ASCP 2020 VIRTUAL

50 Shades of Pink: New Pink Cell Renal Tumors

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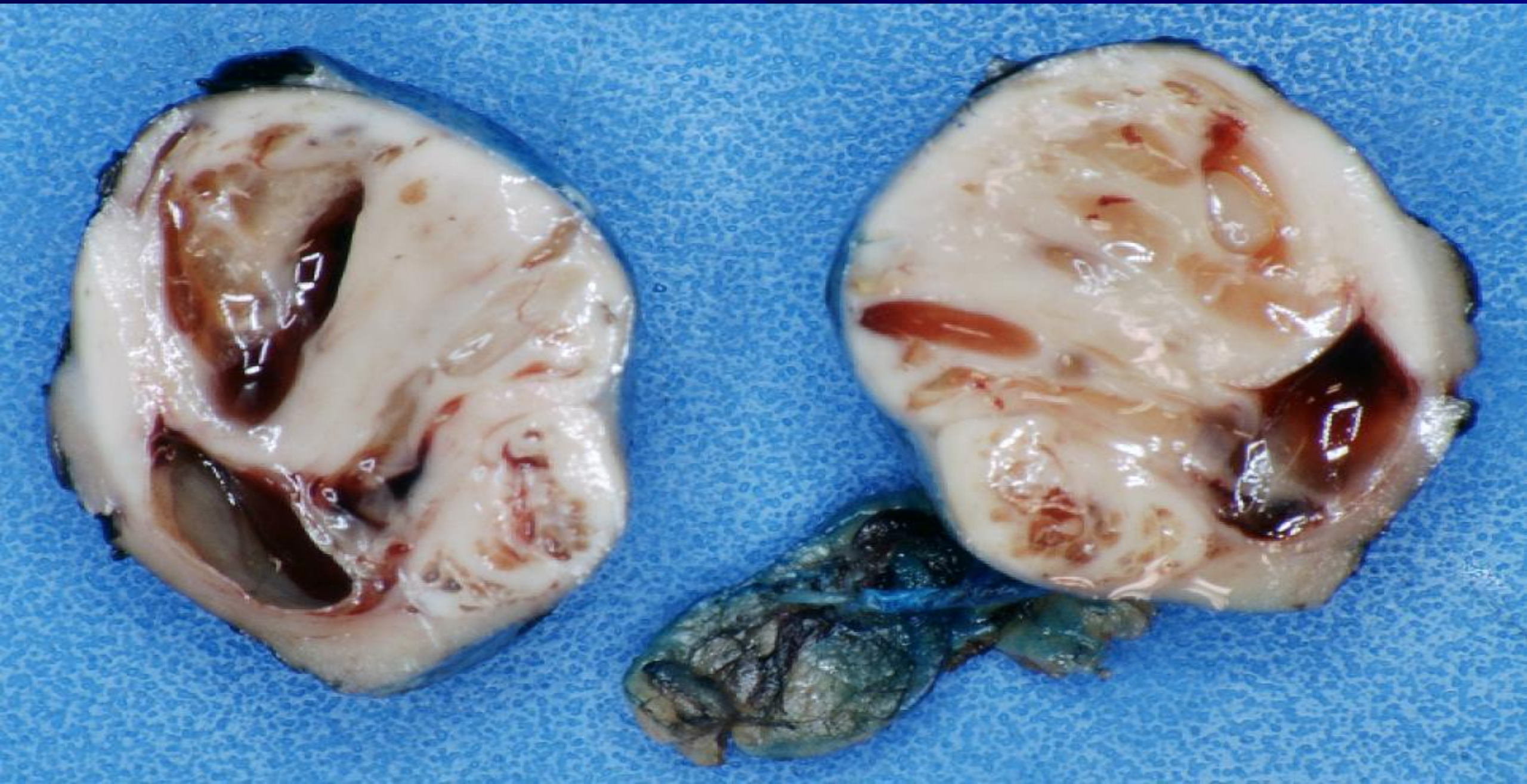
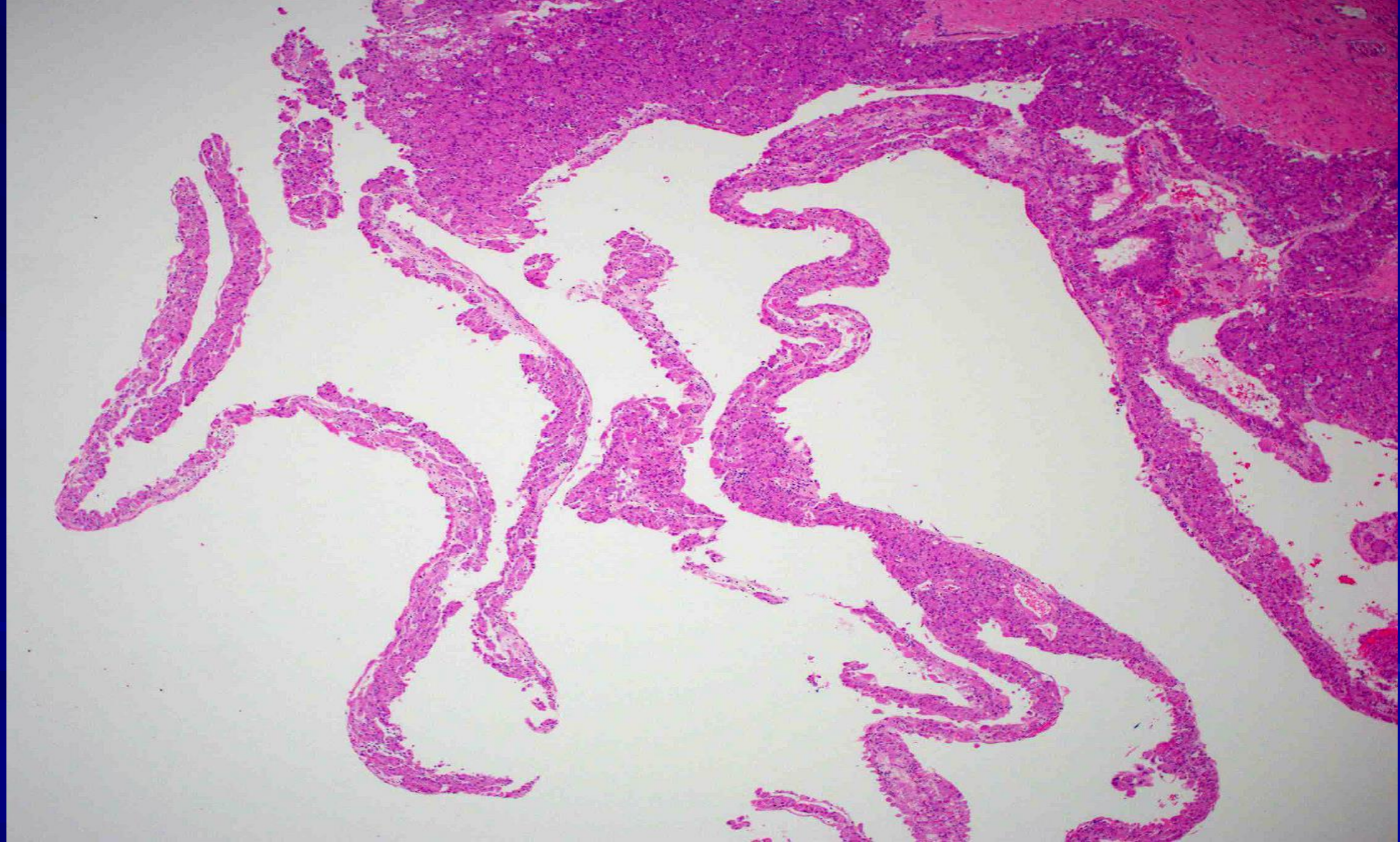
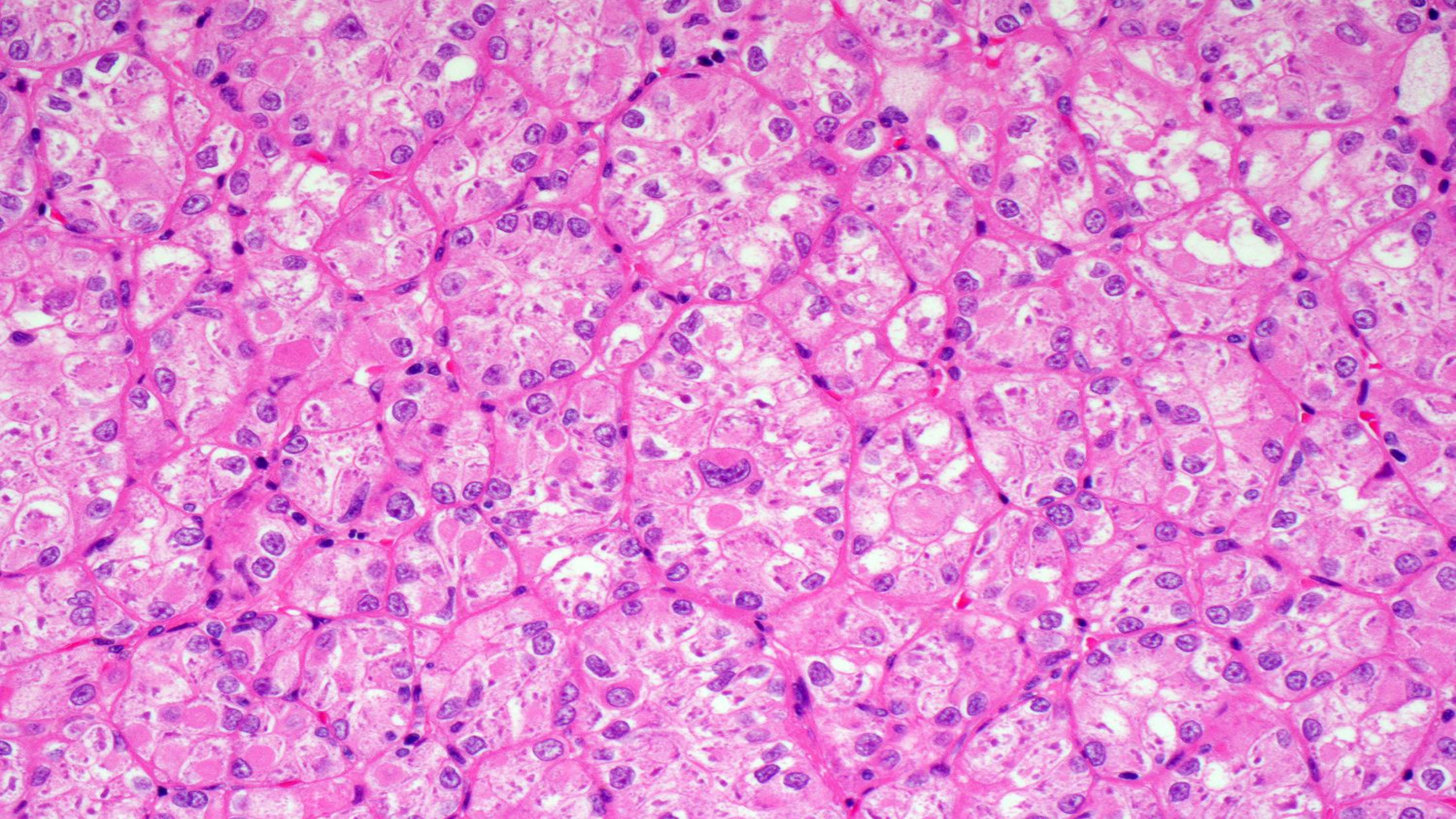
Disclosures

