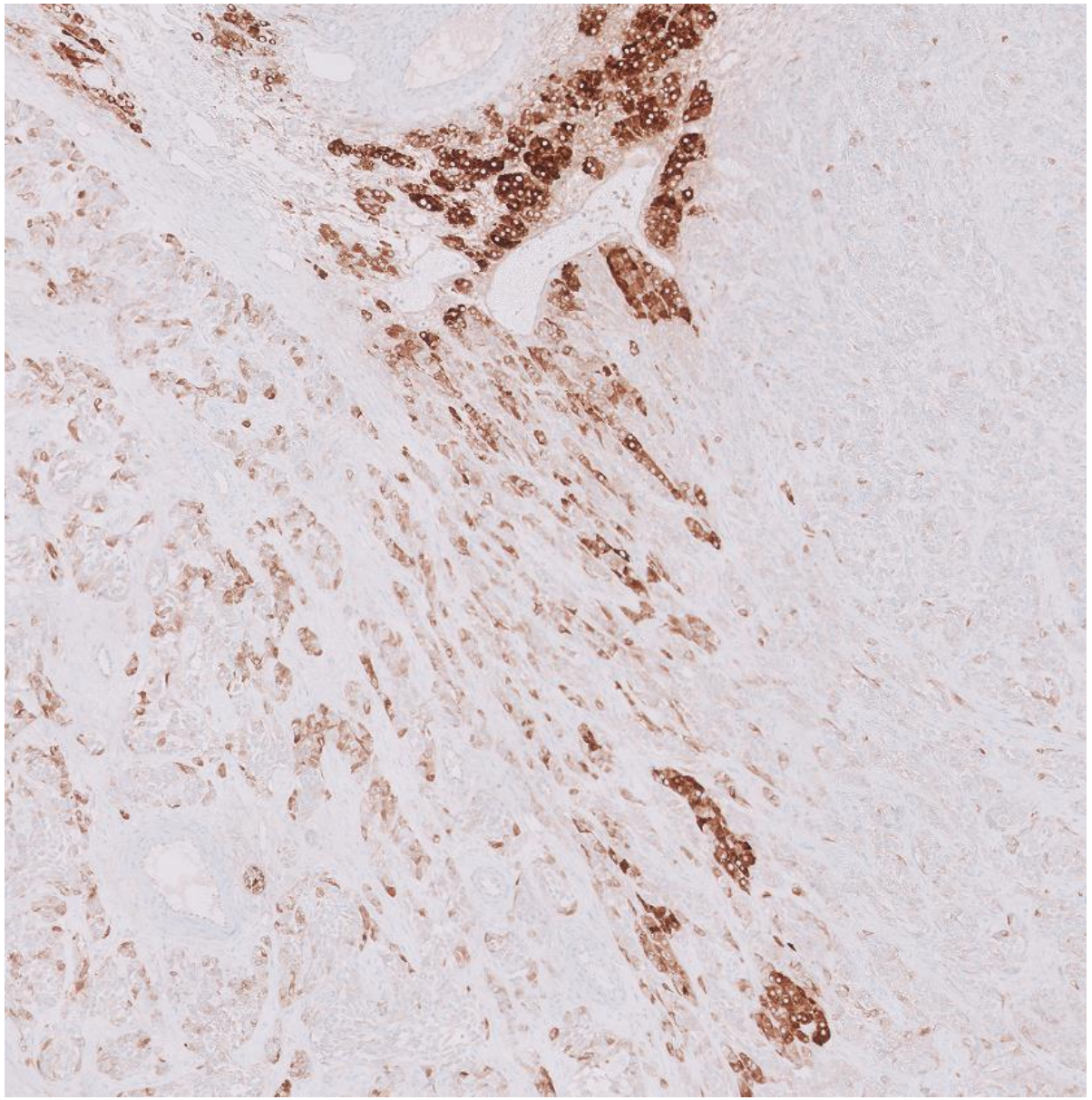
EMA



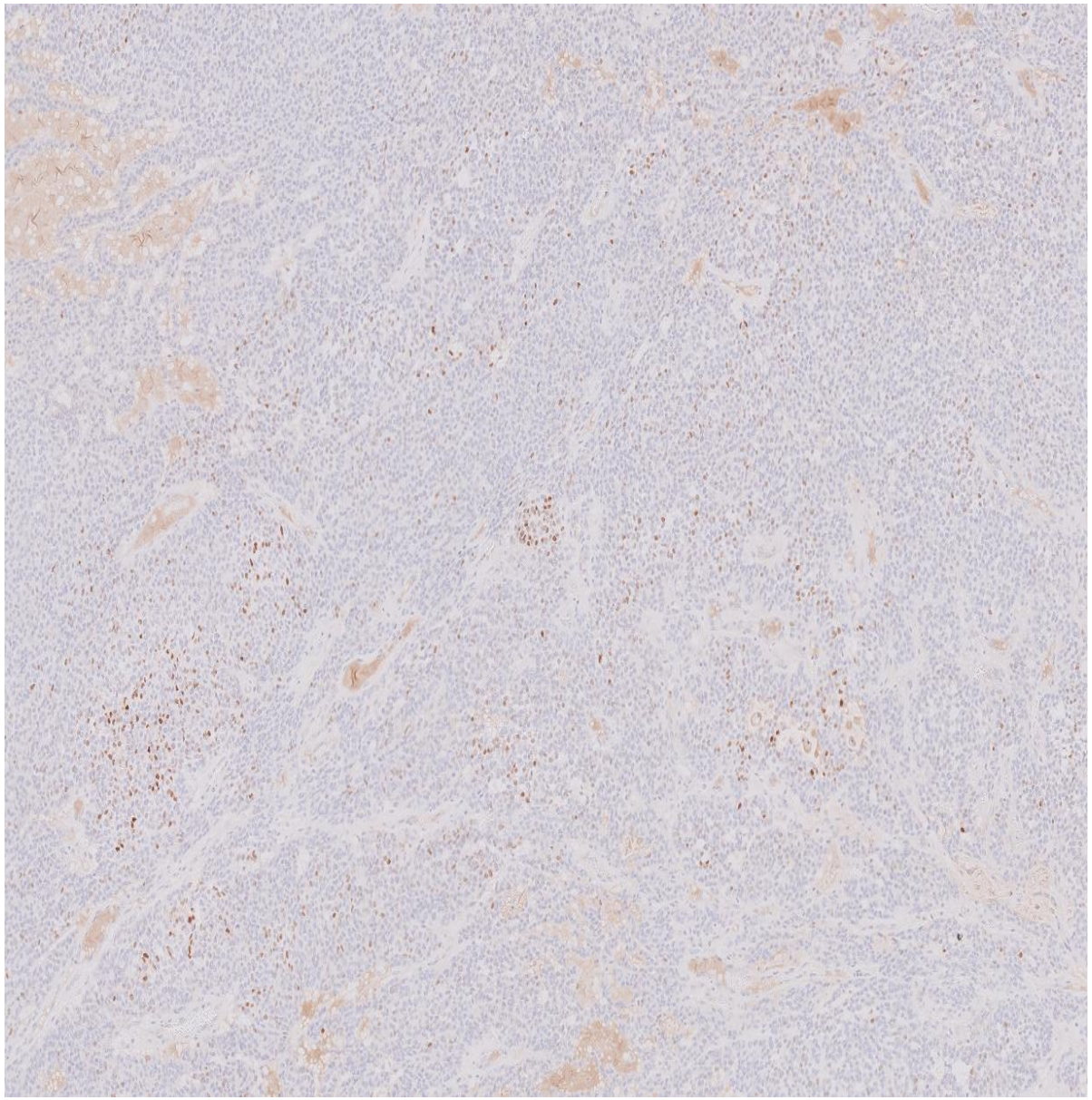
Calretinin



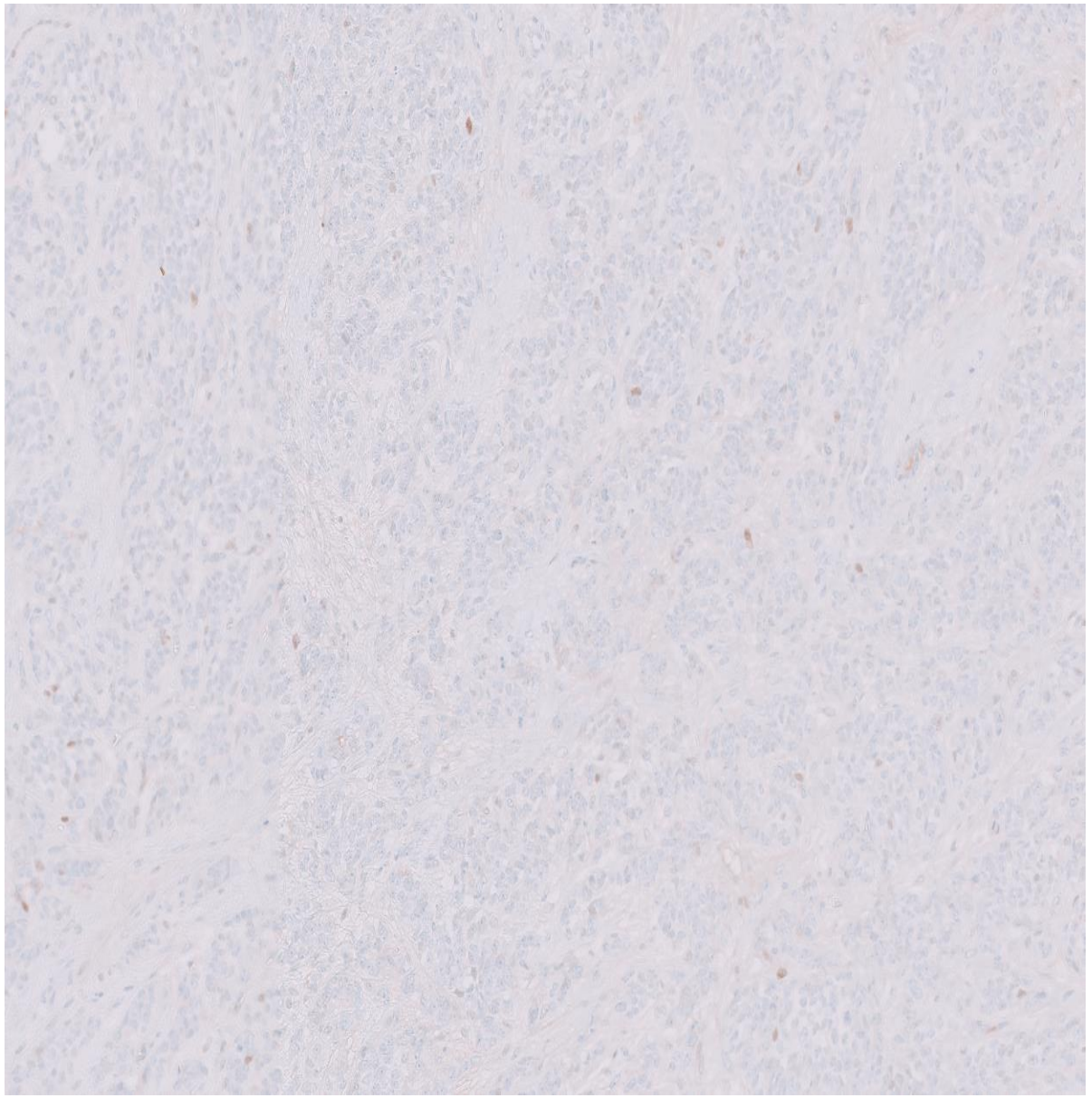
Inhibin



SF1



p53



**Submitted IHC:**

- ER: (2+; 70%)
- PR: (3+; 80%)
- PAX8: negative
- Pankeratin: positive
- CK7: negative
- CK20: negative
- P53: normal/wild-type expression
- CDX2: negative
- Inhibin: partially positive

**IHC performed at Stanford:**

- EMA: negative
- Calretinin: positive
- SF1: partially positive
- CD99: patchy weak positive
- INI: intact expression
- BRG: intact expression

# Differential Diagnosis

- Adult granulosa cell tumor (AGCT)
  - Microfollicular (Call-Exner), insular, trabecular growths
  - Scant cytoplasm, Nuclear grooves
  - FOXL2 mutation
  - ➢ AGCT with brisky mitotic activity?
  - ➢ AGCT with high grade transformation?
- Juvenile granulosa cell tumor
  - Solid areas may show multinodular growth
  - Polygonal cells with ample eosinophilic to clear cytoplasm and round, hyperchromatic nuclei, brisk mitotic activity
  - No associated FOXL2 mutation
- Sertoli-Leydig cell tumor
  - Tubules (in well differentiated tumors), cords (intermediate differentiation), sarcomatoid growth (poorly differentiated) or retiform architecture
  - Follicle-like spaces occasionally seen admixed with typical sertoliform differentiation
  - 3 molecular subtypes: DICER1 mutant; FOXL2 c.402C>G (p.Cys134Trp) mutant; DICER1 / FOXL2 wildtype

# Differential Diagnosis

- Malignant mesothelioma
  - *Papillary growth*
  - *Psammomatous calcifications, ascites common and often multifocal distribution*
  - *IHC: D2-40, WT1, calretinin positive and BAP1 loss (~ 50%); claudin-4 negative*
- Mullerian adenocarcinoma
  - *Well-formed glandular structures*
  - *Endometriosis*
  - *IHC: CK7 and EMA (diffuse) and PAX8 positive*
  - *Mutations characteristic of endometrioid carcinomas (i.e. ARID1A, PTEN, PIK3CA, KRAS, CTNNB1)*
- Mesonephric-like carcinoma
  - *IHC: GATA-3 and TTF-1 positive, ER negative*

*International Journal of Gynecological Pathology*
**36**:240–252, Lippincott Williams & Wilkins, Baltimore
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Original Article

# Granulosa Cell Tumors: Novel Predictors of Recurrence in Early-stage Patients

Sharif Sakr, M.D., Eman Abdulfatah, M.D., Sumi Thomas, M.D., Zaid Al-wahab, M.D., Rafic Beydoun, M.D., Robert Morris, M.D., Rouba Ali-Fehmi, M.D., and Sudeshna Bandyopadhyay, M.D.

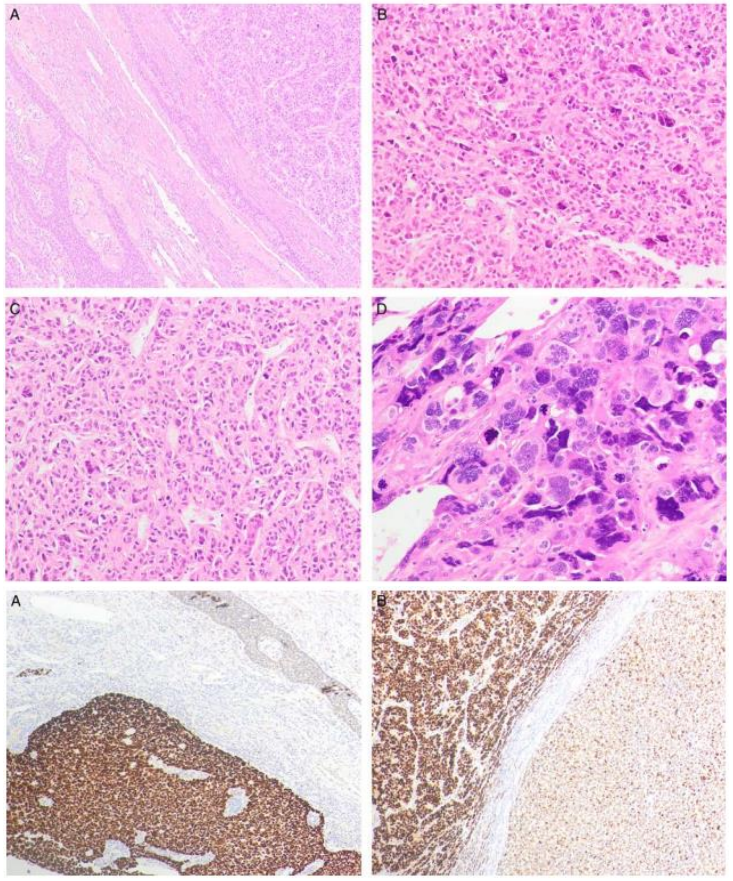
**TABLE 2.** *Correlation of histomorphologic features and tumor characteristics of primary GCT with recurrence*

| Parameter | Variable | n (%) Nonrecurrent (n = 113)* | n (%) Recurrent (n = 12) | *P* |
|---|---|---|---|---|
| Tumor type | Adult | 103 (91.2) | 10 (83.3) | 0.32 |
| | Juvenile | 10 (8.8) | 2 (16.7) | |
| Tumor subtype | Solid | 39 (61.9) | 5 (50.0) | 0.55 |
| | Cystic | 9 (14.3) | 1 (10.0) | |
| | Solid cystic | 15 (23.8) | 4 (40.0) | |
| Tumor size | <10 cm | 43 (47.8) | 6 (60.0) | 0.52 |
| | ≥10 cm | 47 (52.2) | 4 (40.0) | |
| Capsule rupture | Yes | 13 (28.3) | 2 (50.0) | 0.57 |
| | No | 33 (71.7) | 2 (50.0) | |
| Histopathologic type | Diffuse | 45 (61.6) | 7 (70.0) | 0.98 |
| | Nondiffuse types | 28 (38.4) | 3 (30.0) | |
| Mitotic rate | <4/10 HPF | 56 (70.0) | 4 (33.3) | **0.021** |
| | ≥4/10 HPF | 24 (30.0) | 8 (66.7) | |
| Nuclear pleomorphism | Mild | 42 (63.6) | 2 (20.0) | **0.016** |
| | Moderate | 19 (28.8) | 5 (50.0) | |
| | Severe | 5 (7.6) | 3 (30.0) | |

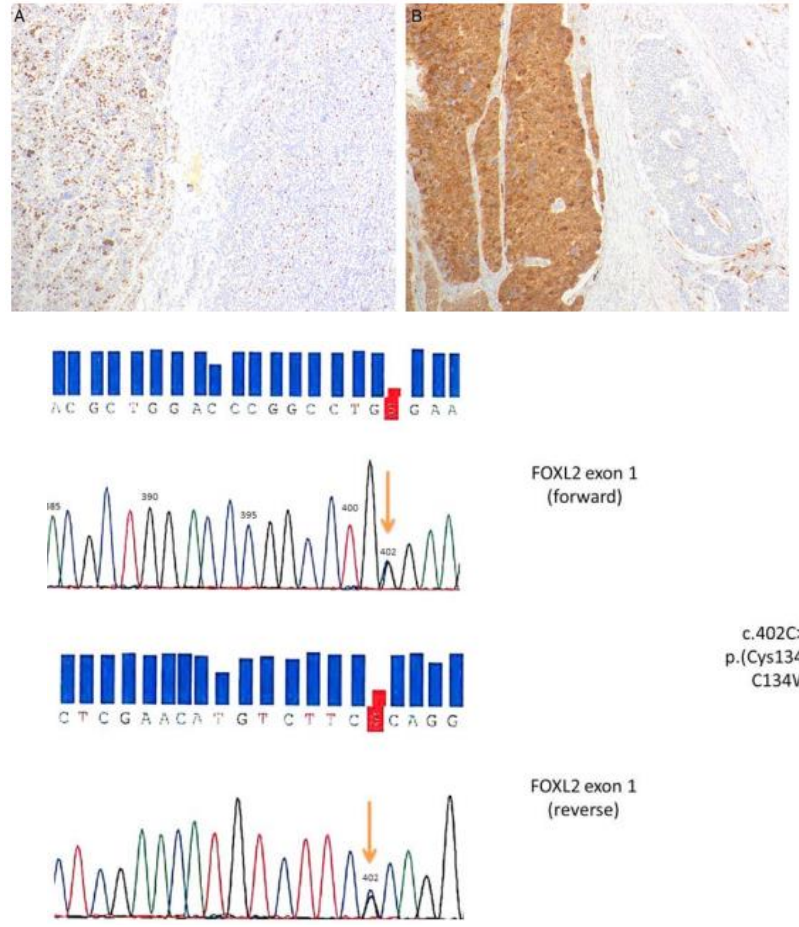
# Adult Granulosa Cell Tumor With High-grade Transformation

## *Report of a Series With FOXL2 Mutation Analysis*

*Yinka Fashedemi, FRCPath,* Michael Coutts, FRCPath,† Olga Wise, FRCPath,‡ Benjamin Bonhomme, PhD,§ Gavin Baker, MSc,‖ Paul J. Kelly, FRCPath,‖ Isabelle Soubeyran, PhD,§ Mark A. Catherwood, PhD,¶ Sabrina Croce, MD,§ and W. Glenn McCluggage, FRCPath‖*




- Distinct low-grade morphology admixed with areas of high-grade morphology
- Striking difference between the p53 staining in the low-grade and high-grade components
- FOXL2 mutation analysis of both the morphologically low-grade and high-grade areas



- Adult granulosa cell tumor?

