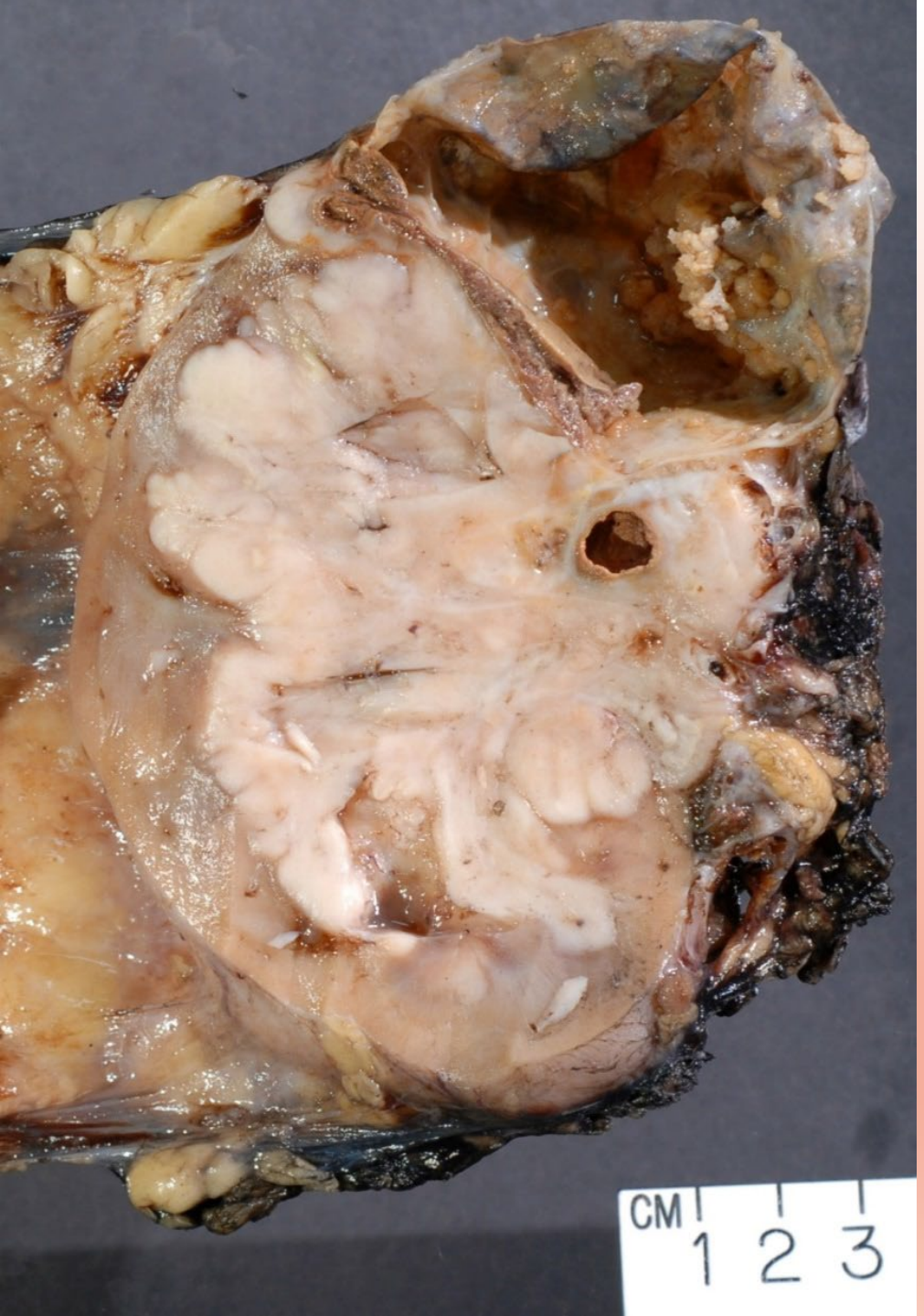
Case Studies in Hereditary Kidney Tumors

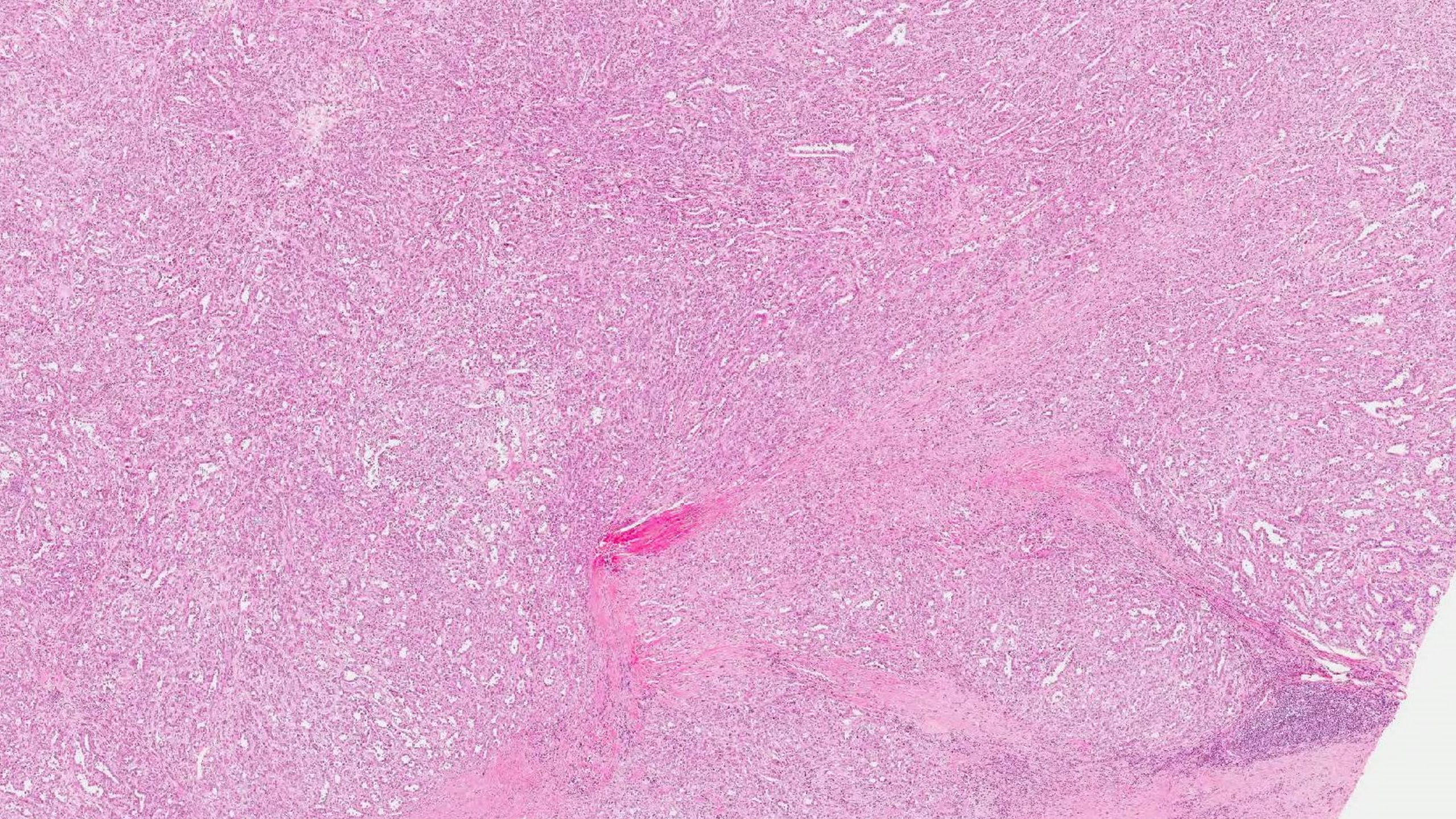
Christopher Przybycin, MD

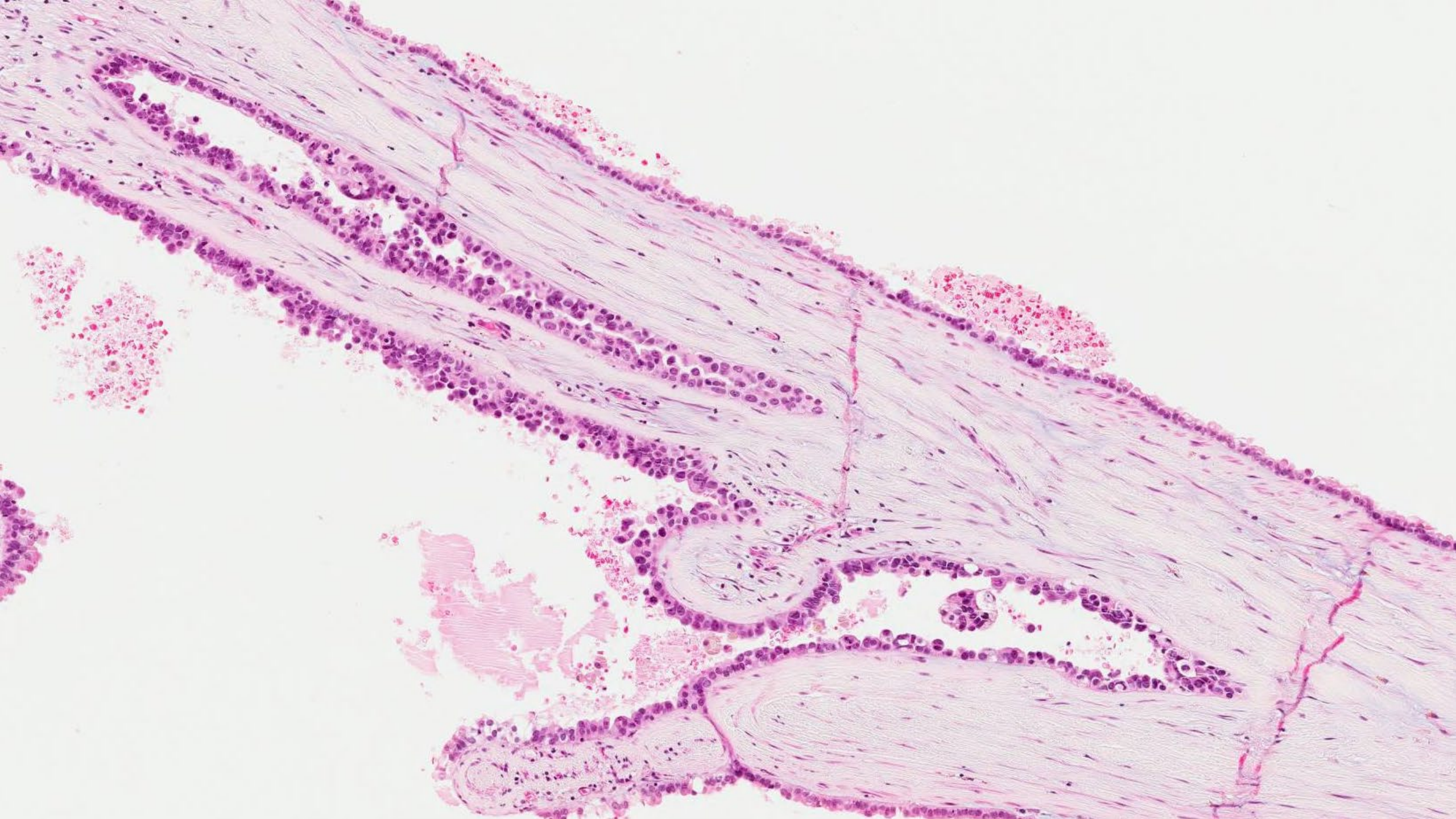
Cleveland Clinic

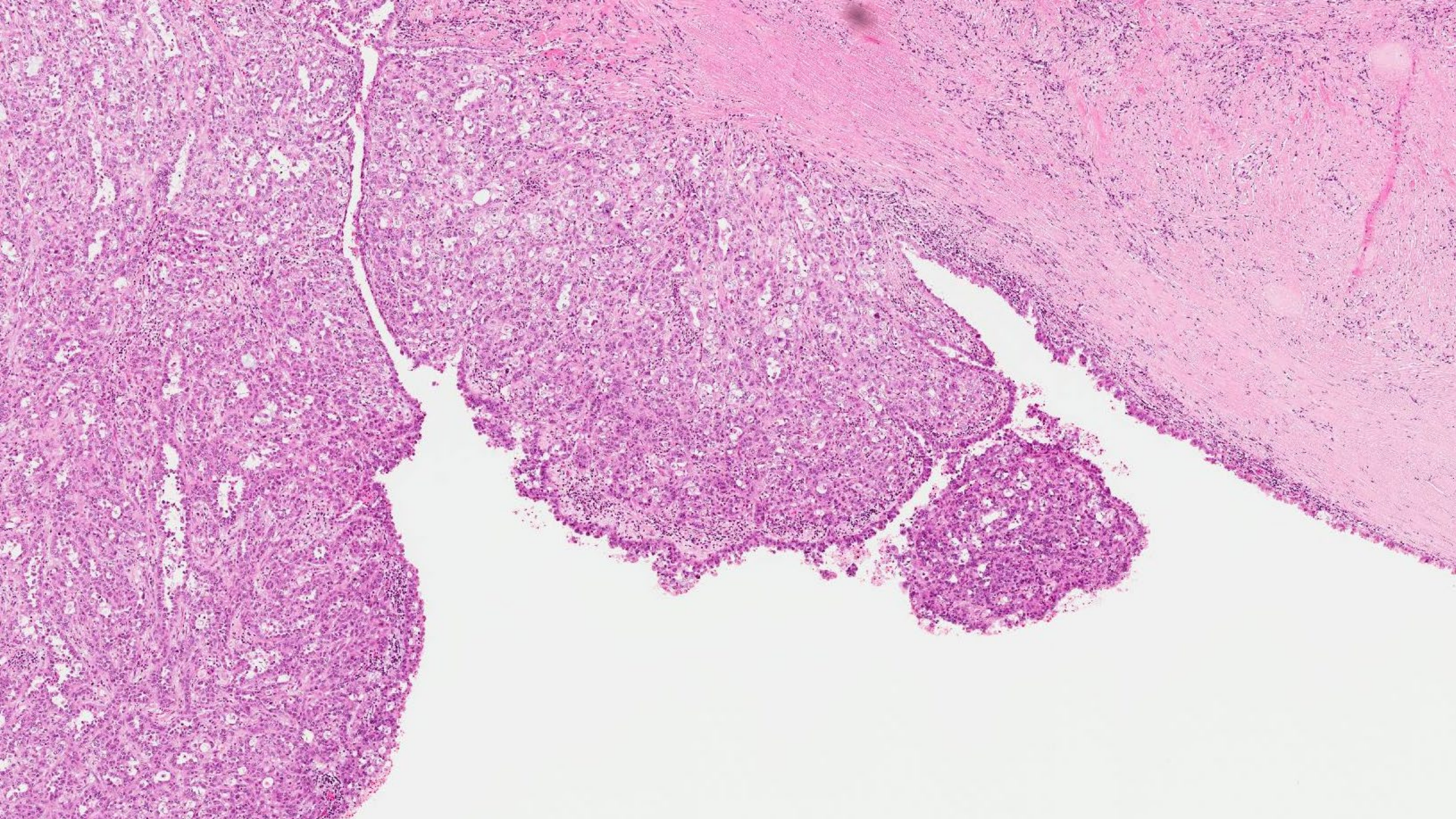
Case 1

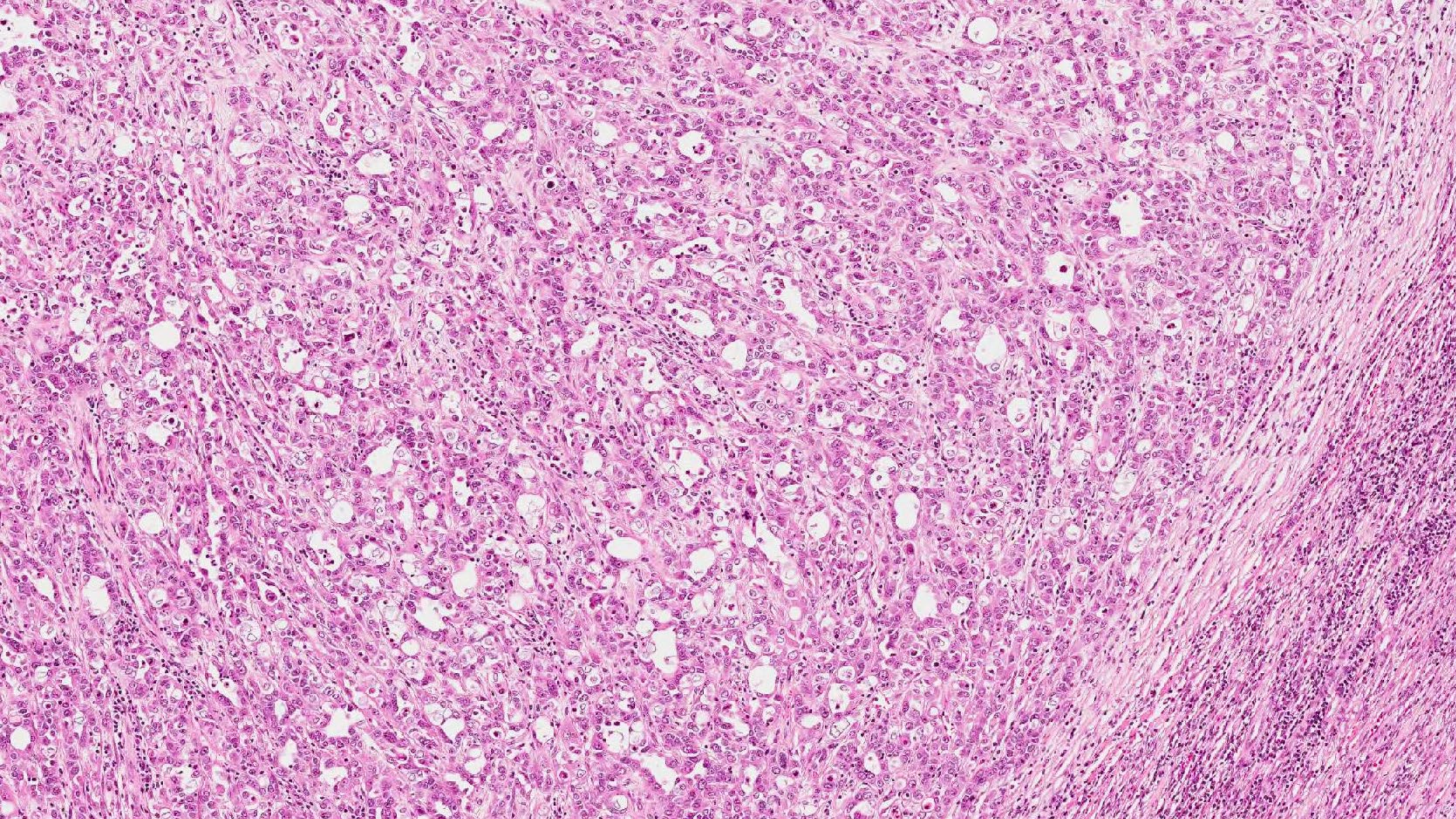


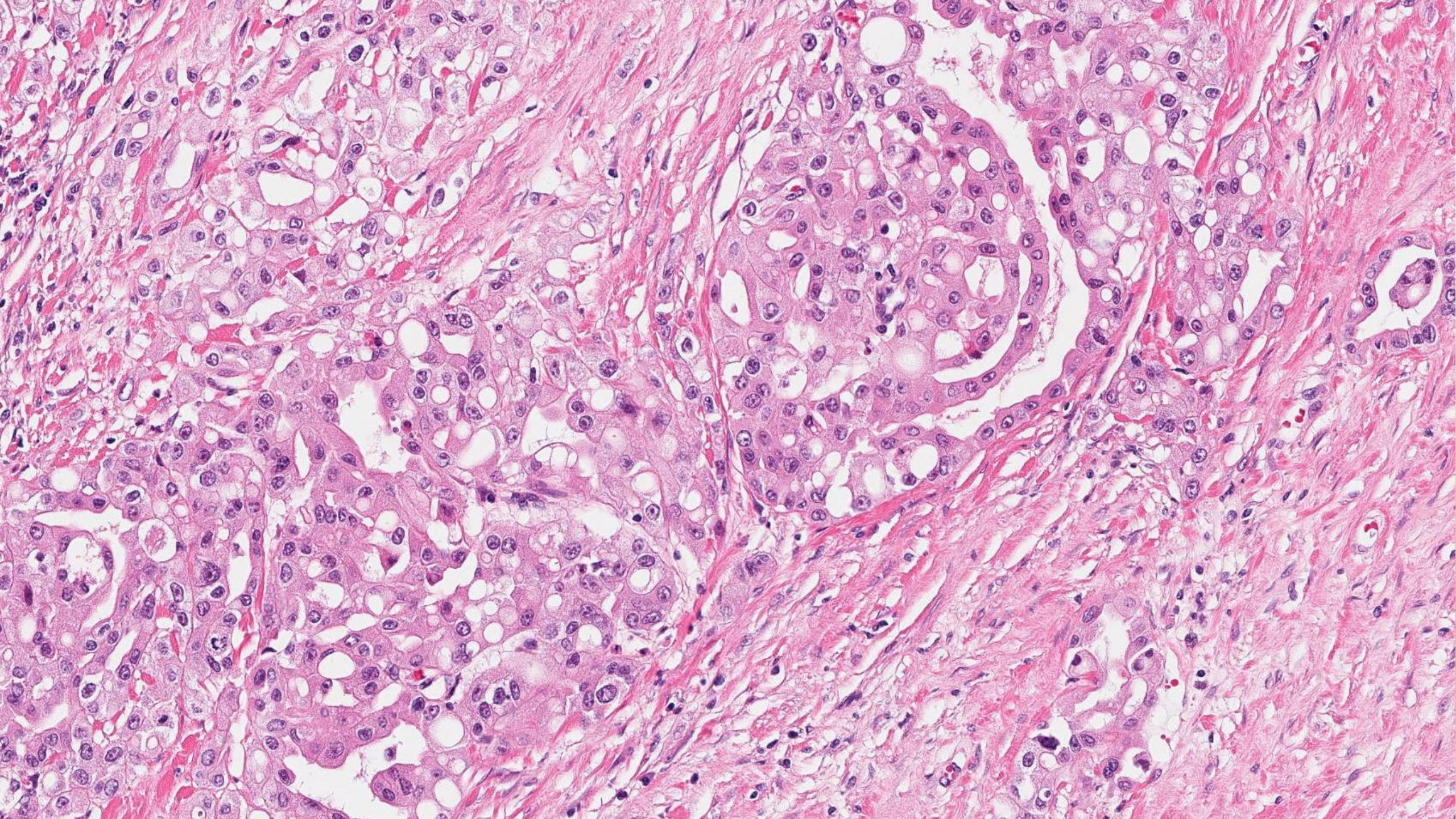
- 48-year-old woman
- Kidney mass

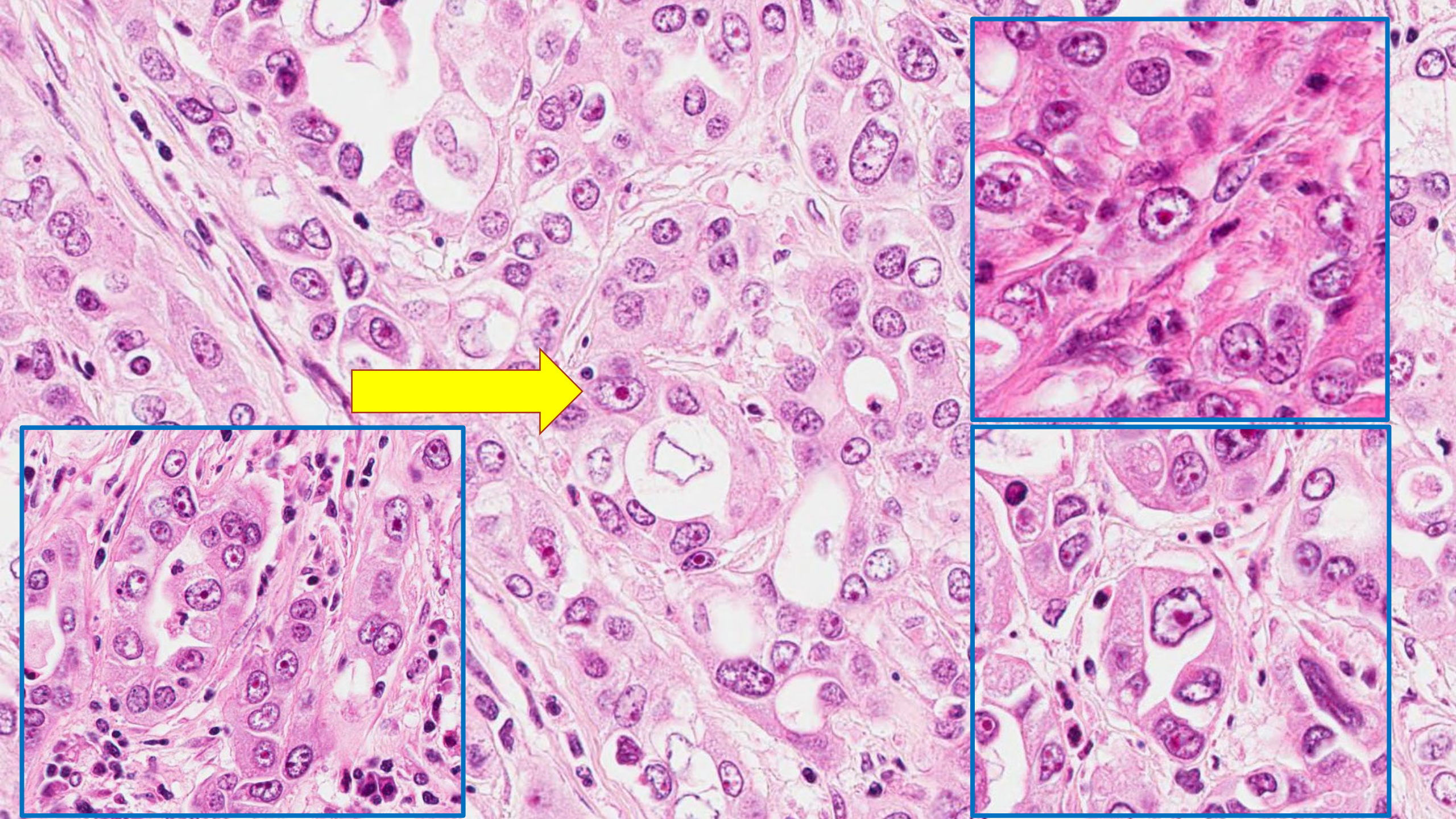


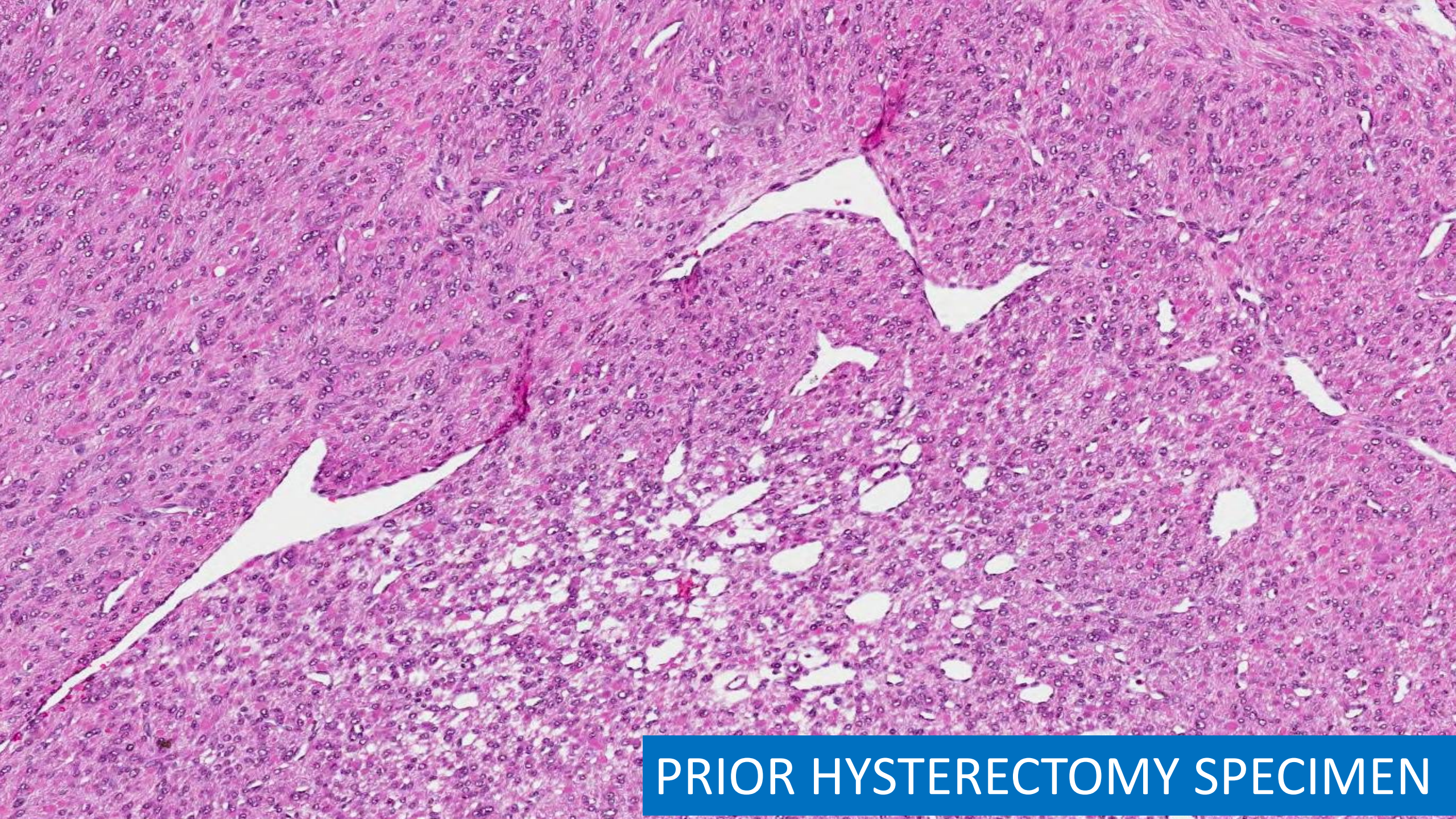


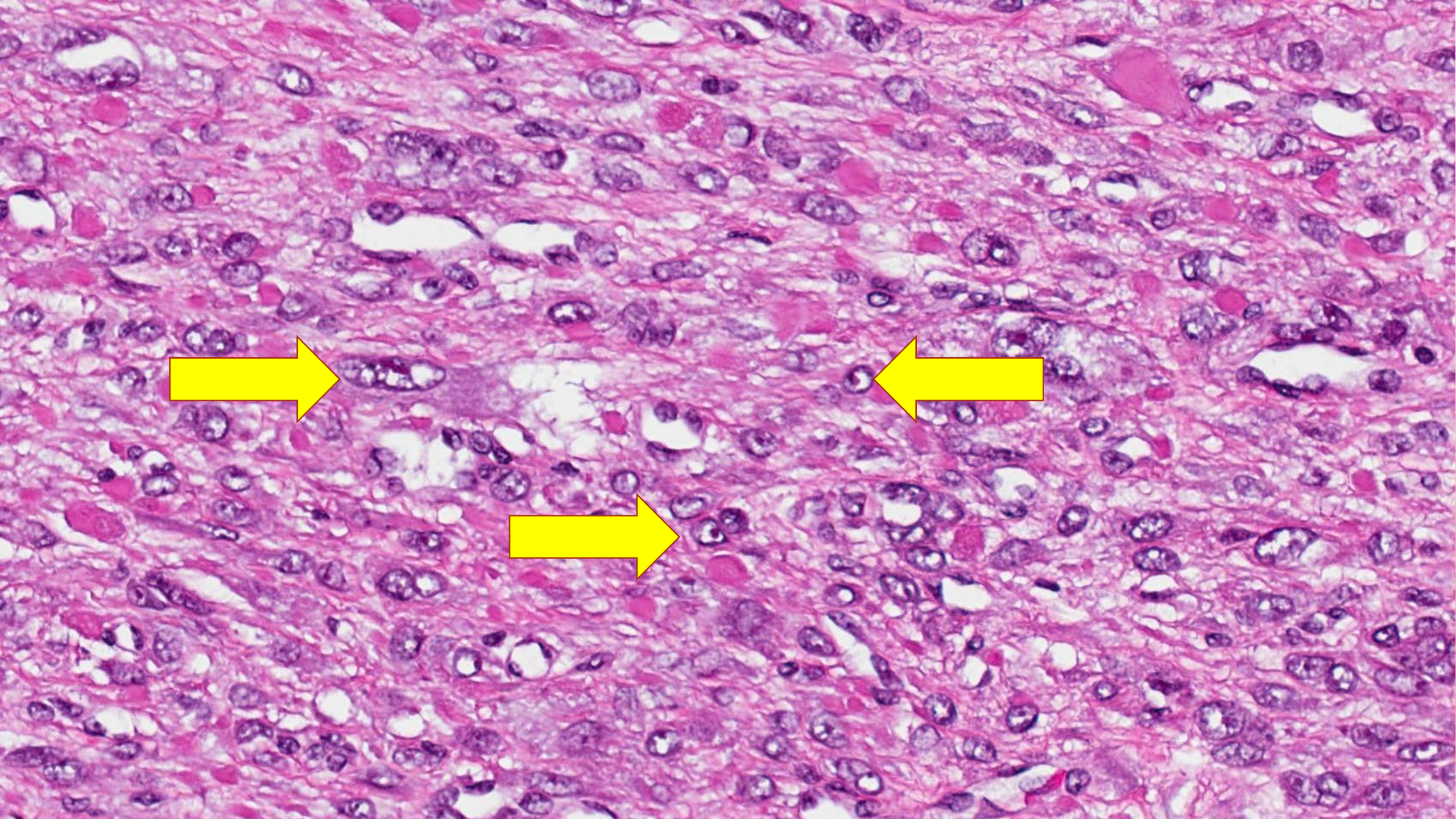






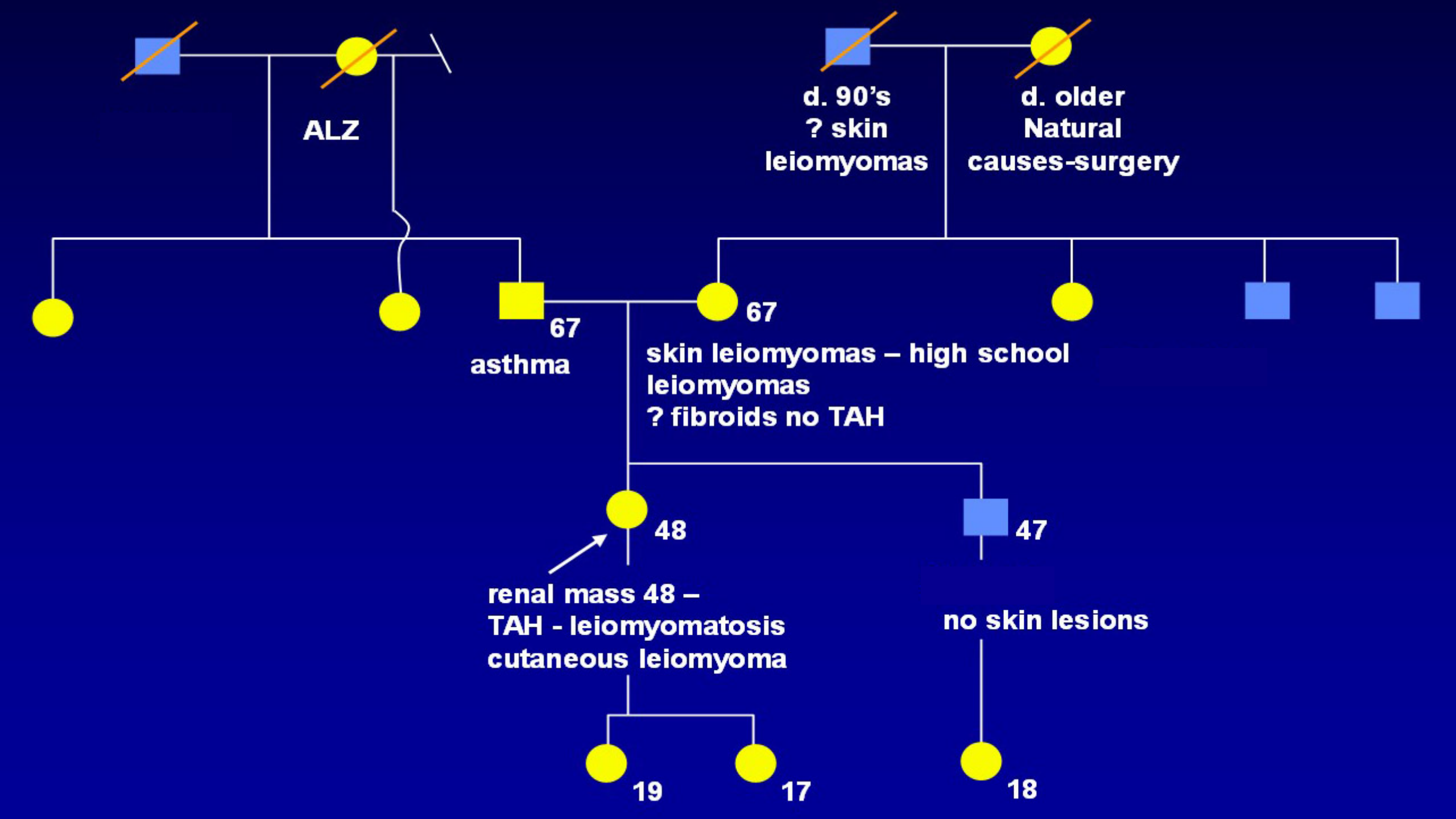



PRIOR HYSTERECTOMY SPECIMEN



Diagnosis

- Fumarate hydratase (FH)-deficient Renal Cell Carcinoma
  - Associated with Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC) syndrome


ALZ
d. 90's
? skin
leiomyomas
d. older
Natural
causes-surgery
67
asthma
67
skin leiomyomas – high school
leiomyomas
? fibroids no TAH
48
47
renal mass 48 –
TAH - leiomyomatosis
cutaneous leiomyoma
no skin lesions
19
17
18

First take-home point

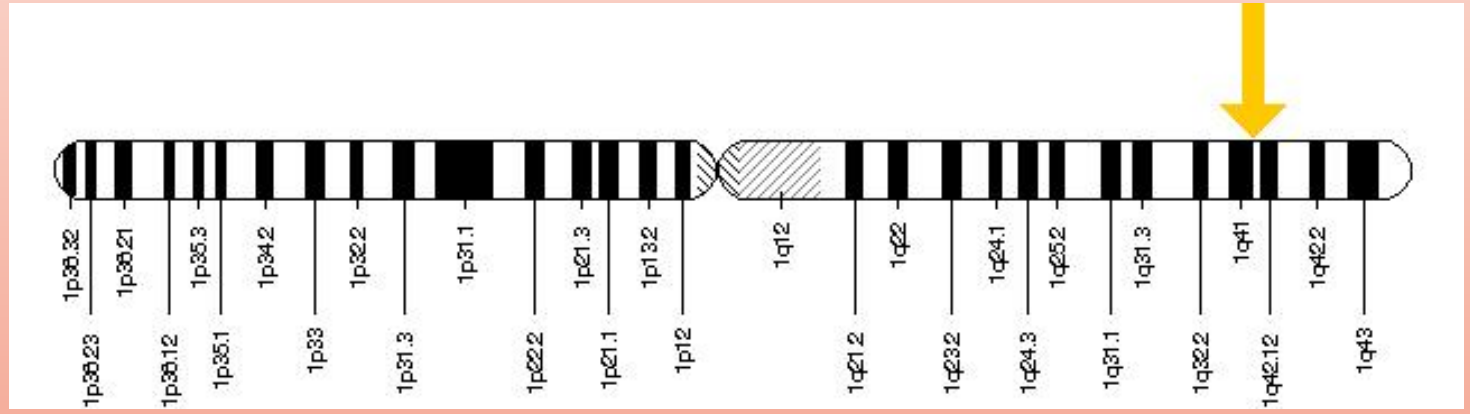
History may not necessarily suggest a hereditary kidney tumor syndrome

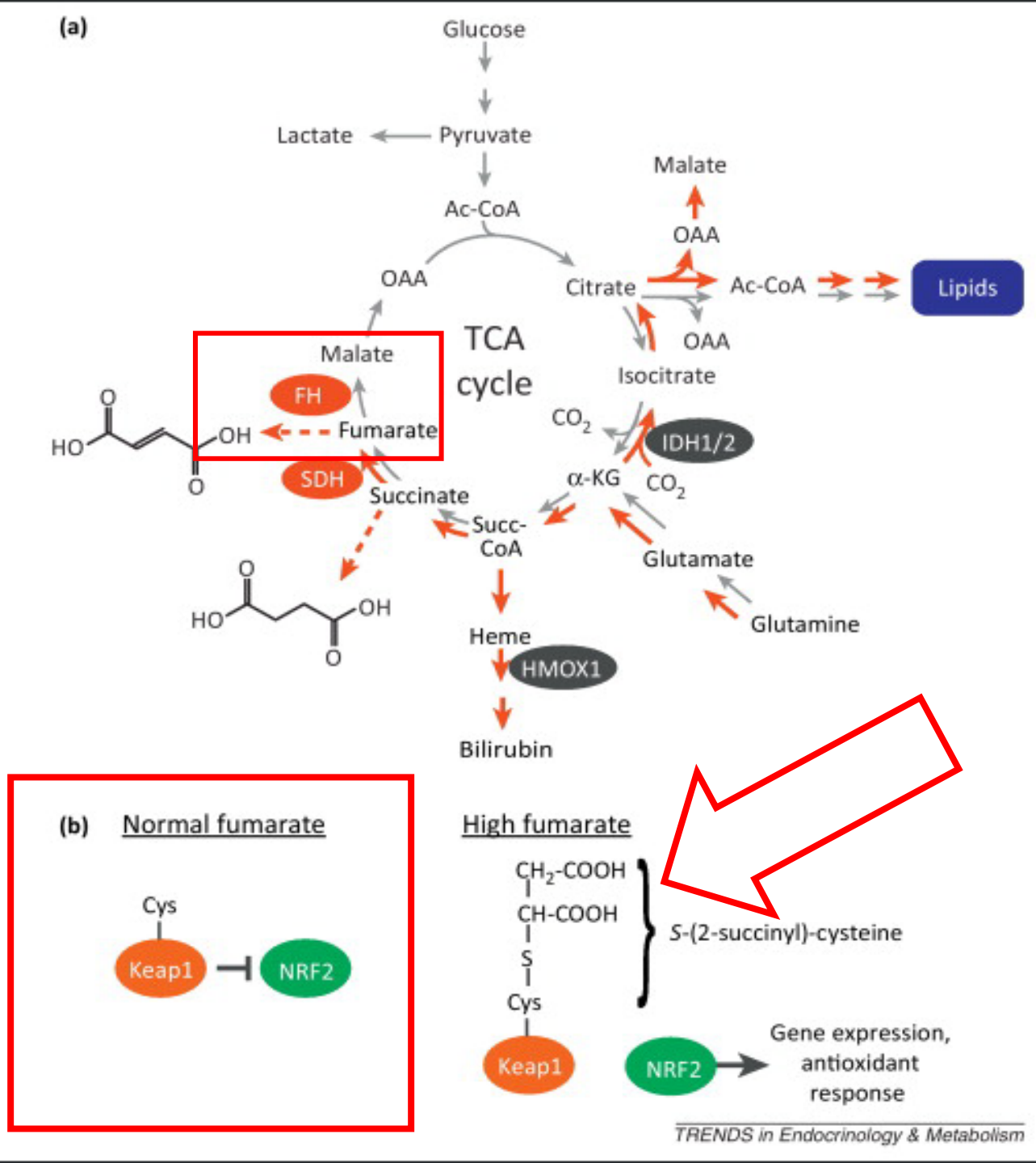
Sequencing for germline Fumarate Hydratase gene mutations

- Tier 1 (hotspot)
  - Negative for *FH* mutation
- Tier 2 (remainder of coding regions of *FH*)
  - Heterozygous for deletion in *FH*

Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome (HLRCC)

- Autosomal dominant syndrome
- Germline mutations in one allele of fumarate hydratase (FH) gene (1q42.3-q43)

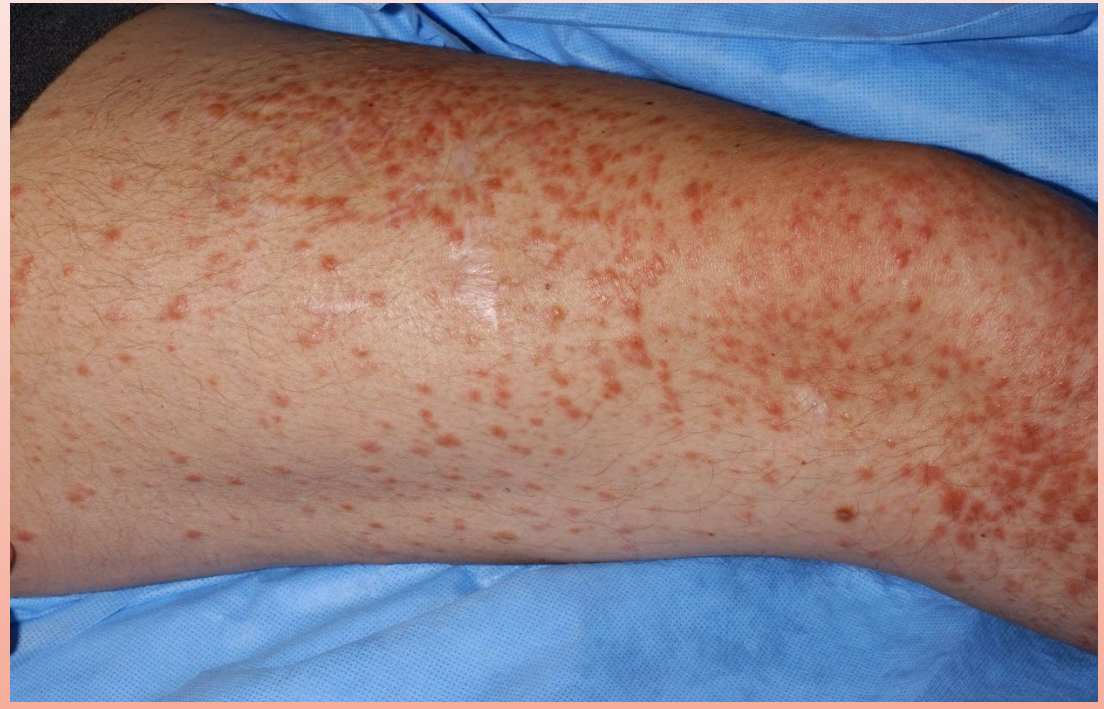




Mullen, A and DeBerardinis, R. Genetically-defined metabolic reprogramming in cancer. *Trends in Endocrinology and Metabolism.* 2012, (23)11; 552-559.