None

37 y/o female, right renal mass 4.5 cm







Your Diagnosis?

1. High grade clear cell RCC with granular cytoplasm
2. Oncocytoma
3. Chromophobe RCC
4. Eosinophilic solid cystic RCC

Three-step Pattern-based Approach to Diagnosis of Renal Tumors

1. Look for predominant pattern at low power

   Pink Cell Tumor

2. Generate differential diagnosis based on the predominant pattern

3. Rule in or out each tumor on the list by looking for a constellation of histological features relatively specific for the tumor

Pink Cell Renal Tumors

Common RCC types

- Clear cell RCC with granular cytoplasm
- Papillary RCC, type 2
- Chromophobe RCC, eosinophilic variant
- Oncocytoma

New RCC entities

- Translocation RCC
- Acquired cystic disease associated RCC
- Succinic dehydrogenase (SDH)-deficient RCC
- Fumarate hydratase (FH)-deficient RCC, including HLRCC/RCC
- *TSC/mTORC* mutated RCC, including eosinophilic solid cystic RCC
- Hybrid oncocytic tumor (HOT) in Birt-Hogg-Dube syndrome (BHD)

Non-epithelial tumors

- Ectopic adrenal cortical tissue
- Epithelioid angiomyolipoma

Three-step Pattern-based Approach to Diagnosis of Renal Tumors

1. Look for predominant pattern at low power

2. Generate differential diagnosis based on the predominant pattern

3. Rule in or out each tumor on the list by looking for a constellation of histological features relatively specific for each tumor

Diagnosis of “Pink Cell Tumors”

Morphological Clues

Tumor/normal interface

Infiltrative vs circumscribed
Entrapped renal tubules

Architectural features

Acinar
Papillary
Tubular
Cystic

Biphasic rosette
Ca oxalate crystals
Hyalinized cores

Cytoplasmic features

Cell borders
Two tone cytoplasm
Cytoplasmic granules
Cytoplasmic vacuoles

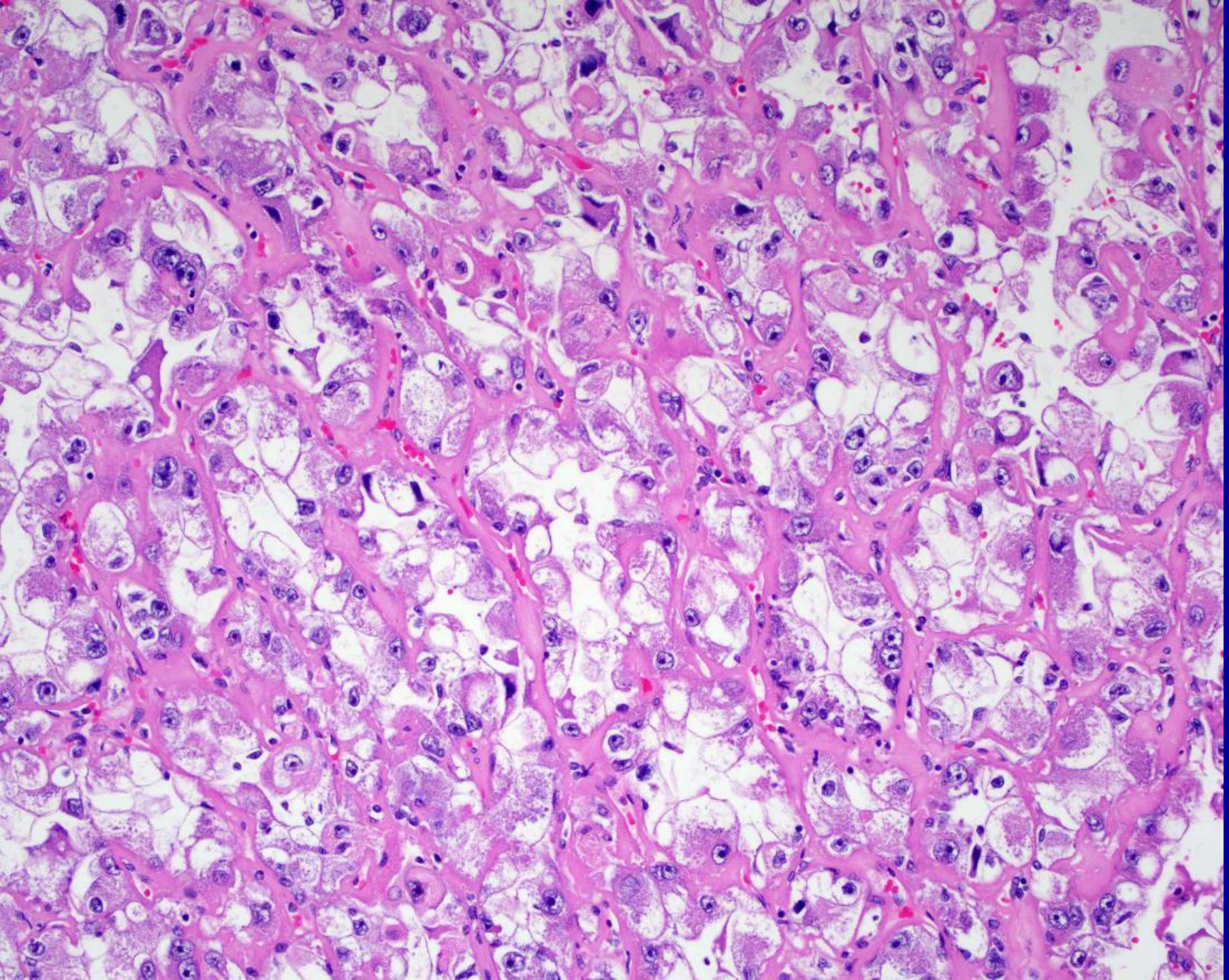
Nuclear features

Raisinoid nuclei
Prominent nucleoli
Perinucleolar halo
Cytoplasmic/nuclear synchronization

Diagnosis of “Pink Cell Tumor”

