


Creating a Cancer-free World. One Person, One Discovery at a Time.

# *New and Emerging Renal Neoplastic Entities: An Update from WHO 2022 Perspective*

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

**Anil V Parwani, MD, PhD, MBA**

The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute


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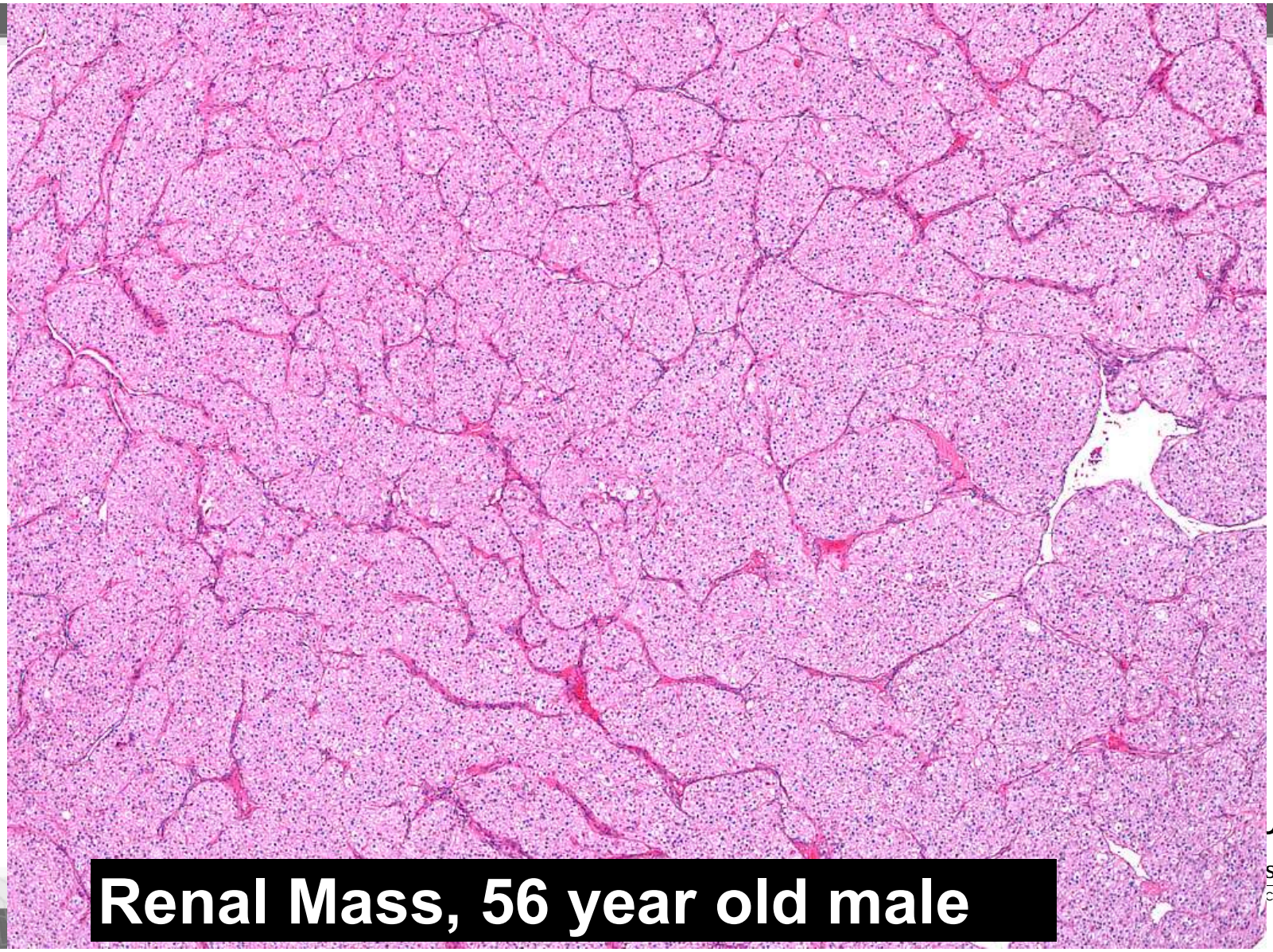

# Renal Mass, 56 year old male

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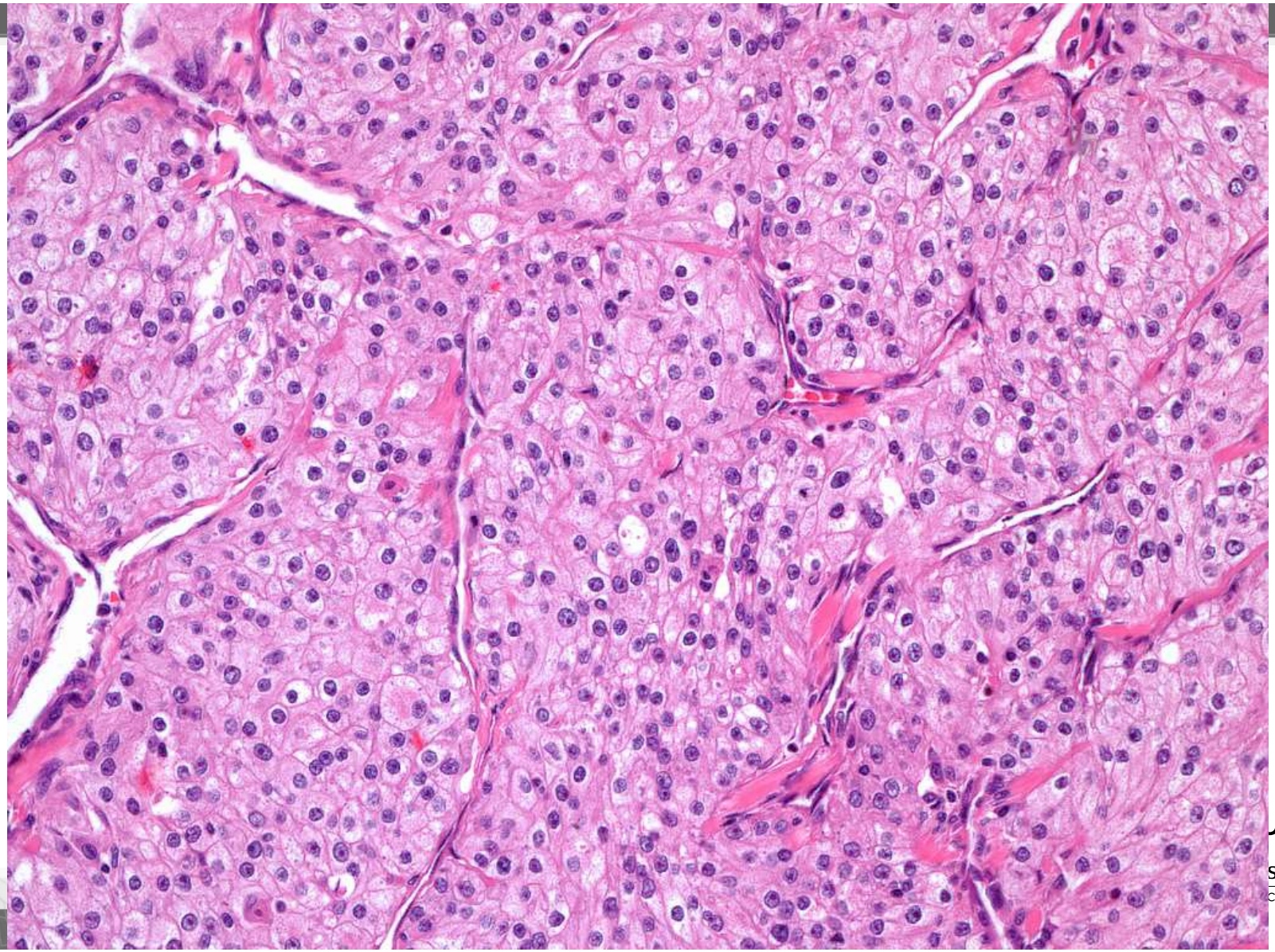

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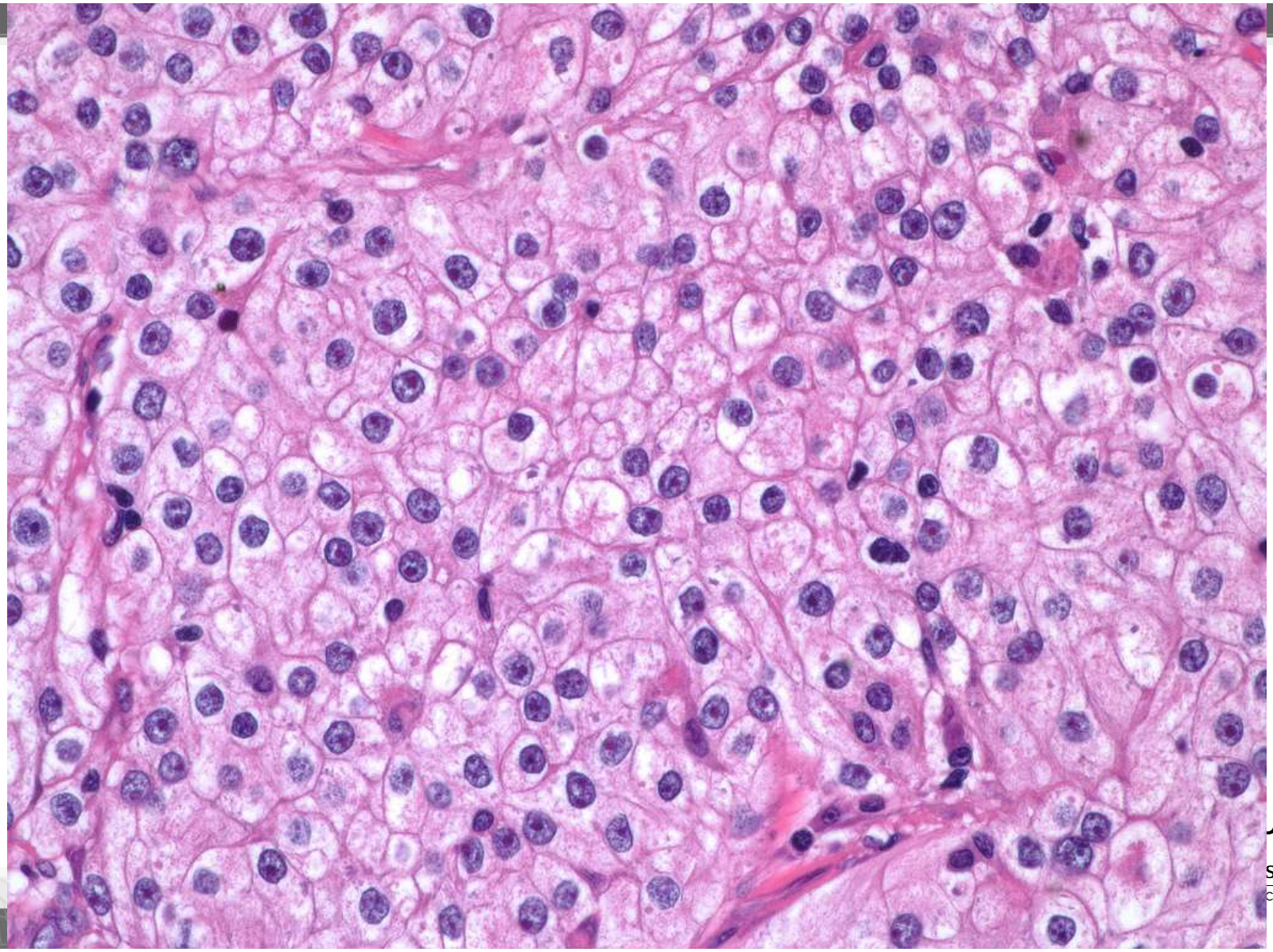

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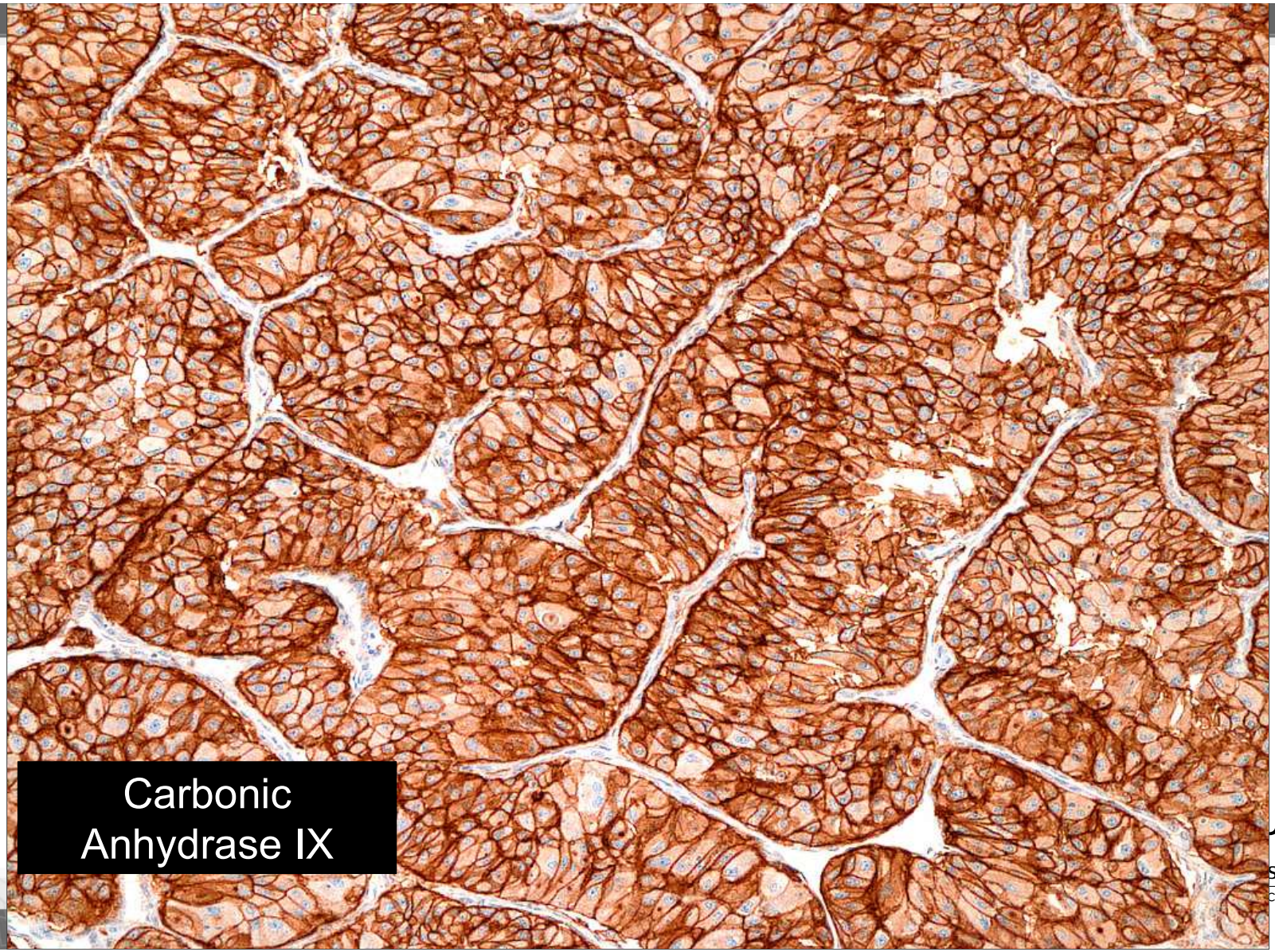


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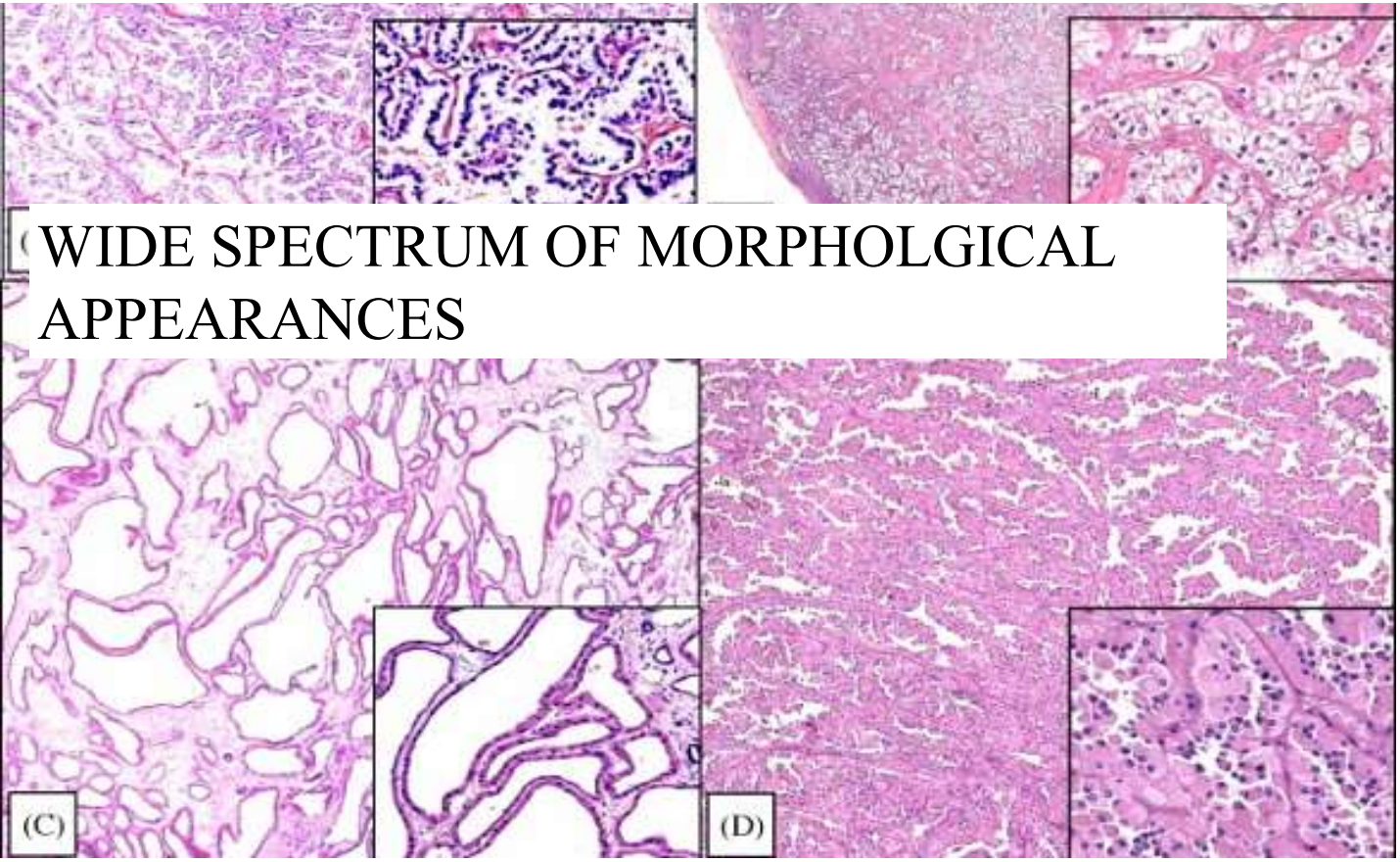
# Renal Cell Carcinoma Classification: Complex, Changing and Evolving WHO 2022 RCC Updates

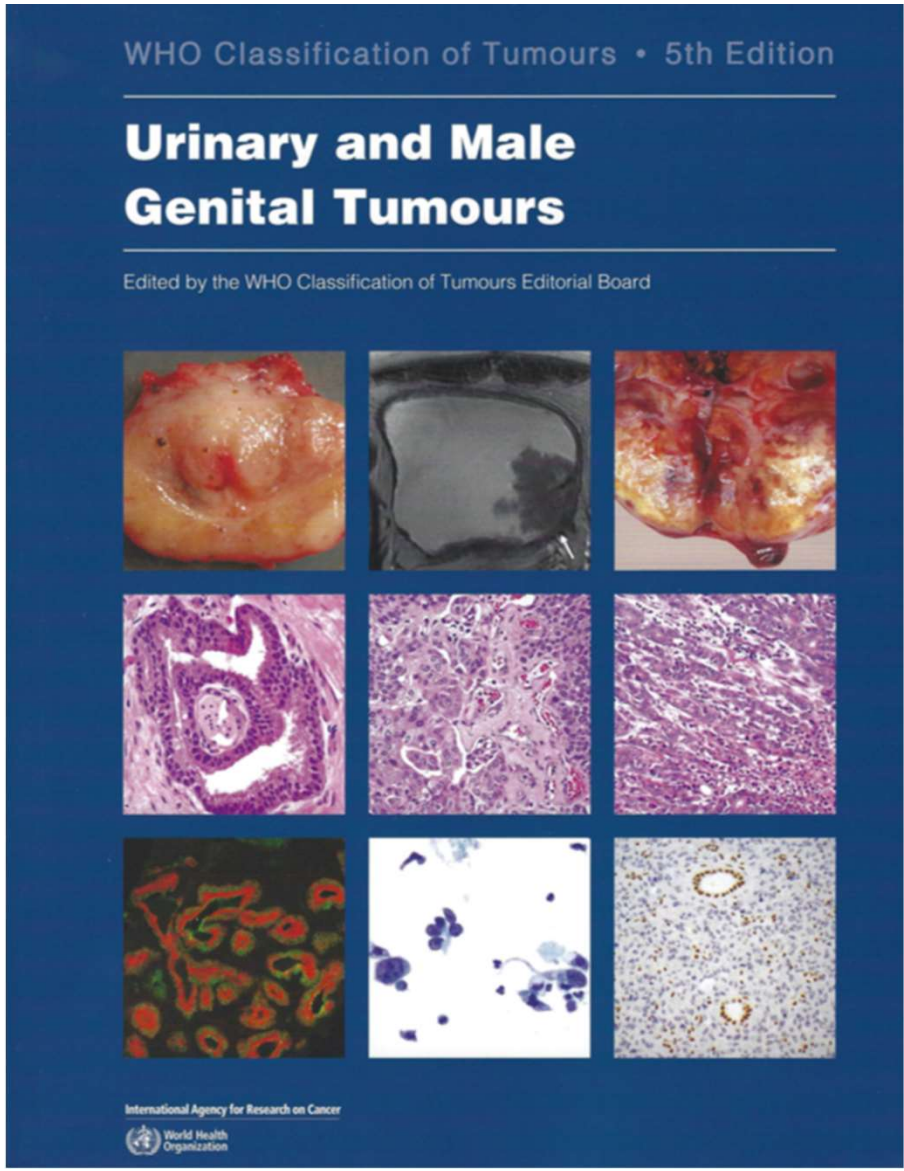



Cytoplasmic features (e.g., clear cell and chromophobe renal cell carcinoma [RCC]), architectural features (e.g., papillary RCC), anatomical location of tumor) and correlation with a specific renal disease background (e.g., acquired cystic disease-associated RCC), but also by characteristic molecular alterations

# Objectives

Objective 1: Provide an overview of the 2022 WHO Classification of Adult Kidney Epithelial Tumors, Prostate cancer and Urothelial cancers

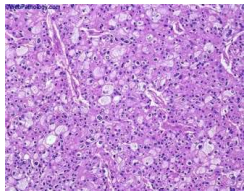
Objective 2: Discuss using a case-based approach, some of the newly described entities with an emphasis on morphology and ancillary testing



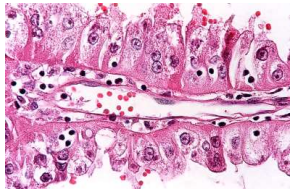
# Renal Epithelial cell tumors

**Enhanced Understanding**

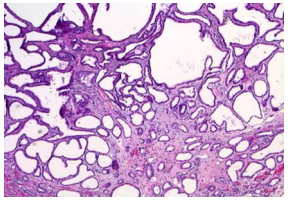
**1996 Heidelberg**



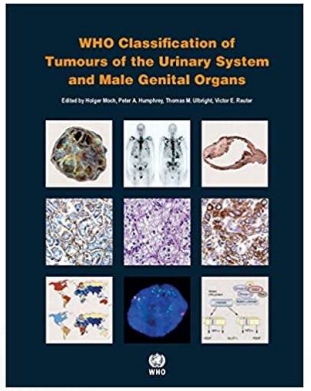
**2004 France**

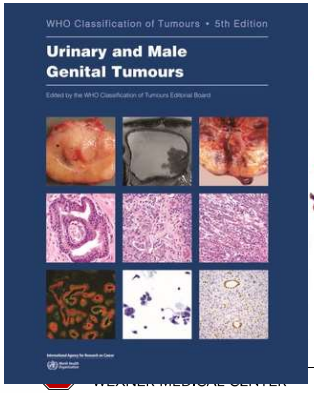


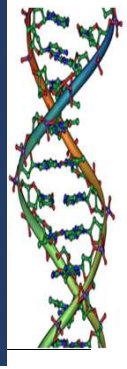
**2012 Vancouver**



**Molecular Pathology**



# WHO CLASSIFICATION OF RENAL CELL TUMORS 2022

**Clear cell renal tumours**
- Clear cell renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential

**Papillary renal tumours**
- Renal papillary adenoma
- Papillary renal cell carcinoma

**Oncocytic and chromophobe renal tumours**
- Oncocytoma of the kidney
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**Collecting duct tumours**
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**Metanephric tumours**
- Metanephric adenoma
- Metanephric adenofibroma
- Metanephric stromal tumour

**Other renal tumours**
- Clear cell papillary renal tumour
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic carcinoma
- Acquired cystic disease associated renal cell carcinoma
- Eosinophilic solid and cystic renal cell carcinoma
- Renal cell carcinoma NOS

**Molecularly defined renal carcinomas**
- TFE3-rearranged renal cell carcinoma
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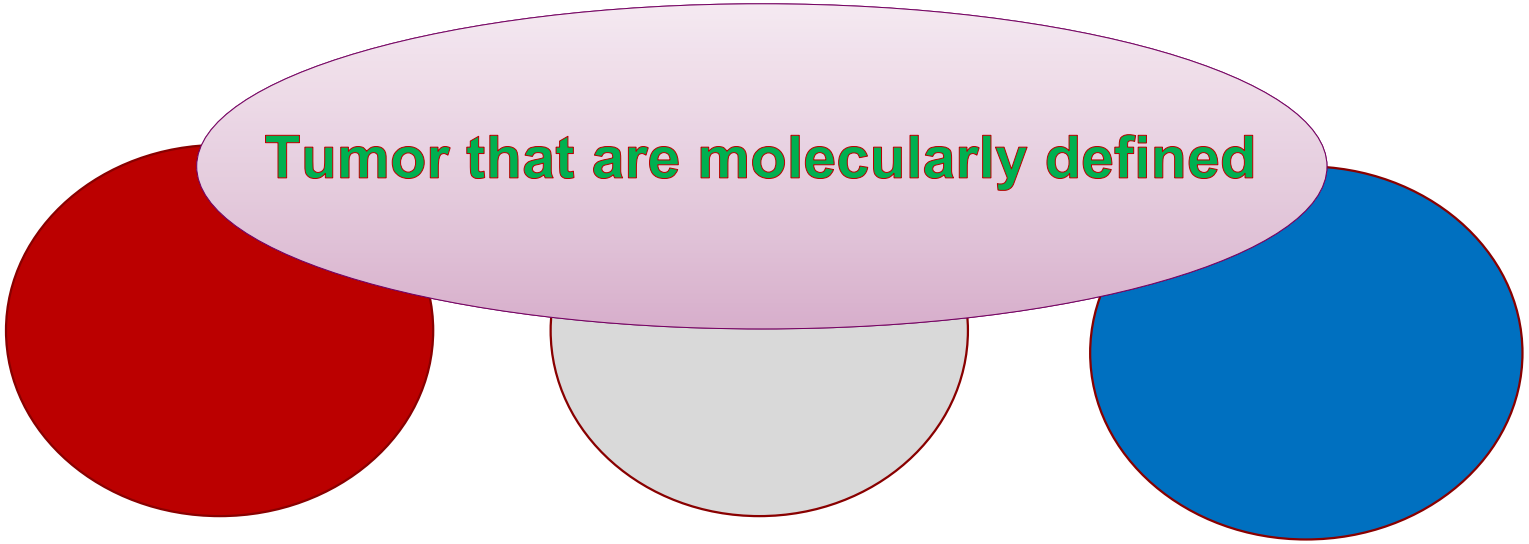
- SMARCB1-deficient renal medullary carcinoma

# RENAL CELL TUMOR CLASSIFICATION 2022




**Tumor cells are pink**
**Oncocytic**
**Eosinophilic**

**Tumor with**
**“clear” cells**

**Tumor with**
**“Blue” cells**

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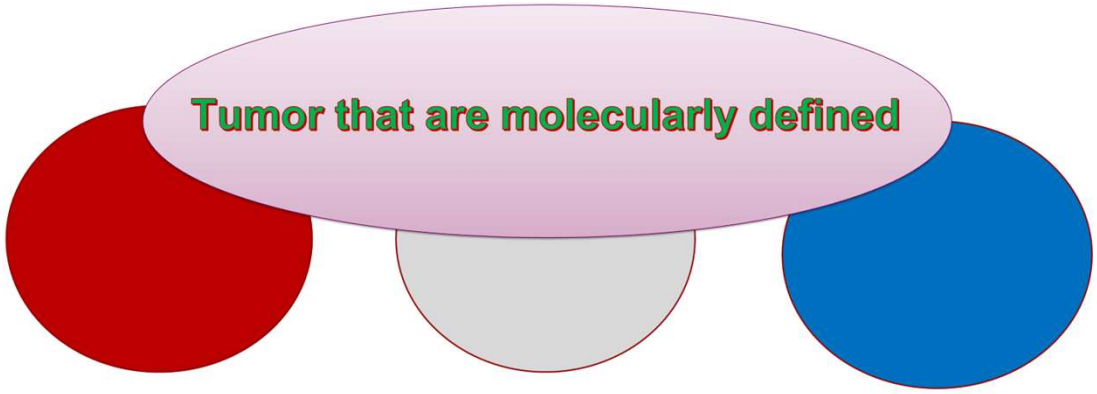


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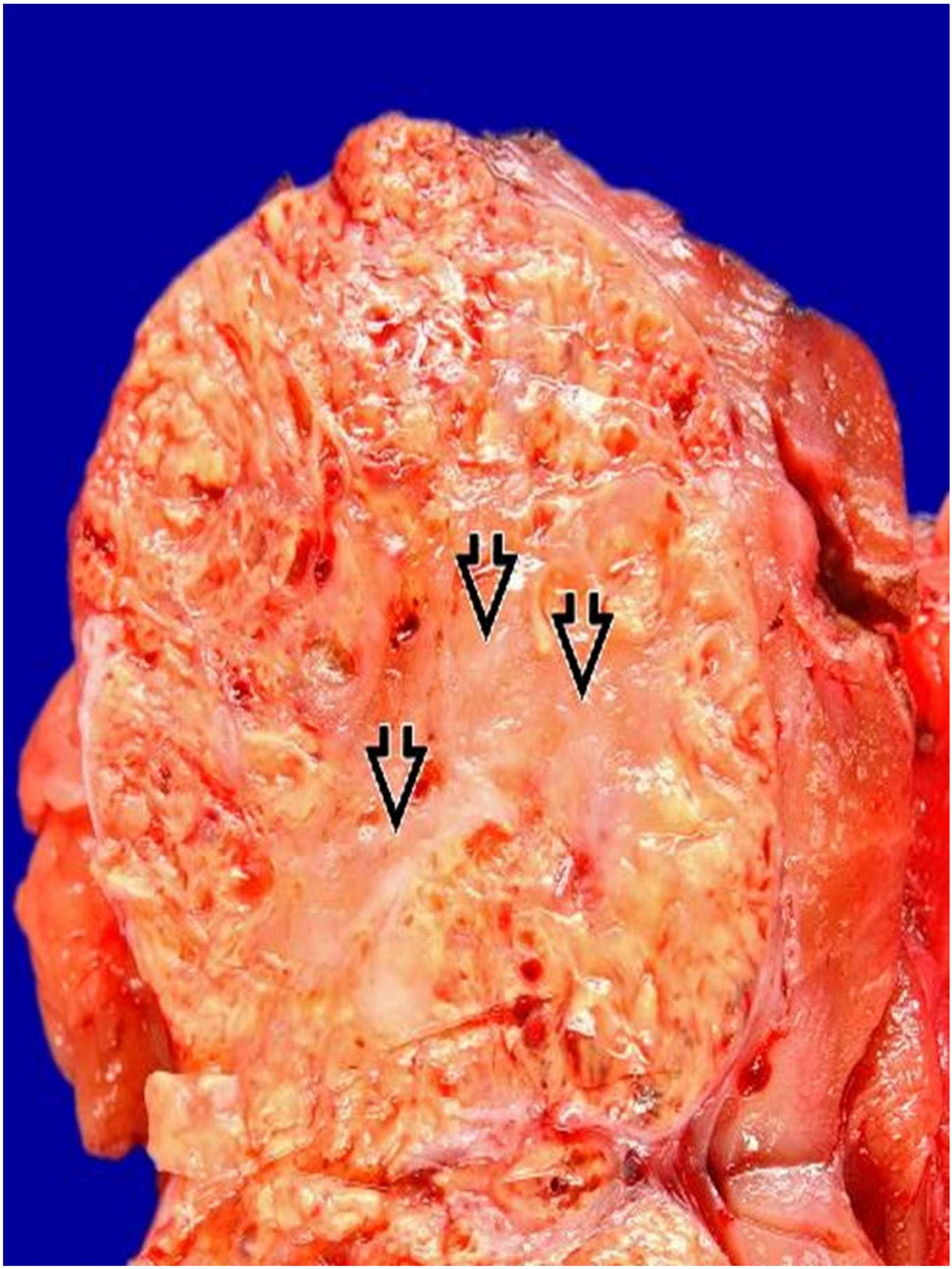
# CASE PRESENTATION

- 56 year old man
- Incidental 4.0 cm mass
- Total nephrectomy done



# WSI KIDNEY CASE NUMBER 2

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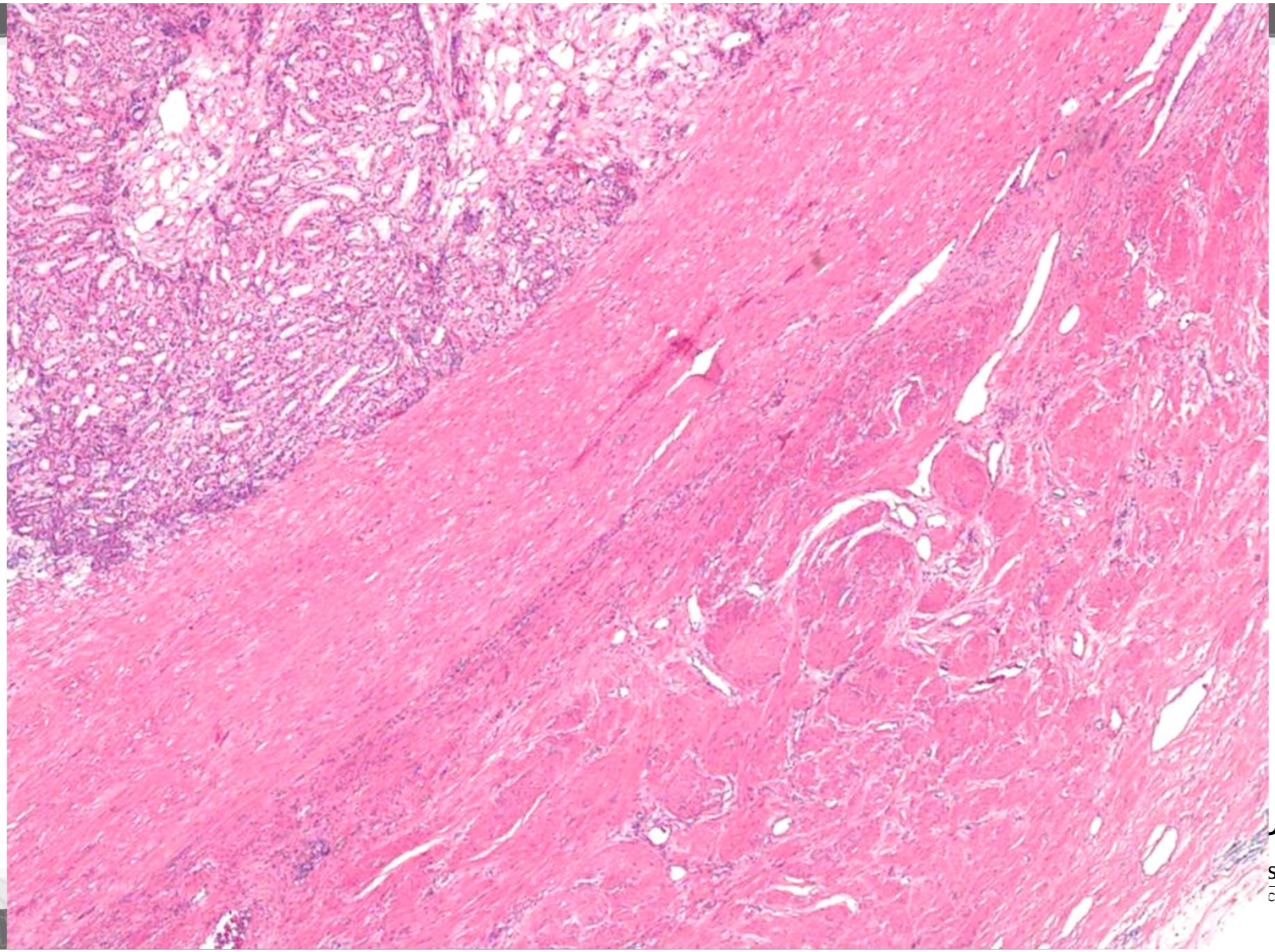