- *FOXL2* mutational analysis has been sent to Mayo Medical Laboratories……

**NEGATIVE FOR *FOXL2* GENE MUTATION IN TARGETED REGION**

# Differential Diagnosis

- Adult granulosa cell tumor
- Juvenile granulosa cell tumor
- Sertoli-Leydig cell tumor
- Malignant mesothelioma
- Mullerian adenocarcinoma
- Mesonephric-like carcinoma
- ……
- Female Adnexal Tumor of Probable Wolffian Origin (FATWO)
- *STK11* Adnexal Tumor

# Female Adnexal Tumor of Probable Wolffian Origin (FATWO)

- Originate from mesonephric duct (wolffian) remnants and arising most commonly in broad ligament
- Location: paratubal, broad ligament > ovary > retroperitoneum
- Wide age range (median: 50 years)
- Admixture of morphologic patterns: Solid, closely packed tubules, sieve-like ± eosinophilic secretions
- **Myxoid matrix is not typical of FATWO**
- Small, round to oval, often pale nuclei with delicate chromatin and inconspicuous nucleoli
- IHC: Cytokeratin and EMA (20%) positive; Calretinin > inhibin (typically patchy and weak) > WT1 positive; PAX8, PAX2, GATA3, and TTF1 typically negative
- No recurrent molecular alterations

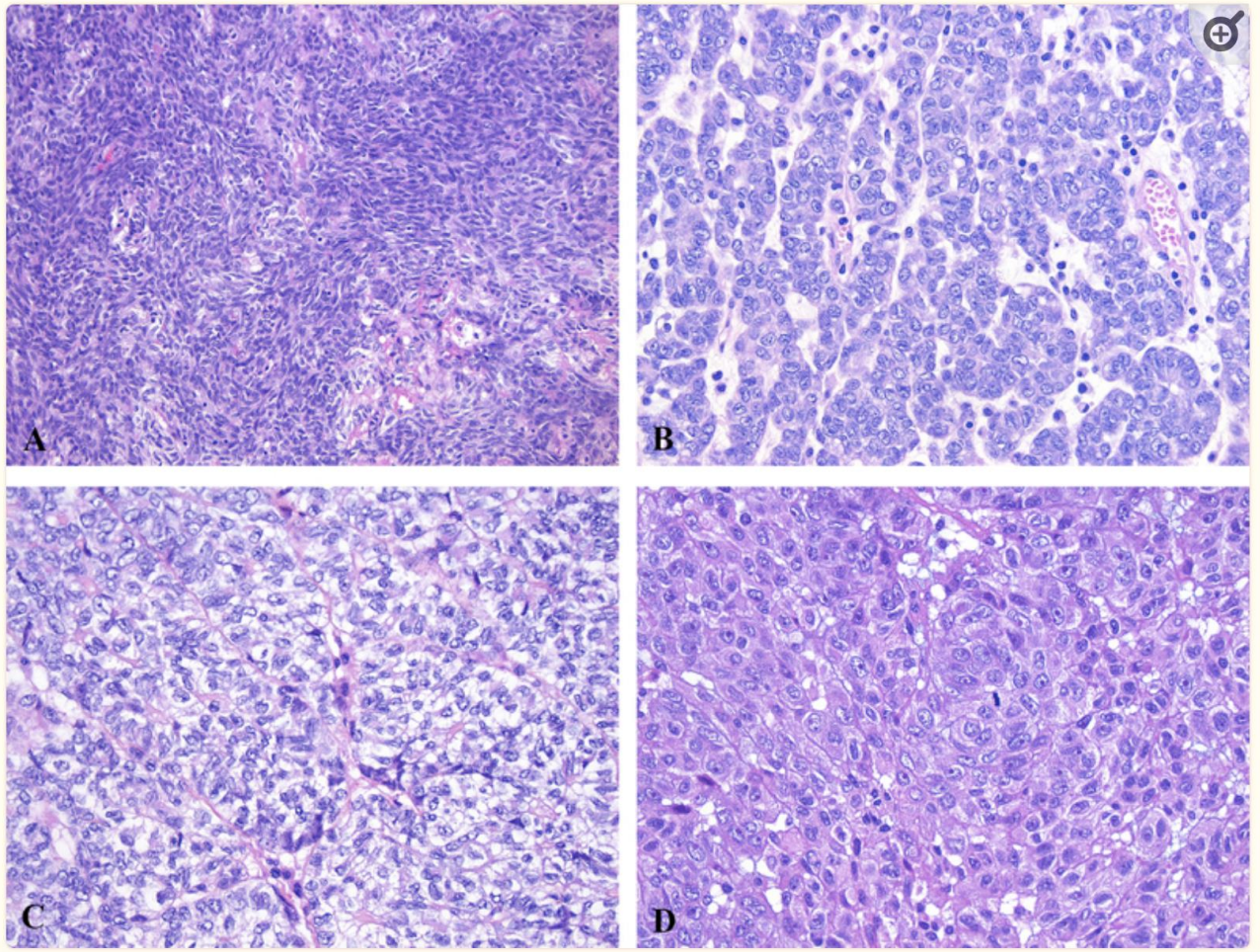
# *STK11* Adnexal Tumor

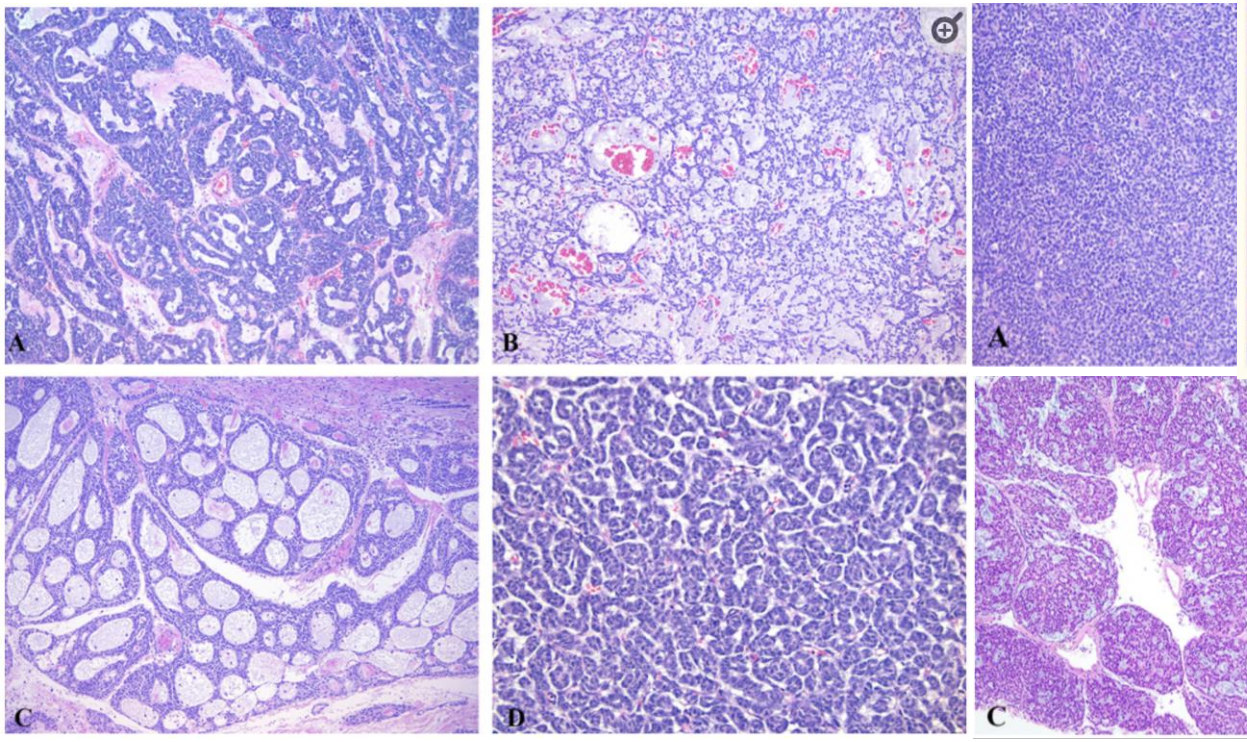
- Paratubal/adnexal location
- Diverse morphological features: Interanastomosing cords and trabeculae but also tubular, cribriform, microacinar nested patterns set in myxoedematous stroma vaguely reminiscent of salivary gland tumors
- Cytologic atypia and mitoses
- Metastatic disease at presentation in ~ 50% of patients
- IHC: positive for cytokeratin, most sex cord markers (inhibin, calretinin, WT1), SF1 negative/focally positive
- *FOXL2* is consistently negative
- ***STK11* molecular alterations**
- Association with Peutz-Jeghers Syndrome in ~ 50%
- Exact histogenesis is unknown

*Am J Surg Pathol.* 2021 August 01; 45(8): 1061–1074. doi:10.1097/PAS.0000000000001677.

# A Distinctive Adnexal (Usually Paratubal) Neoplasm Often Associated with Peutz-Jeghers Syndrome and Characterized by *STK11* Alterations (*STK11* Adnexal Tumor): A Report of 22 Cases

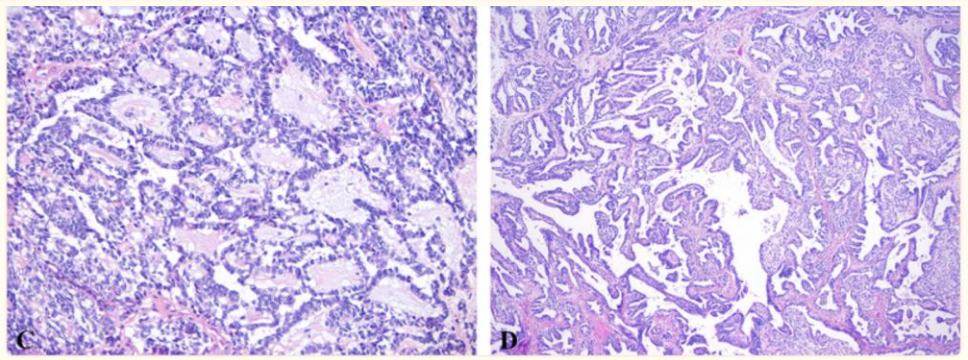
**Jennifer A. Bennett, M.D.[1], Robert H. Young, M.D.[2], Brooke E. Howitt, M.D.[3], Sabrina Croce, M.D.[4], Pankhuri Wanjari, M.S.[1], Chaojie Zhen, B.S.[1], Arnaud Da Cruz Paula, Ph.D[5], Emily Meserve, M.D.[6], J. Kenneth Schoolmeester, M.D.[7], Sofia Westbom-Fremer, M.D.[8], Eduardo Benzi, M.D.[9], Ninad M. Patil, M.D.[9], Loes Kooreman, M.D.[10], Mona El-Bahrawy, M.D.[11], Gian Franco Zannoni, M.D.[12], Thomas Krausz, M.D.[1], W. Glenn McCluggage, FRCPath[13], Britta Weigelt, Ph.D[5], Lauren L. Ritterhouse, M.D., Ph.D[2], Esther Oliva, M.D.[2]**

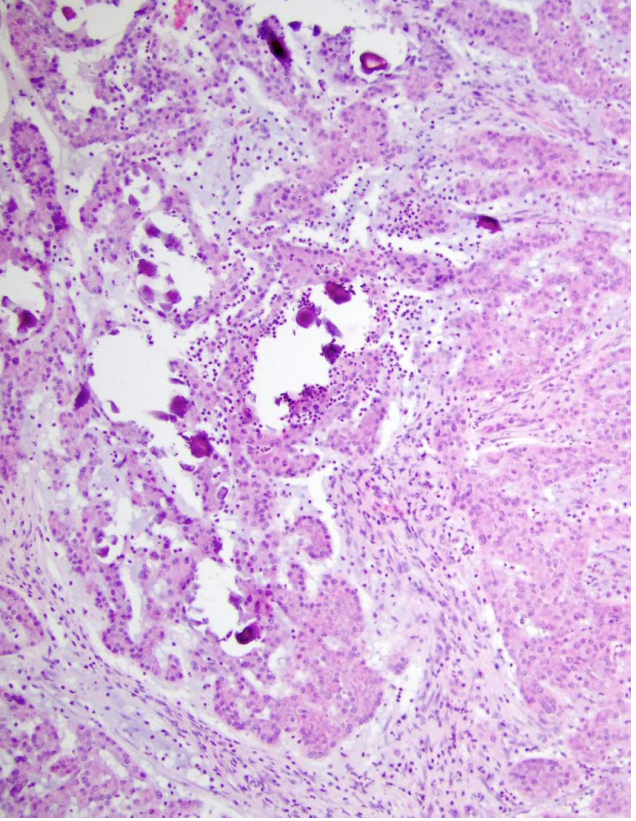


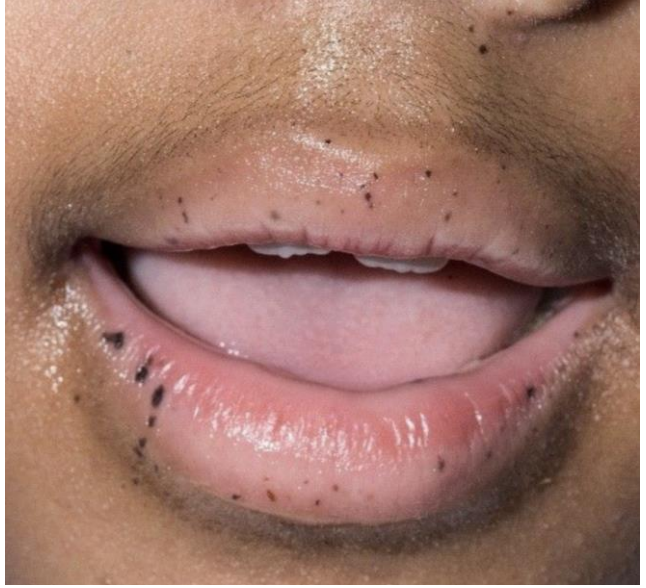



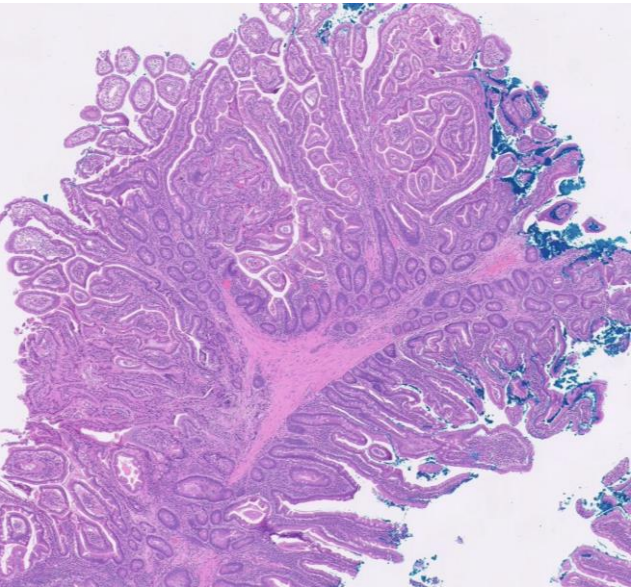


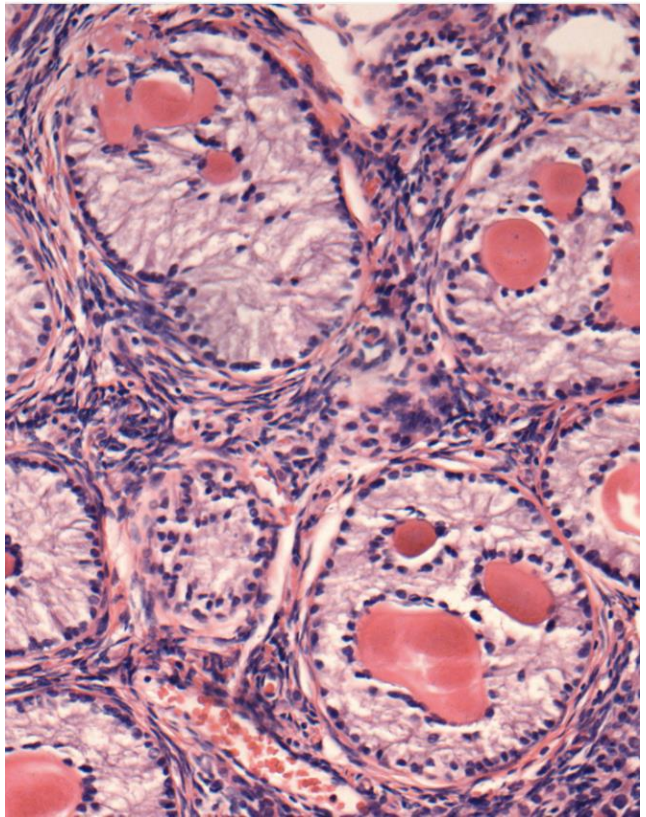












# Peutz-Jeghers Syndrome (PJS)

- Autosomal dominant syndrome, Germline *STK11* mutation
- Presents in 1-3$^{rd}$ decade of life
- GI tract: multiple arborizing hamartomatous polyps
- Mucocutaneous pigmentation (lip most common)
- Distinctive PJ tumors: Sex cord tumor with annular tubules of ovary (SCTAT), Large cell calcifying sertoli tumor of testis, and mucinous tumors
- Cervix: gastric-type adenocarcinoma
- Fallopian tube mucinous metaplasia