HLRCC syndrome clinical manifestations

- Cutaneous leiomyomas (penetrance 75-90%)
- Bulky uterine leiomyomas (penetrance 75-100%)
- Renal cell carcinoma (solitary; penetrance 15-30%)

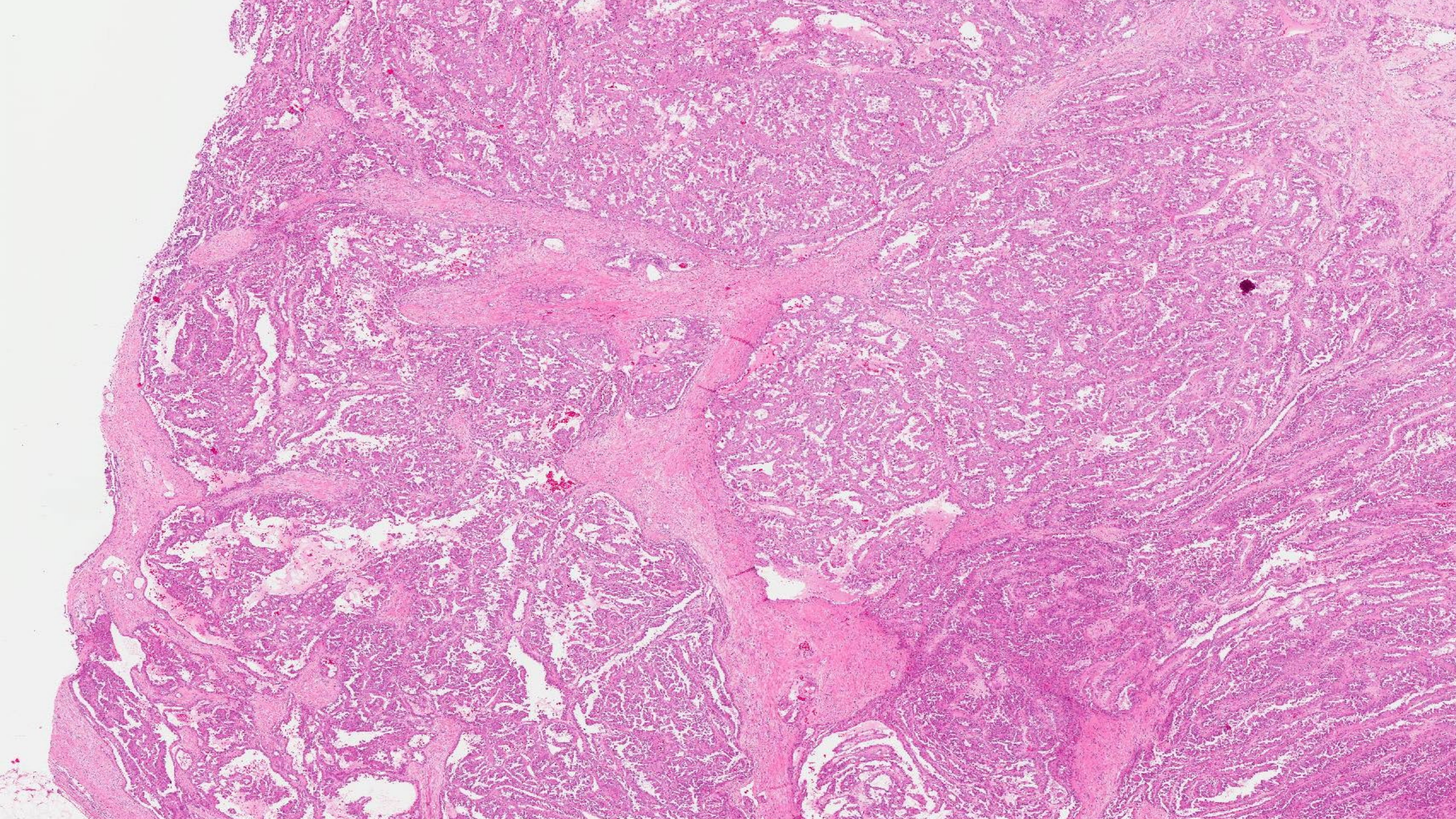


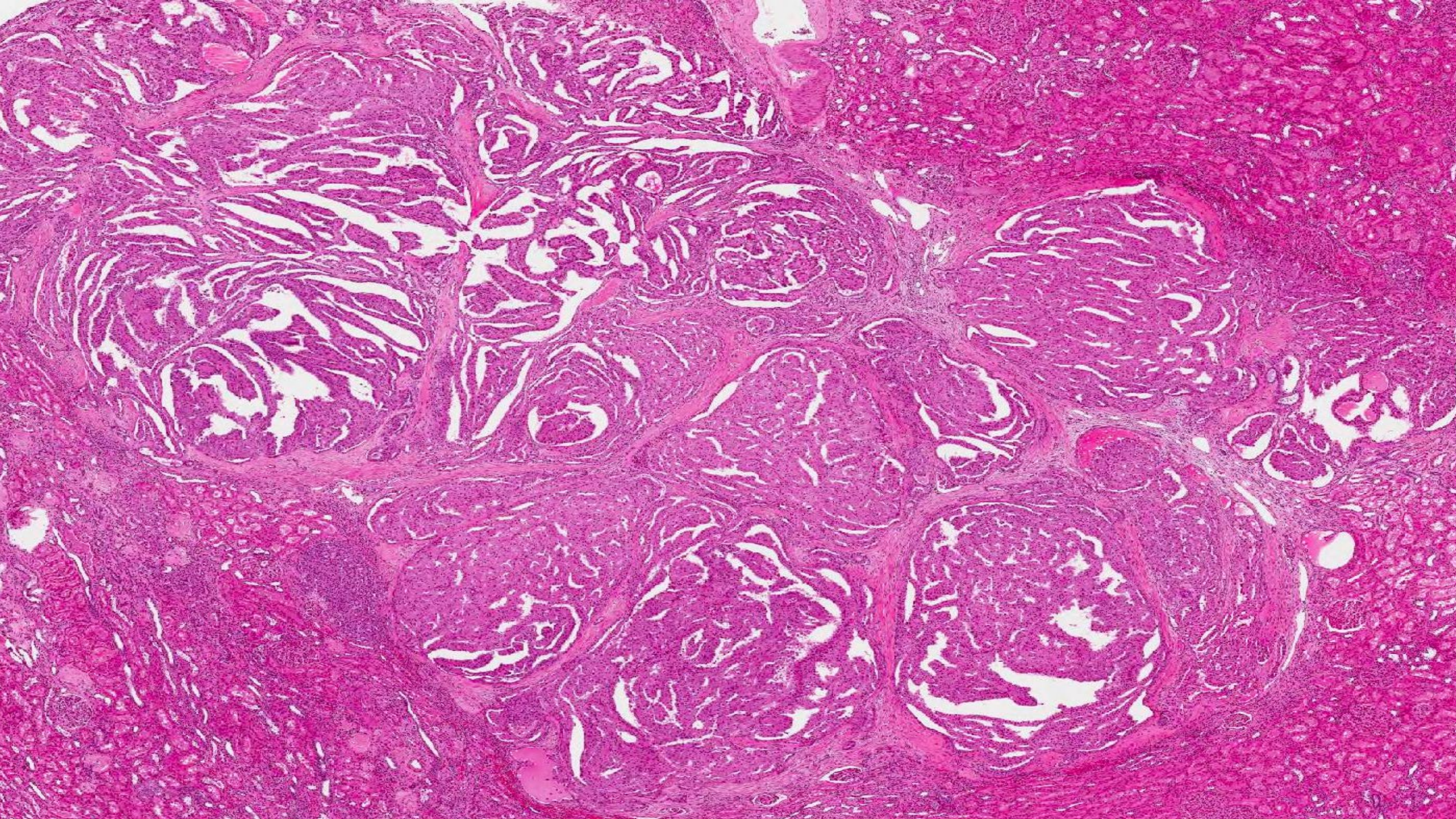
Source: National Cancer Institute
https://nci-media.cancer.gov

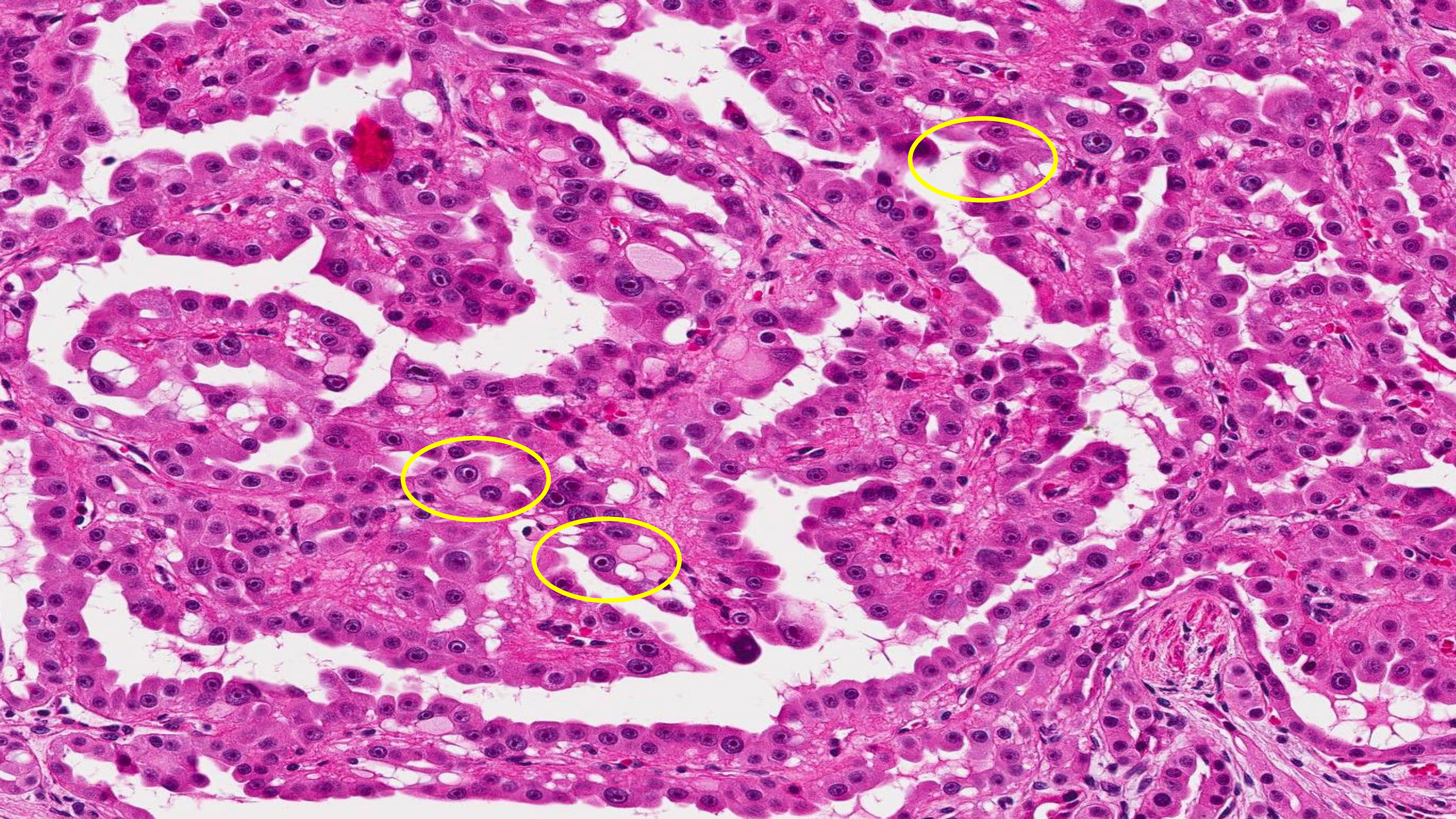
HLRCC Syndrome-associated RCC

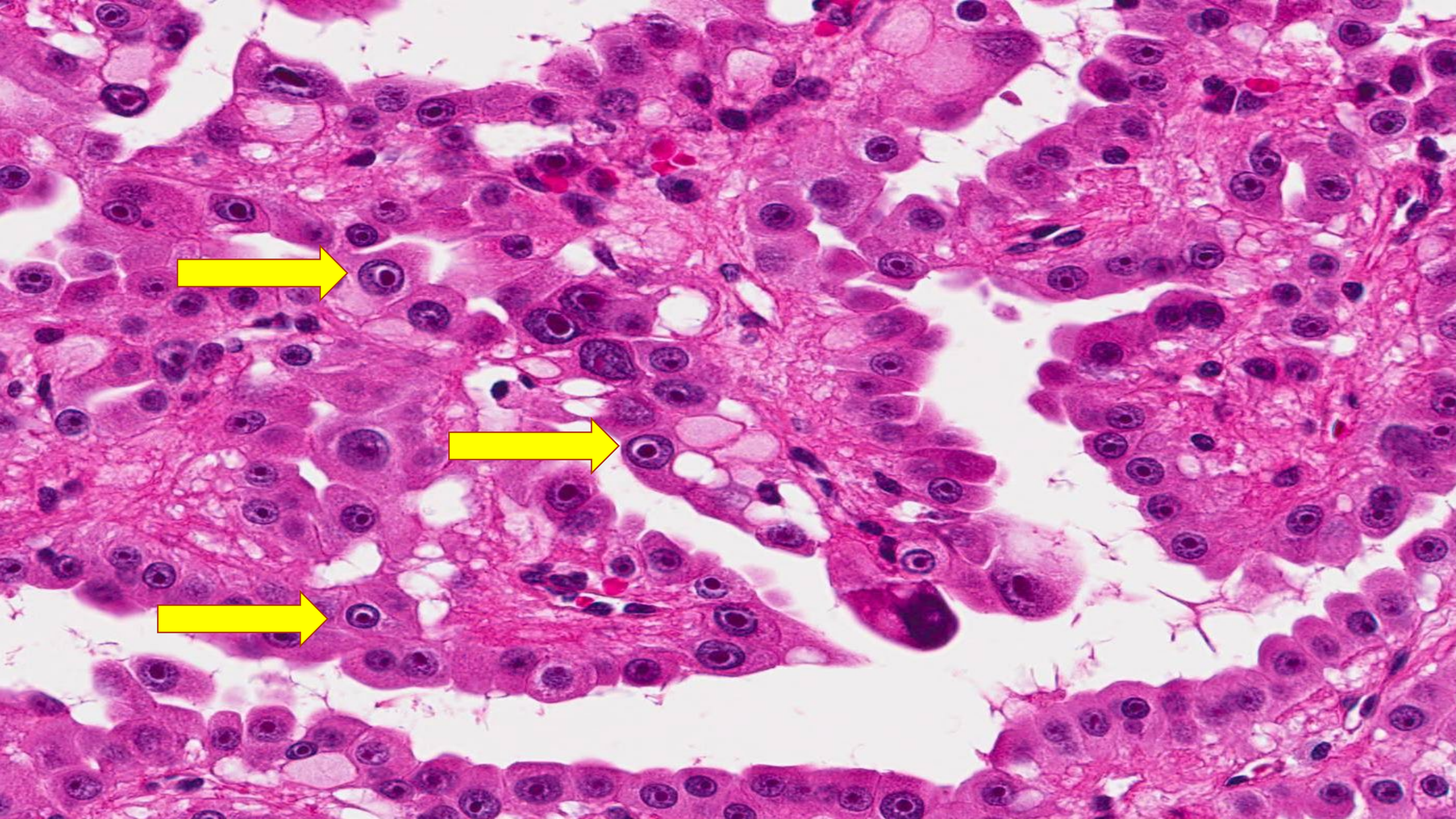
- Merino et al, AJSP 2007
- 40 tumors (38 patients) from HLRCC families with proven *FH* germline mutations

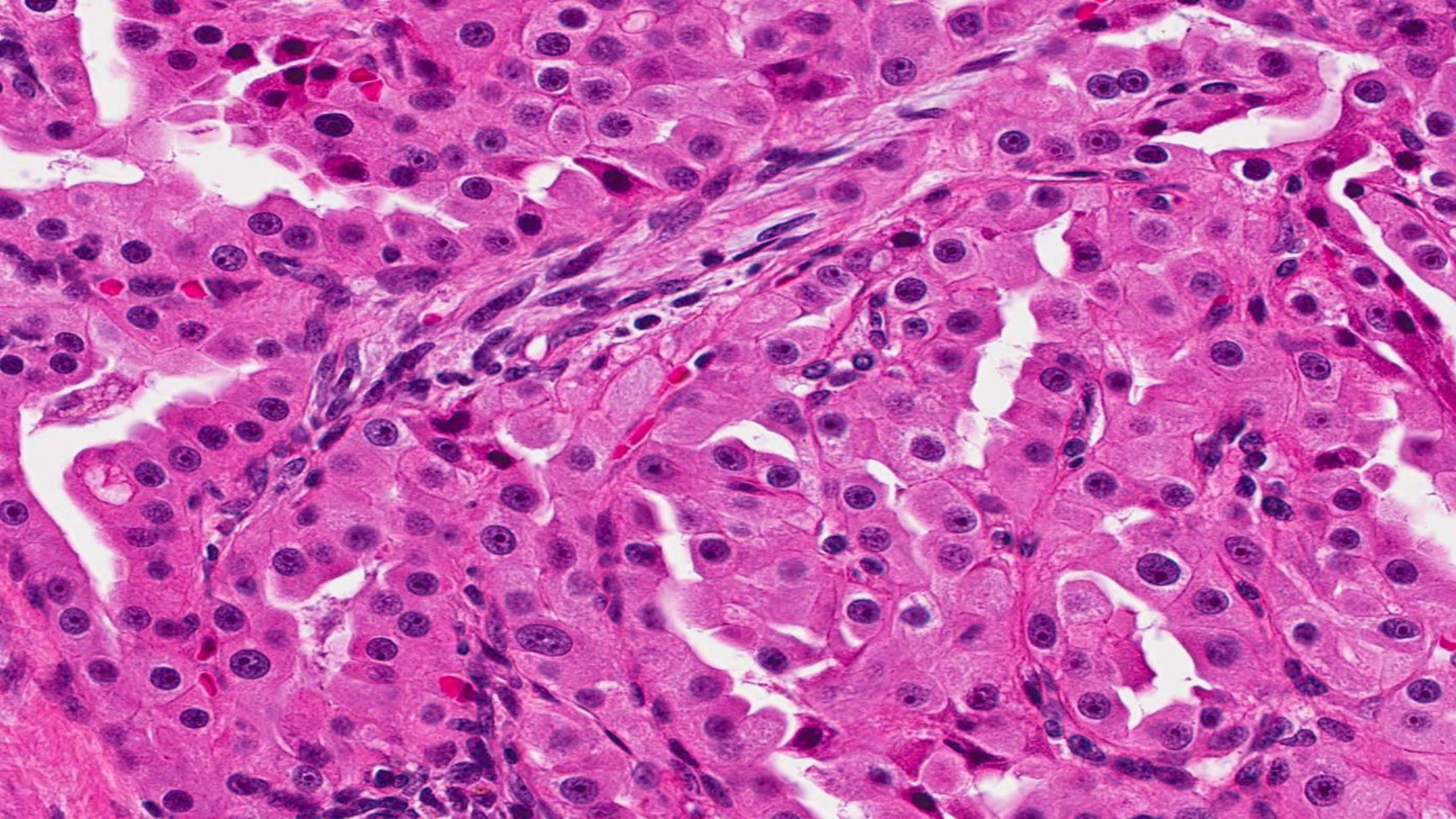
- Characteristic nuclear features
- Variable architecture
- Unilateral and solitary
- High stage, poor prognosis

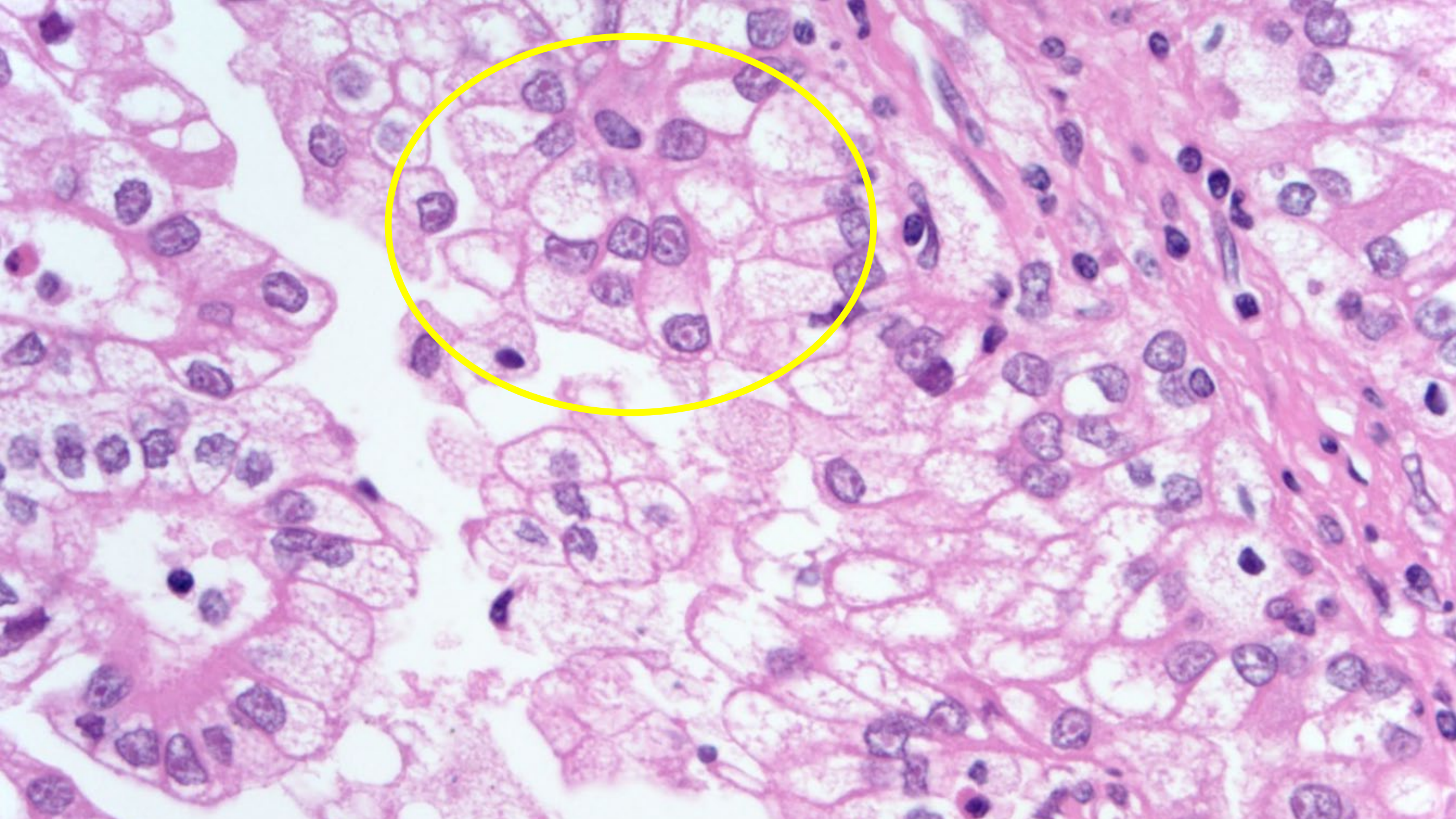


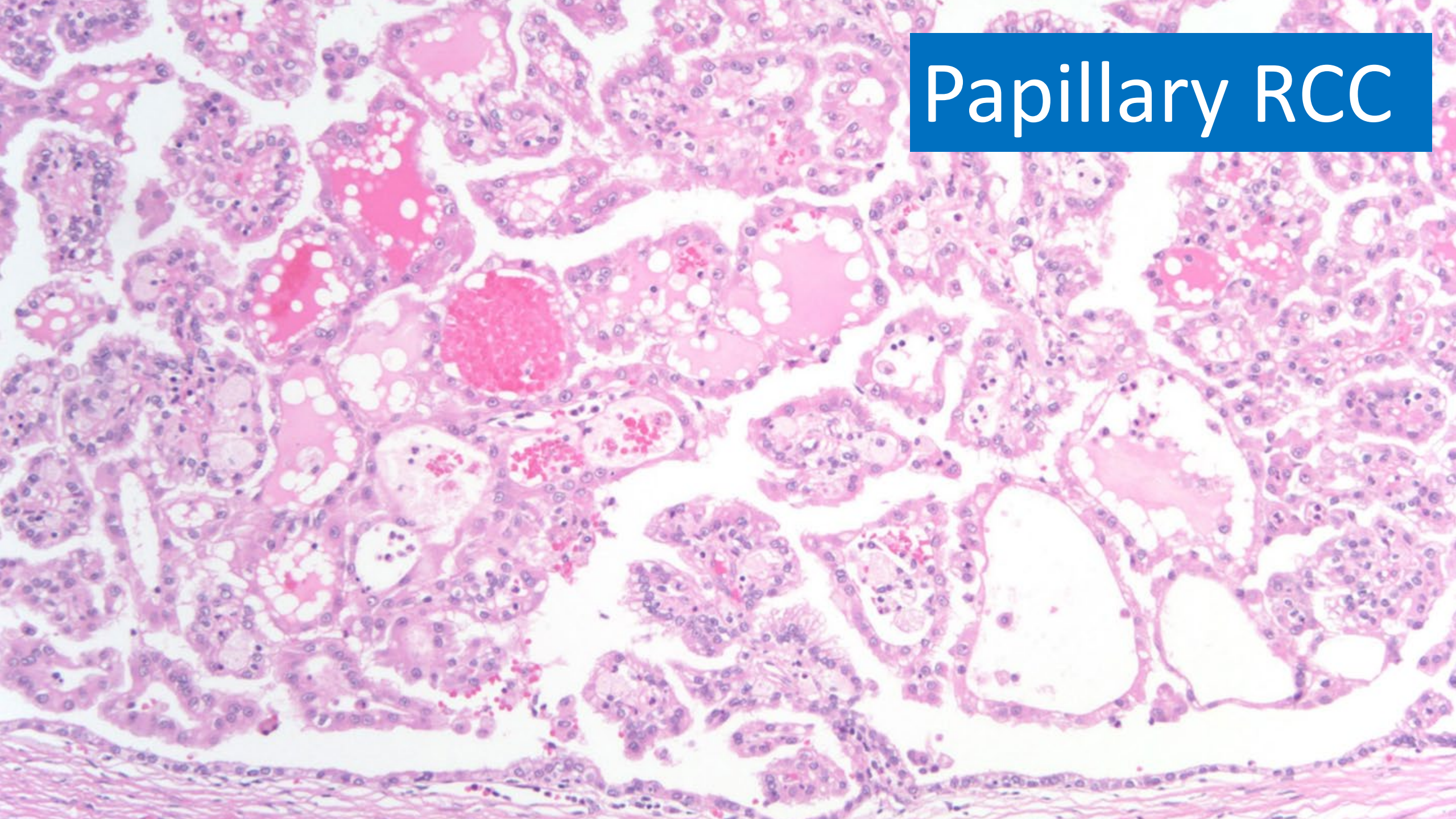






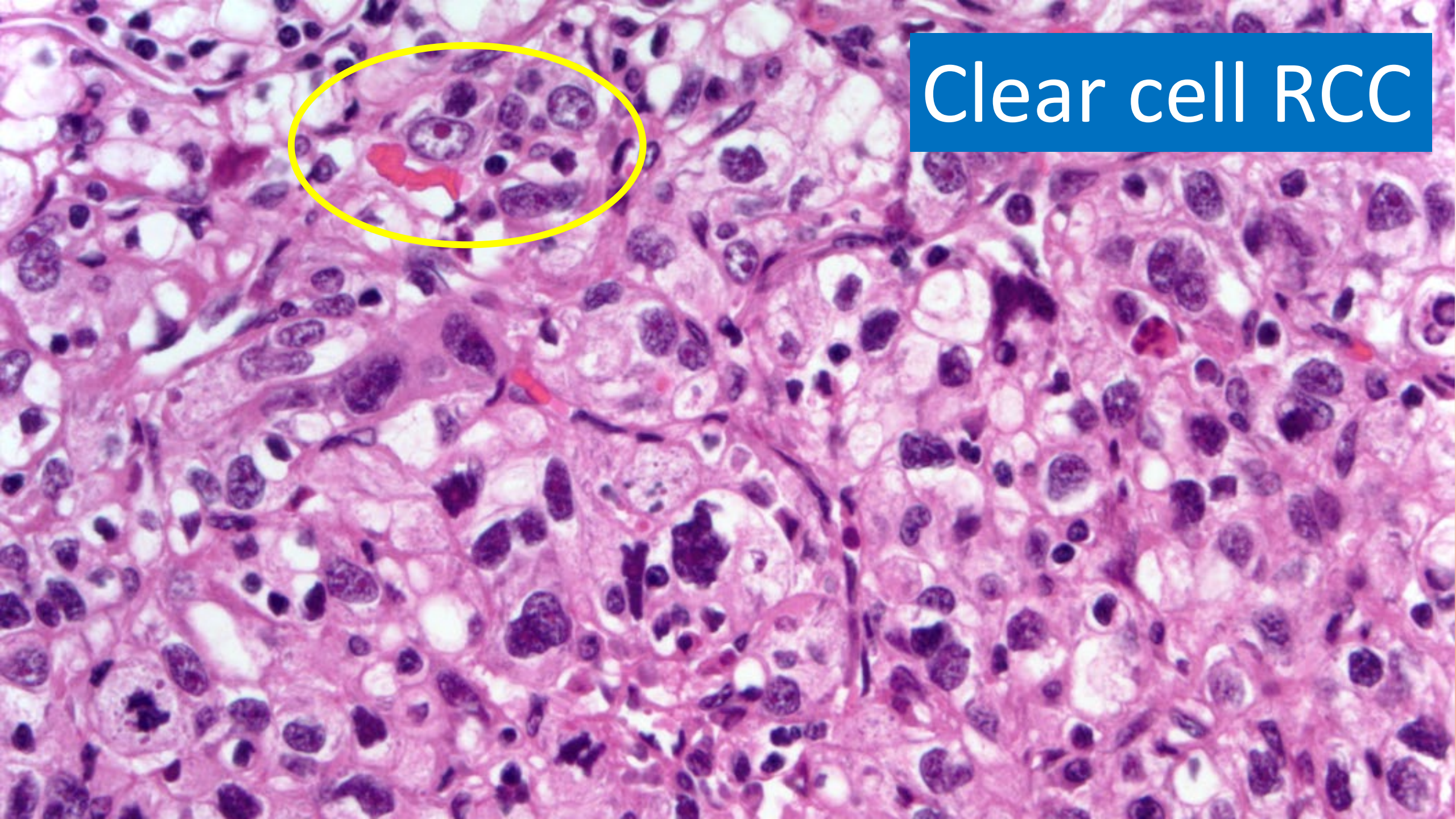


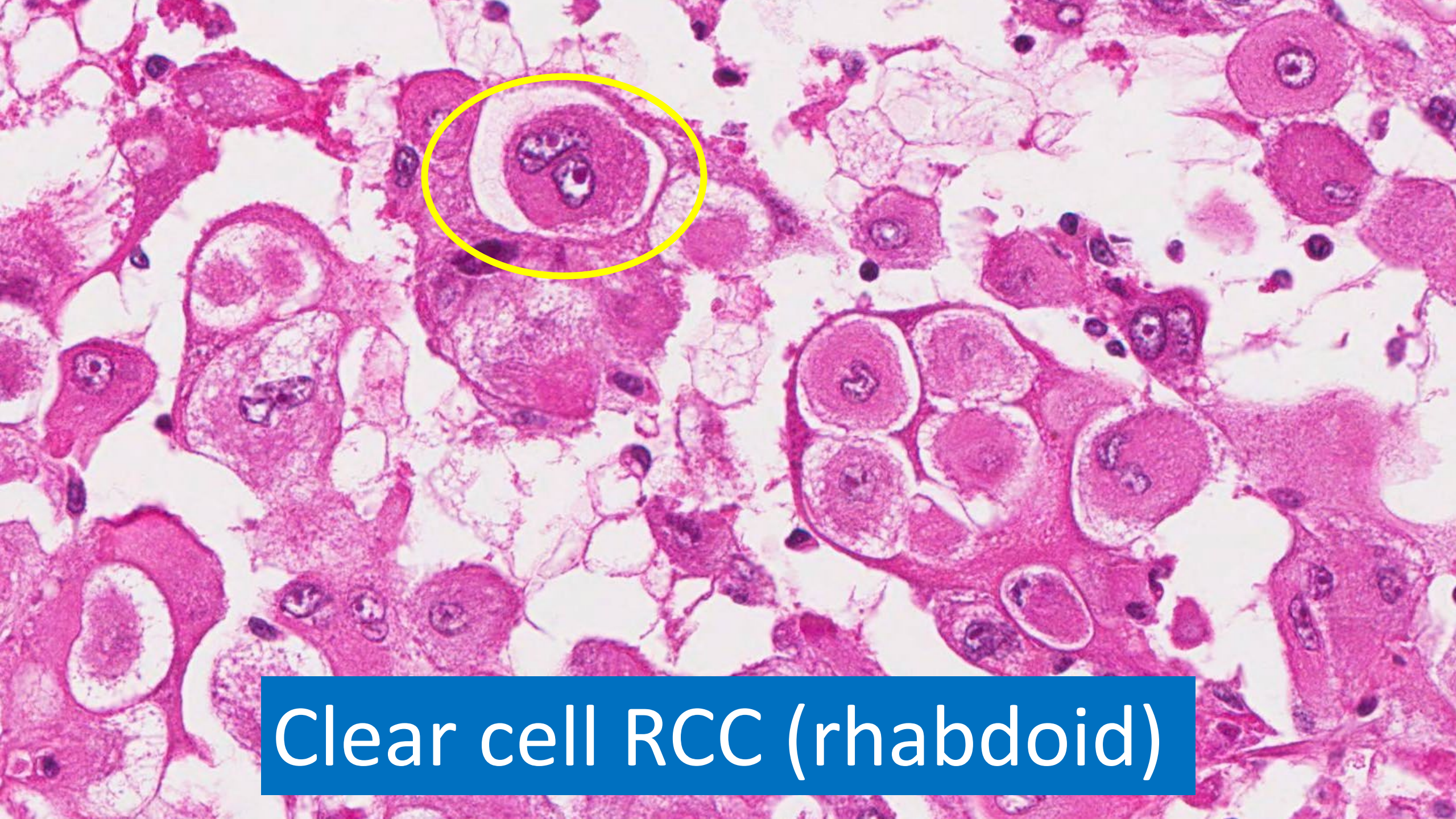



Papillary RCC

Second take-home point

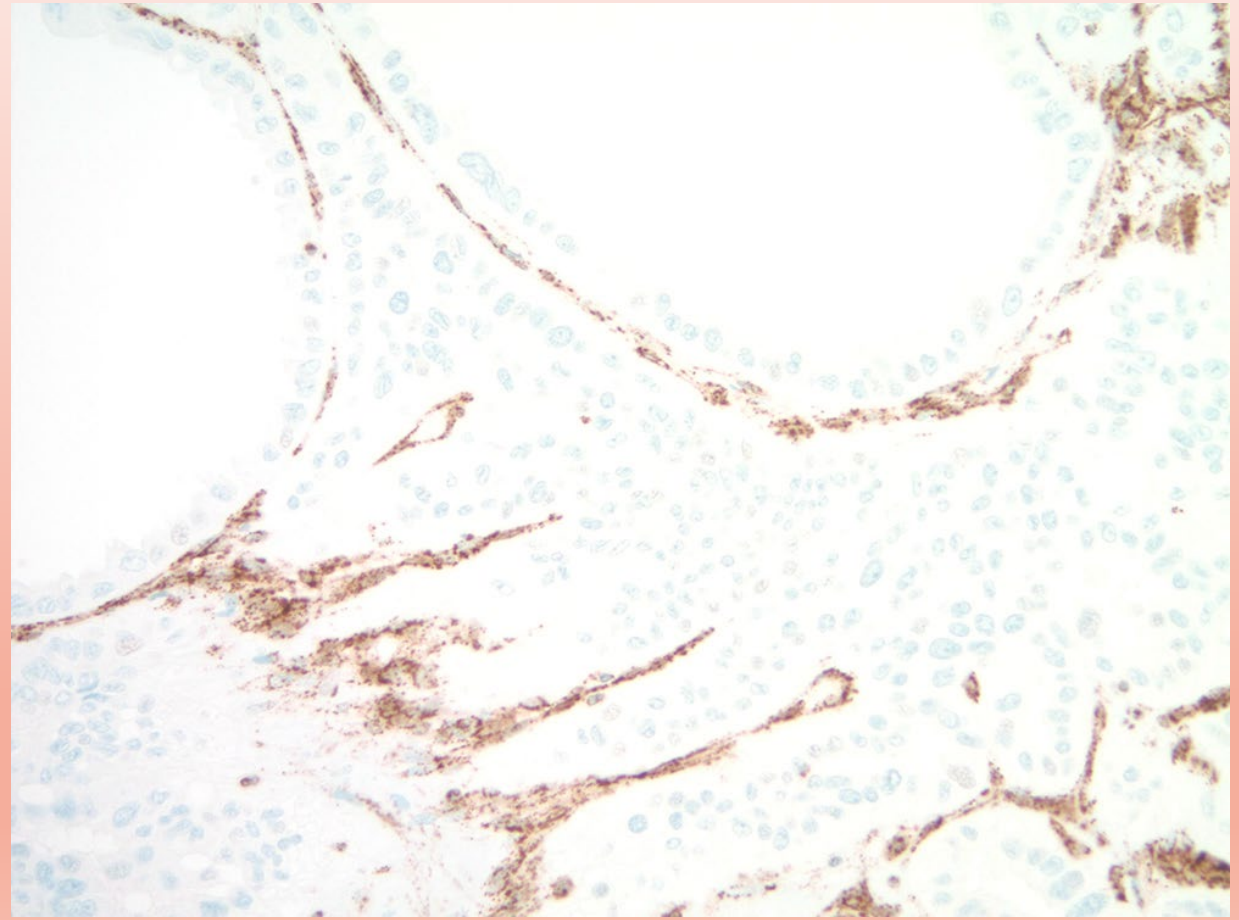
Morphologic context matters


Clear cell RCC


Clear cell RCC (rhabdoid)