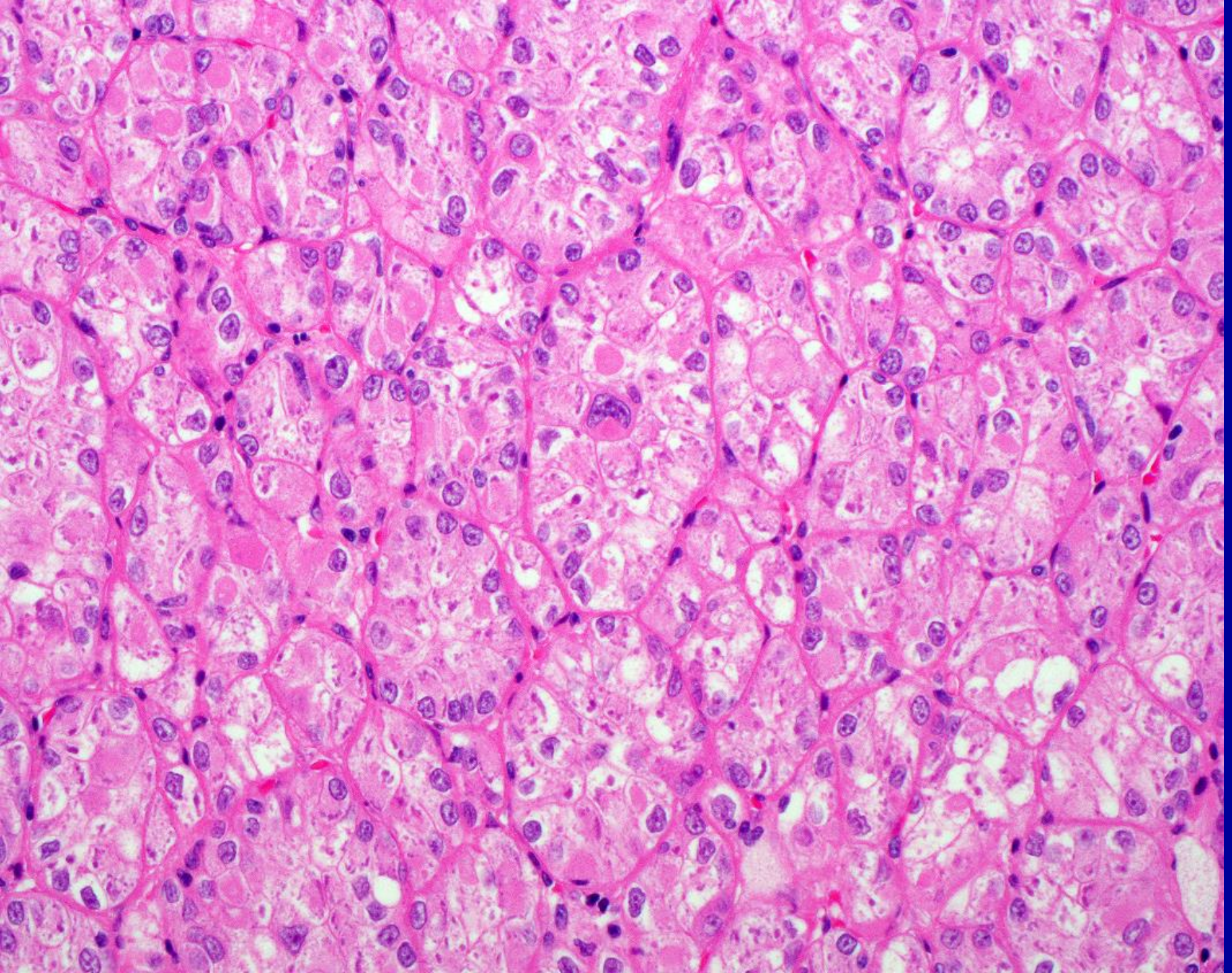
Rule #4

Look for cytoplasmic features



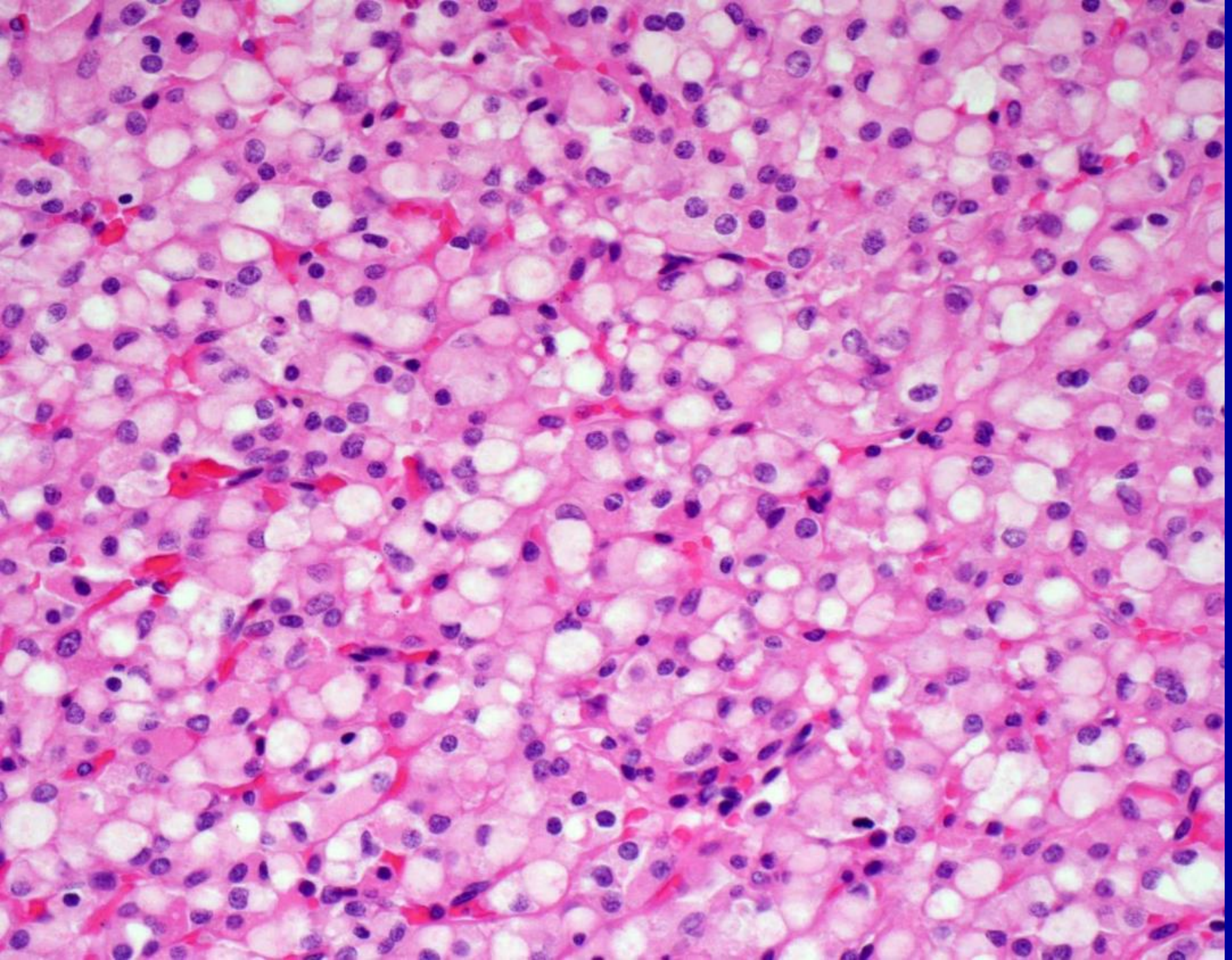
Two tone cytoplasm (partially clear/eosinophilic cytoplasm)