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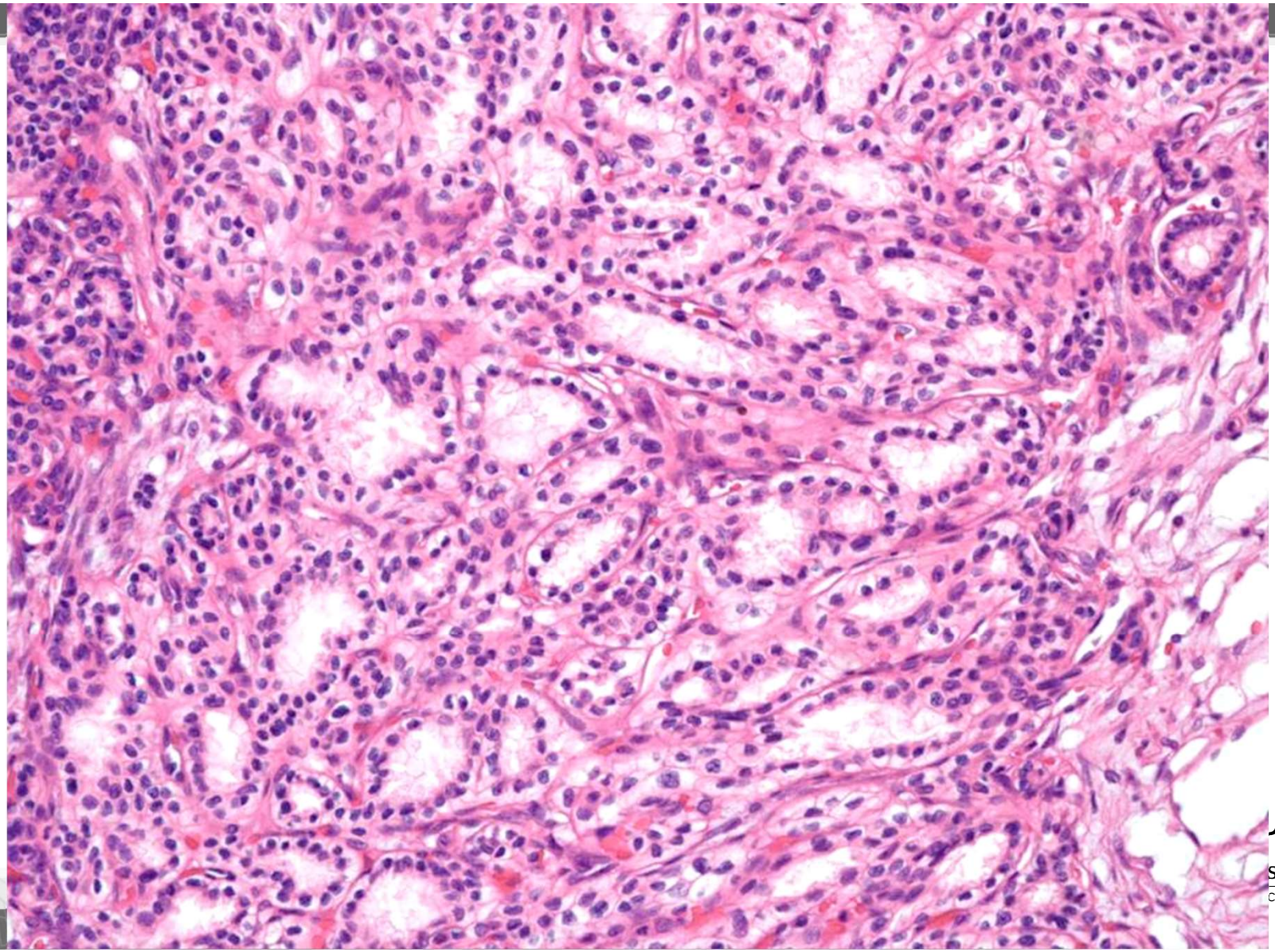

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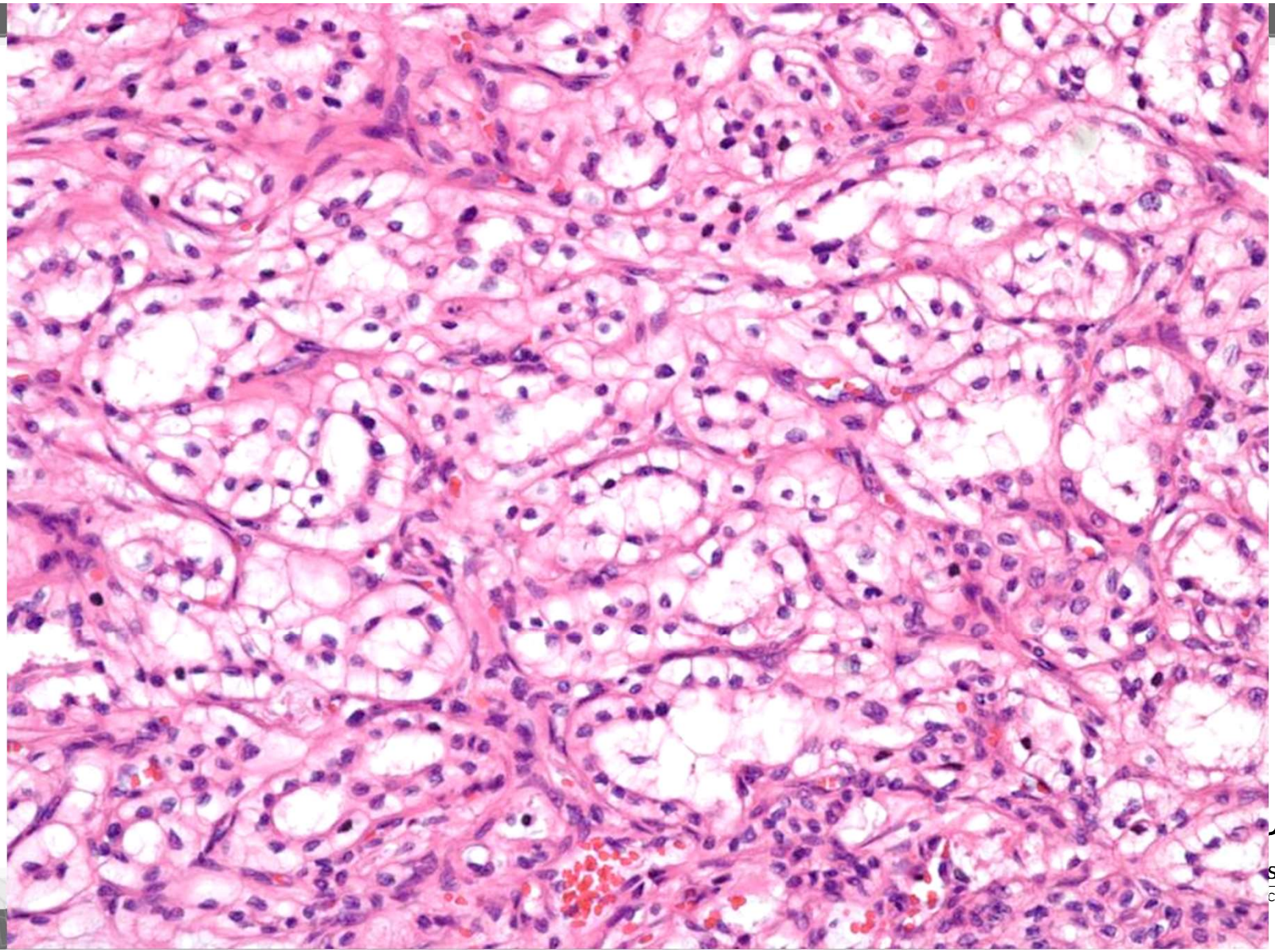

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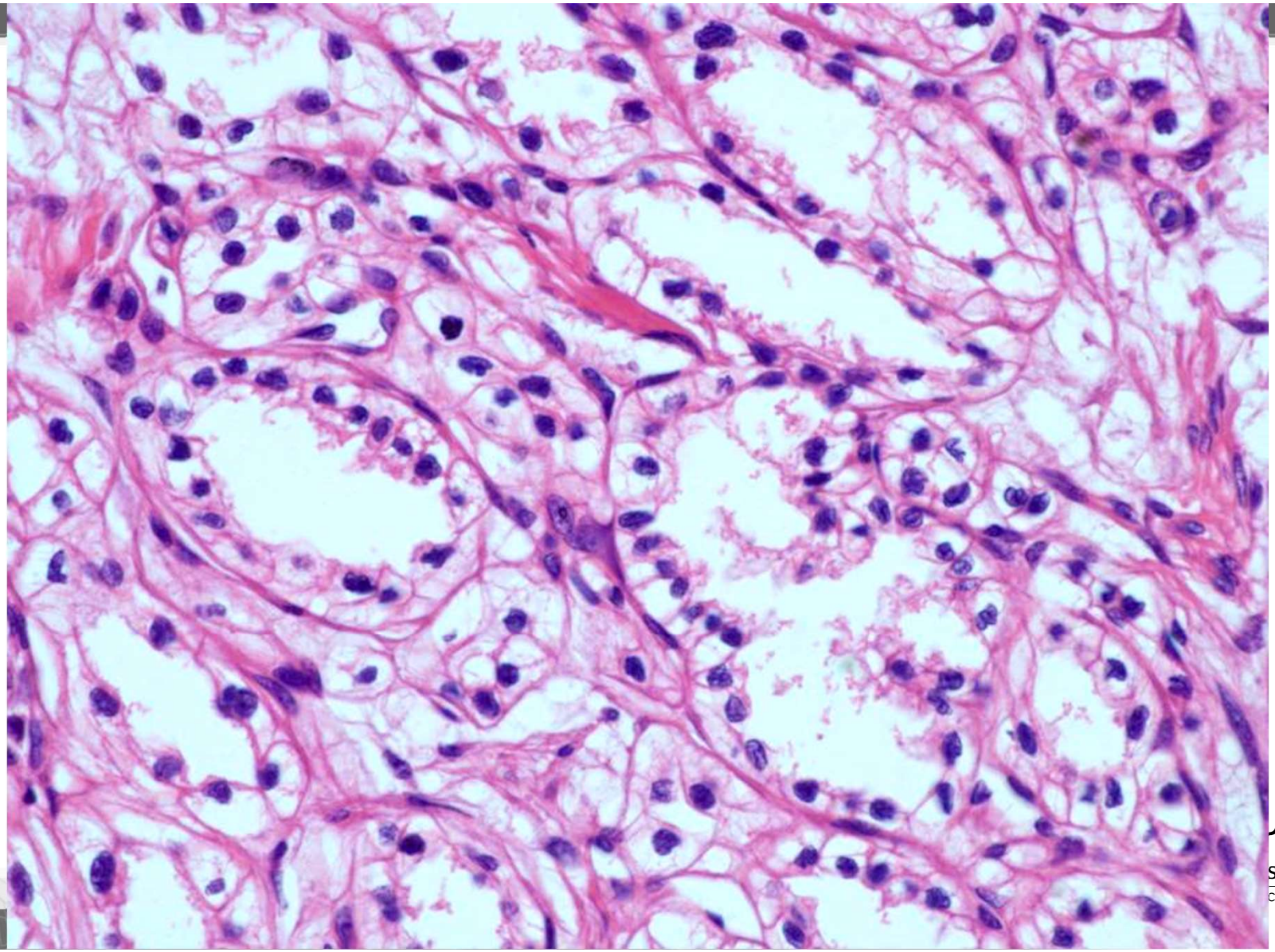

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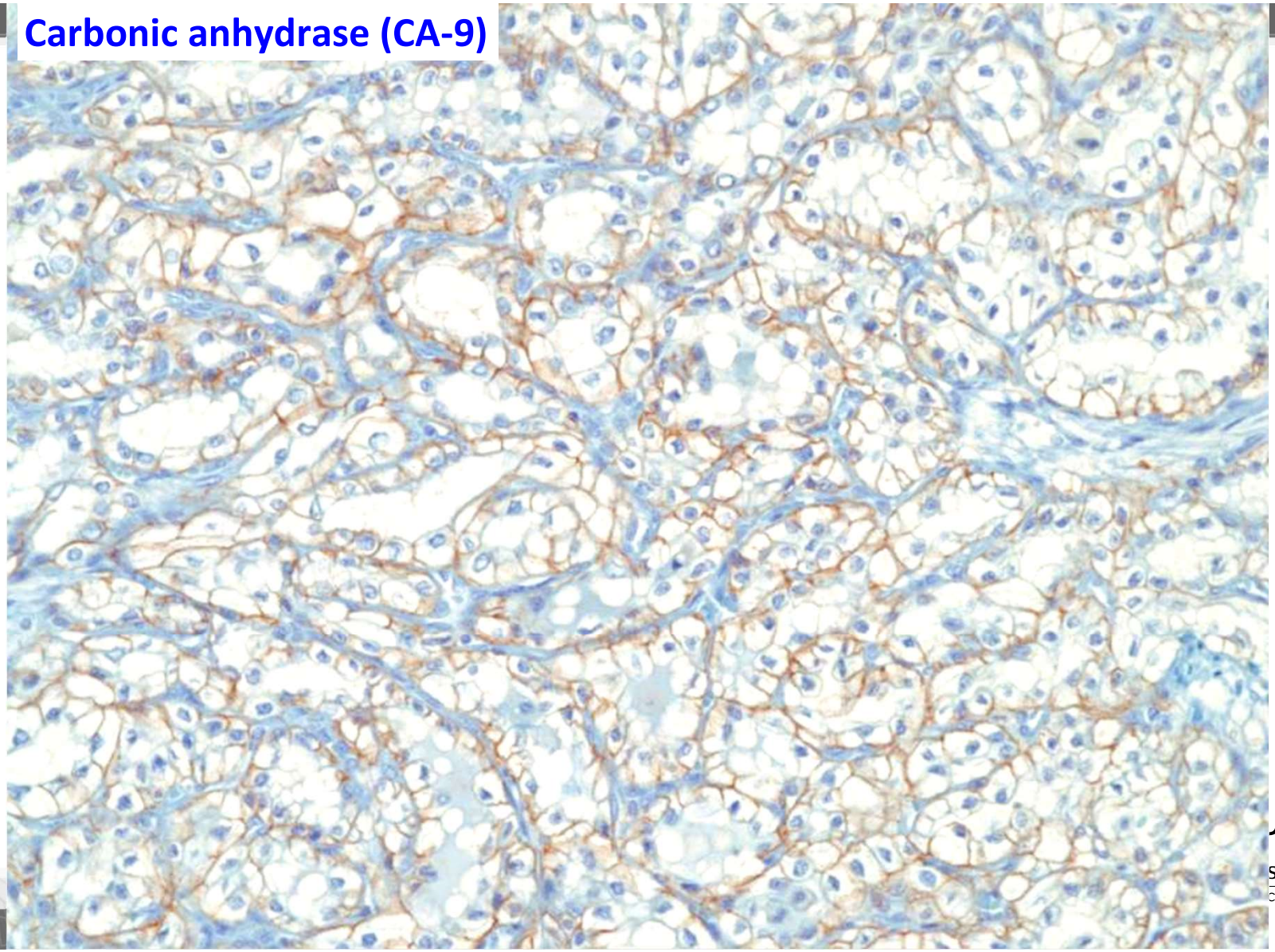
# Carbonic anhydrase (CA-9)



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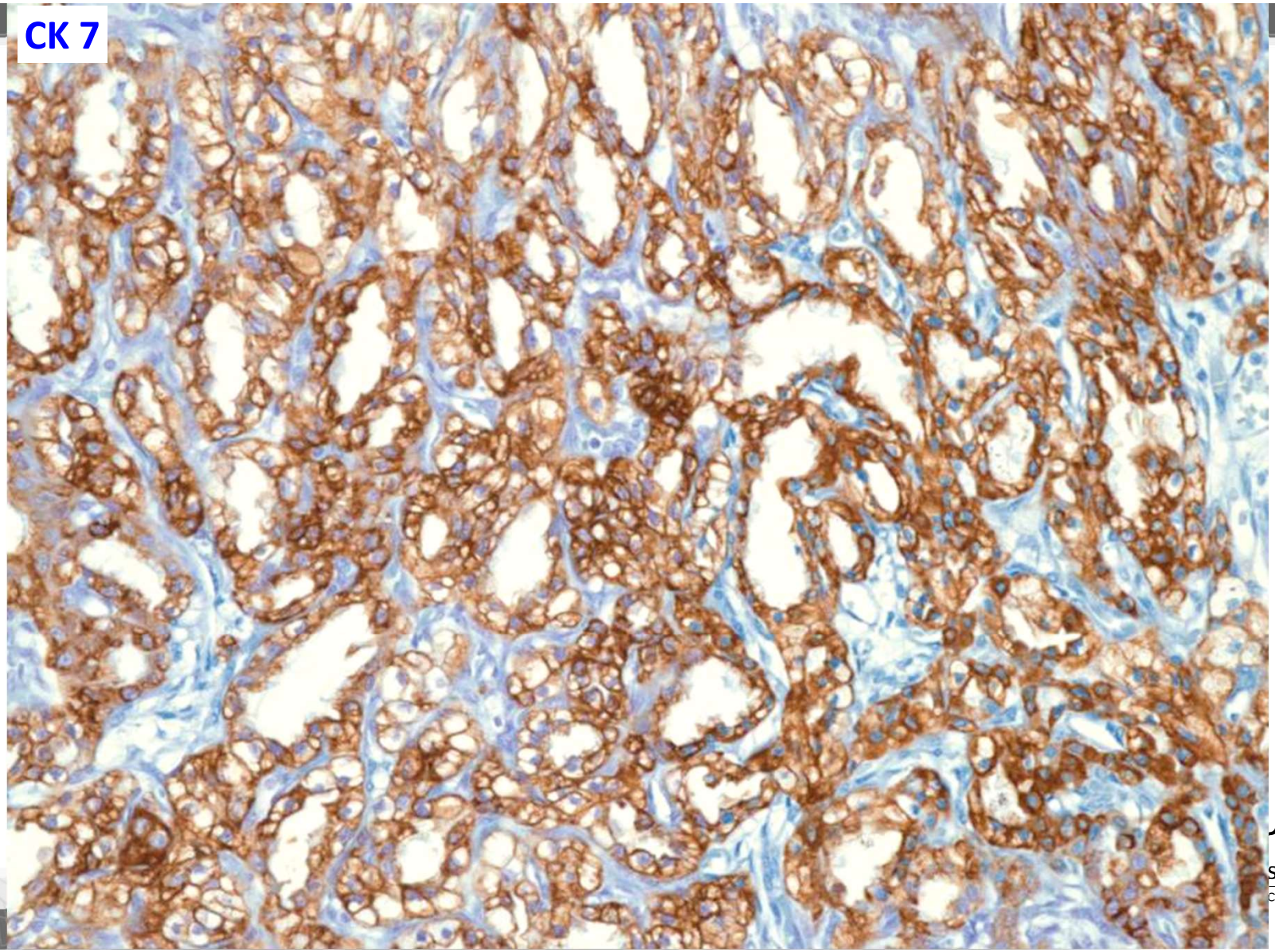


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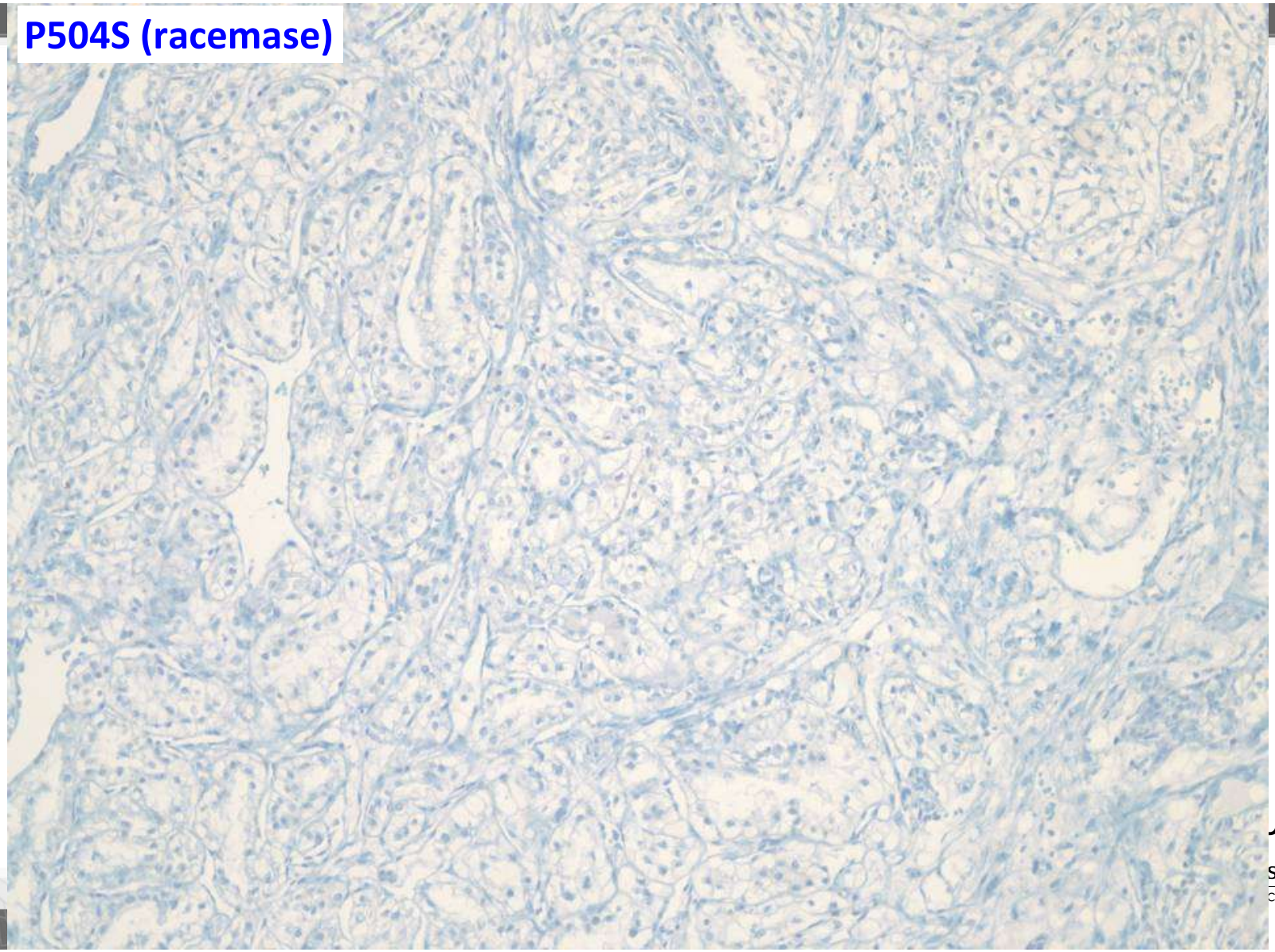
## P504S (racemase)



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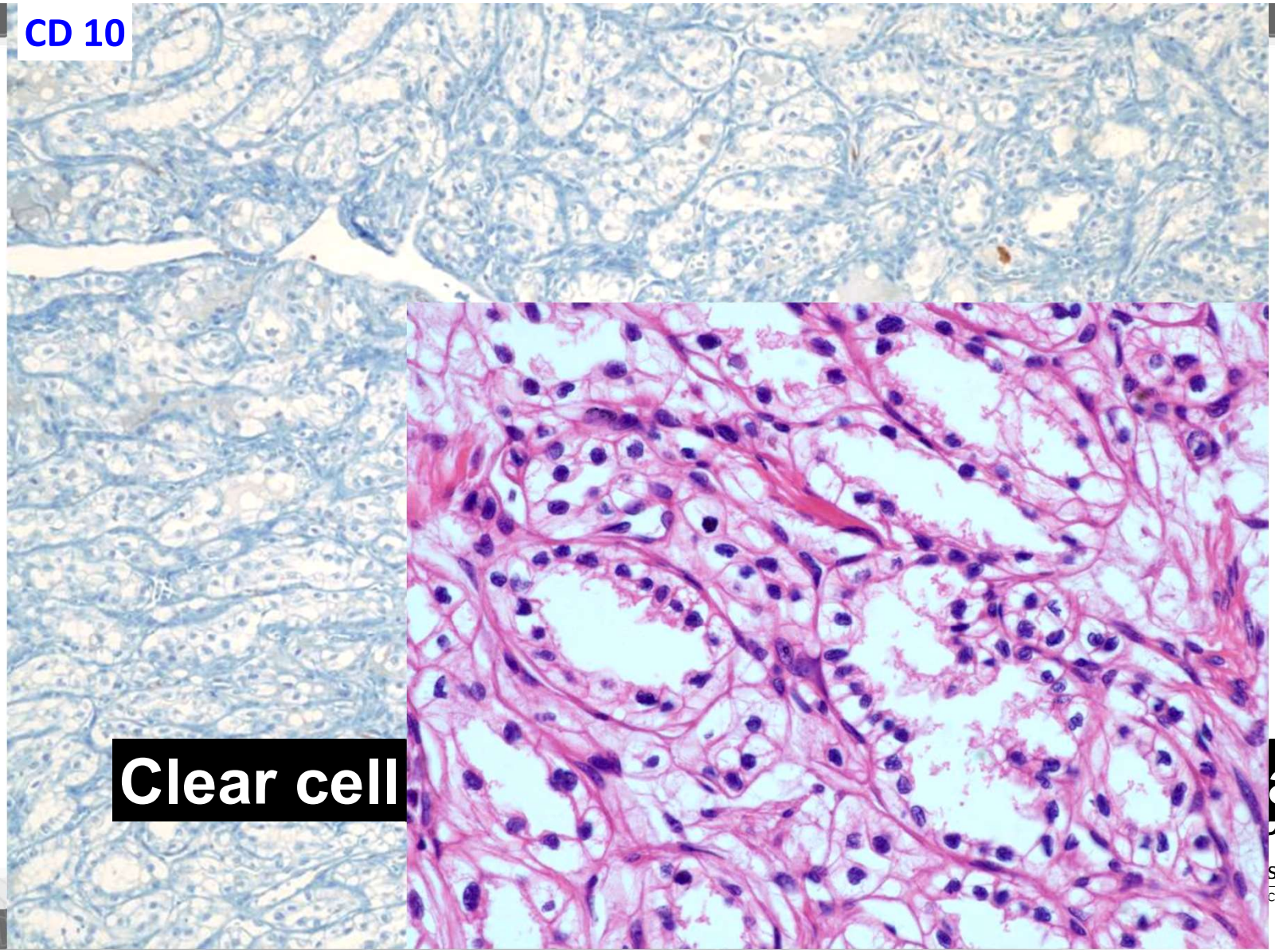

Clear cell

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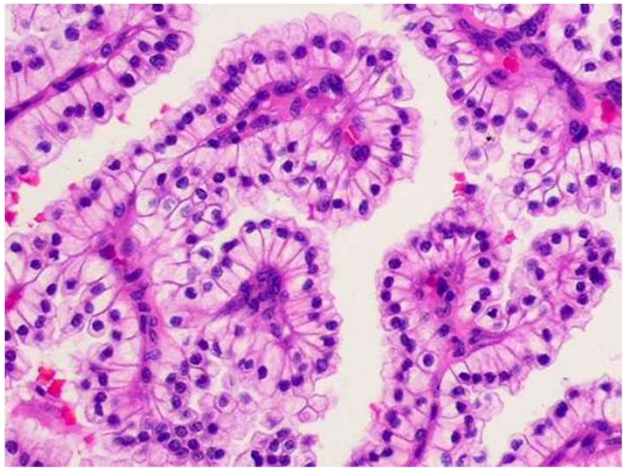
# Clear cell papillary renal cell tumor (CCPRCT) WHO 2022 CLASSIFICATION

***Renamed*** *from carcinoma to tumor due to uniformly indolent behavior.*



- Low-stage, low-grade tumor with tubulo- papillary and cystic architecture composed of clear cells with linearly aligned luminally oriented nuclei.
- Co-express CK7 and CAIX (cup-like), often positive for HMWCK, but negative for CD10, and lack recurrent cytogenetic abnormalities or
- *VHL* gene alterations.

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Wexner Medical Center

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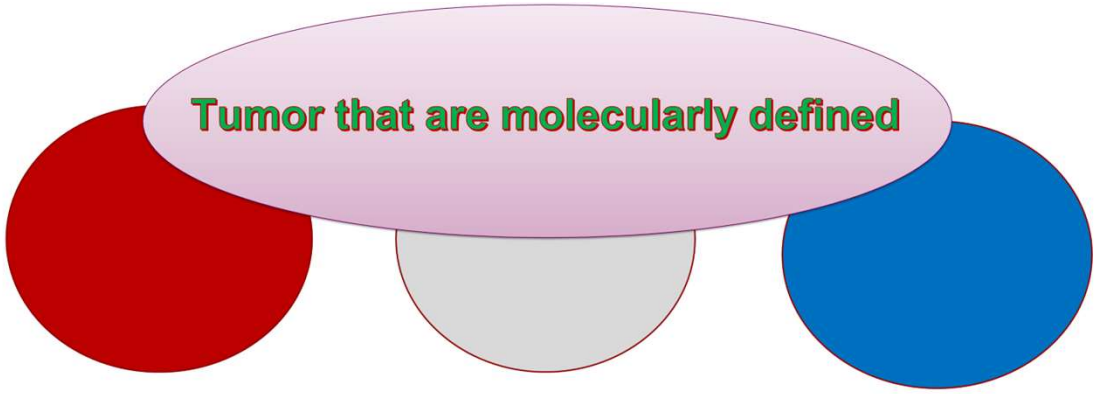
# INTERESTING CASE #2

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Tumor with
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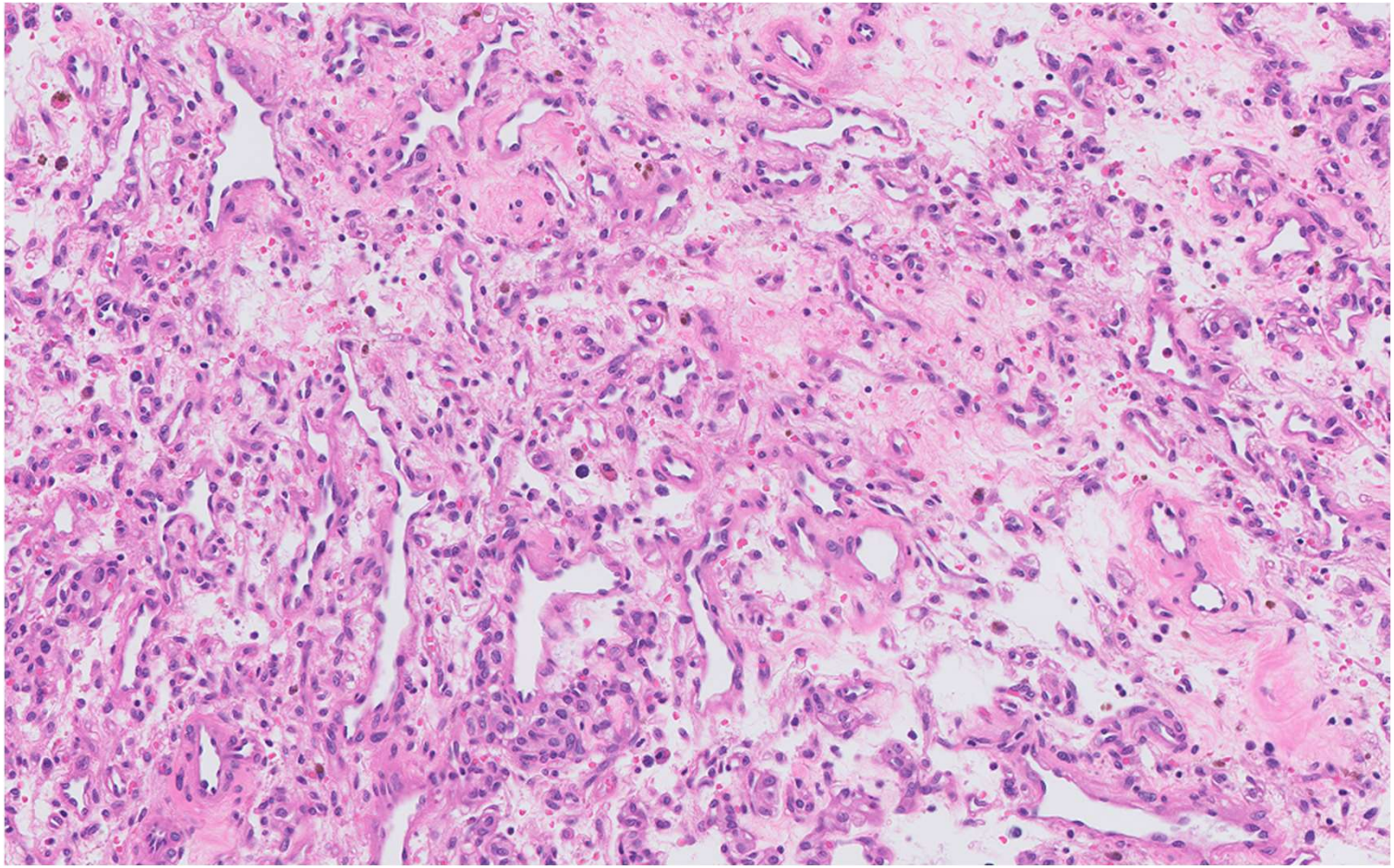
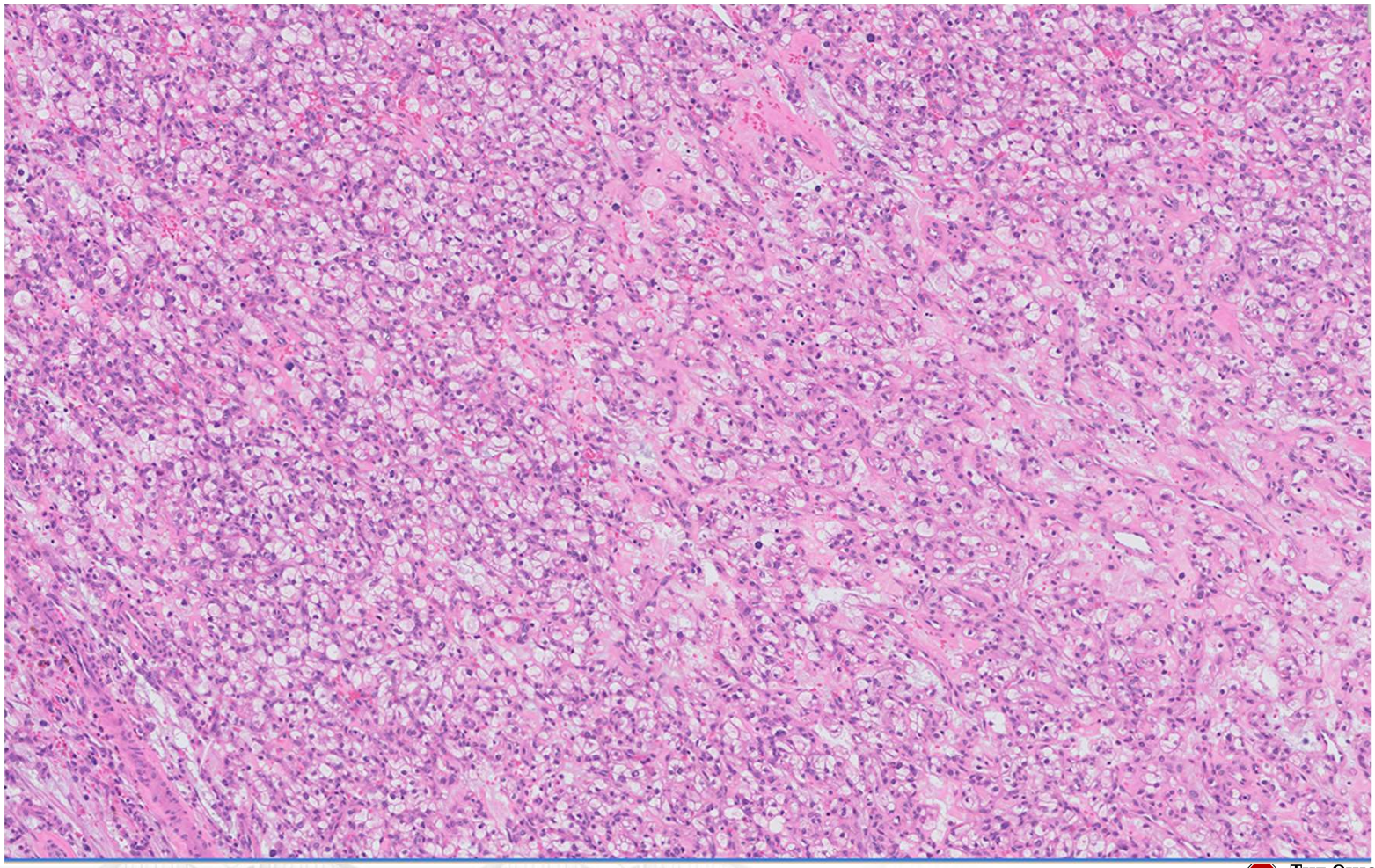
## Case History