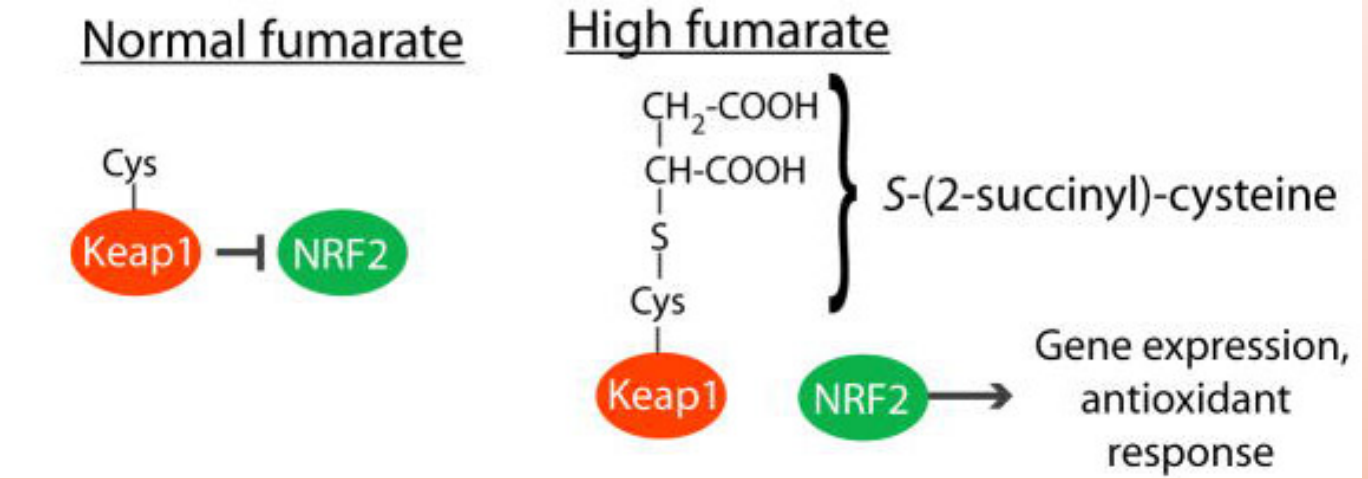
IHC as an aid to diagnosis

- Loss of fumarate hydratase expression
  - Seen in ~75-85% of FH-deficient RCCs



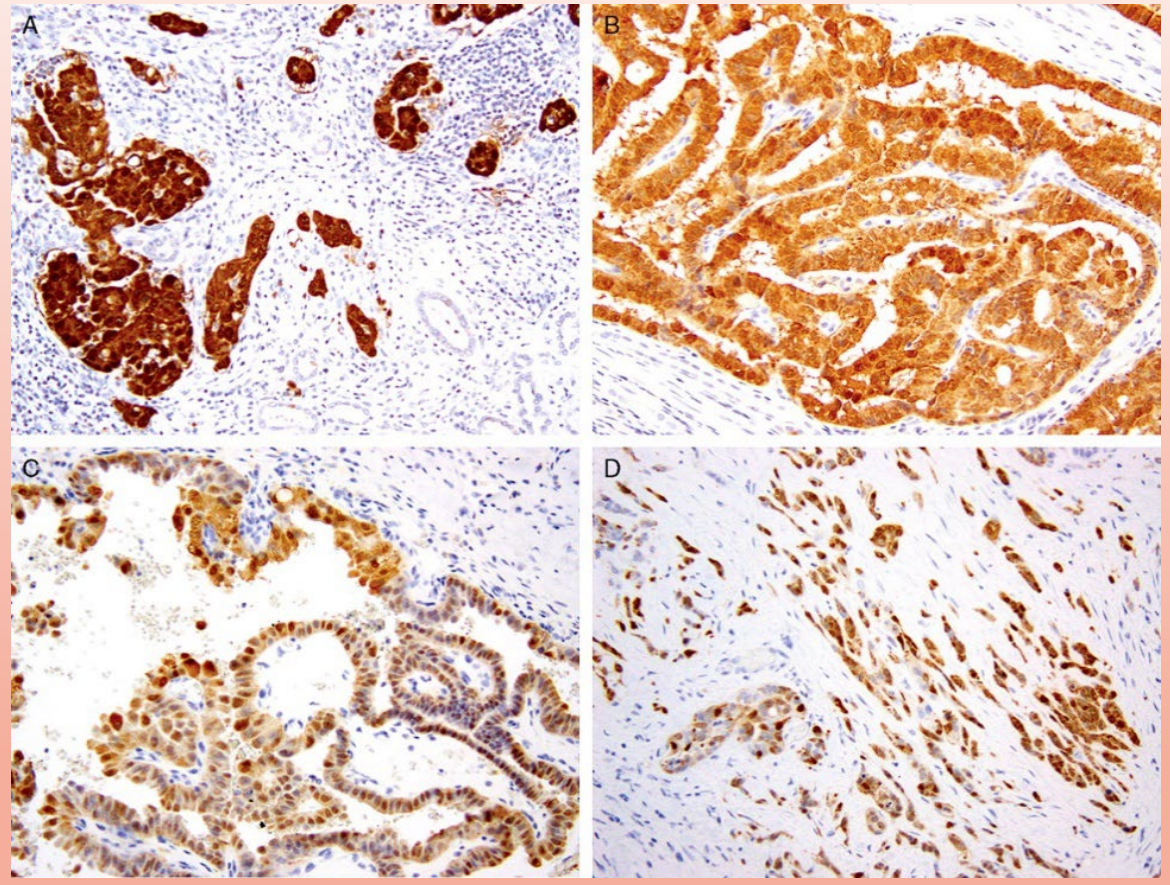
IHC as an aid to diagnosis

- Chen et al, AJSP 2014
- 9 tumors (9 patients)
  - Detected by morphology
- ↑fumarate→succination
  - Bardella et al. J Pathol 2011.
- High stage, poor prognosis, unilateral and solitary, variable architecture, limited clinical history



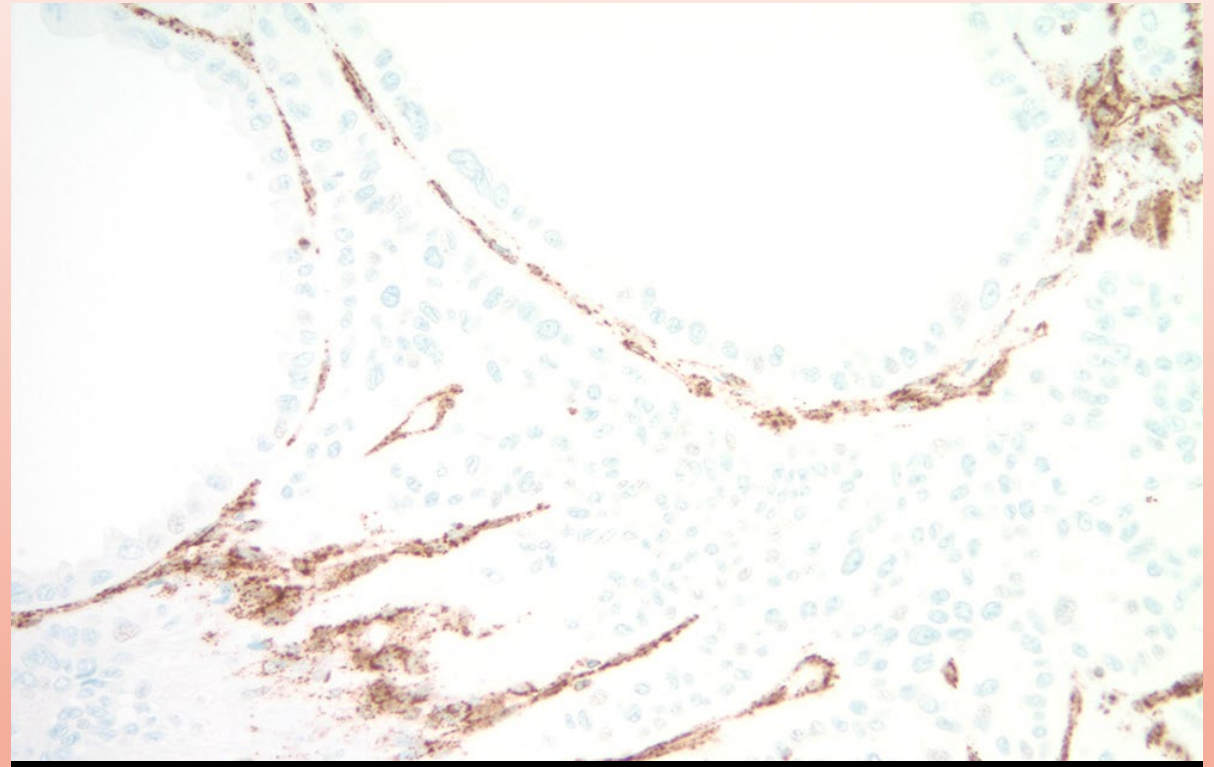
2SC expression: *FH* mutation

- Diffuse 2SC expression (nuclear+cytoplasmic) correlates with *FH* mutation

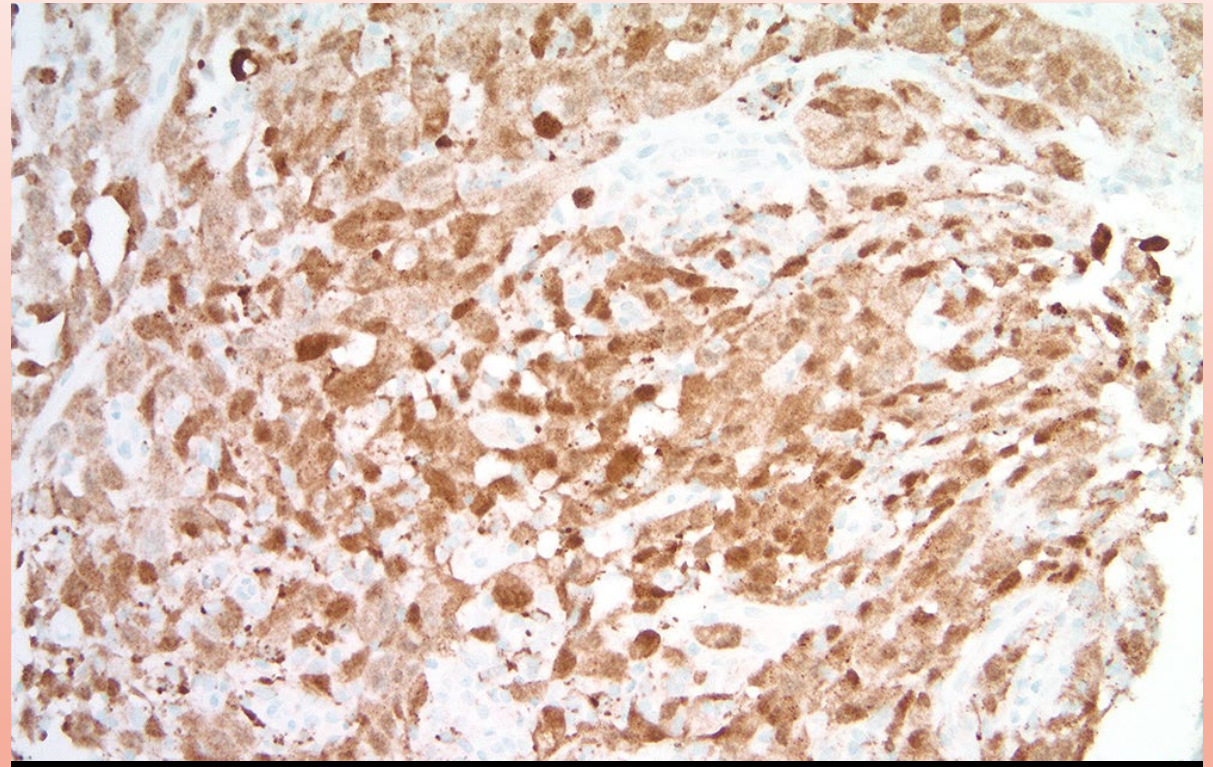


Chen et al. AJSP 2014

FH-deficient RCC



Fumarate hydratase



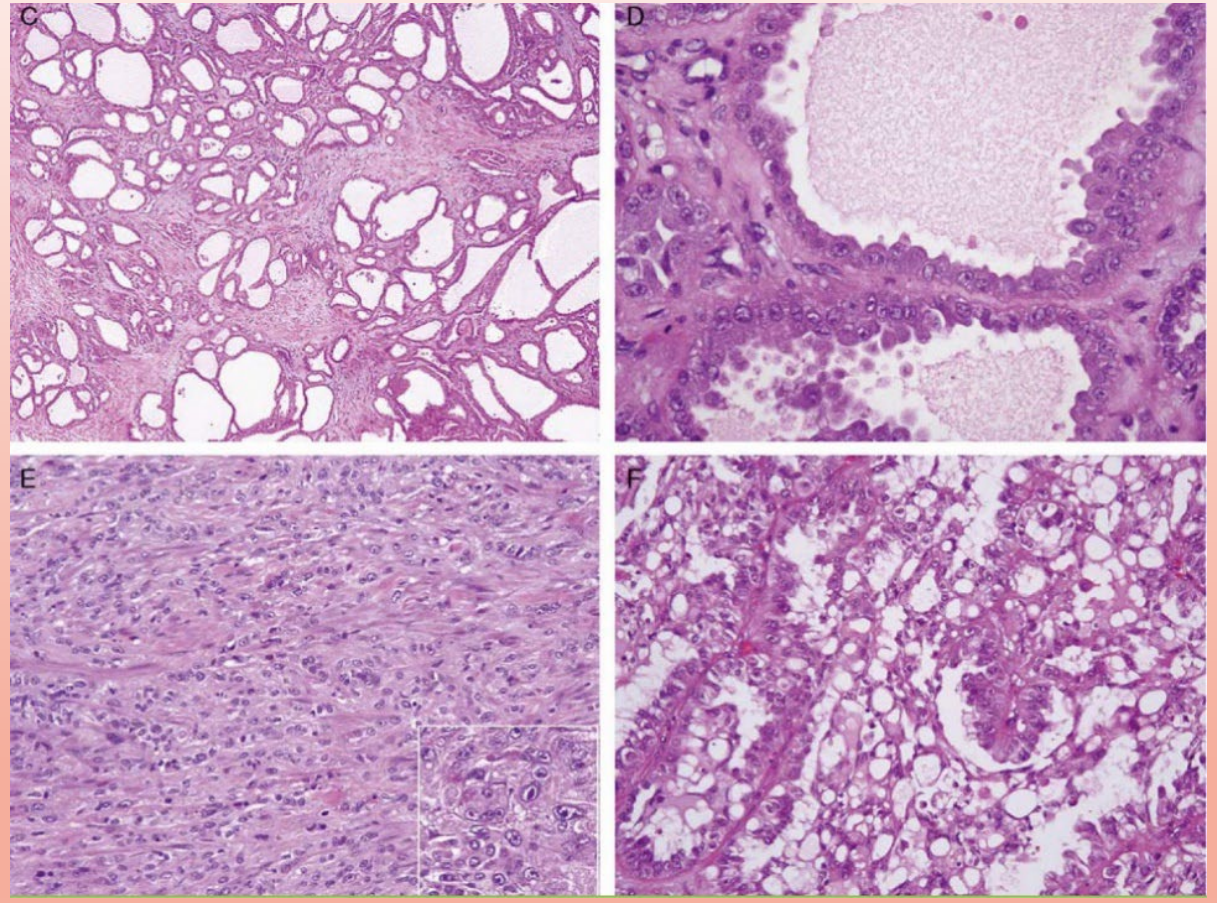
S-(2-succino)-cysteine (2SC)

FH-deficient RCCs

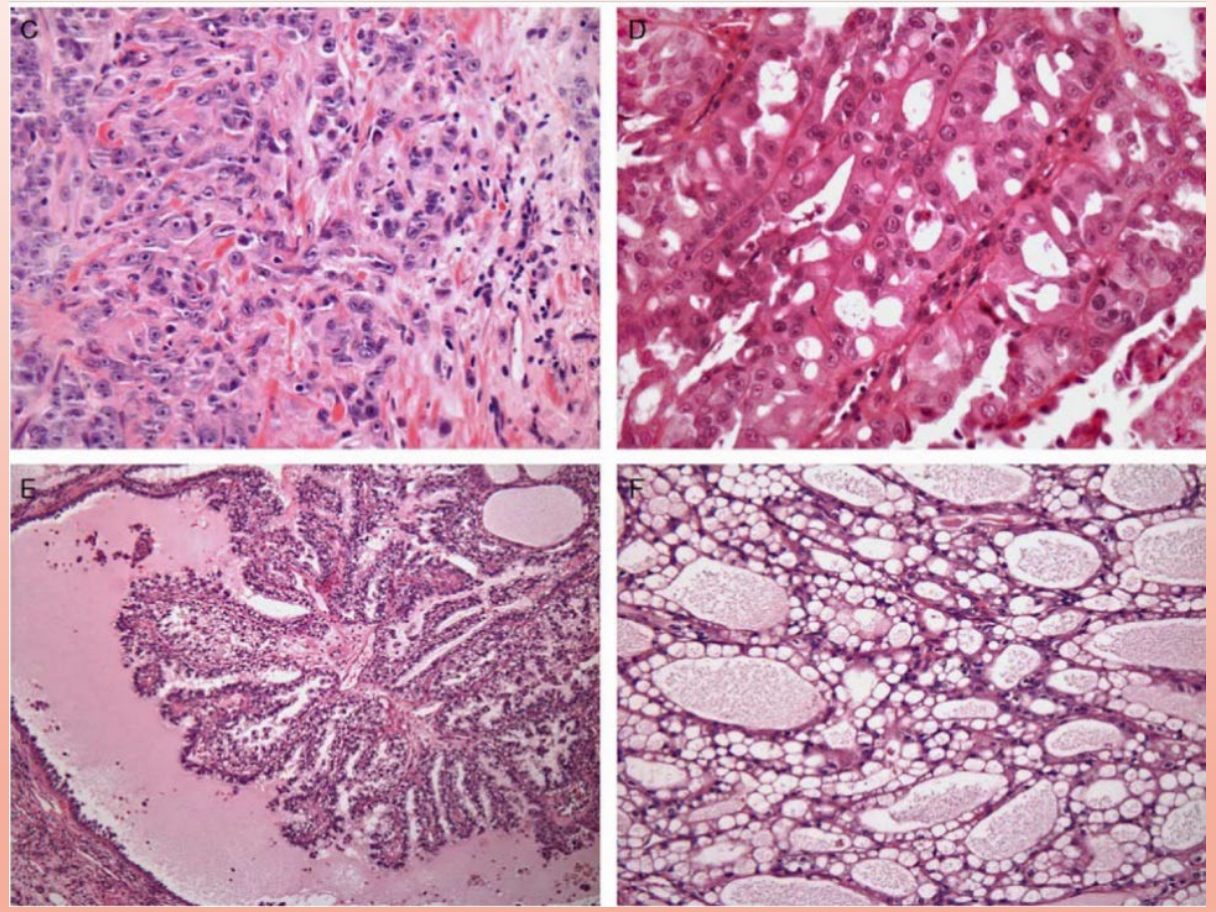
- Trpkov et al *Am J Surg Pathol* 2016;40:865–875
- Screened 124 tumors (118 patients)
- High stage, poor prognosis, unilateral and solitary, variable architecture, limited clinical history

- **FH-/2SC 2+**
  - Correlates with *FH* mutation
  - Highly specific
  - 24/124 (19%) were FH-deficient RCC
  - 8/23 (35%) had known HLRCC

Architectural variability



Chen et al. AJSP 2014

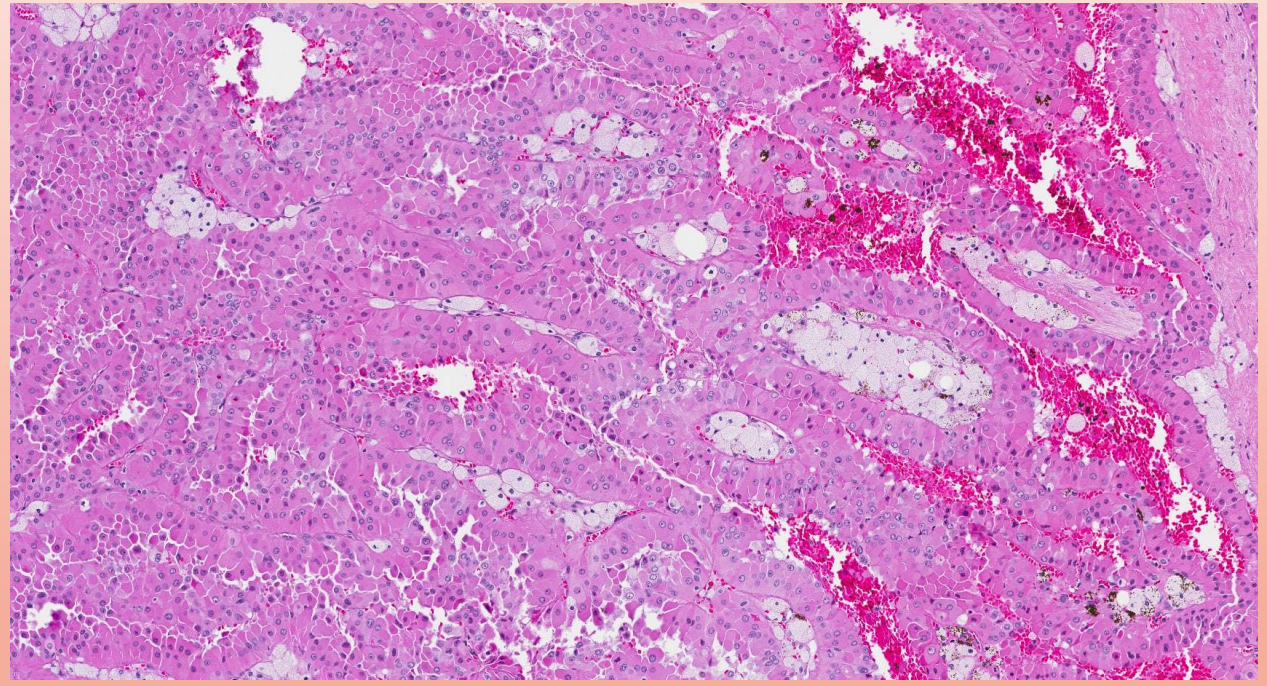


Trpkov et al. AJSP 2016

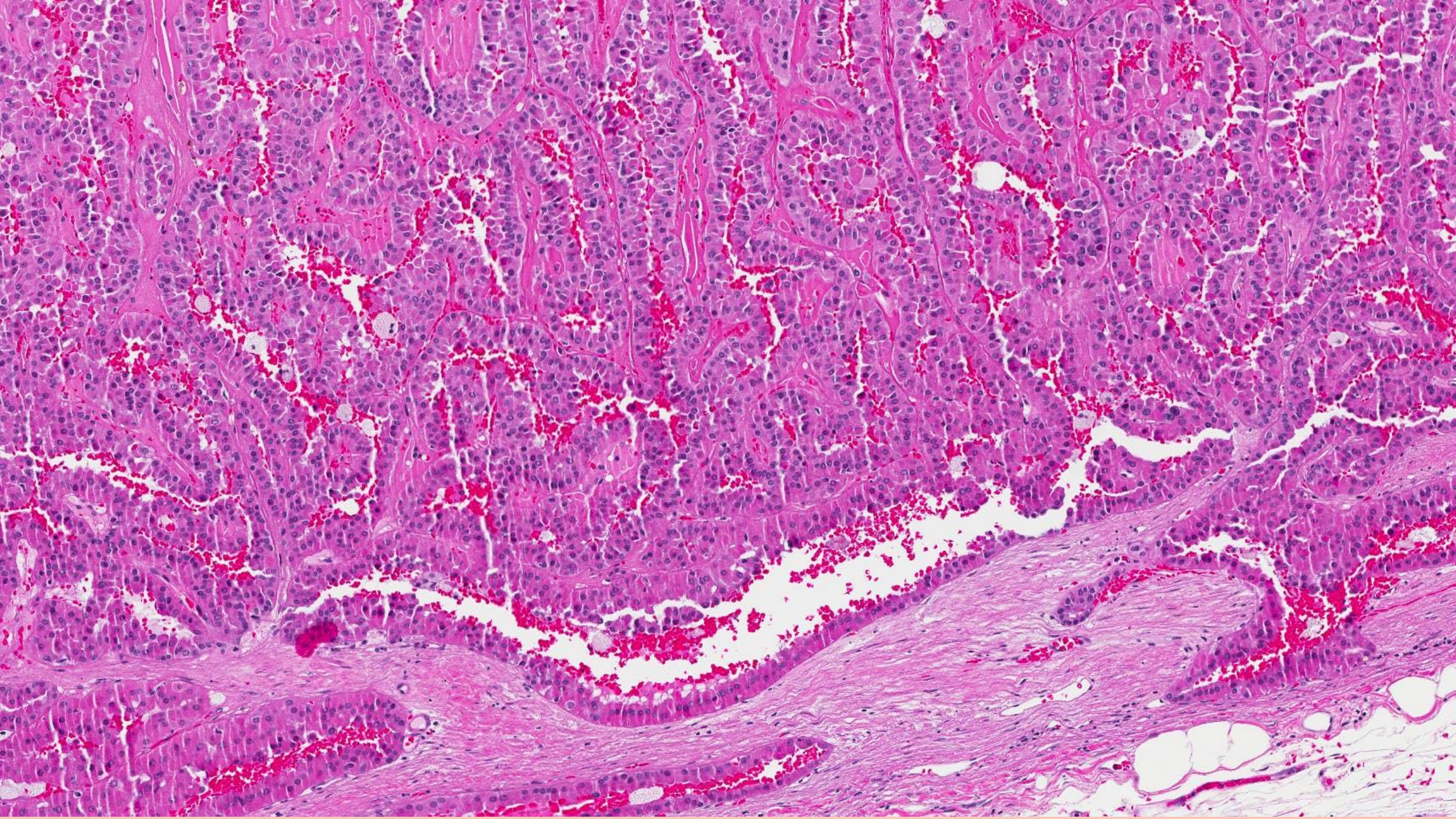
FH-deficient RCC

- Differential diagnosis
  - Papillary RCC, (formerly “type 2”)
  - Collecting duct RCC
  - Medullary RCC
  - Tubulocystic RCC
  - Acquired cystic disease-associated RCC
  - RCC unclassified type (RCC-NOS)

Papillary RCC, “Type 2”

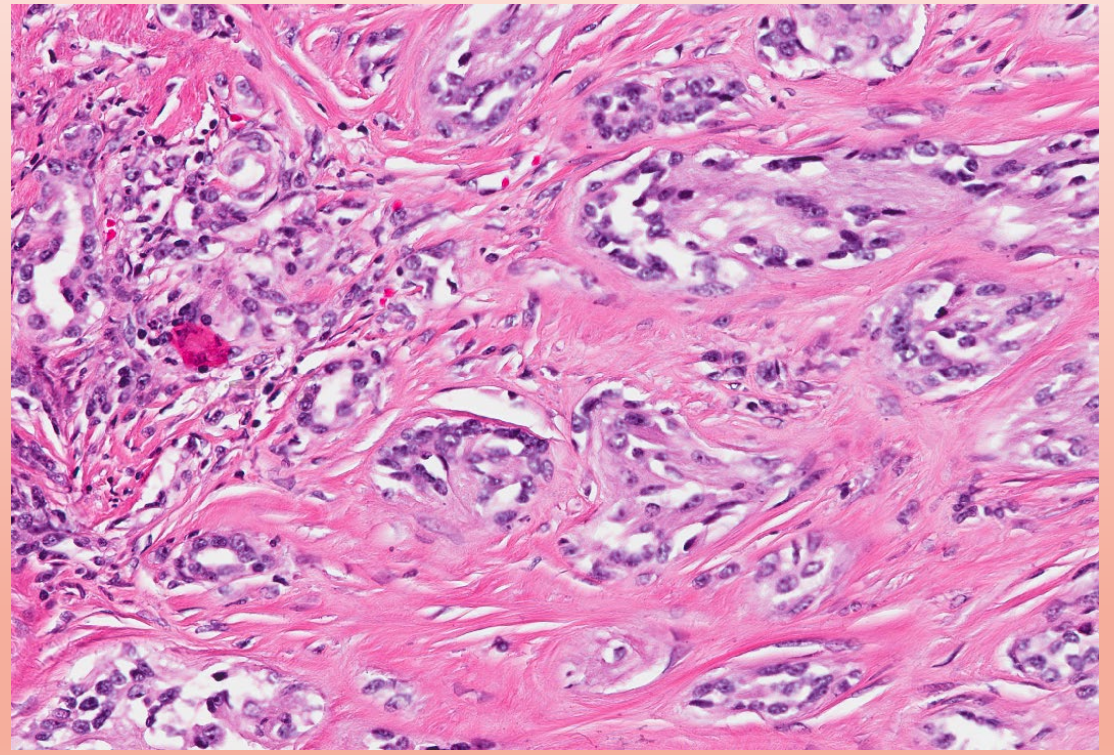


- Vanishing category (no longer typed)
  - Some RCCs removed:
    - FH-deficient RCC
    - Translocation-associated RCCs



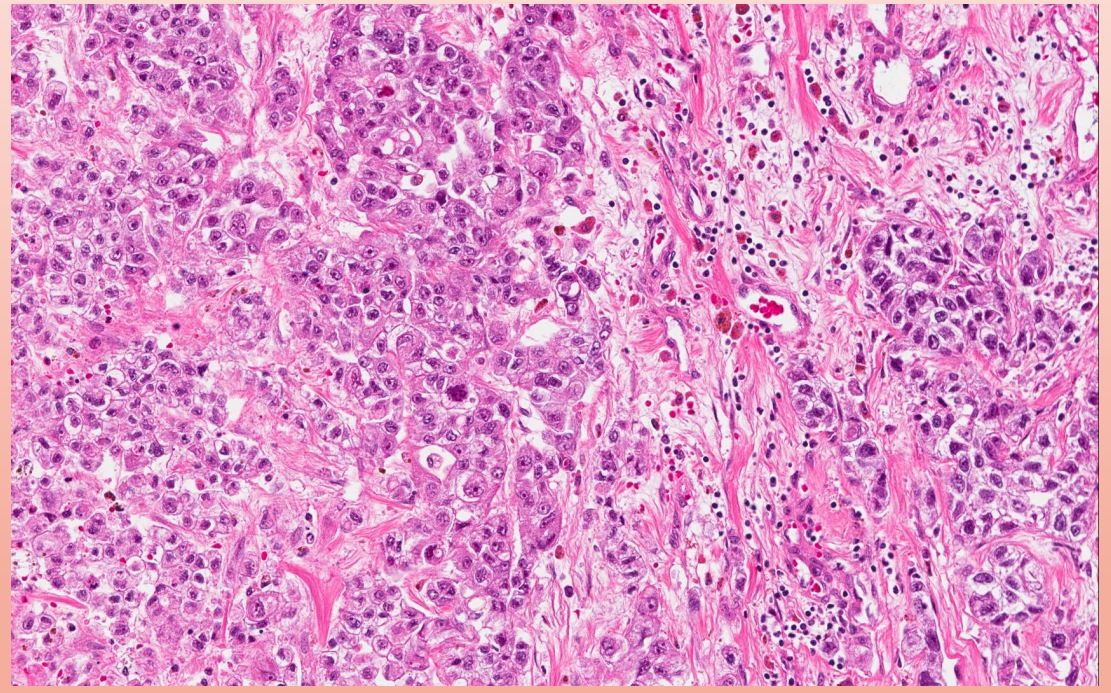
Collecting duct carcinoma

- Diagnosis of exclusion
- Most cases are actually:
  - Urothelial carcinoma
  - FH-deficient RCC
  - Medullary RCC
  - Unclassified RCC



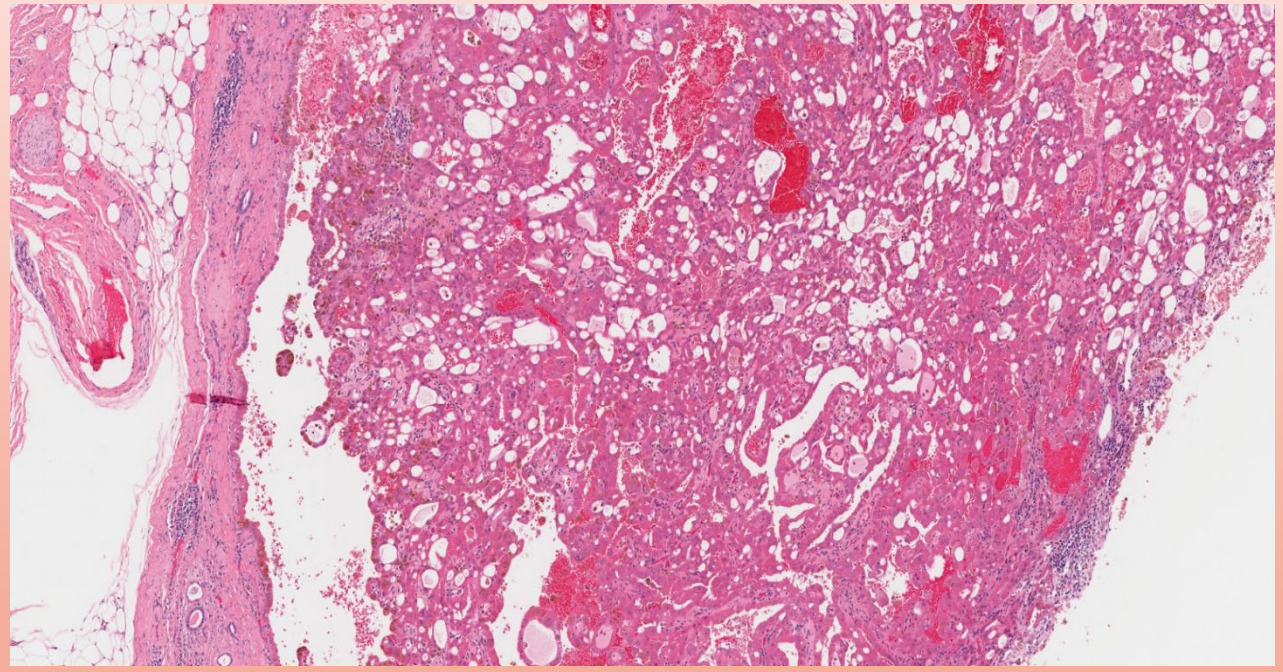
Medullary RCC

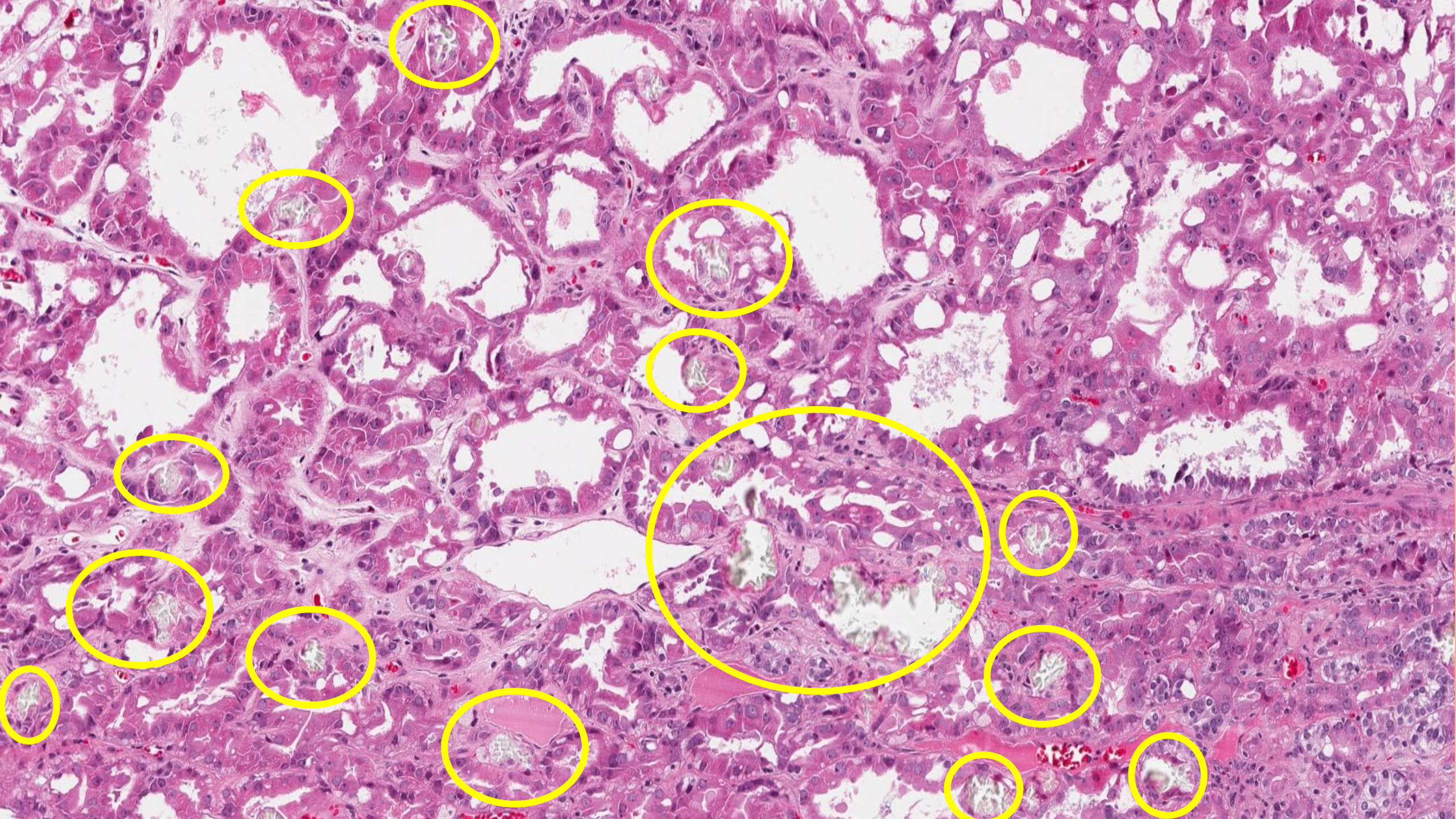
- Young patients with sickle cell trait
- Highly aggressive
- Infiltrative with desmoplasia, +/- sickled RBCs
- INI-1 loss of expression

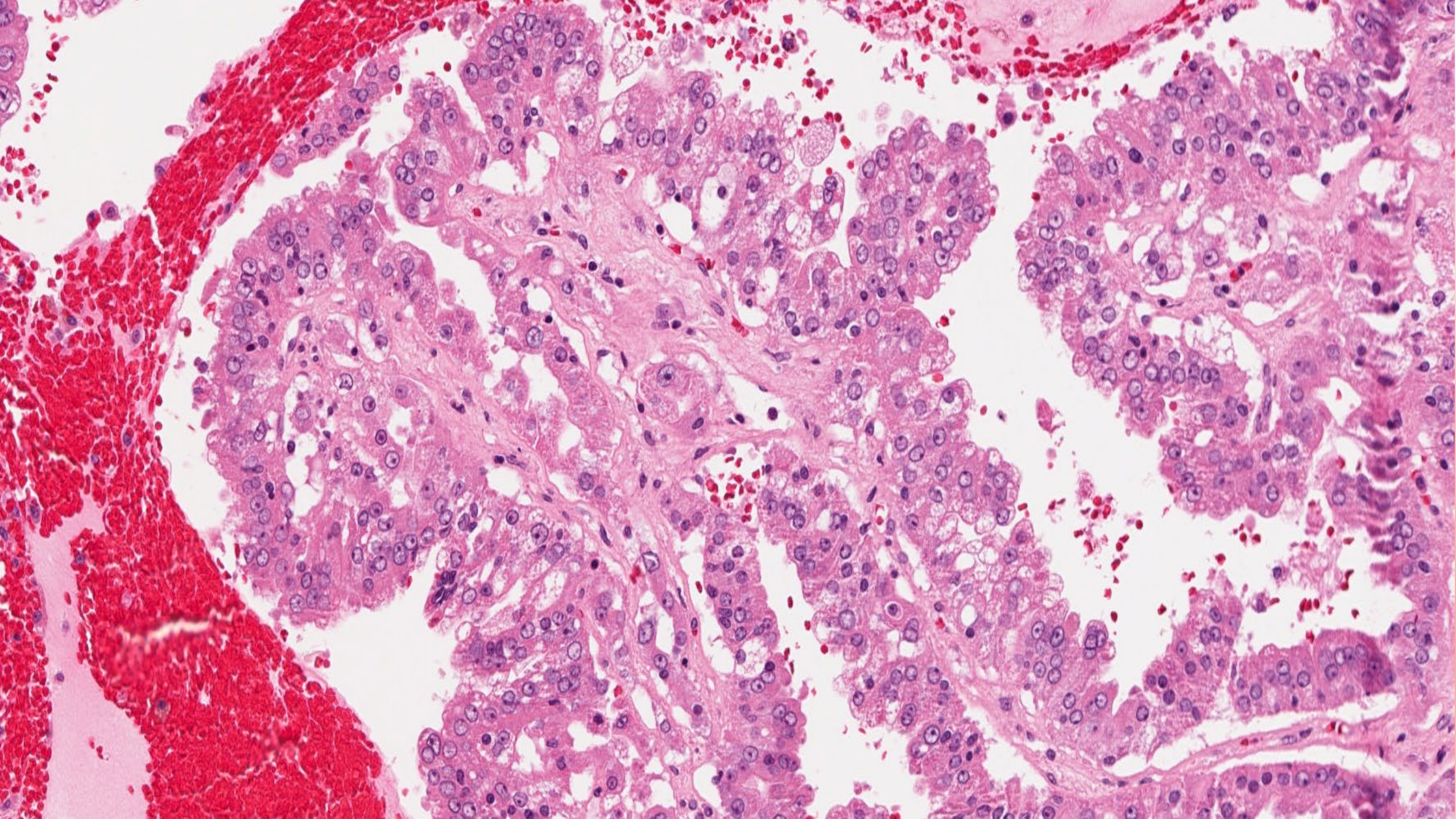


Acquired cystic disease-associated RCC

- ESRD patients on dialysis
- ”Sieve-like” architecture
- Oxalate crystals
- HLRCC-like nuclei/nucleoli





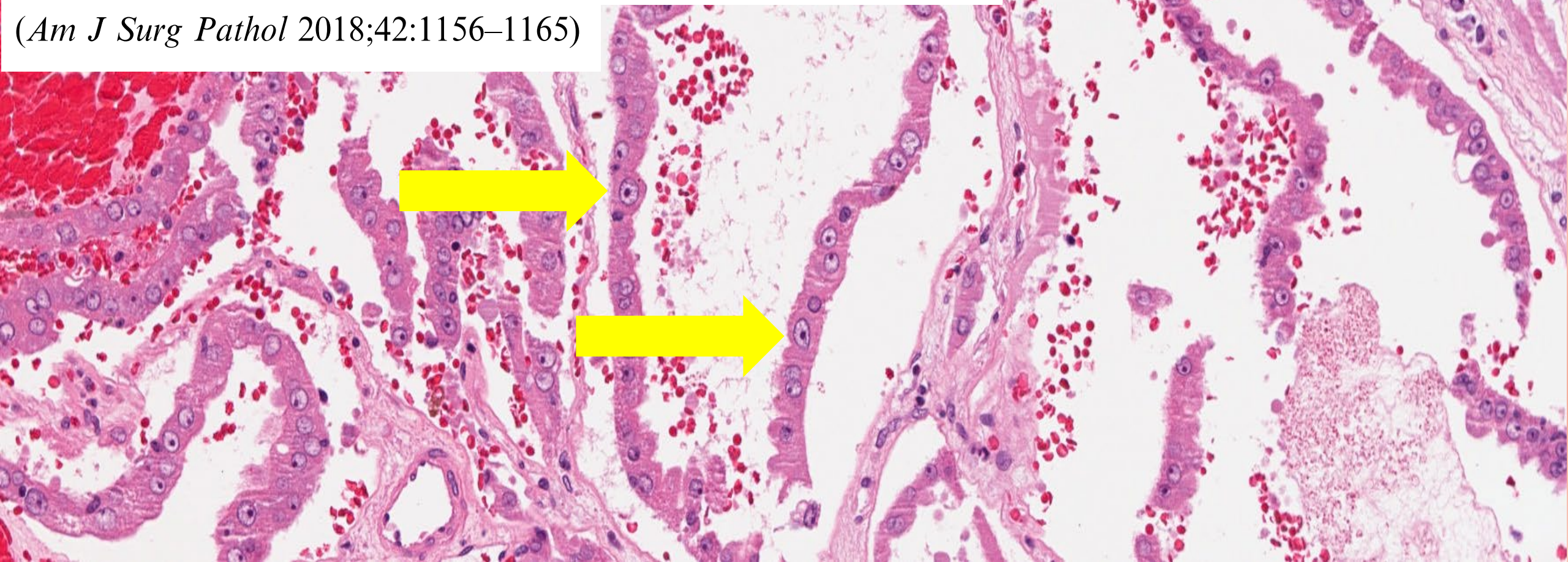


Acquired Cystic Disease-associated Renal Cell Carcinoma (ACD-RCC)