- https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/melanocytic-macules-associated-with-peutz-jeghers-syndrome
- https://www.pathologyoutlines.com/topic/smallbowelpeutzjeghers.html
- https://www.pathologyoutlines.com/topic/testissertolilargecell.html
- WHO Classification of Tumours of Female Reproductive Organs, 5th Edition

# Mutational Profiling STAMP

OVARY AND FALLOPIAN TUBE, LEFT, SALPINGO-OOPHORECTOMY, MUTATIONAL PROFILING BY STAMP (A)

OVARY

-- **POSITIVE FOR *STK11* D53fx**

-- POSITIVE FOR *LZTR1* Q10fs

-- POSITIVE FOR *ATM* c.2921+1G>C

-- POSITIVE FOR *NTRK2* A203T

-- ESTIMATED TUMOR MUTATION BURDEN (TMB): 1.1
MUTATIONS PER MEGABASE

OVARY AND FALLOPIAN TUBE, LEFT, SALPINGO-OOPHORECTOMY (A)

- STK11 Adnexal Tumor (See note)

Note: Although diagnostic considerations include malignant female adnexal tumor of probable Wolffian origin (FATWO), the newly described entity "STK11 Adnexal Tumor" and adult granulosa cell tumor. While there are morphologic and immunophenotypic overlap between FATWO and adult granulosa cell tumor, based on lack of *FOXL2* mutation and positive for *STK11* mutation, "STK11 Adnexal Tumor" is favored. STK11 mutation has been reported in a subset of FATWO and therefore it is not clear if FATWO and "STK11 Adnexal Tumor" are two distinct tumors or if "STK11 Adnexal Tumor" is a subgroup of FATWO that is associated with Peutz-Jeghers syndrome (See ref.1). Given the frequent association with Peutz-Jeghers syndrome, clinical correlation and genetic counseling is suggested.

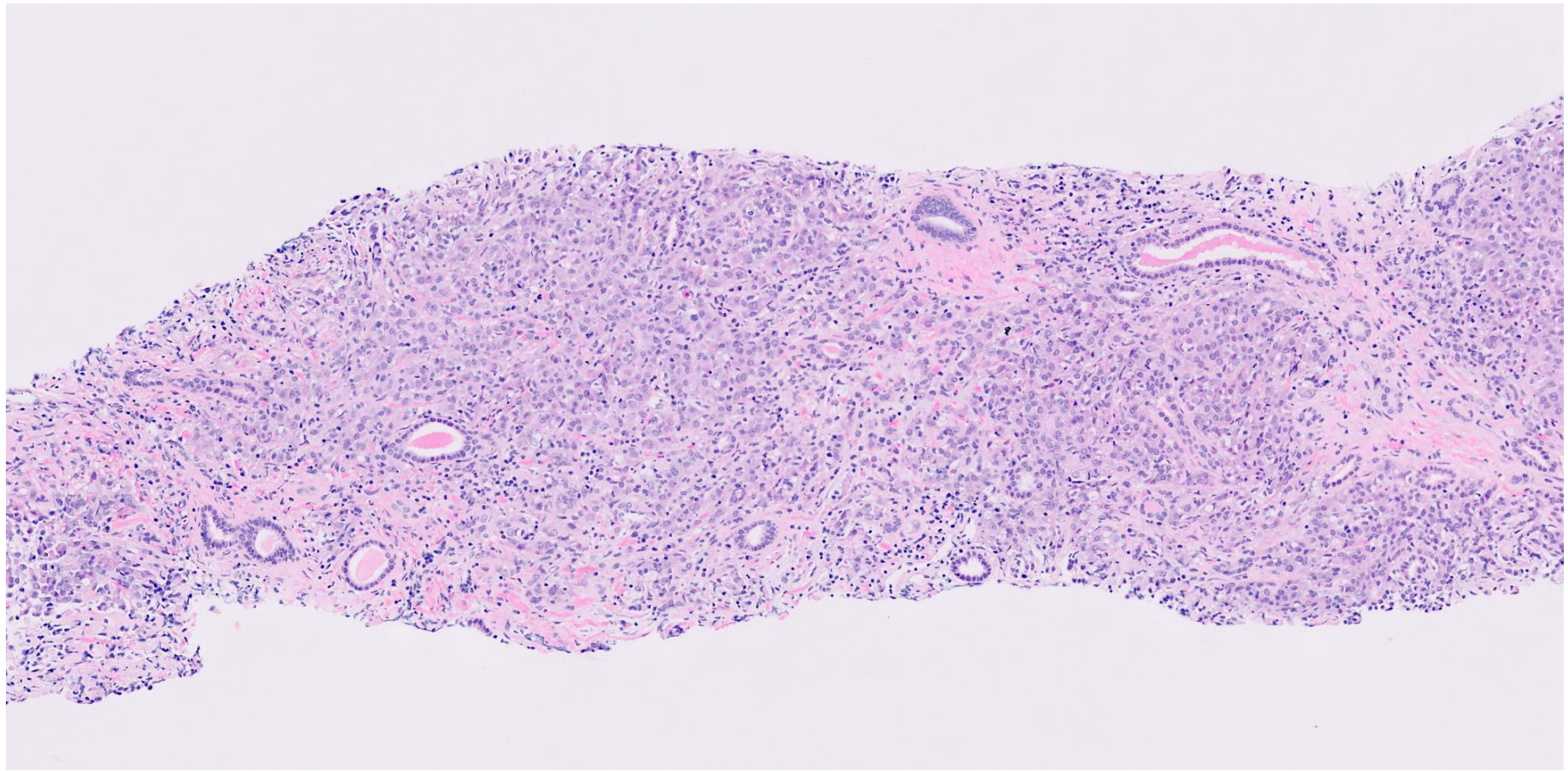
# Take Home Points

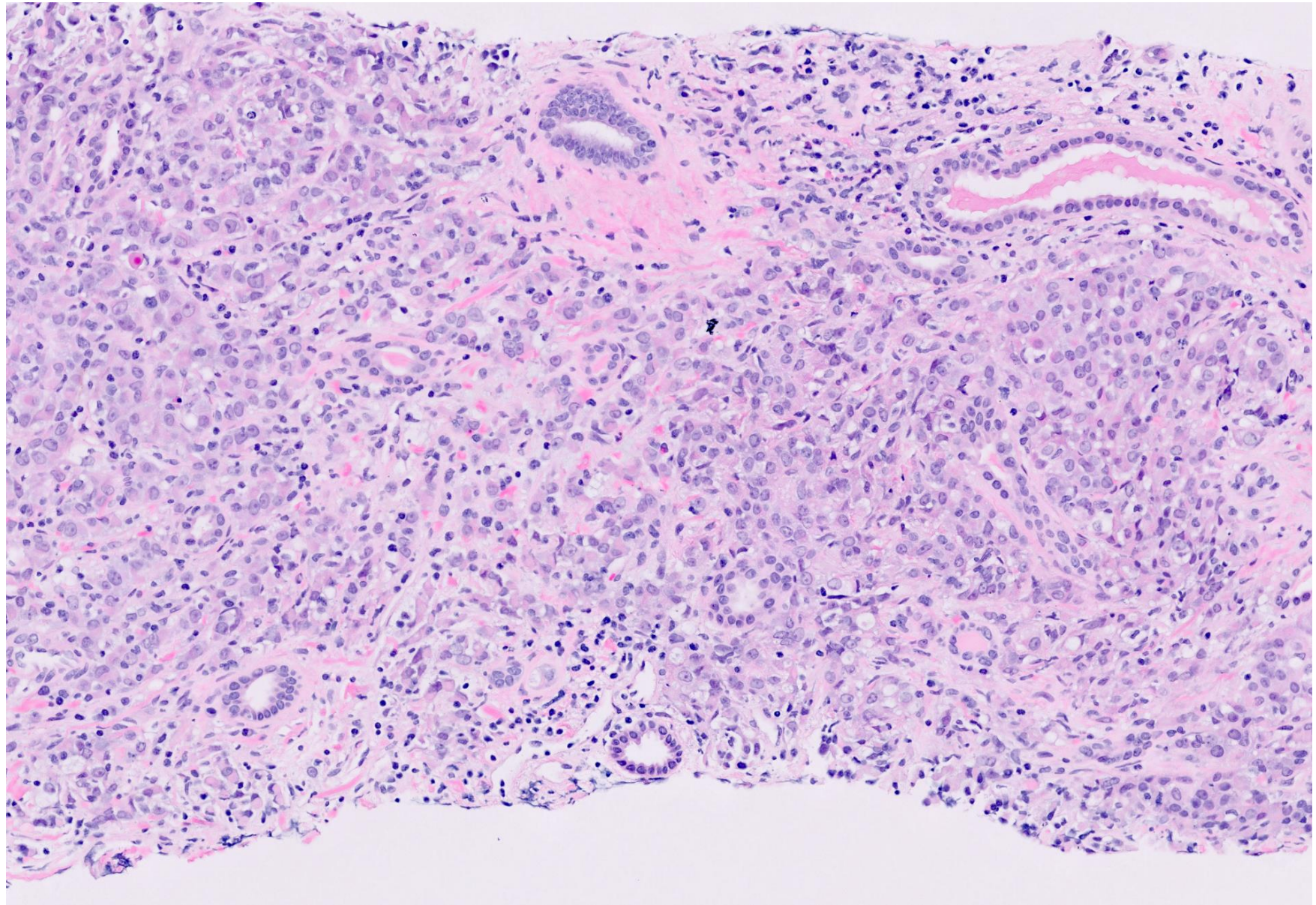
- *STK11* adnexal tumor shows a diverse histologic spectrum, which mimic a variety of tumors
- The presence of aggregate morphological features enriched by the striking myxoid matrix imparts a distinct appearance of *STK11* adnexal tumor
- ~50% *STK11* Adnexal tumor associated with PJS
- Recurrent *STK11* alteration in tumors from both PJS and non-PJS patients

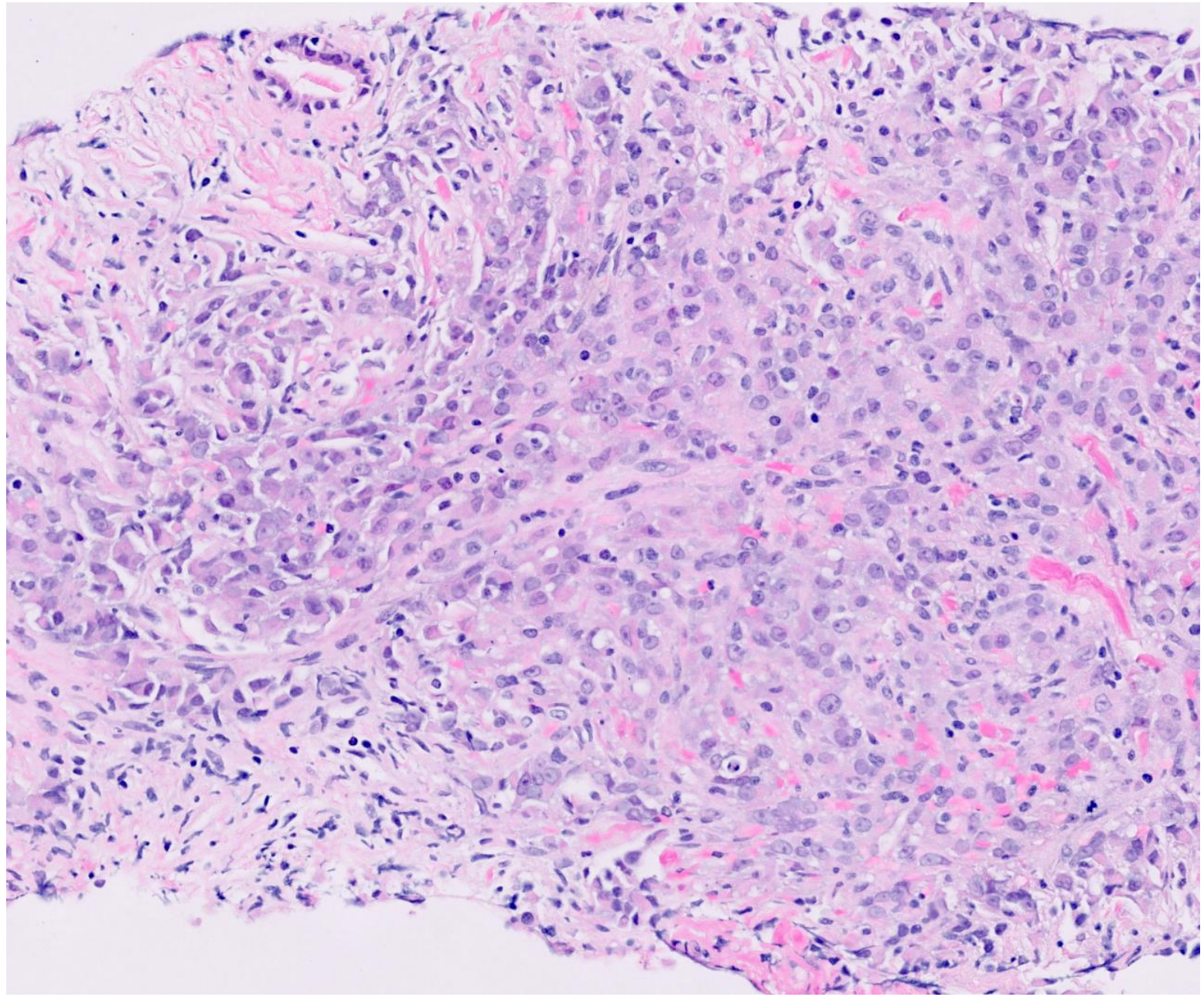
# 23-0707

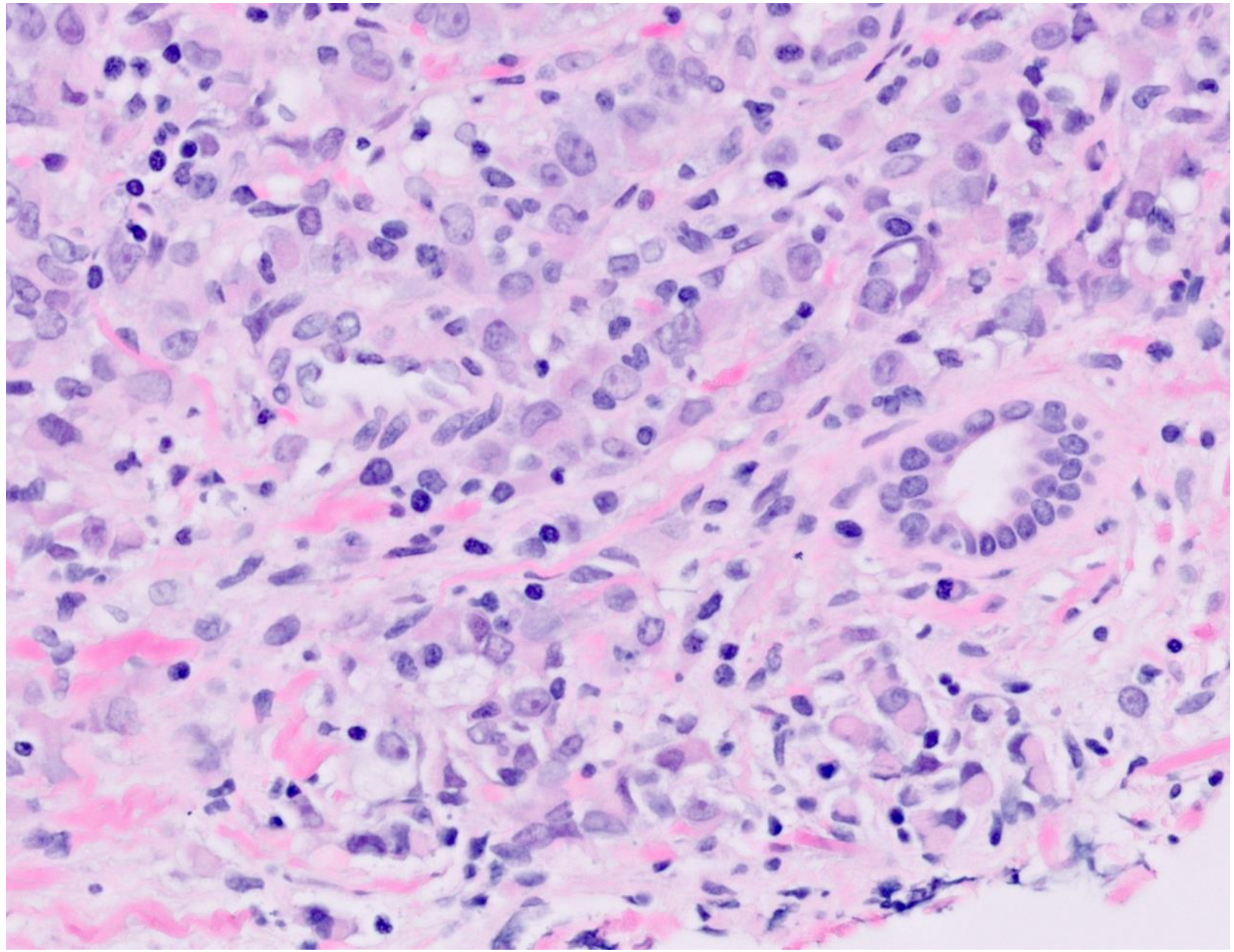
Emily Chan, UCSF
Acknowledgements: Case provided by Bradley Stohr, UCSF