- A 48 year old male presented for evaluation of a left renal mass found incidentally during a previous MRI.
- A follow up MRI of the abdomen revealed a left lower pole 1.6 cm enhancing renal mass concerning for renal cell carcinoma.
- A partial nephrectomy was performed.
- 1.5 x 1.4 x 1.1 cm well-circumscribed, rubbery mass

# Histology Findings





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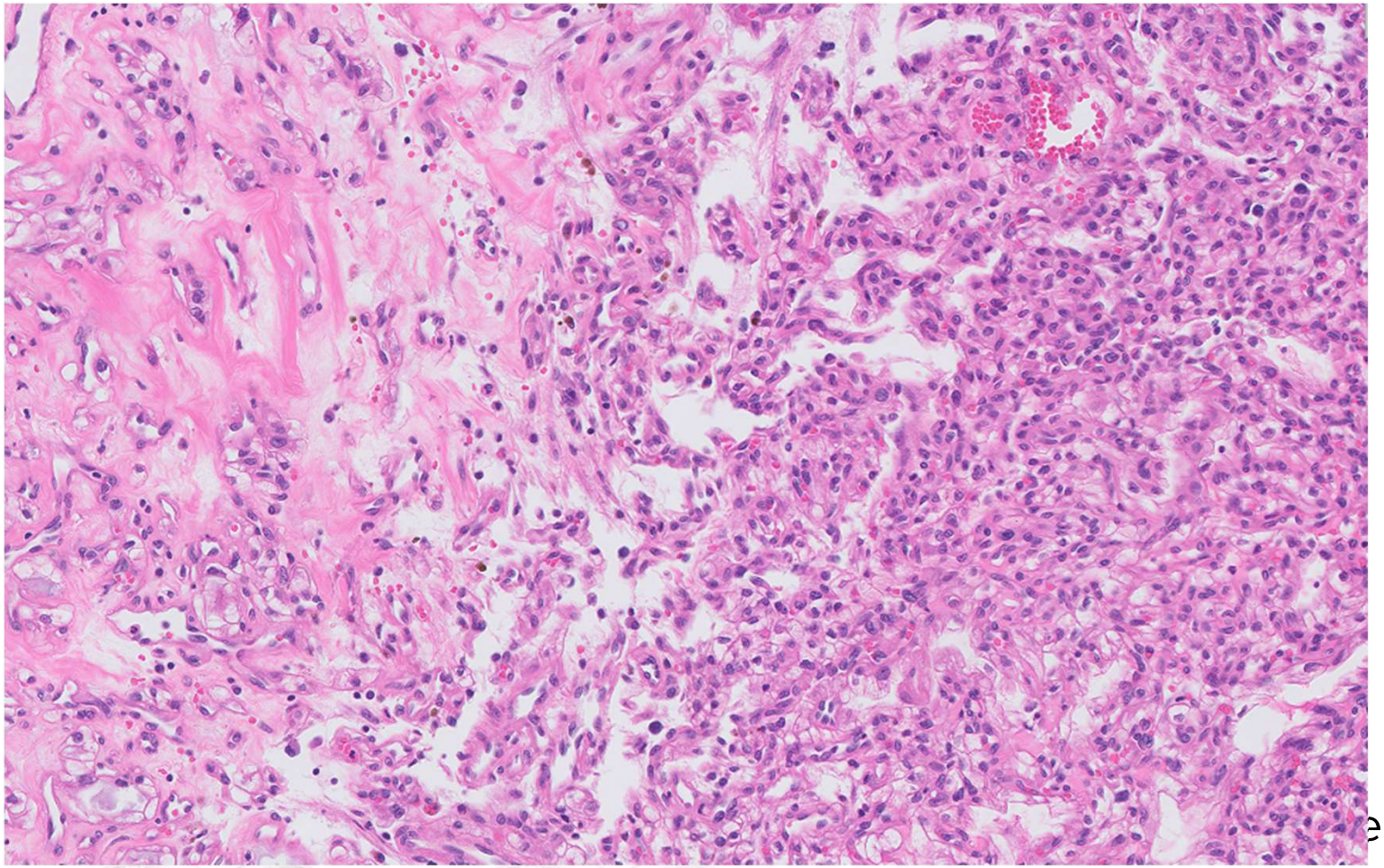
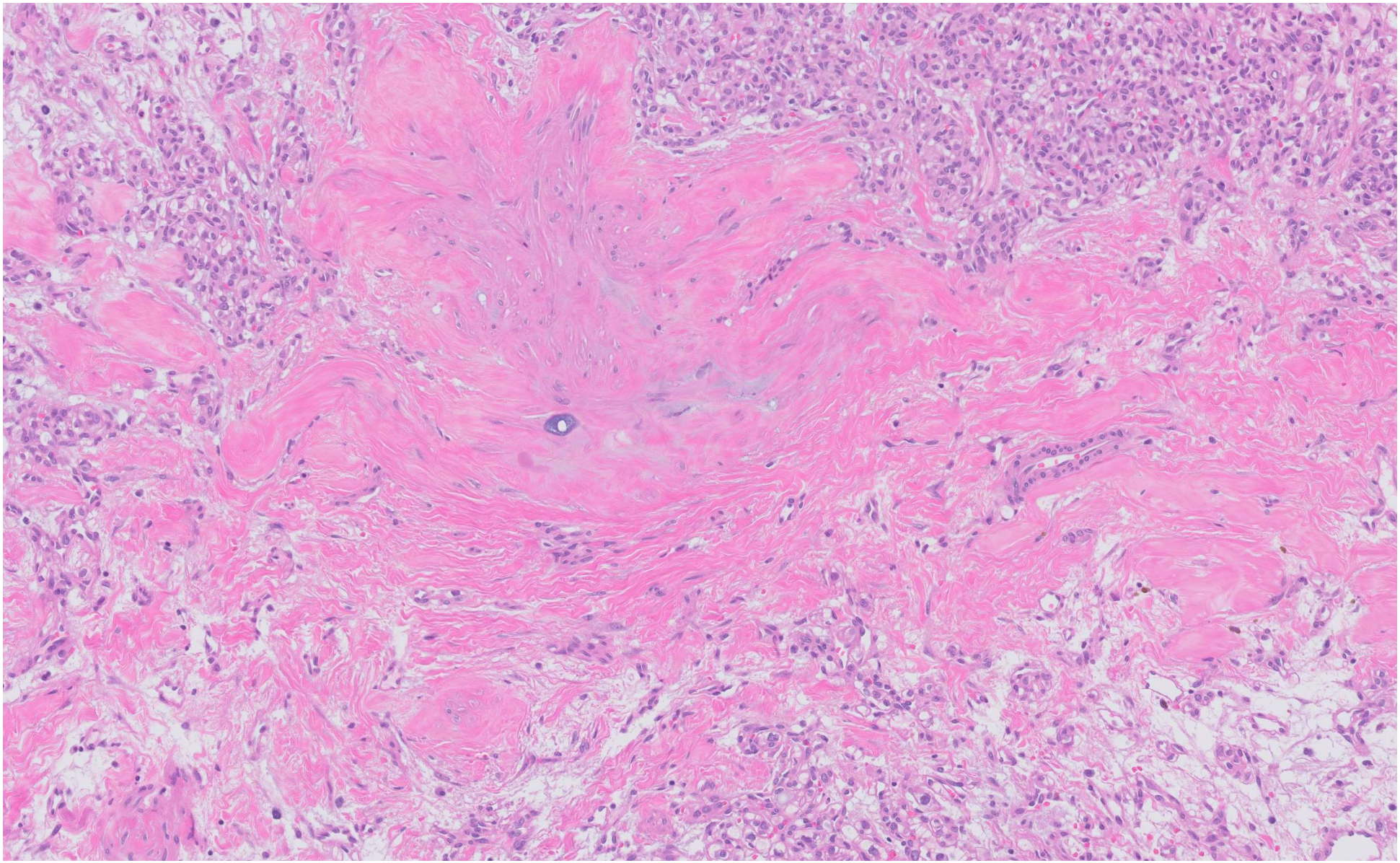
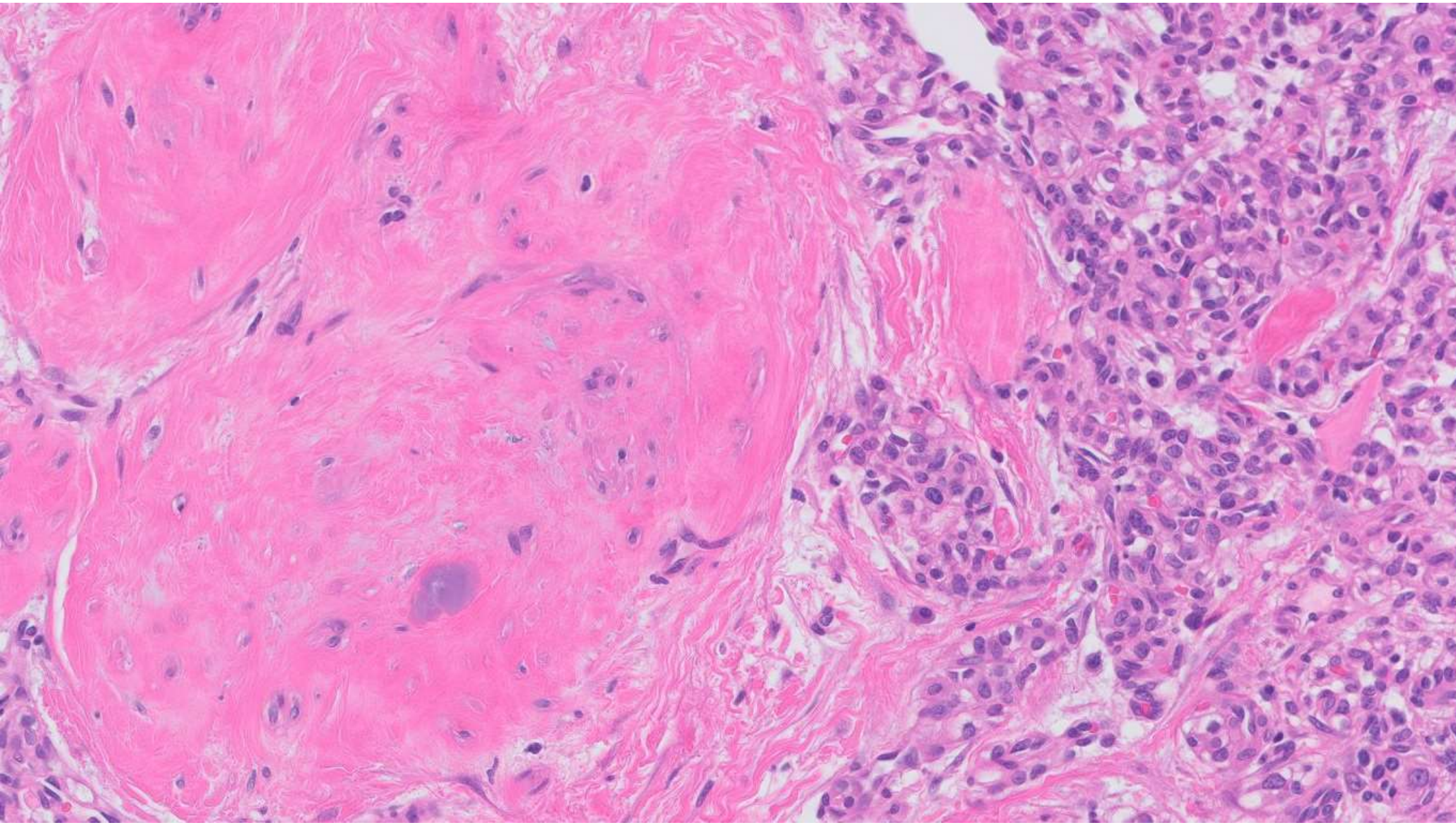
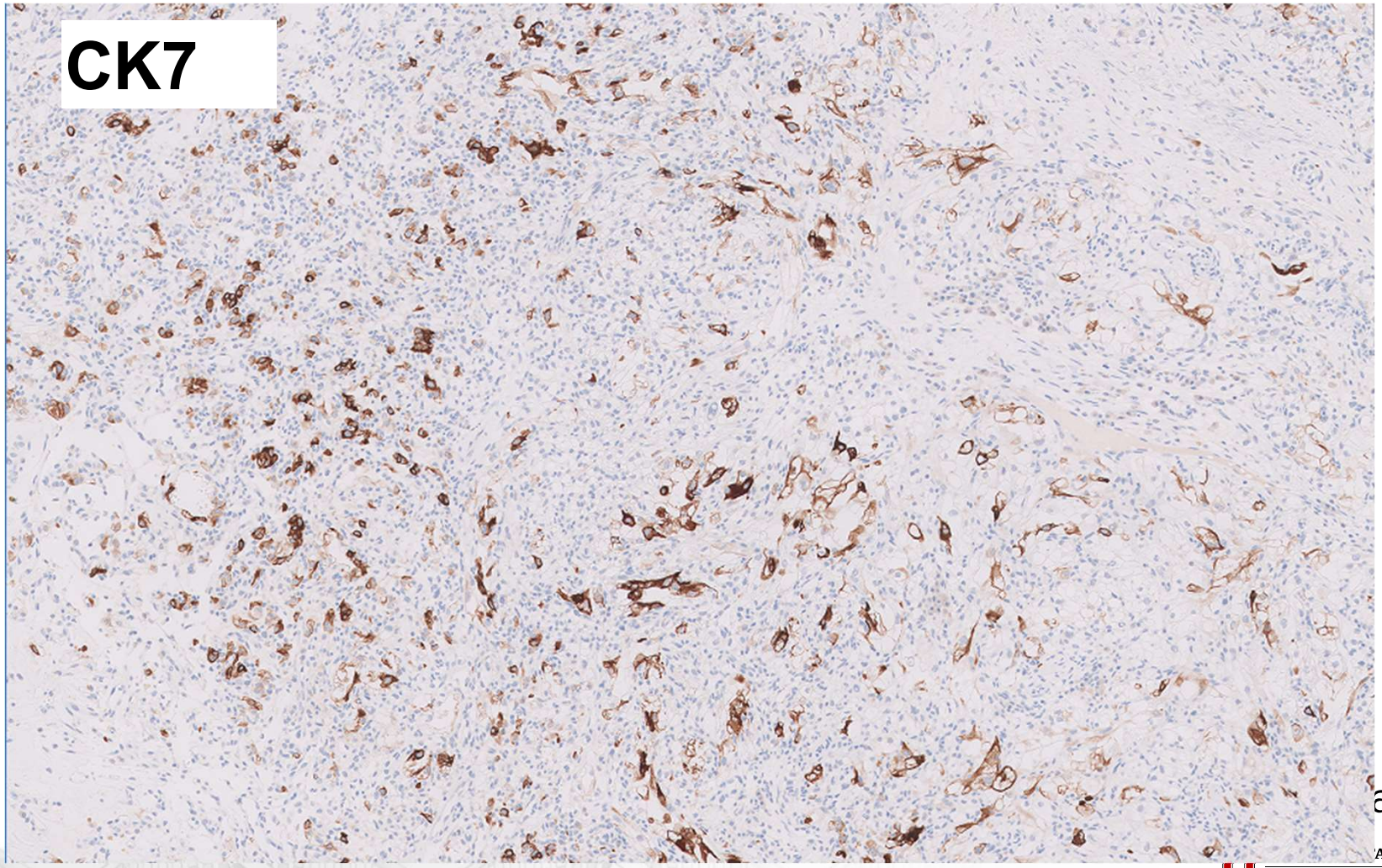
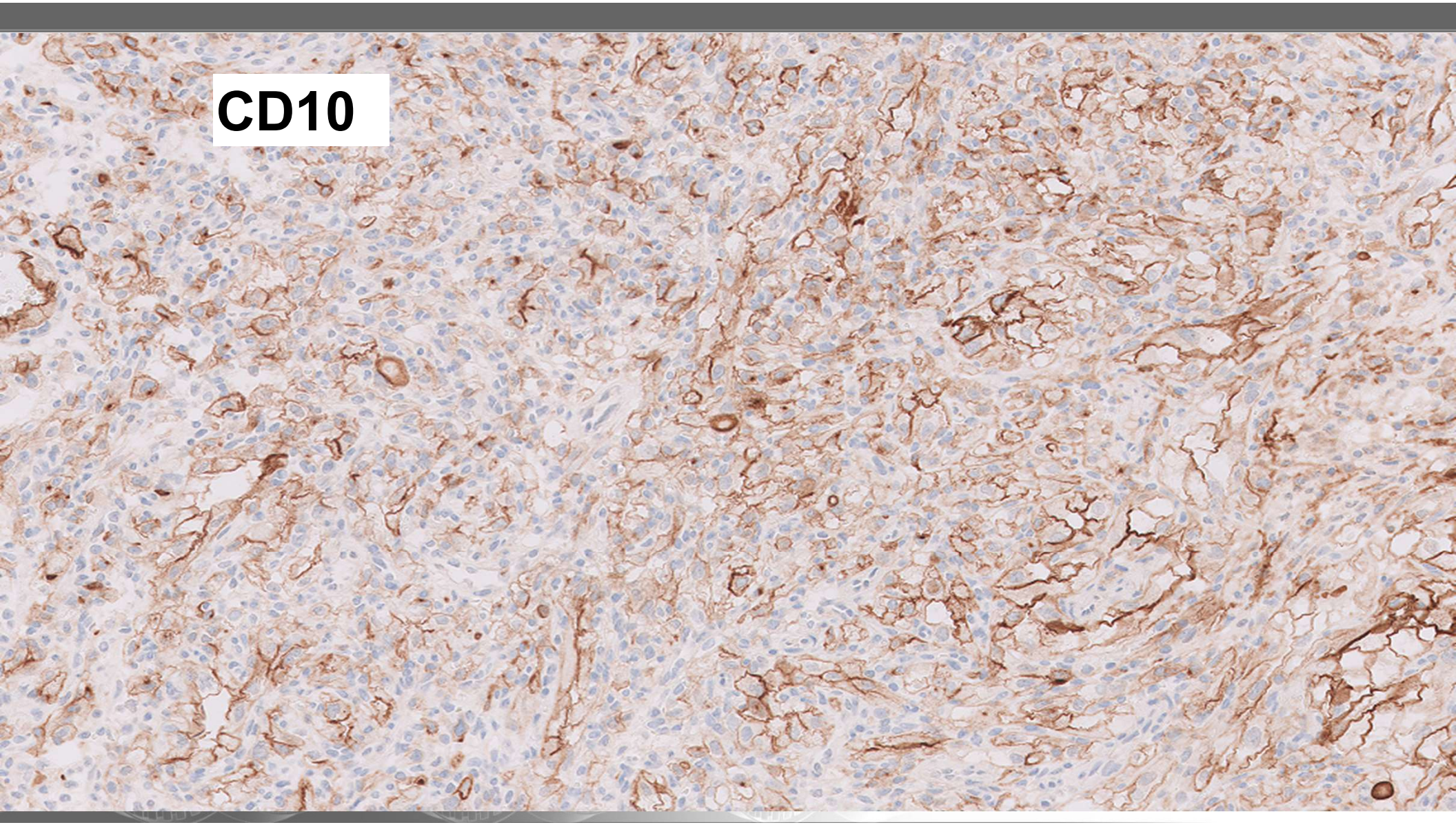
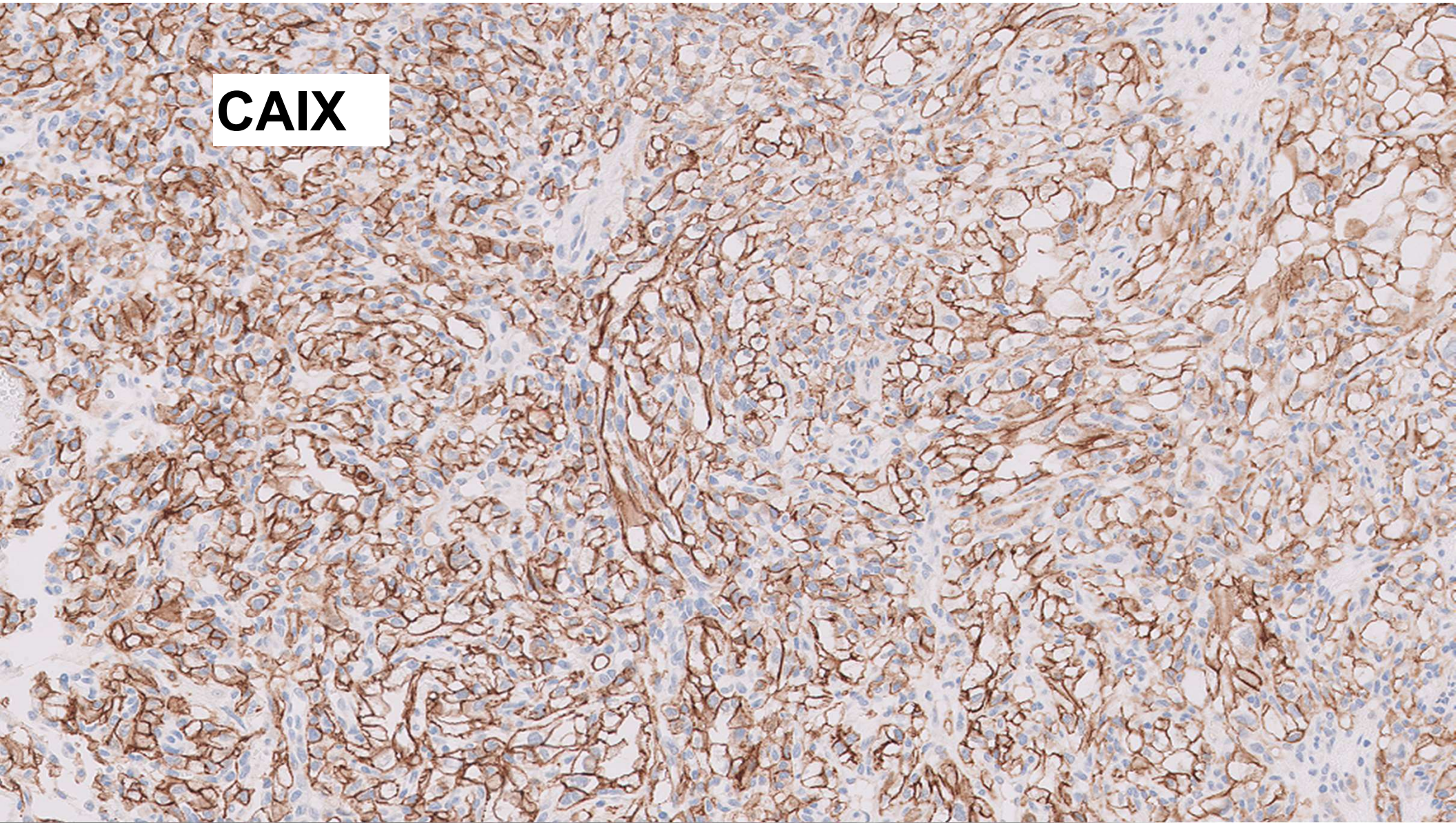




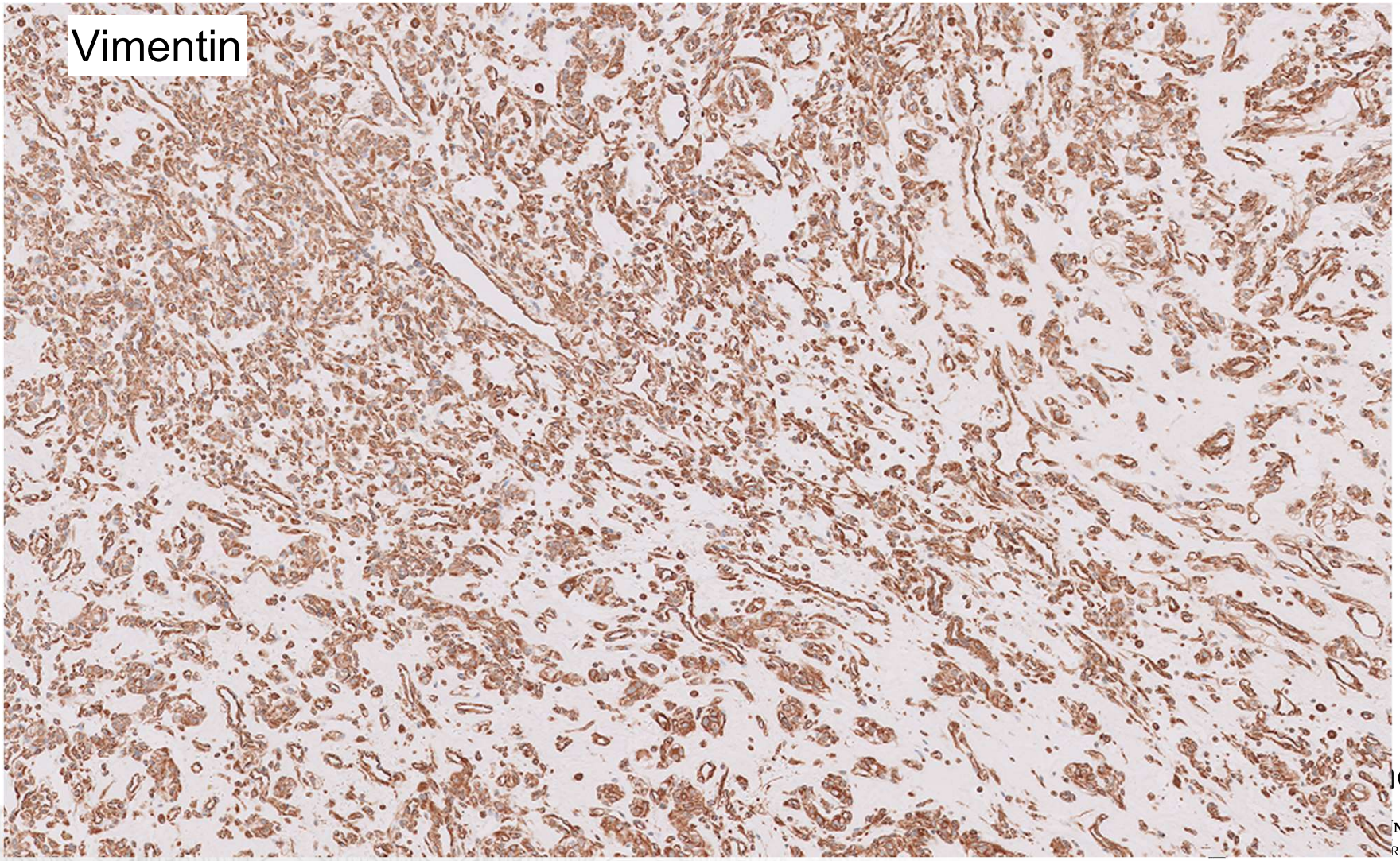



CK7


CD10


CAIX

Vimentin



# What is the most likely diagnosis?

- Renal angiomyoadenomatous tumor
- Clear cell papillary renal cell carcinoma
- Renal cell carcinoma with leiomyomatous stroma
- Papillary renal cell carcinoma

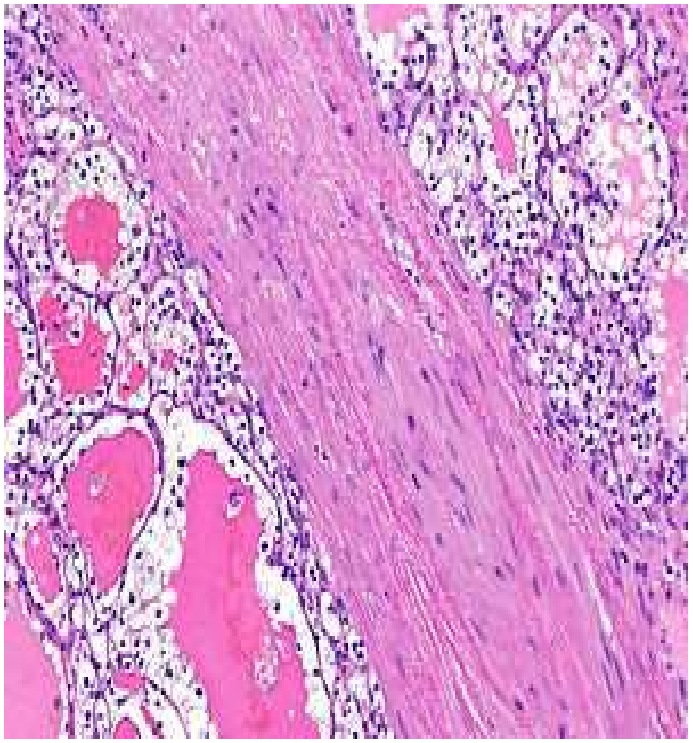
**Renal cell carcinoma with leiomyomatous stroma**

## Case Findings

- IHC: Stained positive for vimentin, CAIX, CK7 (focal), CD10, desmin (highlights muscle in stroma). Negative AMACR
- Molecular testing:
  - FISH study performed, showed no deletion in Chromosome 3p which confirms that this is not clear cell subtype.
- Based on histopathological features, IHC stains, and molecular genetics results, this tumor shows features consistent with renal cell carcinoma with leiomyomatous stroma.

# Discussion

- Renal cell carcinoma with leiomyomatous stroma is a rare entity that is distinct from clear cell renal carcinoma.
- IHC typically positive for **CK7 and CD10**, as well as CAIX, pankeratin, vimentin, and HIF1-alpha
- Differential diagnostic from renal clear cell carcinoma must be done; renal clear cell carcinoma will show deletion of chromosome 3p, VHL mutation, and VHL methylation abnormalities
- Additional differential diagnostic methods may include genetic testing, as renal cell carcinomas with leiomyomatous stroma have shown recurrent mutations of TSC1/TSC2, MTOR, and/or **ELOC, consistent with hyperactive MTOR complex**.



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# ***WHO 2022 Update: Papillary renal tumors***

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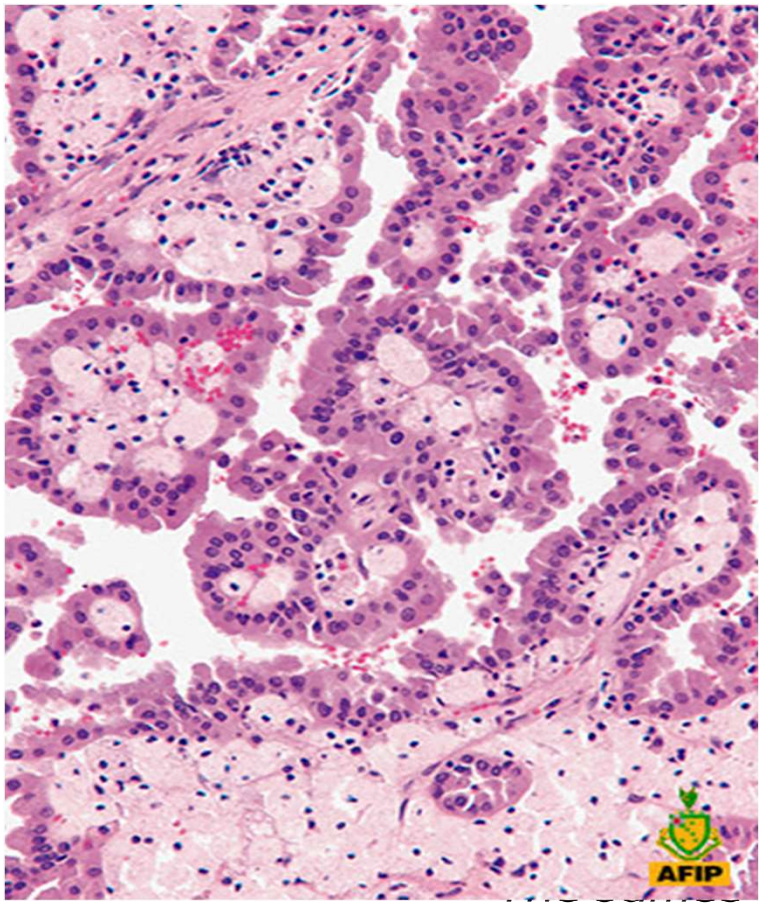
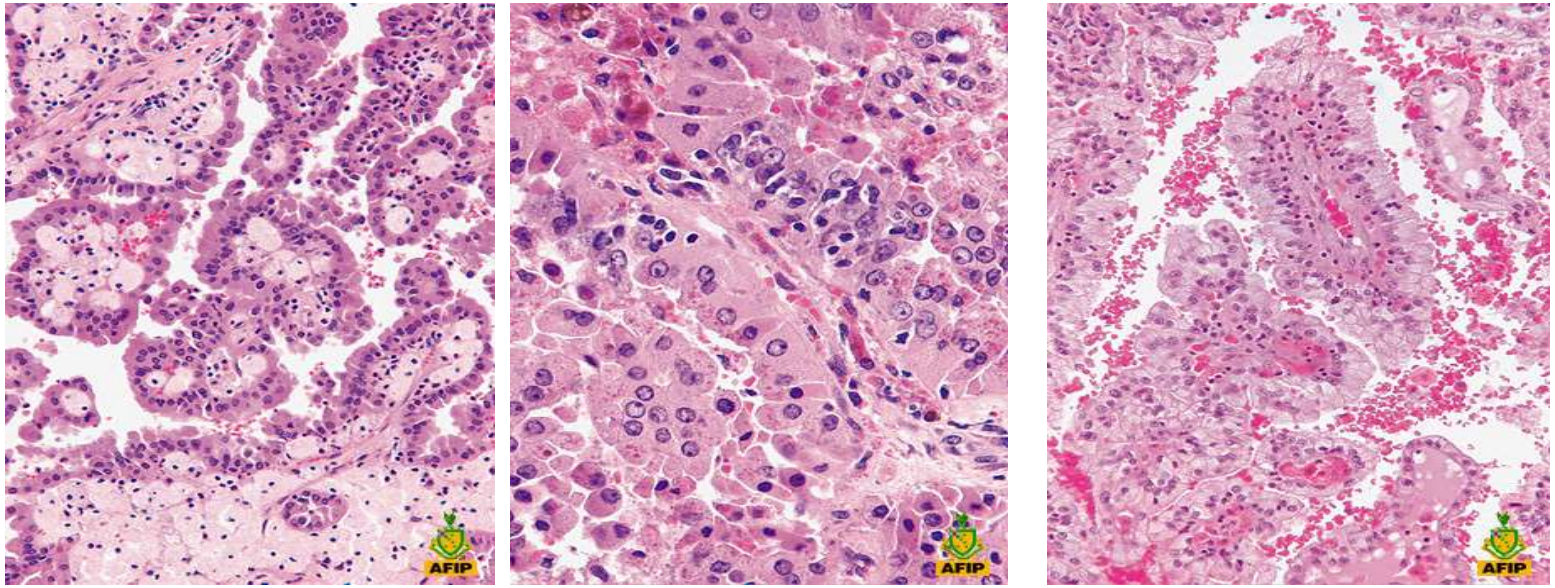
- Papillary renal cell carcinoma



# WSI KIDNEY CASE NUMBER 3

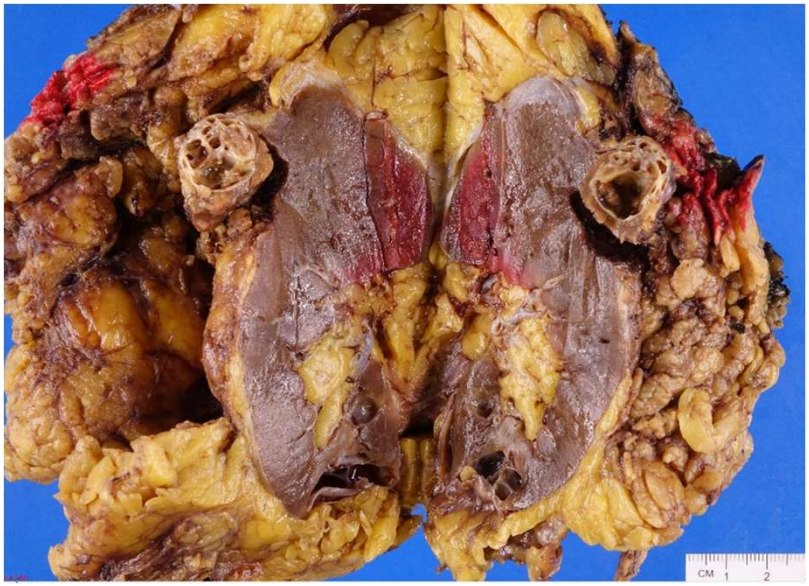
# MORPHOLOGIC TYPING OF PAPILLARY RENAL CELL CARCINOMA (PRCC)