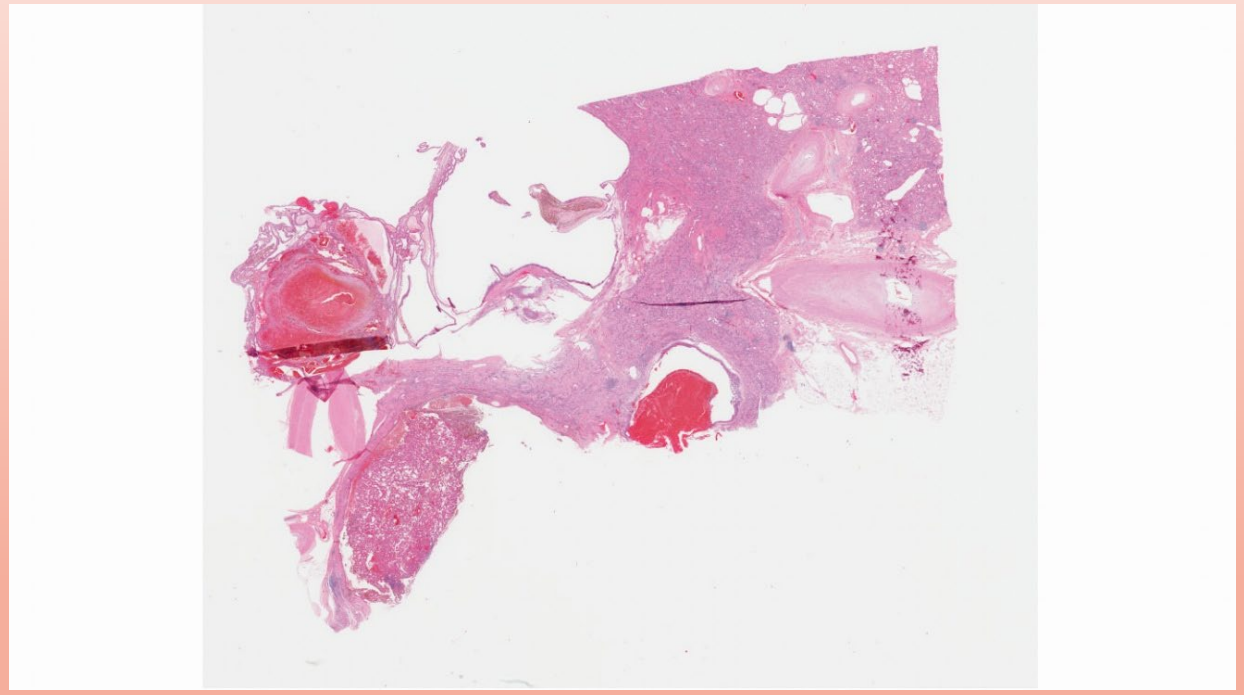
A Multiinstitutional Study of 40 Cases With Clinical Follow-up

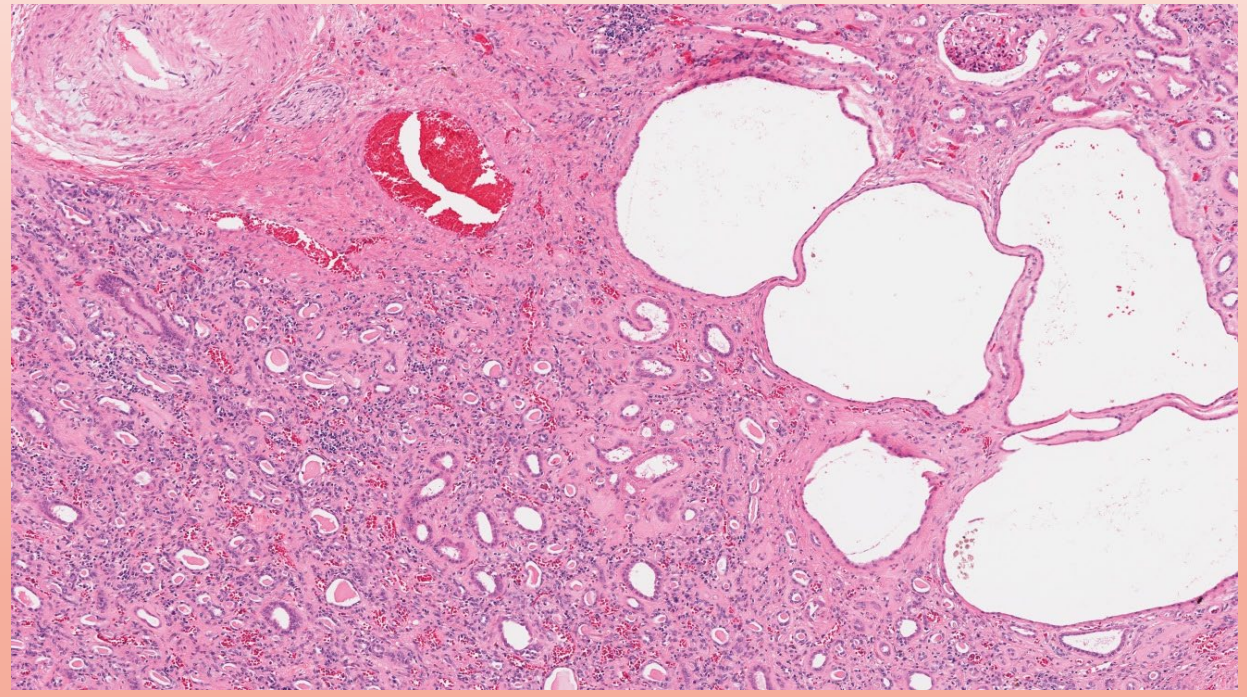
Christopher G. Przybycin, MD, Holly L. Harper, MD,† Jordan P. Reynolds, MD,* Cristina Magi-Galluzzi, MD, PhD,* Jane K. Nguyen, MD, PhD,‡ Angela Wu, MD,§ Ankur R. Sangoi, MD,‖ Peter S. Liu, MD,¶ Saleem Umar, MD,# Rohit Mehra, MD,§ Xiaochun Zhang, MD, PhD,* Roni M. Cox, MD,* and Jesse K. McKenney, MD**

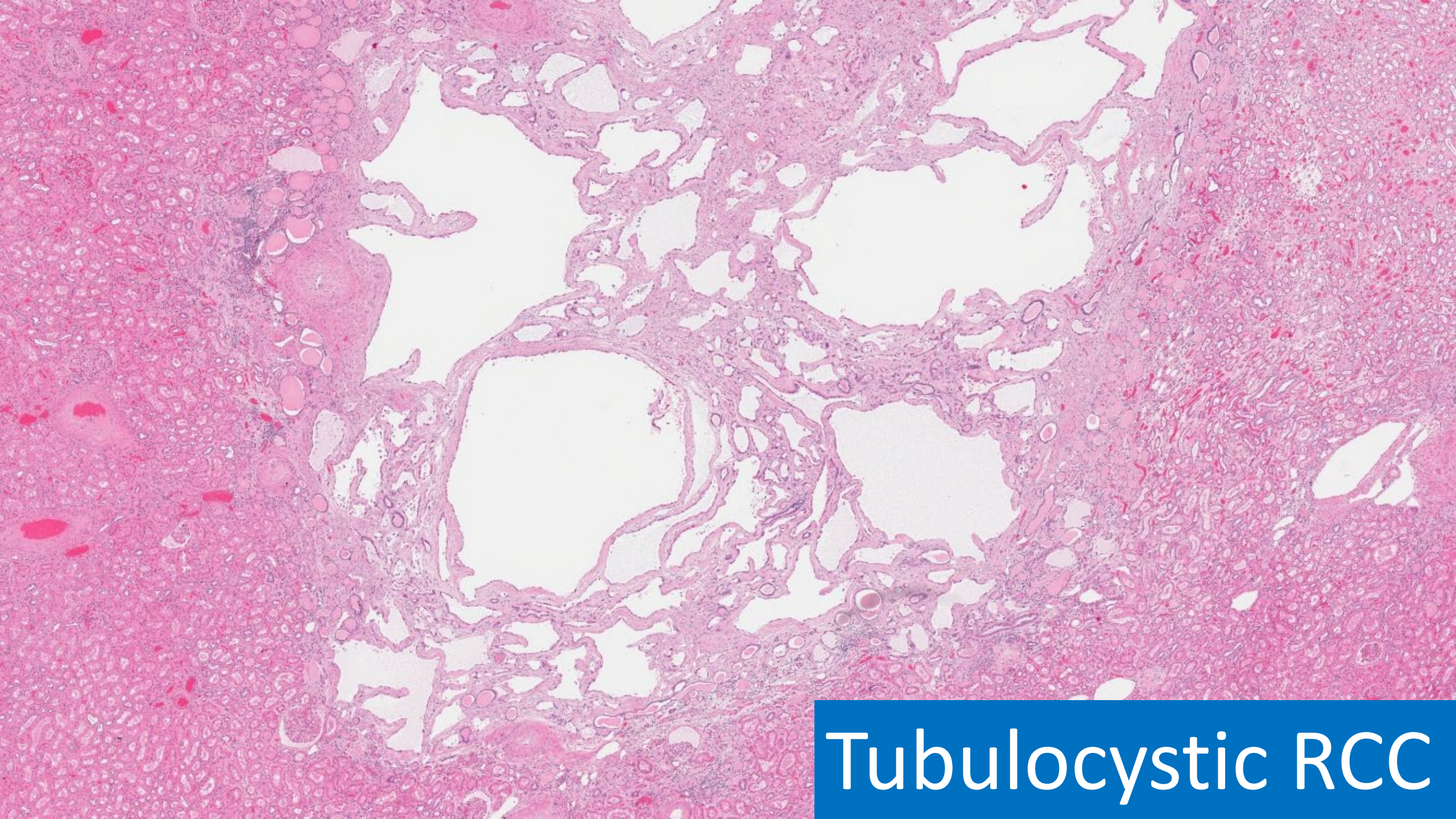
(*Am J Surg Pathol* 2018;42:1156–1165)



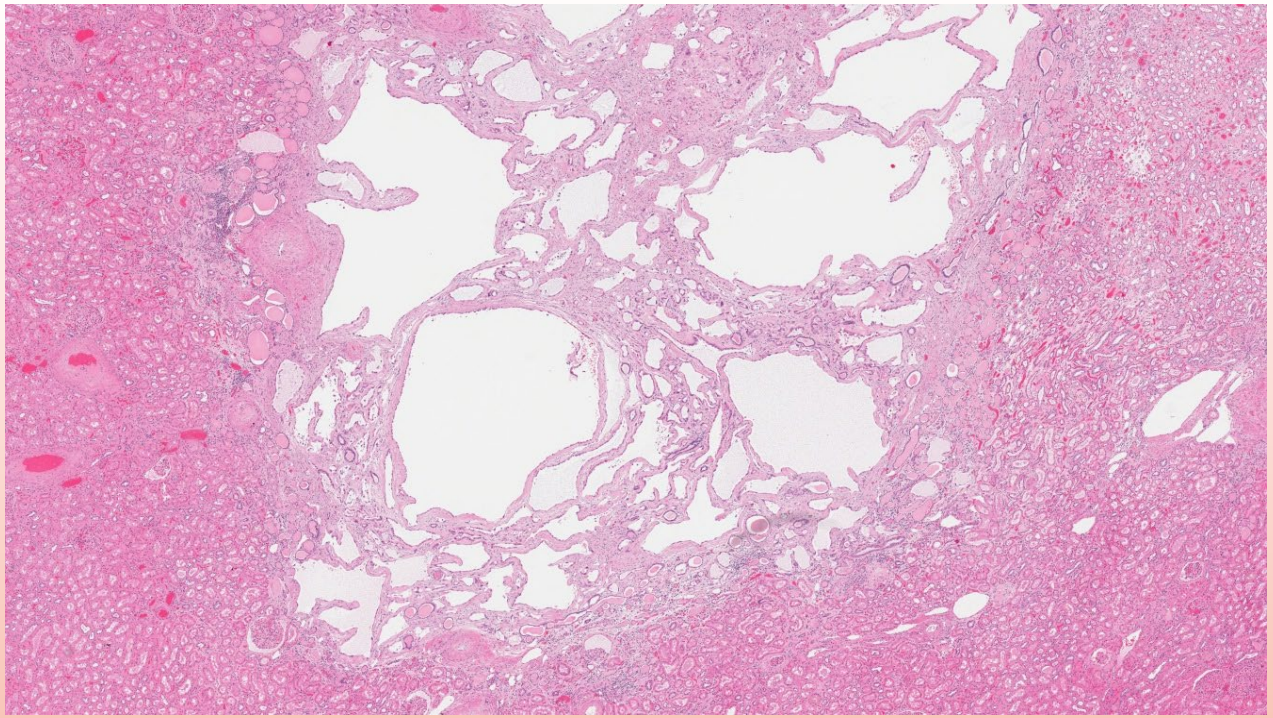
Acquired cystic disease – background kidney



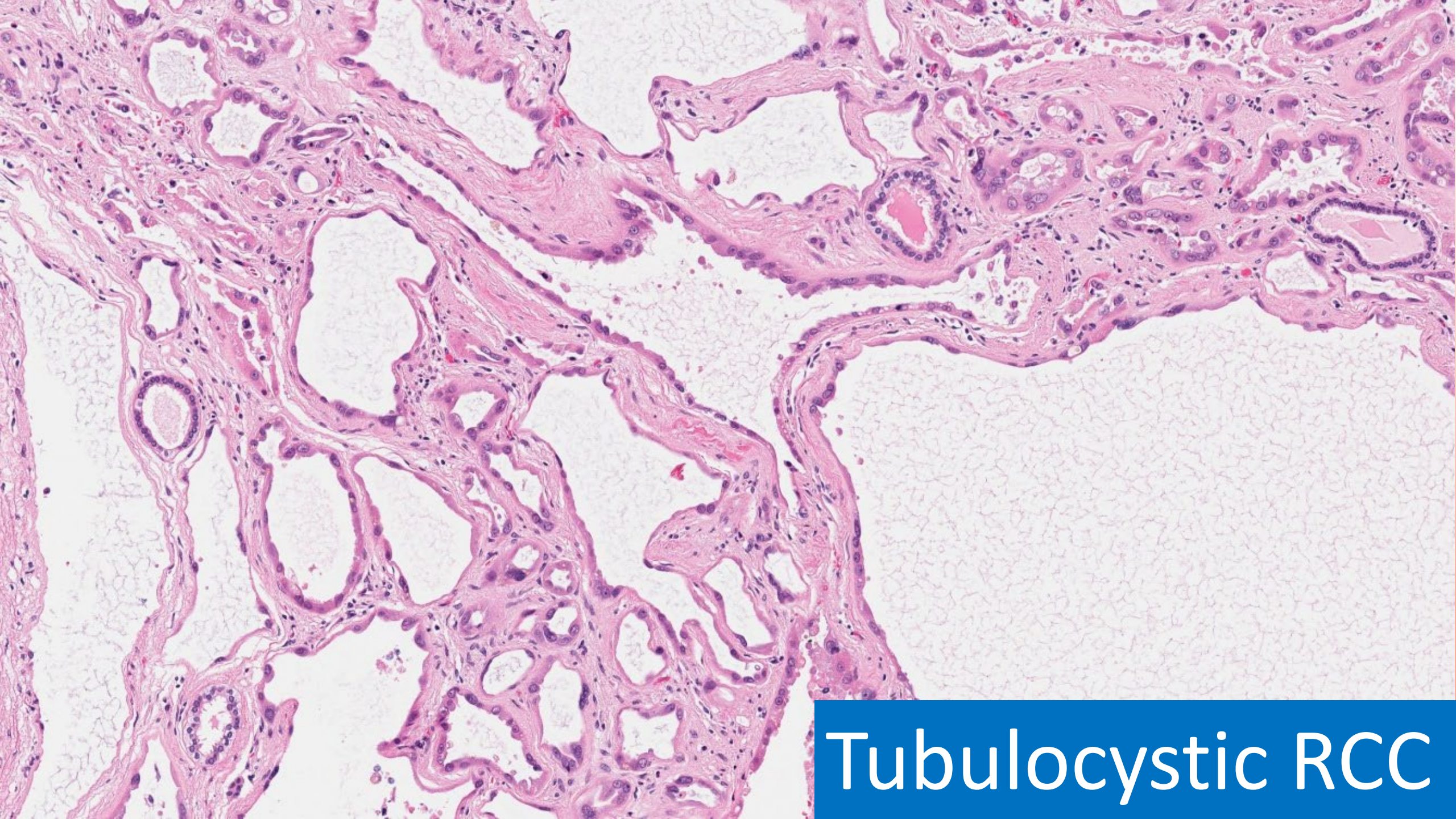



Tubulocystic RCC

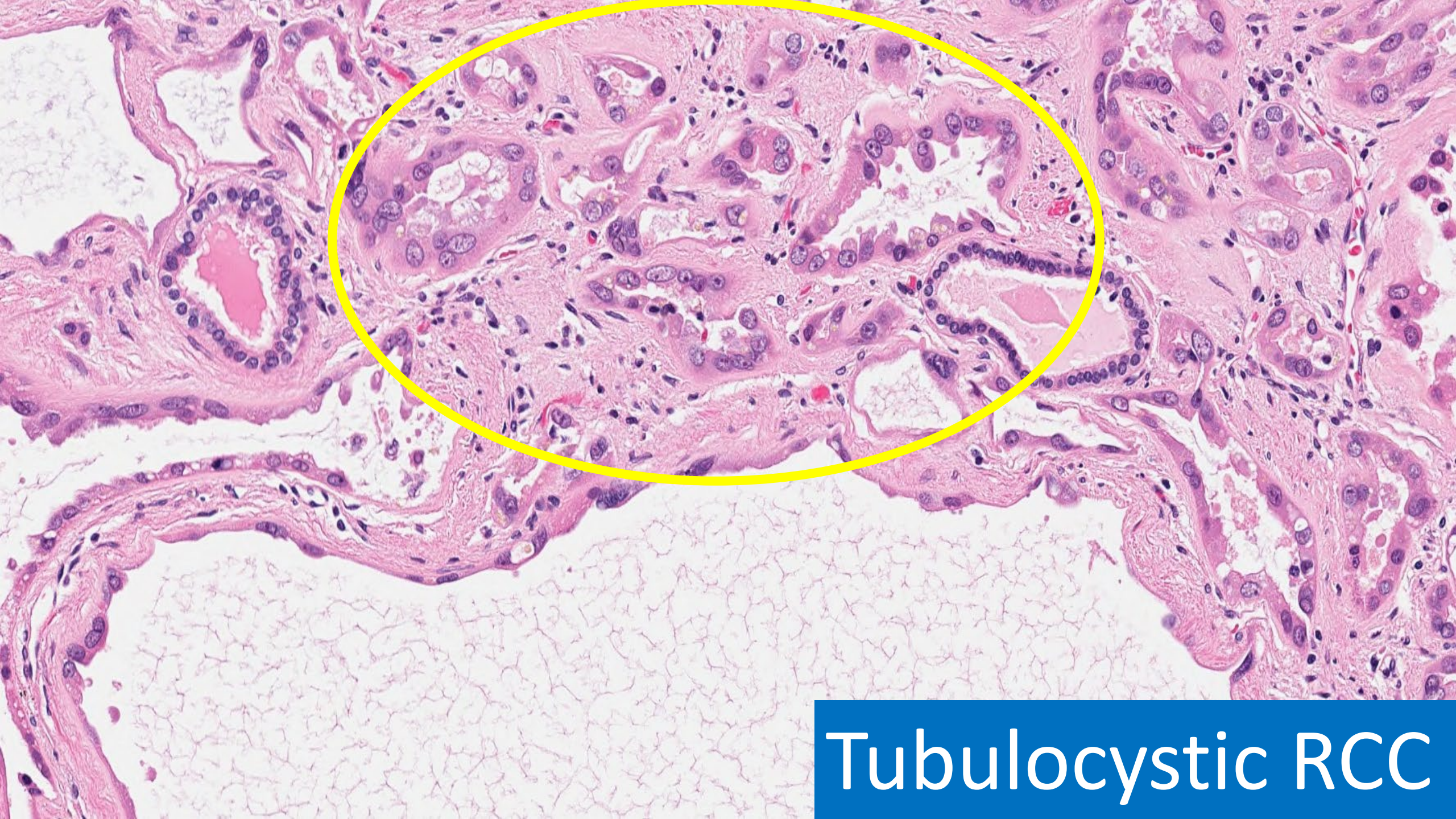
Tubulocystic RCC

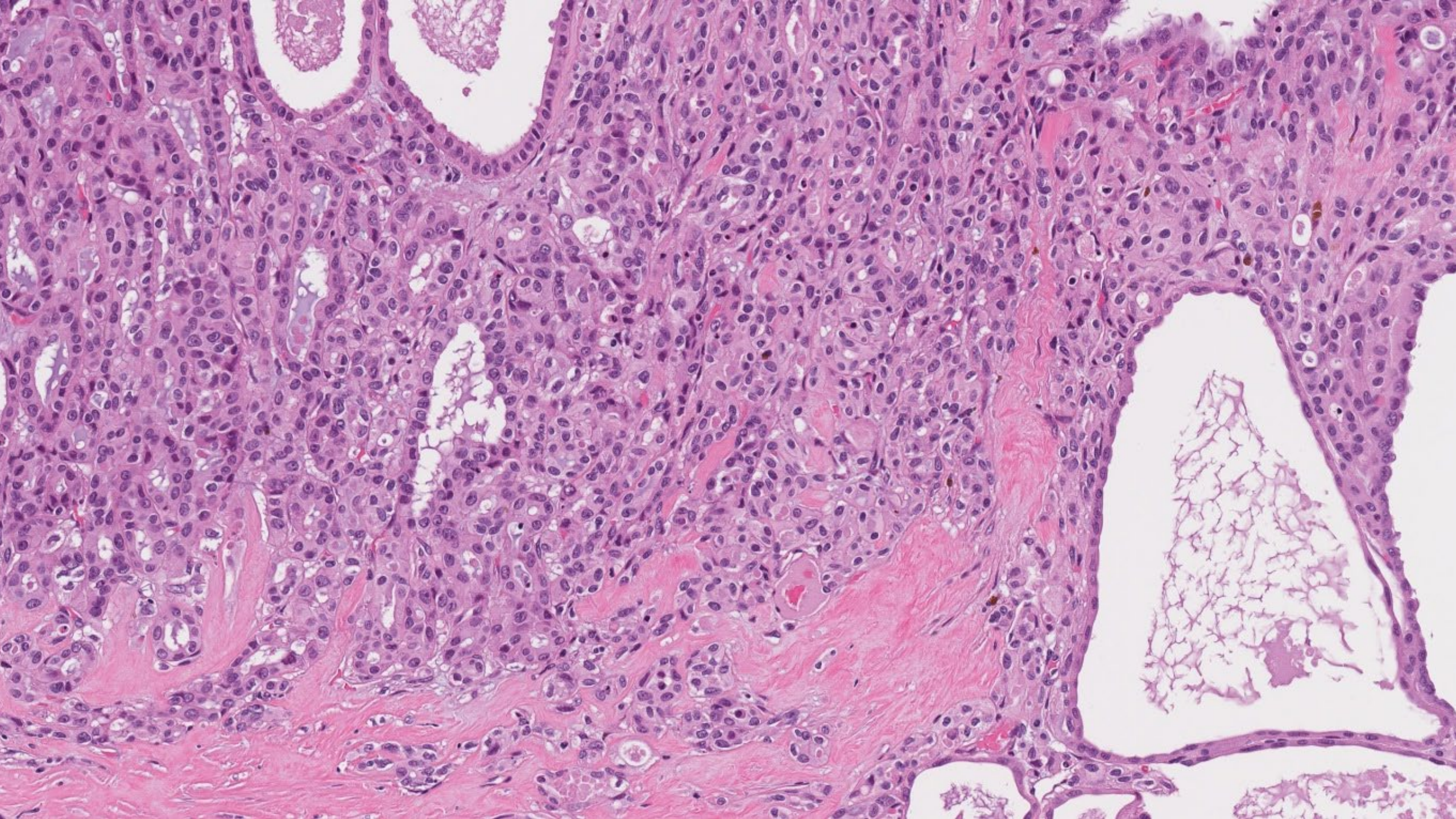


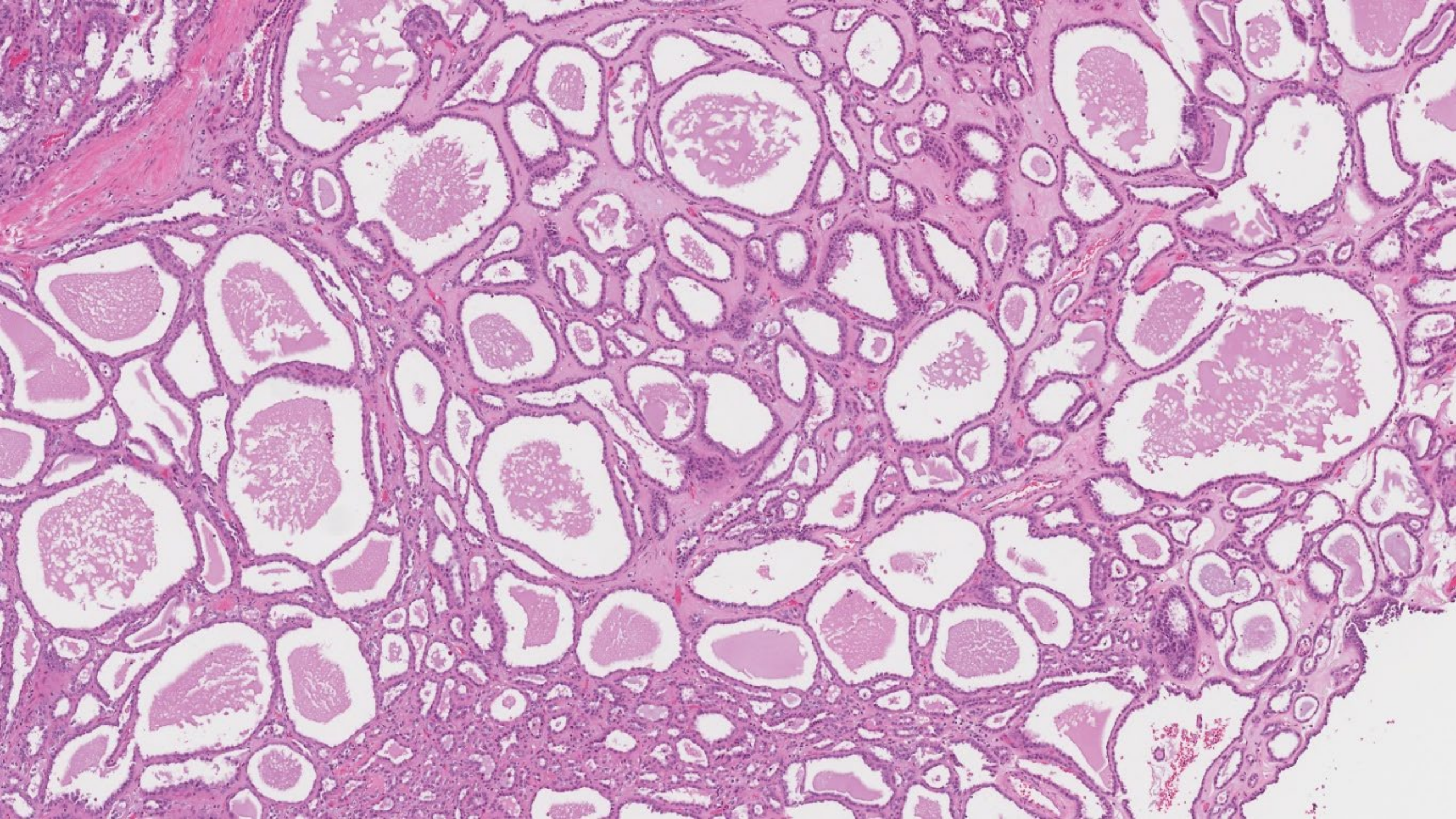
- Rare
- M:F=7:1
- Most pT1, indolent
- Well-circumscribed, sponge-like
- Variably dilated cystic tubules in fibrous stroma
  - Exclusively cystic; no solid areas
  - Flat, hobnail, or cuboidal cells

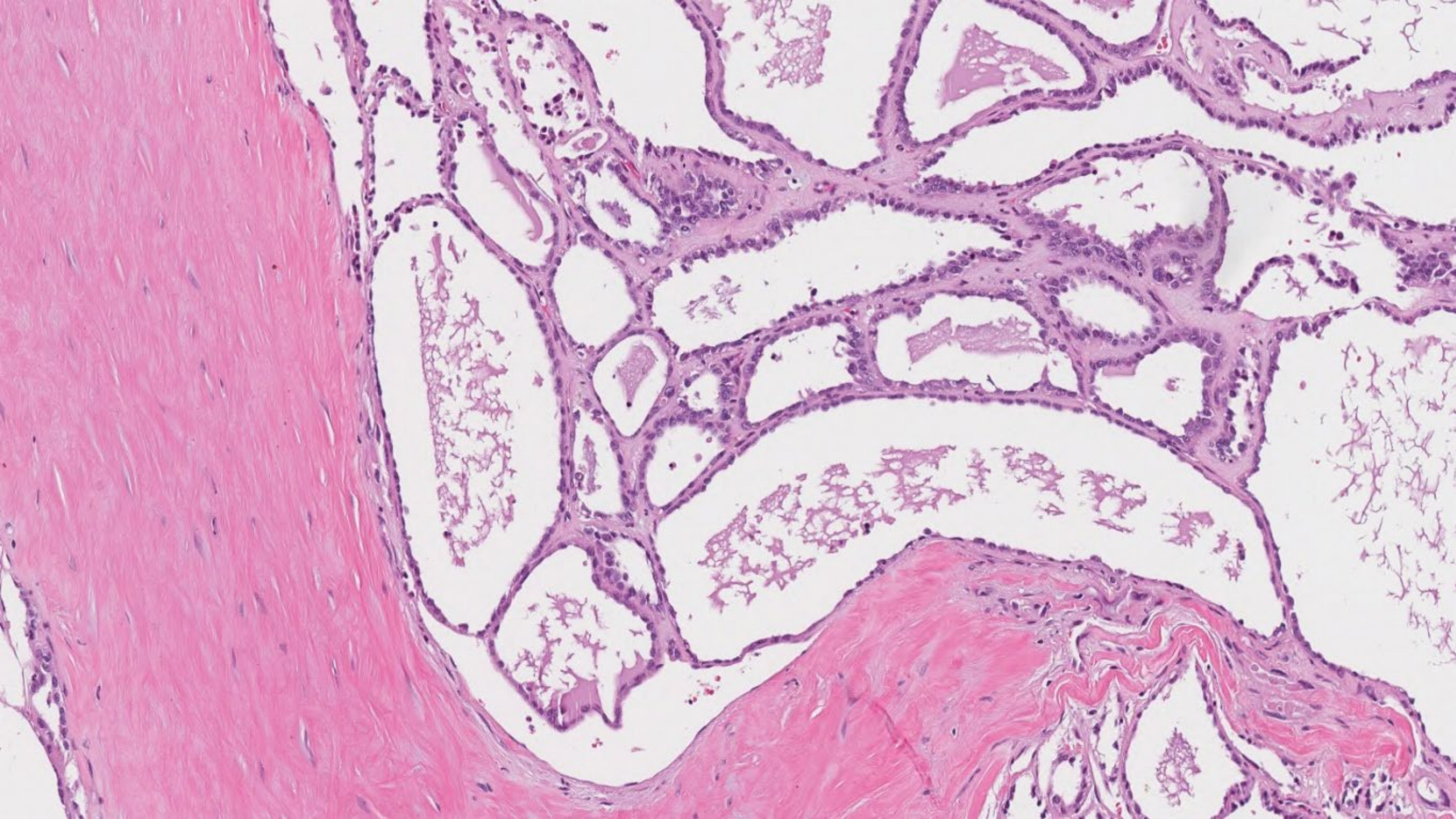


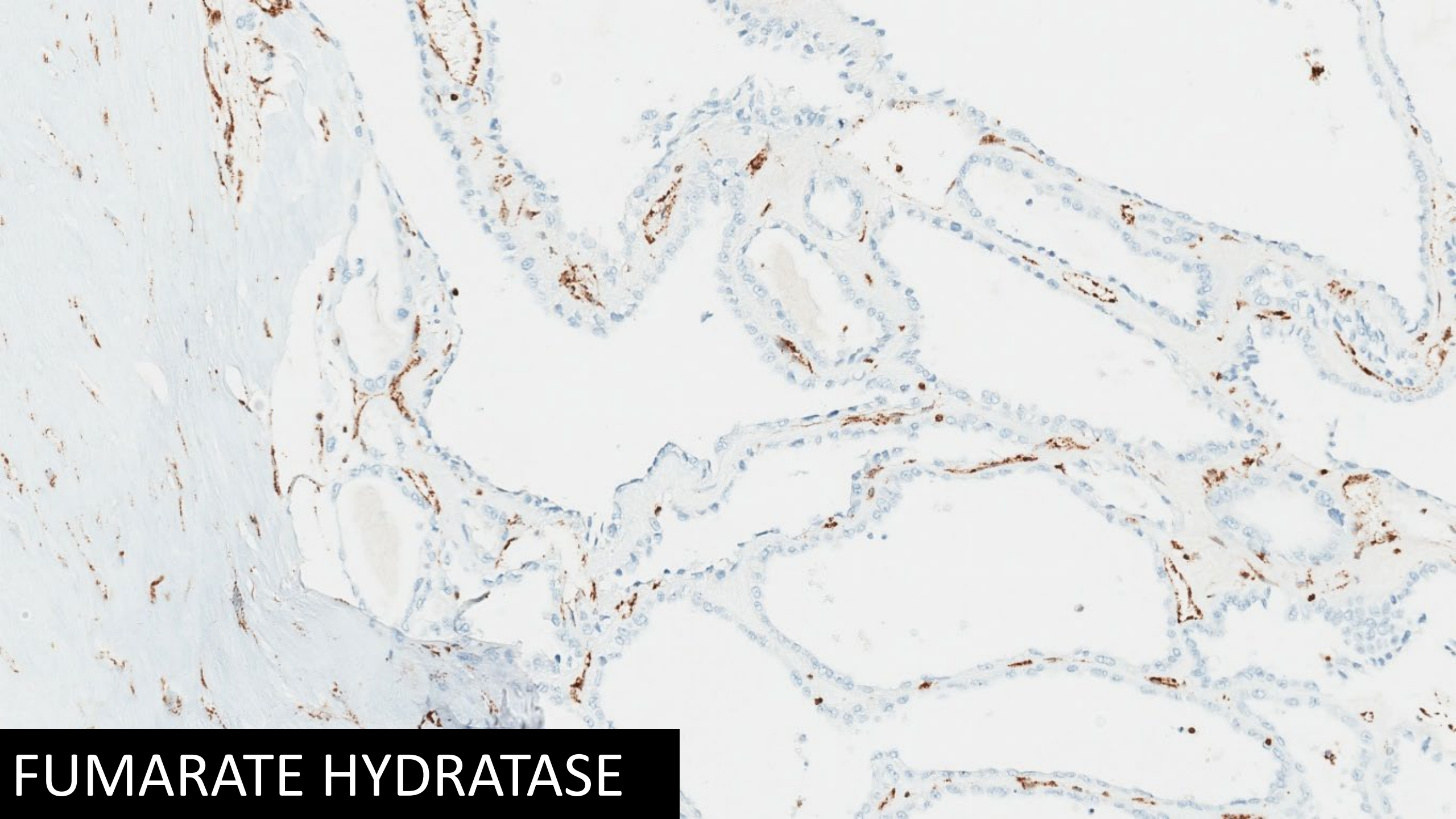
Tubulocystic RCC


Tubulocystic RCC







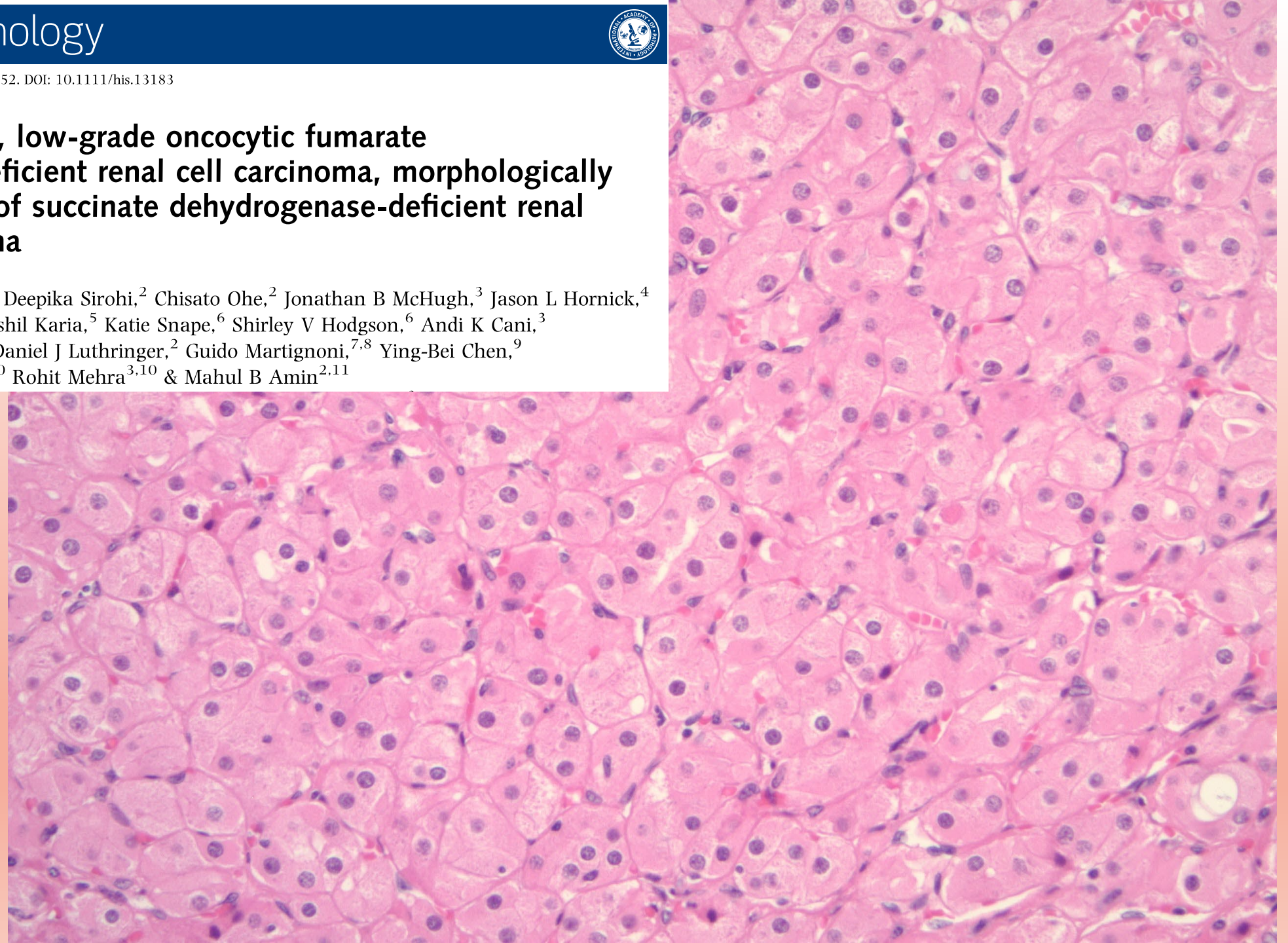

FUMARATE HYDRATASE

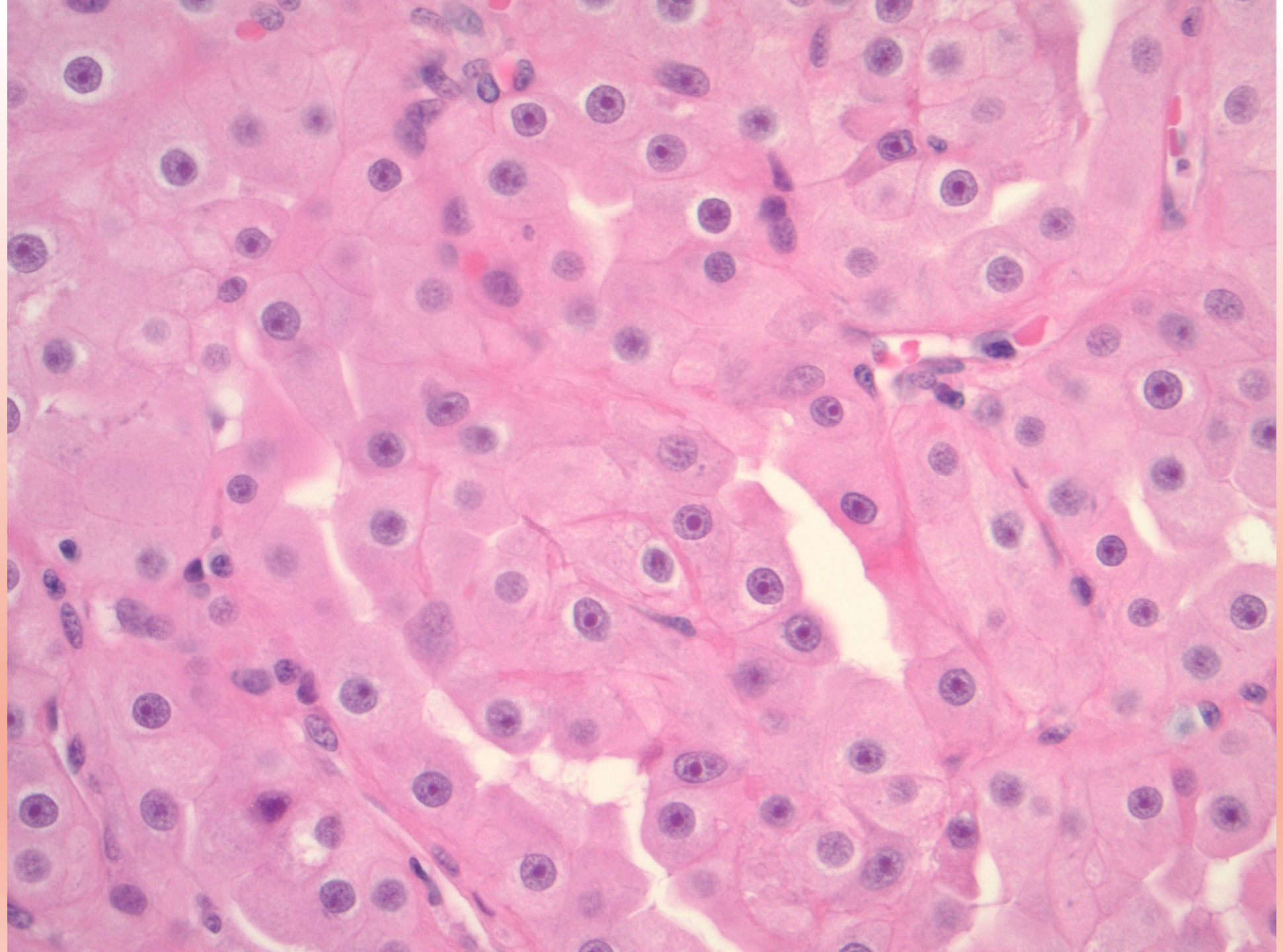
Histopathology

Histopathology 2017, **71**, 42–52. DOI: 10.1111/his.13183

A distinctive, low-grade oncocytic fumarate hydratase-deficient renal cell carcinoma, morphologically reminiscent of succinate dehydrogenase-deficient renal cell carcinoma

Steven C Smith,[1] Deepika Sirohi,[2] Chisato Ohe,[2] Jonathan B McHugh,[3] Jason L Hornick,[4] Jigna Kalariya,[5] Sushil Karia,[5] Katie Snape,[6] Shirley V Hodgson,[6] Andi K Cani,[3] Daniel Hovelson,[3] Daniel J Luthringer,[2] Guido Martignoni,[7,8] Ying-Bei Chen,[9] Scott A Tomlins,[3,10] Rohit Mehra[3,10] & Mahul B Amin[2,11]