Translocation RCC



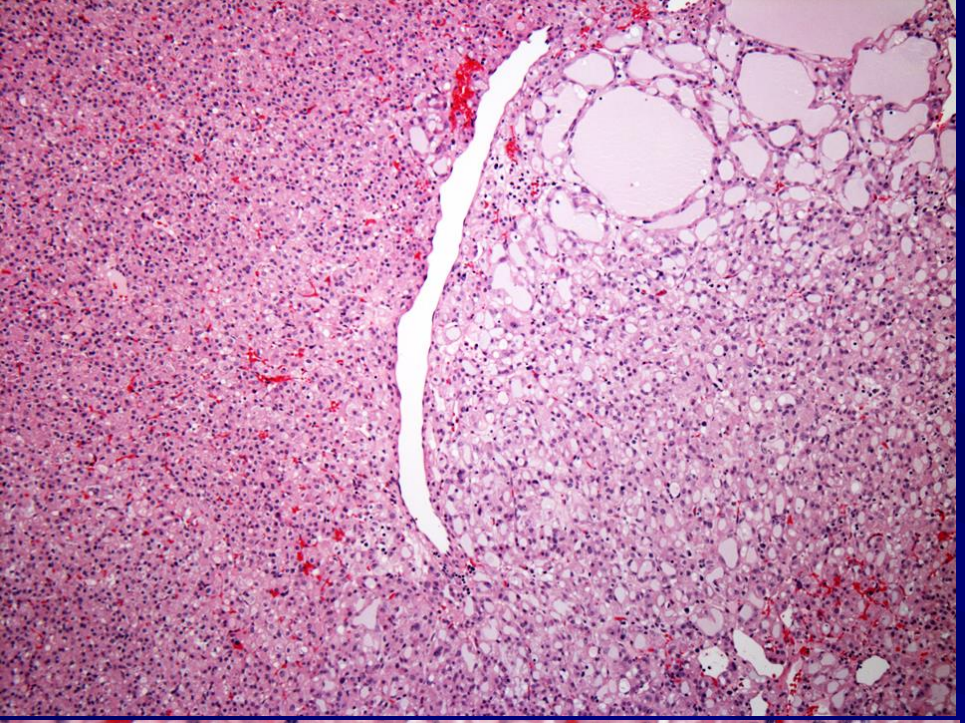
Coarse basophilic cytoplasmic granules (basophilic stippling):

Eosinophilic solid cystic RCC



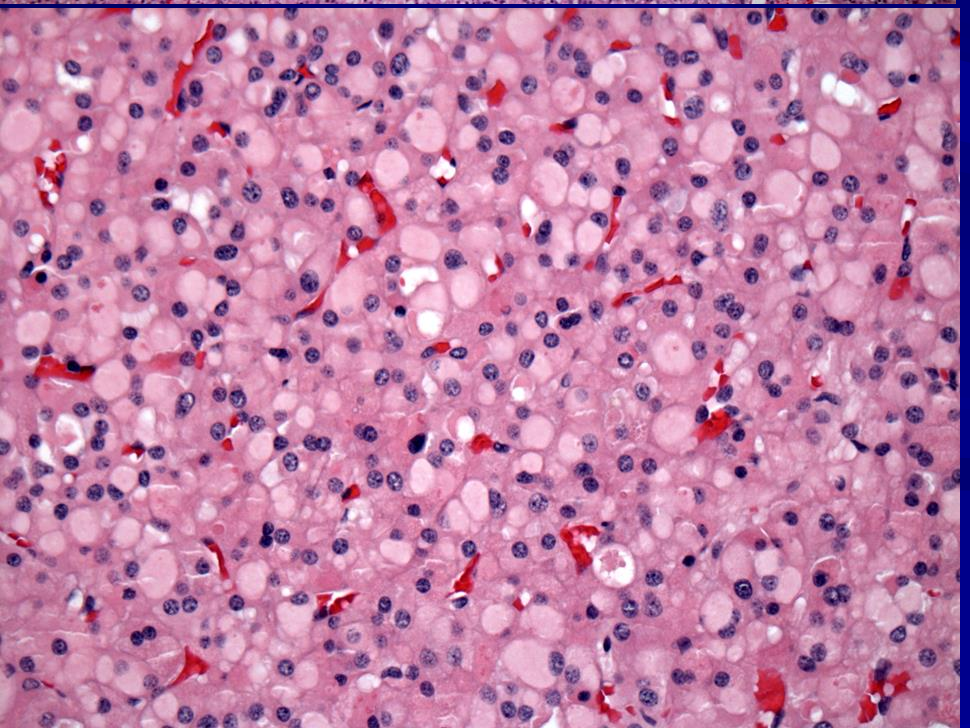
Cytoplasmic vacuoles:

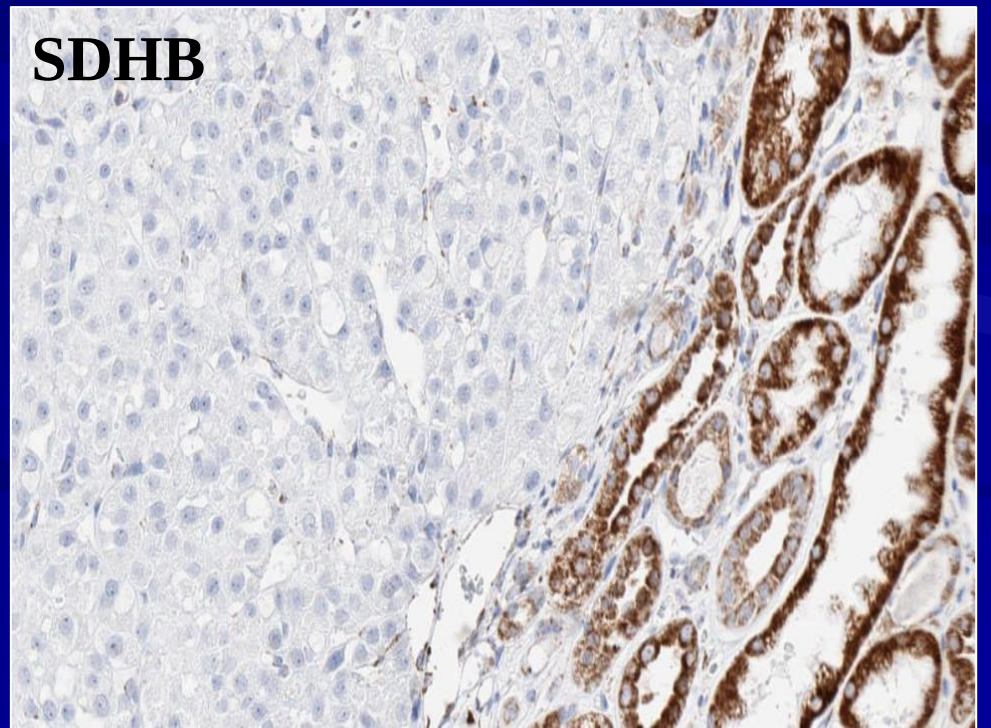
Succinate dehydrogenase (SDH) deficient RCC



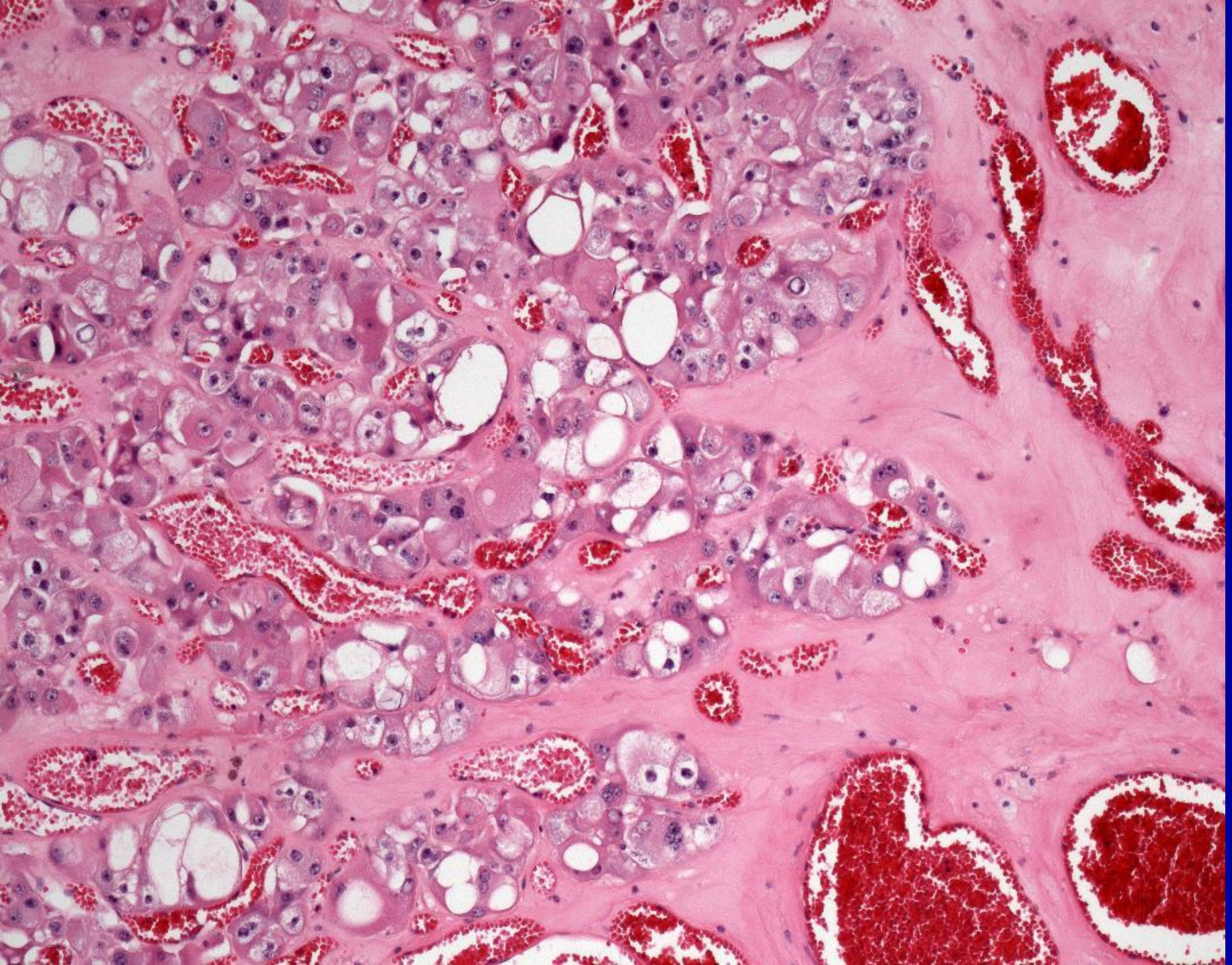
Succinate Dehydrogenase (SDH) Deficient RCC