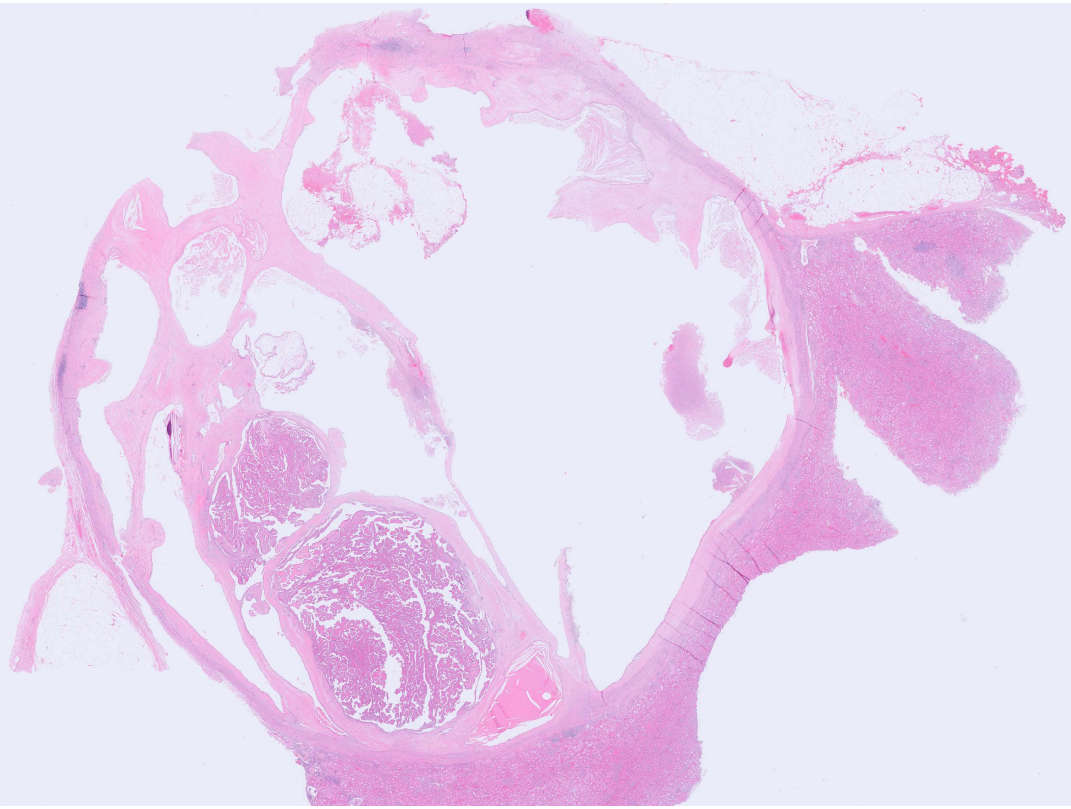

**WHO 2022: No need to Subtype Papillary RCC**

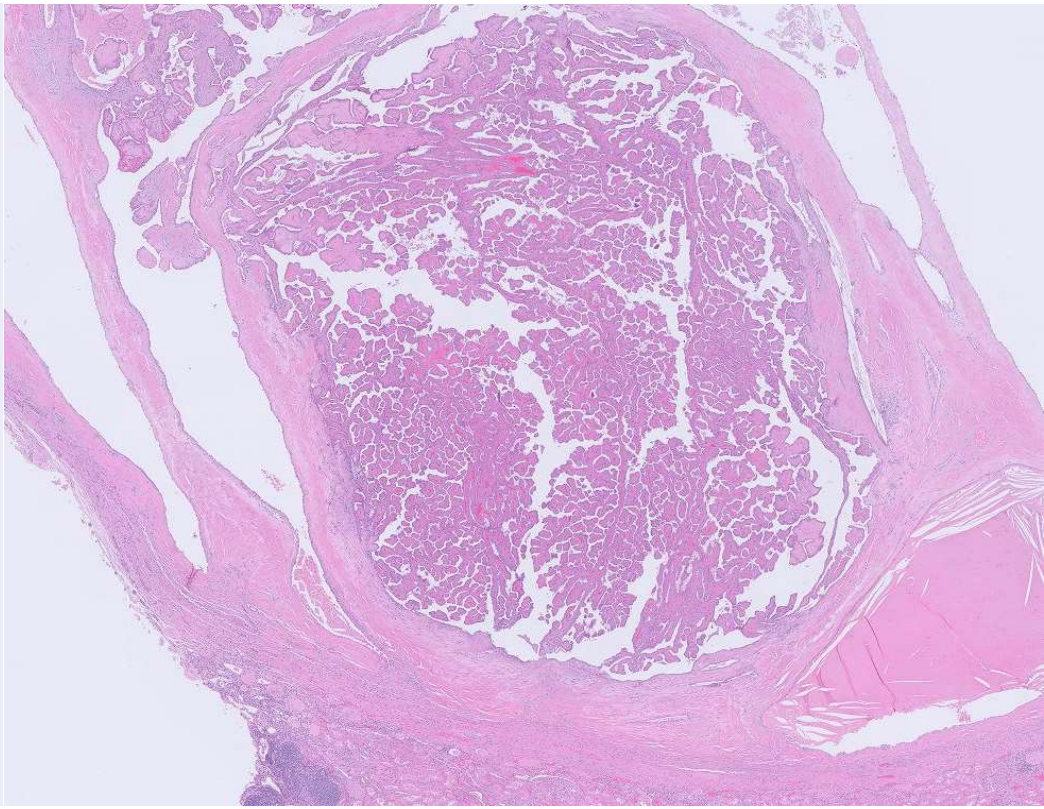
# Case History

- 64-year-old male
- Incidentally found right renal mass
- Hx of gout, HTN, HLD, ED, elevated PSA
- CT  abdo 2.4 x 1.9 cm exophytic slightly hyperdense septated cystic lesion in the interpolar region of the right kidney shows some peripheral thickening and nodularity

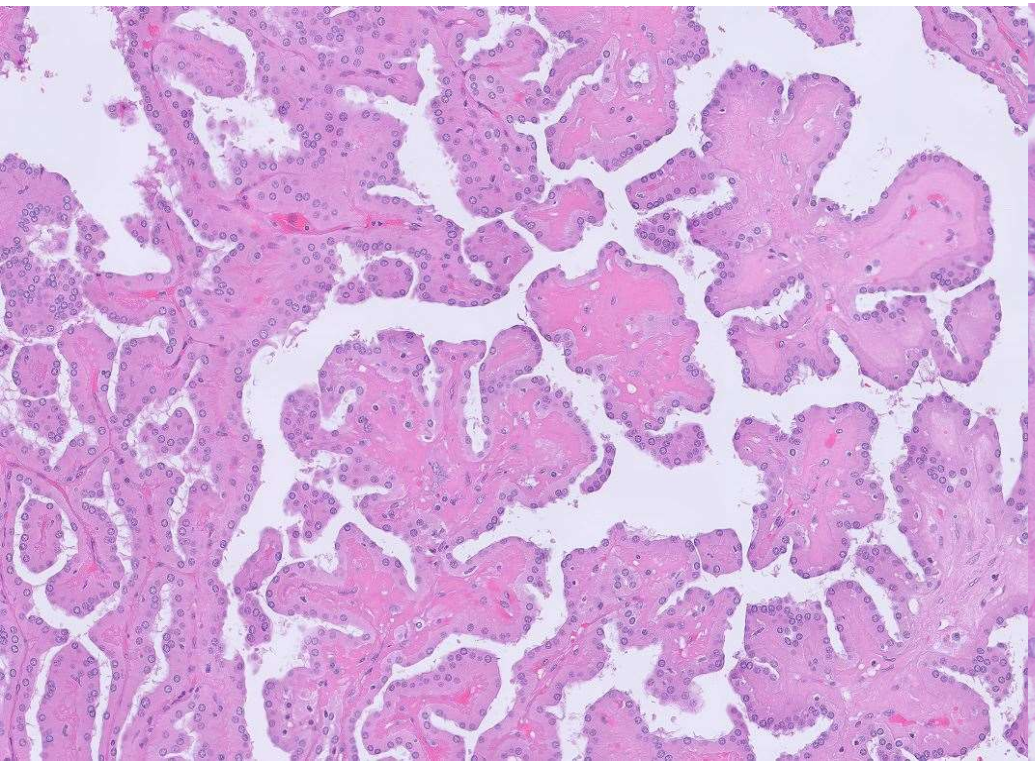


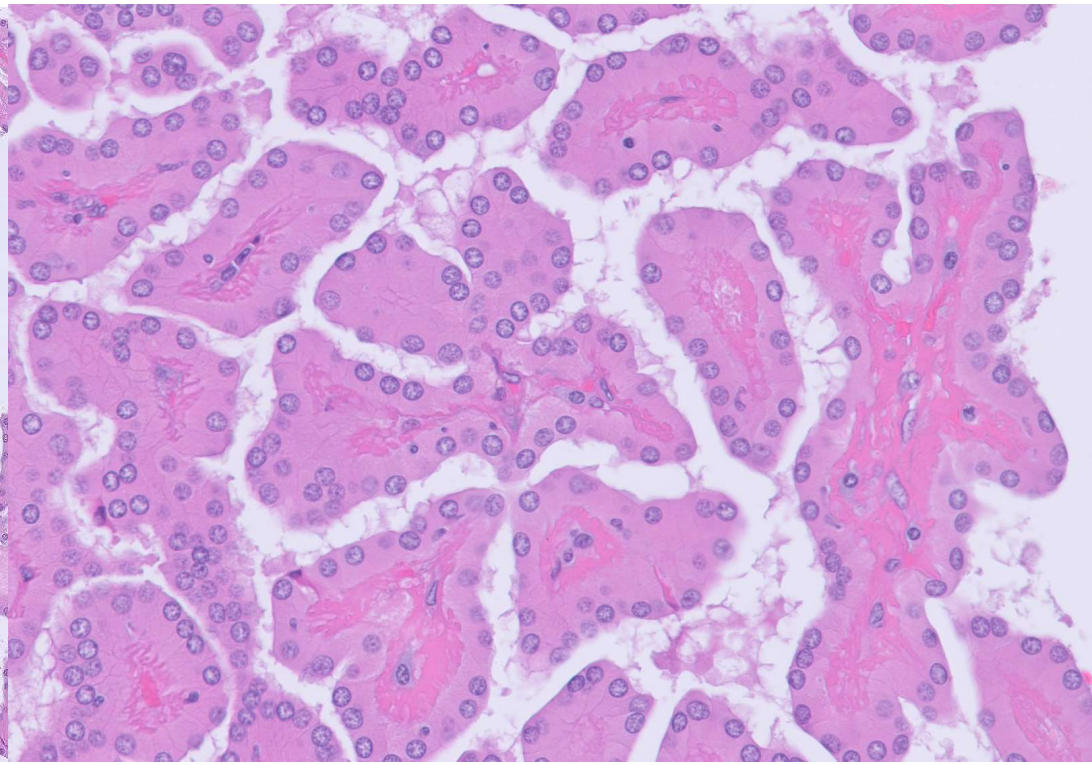
# Pathology- Microscopy



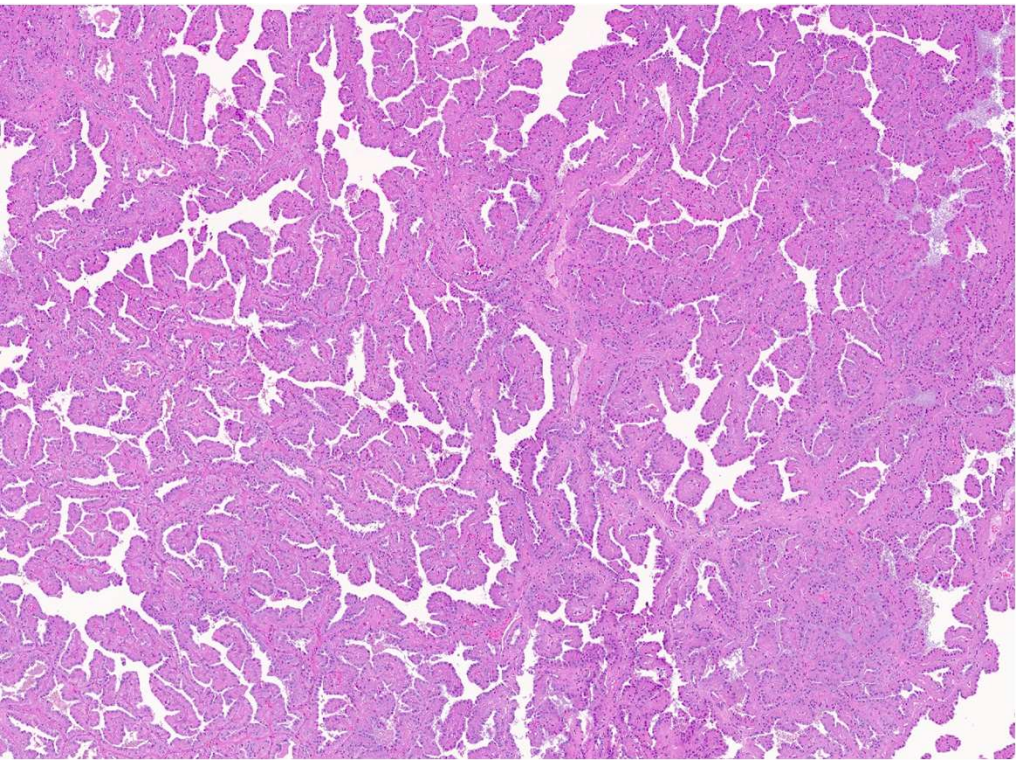


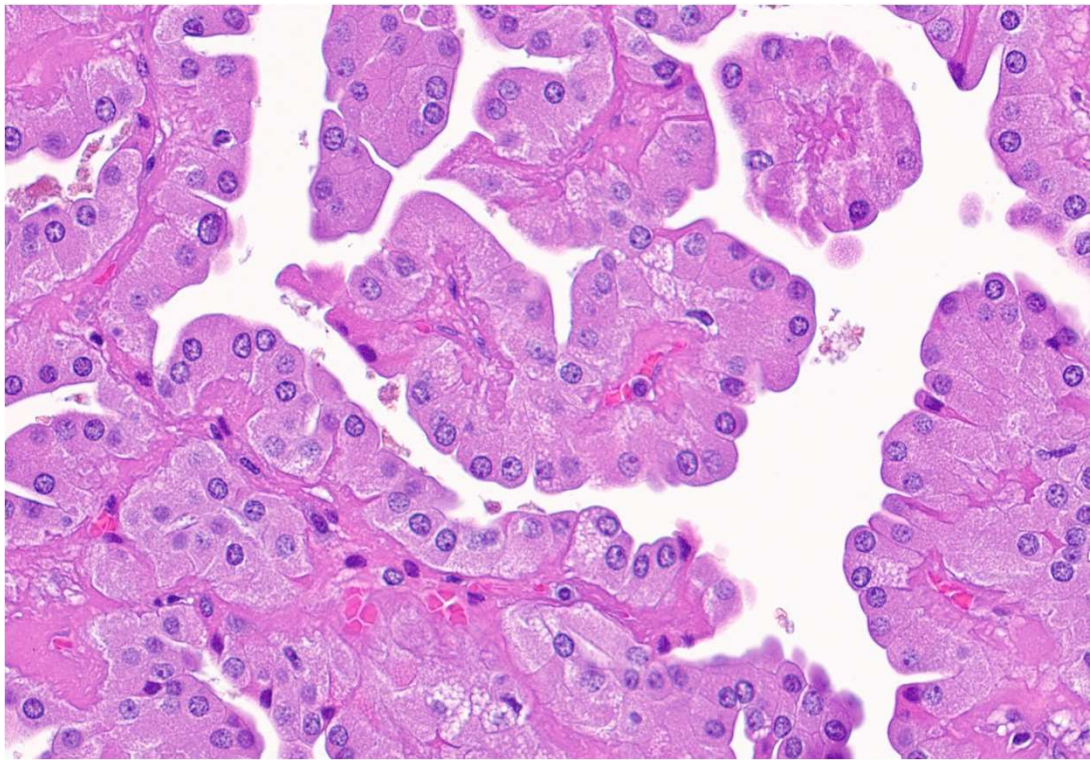
# Pathology- Microscopy



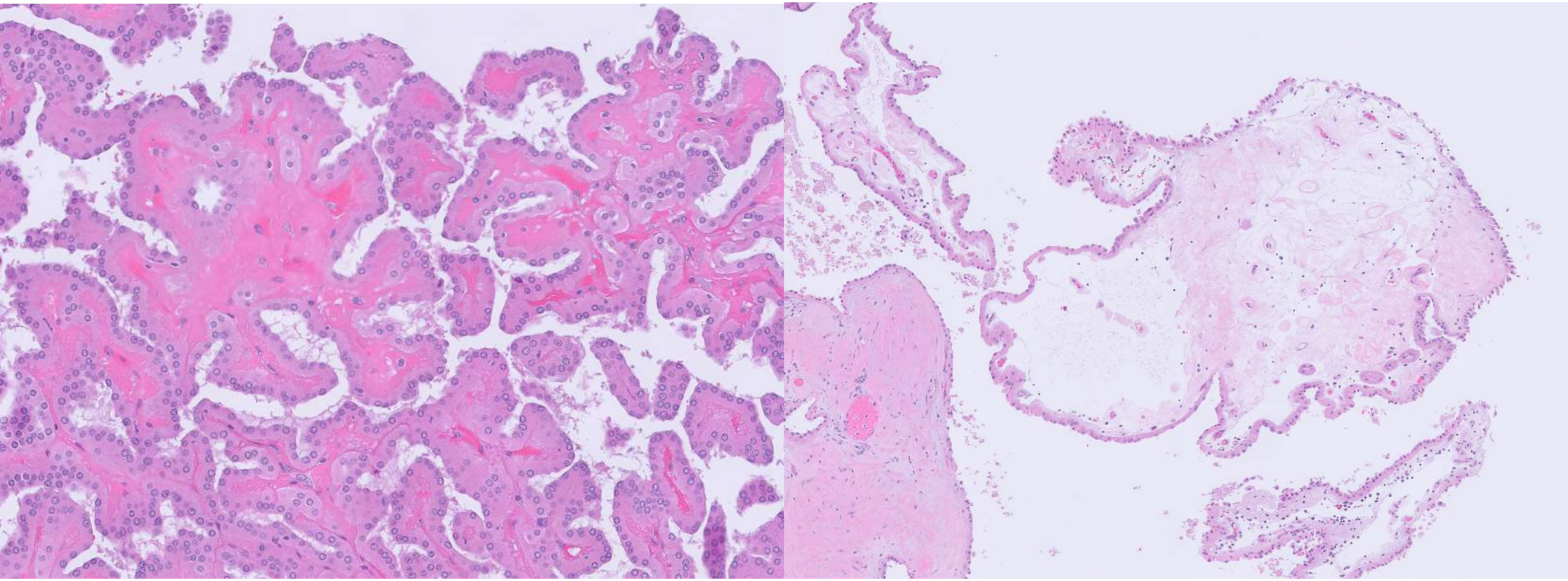


# Pathology- Microscopy

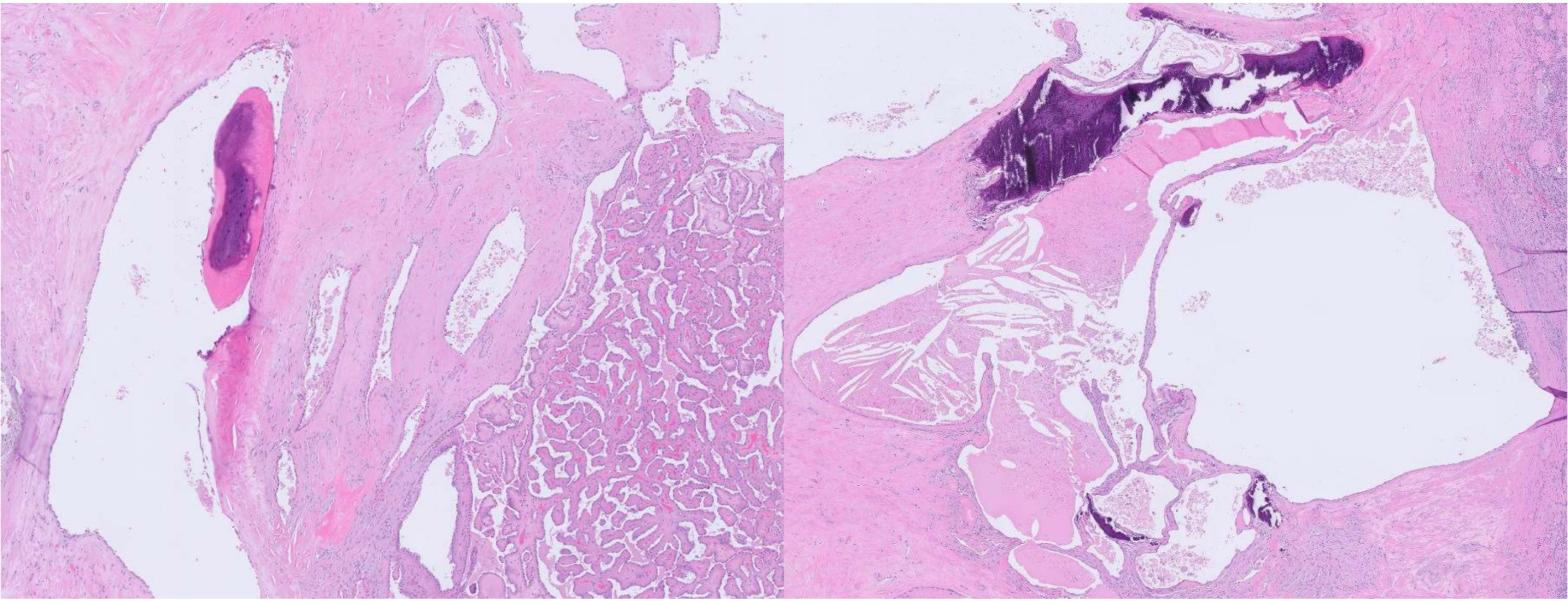




# Pathology- Microscopy

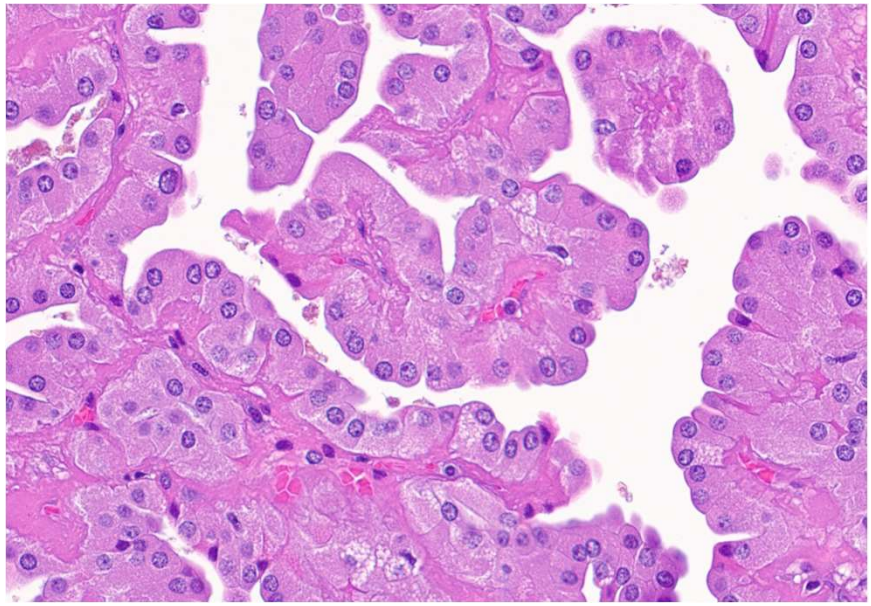


# Pathology- Microscopy

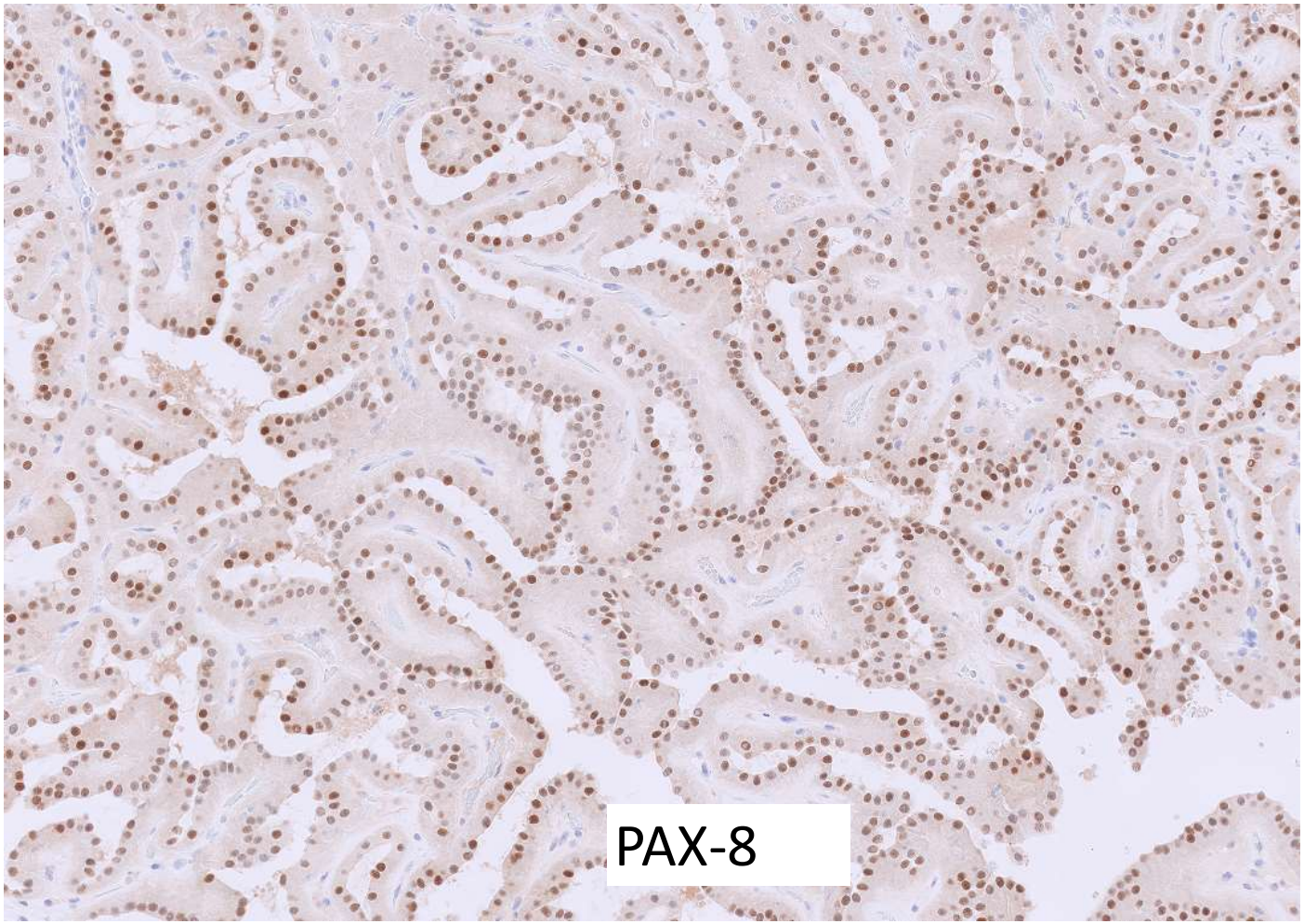


# Pathology- Differential Diagnosis

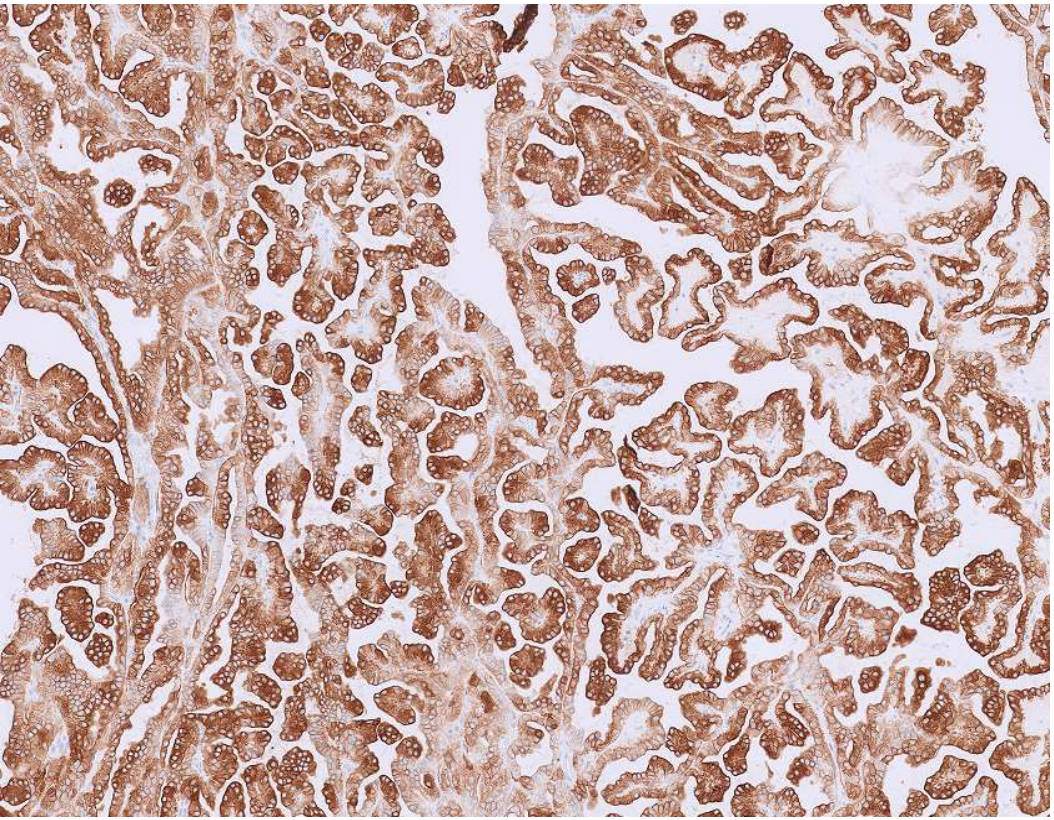
- Papillary RCC subtypes (Type 2 or Oncocytic)
- FH deficient RCC
- Oncocytic tumors
- Papillary adenoma
- PRNRP



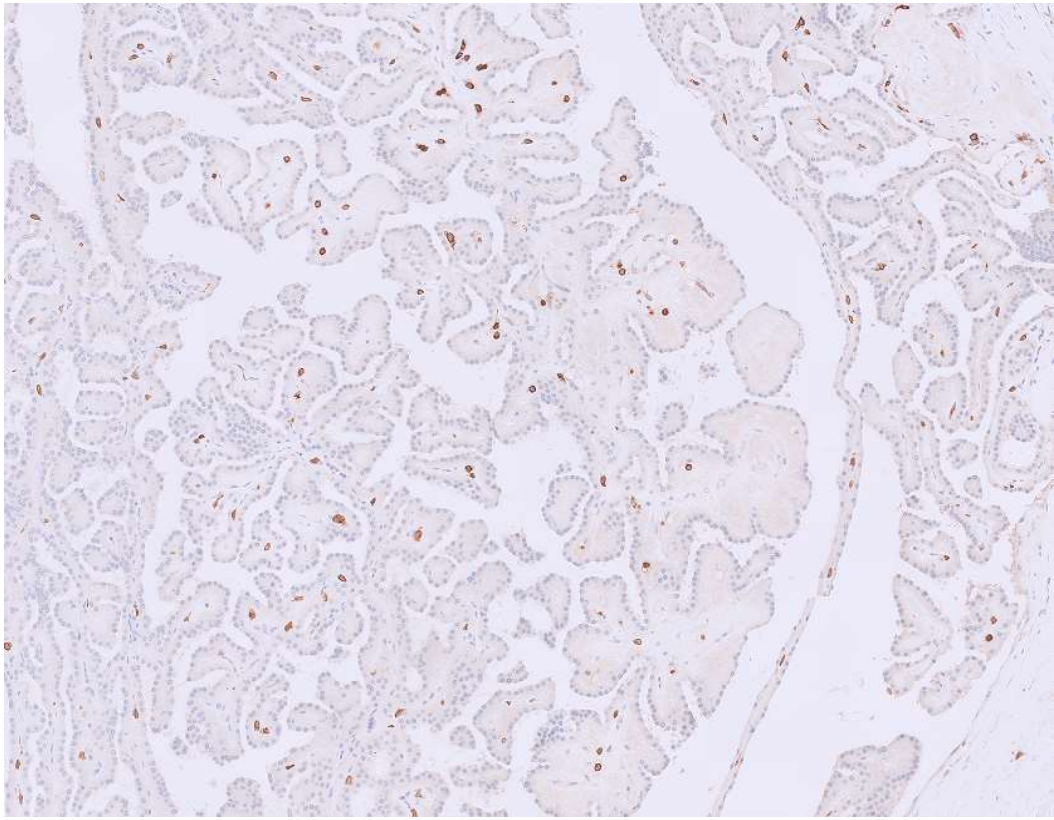
# Pathology- IHC



# Pathology- IHC

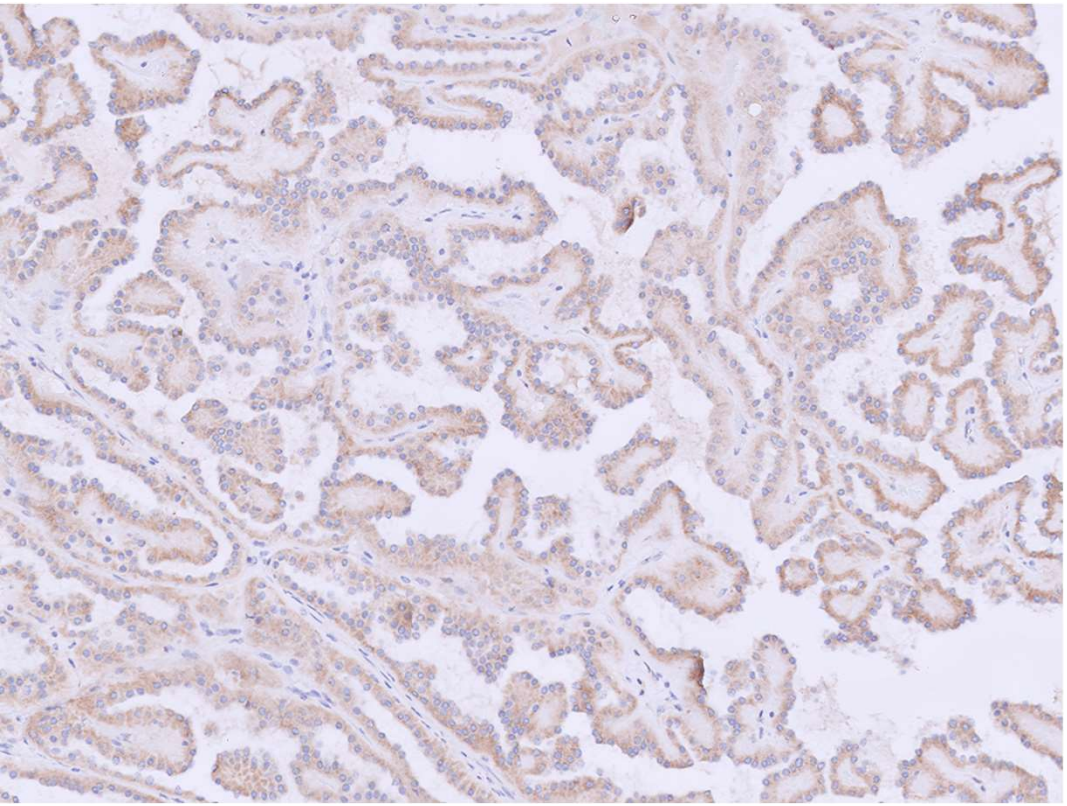


CK 7

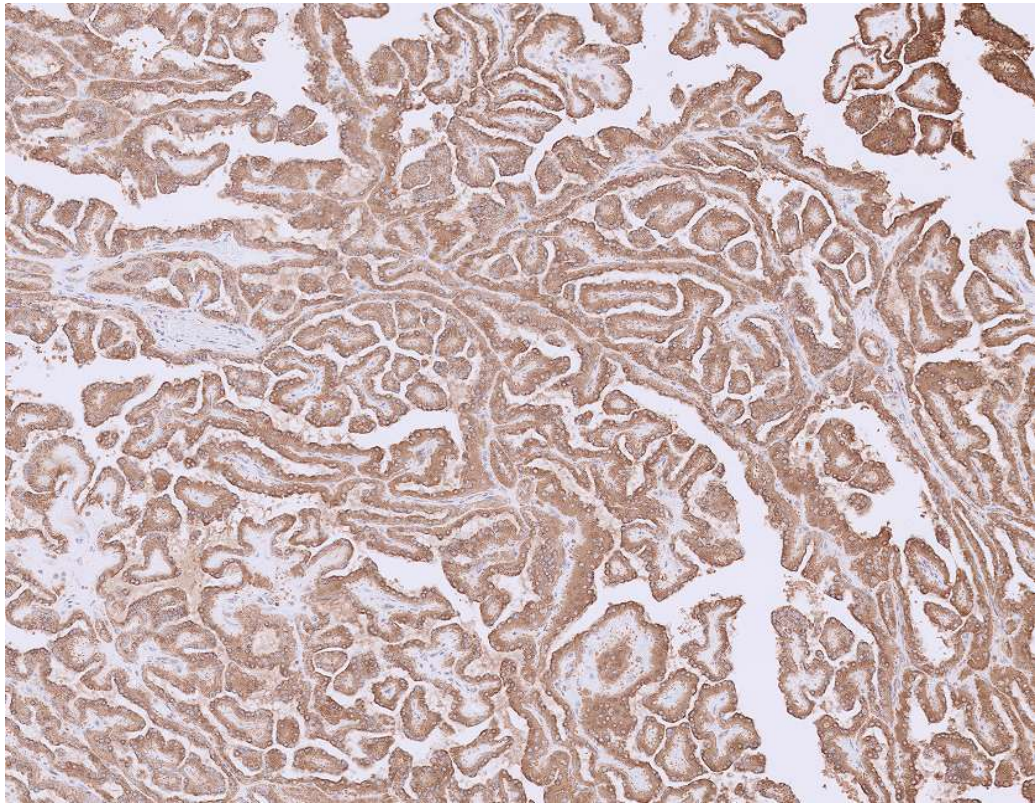


CD 117

# Pathology- IHC

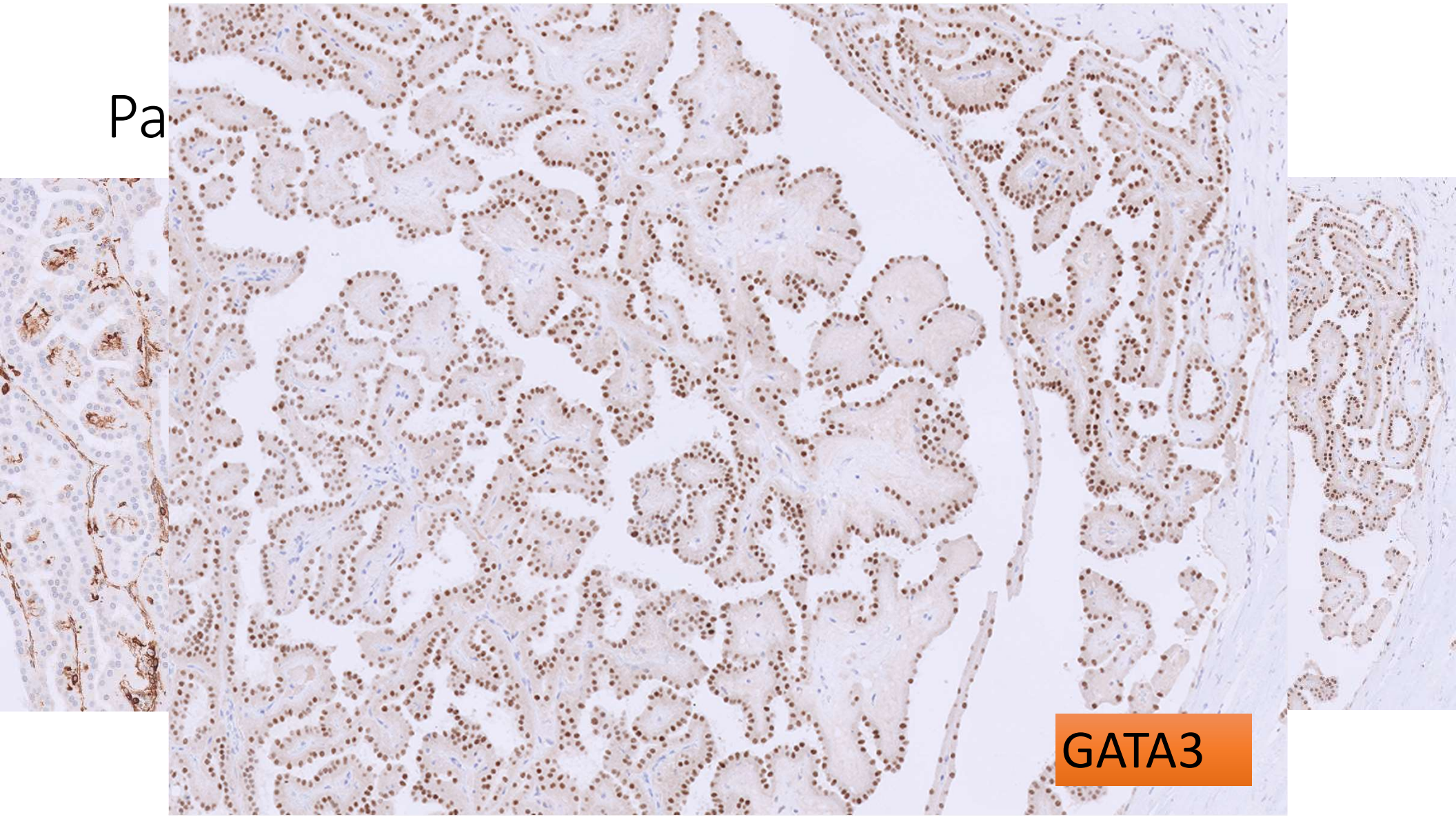


AMACR



FH

Pa



## Genetic testing

**A KRAS exon 2 mutation, KRAS p.G12V (c.35G>T), was detected in this tumor.**

**No mutations detected in exons 3 and 4 of KRAS**

What is your diagnosis?