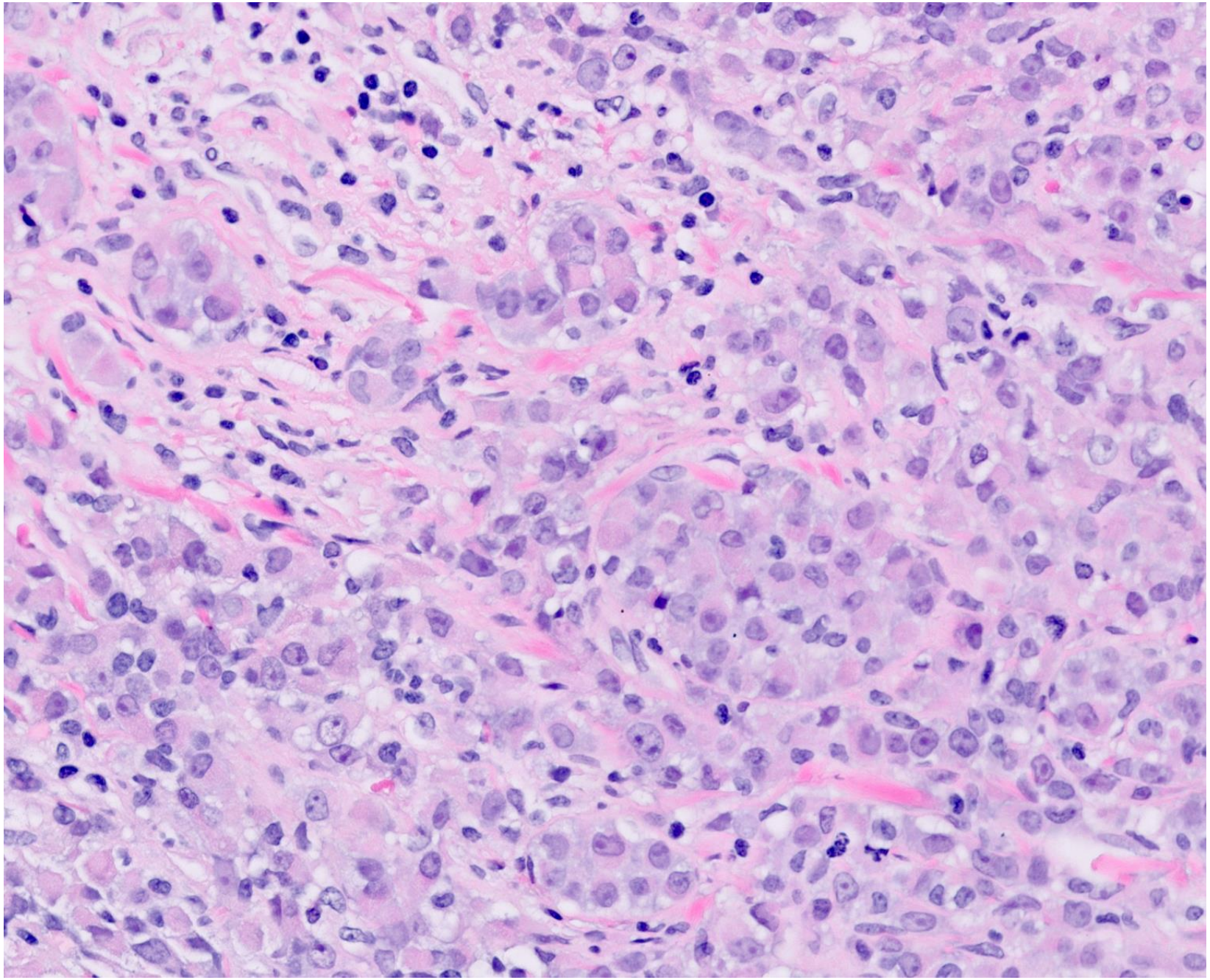
36 year-old woman with 6 cm right kidney mass and several lung nodules, rapidly enlarging











# DIAGNOSIS?

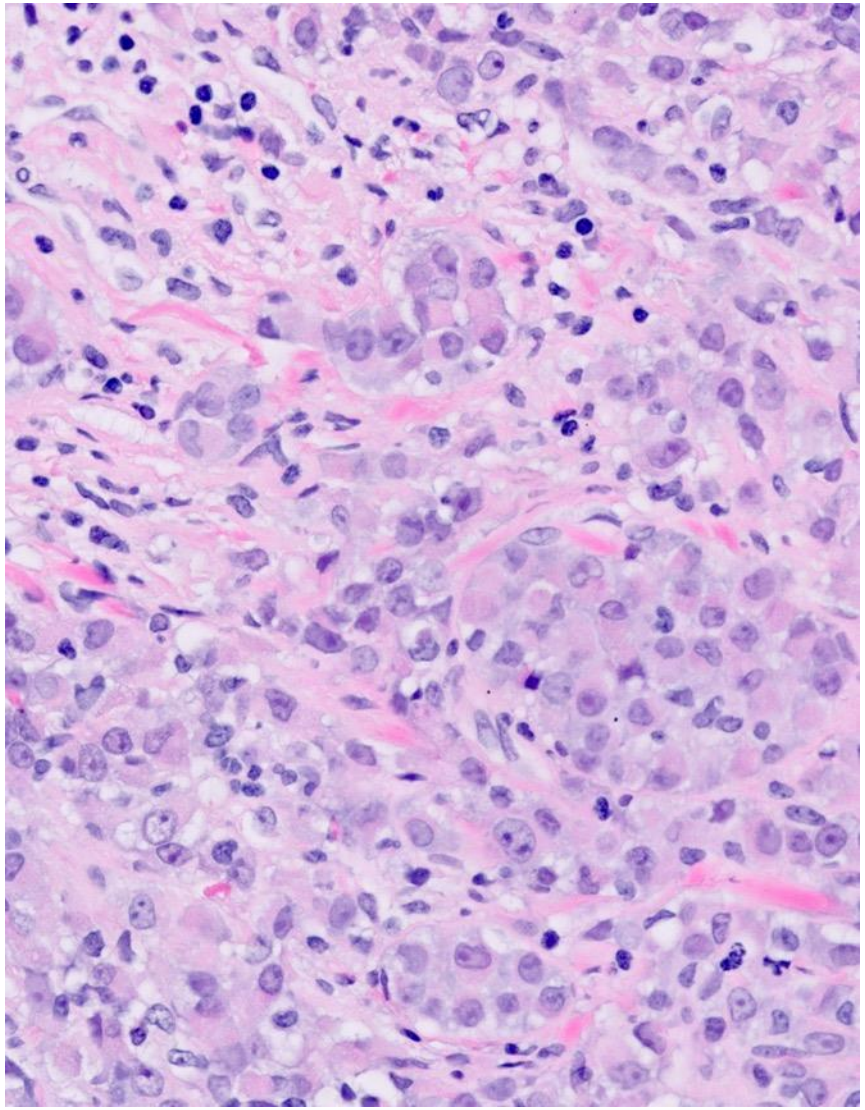
# 36 year-old woman with 6 cm right kidney mass and several lung nodules, rapidly enlarging

Emily Chan, UCSF/Stanford

Acknowledgements: Case provided by Drs. Bradley Stohr and Patrick Devine (molecular), UCSF

# Key features

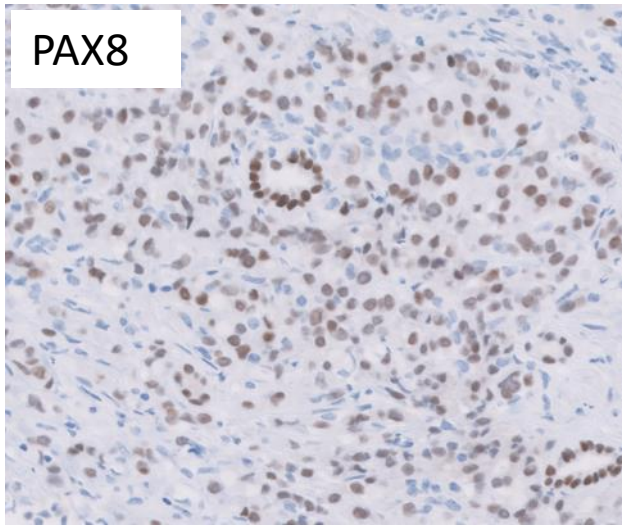
- Young patient
- High-grade/poorly differentiated appearance with infiltrating cords, nests, sheets within a fibrotic/demosplastic stroma
- Rhabdoid features

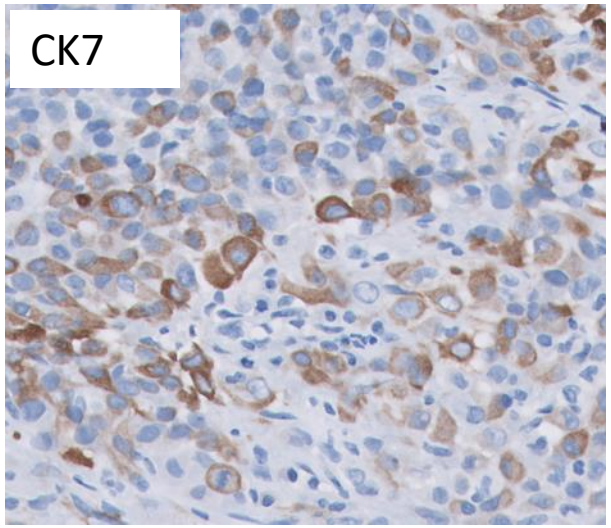


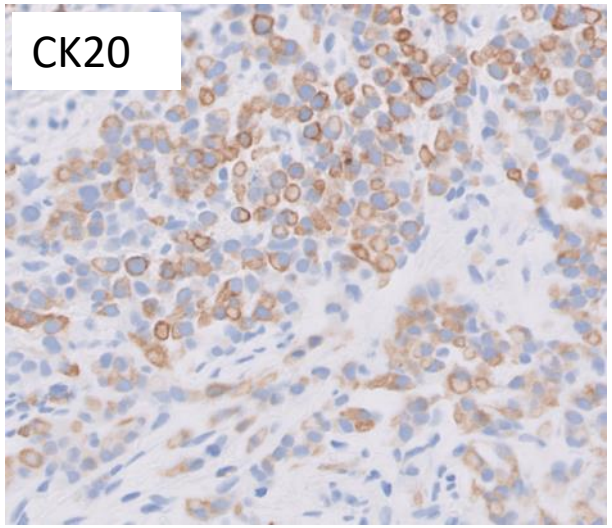
# Differential diagnosis

- Renal cell carcinoma – histologic subtype???
  - Clear cell renal cell carcinoma with rhabdoid features
  - Renal medullary carcinoma (RMC)
  - Collecting duct carcinoma
  - Others (given young age, consider: FH, SDH, translocation, ALK)
- Urothelial carcinoma
- Metastasis

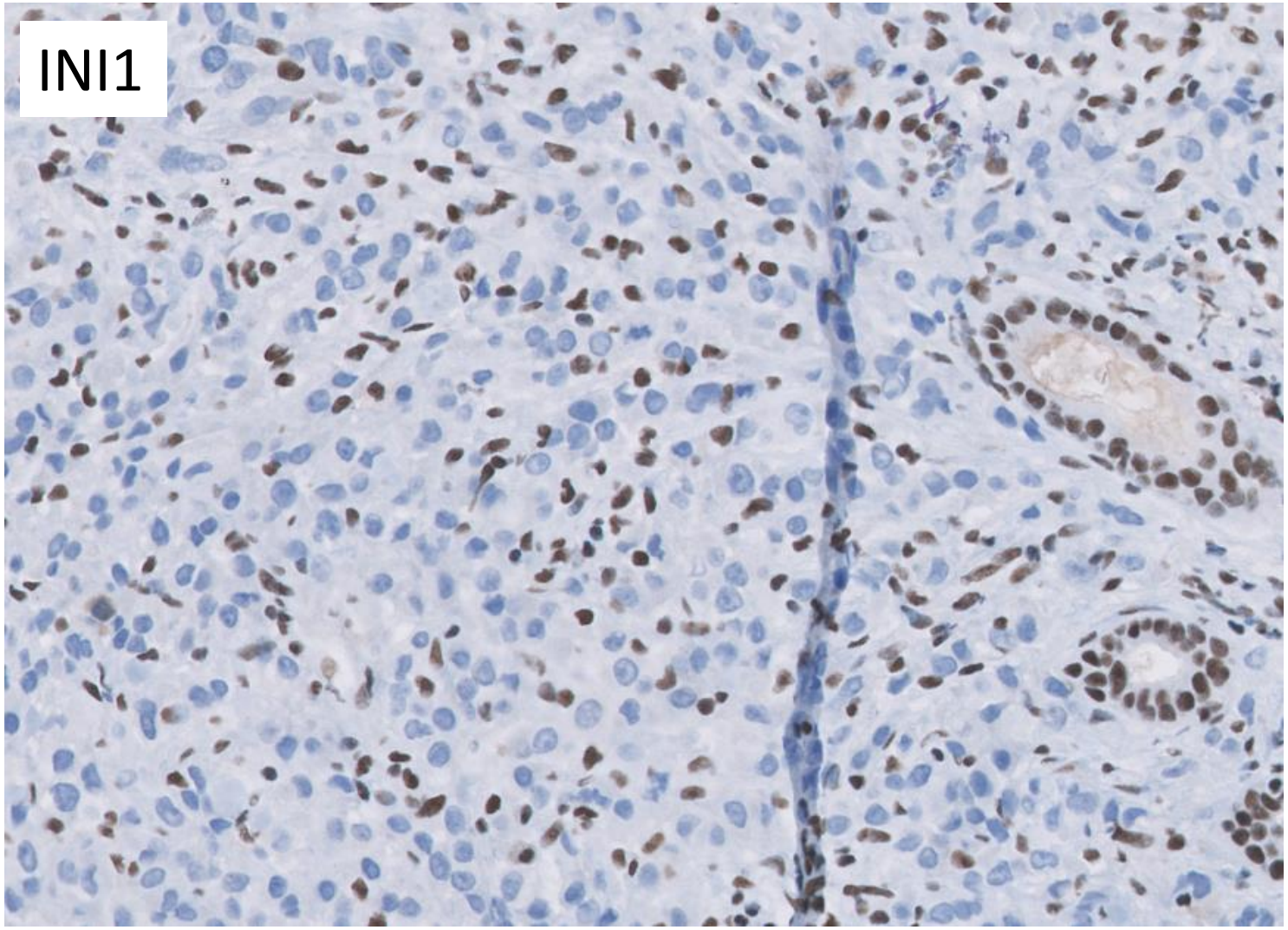
# IPOX




Other negative IHC: TTF1, Synaptophysin, desmin, GATA3, CDX2, CD138, p63


INI1

# DIAGNOSIS: SMARCB1-deficient renal cell carcinoma; see comment.

Comment: Further subtyping requires clinical correlation and the possibilities include:

1. SMARCB1-deficient renal medullary carcinoma, by definition occurs in patients with sickle cell hemoglobinopathies
2. SMARCB1-deficient medullary-like renal cell carcinoma, similar to RMC but occurs in patients without hemoglobinopathy (PMID: 28716439)
3. Unclassified RCC with secondary SMARCB1 loss*

*Secondary SMARCB1 loss can also occur in a variety of RCC subtypes, but these should be classified based on their underlying morphological or genetic subtype.