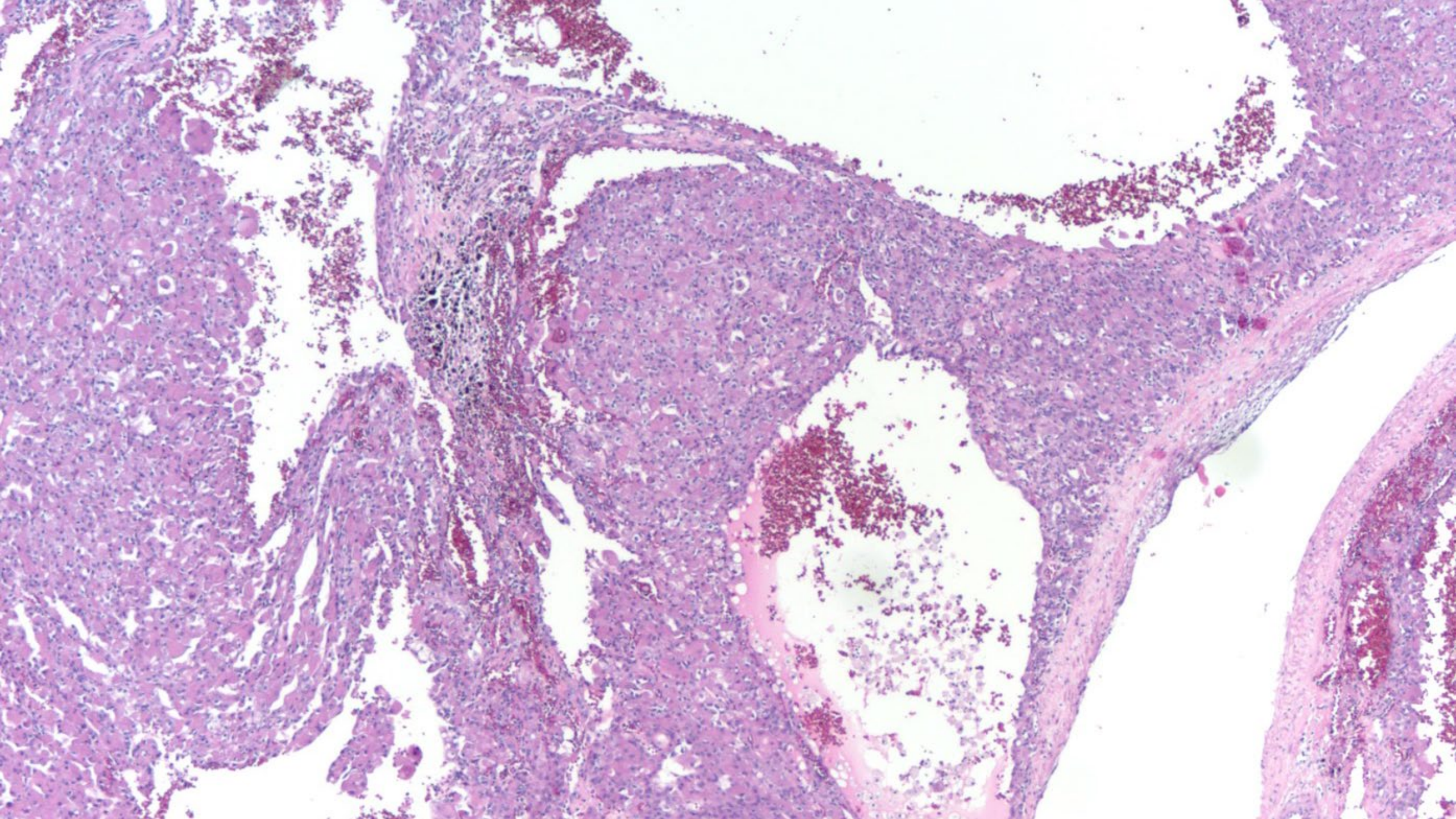


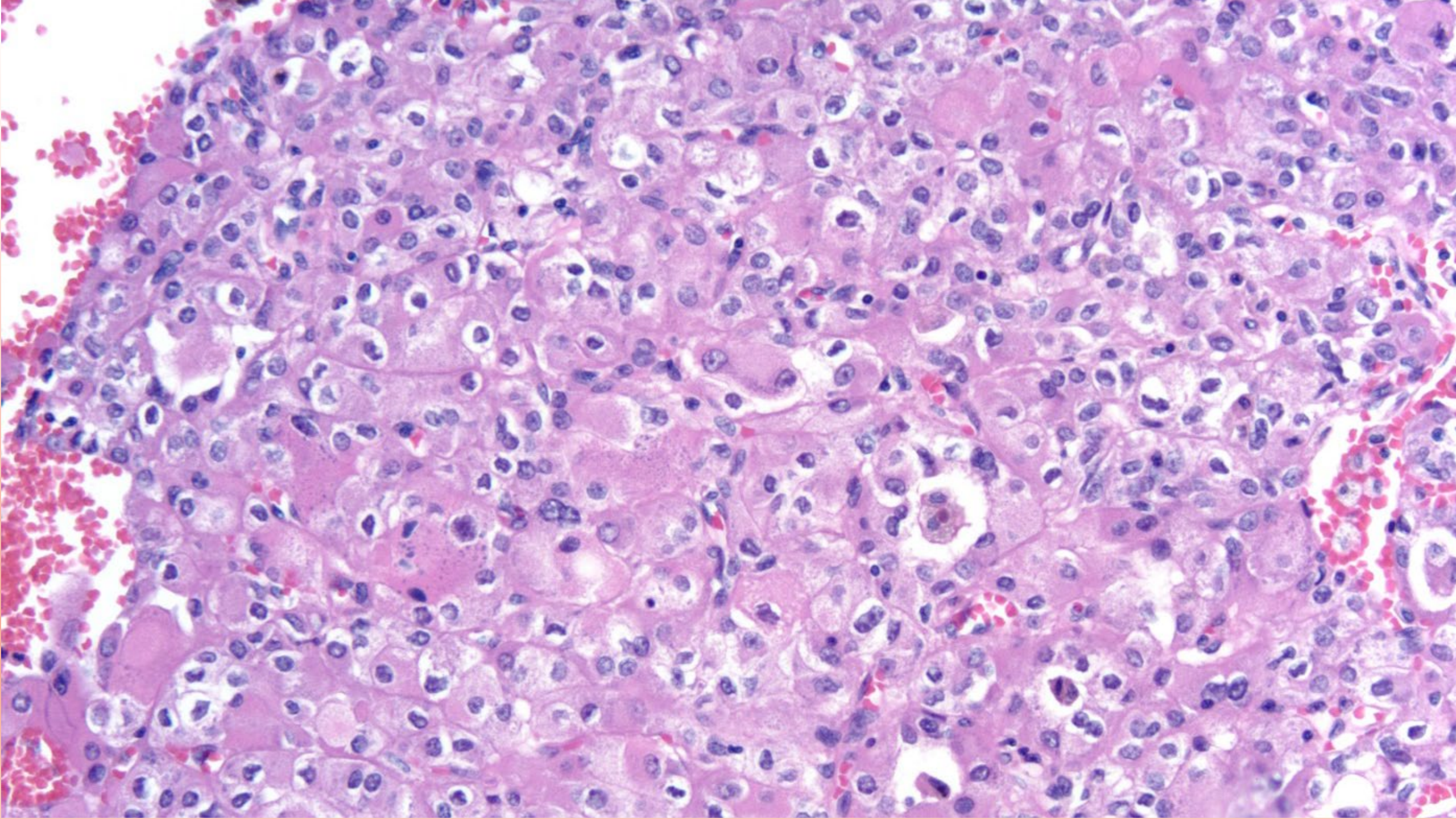
HLRCC-associated RCC

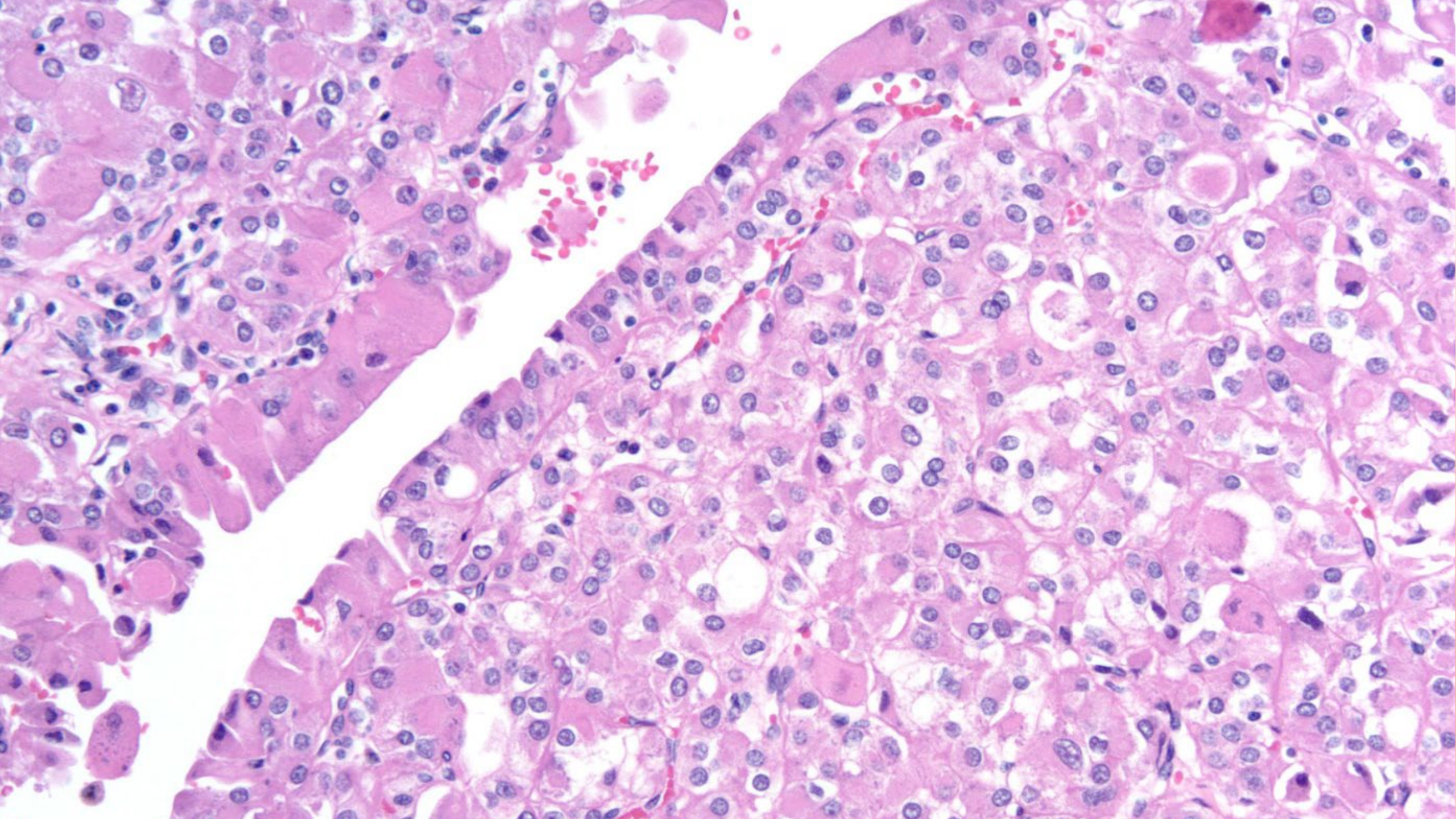
- Challenges and opportunities
  - Incomplete clinical history
  - Solitary, unilateral masses
  - Highly aggressive disease
  - Variable architectural patterns

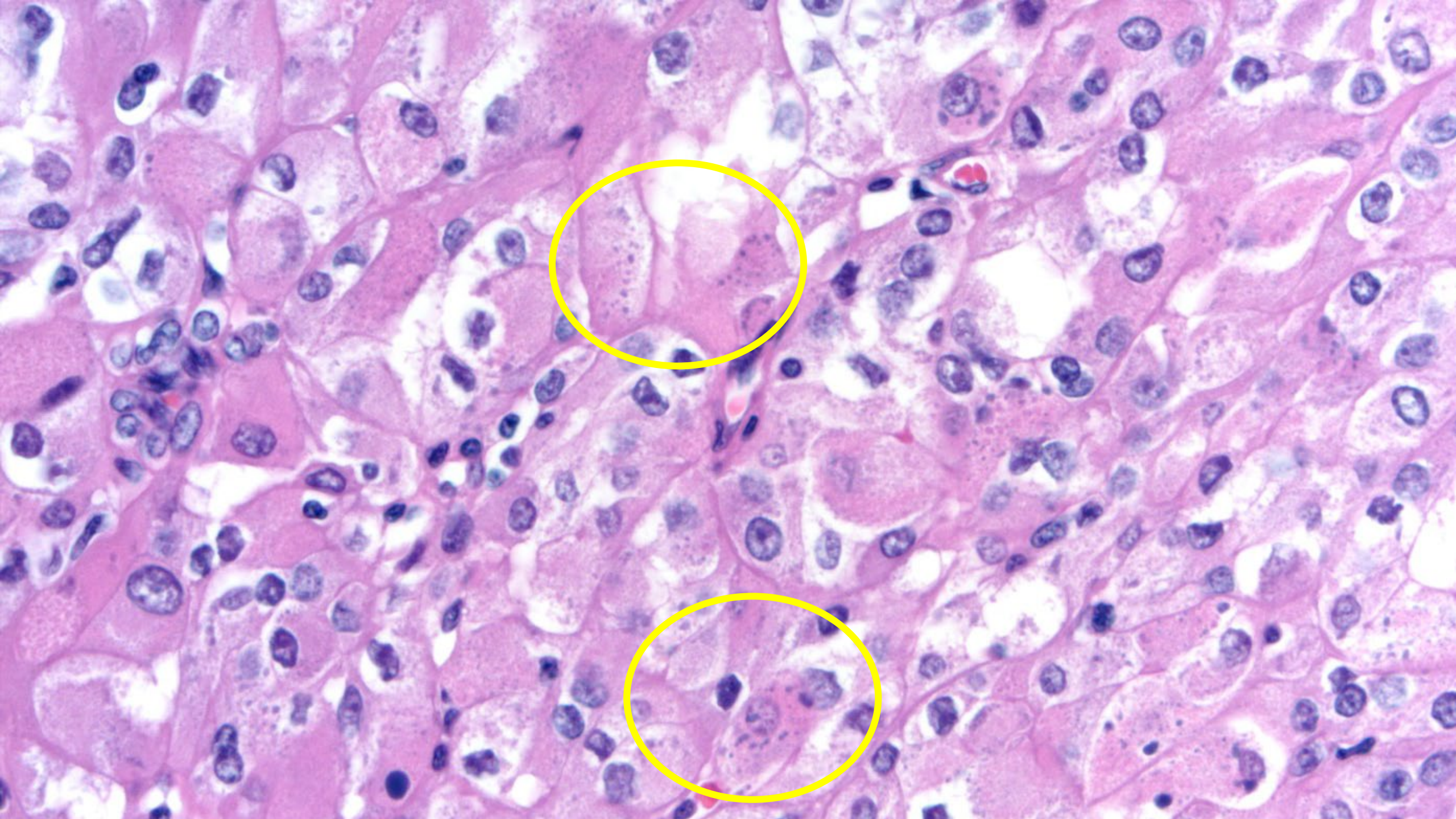
Case 2

Kidney mass, 46 year-old woman

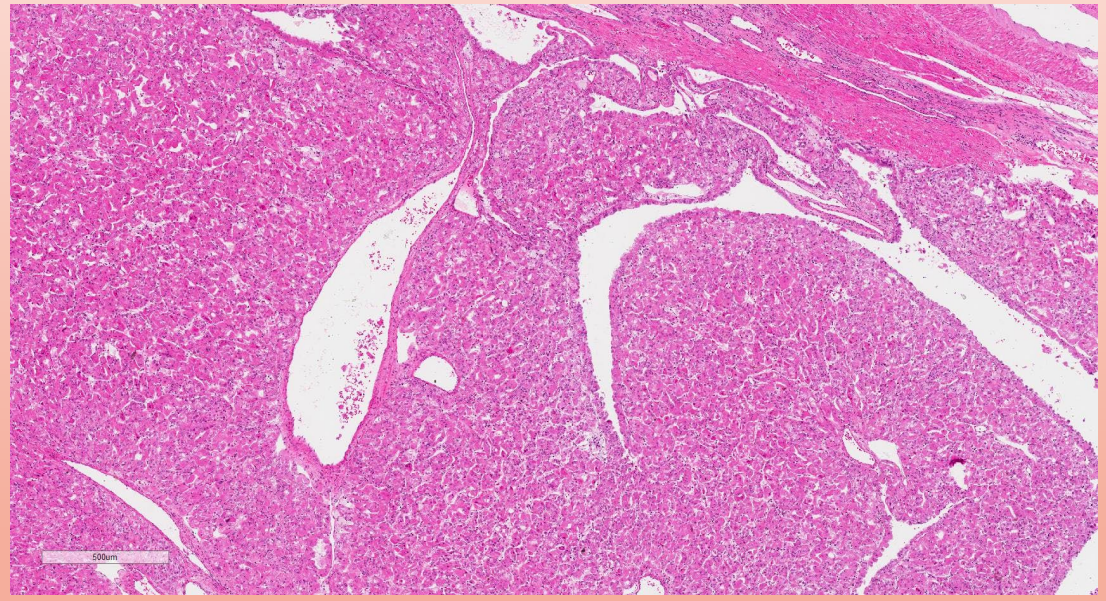


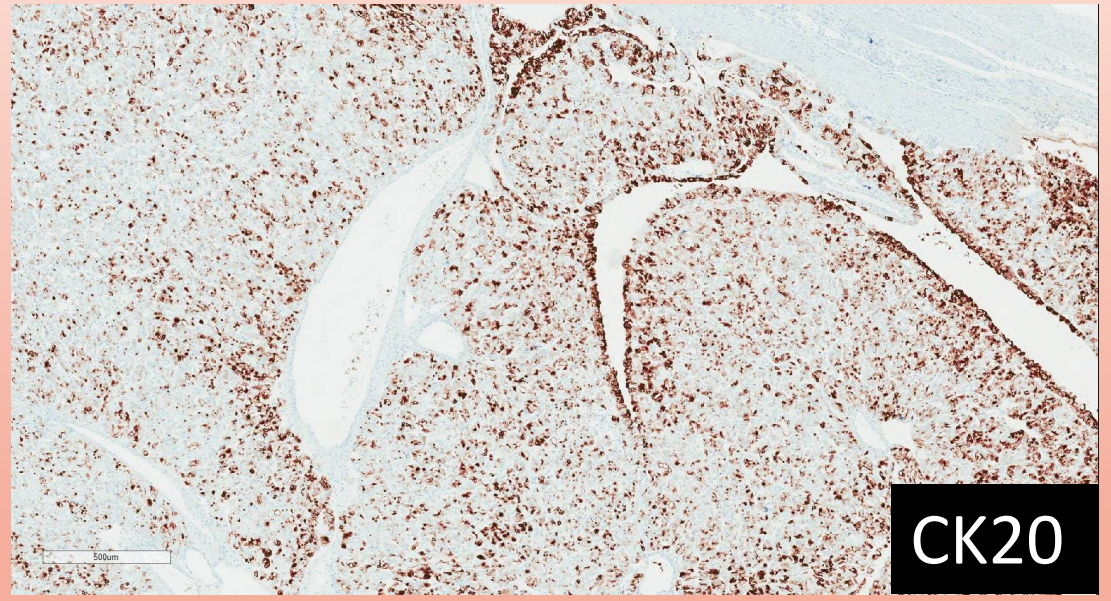






CK20 expression





Trpkov et al. *Am J Surg Pathol* 2016;40:60–71

Differential Diagnosis

- Oncocytic neoplasm
- Chromophobe RCC
- RCC, unclassified type (NOS)
- Epithelioid angiomyolipoma

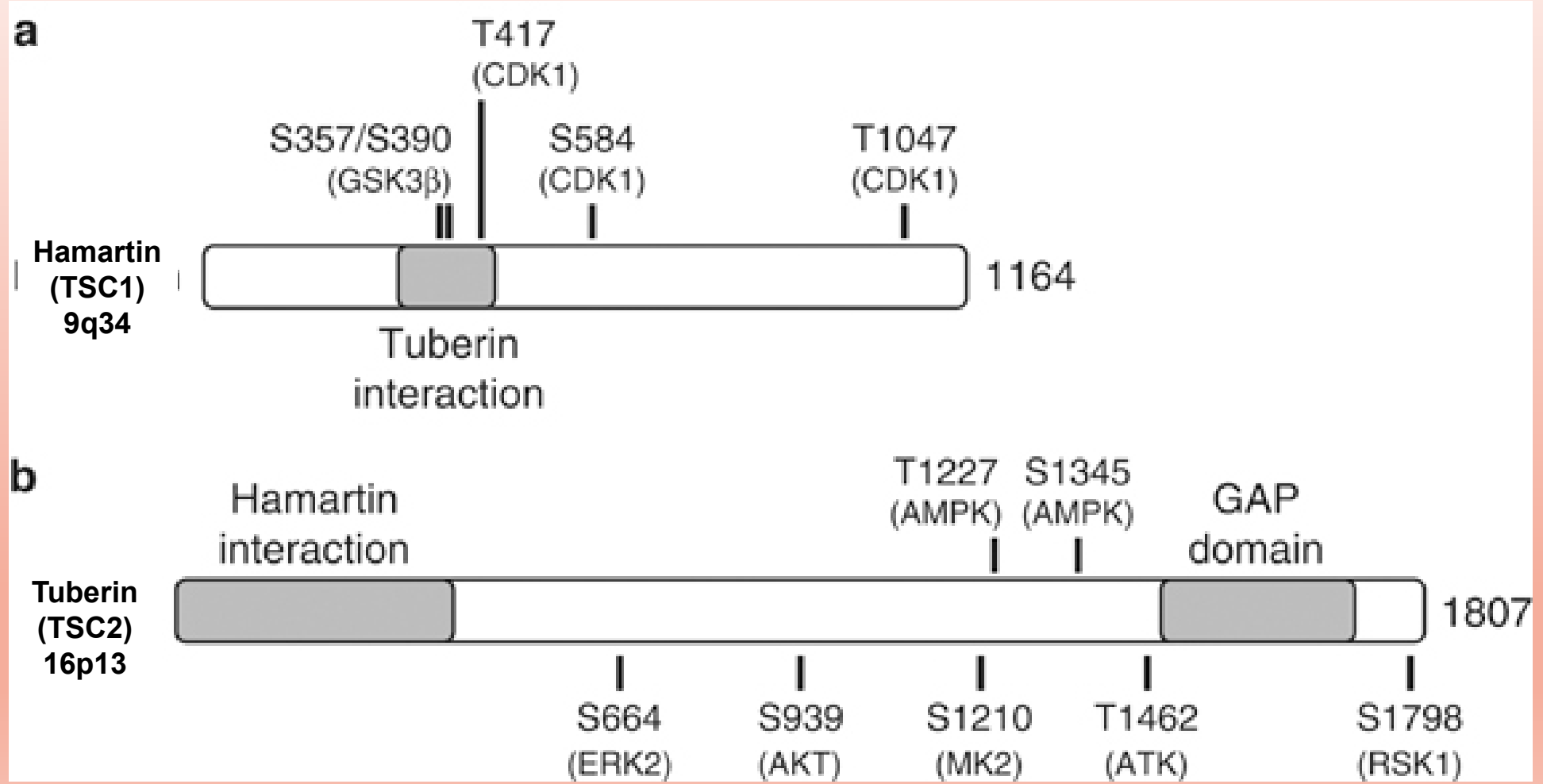
Eosinophilic, Solid, and Cystic Renal Cell Carcinoma (ESC)

- Initially described in Tuberous Sclerosis (6 cases)
  - Subsequent description of 16 sporadic cases (Trpkov et al *Am J Surg Pathol* 2016;40:60–71)
  - PAX8+/CK20+/CK7-/CD117-
  - Initially thought to be indolent
    - Subsequent reports with metastases

Tuberous Sclerosis Complex

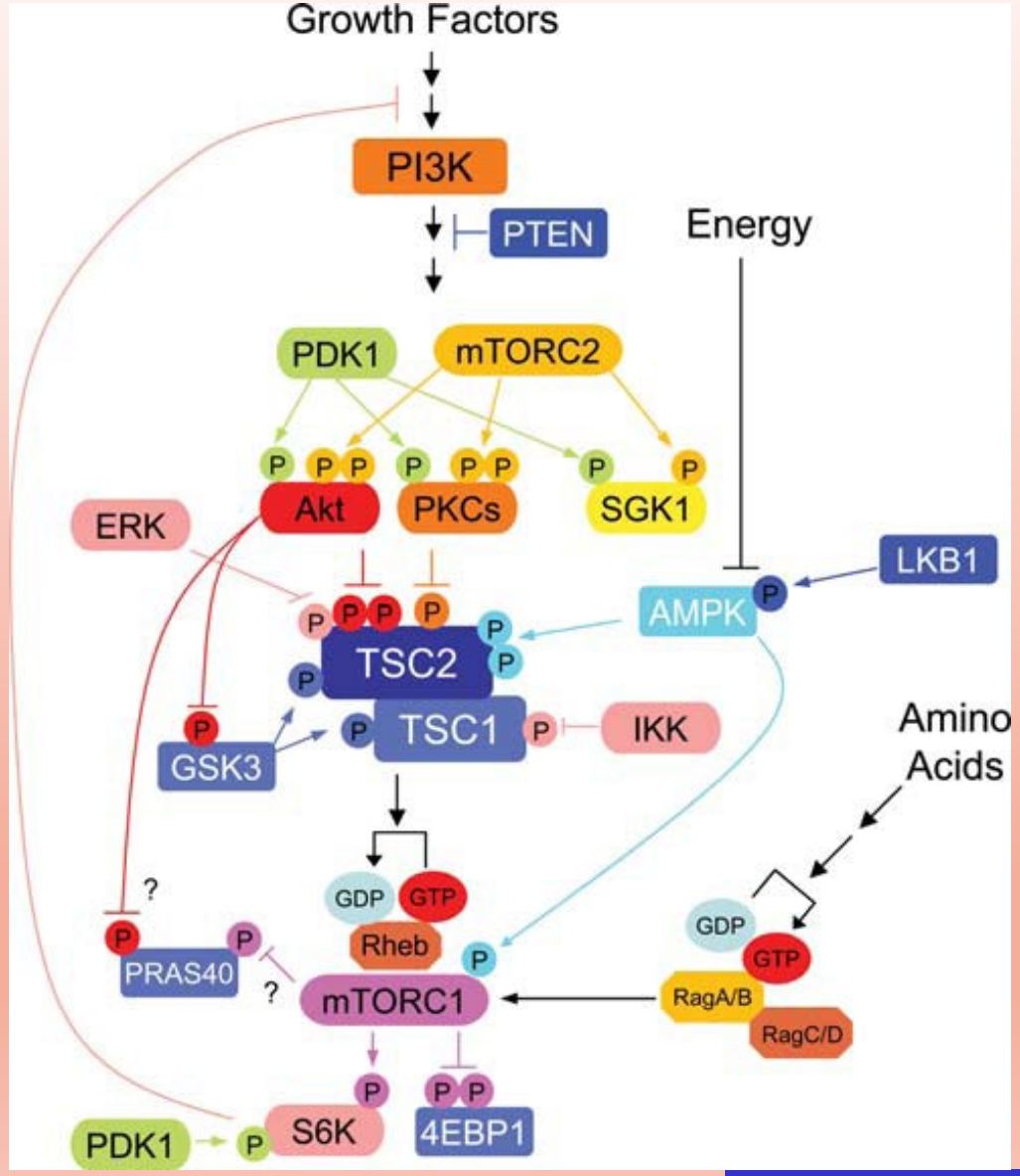
- Autosomal dominant disease
- Clinical presentation
  - Multi-organ involvement
    - CNS: cortical tubers, subependymal giant cell astrocytomas, retinal hamartomas
    - Heart: cardiac rhabdomyomas
    - Kidney/other organs: PEComas, RCCs

Hamartin and Tuberin



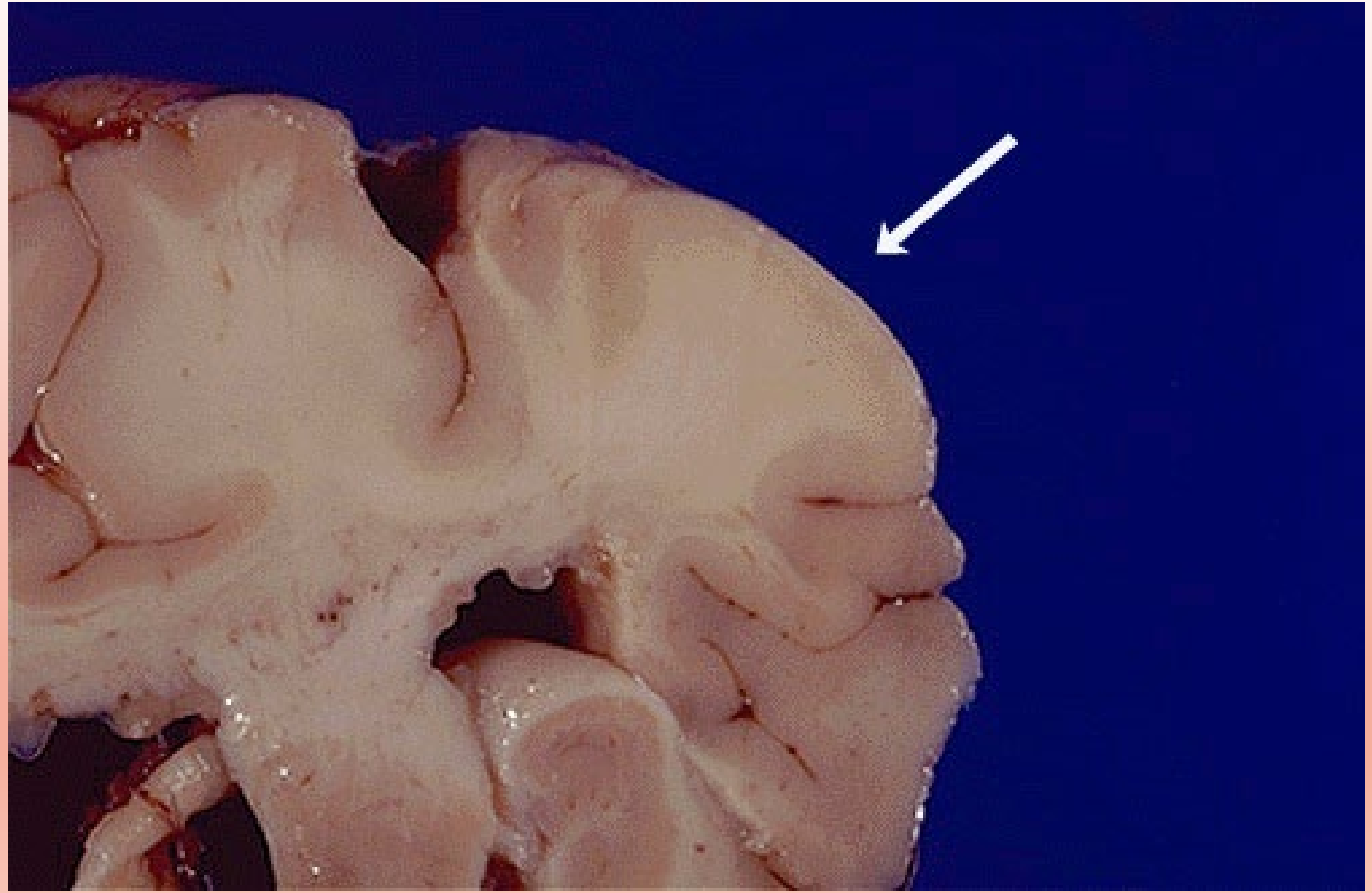
Astrinidis and Henske 2005 Oncogene

Hamartin and Tuberin
Tumor Suppression

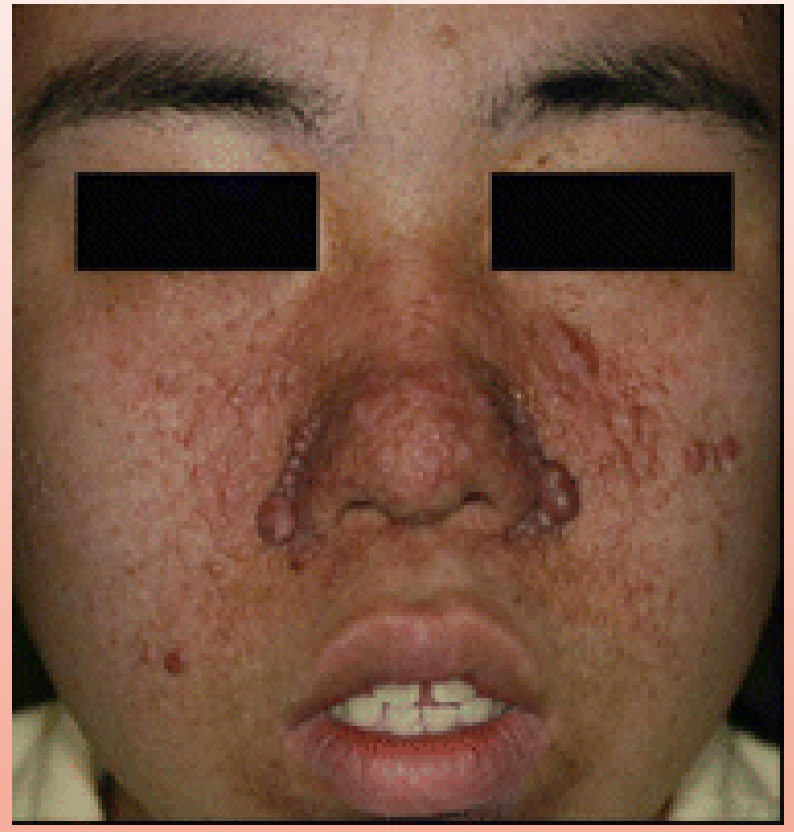


Inoki and Guan, Human Mol Gen, 2009

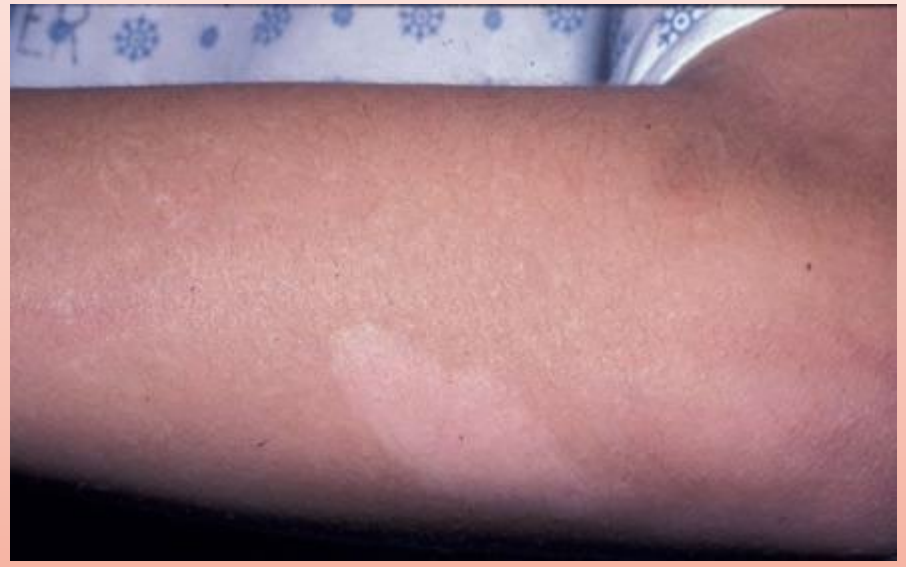
Cortical Tuber in Tuberous Sclerosis



Tuberous Sclerosis

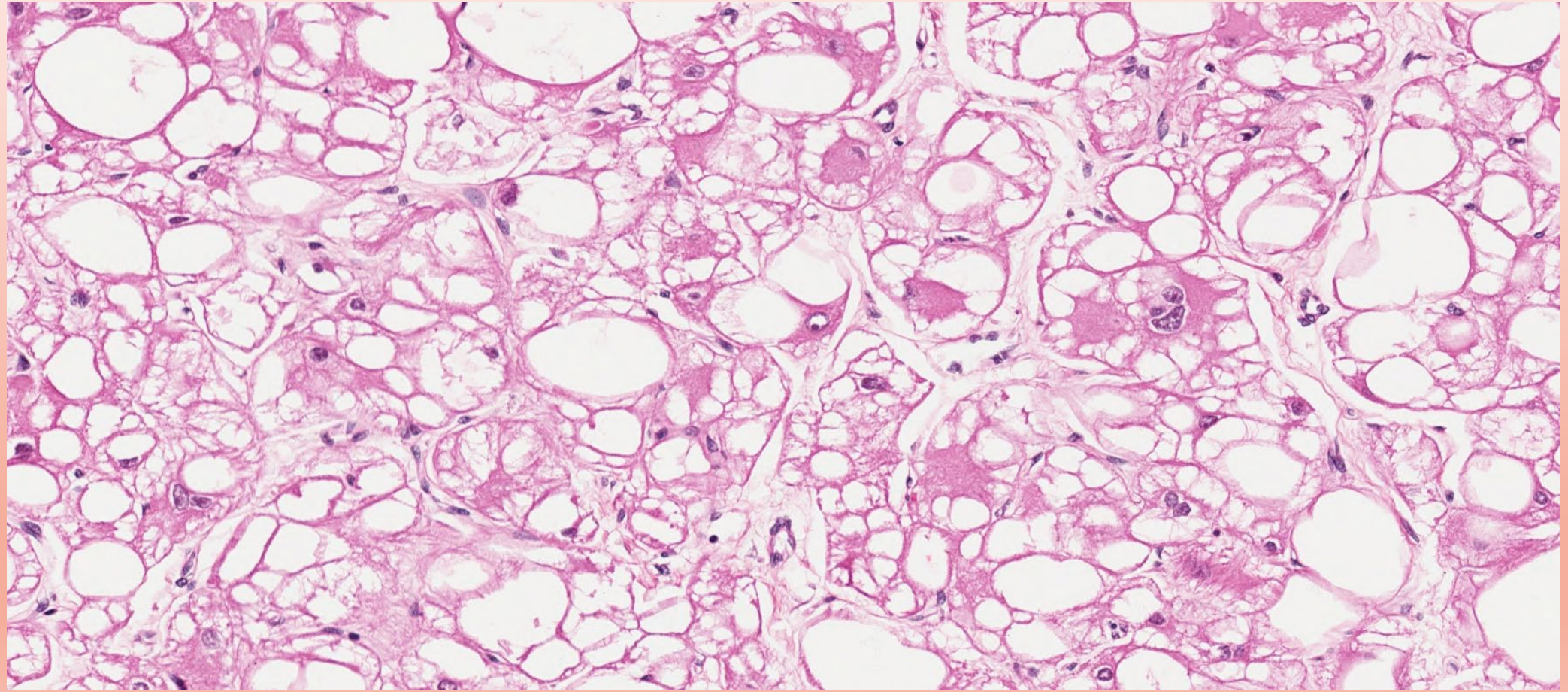


Facial angiofibroma

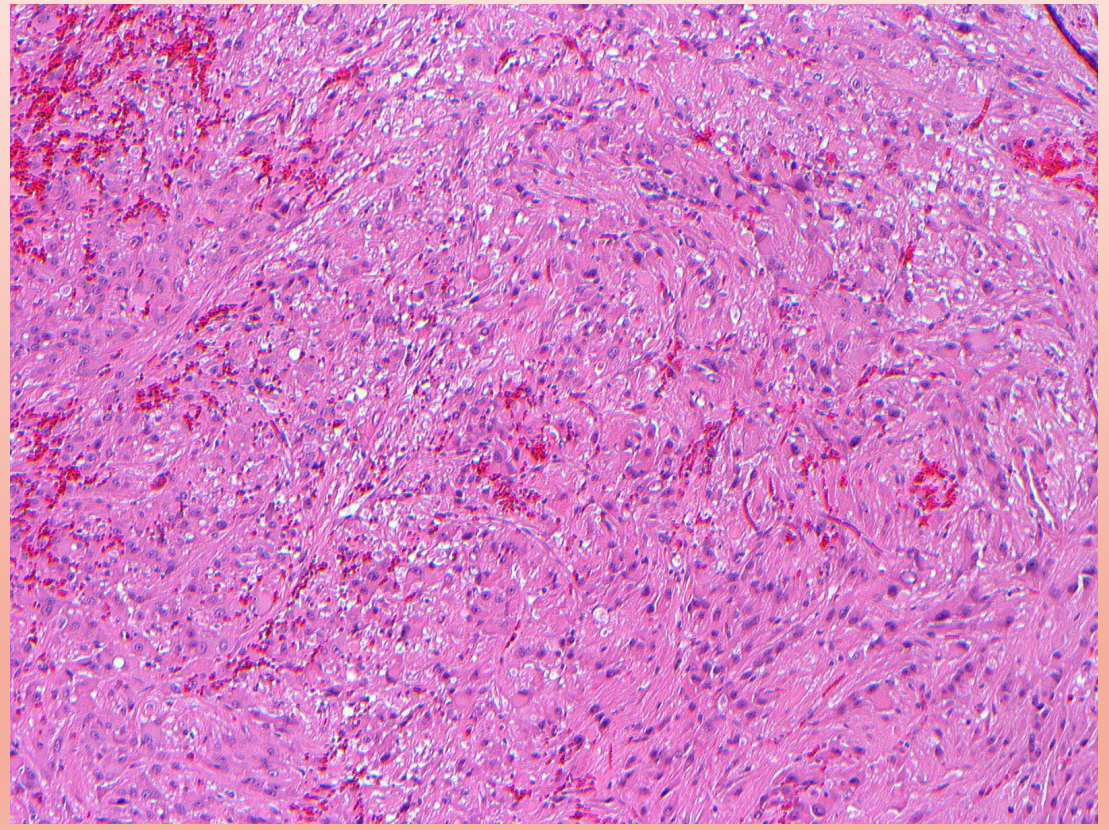


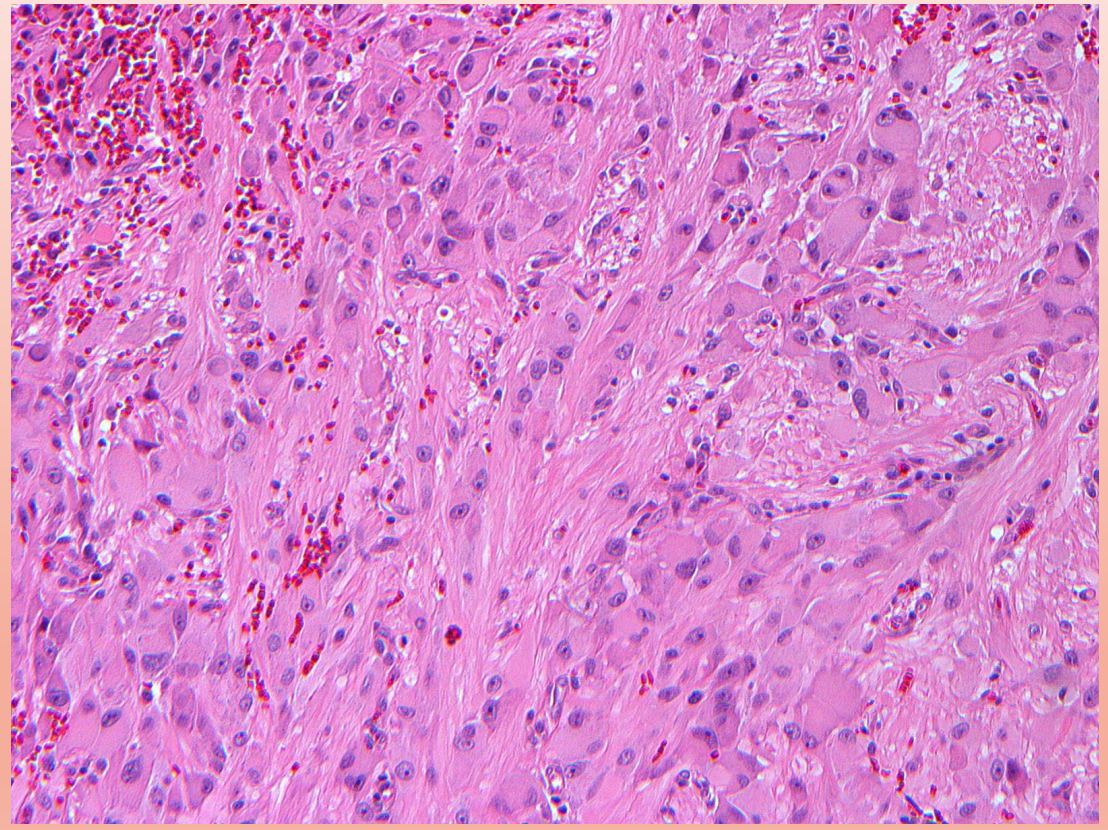
Hypomelanotic macule
(Ash leaf spot)