Papillary Renal Neoplasm With Reverse Nuclear Polarity (PRNRP)

# Papillary Renal Neoplasm With Reverse Nuclear Polarity (PRNRP)

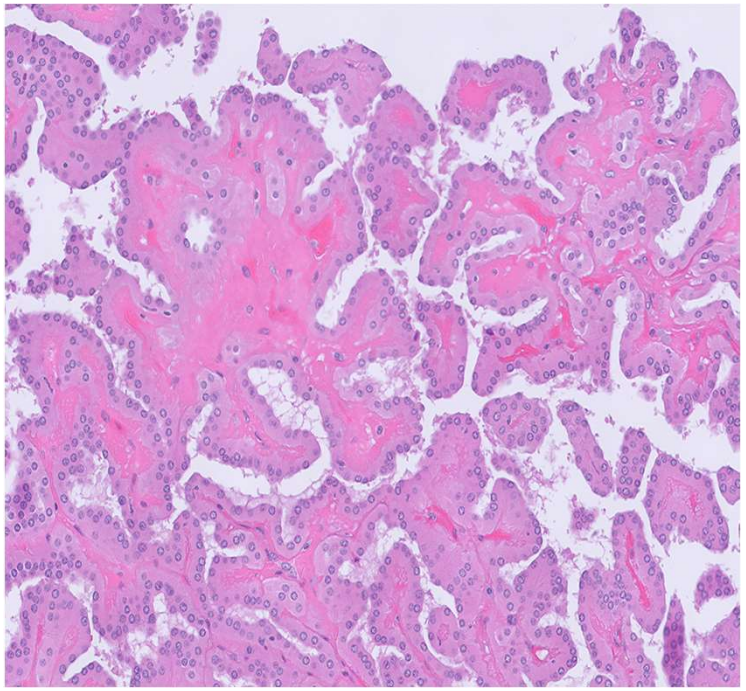
(1) papillary architecture with or without tubulo-papillary/tubular

pattern

(2) monolayered tumor cells with abundant eosinophilic cytoplasm,

(3) nuclei polarized away from basement membrane, and

(4) low ISUP/WHO nuclear grade

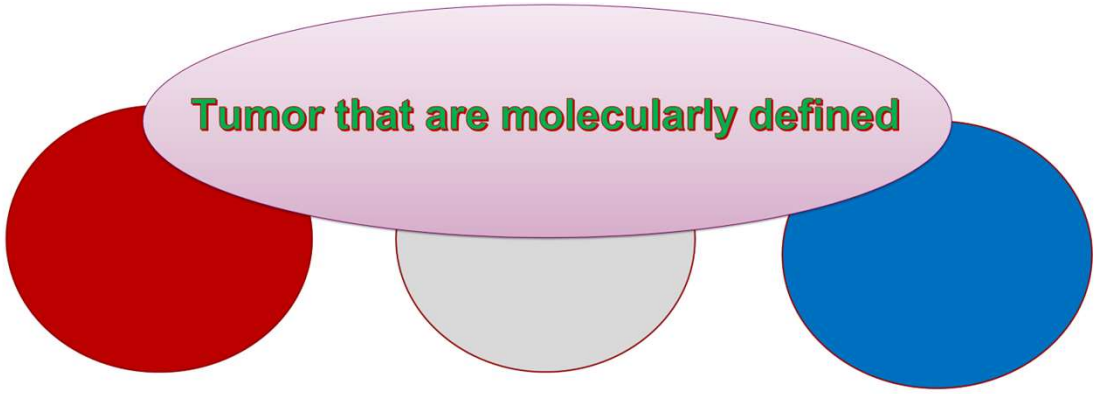


# Take home message for PRNRP

- PRNRP distinct and emerging entity with characteristic morphology, immunoprofile and molecular findings
- GATA 3 expression and KRAS missense mutation
- Based of the available literature, its an indolent renal tumor and should be designated as “Neoplasm” instead of “Carcinoma”
- Needs to be differentiated from PRCC due to its better prognosis and less extensive surgery (PN) would be the appropriate management

# WHO 2022 Renal Tumor Update: Emerging/provisional entities (still not part of the classification as definitive entities)

- Biphasic squamoid alveolar renal cell carcinoma
- Biphasic hyalinising psammomatous renal cell carcinoma
- **Papillary renal neoplasm with reverse polarity**
- Warthin-like papillary renal cell carcinoma
- Thyroid-like follicular carcinoma
- Eosinophilic vacuolated tumor
- Low-grade oncocytic tumor (LOT)



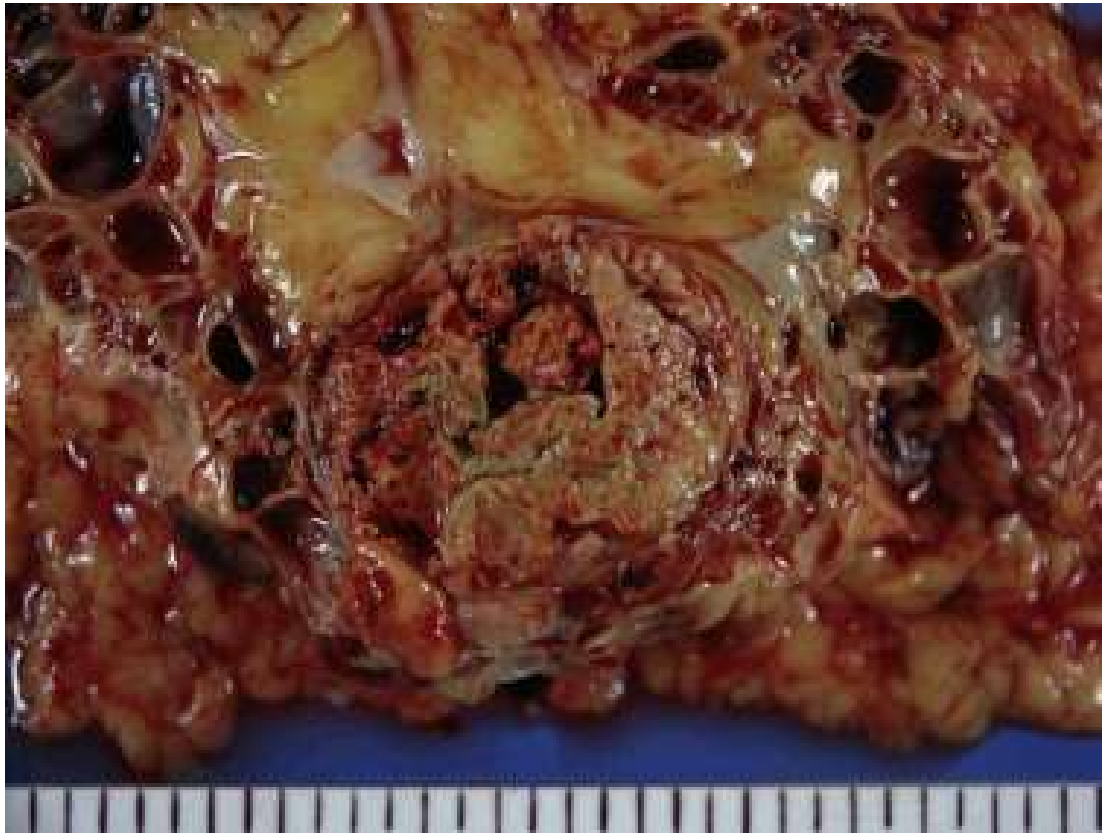

Tumor cells are pink
Oncocytic
Eosinophilic

Tumor with
"clear" cells

Tumor with
"Blue" cells

## CASE HISTORY

- 49 year old female with end stage renal disease
- Presented with a renal mass
- Partial Nephrectomy was performed



# WSI KIDNEY CASE NUMBER 6

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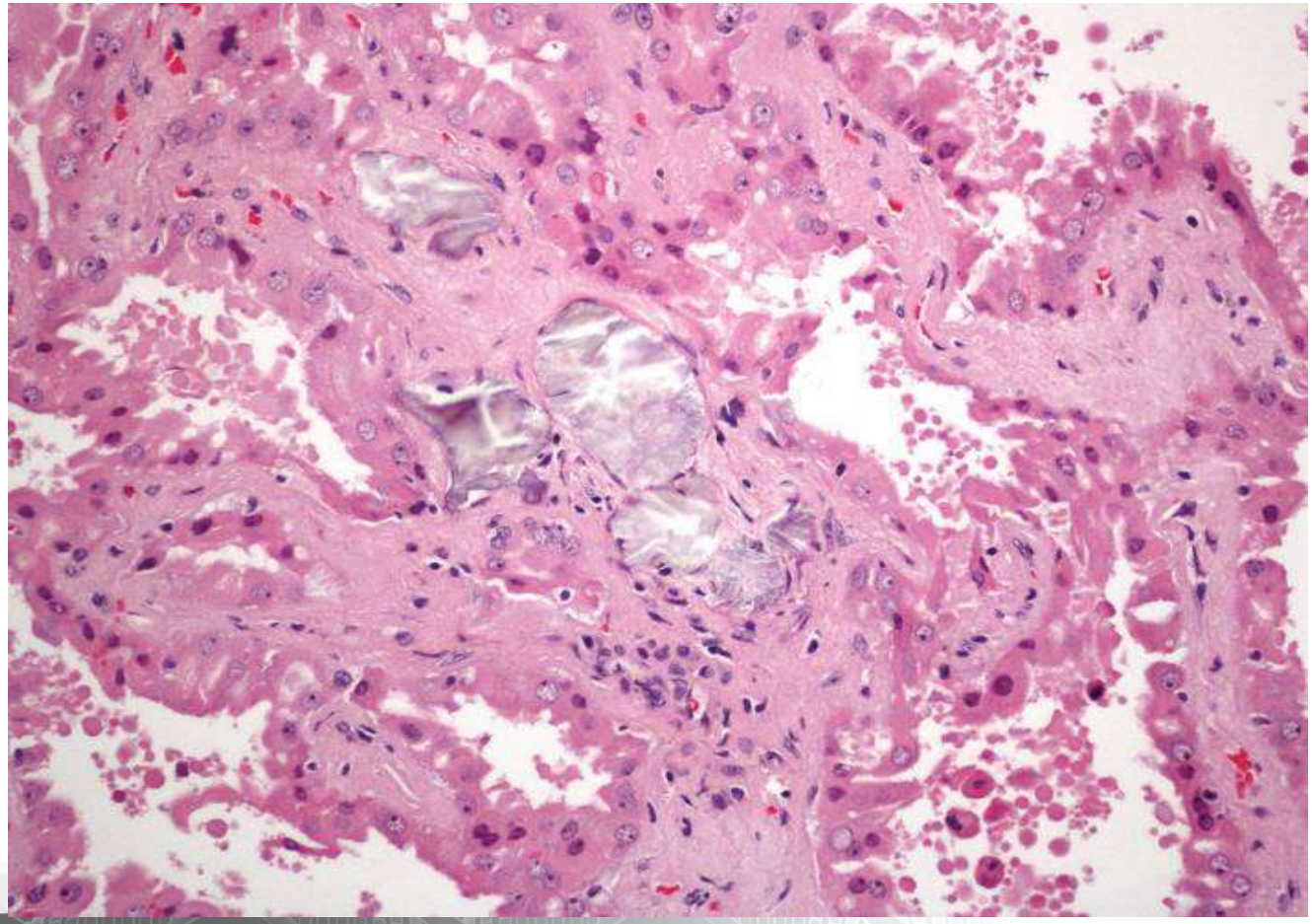
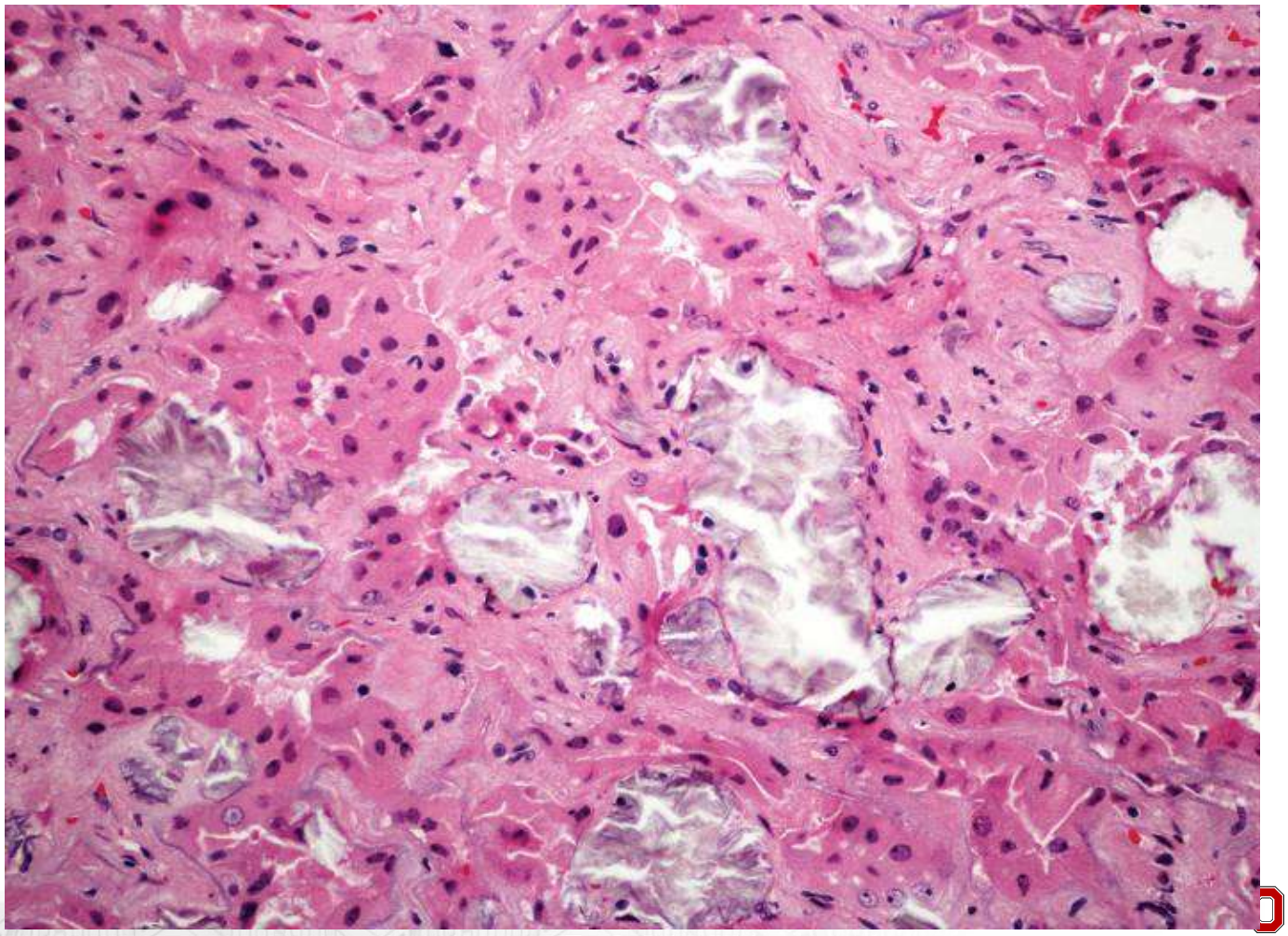
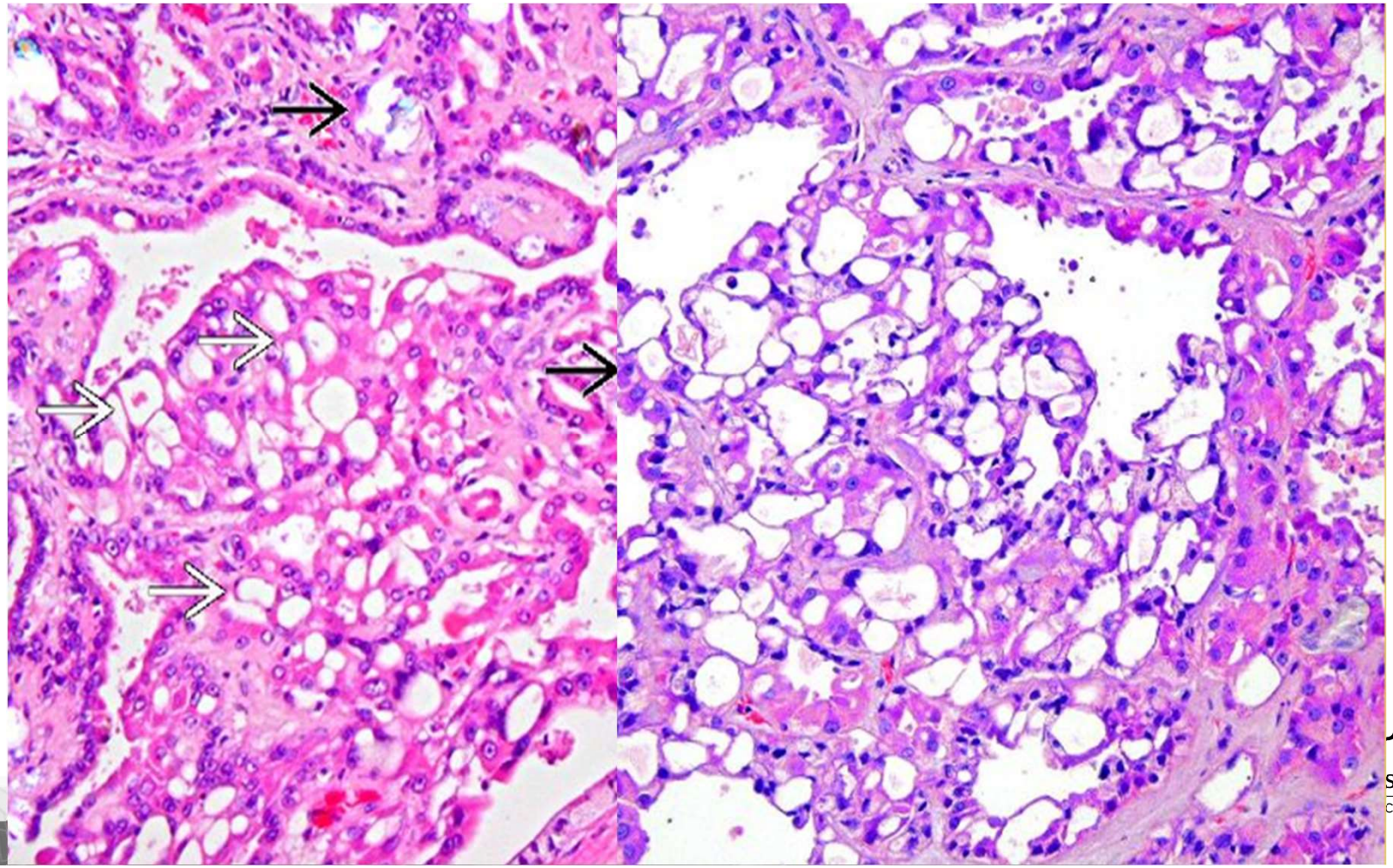
## Variable papillary architecture, abundant eosinophilic cytoplasm & prominent nucleoli



# Characteristic intratumoral oxalate crystals



# Intra/intercellular luminal “holes” imparting a cribriform appearance



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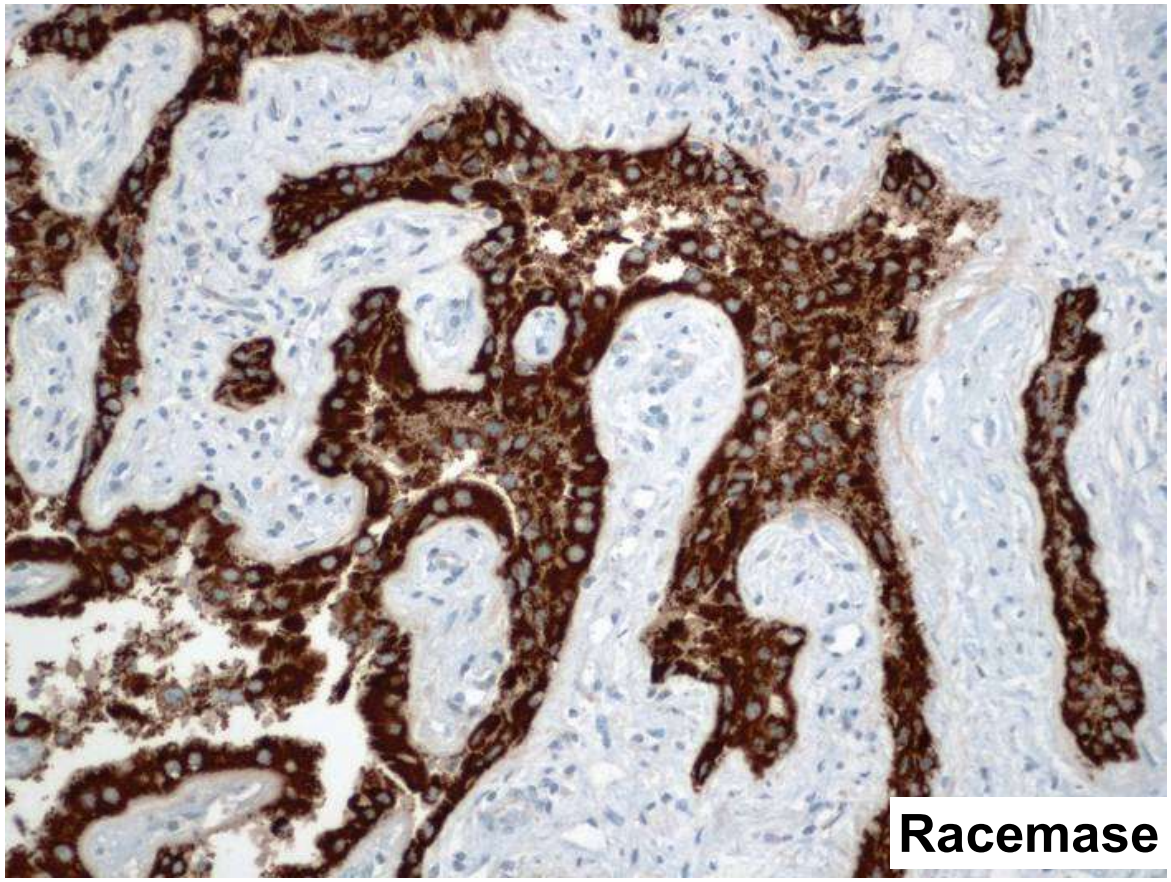
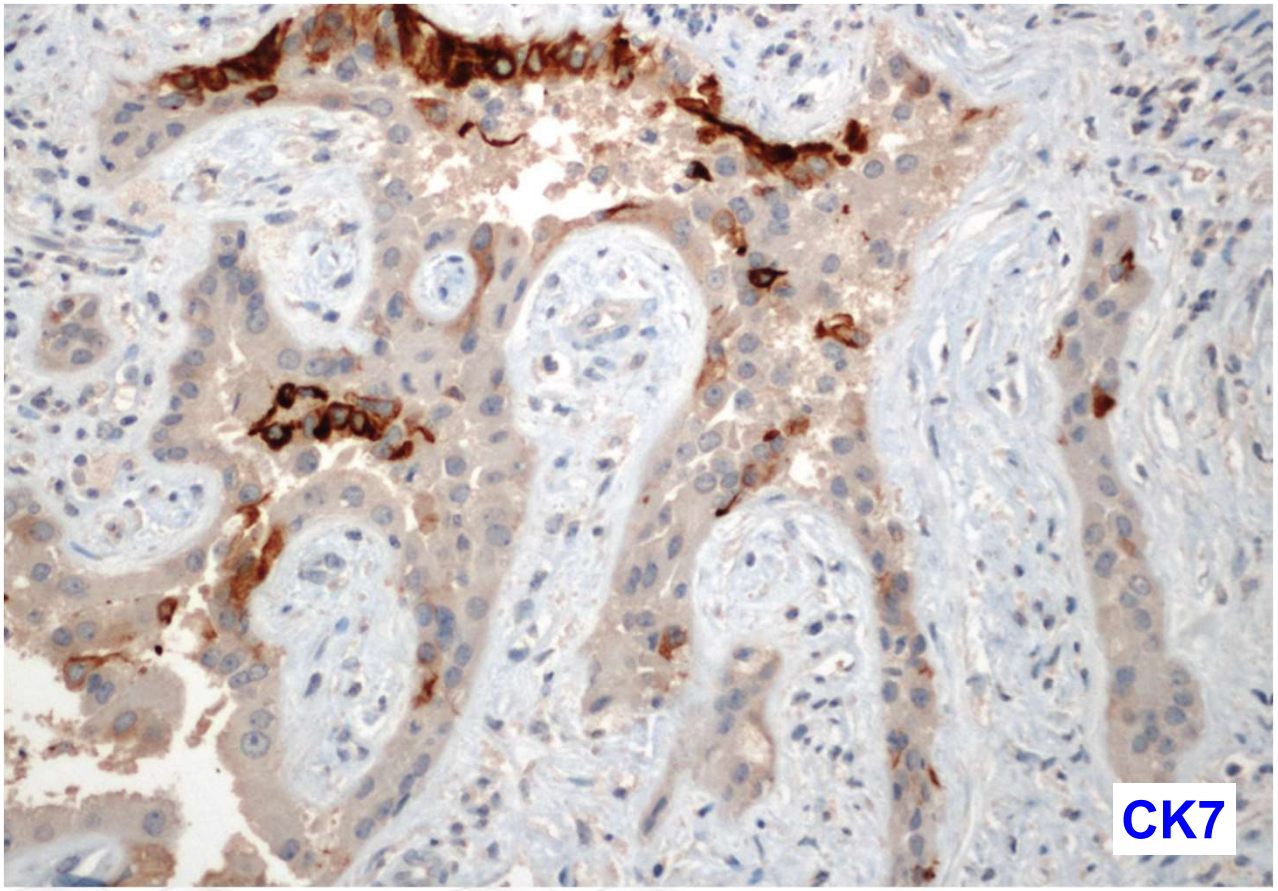
# IHC : Racemase ++, CD10 & RCC +,  CK7 – (or focal +)



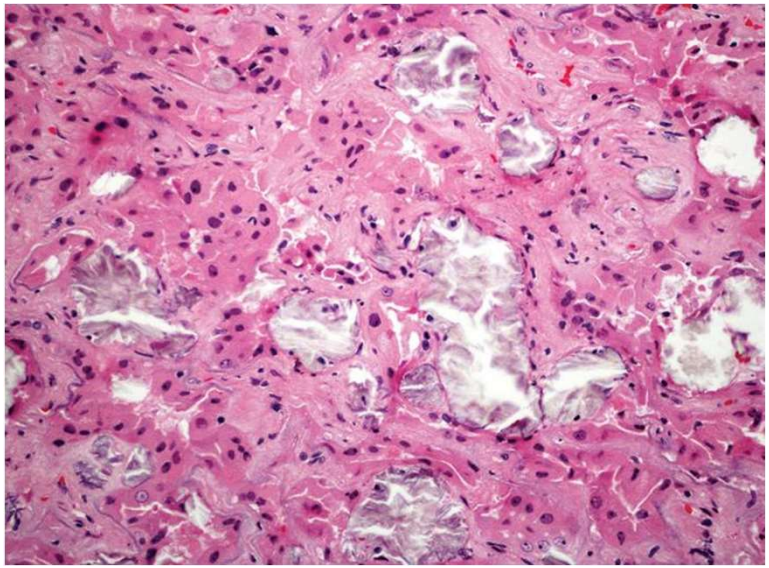
# IHC : Racemase ++, CD10 & RCC +,  CK7 – (or focal +)



## Cytogenetics:

- lack 3p losses
- gains in 1, 2, 3, 10 and 16 reported
- conflicting results with 7, 17 and Y

What is your diagnosis?