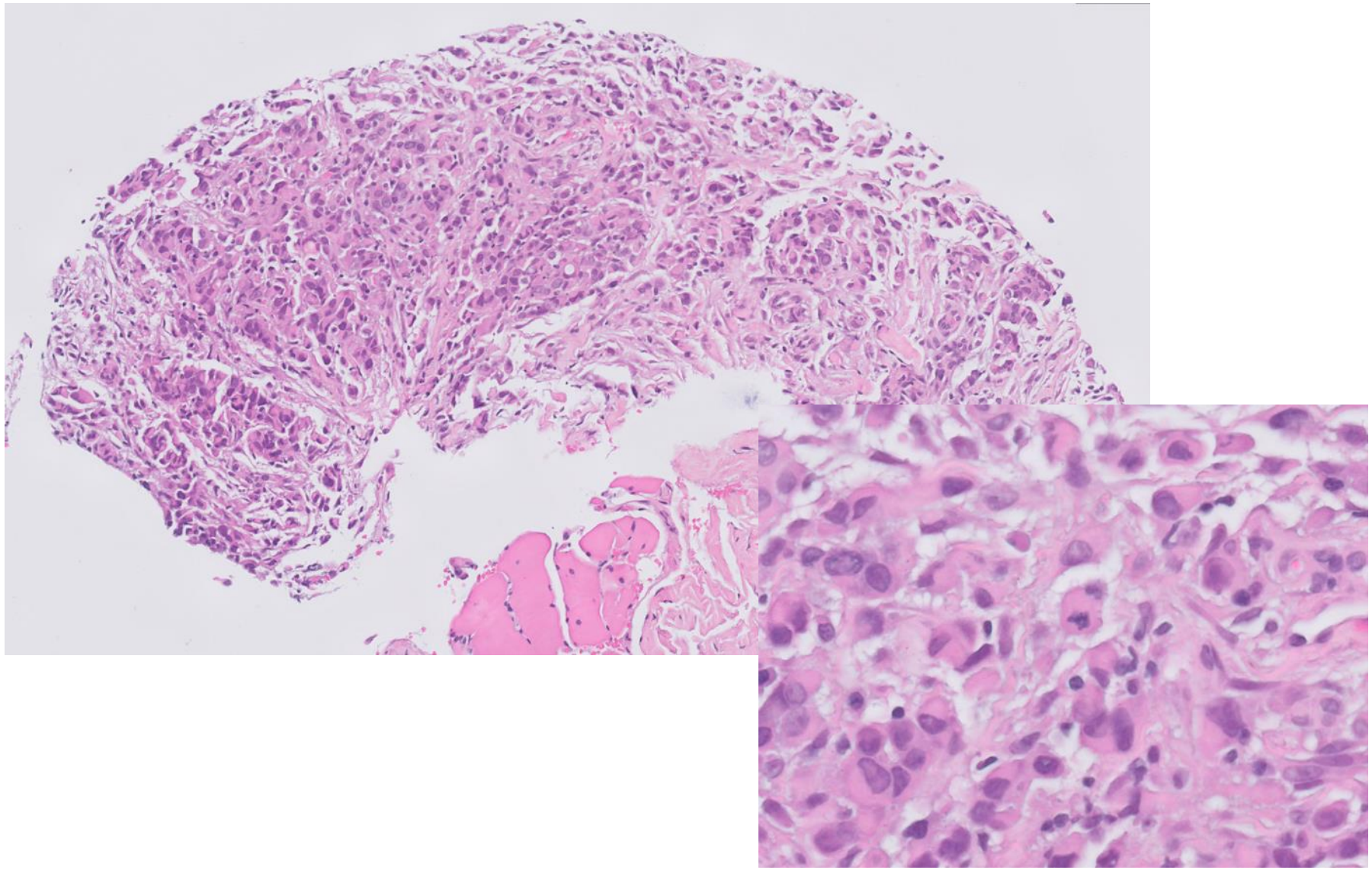
# SMARCB1-deficient Renal Medullary Carcinoma (RMC)

- Young patient, 2:1 M:F, and African ancestry
- Requires hemoglobinopathy for diagnosis (typically sickle cell trait Hb-AS, Hb-SC)
- Loss of nuclear expression of INI1/BAF47
  - CK7 positive, CK20 frequently positive
  - Pitfall: 50% of cases with OCT3/4 expression
- Aggressive tumor
  - Mets at presentation
  - Resistant to conventional RCC therapies
  - Mean survival 4 months

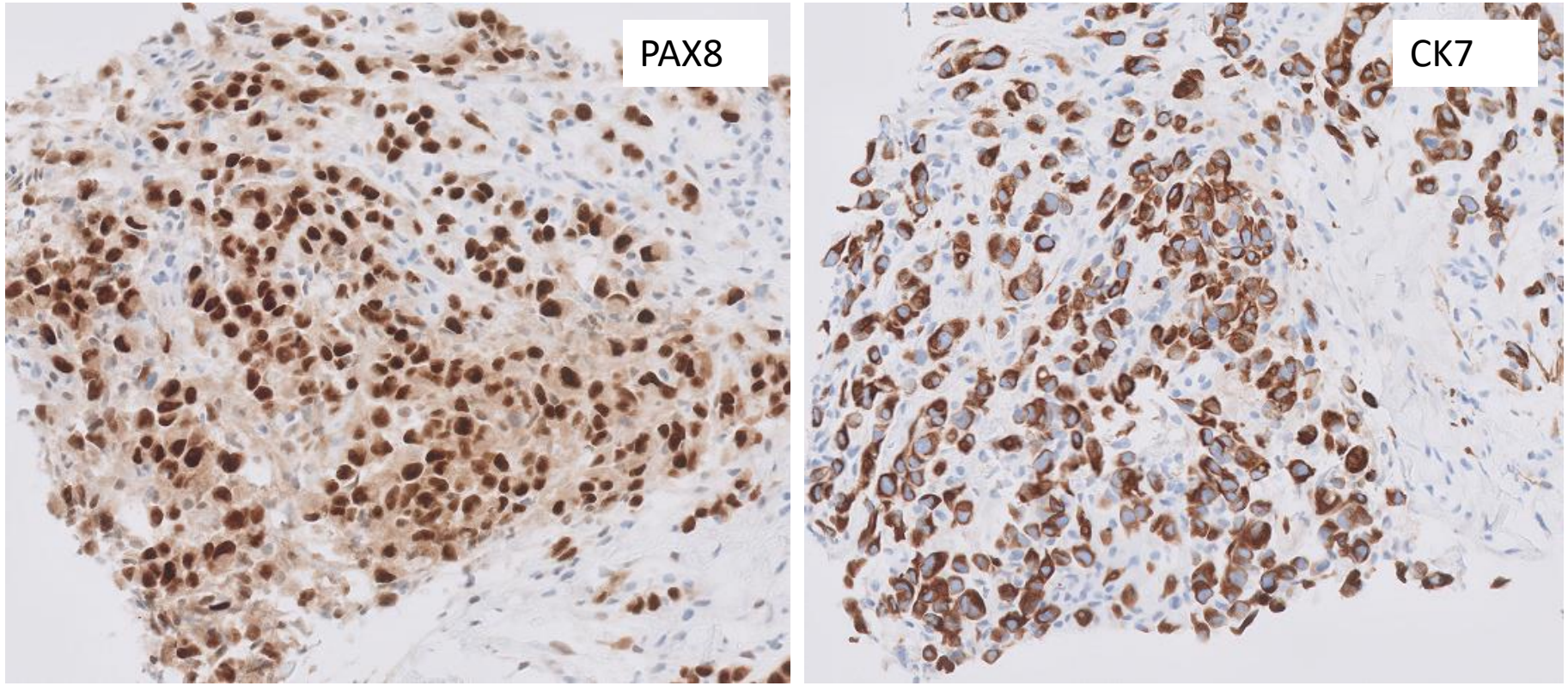
# Patient follow-up

- Subsequent germline testing showed sickle-cell trait
- Patient expired within the year

Story of a similar consult case: young woman with 7 cm left kidney mass and osseous mets. Bx of bone met:



# IPOX

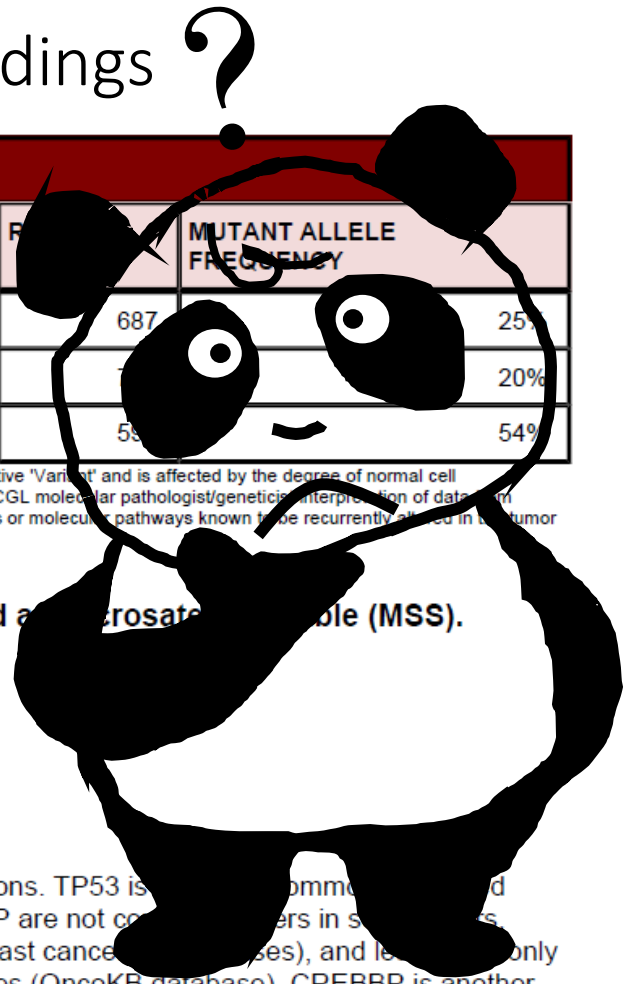



Other negative IHC: CK20, GATA3, mammaglobin, GCDFP, ER/PR, HER2, TTF1, CDX2, arginase, inhibin

# Initially an informal consult which we recommended:

- Likely from kidney, we could do a bunch of immuonstains for further subtyping, OR, given limited sampling, send for UCSF500/molecular testing
- UCSF500 was performed….

# UCSF500 came back with nonspecific findings



**PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS**

| VARIANT | TRANSCRIPT ID | CLASSIFICATION | R | MUTANT ALLELE FREQUENCY |
|---|---|---|---|---|
| TP53 p.Y236* | NM_000546.5 | Pathogenic | 687 | 25 |
| CREBBP p.Q1853* | NM_004380.2 | Likely Pathogenic | | 20% |
| TBX3 p.P661_L677del | NM_016569.3 | Likely Pathogenic | 5 | 54% |

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Vari t' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molec ar pathologist/genetici interpr tion of data m somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecu pathways known t be recurrently a ed in t tumor type.

**2 of 84 tested microsatellites (2.38%) were found to be unstable. This is interpreted a crosat ble (MSS).**

Assessment of microsatellite instability (MSI) by percentage of unstable sites:
<20%: MSI absent (MSS) | 20-30%: MSI equivocal | >30%: MSI present (MSI-High)

**UCSF500 tumor mutation burden: 4.1 mutations/Mb**

## INTERPRETATION

This metastatic carcinoma demonstrates a genomic profile with both common and unusual alterations. TP53 is omm d gene in cancer and therefore not very useful diagnostically. On the other hand, TBX3 and CREBBP are not c ers in s TBX3 is a transcription factor that in the MSK-IMPACT database is most commonly mutated in breast cance ses), and l only in uterine, thyroid, colorectal, and salivary cancers (approximately 1%), among common tumor types (OncoKB database). CREBBP is another transcriptional regulator, and it is best known for its role in lymphoma. Among common solid tumor types in the MSK-IMPACT database, mutations are most often found in bladder, small cell lung, skin and endometrial cancers. The diagnostic consideration of renal cell carcinoma (RCC) is noted. TBX3 and CREBBP are not common drivers in , RCC, found in 1% and 1.6%, respectively, of all RCC in the cBioPortal database. VHL or PBRM1 mutation characteristic of clear cell RCC is not identified. Notably, unlike many other tumor types, TP53 mutation is uncommon in RCC (5.4% of all RCC in cBioPortal).

Copy number analysis shows a flat profile without identifiable copy number alterations. Large-scale copy changes include losses of chromosomes 9p, 17p, 22 and Xp; gain of chromosome 17q. This is not consistent with the copy number pattern seen in chromophobe RCC (loss of chromosomes 1, 2, 6, 10, 13, 17 and 21) or papillary RCC (gain of chromosomes 7, 17, 12, 16, 17 and 3).

# UCSF500 came back with nonspecific findings

| PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS | | | | |
|---|---|---|---|---|
| VARIANT | TRANSCRIPT ID | CLASSIFICATION | READS | MUTANT ALLELE FREQUENCY |
| TP53 p.Y236* | NM_000546.5 | Pathogenic | 687 | 25% |
| CREBBP p.Q1853* | NM_004380.2 | Likely Pathogenic | 752 | 20% |
| TBX3 p.P661_L677del | NM_016569.3 | Likely Pathogenic | 591 | 54% |

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

**2 of 84 tested microsatellites (2.38%) were found to be unstable. This is interpreted as Microsatellite Stable (MSS).**

Assessment of microsatellite instability (MSI) by percentage of unstable sites:
<20%: MSI absent (MSS) | 20-30%: MSI equivocal | >30%: MSI present (MSI-High)

**UCSF500 tumor mutation burden: 4.1 mutations/Mb**

**Loss of chromosome 22**

## INTERPRETATION

This metastatic carcinoma demonstrates a genomic profile with both common and unusual alterations. TP53 is the most commonly mutated gene in cancer and therefore not very useful diagnostically. On the other hand, TBX3 and CREBBP are not common drivers in solid tumors. TBX3 is a transcription factor that in the MSK-IMPACT database is most commonly mutated in breast cancer (4% of cases), and less commonly in uterine, thyroid, colorectal, and salivary cancers (approximately 1%), among common tumor types (OncoKB database). CREBBP is another transcriptional regulator, and it is best known for its role in lymphoma. Among common solid tumor types in the MSK-IMPACT database, mutations are most often found in bladder, small cell lung, skin and endometrial cancers. The diagnostic consideration of renal cell carcinoma (RCC) is noted. TBX3 and CREBBP are not common drivers in , RCC found in 1% and 1.6%, respectively, of all RCC in the cBioPortal database. VHL or PBRM1 mutation characteristic of clear cell RCC is not identified. Notably, unlike many other tumor types, TP53 mutation is uncommon in RCC (5.4% of all RCC in cBioPortal).

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# UCSF500 of initial in-house case (because we sequence everything)

| PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS | | | | |
|---|---|---|---|---|
| VARIANT | TRANSCRIPT ID | CLASSIFICATION | READS | MUTANT ALLELE FREQUENCY |
| No pathogenic or likely pathogenic alterations identified. | | | | |

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

**3 of 70 tested microsatellites (4.29%) were found to be unstable. This is interpreted as Microsatellite Stable (MSS).**

Assessment of microsatellite instability (MSI) by percentage of unstable sites:
<20%: MSI absent (MSS) | 20-30%: MSI equivocal | >30%: MSI present (MSI-High)

**UCSF500 tumor mutation burden: 4.8 mutations/Mb**

**Loss of chromosome 22**

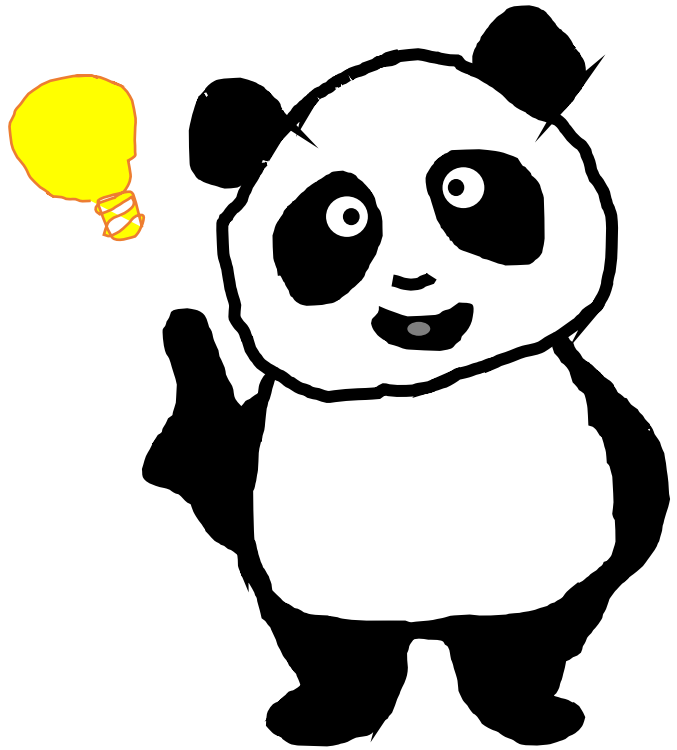
## INTERPRETATION

Tumor only sequencing of this SMARCB1-deficient renal cell carcinoma reveals no pathogenic or likely pathogenic alterations in any of the 529 genes targeted for sequencing on the UCSF500 panel despite good sequencing coverage (571x mean target coverage). This includes SMARCB1/INI1/BAF47, although silencing of SMARCB1 expression has been noted to occur via microRNA-mediated downregulation of SMARCB1 mRNA in a significant number of tumors (Ref.1-2). These results may also reflect one of three possibilities: 1) that this is a neoplasm that harbors genetic alteration(s) not captured for sequencing by this assay, 2) that the relative fraction of neoplastic cells in the extracted tissue sample used for sequencing is very low beyond the limits of detection by this assay, or 3) the absence of a clonal neoplasm within the area sequenced. See Test Limitations described below.

Copy number analysis reveals few large scale chromosomal alterations including a gain of distal 19q and a loss of interstitial 22q. No focal amplifications or homozygous/biallelic deletions are identified.

# Where is SMARCB1 located in the genome…?

- Chromosome 22!
- How is SMARCB1 typically inactivated in RMC??