- Rare
- Germline mutations in SDH subunit A, B, C and D
- Paraganglioma/pheochromocytoma/pediatric gastric GIST
- Majority indolent but may dedifferentiate and metastasize



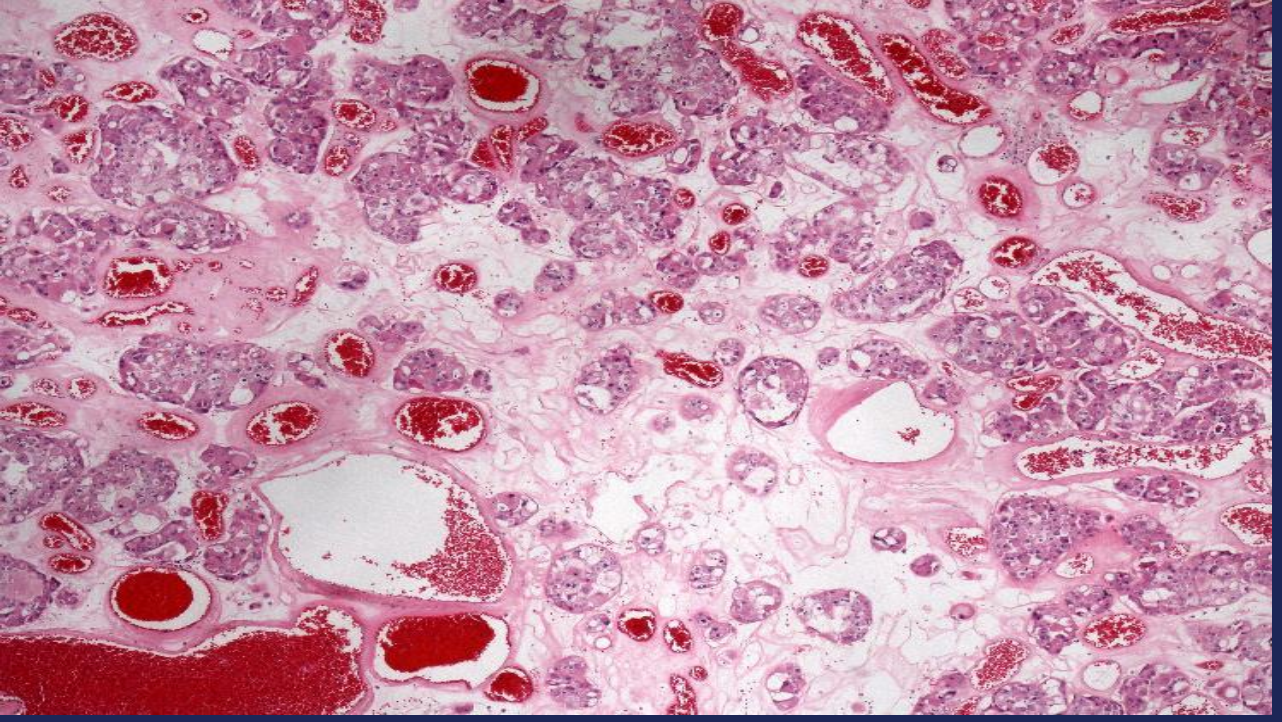


- "Oncocytoma"-like
- Cytoplasmic vacuoles
- Negative SDHB IHC



Marked cytoplasmic vacuolation:

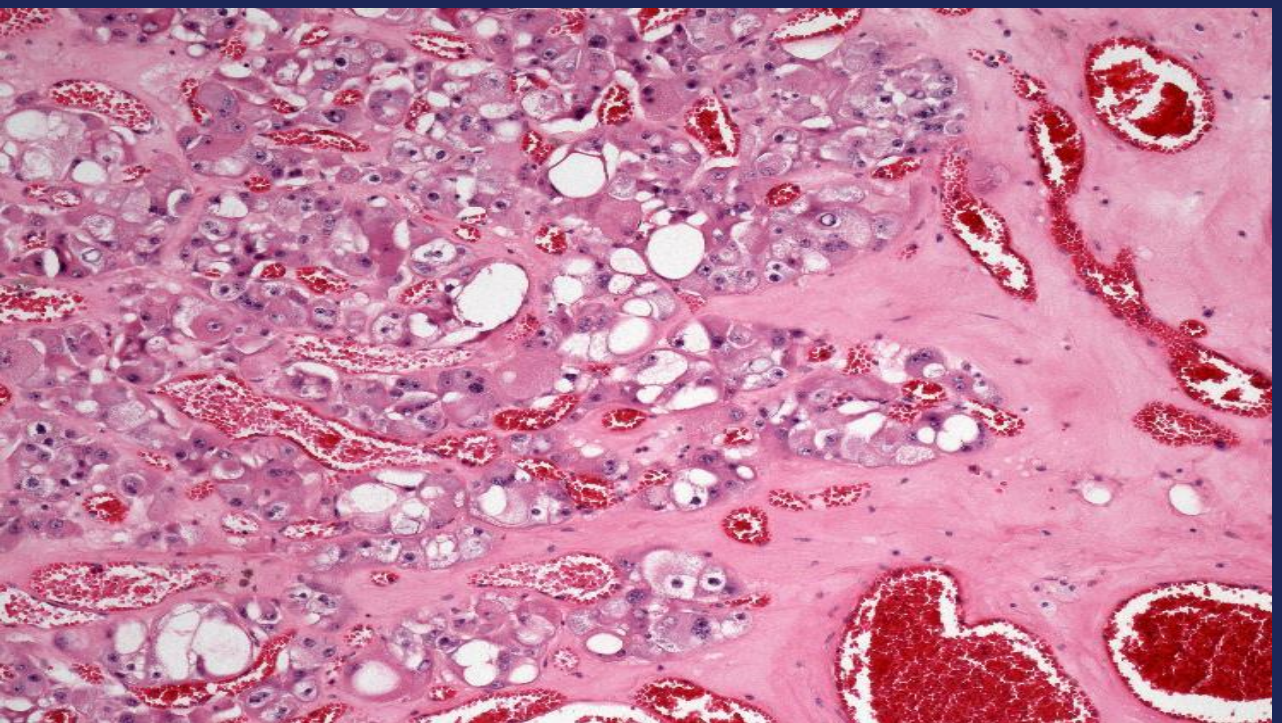
RCC with mutations in *TSC* and *mTORC1* genes