**Acquired cystic kidney disease (ACD) associated renal cell carcinoma**

# Acquired cystic kidney disease (ACD) associated renal cell carcinoma

- **Macroscopically, the disease exclusively occurs in ACD and may arise as a dominant mass or non-dominant masses.**

- **Incidental diagnosis in ACD follow-up**

- **Nonaggressive and low pT stage**

- **Exclusively in ACD patients**

# WHO CLASSIFICATION OF RENAL CELL TUMORS 2022

**Clear cell renal tumours**
- Clear cell renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential

**Papillary renal tumours**
- Renal papillary adenoma
- Papillary renal cell carcinoma

**Oncocytic and chromophobe renal tumours**
- Oncocytoma of the kidney
- Chromophobe renal cell carcinoma
- Other oncocytic tumours of the kidney

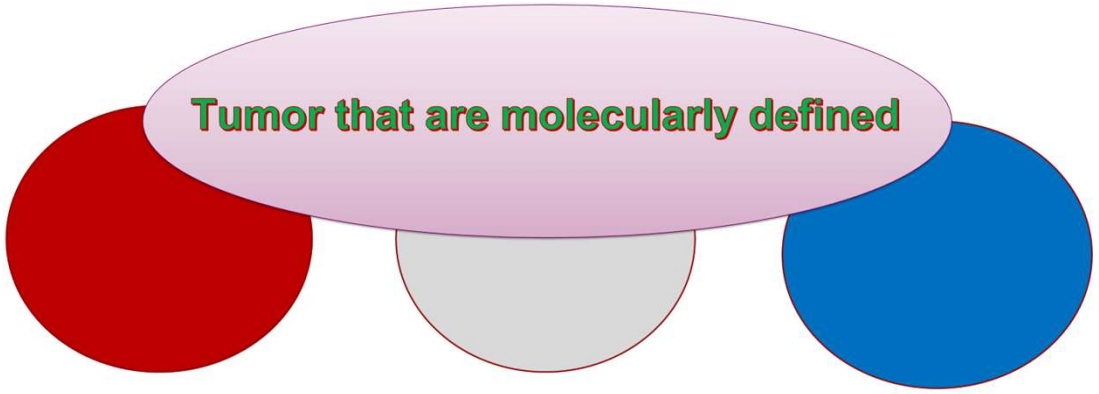
**Collecting duct tumours**
- Collecting duct carcinoma

**Metanephric tumours**
- Metanephric adenoma
- Metanephric adenofibroma
- Metanephric stromal tumour

**Other renal tumours**
- Clear cell papillary renal tumour
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic carcinoma
- Acquired cystic disease associated renal cell carcinoma
- Eosinophilic solid and cystic renal cell carcinoma
- Renal cell carcinoma NOS

**Molecularly defined renal carcinomas**
- TFE3-rearranged renal cell carcinoma
- TFEB-rearranged renal cell carcinoma
- ELOC (formerly TECEB1)-mutated renal cell carcinoma
- Fumarate hydratase-deficient renal cell carcinoma
- Succinate dehydrogenase-deficient renal cell carcinoma
- Alk-rearranged renal cell carcinoma
- SMARCB1-deficient renal medullary carcinoma

# INTERESTING CASE #6




Tumor cells are pink
Oncocytic
Eosinophilic

Tumor with
"clear" cells

Tumor with
"Blue" cells

# WSI KIDNEY CASE NUMBER 7

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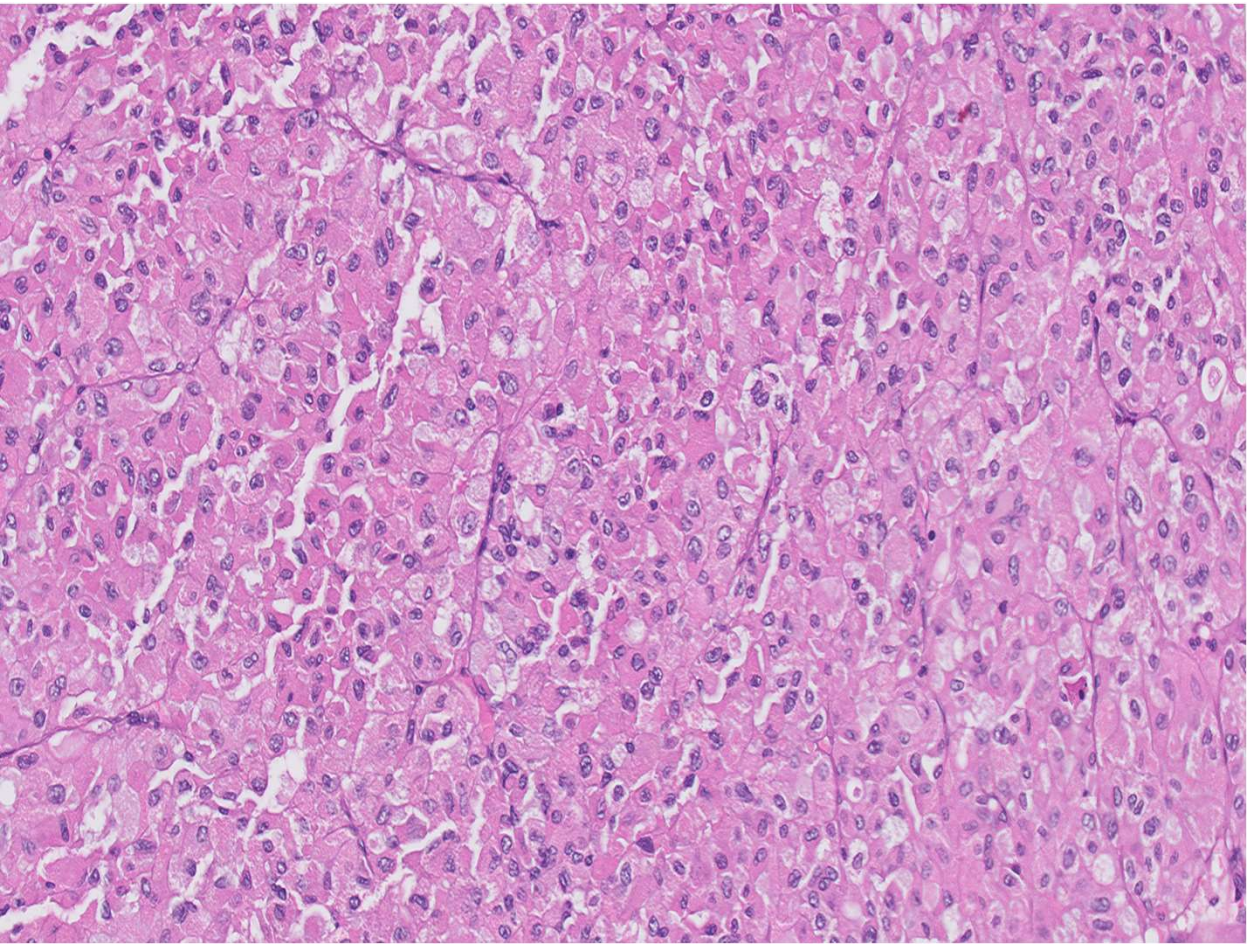
# Case History

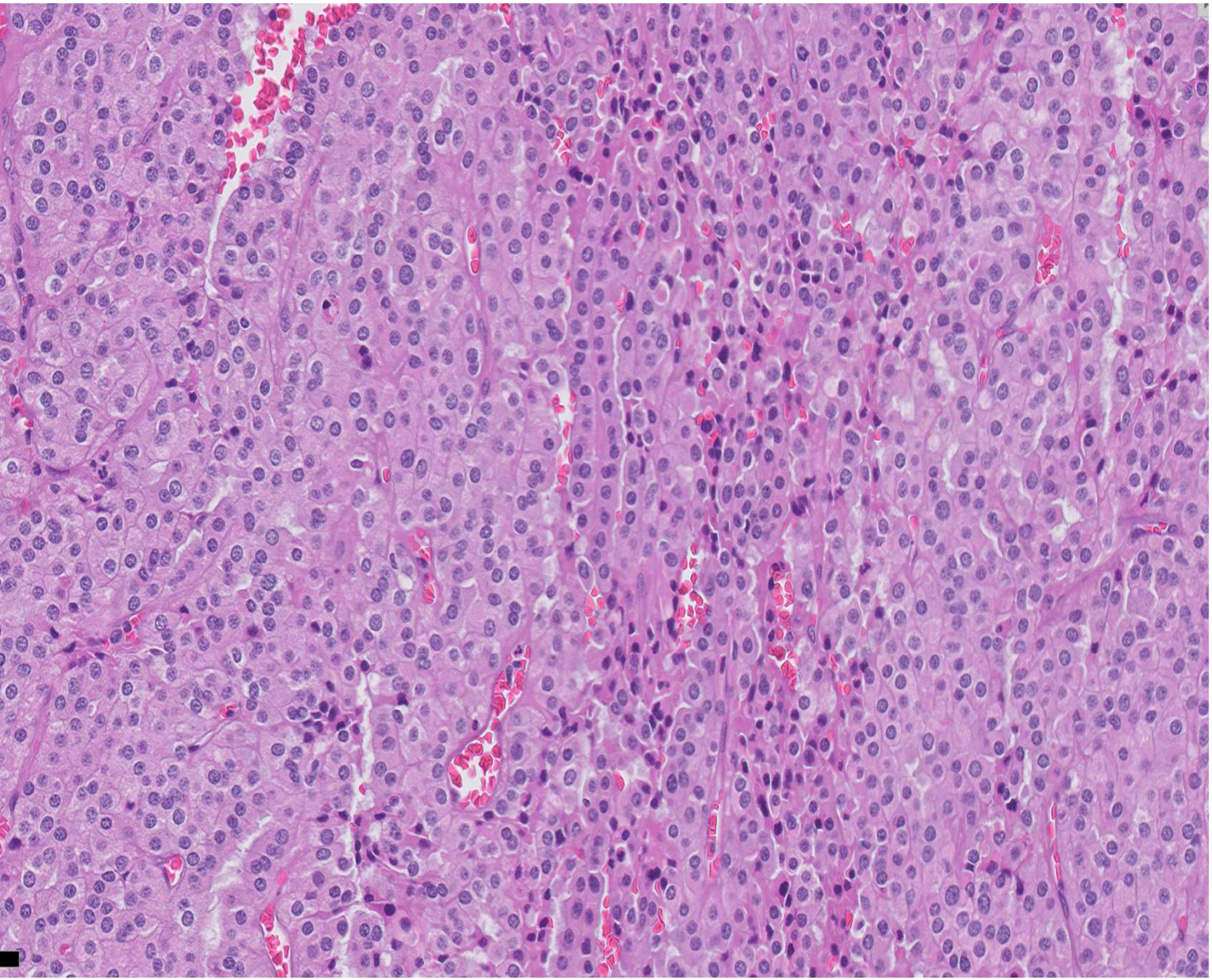
- 31 y.o. year old male with a history of multifocal retroperitoneal

- Ct abdomen and pelvis with and without contrast showed a 2.5 cm x 3.1 cm heterogeneous enhancing mass in the posterior mid pole of the right kidney

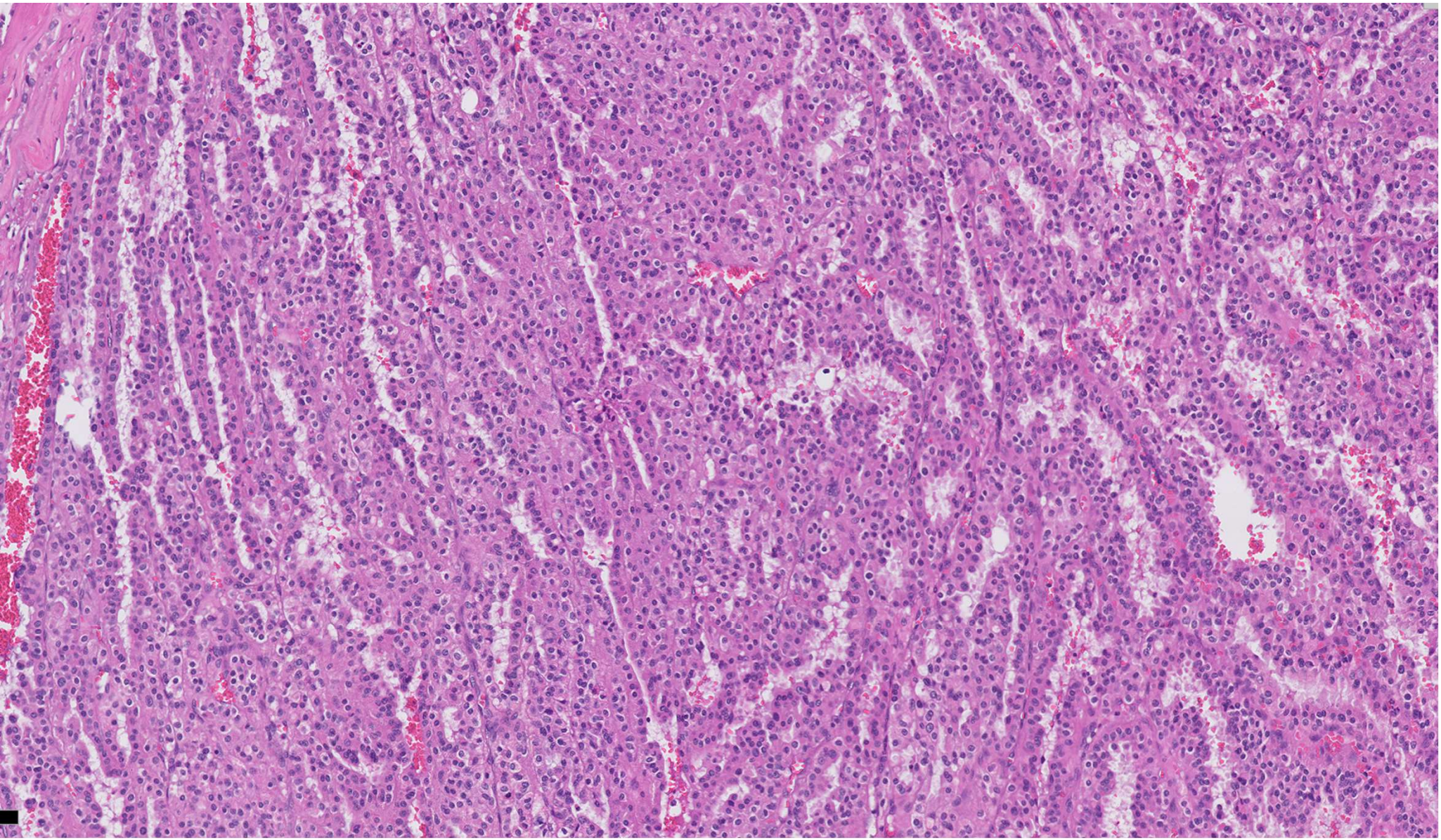
- Status post robotic assisted radical nephrectomy

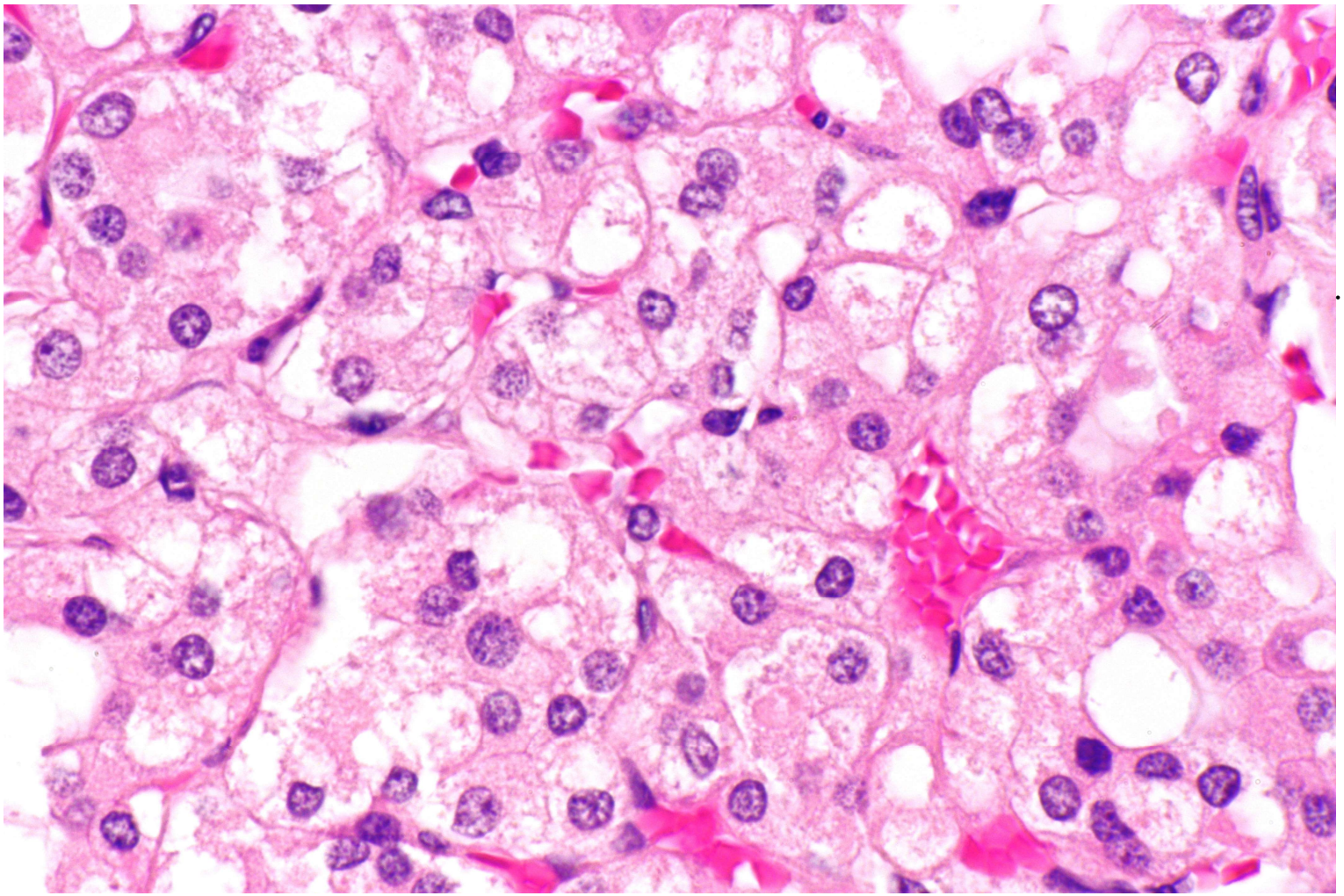


- Tumors are usually well circumscribed and take on a tubular or nested cellular growth pattern
- Tumor cells are cuboidal to oval in shape, contain smooth nuclei, diffuse chromatin, and lack a nucleoli



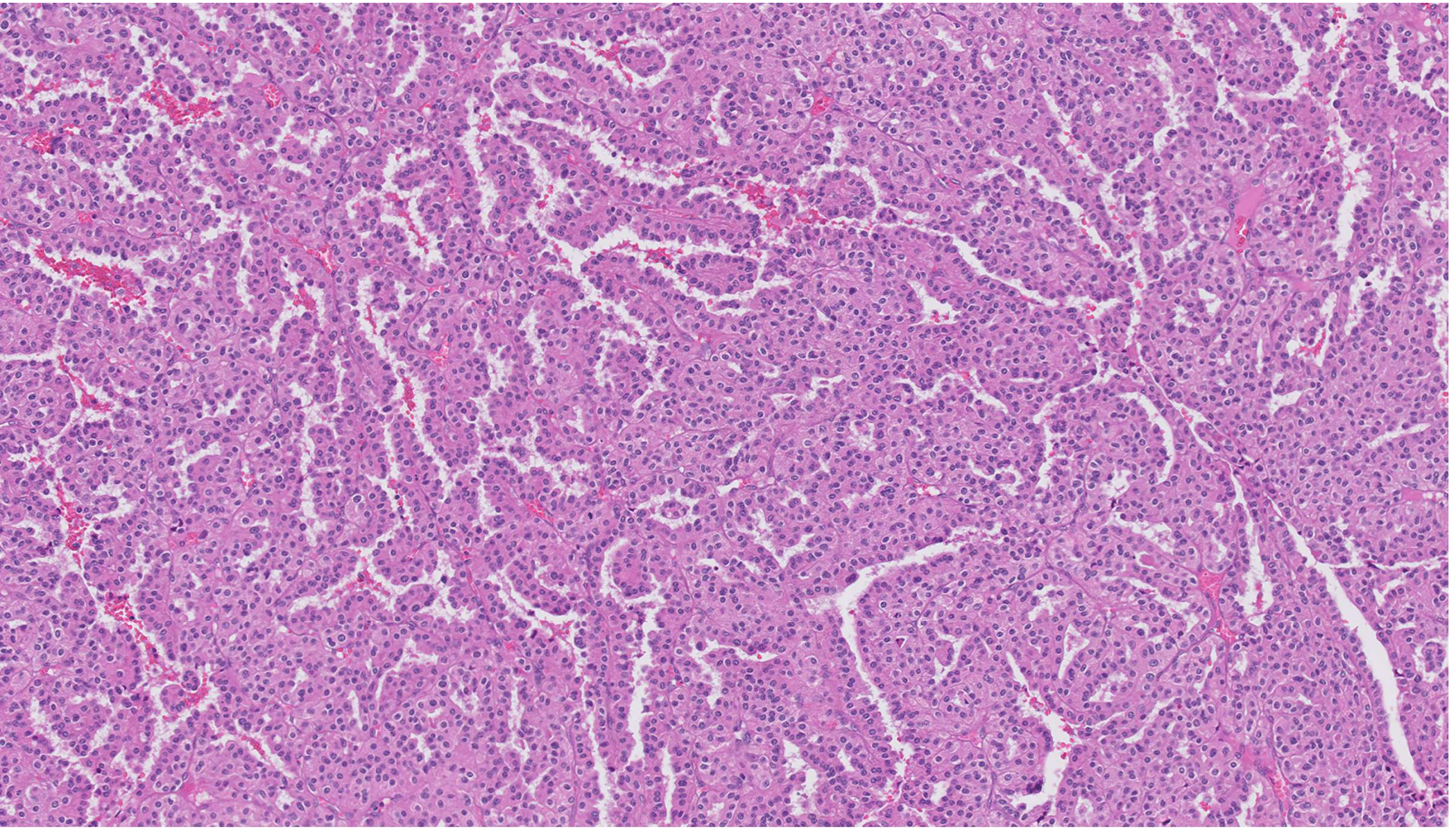
- Mast cells are seen intratumorally
- There is a presence of pale eosinophilic cytoplasm with enlarged mitochondria

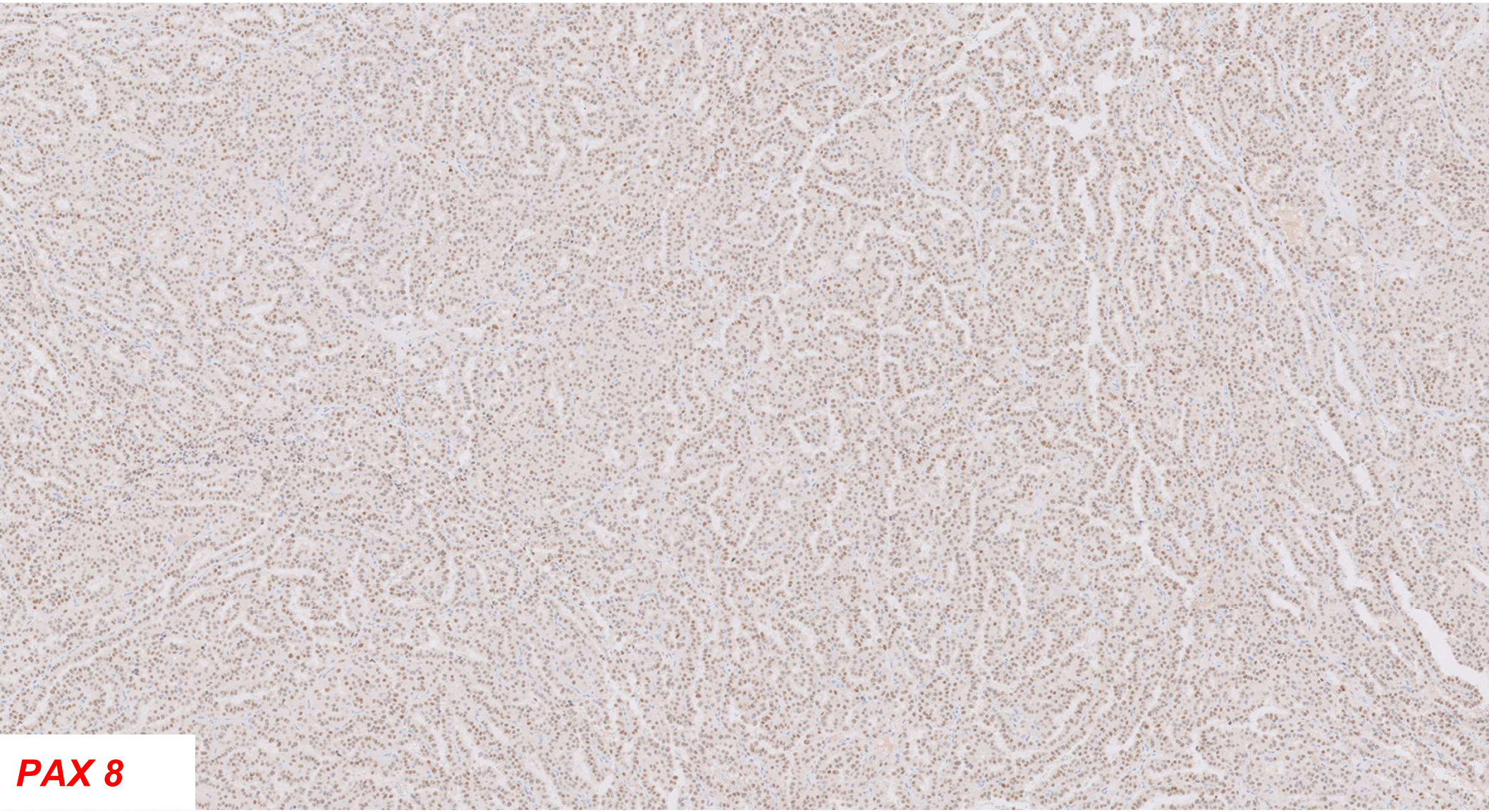


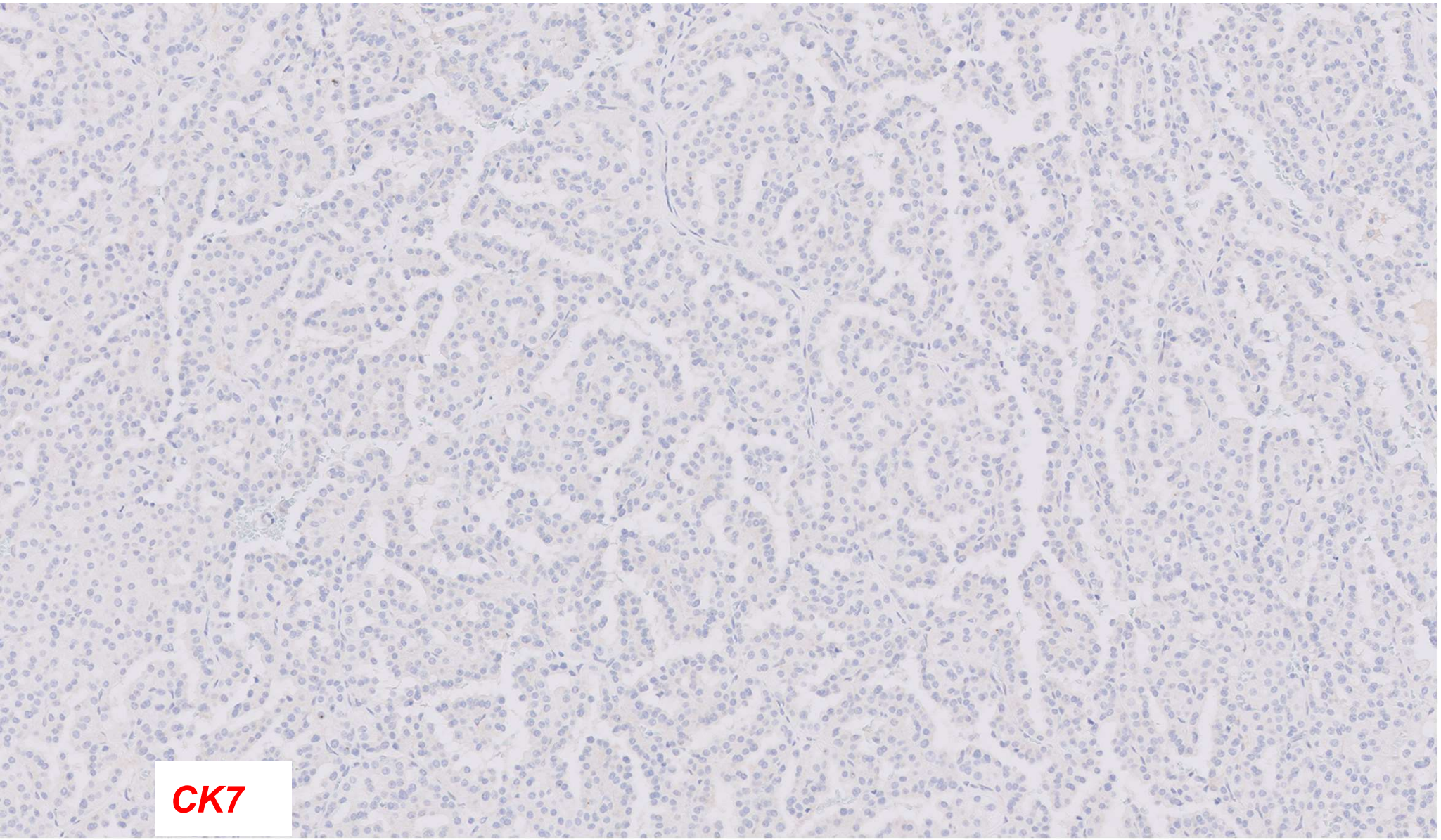


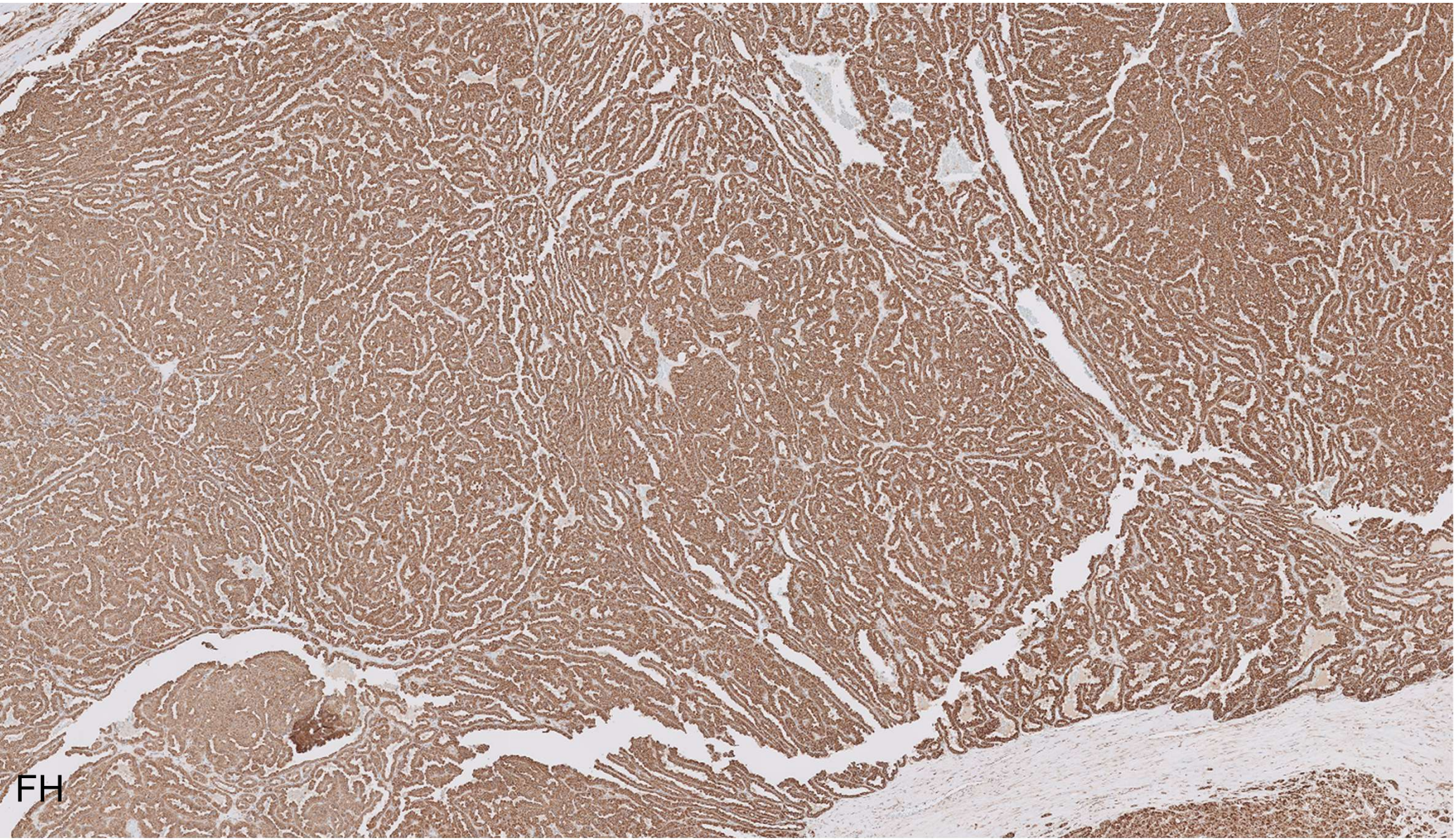
**Characterized by flocculant cytoplasmic inclusions / vacuoles**

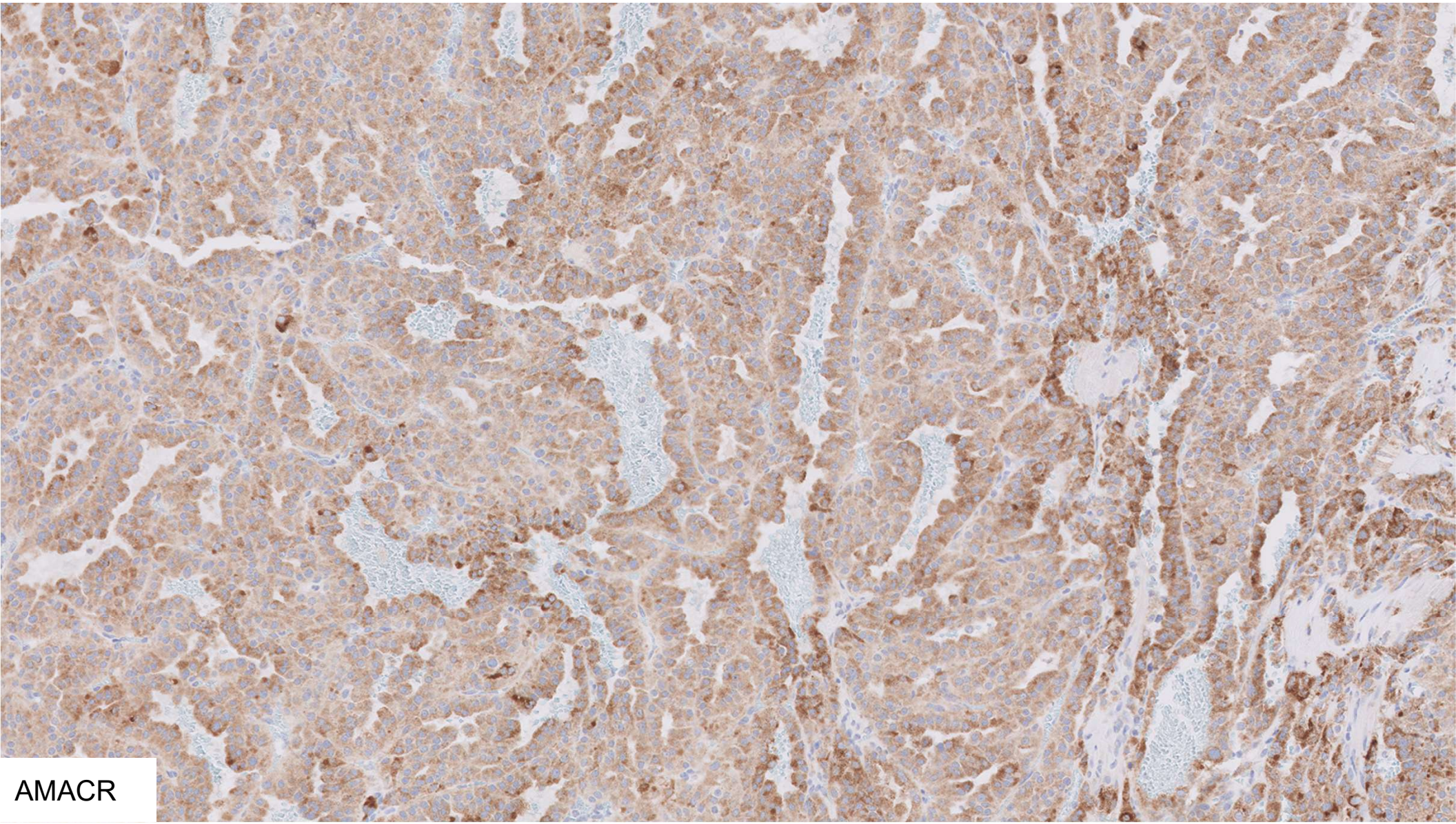
https://commons.wikimedia.org/wiki/File:SDH-deficient_renal_cell_carcinoma_-_very_high_mag.jpg

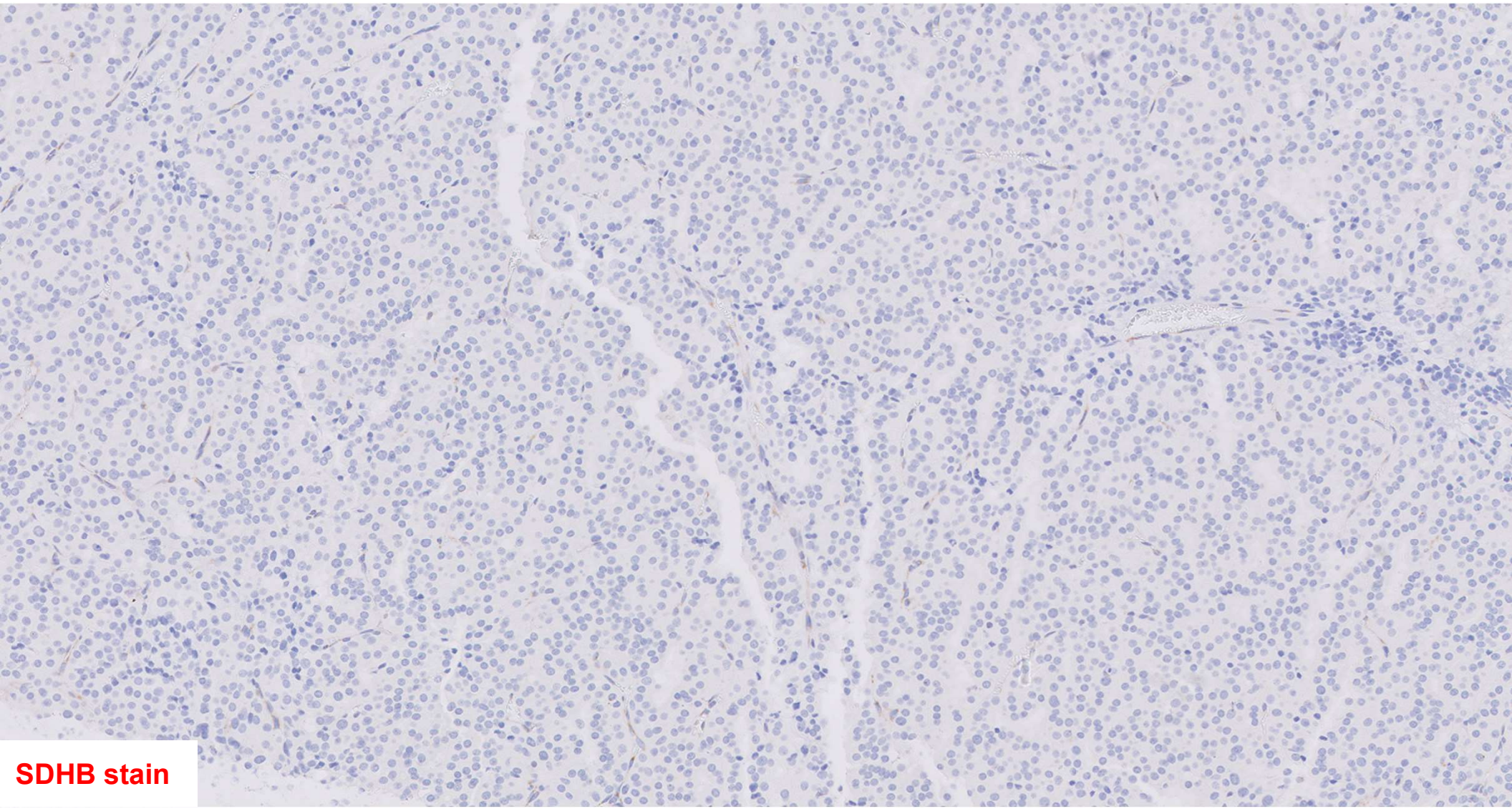



PAX 8


CK7


FH


AMACR


SDHB stain

# What is the most likely diagnosis?

A. Oncocytoma

B. Chromophobe renal cell carcinoma

C. Renal cell carcinoma – succinate dehydrogenase deficient

D. Clear cell renal carcinoma – eosinophilic variant

E. Hereditary leiomyomatosis

F. Papillary Renal cell carcinoma

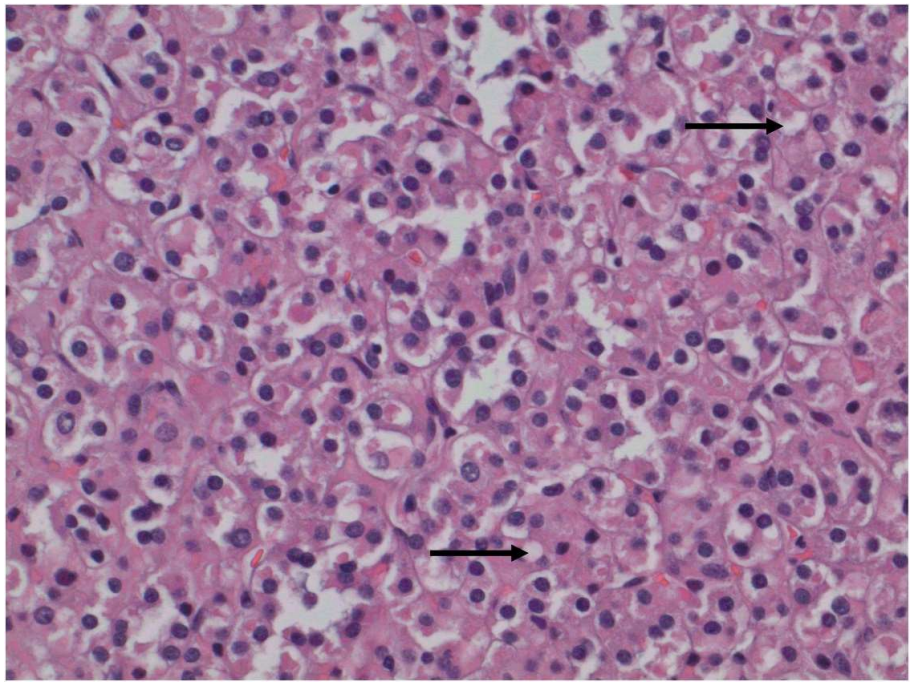
**Renal cell carcinoma – succinate dehydrogenase deficient**