# SMARCB1 status of 38 cases of RMC

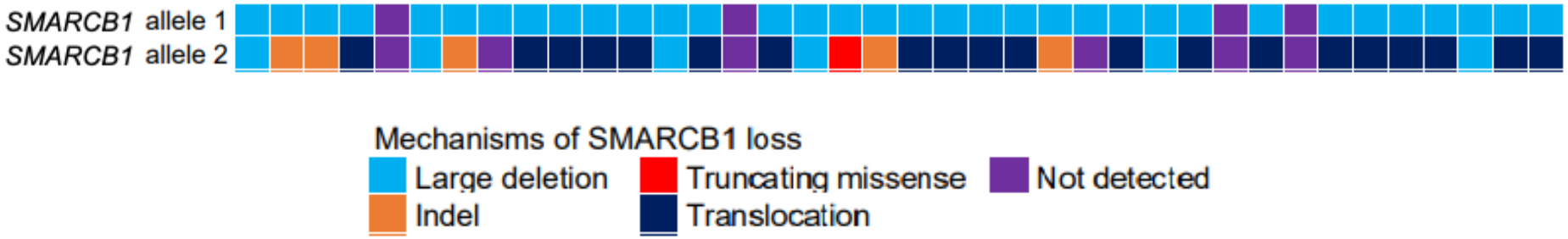
CellPress

Cancer Cell

Article

## Comprehensive Molecular Characterization Identifies Distinct Genomic and Immune Hallmarks of Renal Medullary Carcinoma

Pavlos Msaouel,[1,2,22,*] Gabriel G. Malouf,[3,4] Xiaoping Su,[5] Hui Yao,[5] Durga N. Tripathi,[2] Melinda Soeung,[6] Jianjun Gao,[1] Priya Rao,[7] Cristian Coarfa,[8] Chad J. Creighton,[5,8] Jean-Philippe Bertocchio,[1,2] Selvi Kunnimalaiyaan,[9] Asha S. Multani,[10] Jorge Blando,[11] Rong He,[1] Daniel D. Shapiro,[12] Luigi Perelli,[1] Sanjana Srinivasan,[6,13] Federica Carbone,[1] Patrick G. Pilié,[1] Menuka Karki,[2] Riyad N.H. Seervai,[2,14] Bujamin H. Vokshi,[3,4] Dolores Lopez-Terrada,[15] Emily H. Cheng,[16] Ximing Tang,[17] Wei Lu,[17] Ignacio I. Wistuba,[17] Timothy C. Thompson,[1] Irwin Davidson,[4] Virginia Giuliani,[13,18] Katharina Schlacher,[9] Alessandro Carugo,[13,18] Timothy P. Heffernan,[13,18] Padmanee Sharma,[1,11] Jose A. Karam,[12,17] Christopher G. Wood,[12] Cheryl L. Walker,[2,19,20,21,*] Giannicola Genovese,[1,6,*] and Nizar M. Tannir[1,*]

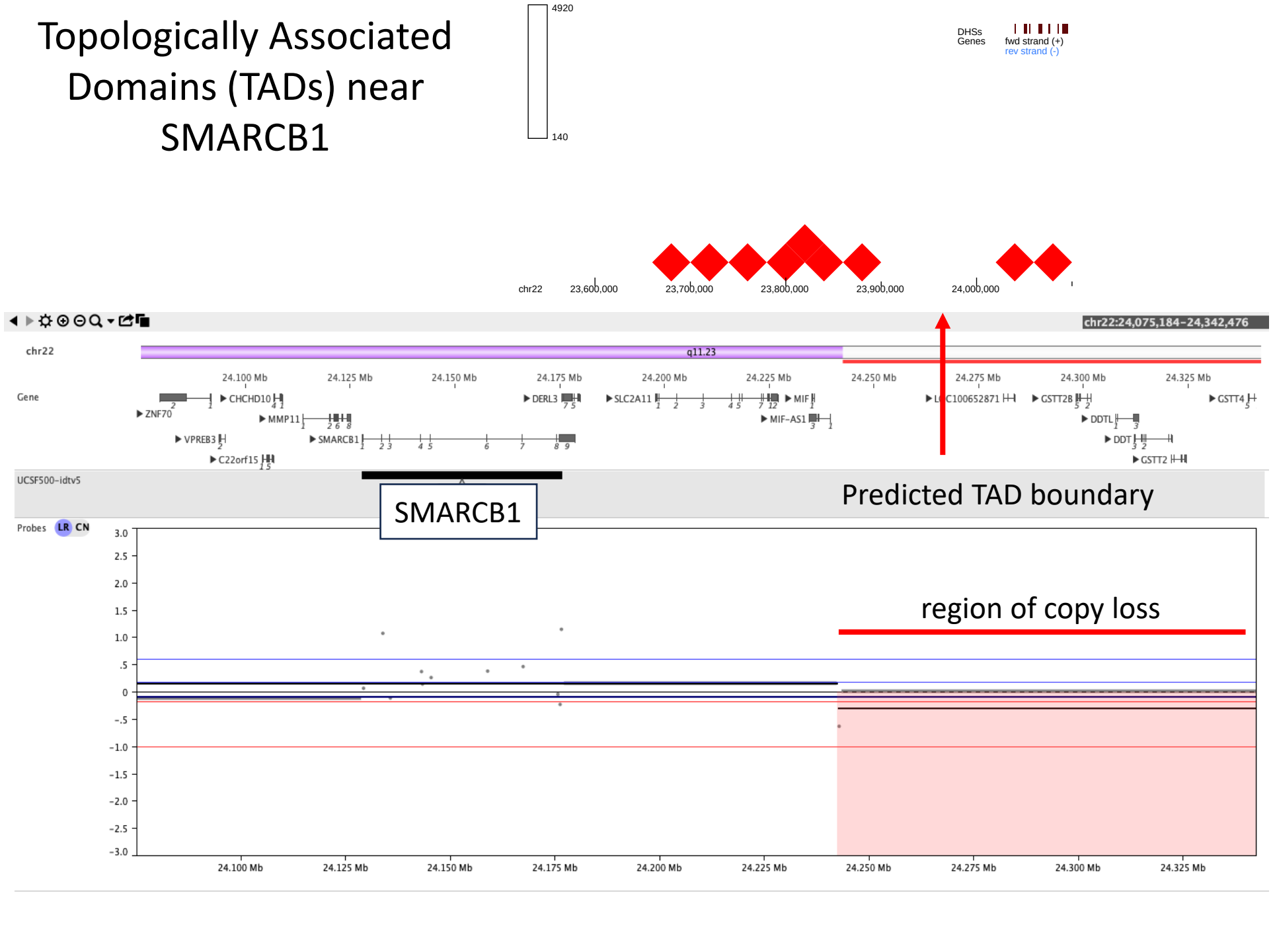



- Translocation with hemizygous loss of other allele (~55%)
- Homozygous loss of SmarcB1 (~30%)
- Only one case had a mutation
- No structural or copy number alterations: 15%

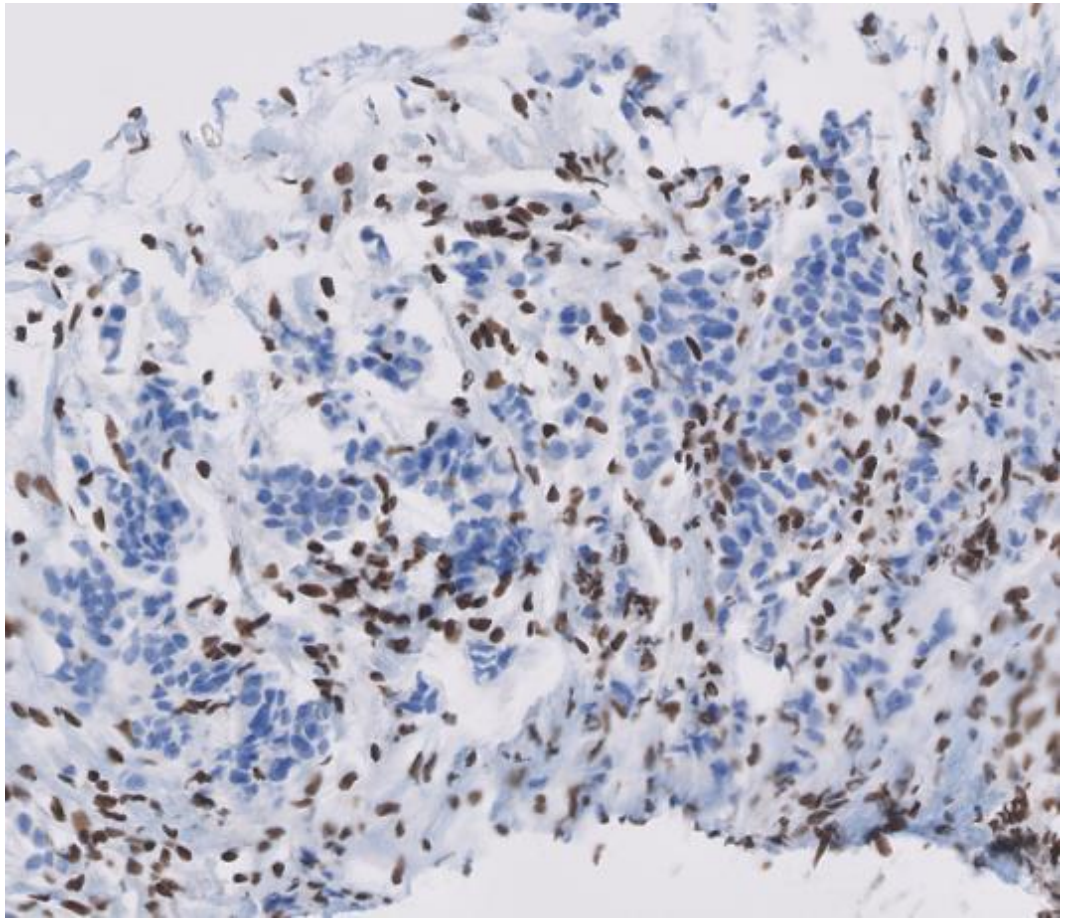
# Further conversation with molecular pathologist regarding original case with interstitial 22q loss:

- “The predicted deletion would overlap with the right end of the TAD (topologically associating domain) containing SMARCB1 and potentially extend into the adjacent TAD. This is one potential mechanism of globally dysregulating many genes at once and may be a source of the down regulation of SMARCB1 protein expression. ”
- Other mechanisms of SMARCB1 loss also possible: promoter swapping, disruption of TAD boundaries, microRNA silencing, etc.

# Topologically Associated Domains (TADs) near SMARCB1



# INI1/BAF47 in second case



Subsequently also revealed to have family history of kidney tumors and sickle-cell trait

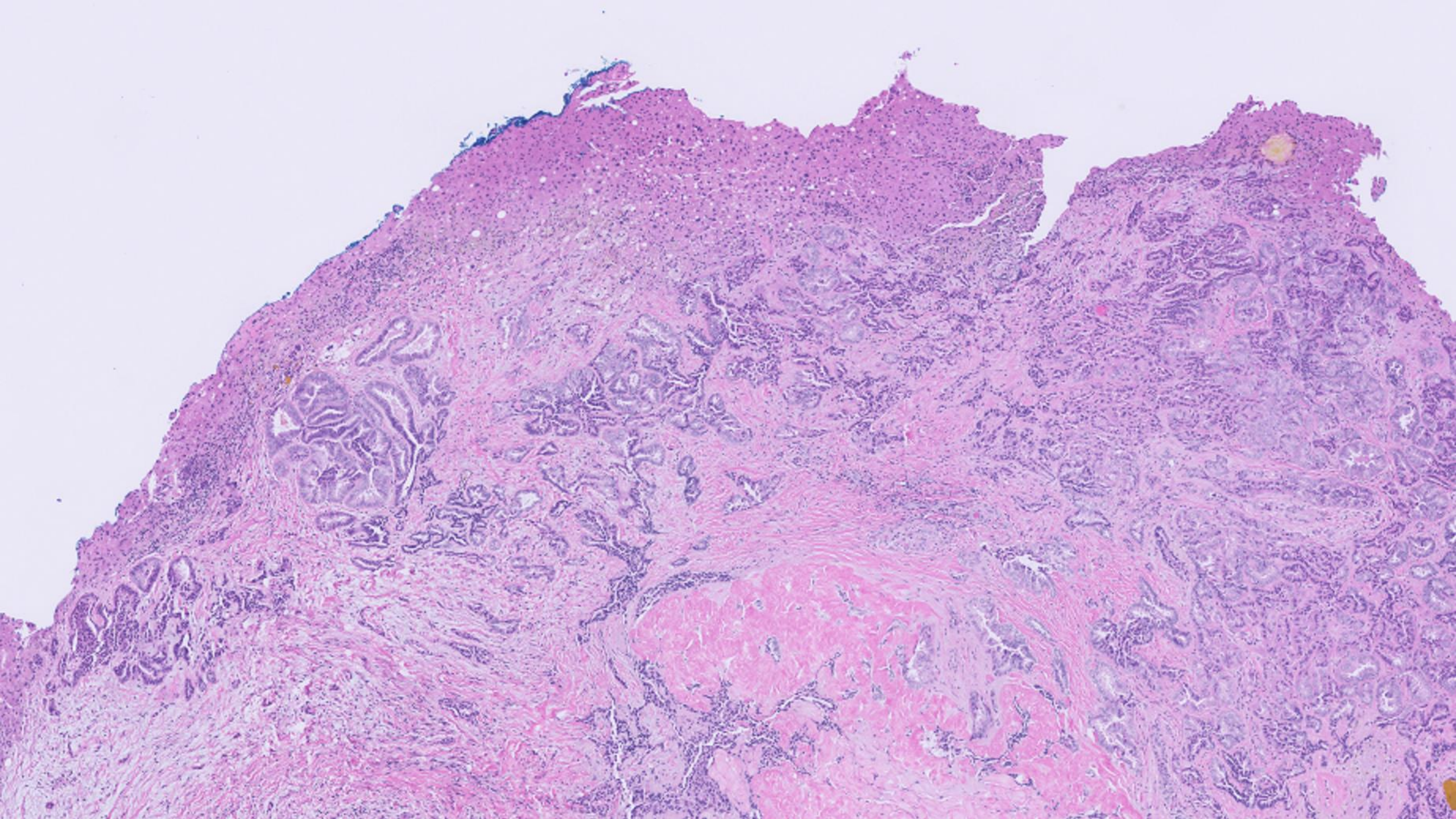
# Take-home points – SMARCB1-Deficient Renal Medullary Carcinoma

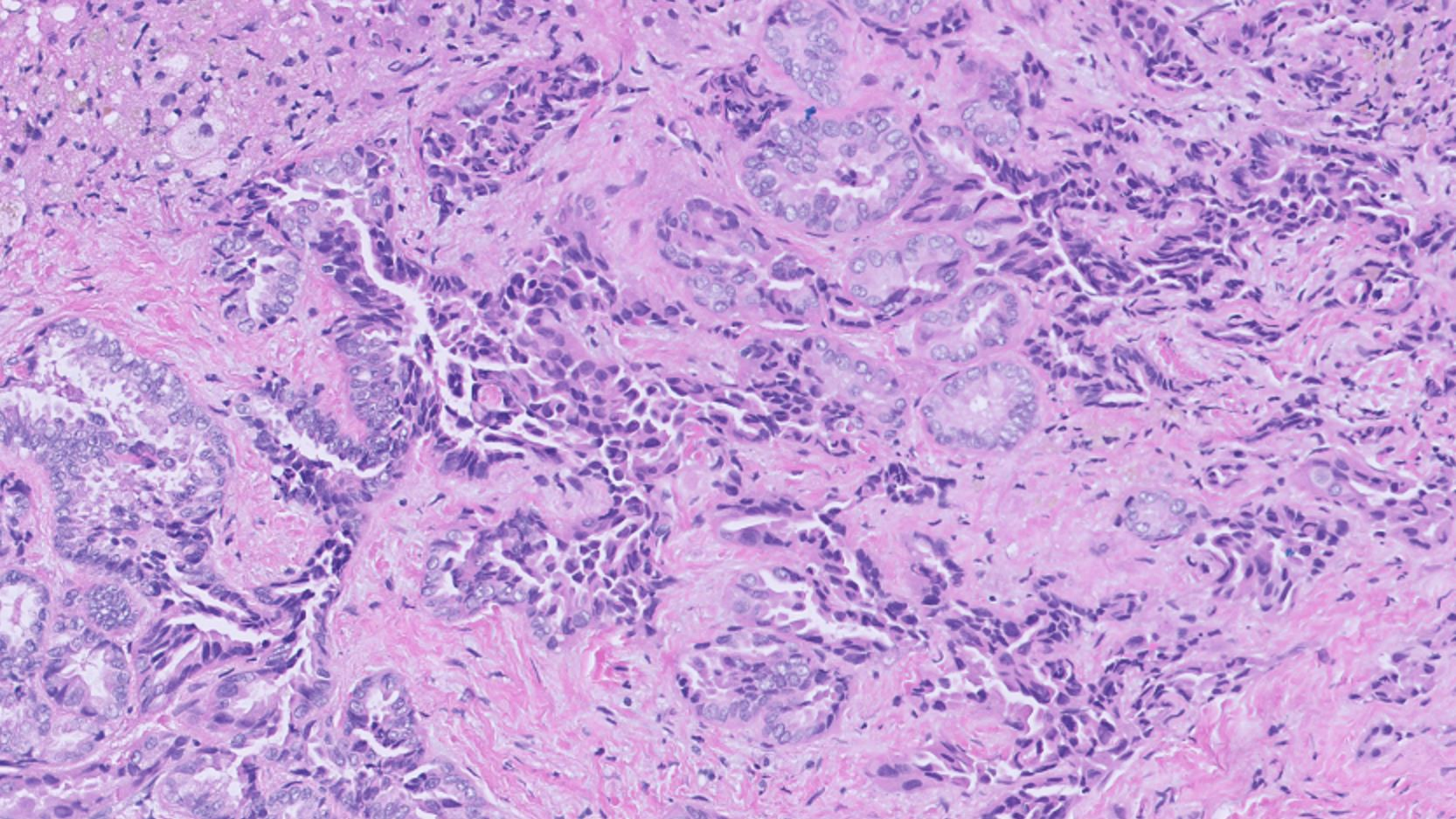
- Young patient, African ancestry, poorly differentiated/rhabdoid histology
- Requires identification of hemoglobinopathy
  - otherwise consider SMARCB1-deficient medullary-like RCC, or other RCC with secondary SMARCB1 loss
- SMARCB1 deficiency best identified by INI1/BAF47 IHC
  - SMARCB1-deficient RCC is rare CK7/CK20+ RCC
  - avoid OCT3/4+ pitfall
- NGS testing may obscure evidence of SMARCB1 deficiency (i.e., UCSF500 is not always the answer : )
  - Divide biopsies into two cassettes when grossing if possible