Tuberous sclerosis – Cardiac rhabdomyoma



Tuberous sclerosis – Subependymal giant cell astrocytoma

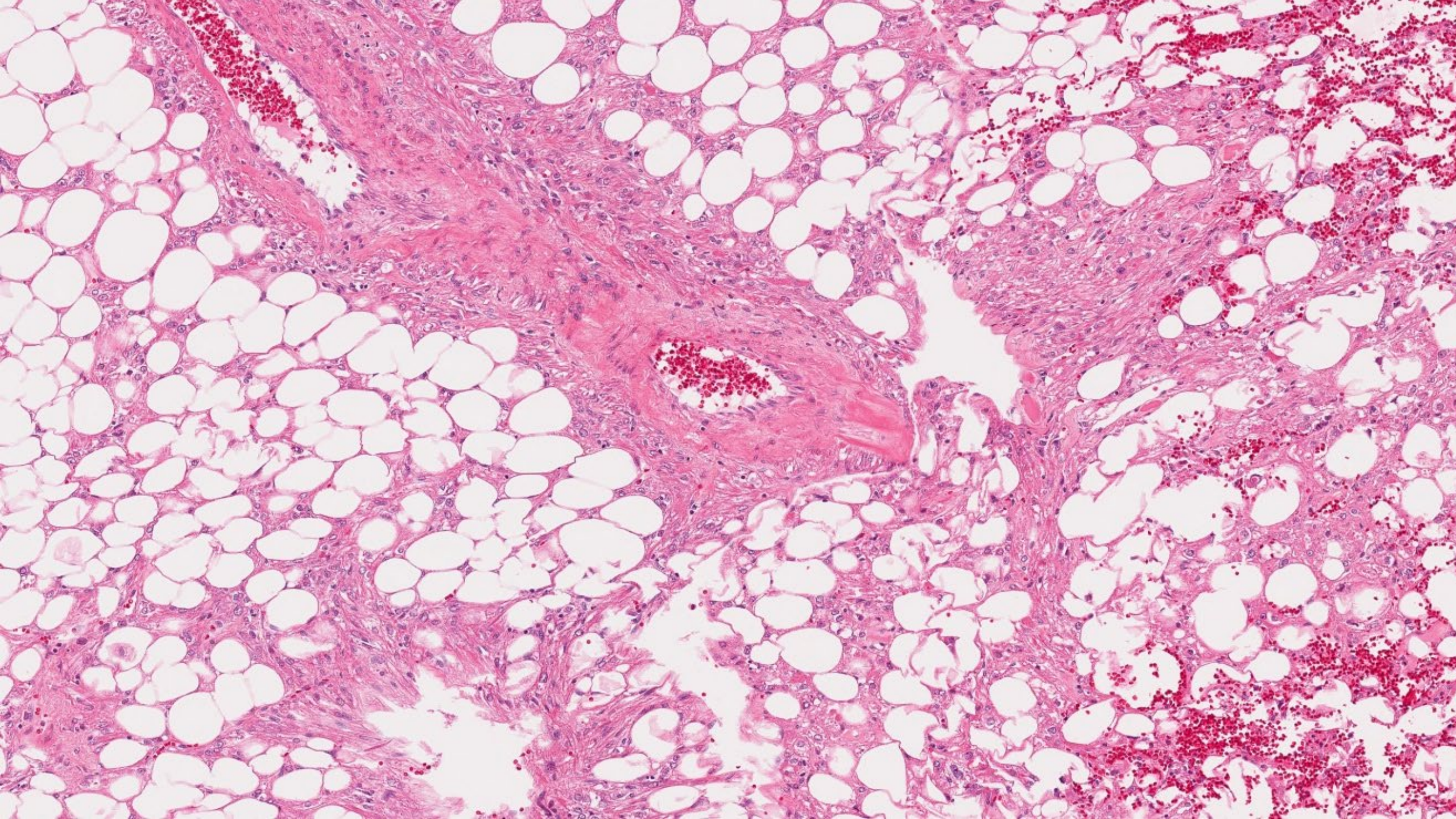




Photos courtesy Dr. Richard Prayson

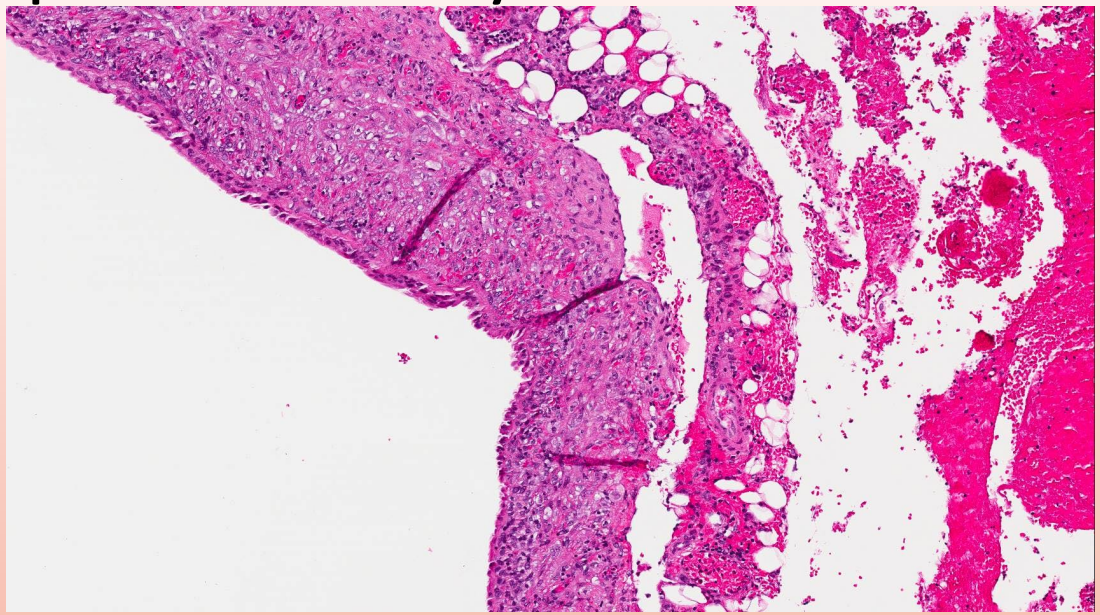
Renal manifestations of TS

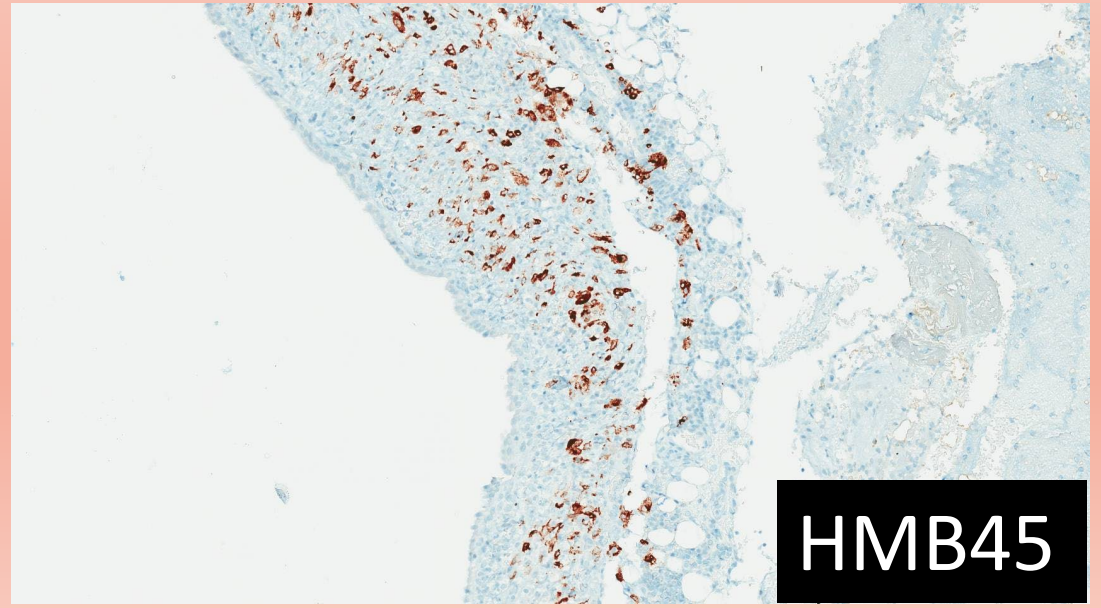
- Renal cysts - 45%
- Angiomyolipomas (spindled and/or epithelioid) - 80%
- Renal cell carcinomas/epithelial tumors
  - ESC-RCC
  - RCC with Fibromyomatous Stroma
  - Oncocytic tumors (EVT/LOT)



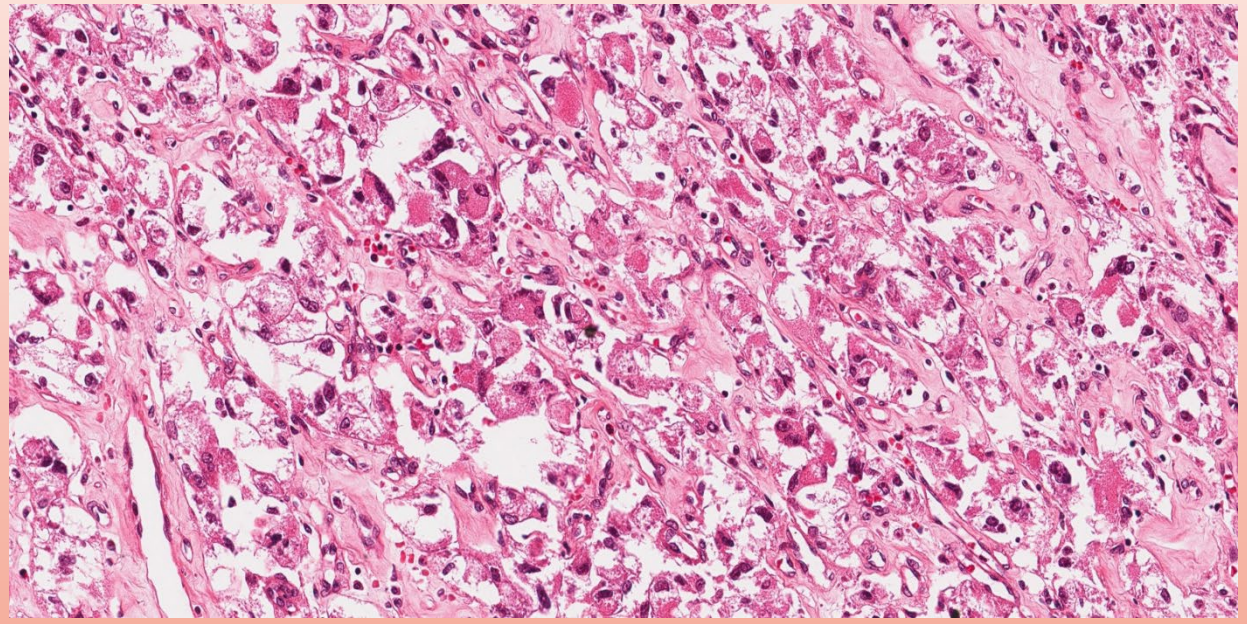
Angiomyolipoma with epithelial cysts (AMLEC)

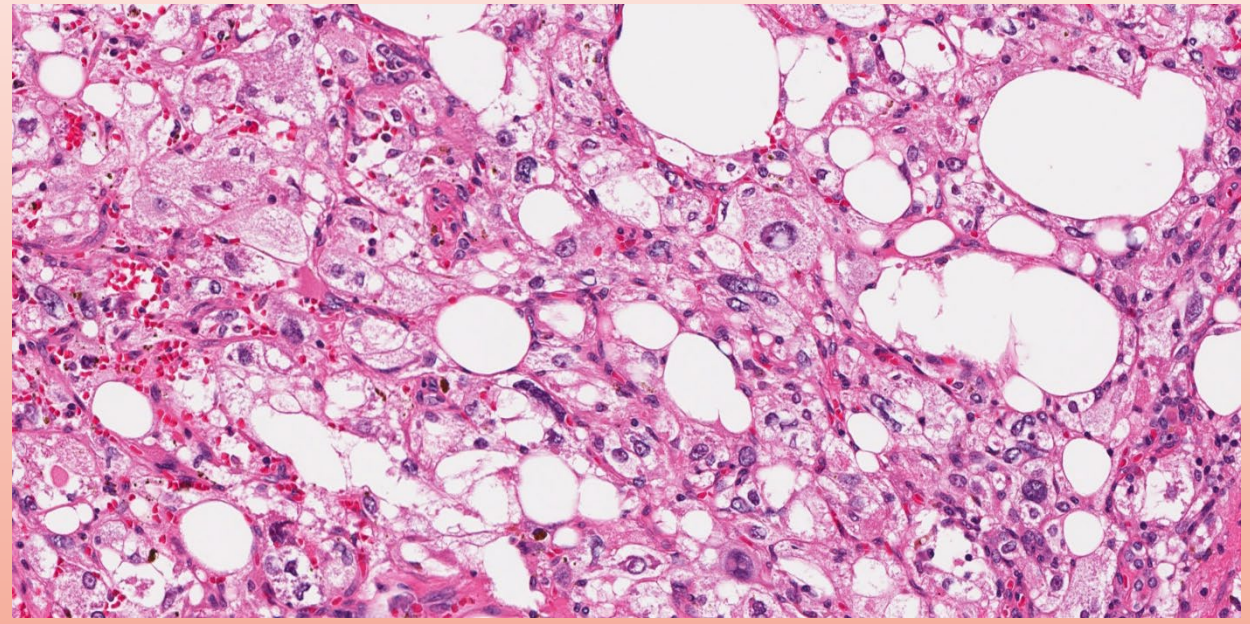
- Fine et al. *Am J Surg Pathol* 2006;30:593–599
- Occurs in tuberous sclerosis **and sporadically**
- Benign prognosis
- 3 components
  - 1) epithelial cysts lined by cuboidal to hobnail cells
  - 2) a compact subepithelial ‘‘cambium-like’’ layer of cellular, Mullerian-like AML stroma with prominent admixed chronic inflammation
  - 3) muscle-predominant AML with associated dysmorphic blood vessels exterior to the cellular subepithelial stroma.





Epithelioid AML

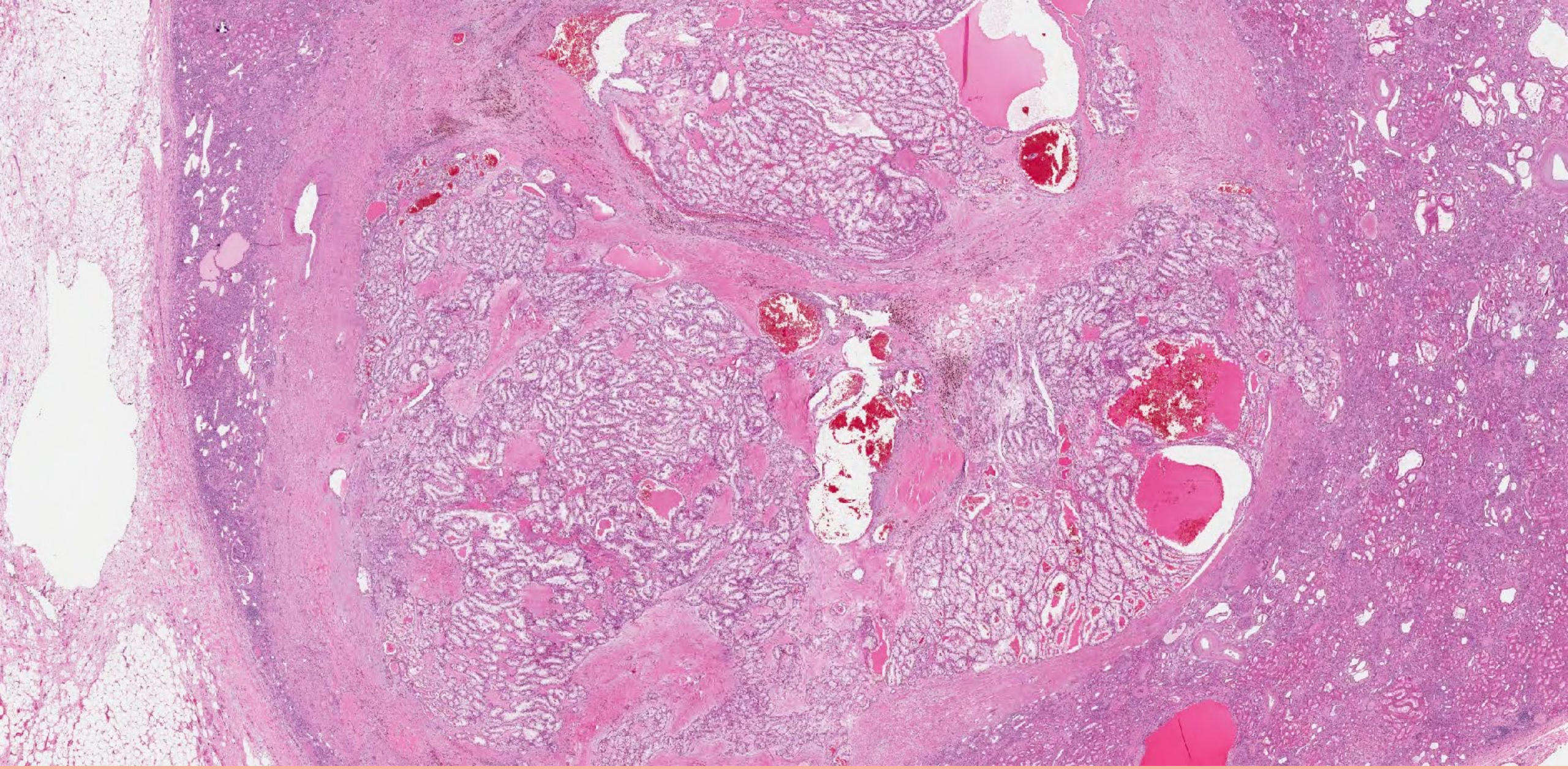


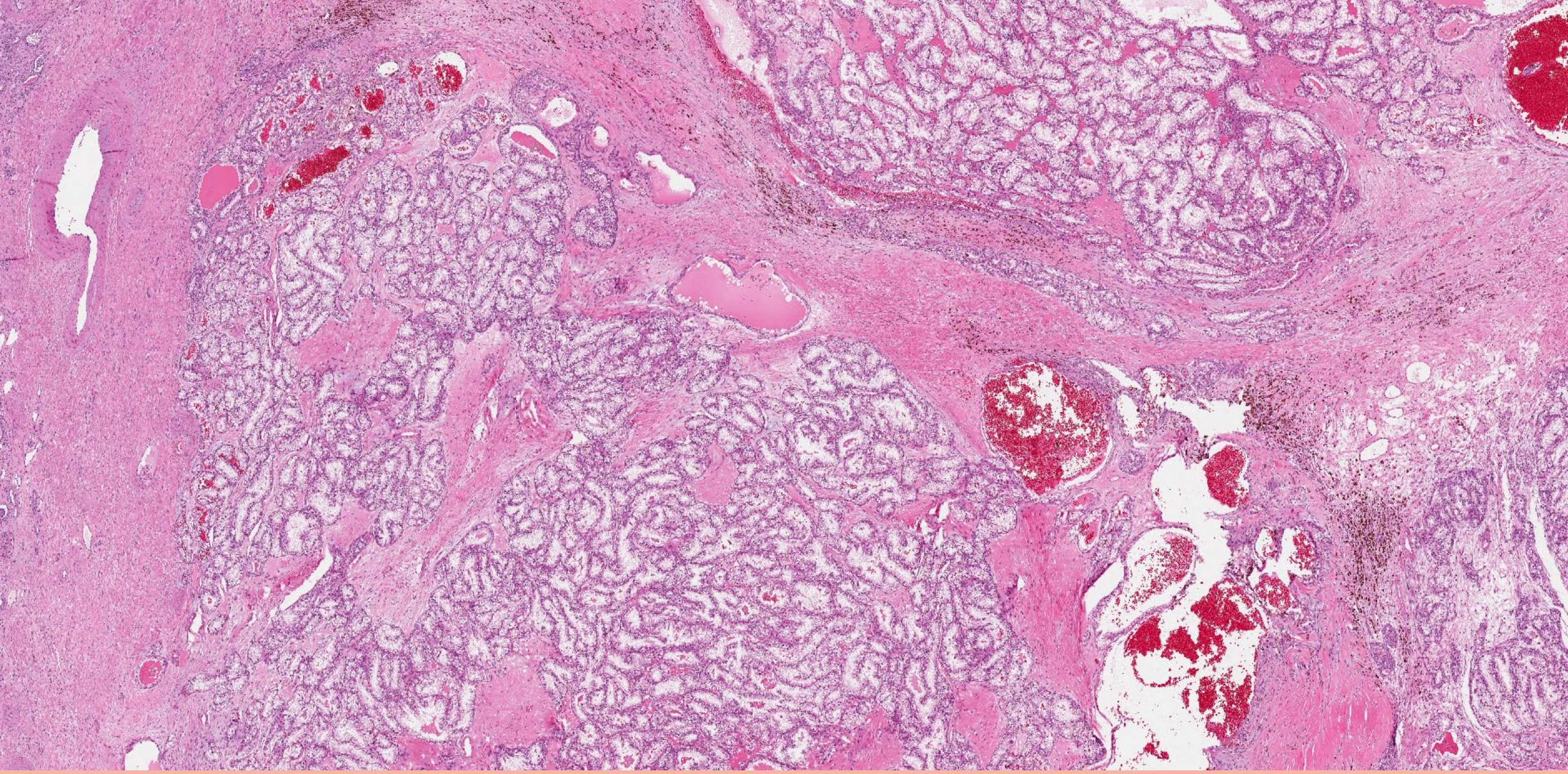


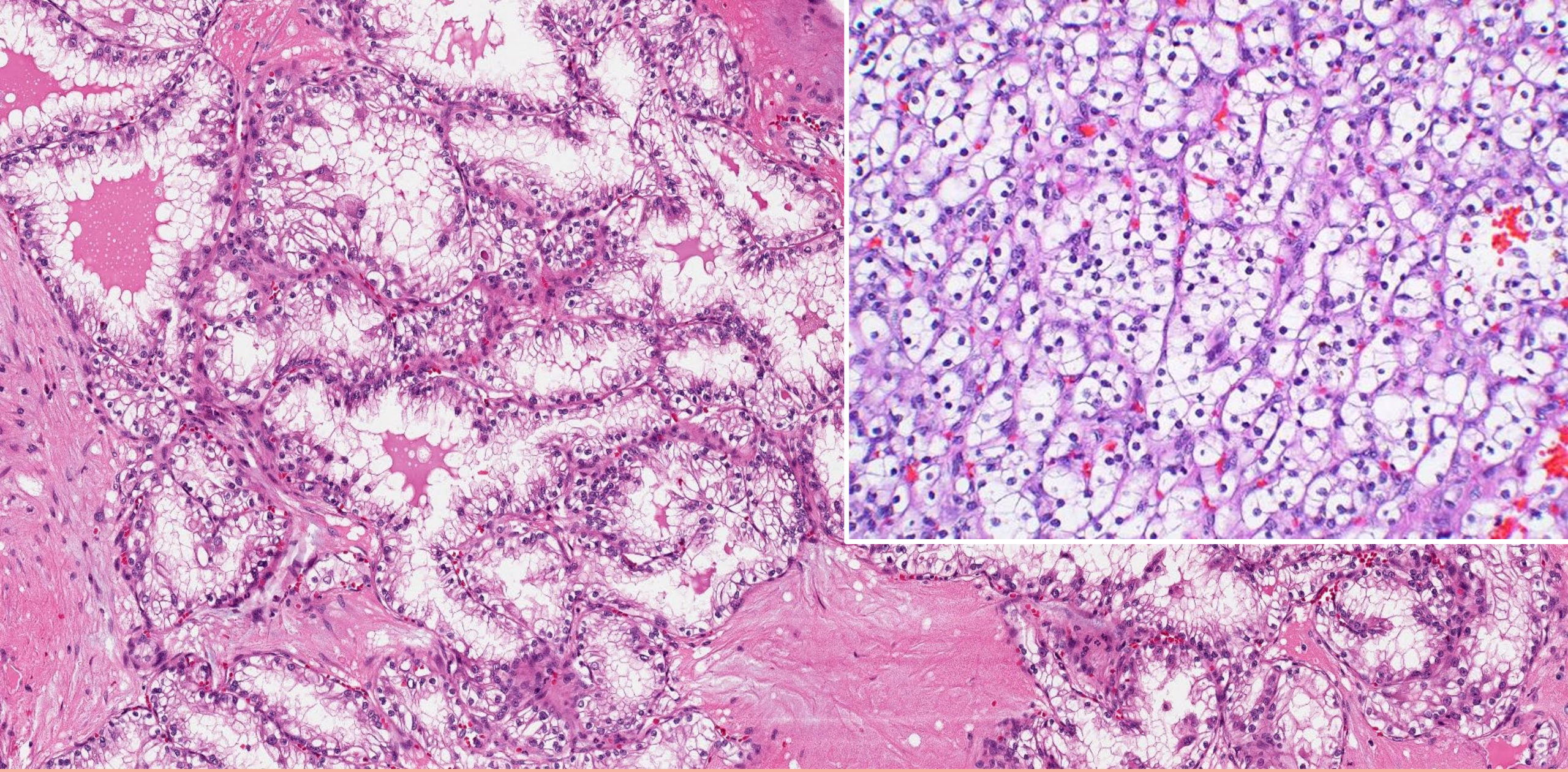
PAX8-, HMB45+, CATHEPSIN K+

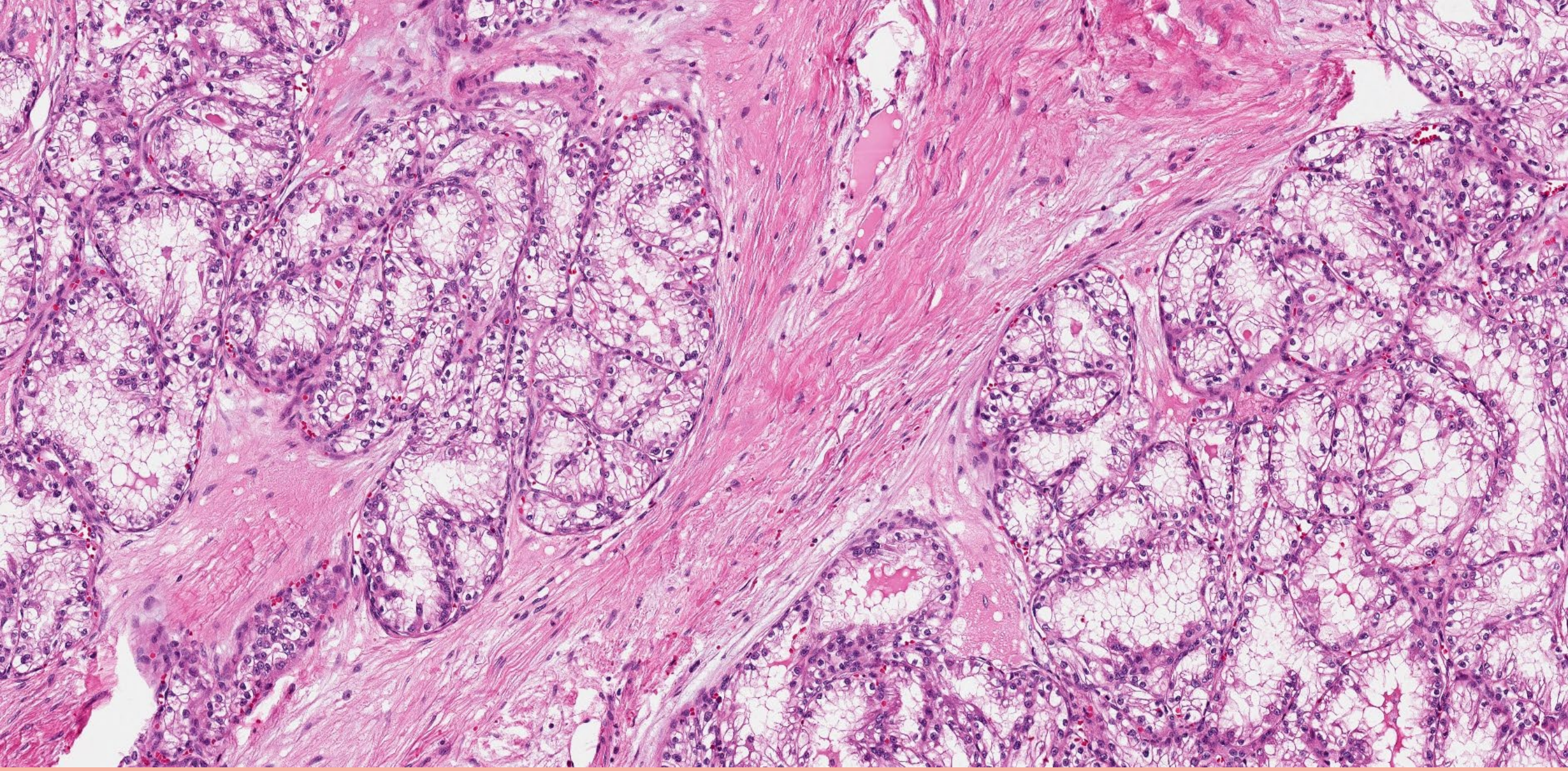
Epithelioid angiomyolipoma

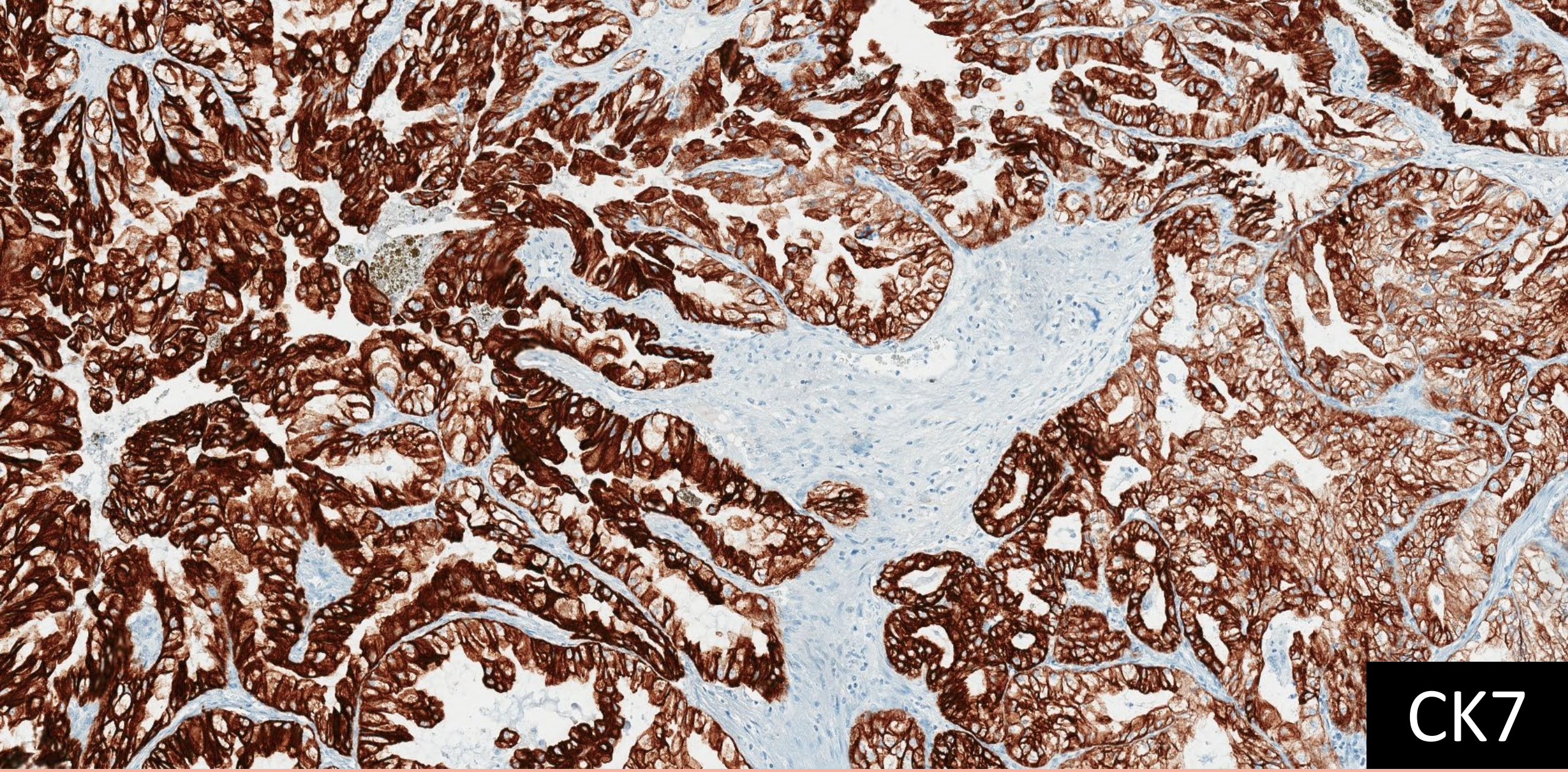
- He et al (Mod Path 2013)
  - 20 pooled cases from 3 institutions
  - Consecutive cases with >80% epithelioid
  - Incidence: 4.6% of renal AMLs
  - One patient died of disease (5%)
    - mean f/u 82 mo










CK7

- Multiple previous names:
  - “Renal angiomyoadenomatous tumor (RAT)”
  - “RCC with (angio)leiomyomatous stroma”
  - “RCC with diffuse CK7 positivity”
  - “Clear cell RCC with smooth muscle stroma”

ELOC-mutated RCC (Renal Cell Carcinoma with Fibromyomatous Stroma)

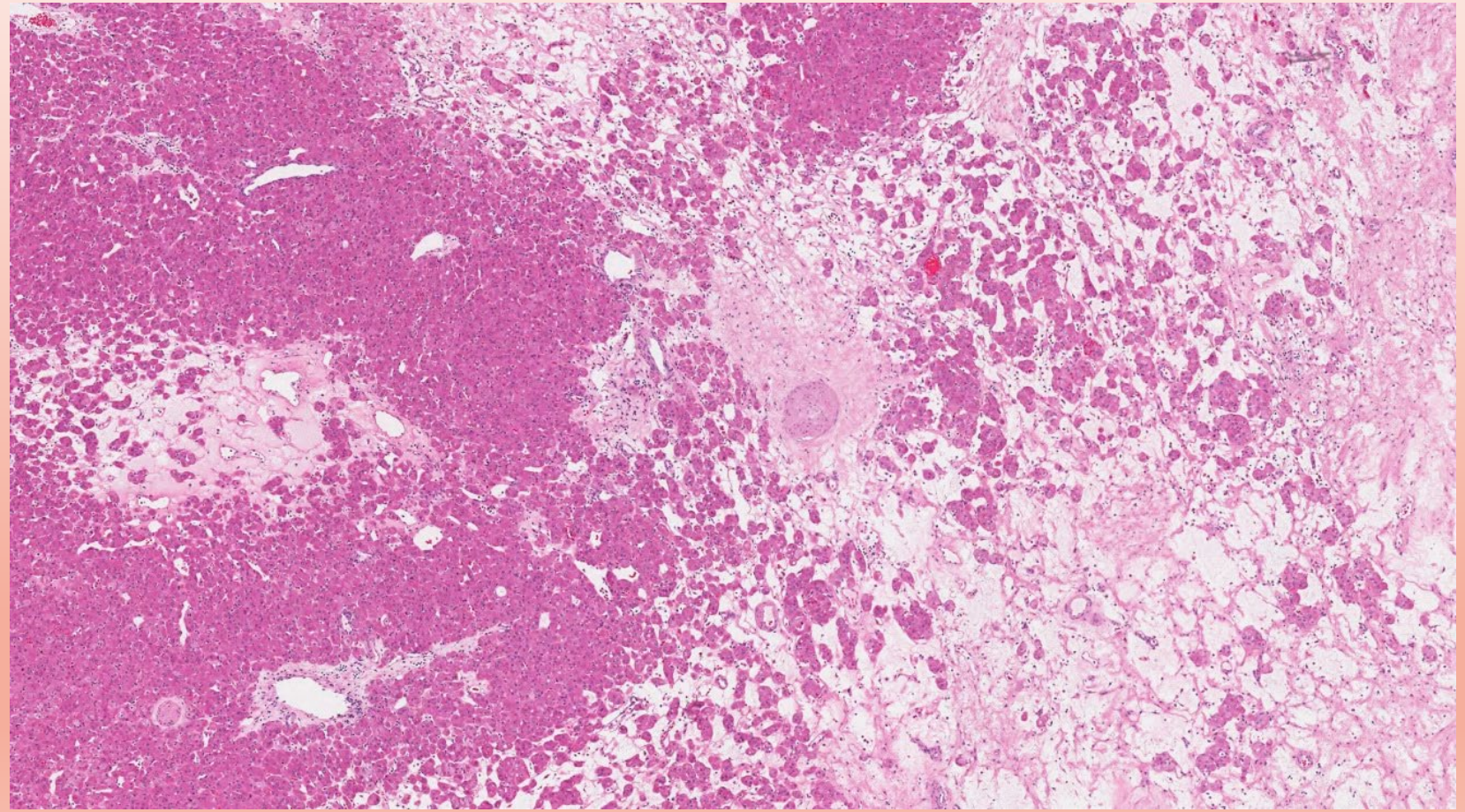
- *TSC1/TSC2/MTOR/ELOC(TCEB1)* mutations (no *VHL*/3p mutations)
  - Most cases sporadic/rarely tuberous sclerosis
- CK7+/CAIX+/CD10+/Vimentin+
- Usually indolent (with exceptions)

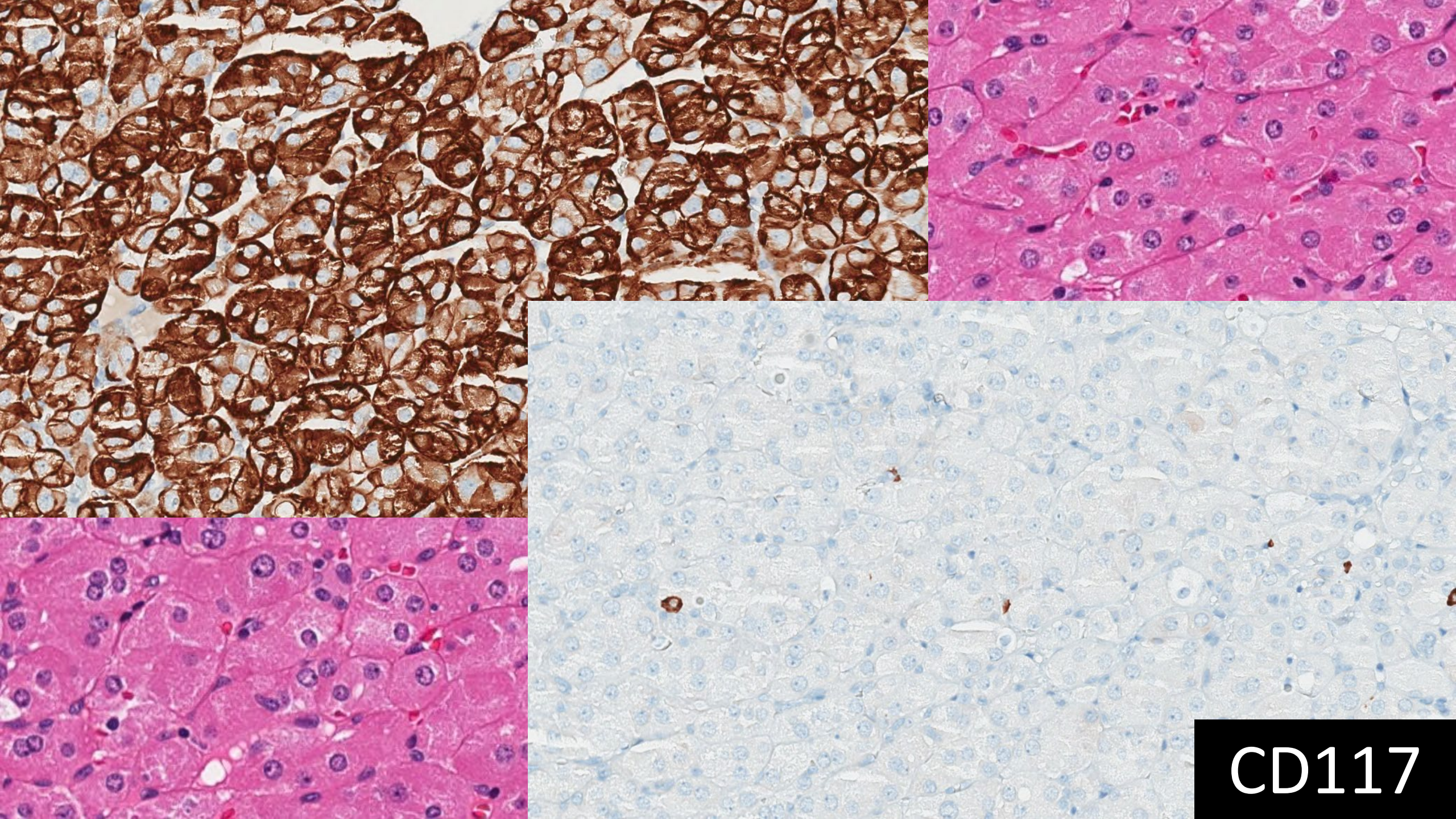
Eosinophilic tumors in Tuberous Sclerosis*

- Low-grade oncocytic tumor (LOT)
- Eosinophilic vacuolated tumor (EVT)

*Also arise sporadically

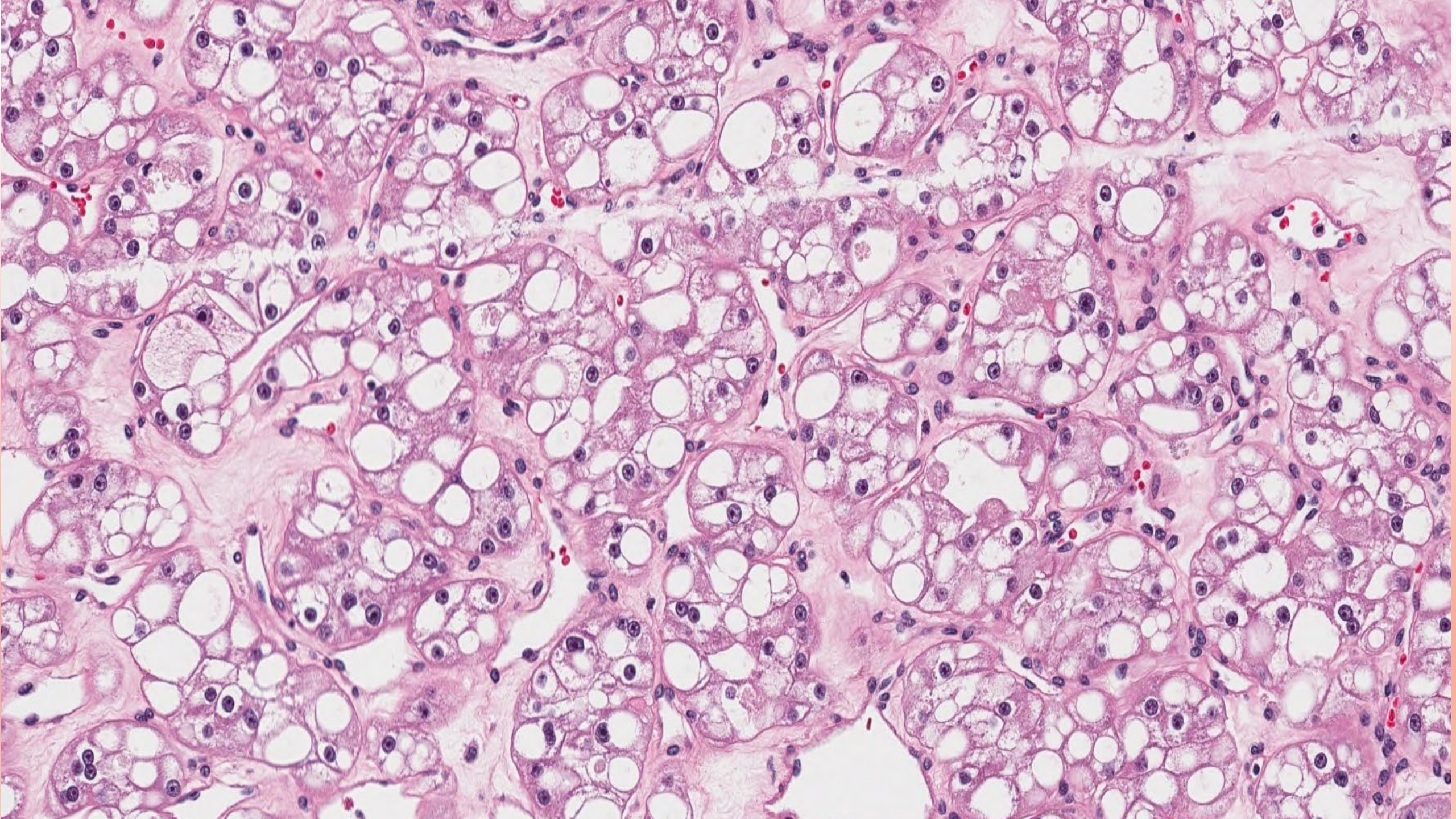
Low-grade oncocytic tumor (LOT)