## Renal cell carcinoma – succinate dehydrogenase deficient

- IHC: Positive for PAX8, AMACR, CD10 (focal); negative for SDHB, CAIX, CK7, CD117; FH - no loss

# Renal cell carcinoma – succinate dehydrogenase deficient

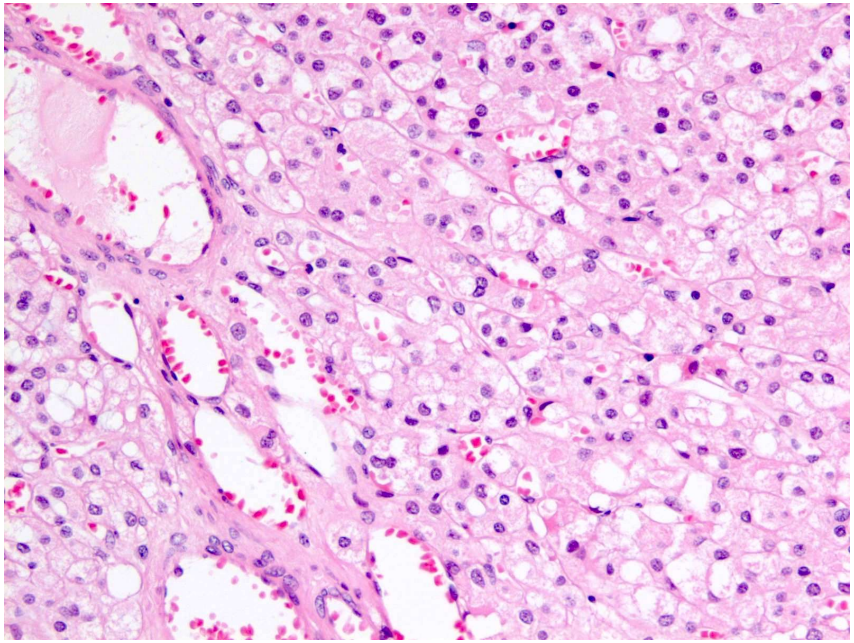
- The most common germline mutations seen in SDH deficient renal cell carcinoma RCC) are SDHB and SDHC mutations respectively
- SDH deficient RCC is a rare subtype representing 0.05% – 0.2% of all of RCC
- There is a prevalence of 1.75:1 ratio of men to women
- The mean age of SDH deficient RCC is ~38-40 years old
- 26% of cases present bilaterally



https://www.sciencedirect.com/science/article/pii/S2214442021003259

## Renal cell carcinoma – succinate dehydrogenase deficient

- Recognition of this subtype can be done primarily on morphology and confirmed with IHC
- Metastasis is seen in ~⅓ of cases.
- If diagnosed, patients and immediate relatives should be screened for SDH deficient tumors (e.g RCC, paragangliomas, pheochromocytomas, gastrointestinal stromal tumors)

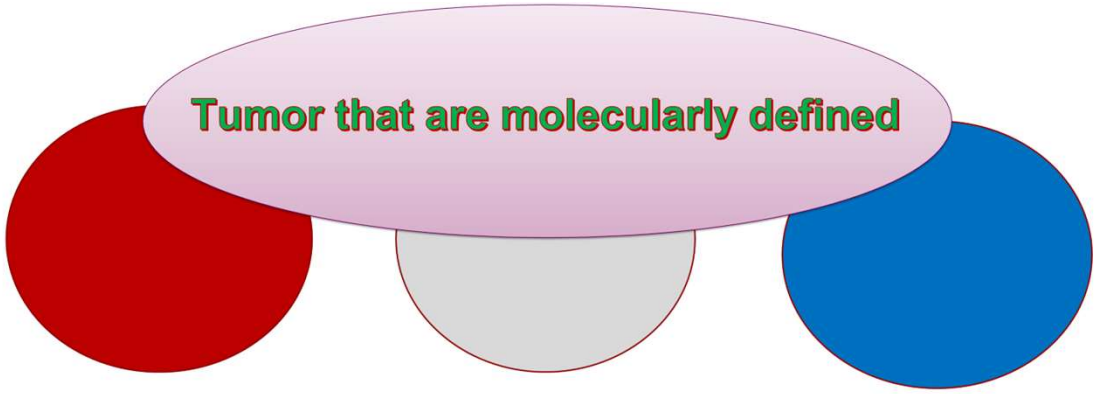


# MOLECULARLY DEFINED RCCs: WHO 2022

## *Novel molecularly defined epithelial renal tumors*

- TFE3-rearranged renal cell carcinomas
- TFEB-altered renal cell carcinomas
- ELOC (formerly TCEB1)-mutated renal cell carcinoma
- Fumarate hydratase-deficient renal cell carcinoma
- Succinate dehydrogenase-deficient renal cell carcinoma
- ALK-rearranged renal cell carcinomas
- SMARCB1-deficient renal medullary carcinoma

# INTERESTING CASE #7

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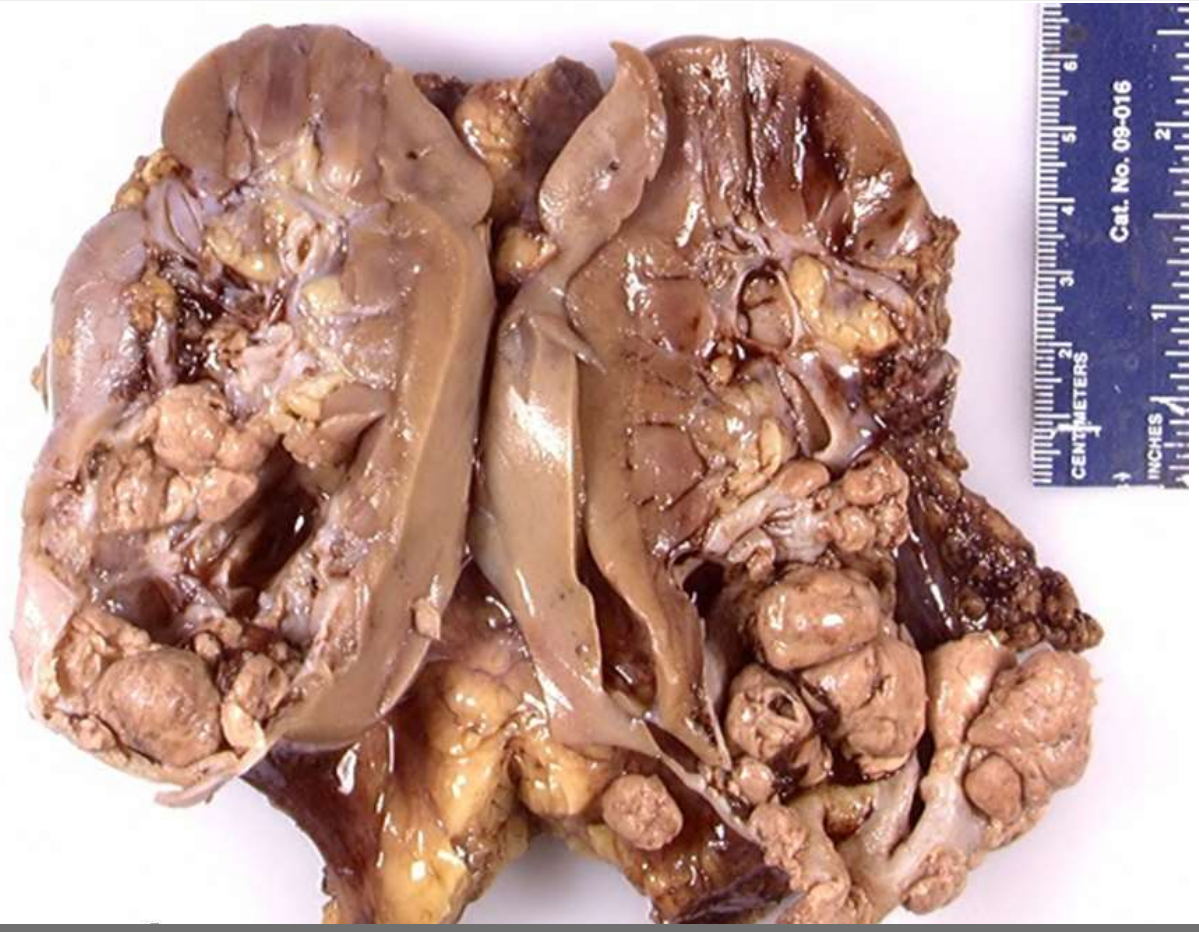


# 26 year old 14 week pregnant female with a 5.5 cm renal mass

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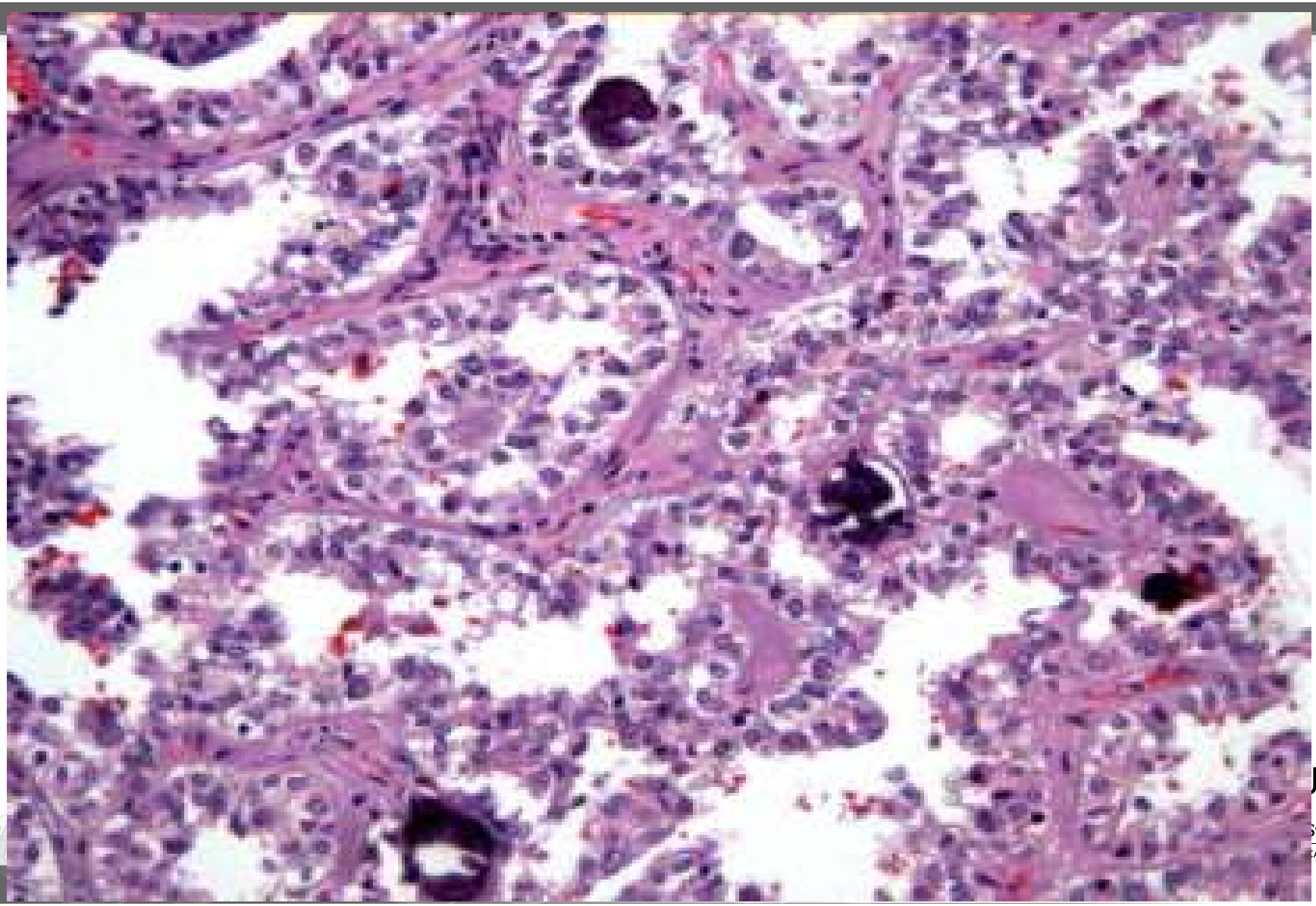

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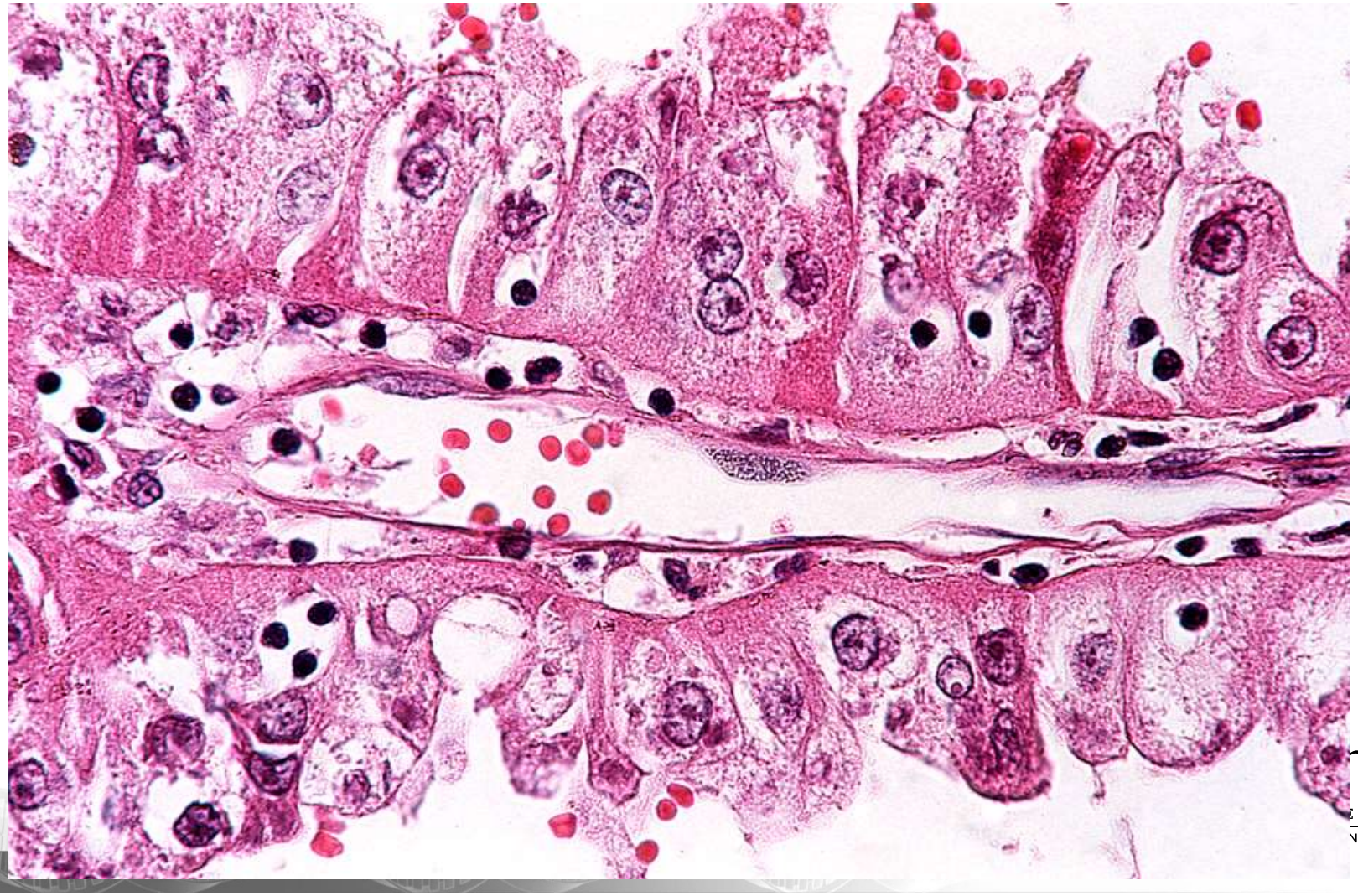
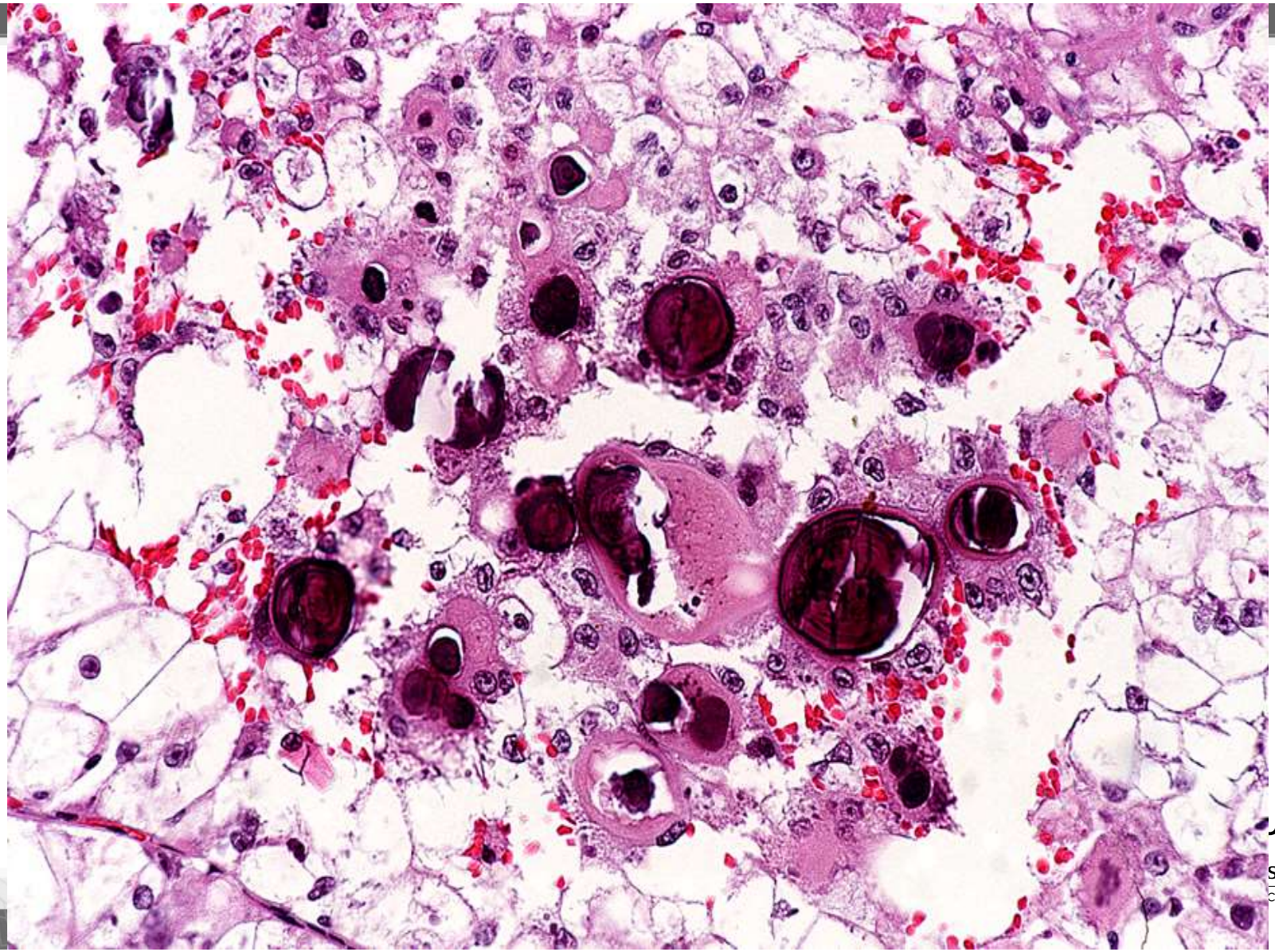
# RCC with Xp11.2





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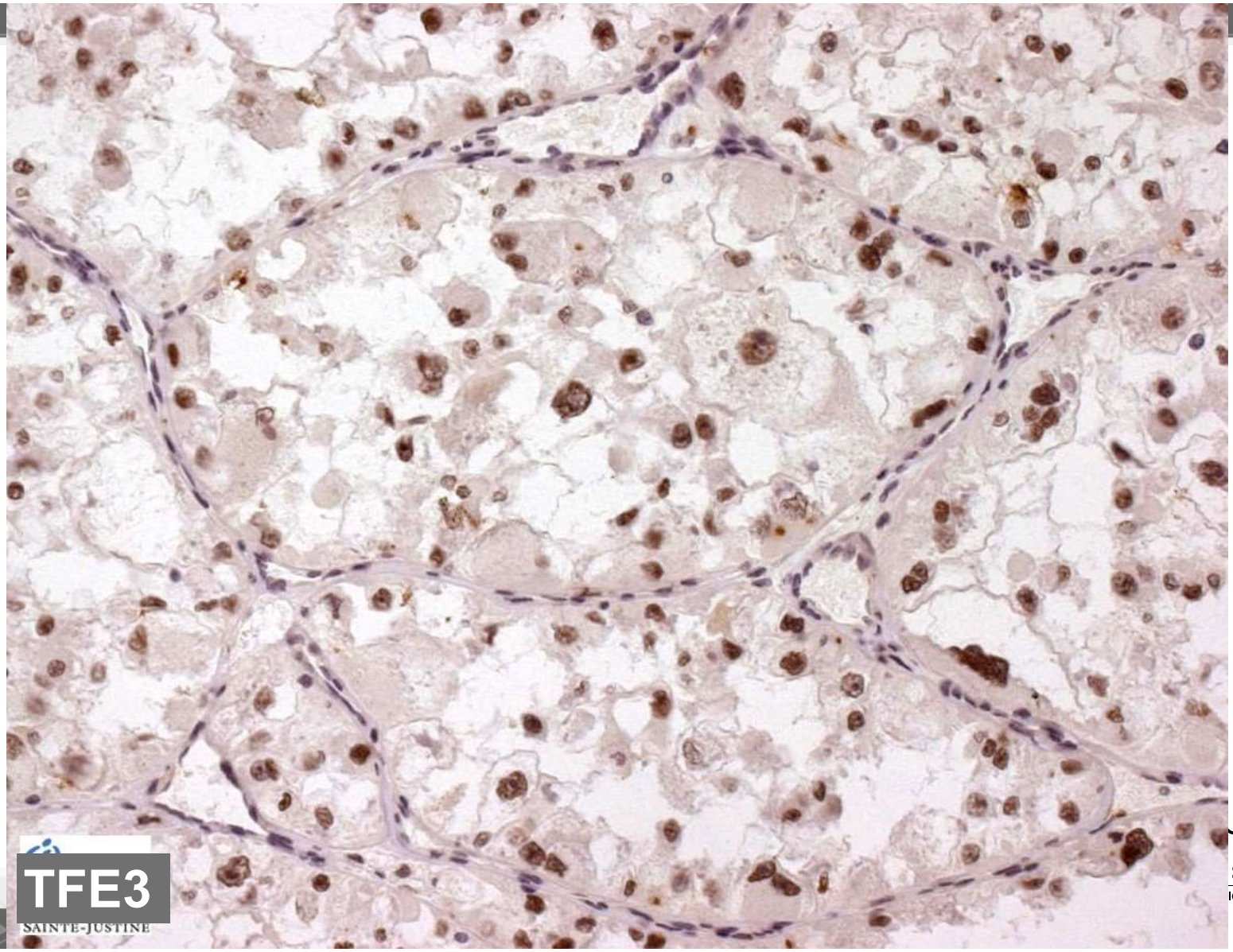


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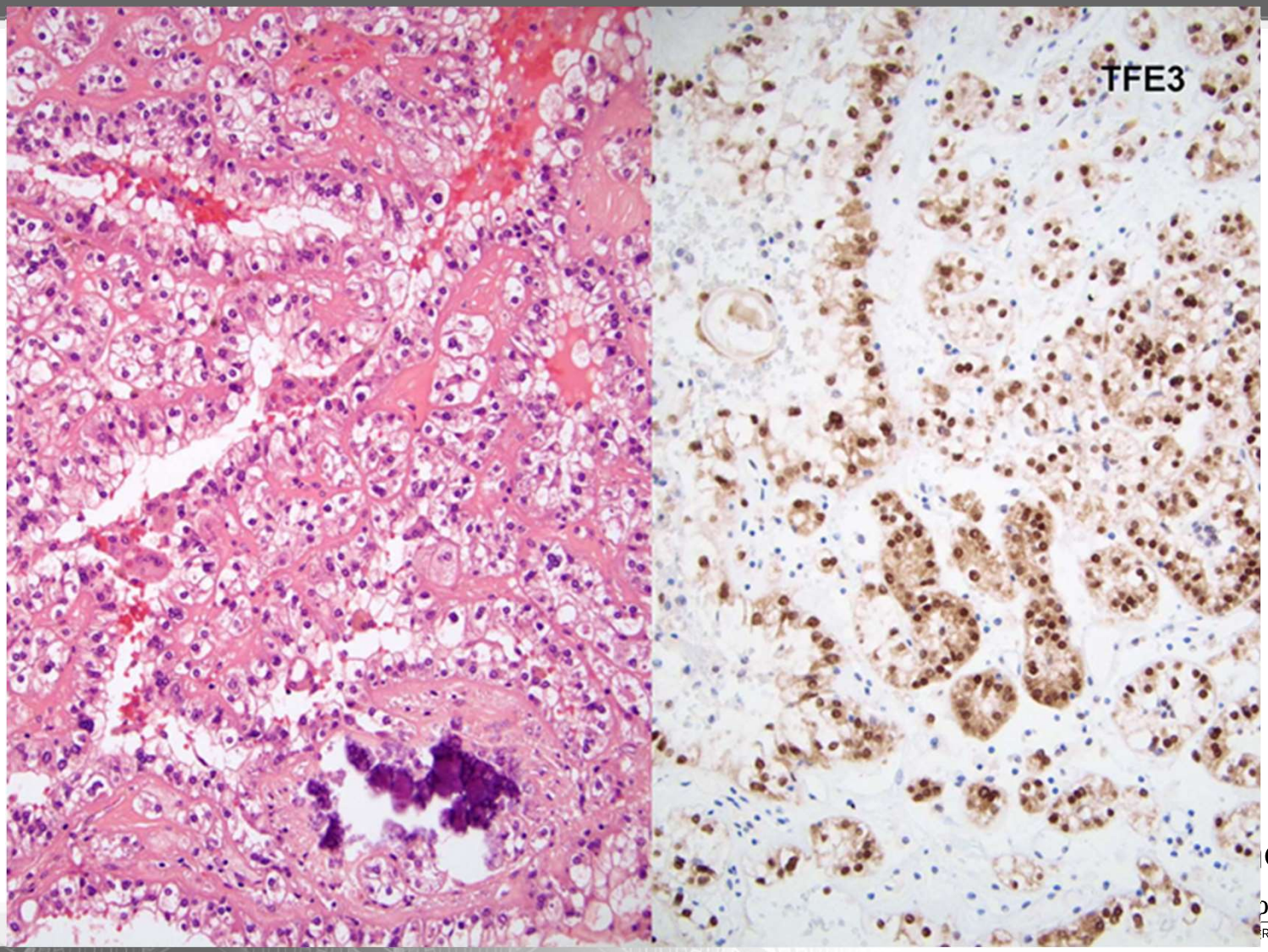


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R MEDICAL CENTER

# WHAT IS YOUR DIAGNOSIS?

## *TFE3*-rearranged RCC (formerly named MiTF family Xp11 translocation RCC)

# Xp11 Translocation Carcinoma-Clues

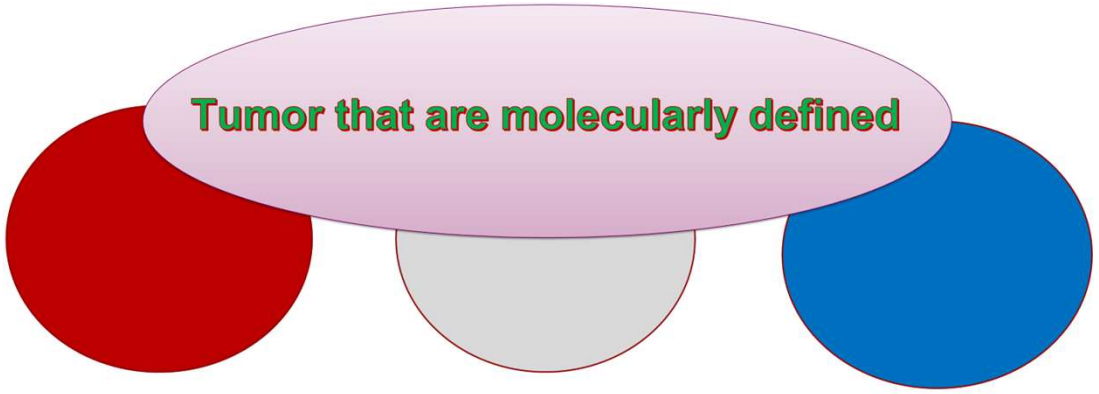
- Young patient
- Papillary architecture with clear cytoplasm
- Psammoma bodies
- Minimal immunoreactivity for Cytokeratin, EMA, Vimentin

# MOLECULARLY DEFINED RCCs: WHO 2022

## *Novel molecularly defined epithelial renal tumors*

- TFE3-rearranged renal cell carcinomas
- TFEB-altered renal cell carcinomas
- ELOC (formerly TCEB1)-mutated renal cell carcinoma
- Fumarate hydratase-deficient renal cell carcinoma
- Succinate dehydrogenase-deficient renal cell carcinoma
- ALK-rearranged renal cell carcinomas
- SMARCB1-deficient renal medullary carcinoma

# INTERESTING CASE #8




Tumor cells are pink
Oncocytic
Eosinophilic

Tumor with
"clear" cells

Tumor with
"Blue" cells

# Case History

- A female in her early 40's with history of ESRD due to diabetic nephropathy presents with an exophytic solid mass in the lower pole of the left kidney.

- The CT scan showed a mass measuring approximately 4.3 x 4.3 x 4.9 cm.

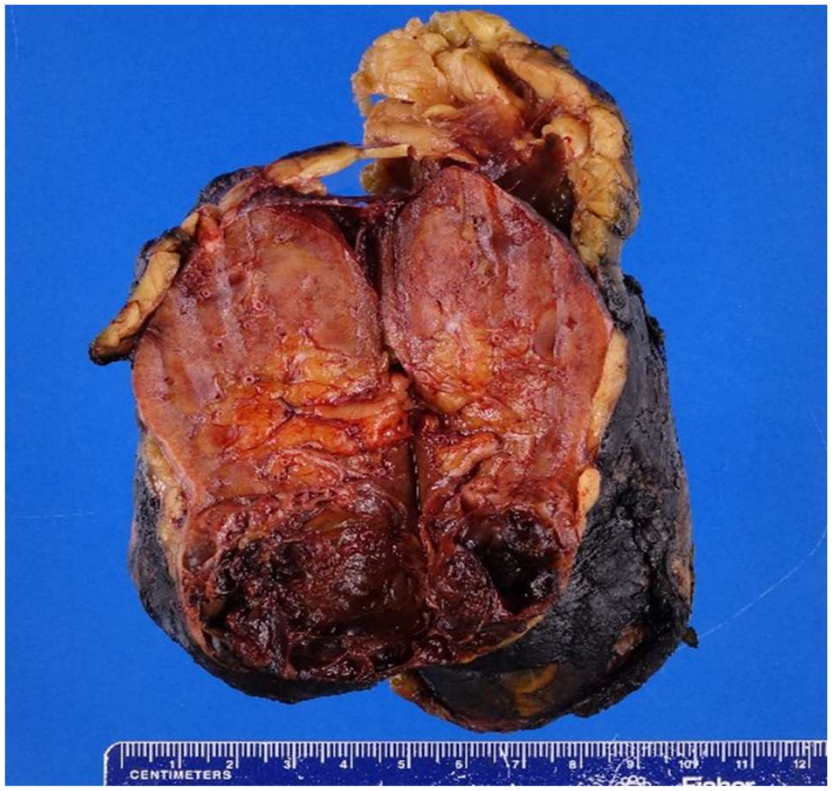
- An image guided biopsy was performed, allowing consensus for a radical nephrectomy.

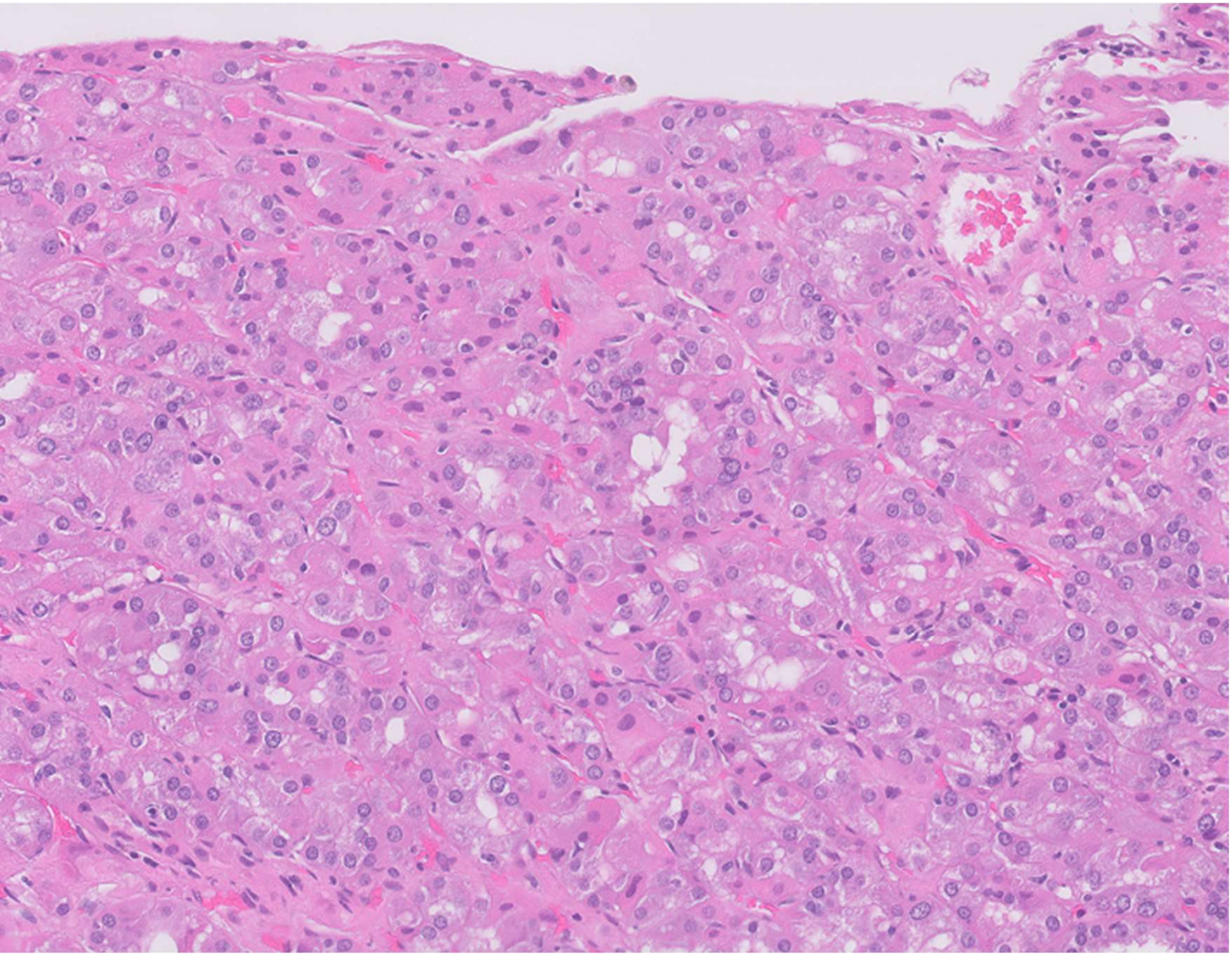
# Gross Examination

Located in the lower pole is a well-circumscribed, partially hemorrhagic, multicystic mass with no discernible solid component that measures 4.5 x 4.2 x 3.5 cm.