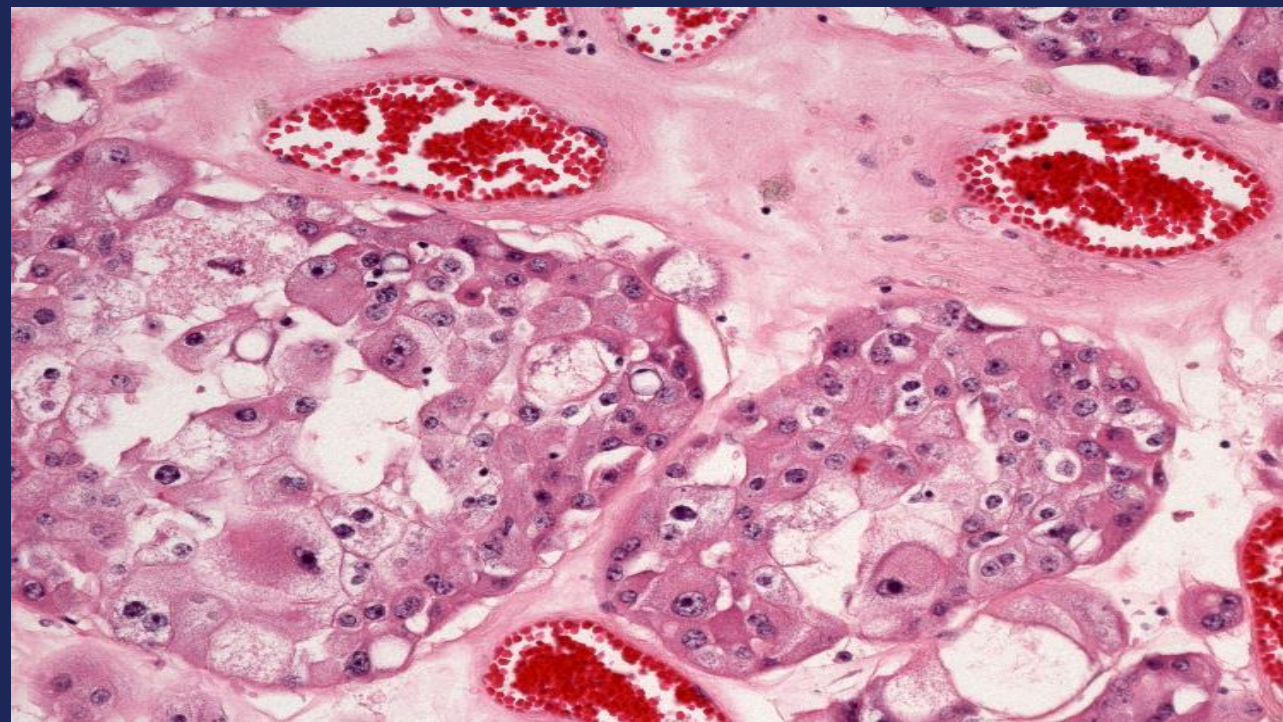


RCC with Eosinophilic and Vacuolated Cytoplasm Harbors Mutations in *TSC/mTORC1* genes

- 7 unclassified oncocytic tumors
- 3/5 somatic inactivating mutations of *TSC2*
- 2/5: activating mutations of *mTORC1*

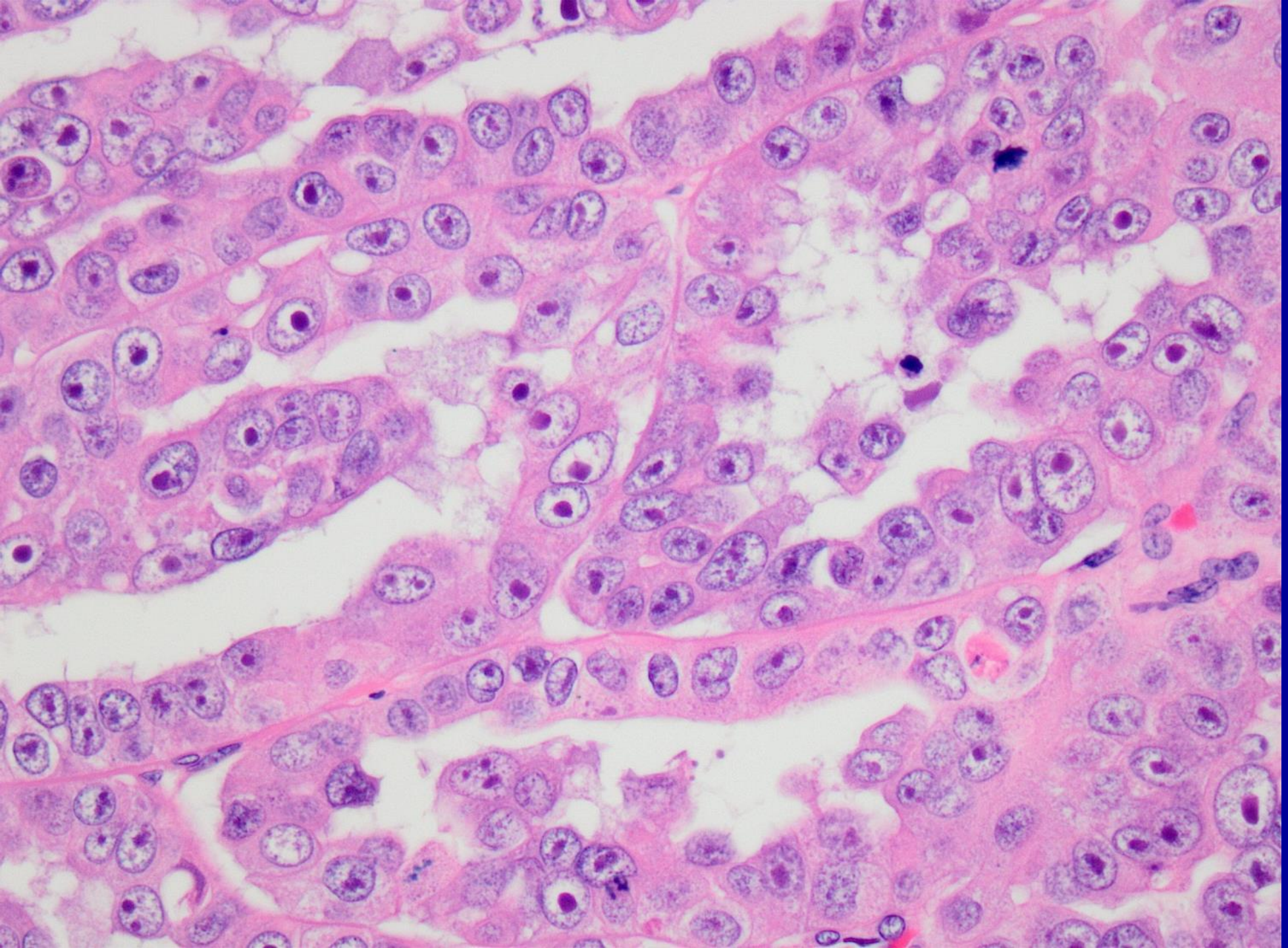
Chen YB et al, AJSP, 2019





Diagnosis of “Pink Cell Tumor”
Rule #5

Look for nuclear features



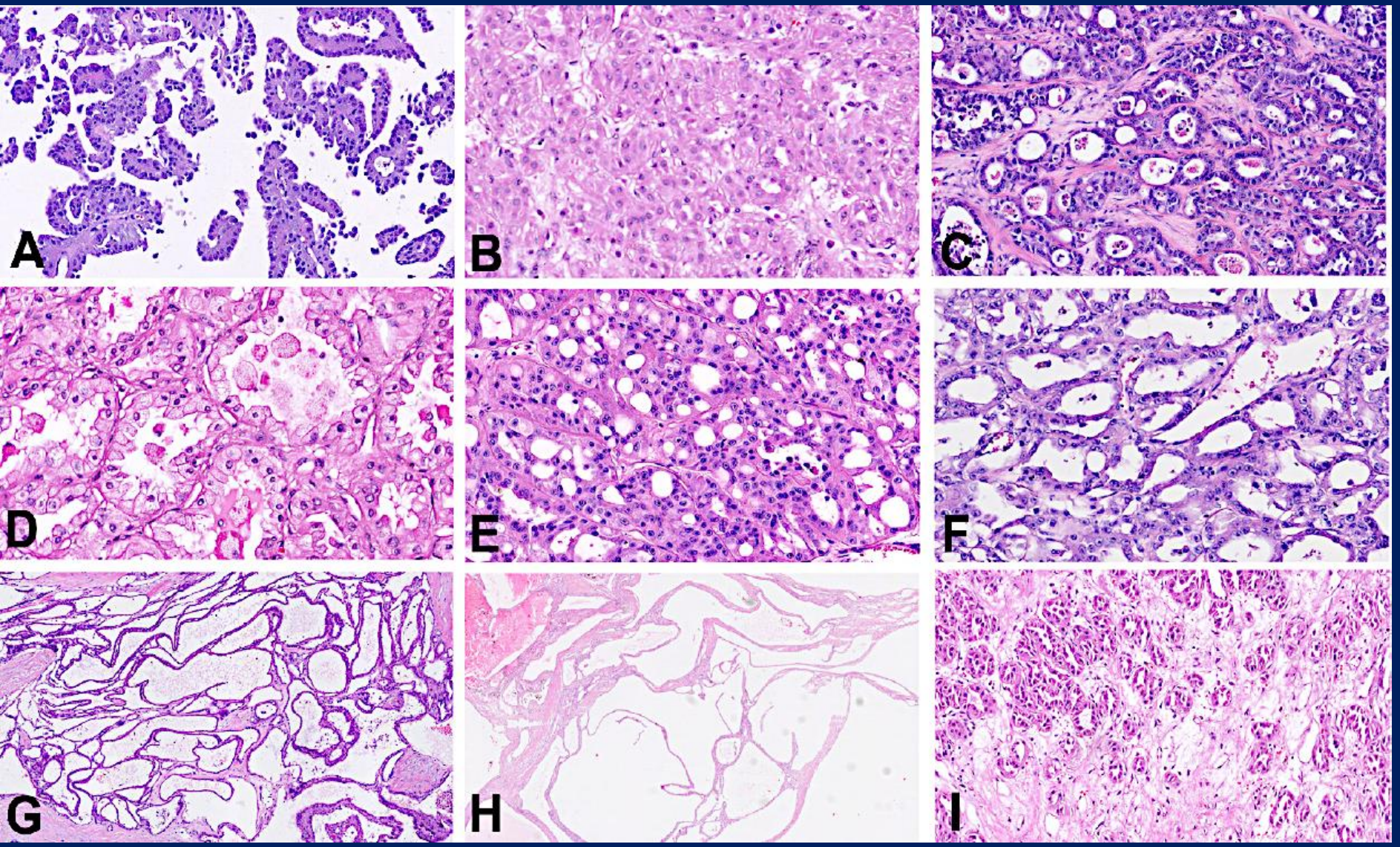
Prominent nucleoli with perinucleolar clearing (resembling CMV inclusions or melanoma nuclei)