CD117

Low-grade oncocytic tumor (LOT)

- ? Relationship to TS
  - But some have TSC/MTOR mutations
- Indolent prognosis
- Provisional entity



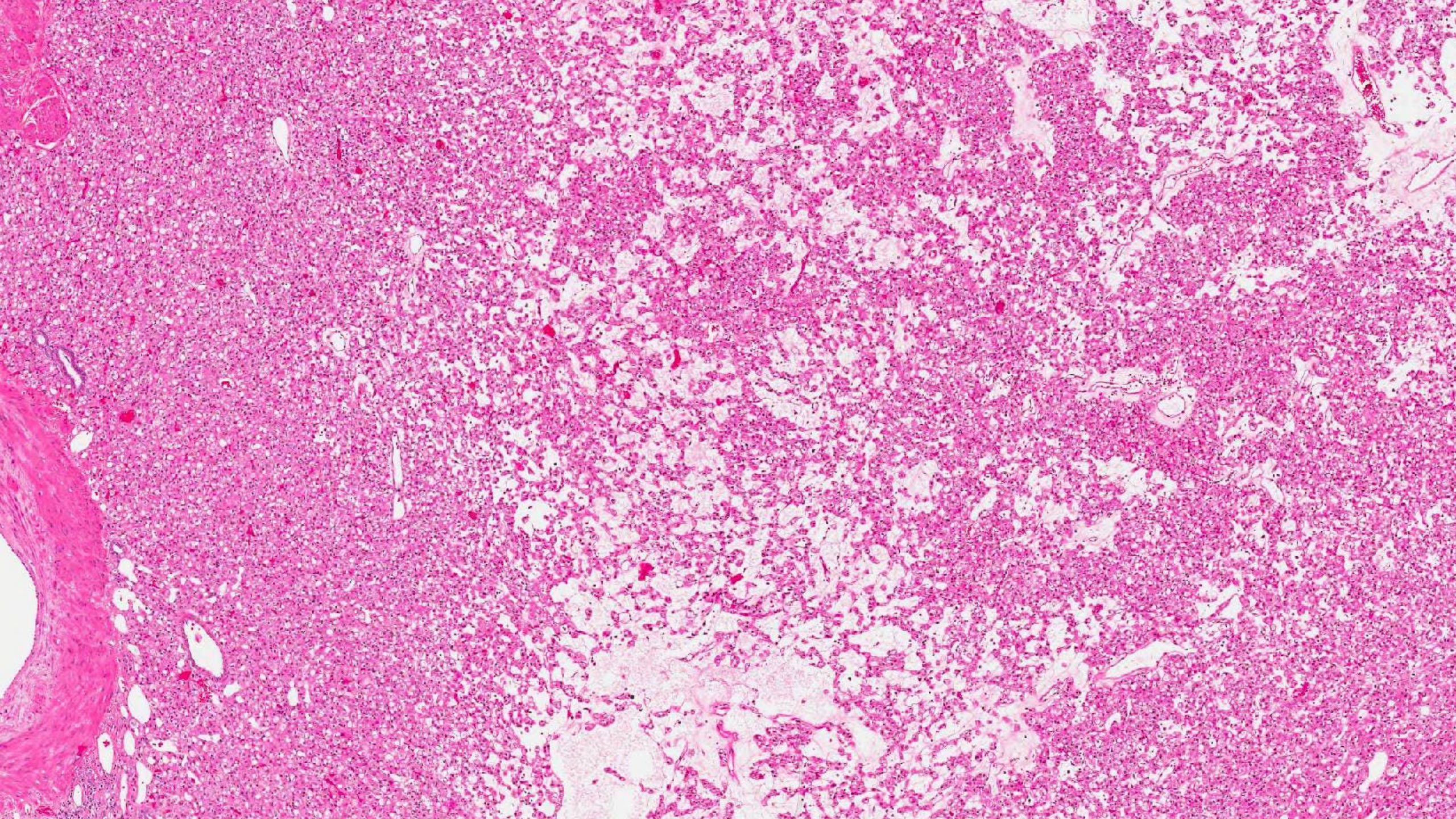
Eosinophilic Vacuolated Tumor

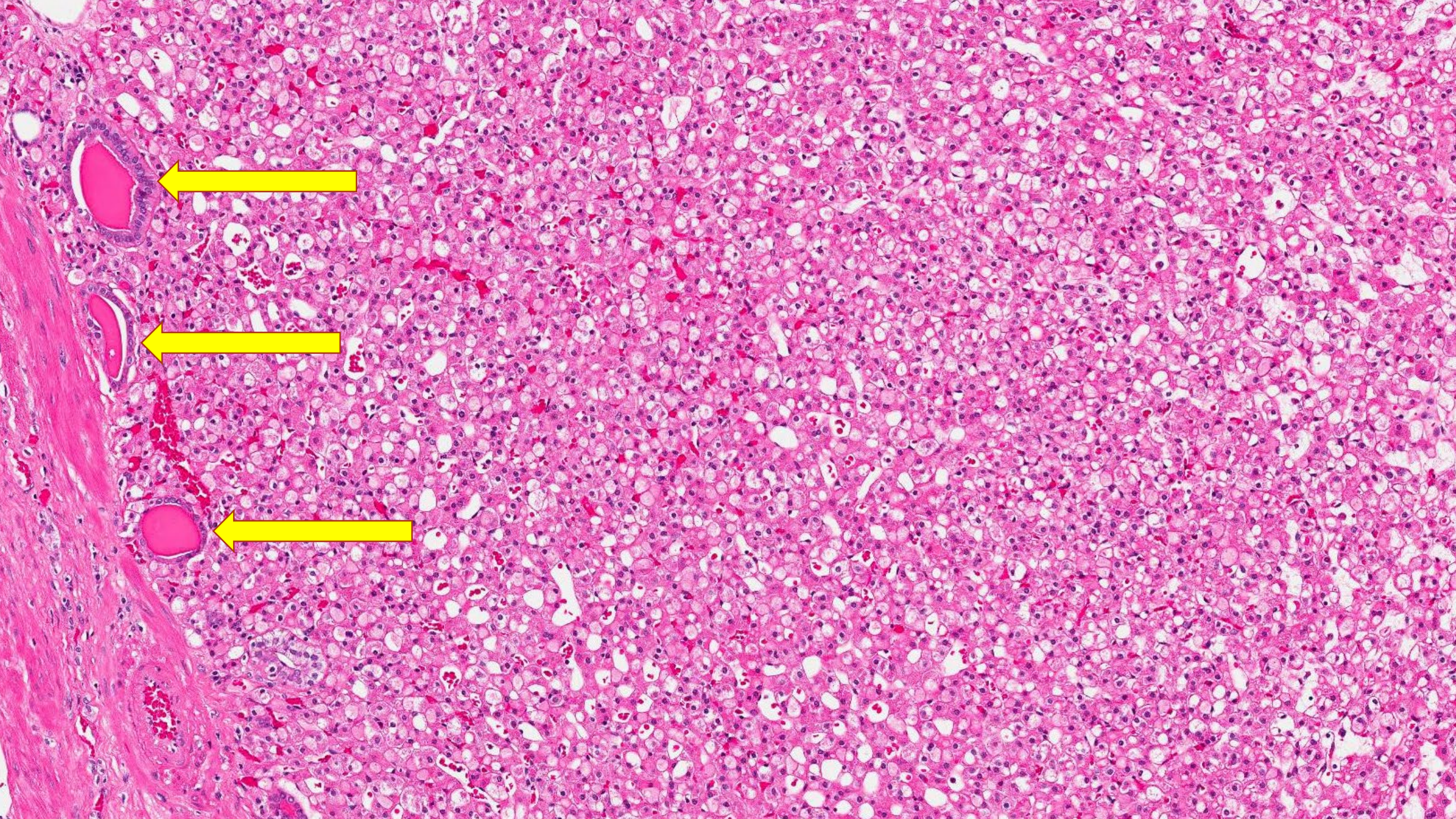
- Formerly “High-grade oncocytic tumor (HOT)”
- TS patients and sporadic
- Indolent behavior
- CD117+/-, Cathepsin K +/-, CK7 focal,
- *TSC/MTOR* mutations
- Emerging entity

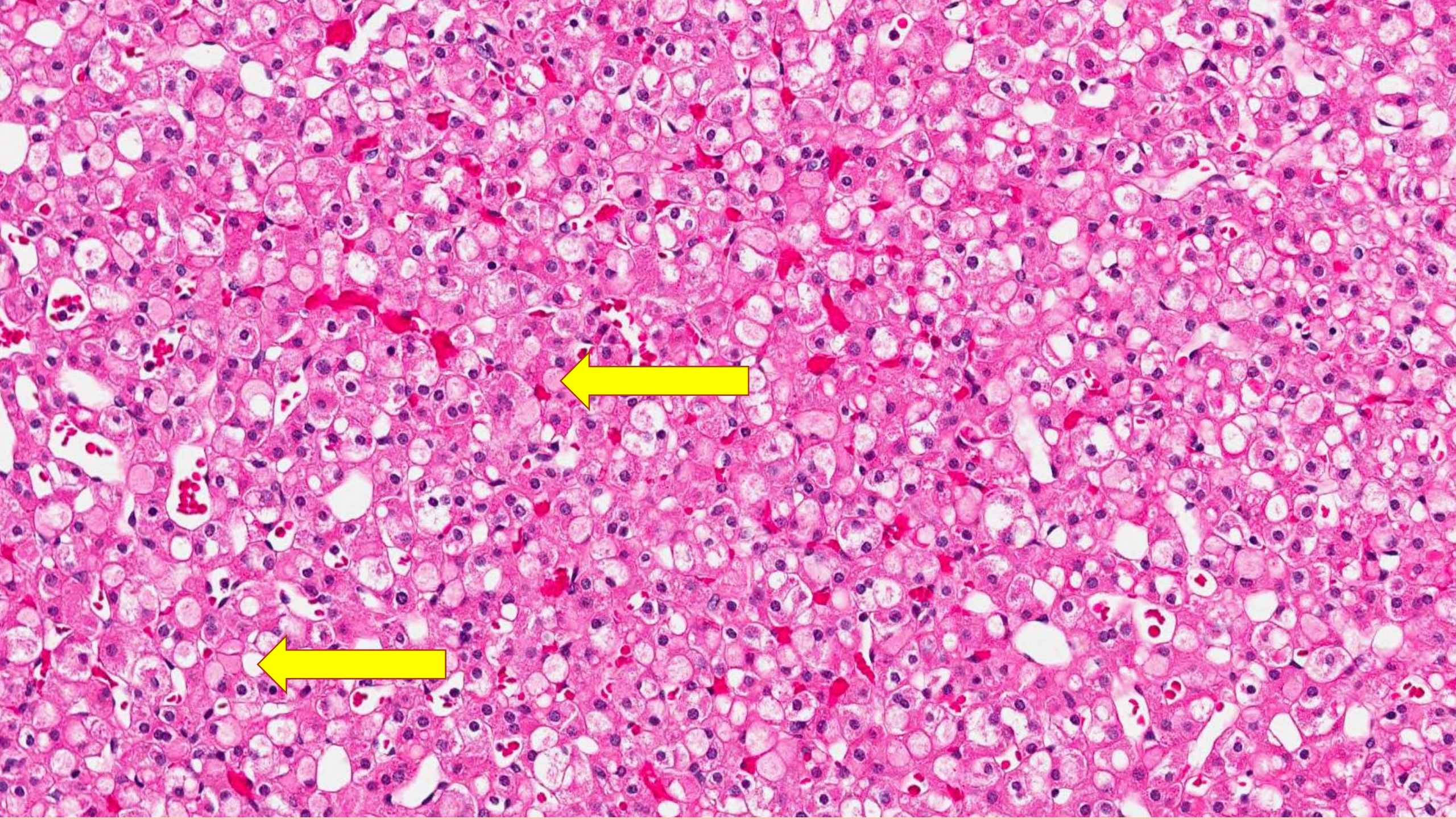
Case 3

Clinical history

- 57-year-old man with a kidney mass





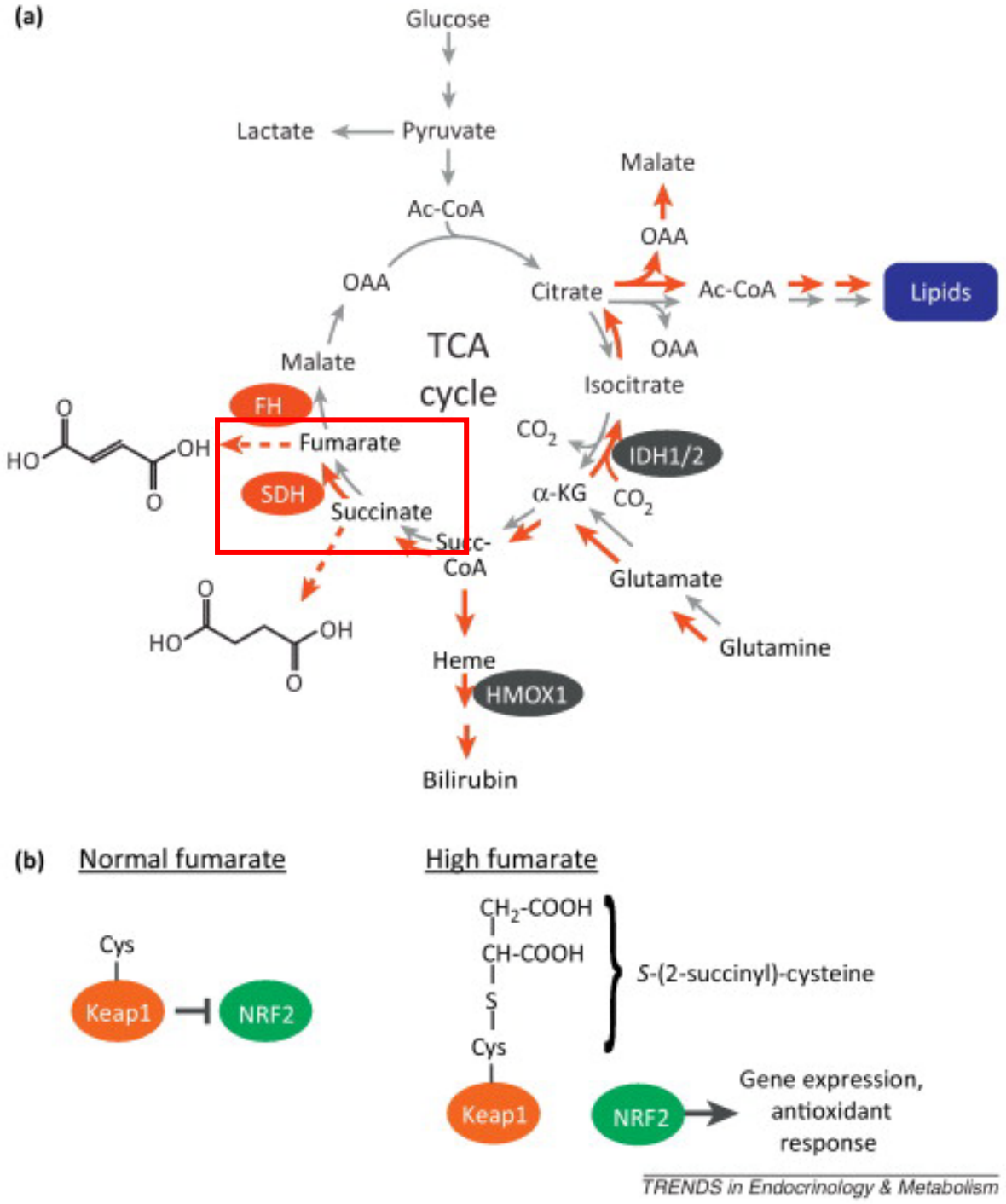


Differential diagnosis

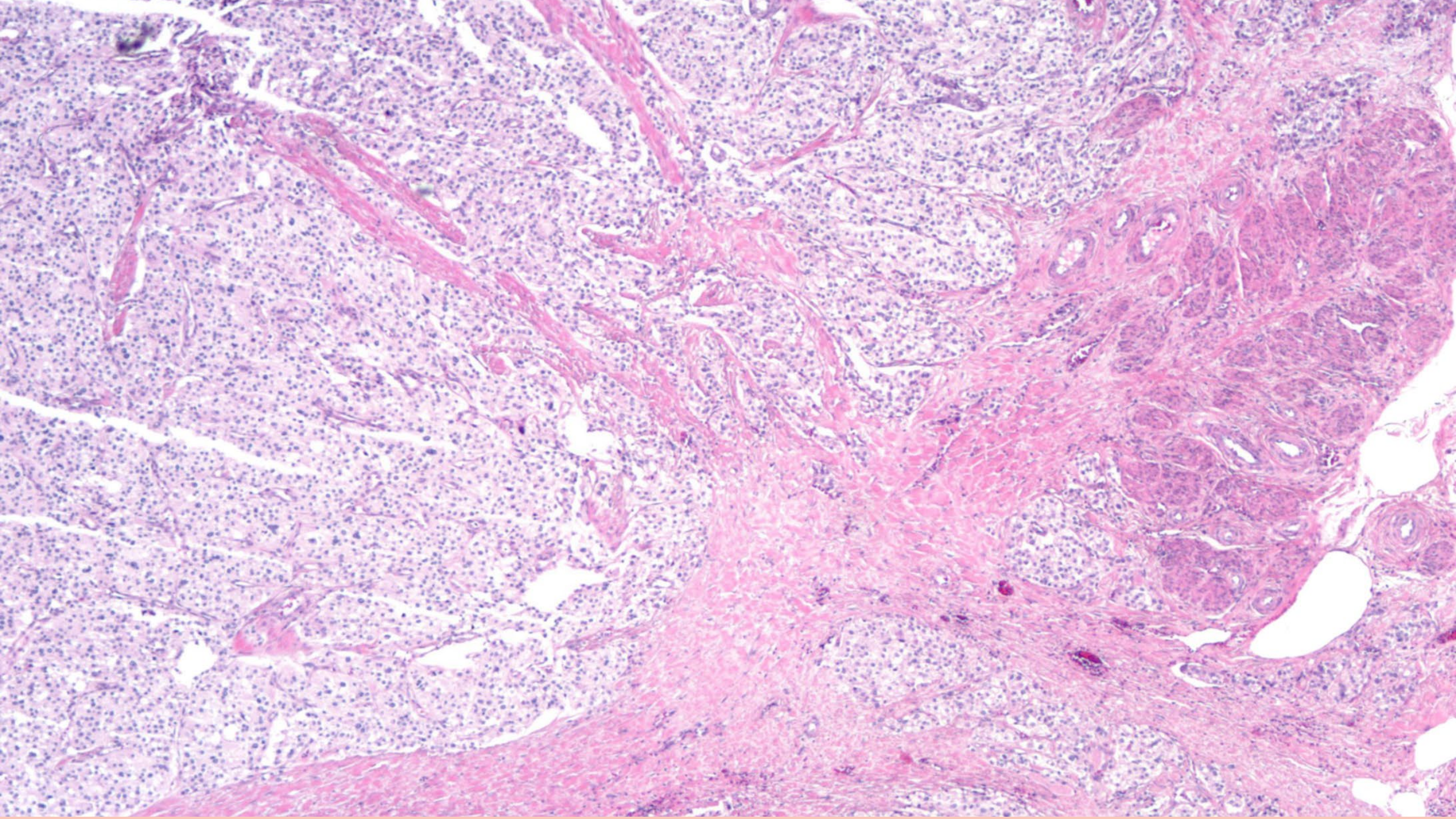
- Oncocytoma
- Chromophobe renal cell carcinoma, eosinophilic variant

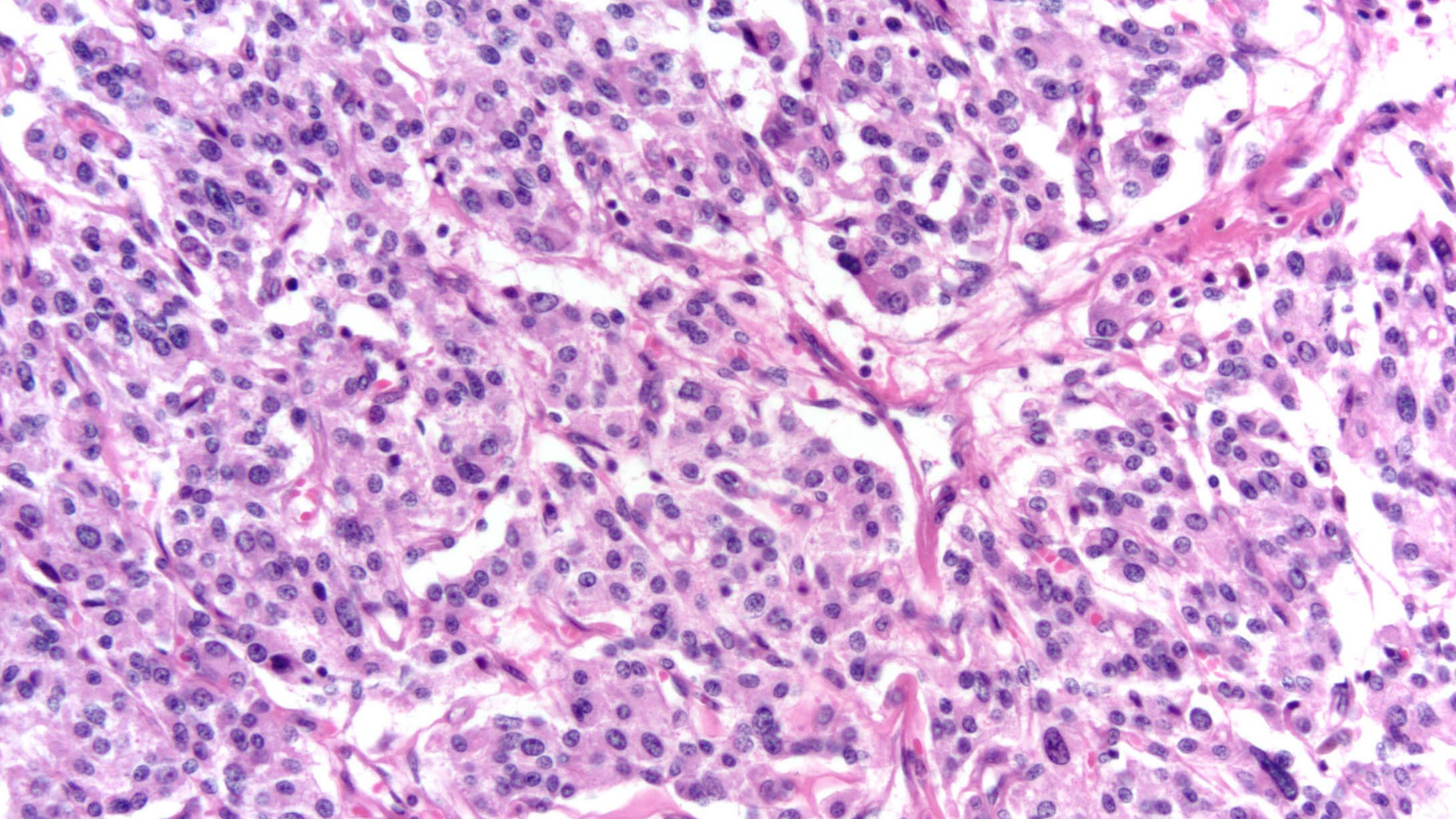
Succinate dehydrogenase (SDH) – deficient RCC

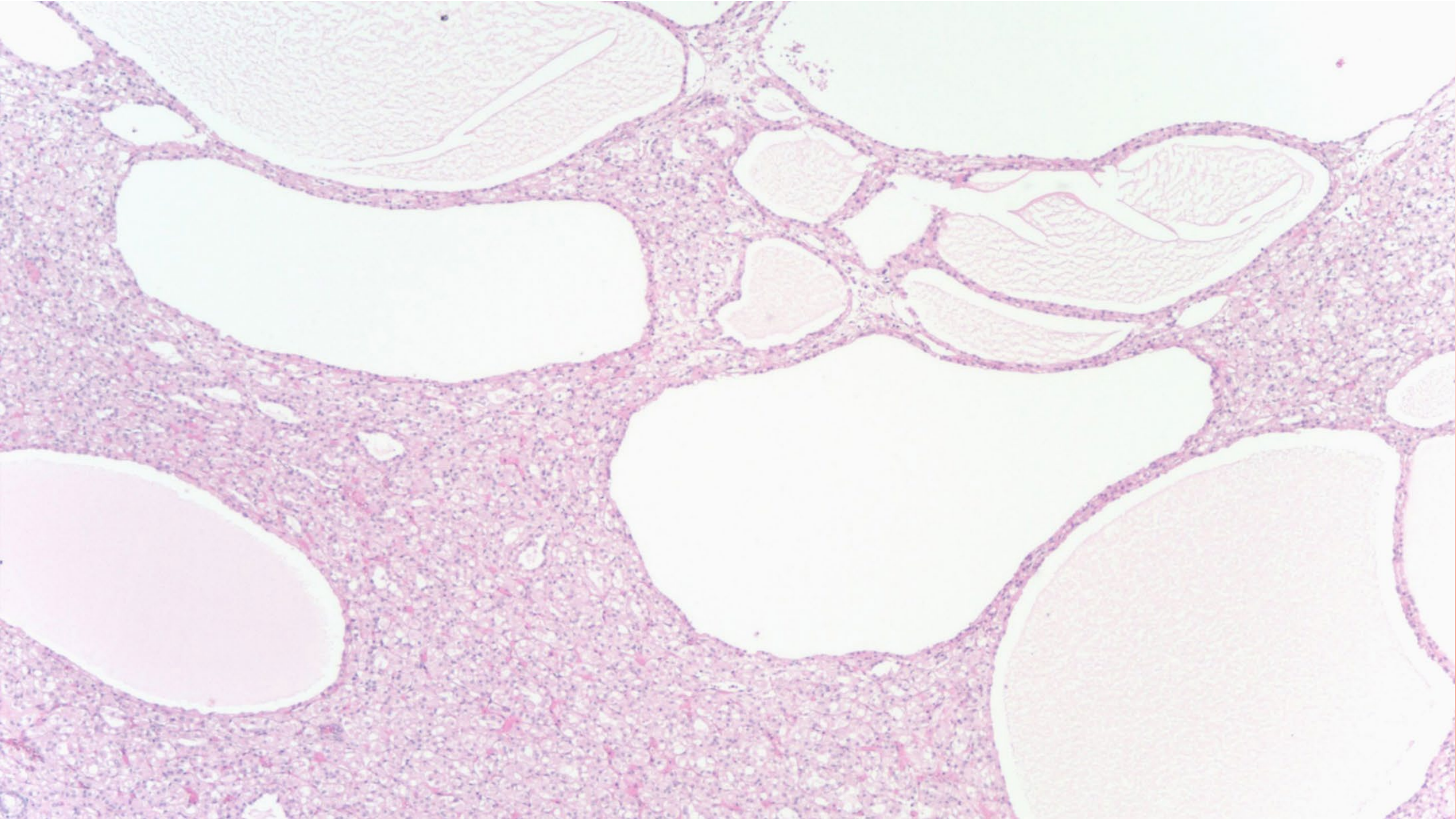
- RCCs associated with germline SDH mutations (usually SDHB)
  - Hereditary pheochromocytoma/paraganglioma syndromes
    - Pheochromocytomas/paragangliomas/pediatric-type (type 2) GISTs
- Young adults
- Usually (not always) indolent if low-grade nuclei and no necrosis
- CD117-/CK7 focal to -/cytokeratins focal to -

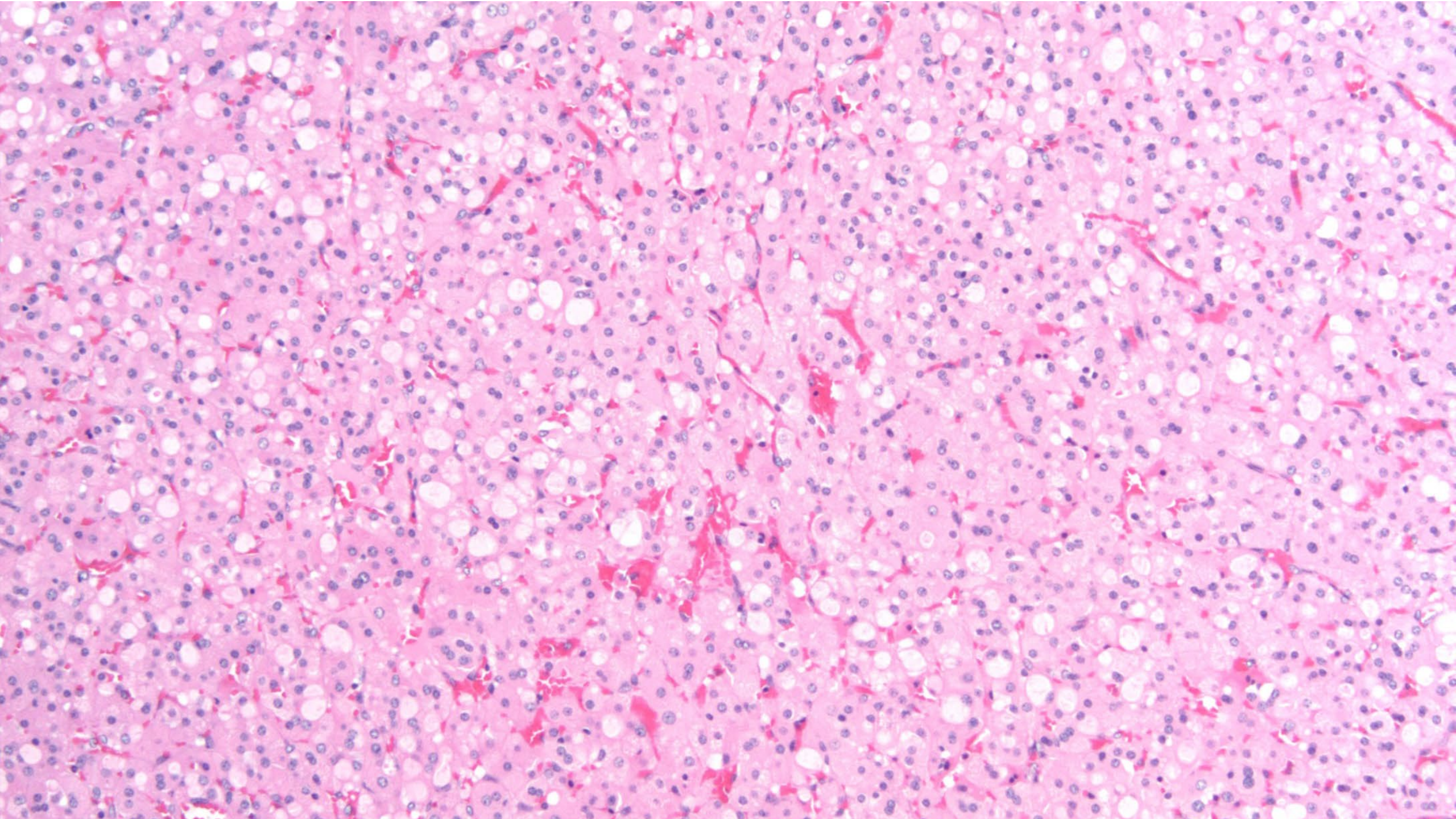


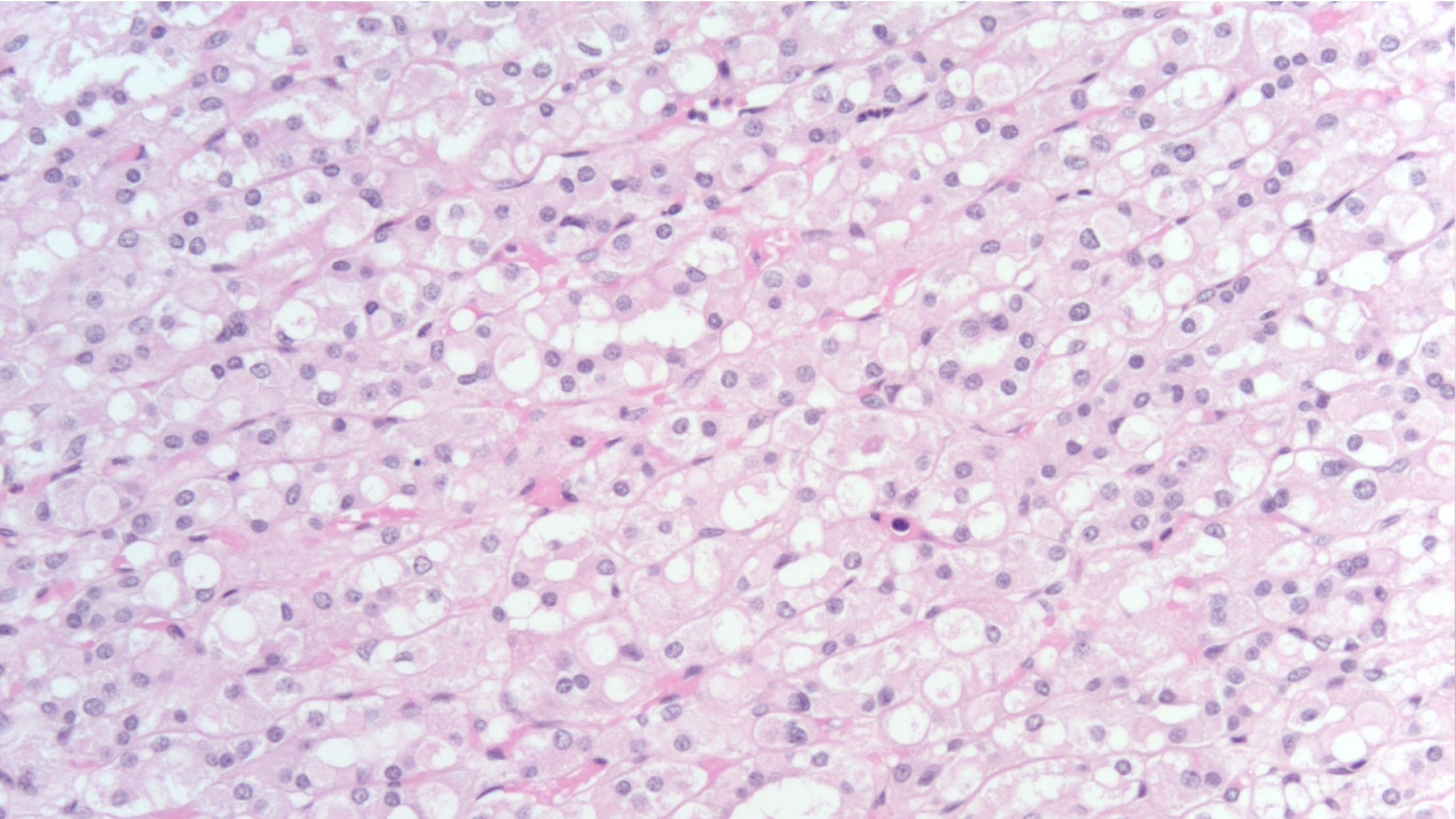
- Mullen, A and DeBerardinis, R. Genetically-defined metabolic reprogramming in cancer. *Trends in Endocrinology and Metabolism.* 2012, (23)11; 552-559.