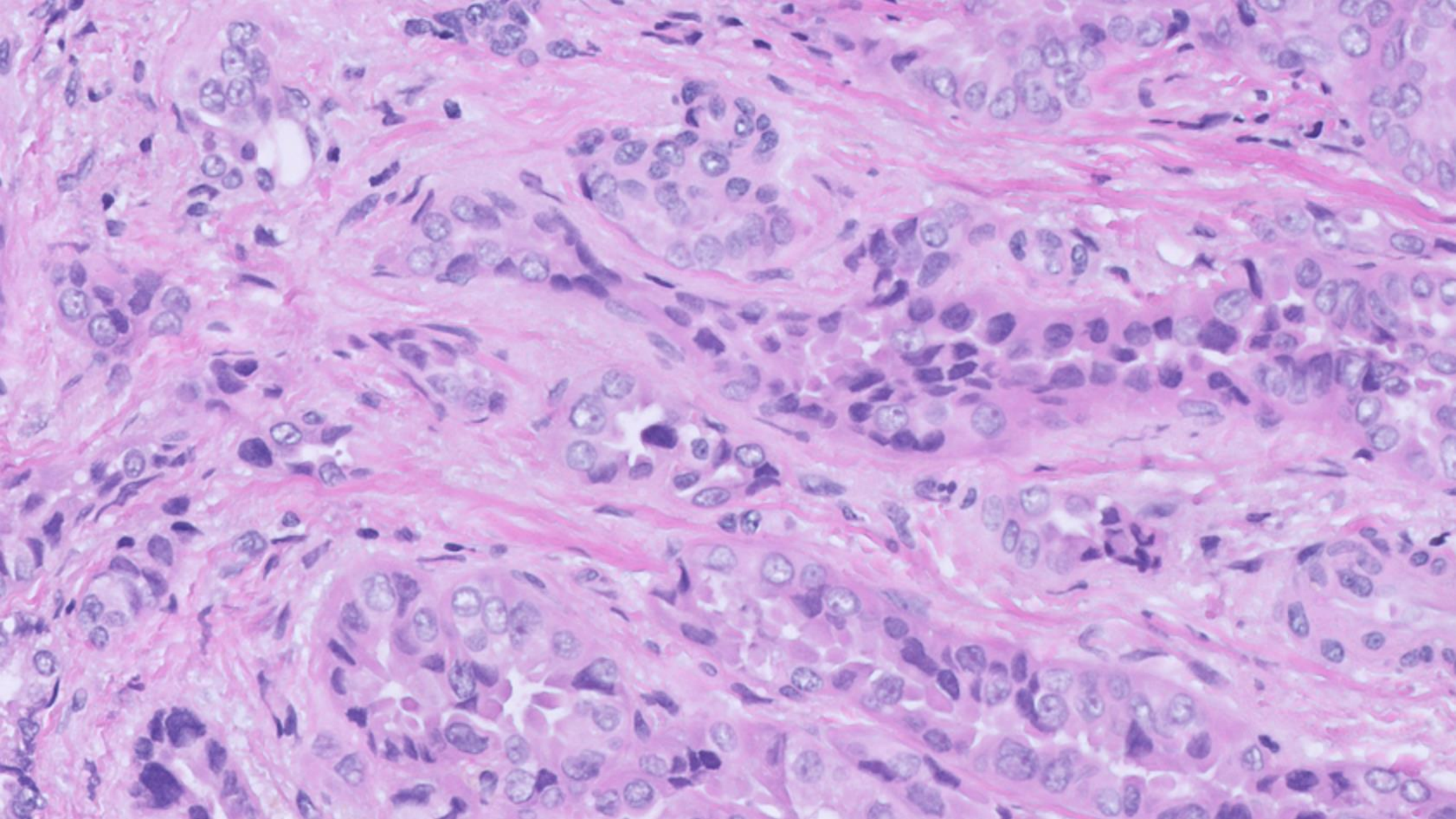
23-0708

**Cindy Wang; Stanford**

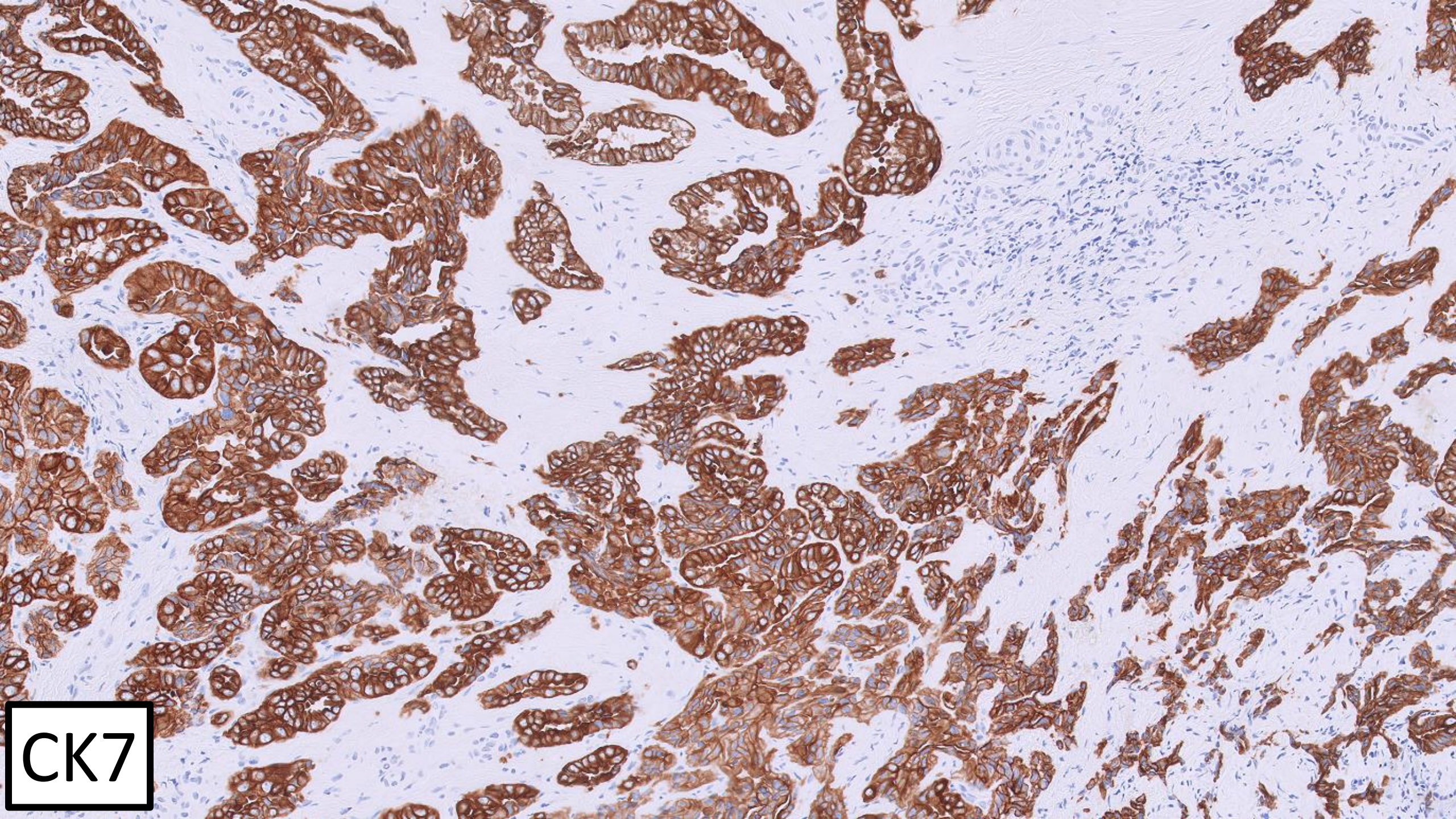
58 yo F with tail of pancreas mass and multiple liver lesions.