RCC in hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

Renal Cell Carcinoma in Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC)

- Autosomal dominant
- Germ-line mutation in fumarate hydratase gene (*FH*, 1q42.3-q43)
- Young patients with multiple skin leiomyomas or early uterine fibroids
- RCC resembles “type 2” PRCC or collecting duct RCC
- Very poor prognosis; up to 50% with metastasis at diagnosis

HLRCC often has multiple patterns in the same tumor

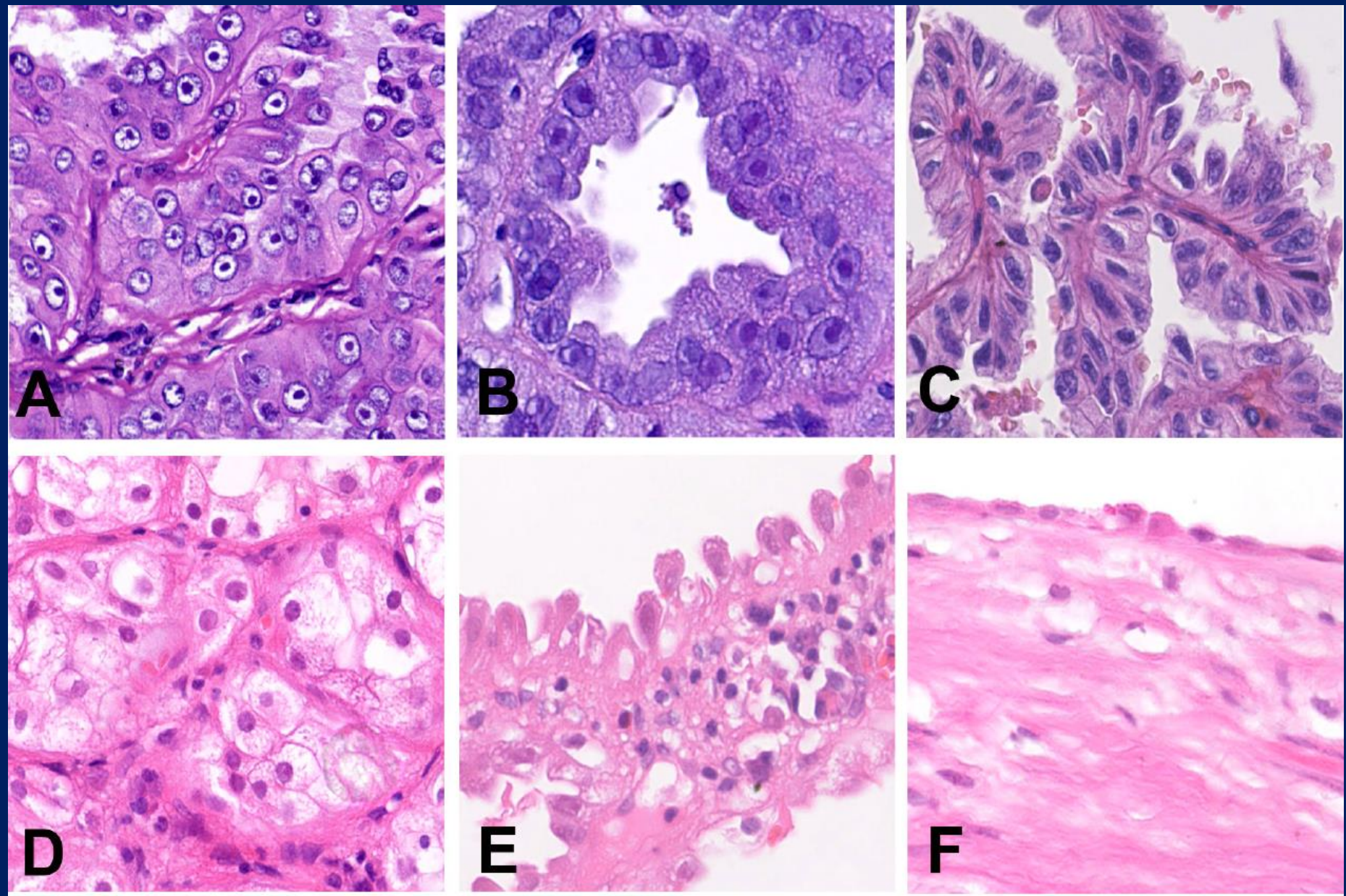


- Papillary
- Tubular
- Tubulocystic
- Cribriform
- Solid

Polymorphous patterns: 1st clue for HLRCC

Nuclear Features

(Pan X et al, J Clin Pathol, 2019)



Low grade morphology

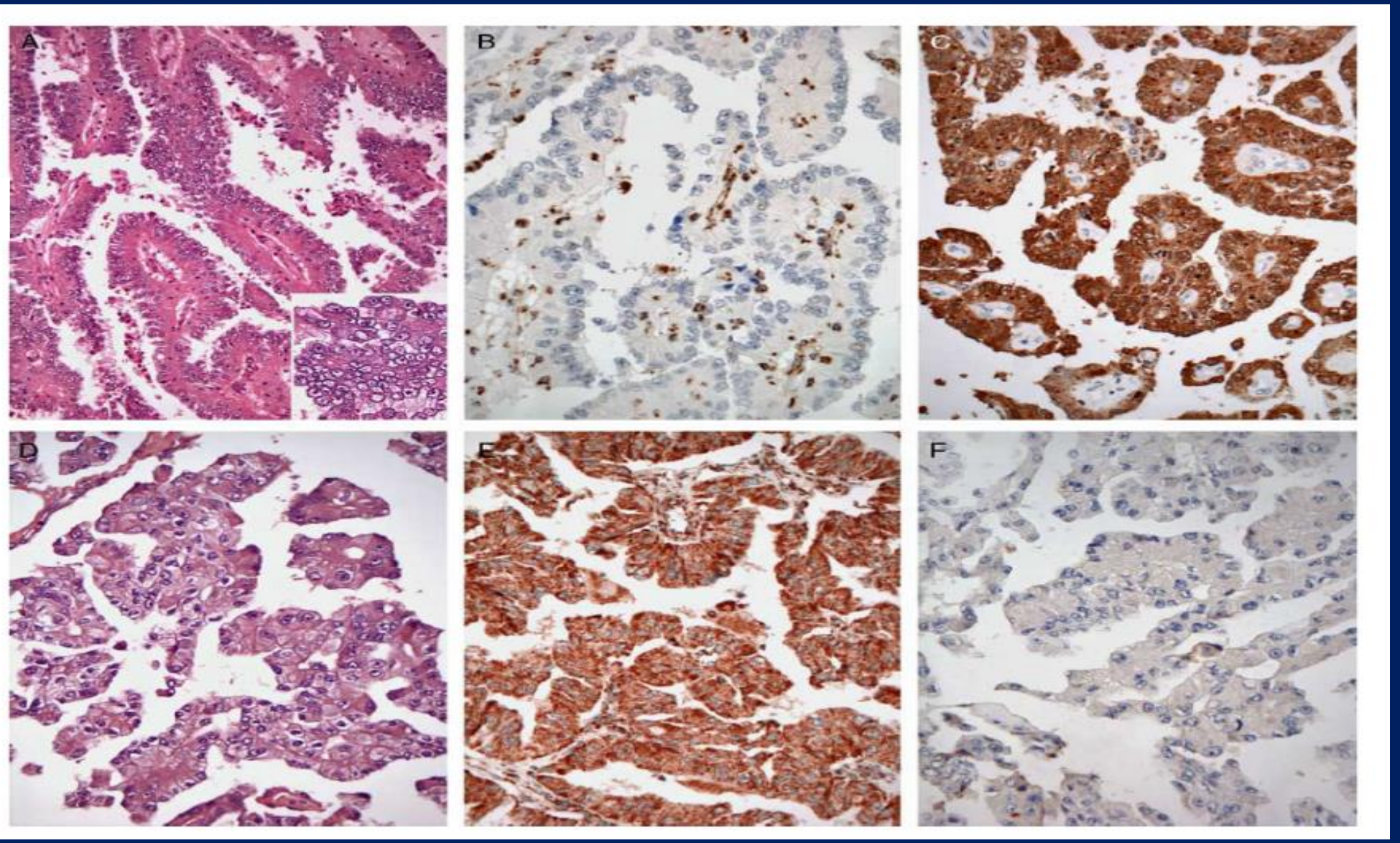
To Confirm the Diagnosis…

1. Sequence *FH* gene, *or*
2. Surrogate IHC markers
   - ✓ FH (loss or reduced expression)
   - ✓ S -(2-succinyl) cysteine protein (2SC) (strong increased expression)