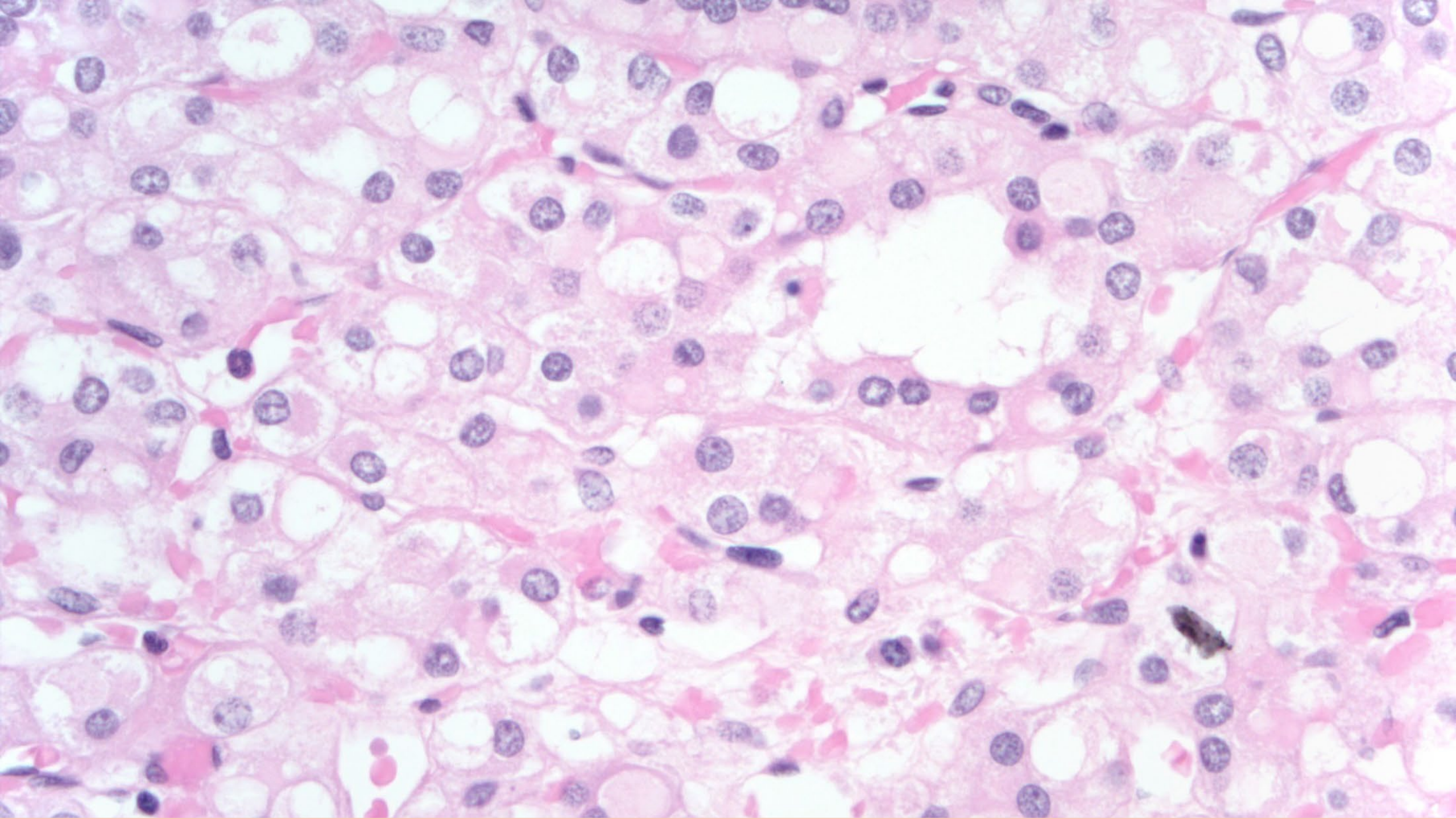


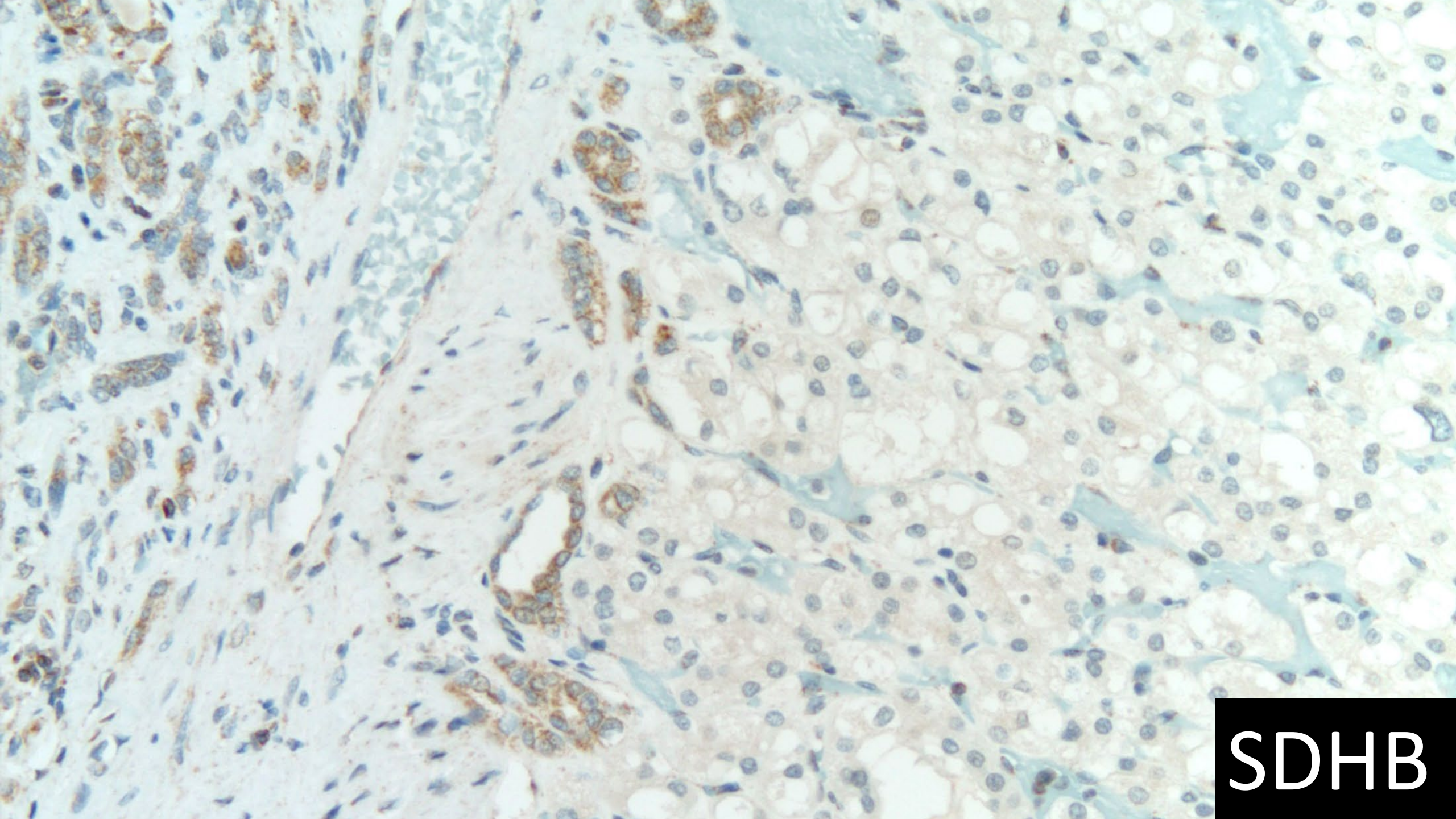










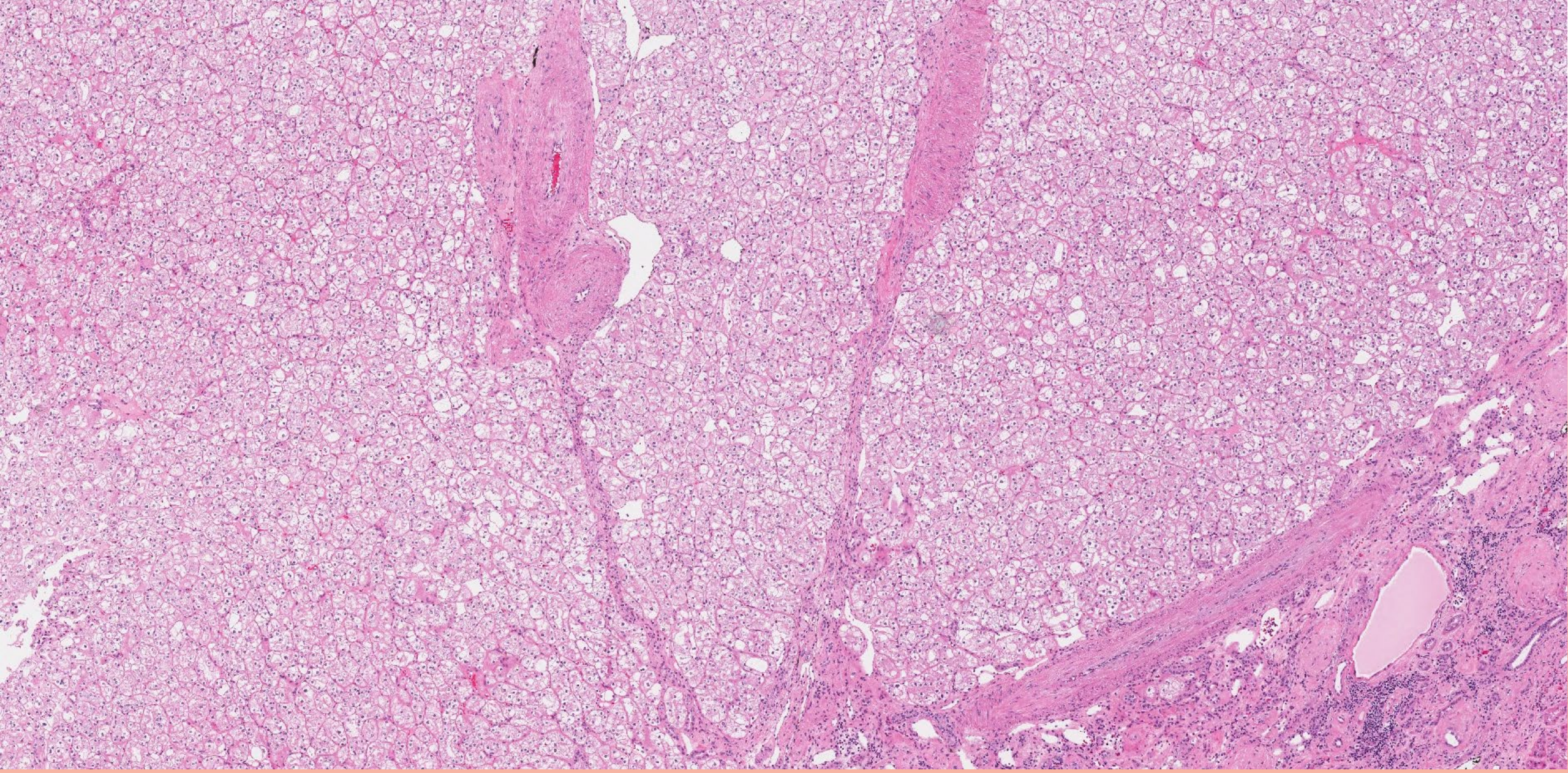

SDHB

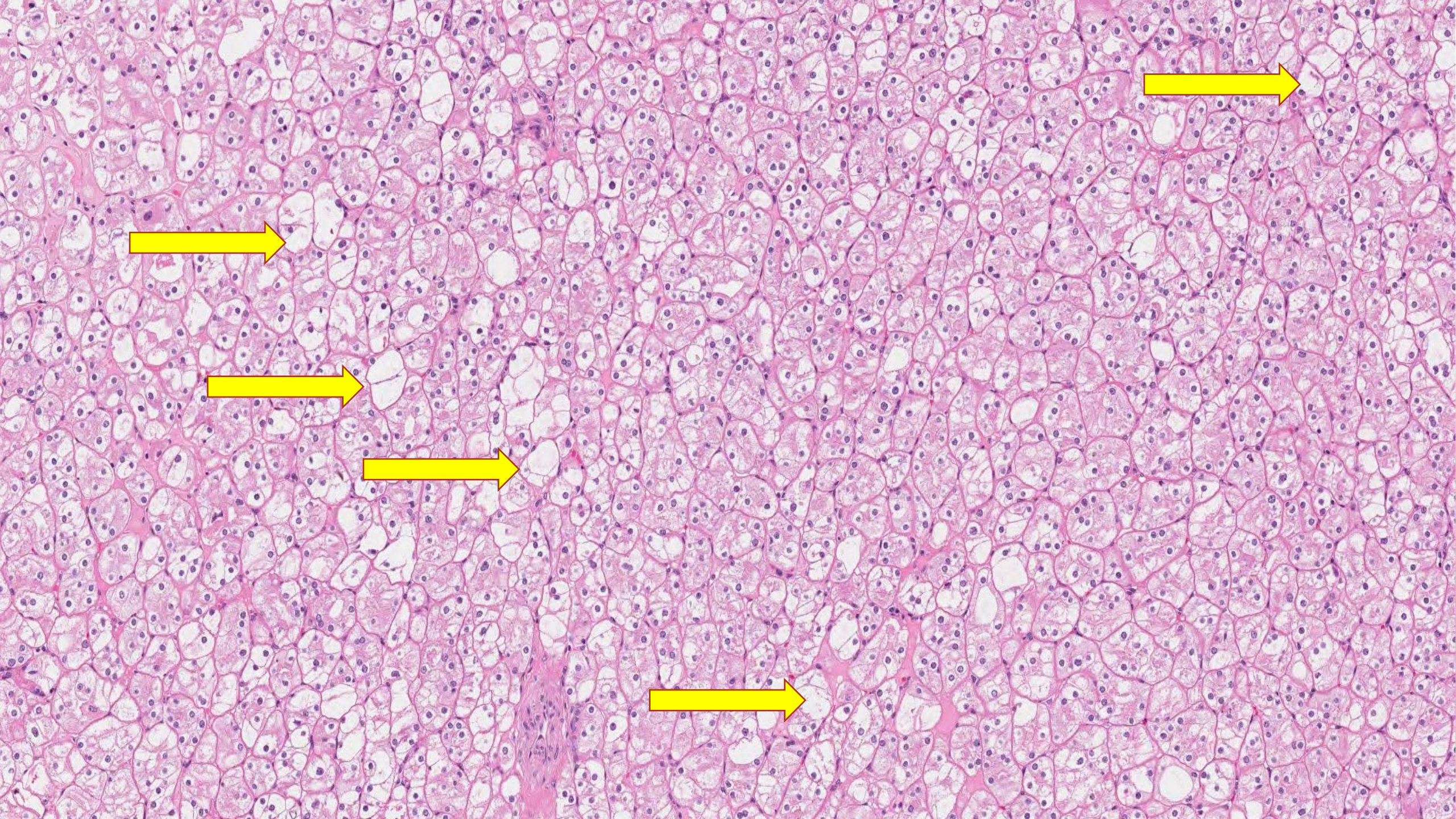
SDH-deficient RCCs

- Largest series: Gill et al AJSP 2015:
  - 36 total cases from 27 patients (21 new cases + 15 previous cases)
  - Mean age = 37 years
  - 4/27 (15%) patients with multifocal tumors in one kidney
  - 7/27 (26%) patients with bilateral disease
  - 4/27 (15%) had SDH-deficient GISTs
  - 4/27 (15%) had paragangliomas
- 9 patients developed metastases
  - 4 of these died of disease (ISUP grade ≥ 3, usually necrotic)

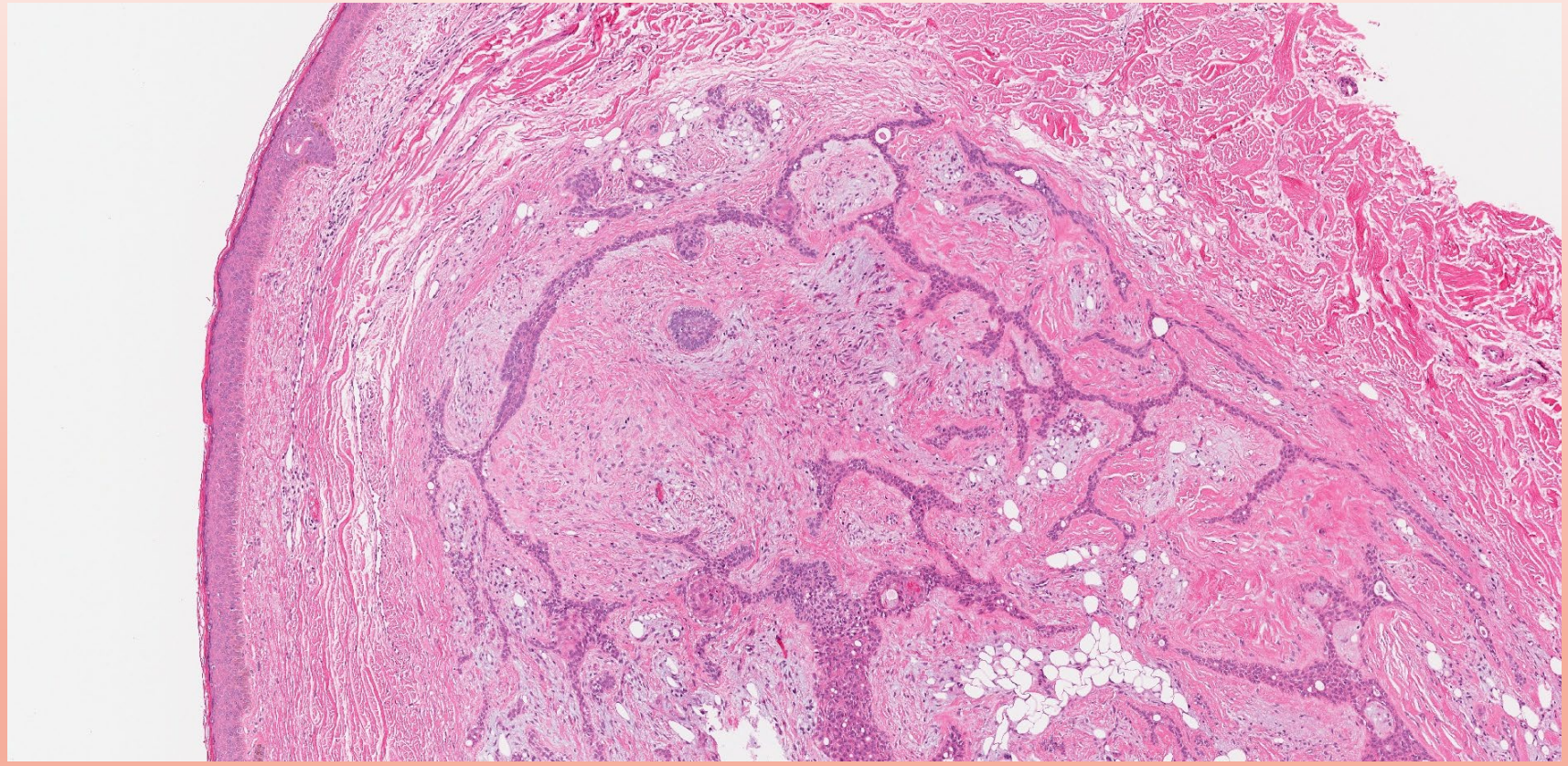
Clinical history

- 68-year-old man with multiple kidney masses





Previous skin biopsy - Fibrofolliculoma



Birt-Hogg-Dubé syndrome

- Autosomal dominant, variable penetrance
  - Skin tumors (fibrofolliculomas, trichodiscomas, etc.)
  - Lung blebs → pneumothorax
  - Kidney tumors
- Mutations in the Folliculin gene – chromosome 17
  - Folliculin protein – binds to folliculin interacting proteins 1 and 2 (FNIP1, FNIP2)
  - FINP1 binds an AMP-kinase that normally inhibits mTOR

Birt-Hogg-Dubé syndrome

- Skin lesions – frequent; 3rd decade
- Kidney tumors – 20-25% of patients; 6th decade
  - Chromophobe RCC, oncocytomas, hybrid oncocytic tumors
  - Frequently multiple/bilateral (~50%)
  - Background oncocytosis

Hybrid Oncocytic Tumor in Birt-Hogg-Dubé syndrome

- GUPS Proposal:
  - Hybrid Oncocytic Tumor reserved only for hereditary cases (as in Birt-Hogg-Dubé syndrome) with characteristic “checkerboard” appearance
    - **Trpkov K, et al. New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol. 2021 Jul;34(7):1392-1424. Epub 2021 Mar 4. PMID: 33664427.**

Additional hereditary RCC considerations

von Hippel-Lindau Disease

- Autosomal dominant – high penetrance for RCC (>70%)
- Multi-organ involvement
  - Hemangioblastomas of CNS (mean age 25-30)
  - Renal cysts, clear cell RCC (mean age 37), clear cell nodules
  - Adrenal pheochromocytoma
  - Pancreatic cysts, islet cell tumors
  - Papillary cystadenomas of the epididymis/broad ligament; Endolymphatic sac tumors of the ear

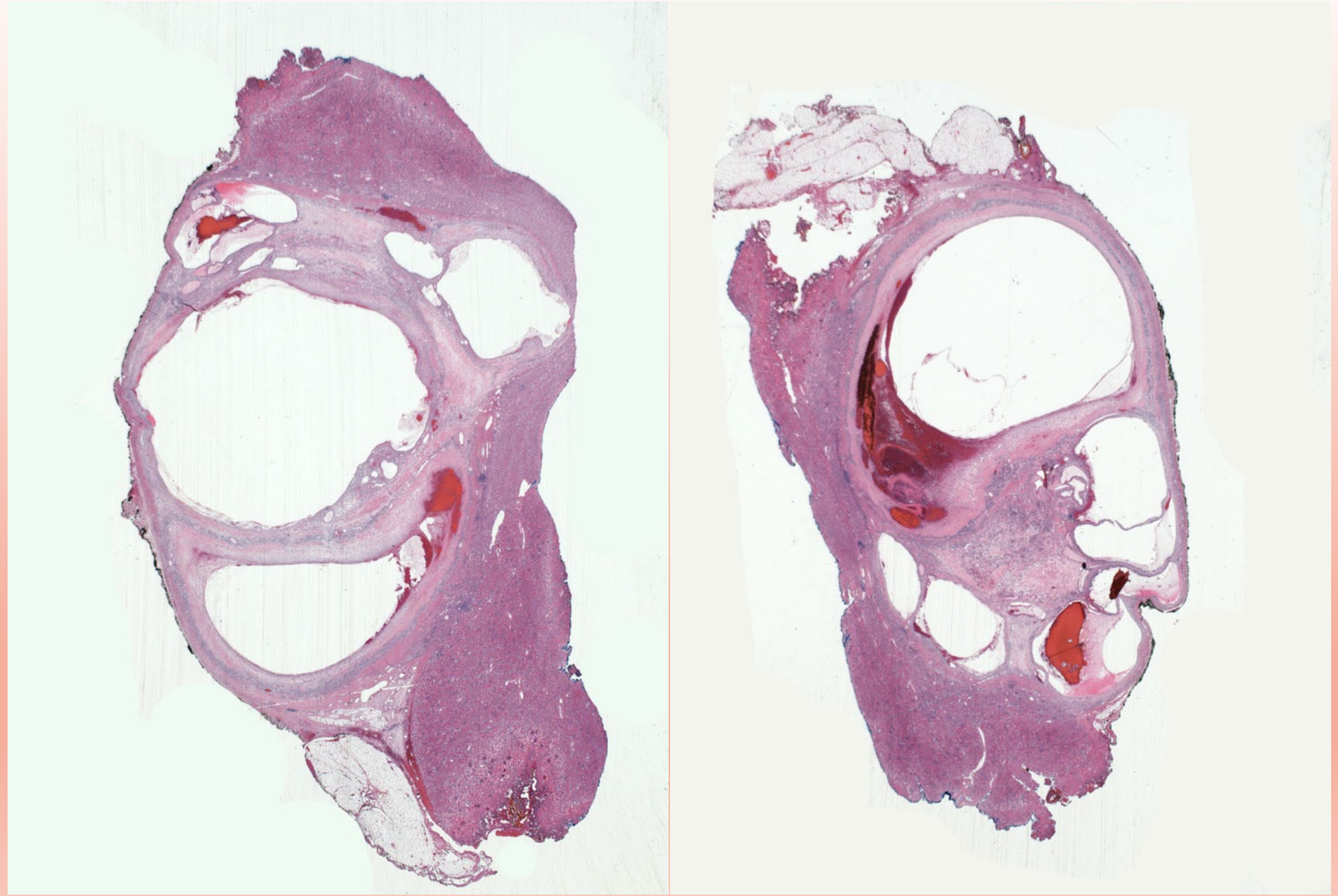
von Hippel-Lindau Disease

- Types: + or – pheochromocytoma
  - Type 1: No pheo
    - Loss of function mutations
  - Type 2: High risk for pheochromocytoma
    - 2A: Low risk for RCC
    - 2B: High risk for RCC
    - 2C: Pheochromocytoma only
    - Missense mutations – partial VHL protein function

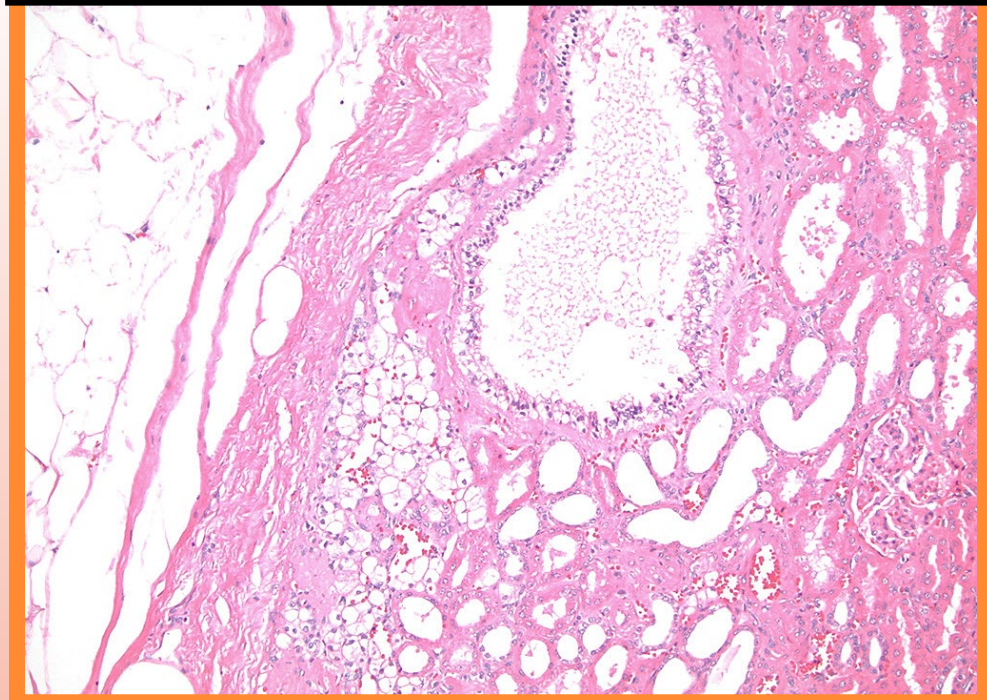
von Hippel-Lindau Disease

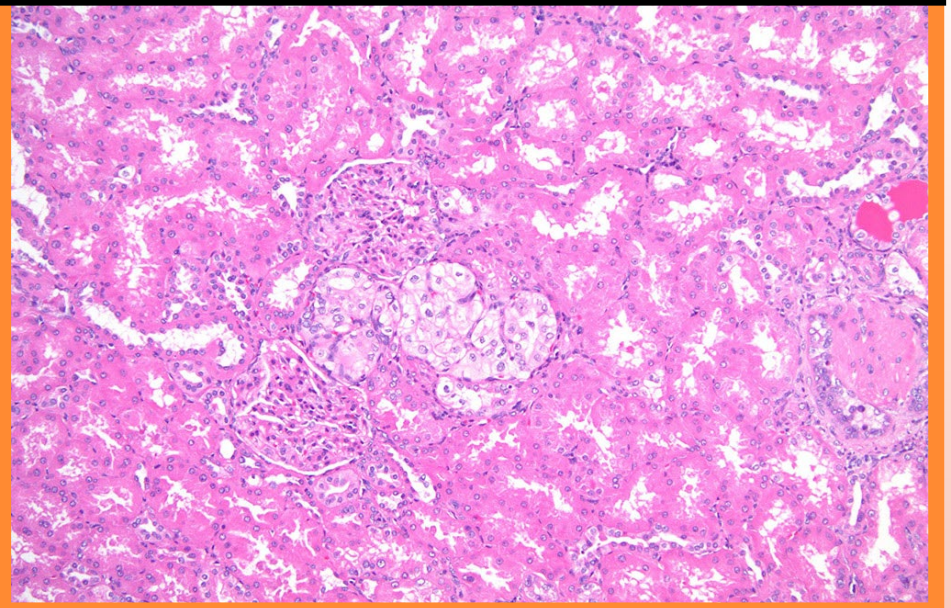
- RCCs in VHL disease
  - Almost always clear cell RCC
  - Multifocal and bilateral
  - Detected at small size
- Other renal findings
  - Clear cell nodules
  - Clear cell papillary renal cell tumor-like lesions
  - Cysts (unilocular or multilocular, benign or atypical)

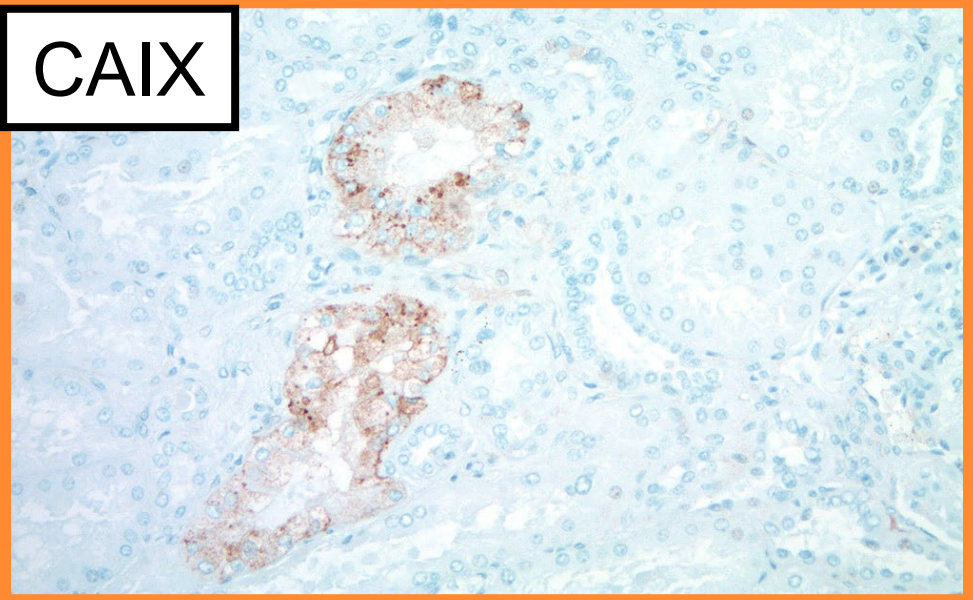
von Hippel-Lindau: Associated Cysts

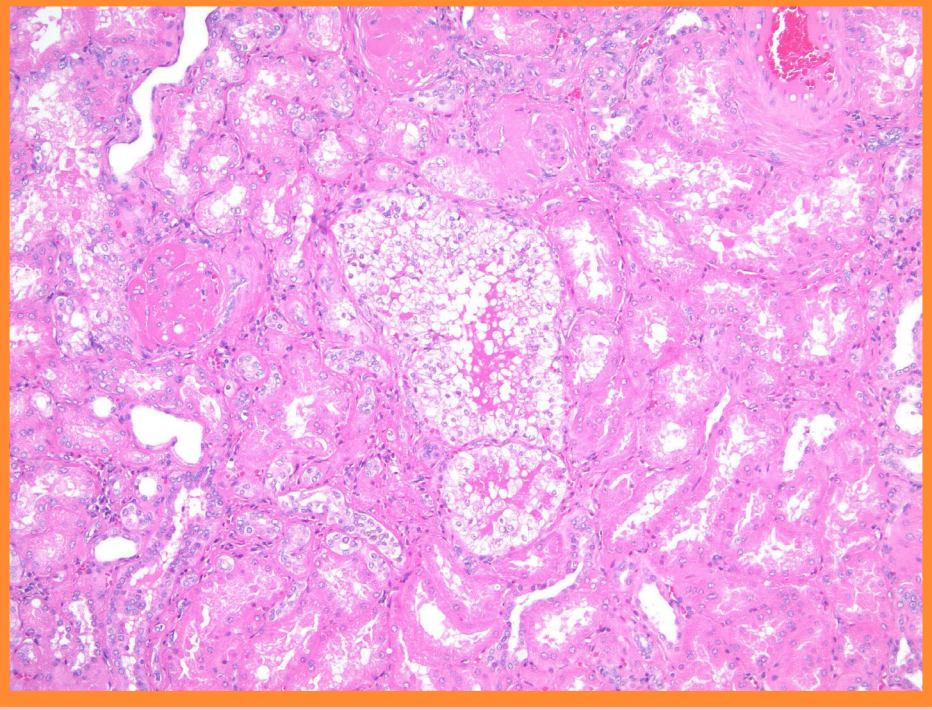


von Hippel-Lindau: Microscopic Tumorlets

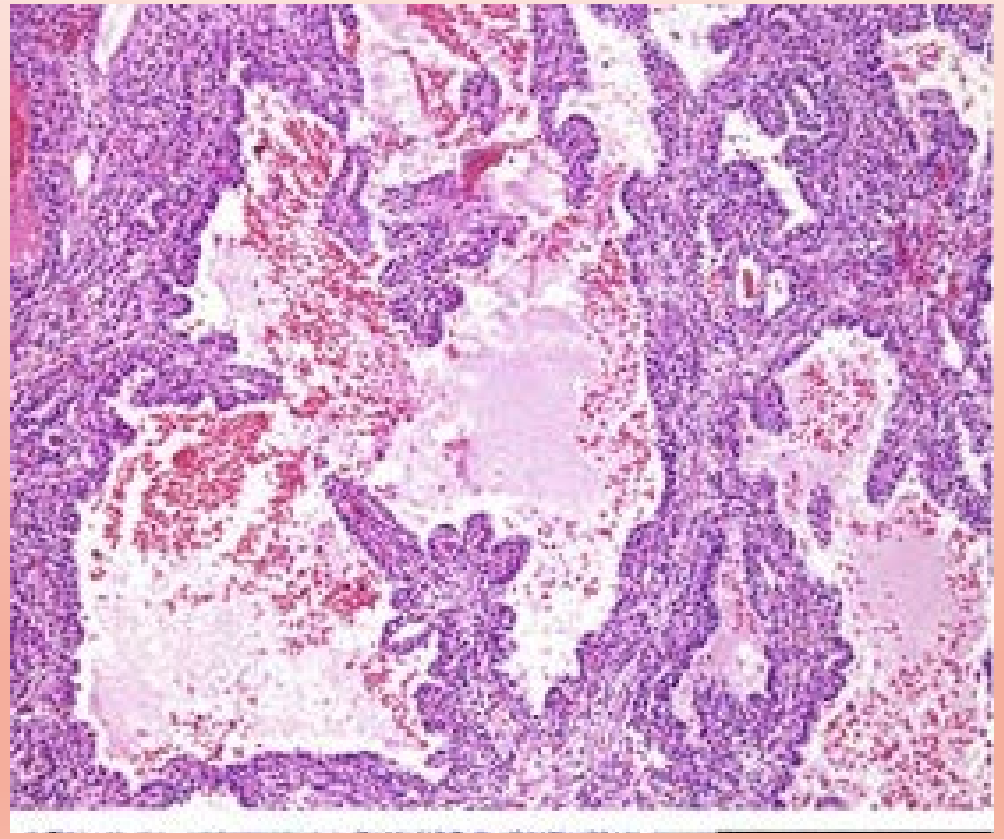








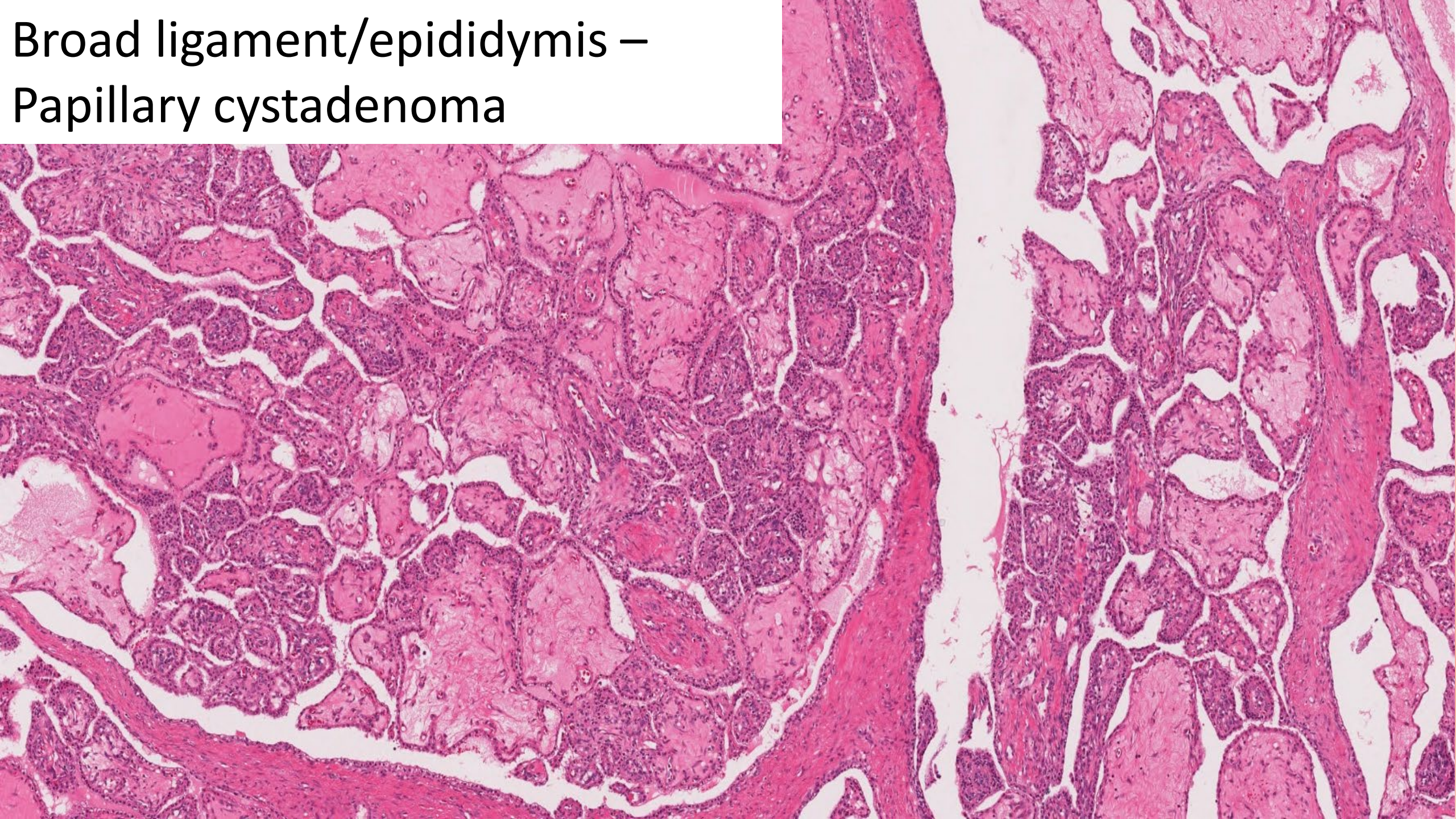
Tumors with similar histology in vHL

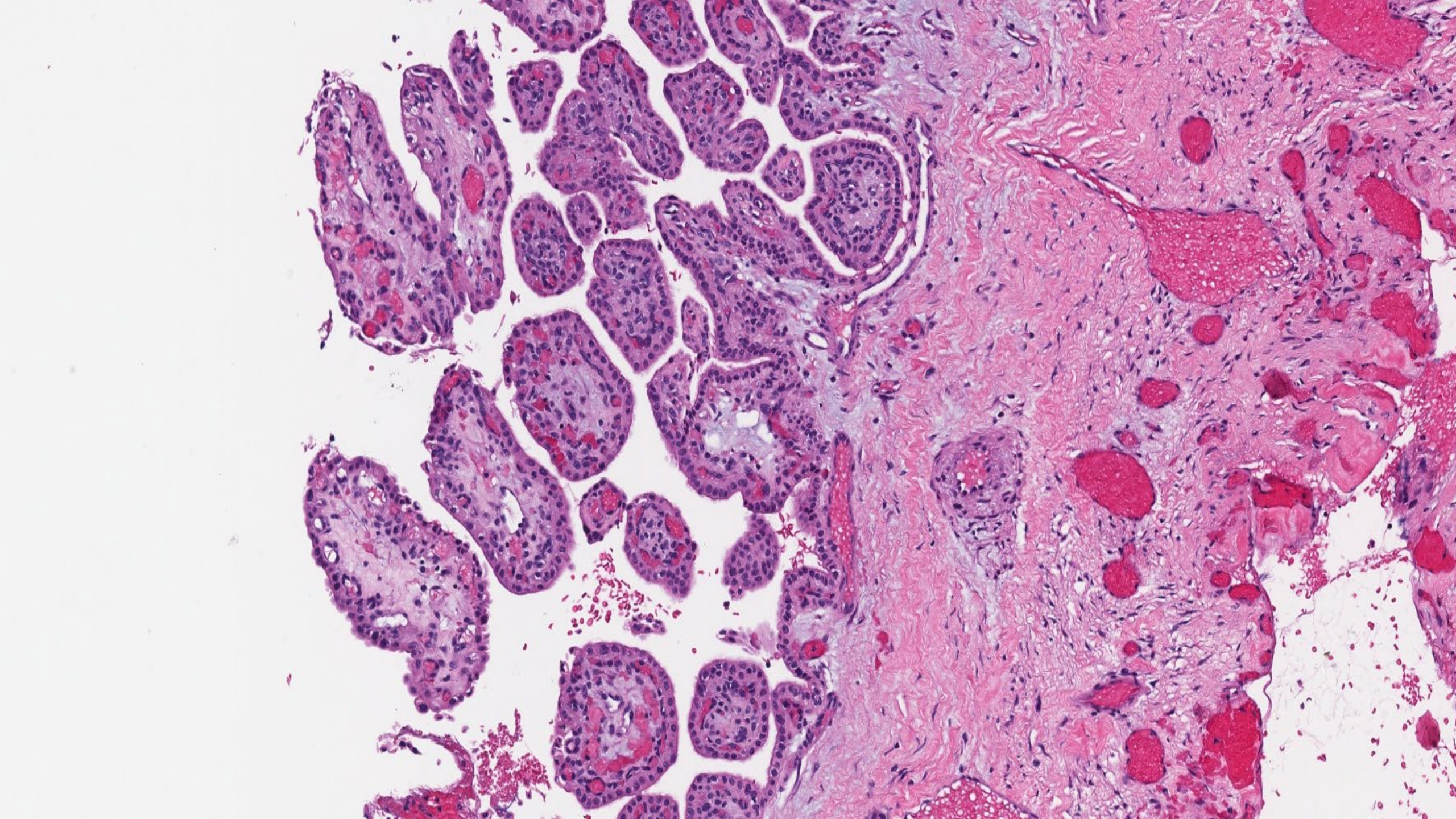


Williamson et al. Am J Surg Pathol 2013;1131-1139

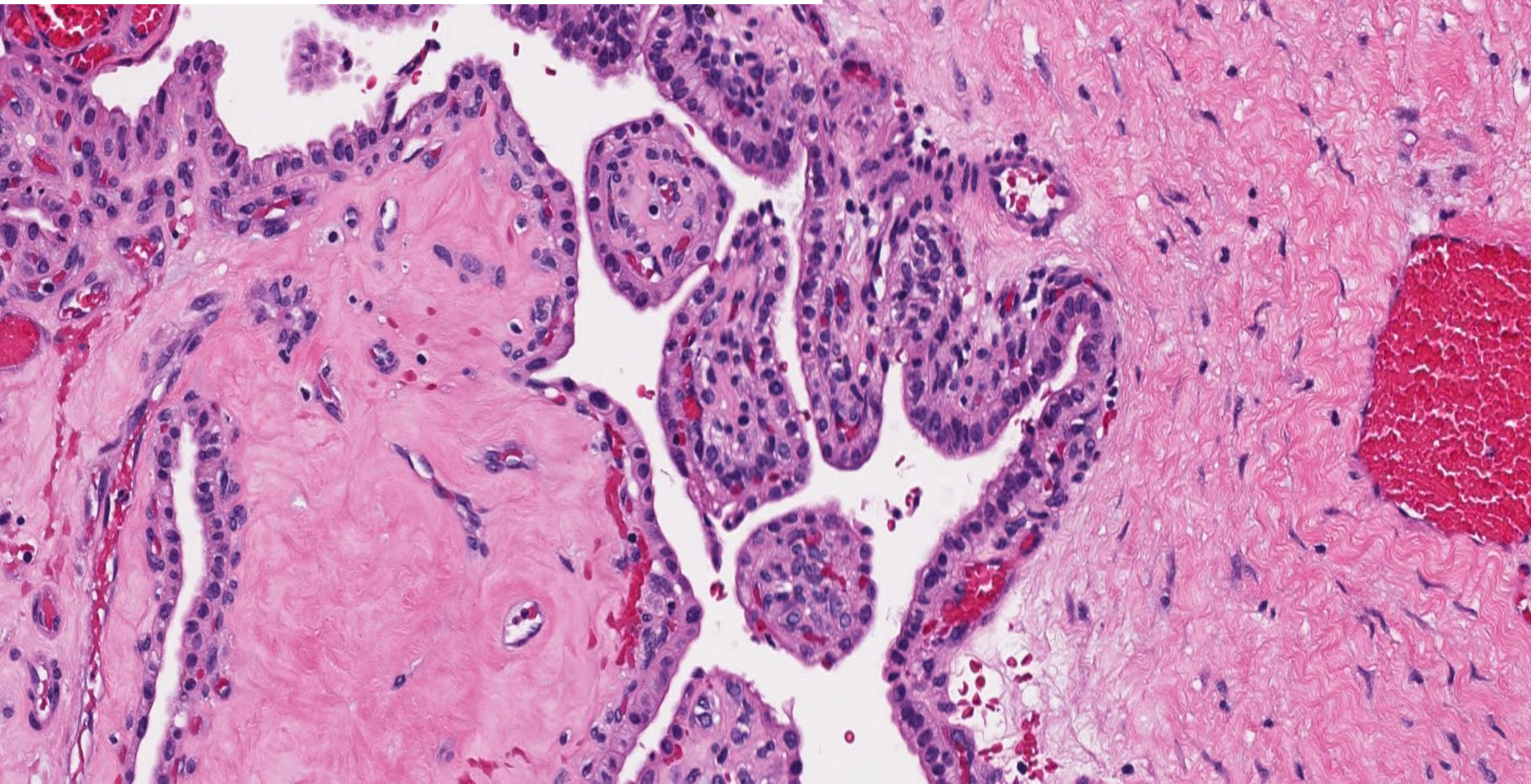
- Kidney – Clear cell tumors with morphology resembling clear cell papillary renal cell tumor
- Broad ligament and epididymis – Papillary cystadenoma
- Middle ear – Endolymphatic sac tumor

Broad ligament/epididymis – Papillary cystadenoma

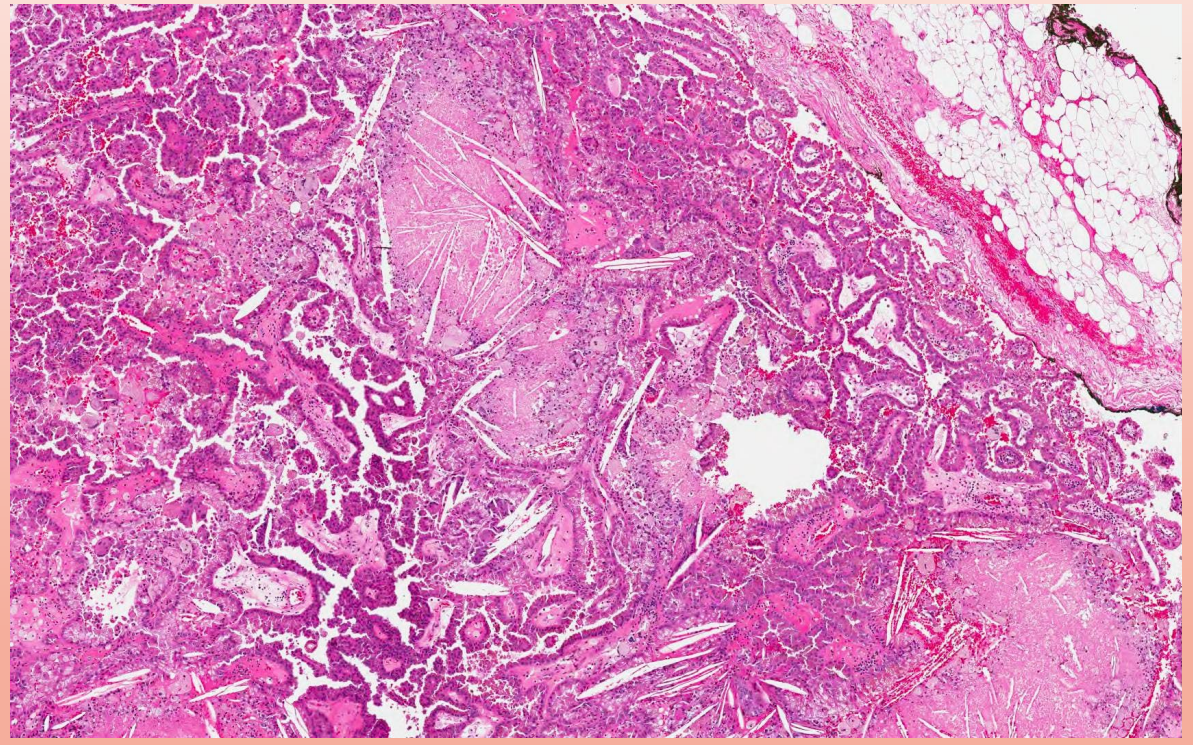




Endolymphatic sac tumor



Hereditary papillary RCC



- Autosomal dominant
- Multifocal/bilateral papillary RCC & adenomas
- 90% develop RCC by age 80
- *MET* gene mutations
- “Type 1”

Summary – Hereditary Renal Neoplasia

- Hereditary kidney tumors have characteristic morphology
- Careful attention to morphology + judicious use of immunostains can help with diagnosis
- Clinical history often does not suggest hereditary basis
  - Often first recognized by the pathologist