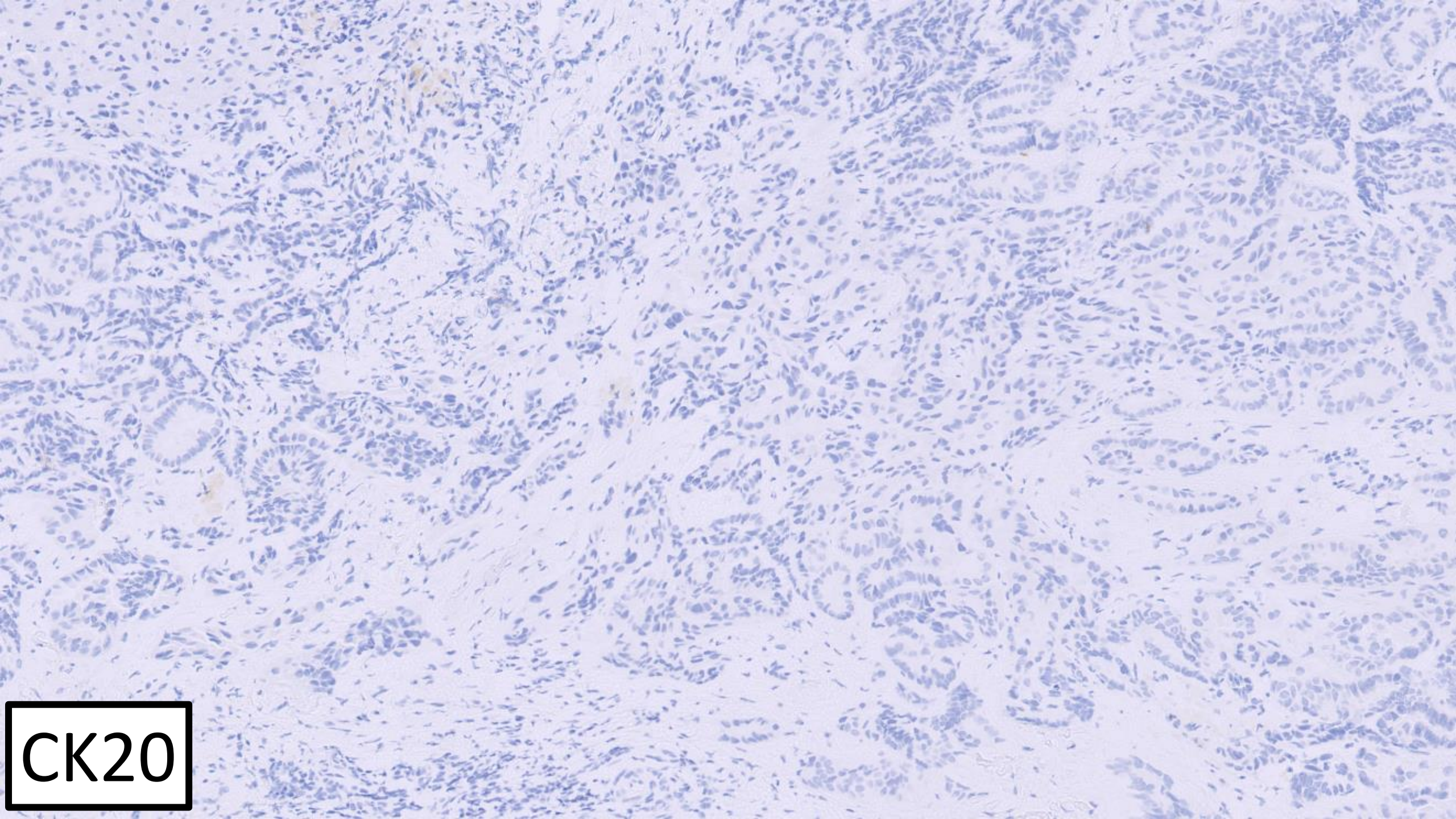


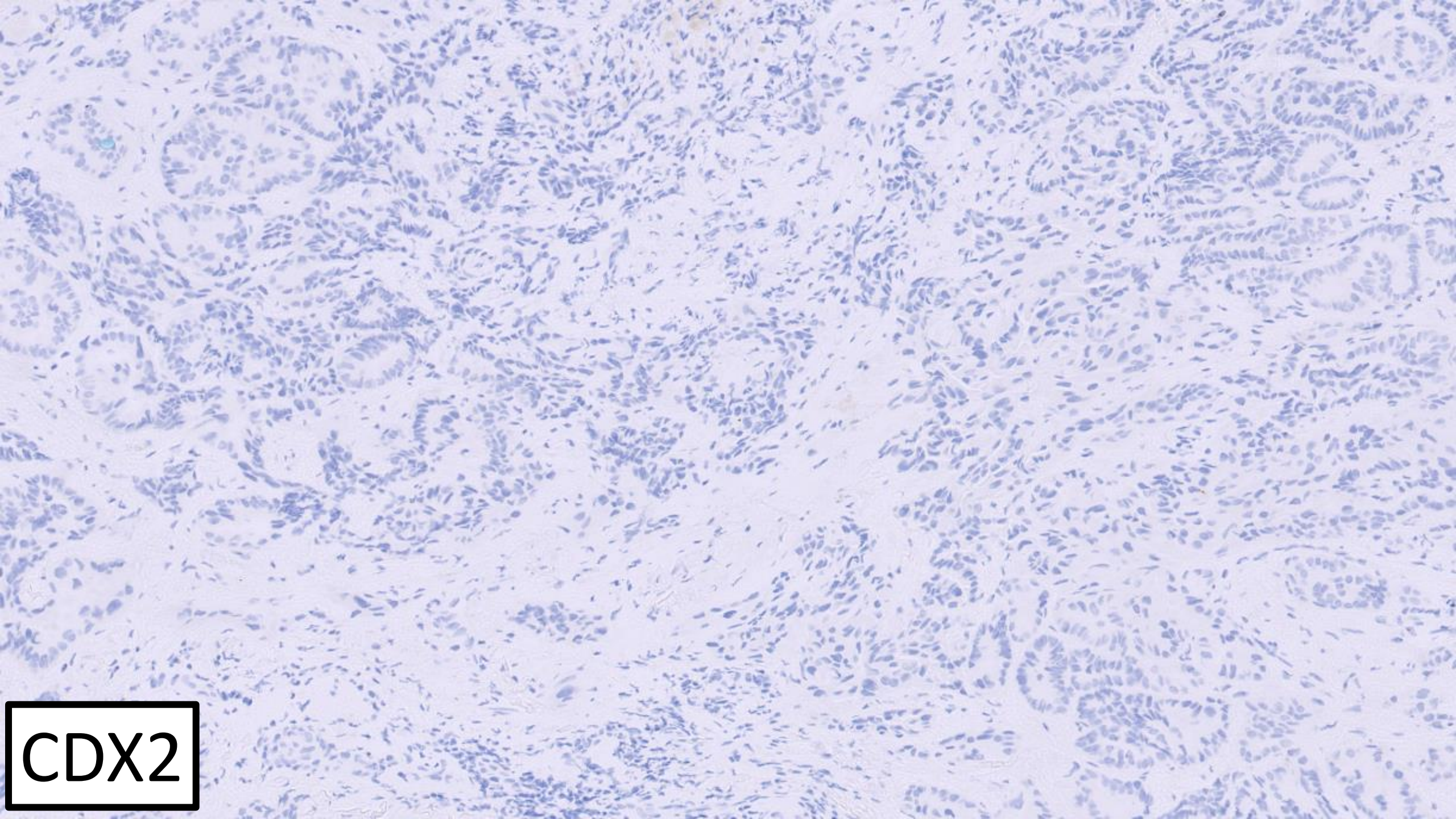




# DIAGNOSIS?


CK7

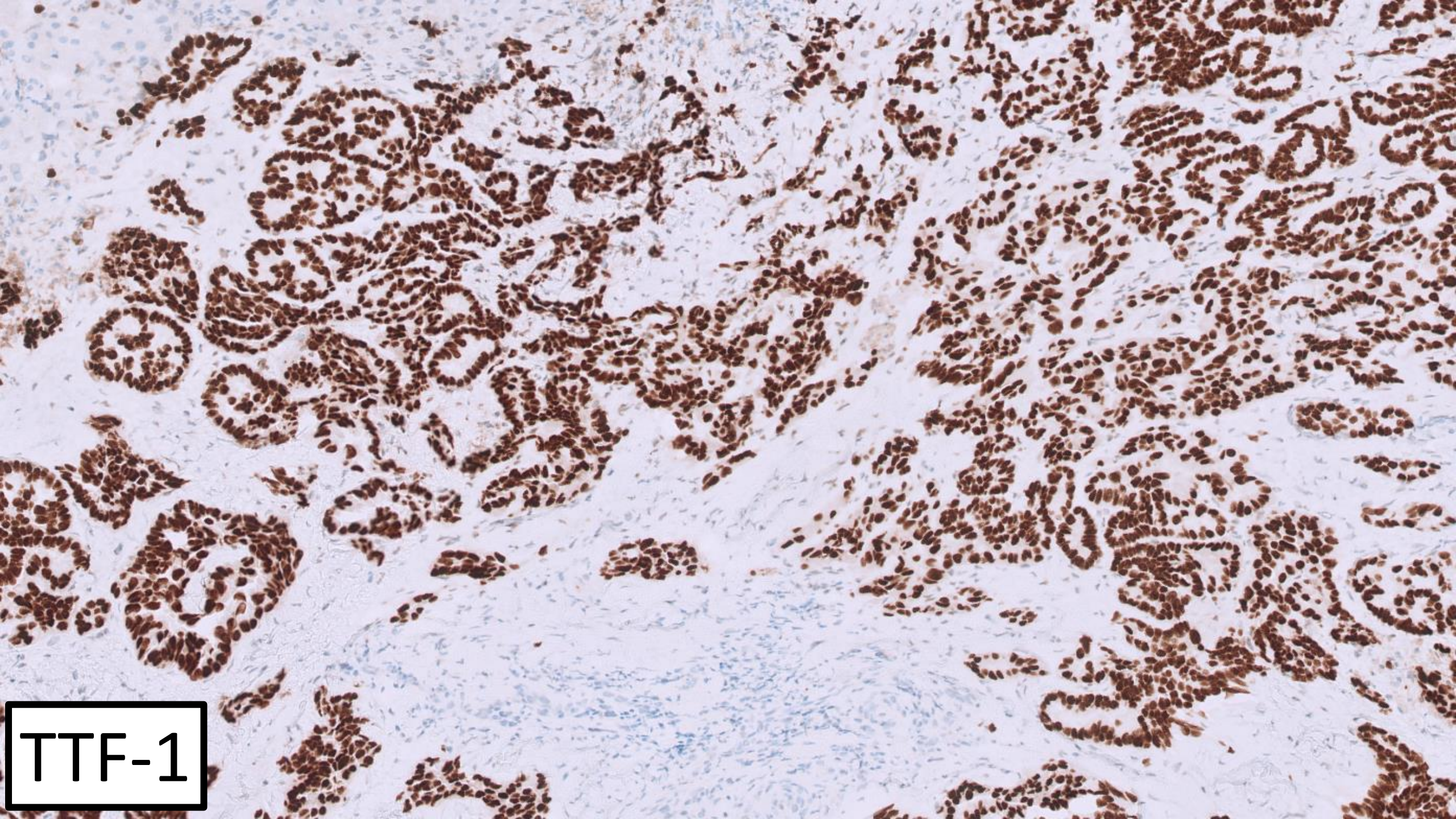

CK20

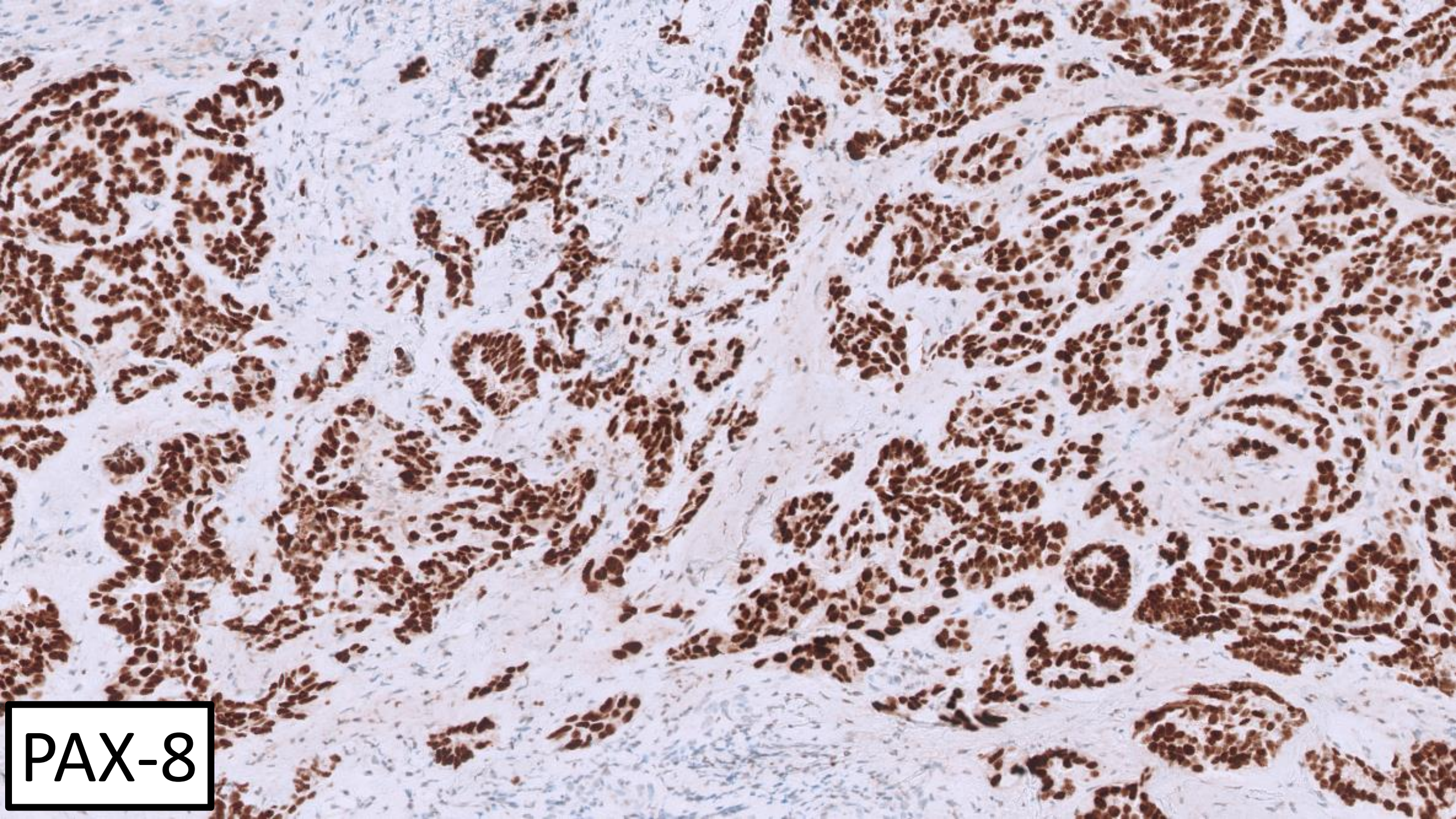

CDX2

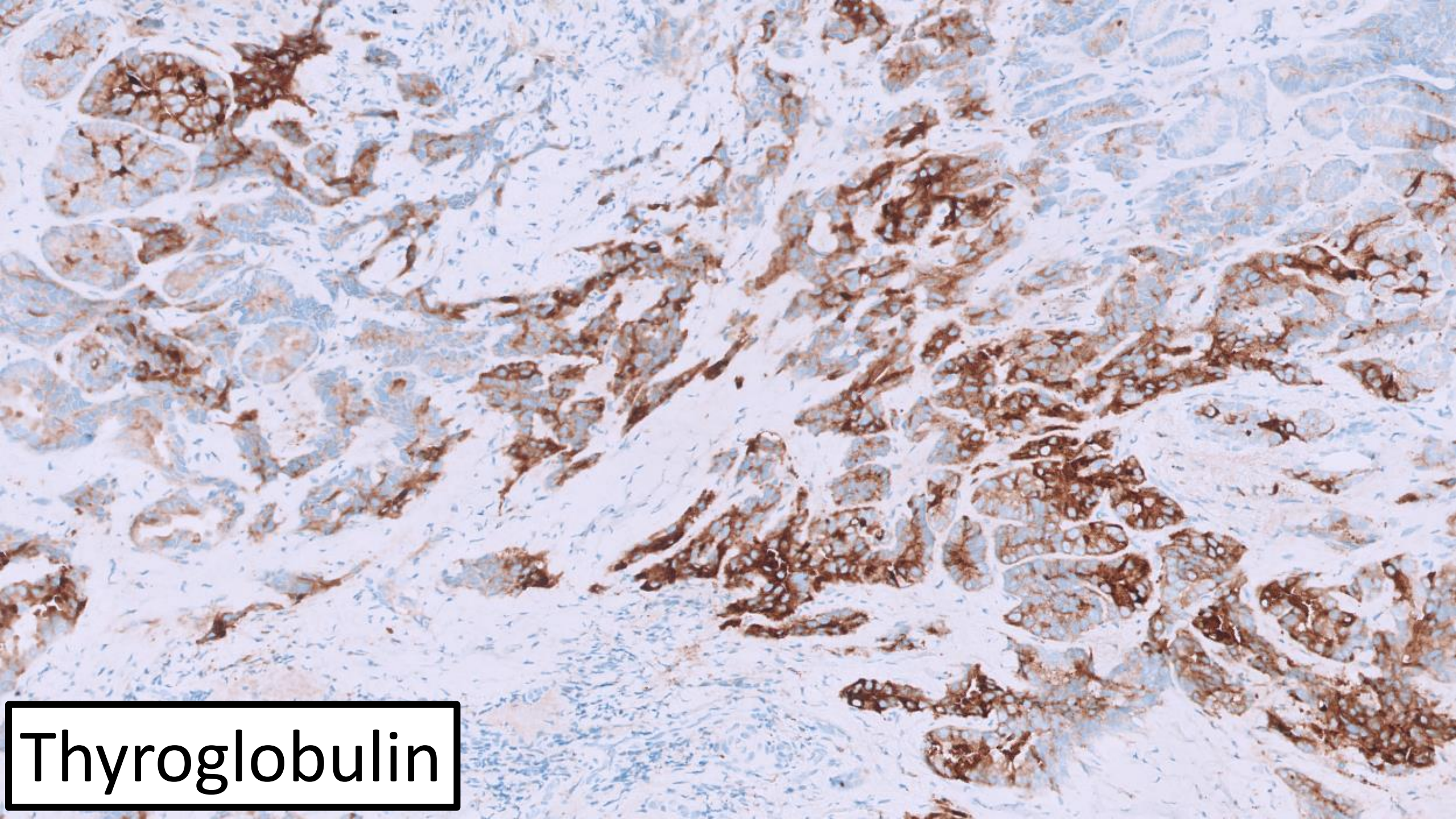
# What’s your diagnosis now?

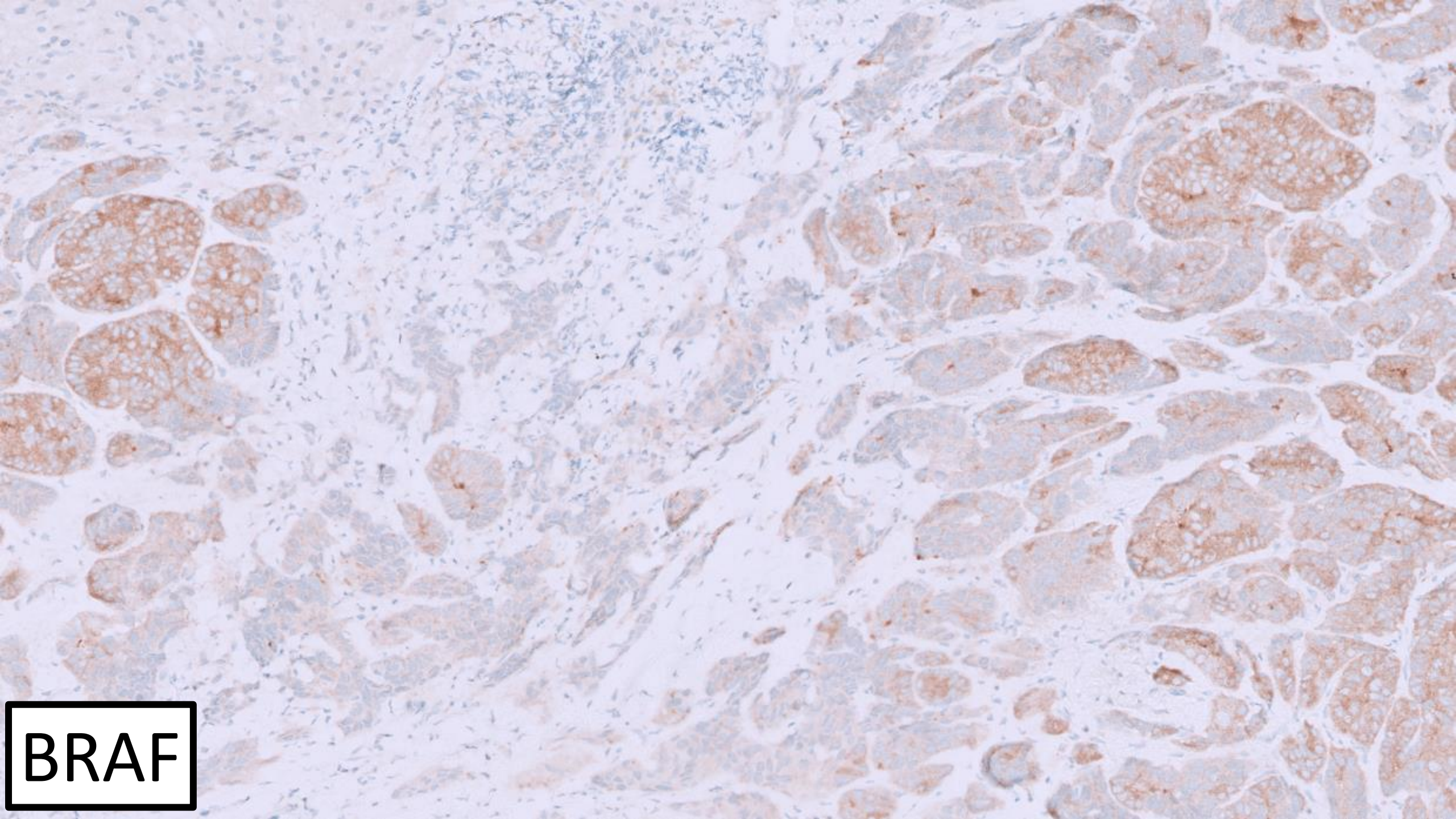
# Chart Review

- Remote history of metastatic PTC s/p thyroidectomy radioactive iodine (RAI) ablation (2011)
- Increasing size of pancreatic tail mass by serial CTs
- FNA of mass shows “adenocarcinoma, pancreatobiliary type”
- New small liver lesions


TTF-1


PAX-8


Thyroglobulin


BRAF

# Final diagnosis
# metastatic papillary thyroid carcinoma

Informed the surgeon and cytopathology

# Better prognosis and more treatment options

# Pancreatic metastasis from papillary thyroid cancer: a case report and literature review

Sang Hwa Song[1], Young Hoe Hur[1], Chol Kyoon Cho[1,2], Yang Seok Koh[1,2], Eun Kyu Park[3], Hee Joon Kim[3], Sang Hoon Shin[3], Sung Yeol Yu[3], Chae Yung Oh[3]

[1]Department of Surgery, Chonnam National University Hwasun Hospital, Hwasun, Korea
[2]Department of Surgery, Chonnam National University Medical School, Gwangju, Korea
[3]Department of Surgery, Chonnam National University Hospital, Gwangju, Korea

# Case report:

- 51 yo male with PTC s/p thyroidectomy and RAI
- 6 years later CT picked up incidental 4.7 cm solid and cystic mass in the pancreatic tail
- Distal pancreatectomy confirmed metastatic PTC

# Discussion

- “Distant [PTC] metastases are uncommon and usually occur in the bones, lungs, and thoracic lymph nodes”
- “Pancreatic metastasis from papillary thyroid cancer (PTC) is extremely rare; only 18 cases have been reported in the literature”
- “Diagnosis is difficult due to the occurrence of pancreatic metastasis after a long period and lack of specific imaging findings”
- “In some studies, the characteristics of pancreatic metastatic tumors are similar to those of primary pancreatic tumors. [Often] mimic primary pancreatic tumors and have been reported to appear as a solitary pancreatic mass in imaging studies.”

Song SH, Hur YH, Cho CK, Koh YS, Park EK, Kim HJ, Shin SH, Yu SY, Oh CY. Pancreatic metastasis from papillary thyroid cancer: a case report and literature review. Korean Journal of Clinical Oncology. 2023 Jun;19(1):32.

Table 1. Summary of cases of pancreatic metastasis from PTC

| First author | Age (yr) | Sex | Histology/stage | RAI | Imaging study | Imaging characteristics | Location in pancreas | Years from metastasis | Treatment | Recurrence or metastasis after surgery |
|---|---|---|---|---|---|---|---|---|---|---|
| Stein [11] | 39 | F | PTC/NA | No | ERCP, CT | Hypervascular on arteriography 5 cm isodense lesion | Head | 7 | NA | NA |
| | 53 | M | TCPTC/NA | Yes | MRI | 3×4 cm, well circumscribed | Head | 1 | PD | NA |
| | 67 | M | TCPTC/NA | Yes | PETCT, EUS | Hypermetabolic, hypodense mass 1.5×1.1 cm well defined hypoechoic, homogeneous mass | Head | 7 | NA | NA |
| | 82 | M | PTC/NA | Yes | EUS | NA | Neck | 5 | NA | NA |
| | 67 | F | FVPTC/pT2N1c | Yes | CT, MRCP | 1.8×1.5 cm hypovascular lesions, T1 and T2 hypointense, faint enhancement, well-circumscribed | Neck | 7 | NA | NA |
| | 66 | M | PTC/NA | NA | PET-CT, CT | 6.2×5.8 cm heterogeneously enhancing mass with clear border hypometabolic | Body and tail | 11 | DPS | NA |
| | 46 | M | TCPTC/NA | Yes | PET-CT | 3 cm well-circumscribed | Head | 3 | Pancreatic head mass resection | No recurrence |
| Meyer [6] | 67 | M | PTC/pT4N0 | Yes | CT | Capsulated cystic mass | Head | 5 | DP | 53 mo |
| Angeles-Angeles [4] | 72 | M | PTC/NA | NA | CT | 8.5 cm non encapsulated, well circumscribed | Body and tail | NA | DPS | NA |
| Borschitz [5] | 61 | M | PTC/pT3N1 | Yes | PETCT, MRI | Hypermetabolic isodense well circumscribed lesion | Body | 15 | DP | 9 mo |
| | 44 | F | FVPTC/pT3N1a | Yes | PETCT, MRI | Hypermetabolic, T1 hypointense, T2 intermediate well-circumscribed | Head | 10 | Enucleation | 42 mo |
| Alzahrani [13] | 55 | M | PTC/pT4aN1b | Yes | PETCT, MRI | 1.7 cm well circumscribed hypermetabolic | Head | 8 | Sorafenib | No surgery |
| Davidson [7] | 84 | F | TCPTC/pT3N1b | Yes | PETCT, CT | Hypermetabolic, well circumscribed 1.1 cm enhancing mass | Body | 2 | NA | NA |
| Cho [2] | 81 | M | PTC/NA | Yes | PETCT, MRCP | Hypermetabolic lesion 1×0.8 cm T1 hypointense, slightly T2 hyperintense, diffusion restriction, peripheral enhancement | Head/body | 10 | Systemic treatment | NA |
| Ren [3] | 47 | M | PTC/NA | Yes | US, CT | 4×3 cm pancreatic space occupying lesions with main ductal dilation | Body and tail | 0 | DPS | No recurrence |
| Rossi [8] | 60 | M | PTC/NA | No | CT, MRI, EUS | 2 cm hypoechoic lesion and intraductal growth | Head | 15 | PD | NA |
| Tramontin [9] | 73 | M | PTC/pT4aN1b | Yes | PETCT | 2.8 cm mass | Head | 6 | PD | NA |
| Wong [10] | 75 | M | PTC/NA | Yes | PETCT | Hypodense, well circumscribed lesion with atrophy of distal pancreas hypermetabolic | Body and tail | 7 | NA | NA |
| Present case | 51 | M | PTC/pT3N1b | Yes | CT, MRCP, PETCT | Well circumscribed dominant cystic mass of 5.6 cm with a 2.6 cm mural enhancing solid portion on the posterior wall with diffusion restriction, hypermetabolic | Tail | 6 | DPS | No recurrence |

# Discussion

- “Distant [PTC] metastases are uncommon and usually occur in the bones, lungs, and thoracic lymph nodes”
- “Pancreatic metastasis from papillary thyroid cancer (PTC) is extremely rare; only 18 cases have been reported in the literature”
- “Diagnosis is difficult due to the occurrence of pancreatic metastasis after a long period and lack of specific imaging findings”
- “In some studies, the characteristics of pancreatic metastatic tumors are similar to those of primary pancreatic tumors. [Often] mimic primary pancreatic tumors and have been reported to appear as a solitary pancreatic mass in imaging studies.”
- “EUS-guided biopsy may be an appropriate diagnostic method, which has a sensitivity of 80% to 90%, a specificity of nearly 100%, and an accuracy in diagnosing metastatic lesions of 89%”
- “When the metastatic pancreatic lesion is a single metastatic tumor, pancreatectomy can increase the 5-year survival rate up to 31%”

Song SH, Hur YH, Cho CK, Koh YS, Park EK, Kim HJ, Shin SH, Yu SY, Oh CY. Pancreatic metastasis from papillary thyroid cancer: a case report and literature review. Korean Journal of Clinical Oncology. 2023 Jun;19(1):32.

# QR Code: EVALUATION QR CODE! Hold smartphone camera on code