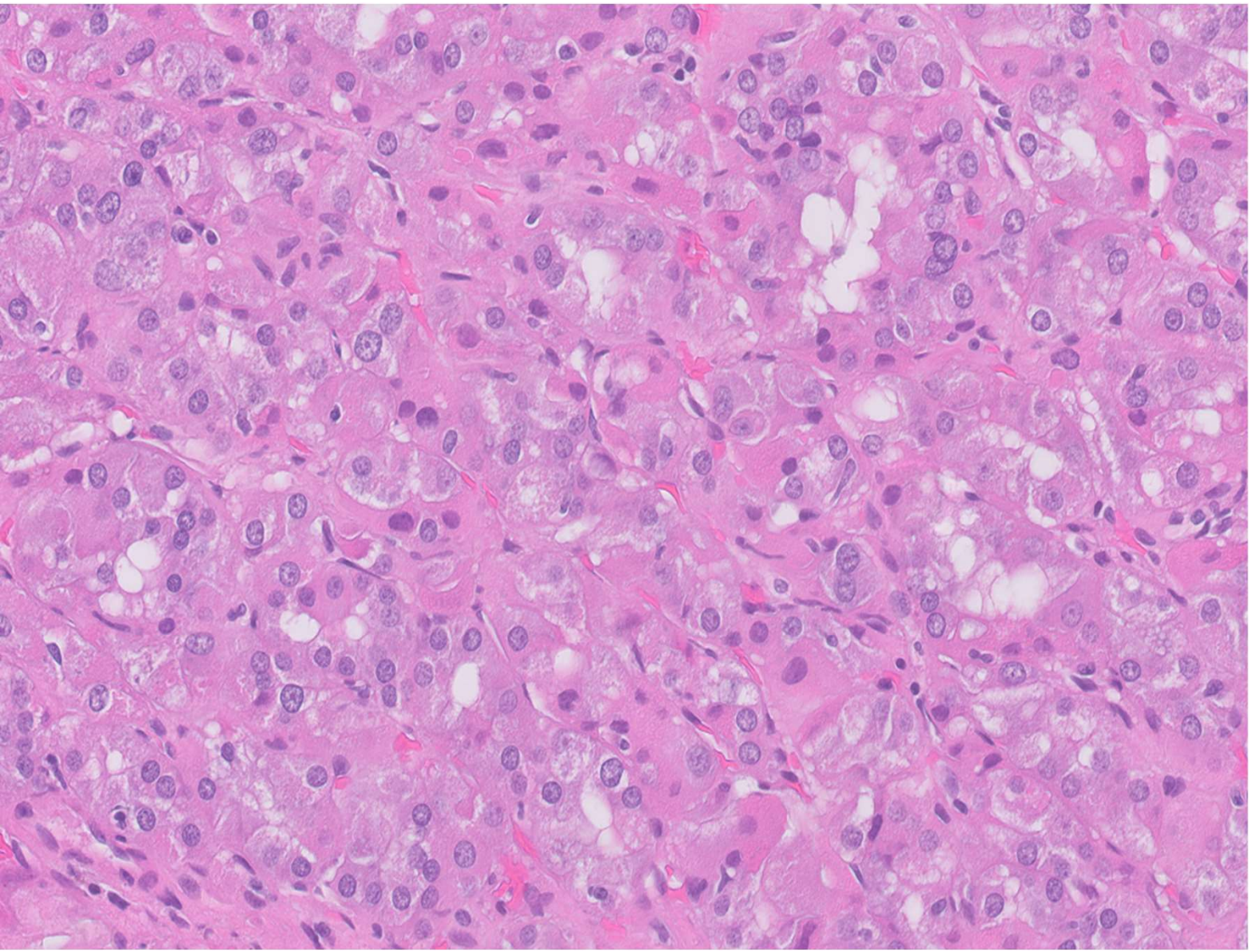
The cysts contains clear or bloody fluid.

The tumor abuts the renal sinus fat, pelvicalyceal system, and inked outer surface but does not involve them.



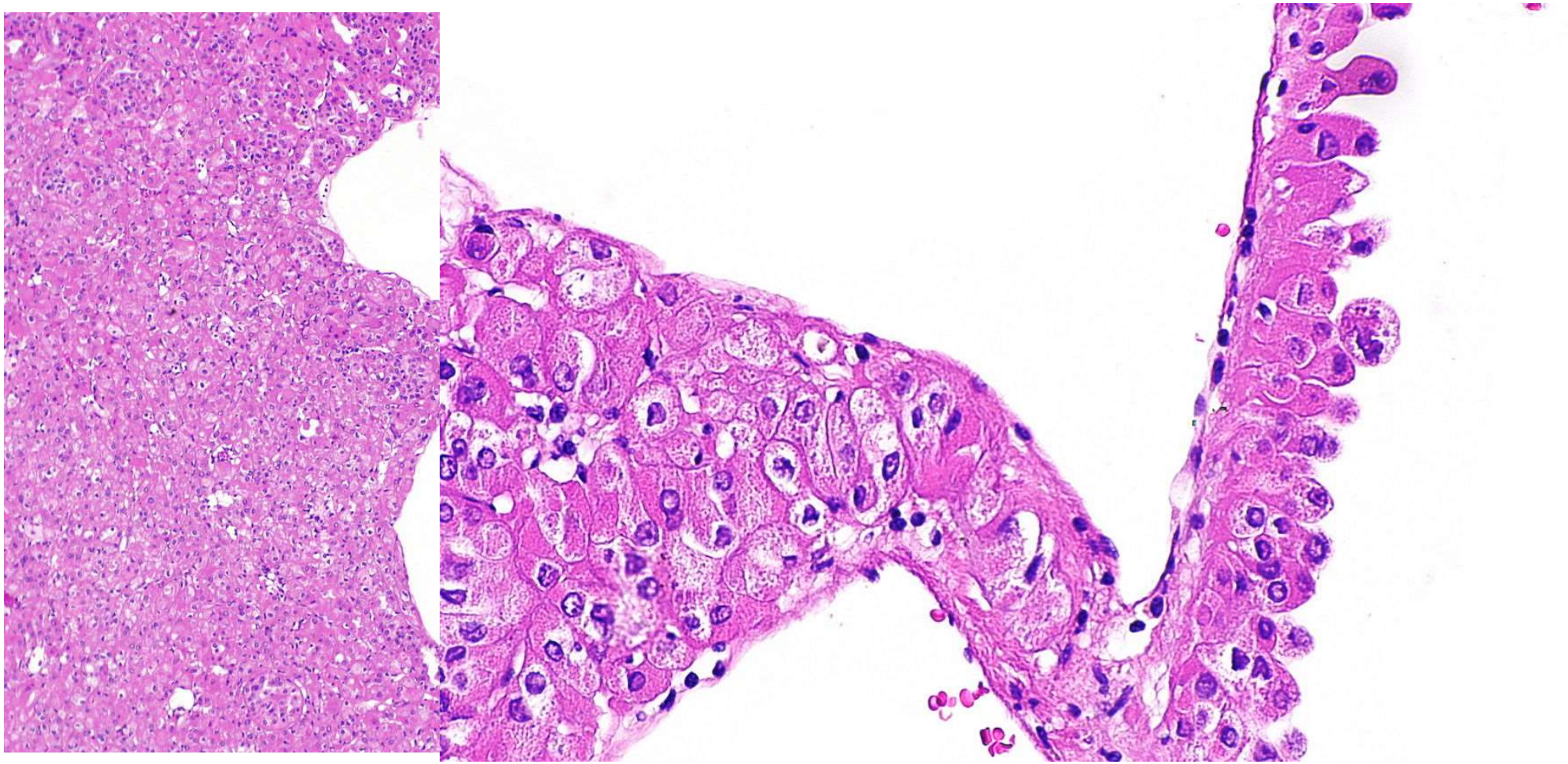


Granular eosinophilic cytoplasm
- No distinct cell borders

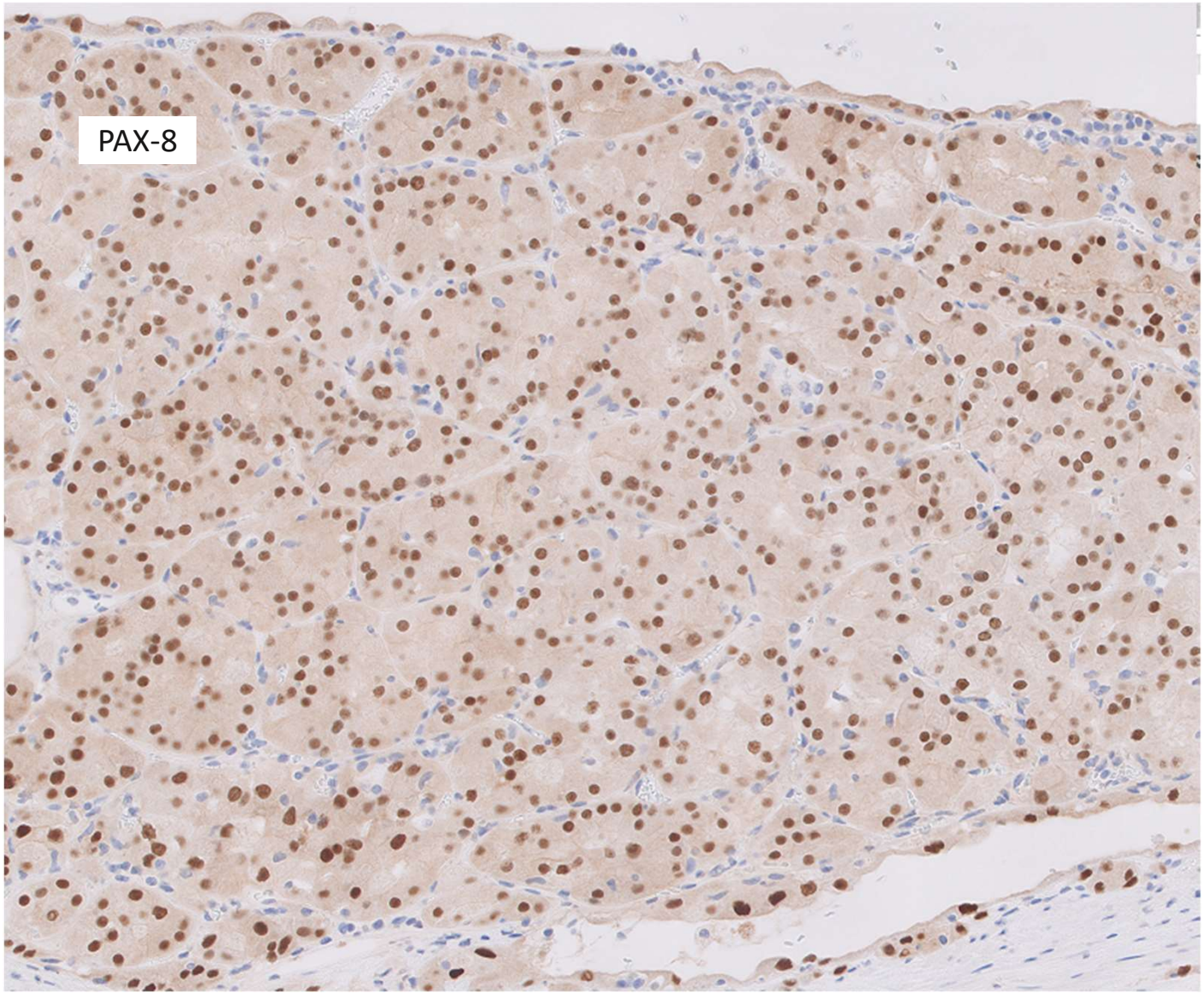


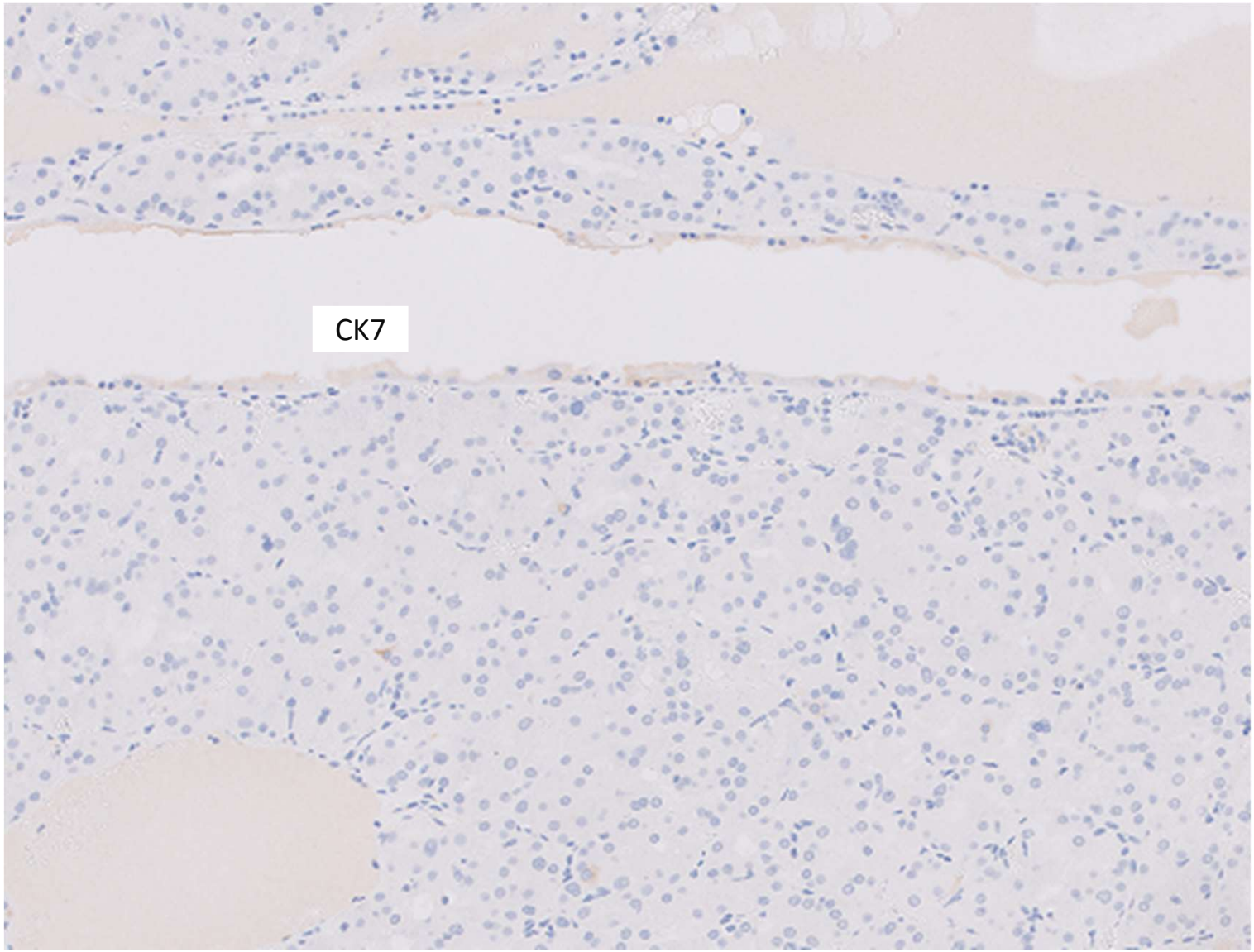
Finely granular intracytoplasmic stippling/inclusions

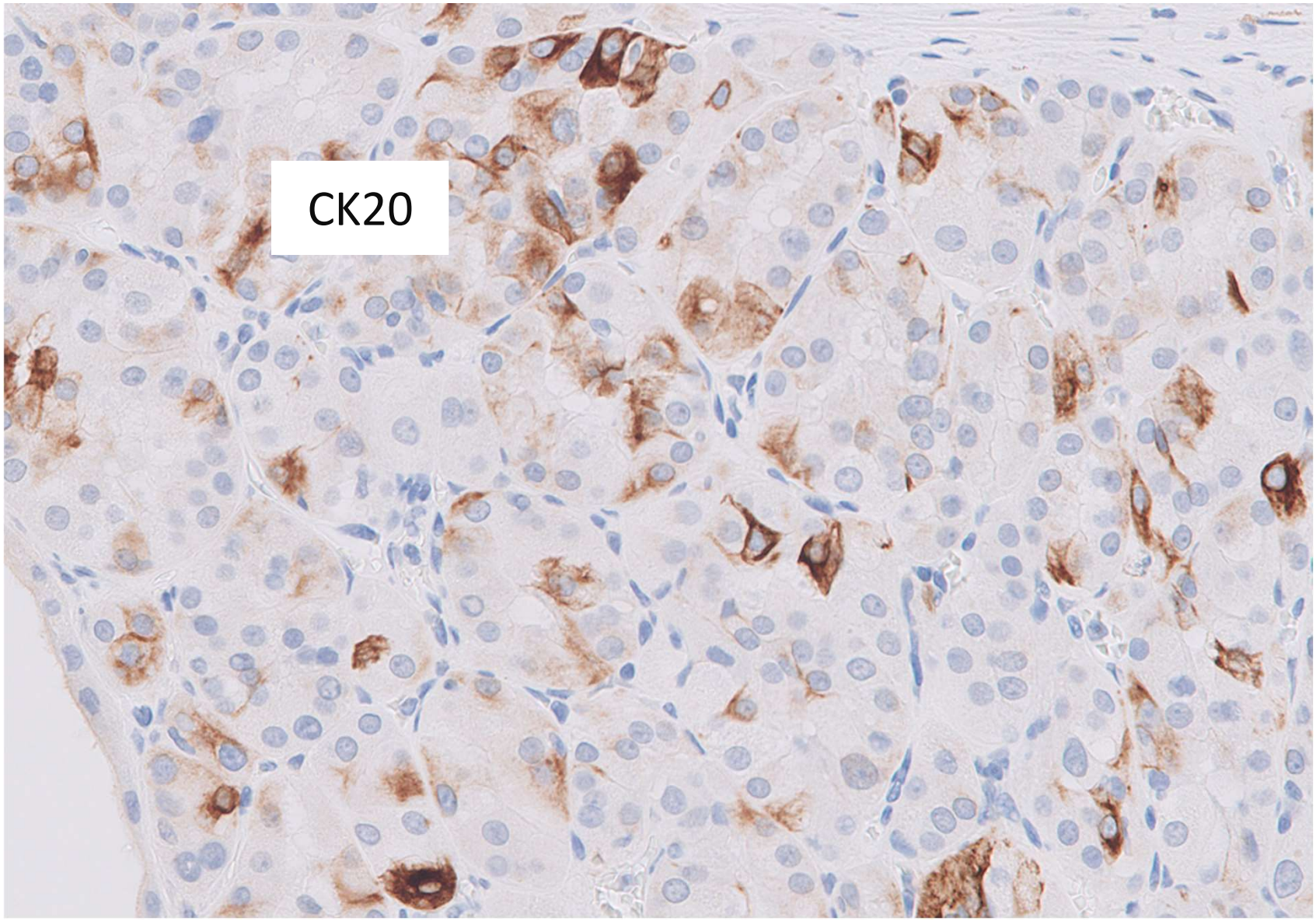
- Occasional binucleations/
- multinucleations
- Cytoplasmic vacuolization

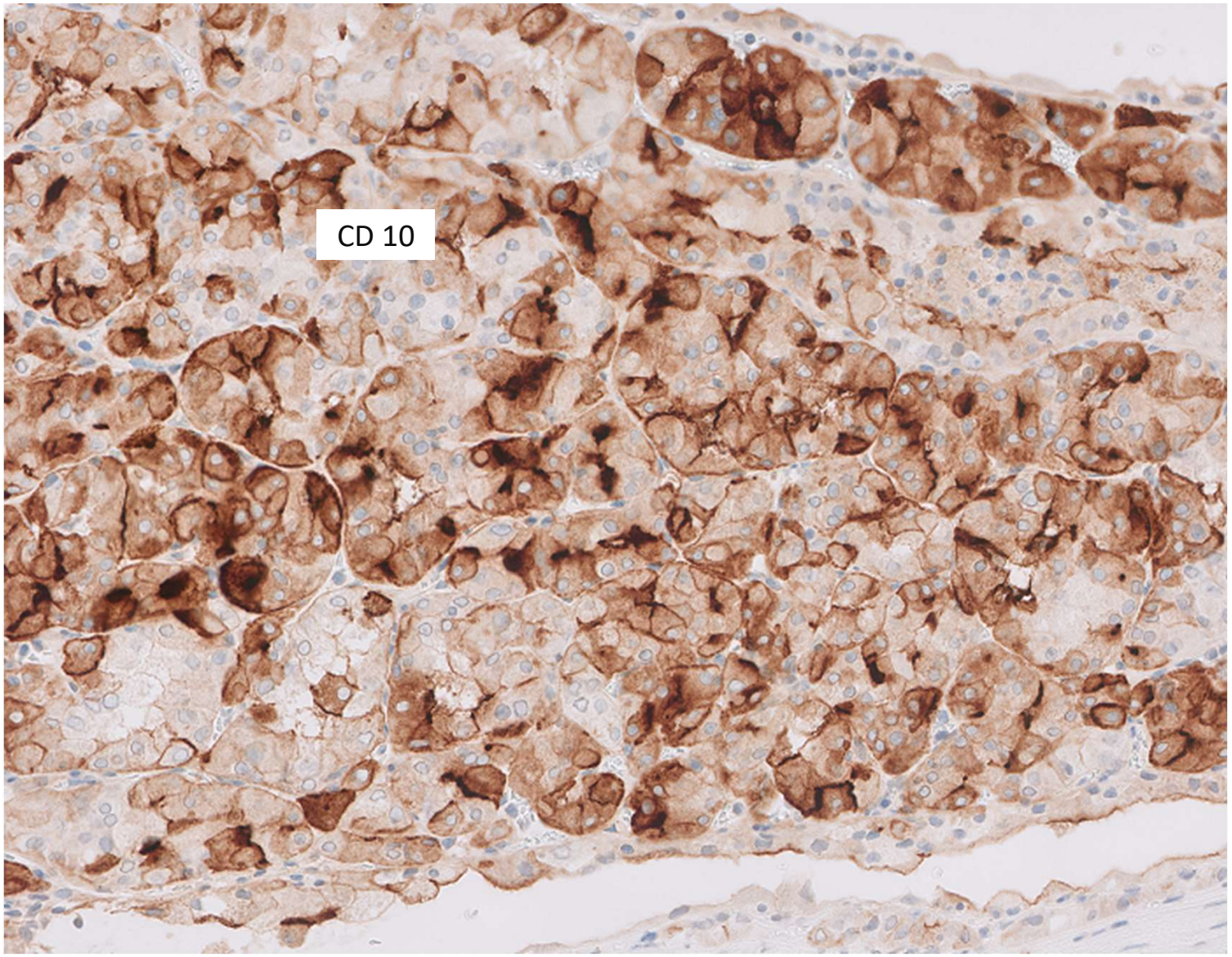


**Both solid and cystic characteristics**


PAX-8


CK7


CK20


CD 10

# What is Your Diagnosis

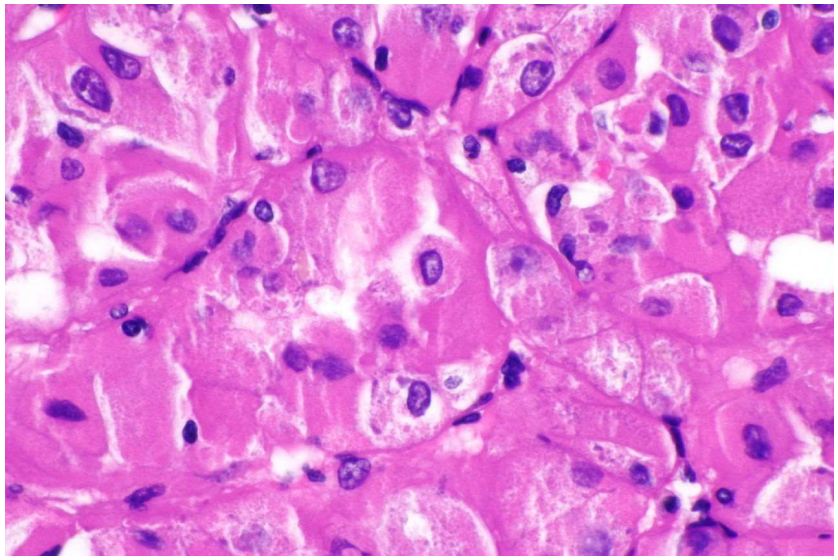
A. MiT family translocation renal cell carcinoma

B. Oncocytoma

C. Chromophobe renal cell carcinoma (eosinophilic type)

D. Clear cell renal cell carcinoma

E. Eosinophilic solid and cystic renal cell carcinoma



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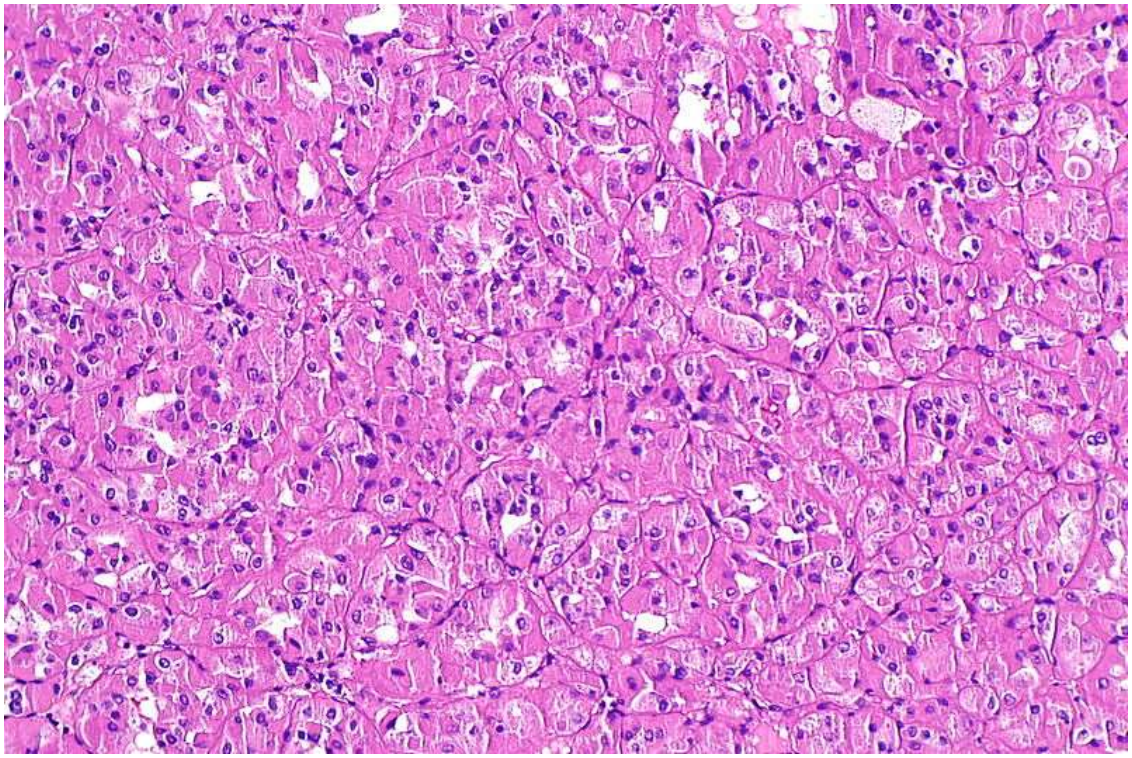
**Eosinophilic solid and cystic renal cell carcinoma**

# Eosinophilic Solid and Cystic Renal Cell Carcinoma

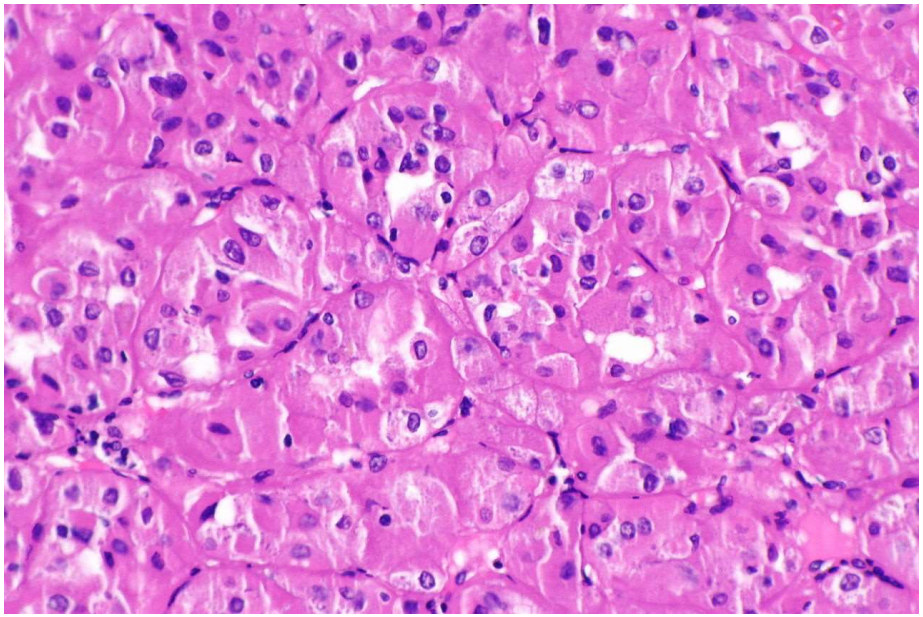
- - - Positive: FH, SDHB, CD10, CAM 5.2, Vimentin, PAX8, CAIX (granular, non-membranous staining), CK20, AMACR, RCC, patchy AE1/E3
- Negative: Melan A, CK7, Inhibin, HMB45



https://commons.wikimedia.org/wiki/File:Eosinophilic,_solid_and_cystic_renal_cell_carcinoma_-_solid_--_intermed_mag.jpg

# Eosinophilic Solid and Cystic Renal Cell Carcinoma

- Gross examination of ESC RCC tumors generally reveal both solid and cystic characteristics, which could also reveal variable hemorrhage with associated necrosis.
- Upon microscopic examination, eosinophilic cytoplasm and prominent granular cytoplasmic stippling/inclusions within cells are generally seen.
- Nuclei are viewed having round to oval, with mild pleomorphism and variably prominent nucleoli.
- Positivity is generally seen on IHC stains such as PAX-8, **CK20**, AMACR, Vimentin and show general negativity in CK7, CAIX, and CD117.
- ESC RCC has been shown **to harbor TSC mutations** as well.



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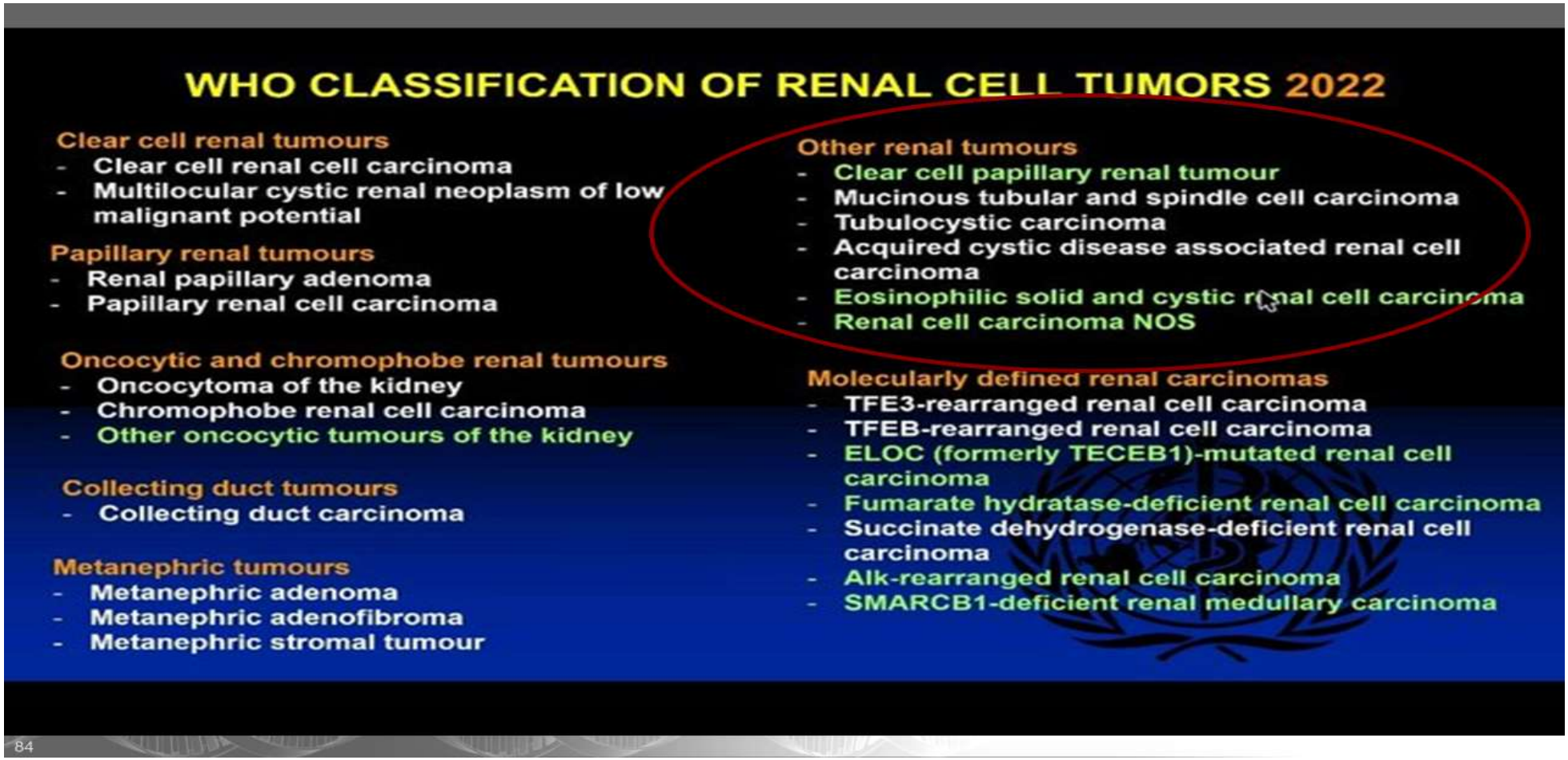
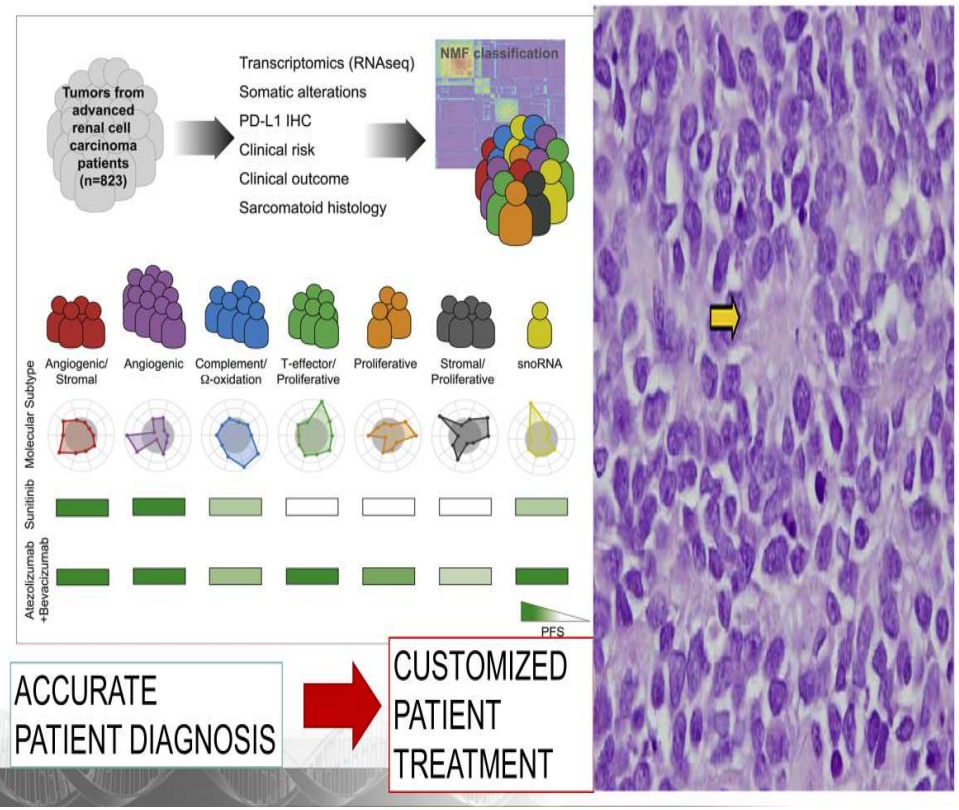
https://www.sciencedirect.com/science/article/pii/S0302283822024678#t0005

# Eosinophilic solid and cystic (ESC) RCC is a unique indolent entity that has been seen to mostly affect females



# 2022 WHO Classification of Renal Tumors




- **In the 2022 WHO classification of renal tumors, a molecularly driven renal tumor classification has been introduced**
- **Novel molecularly defined epithelial renal tumors, e.g. SMARCB1-deficient medullary RCC, *TFEB*-rearranged RCC, *ALK*-rearranged RCC, and *ELOC*-mutated RCC**

https://onlinelibrary.wiley.com/doi/10.1111/his.14700

# Thank You

The James

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