FH 2SC

FH deficient RCC

FH retained RCC



FH-/2SC+: FH deficiency, strongly correlates with *FH* mutation and HLRCC syndrome

Trpkov AJSP 2016

HLRCC

Genetically confirmed germline mutation in *FH* gene

FH deficient RCC

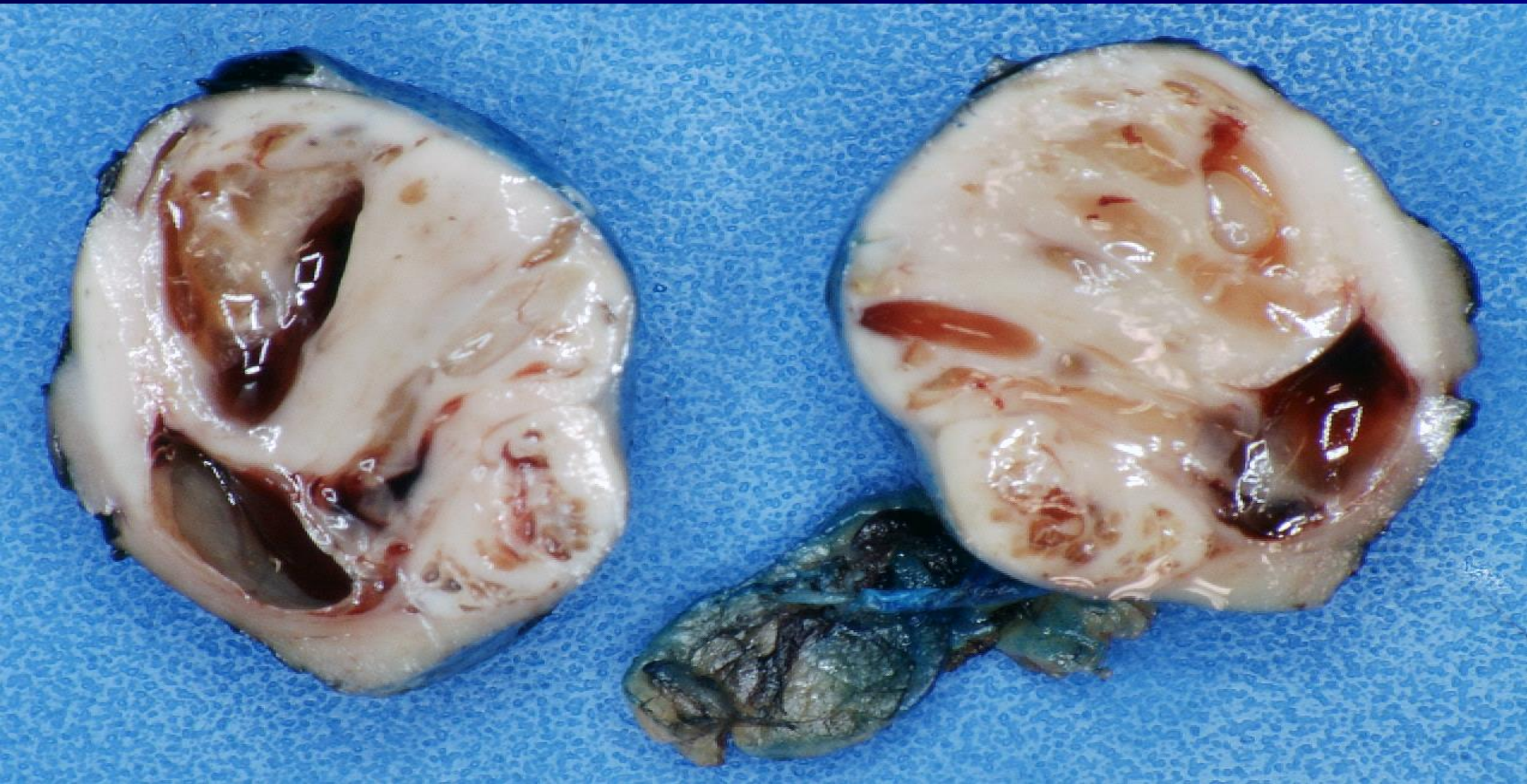
1) Morphology compatible with HLRCC

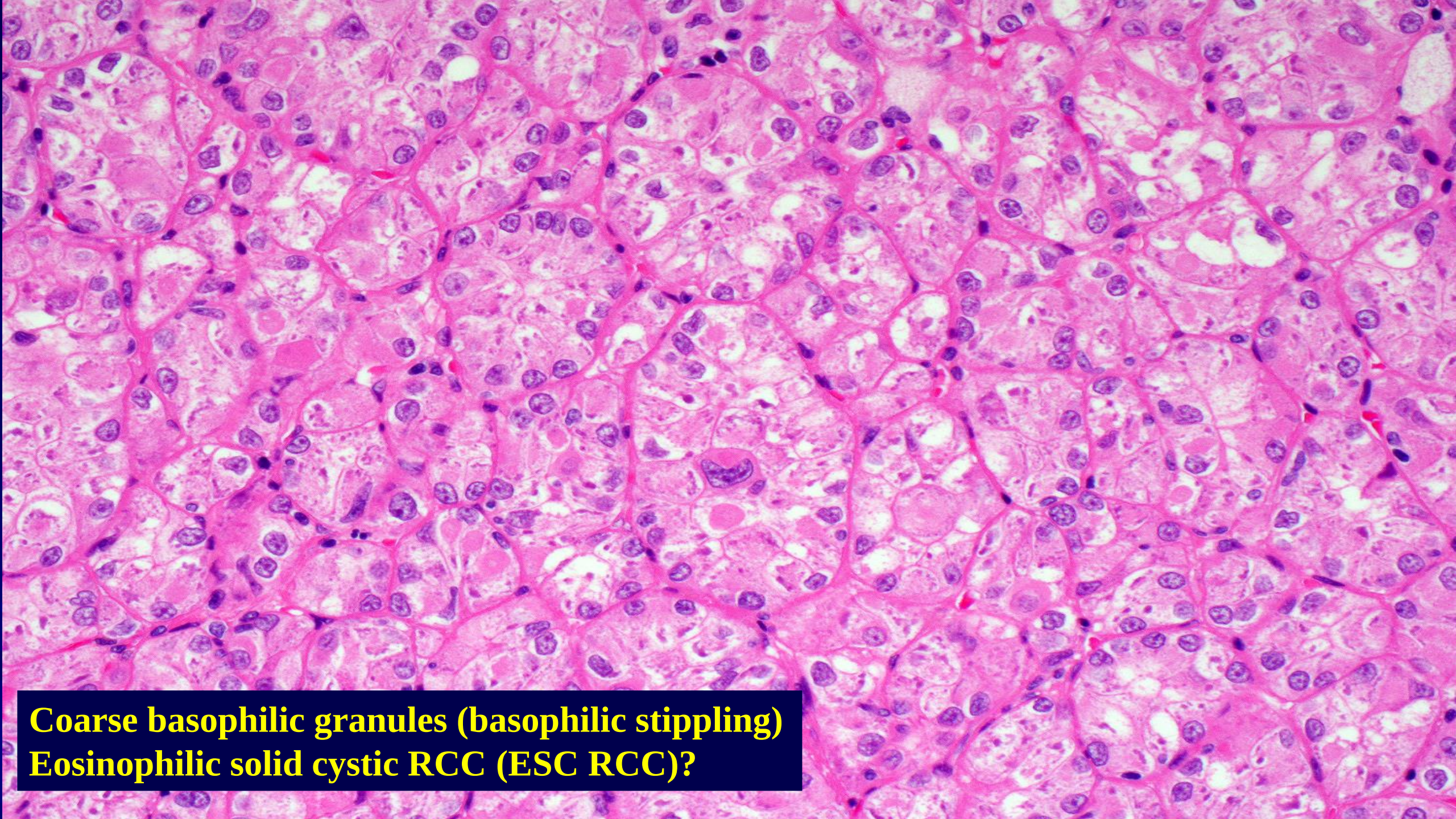
2) IHC: FH -, and/or 2SC +

3) Clinical and family history of skin and uterine leiomyomas: uncertain

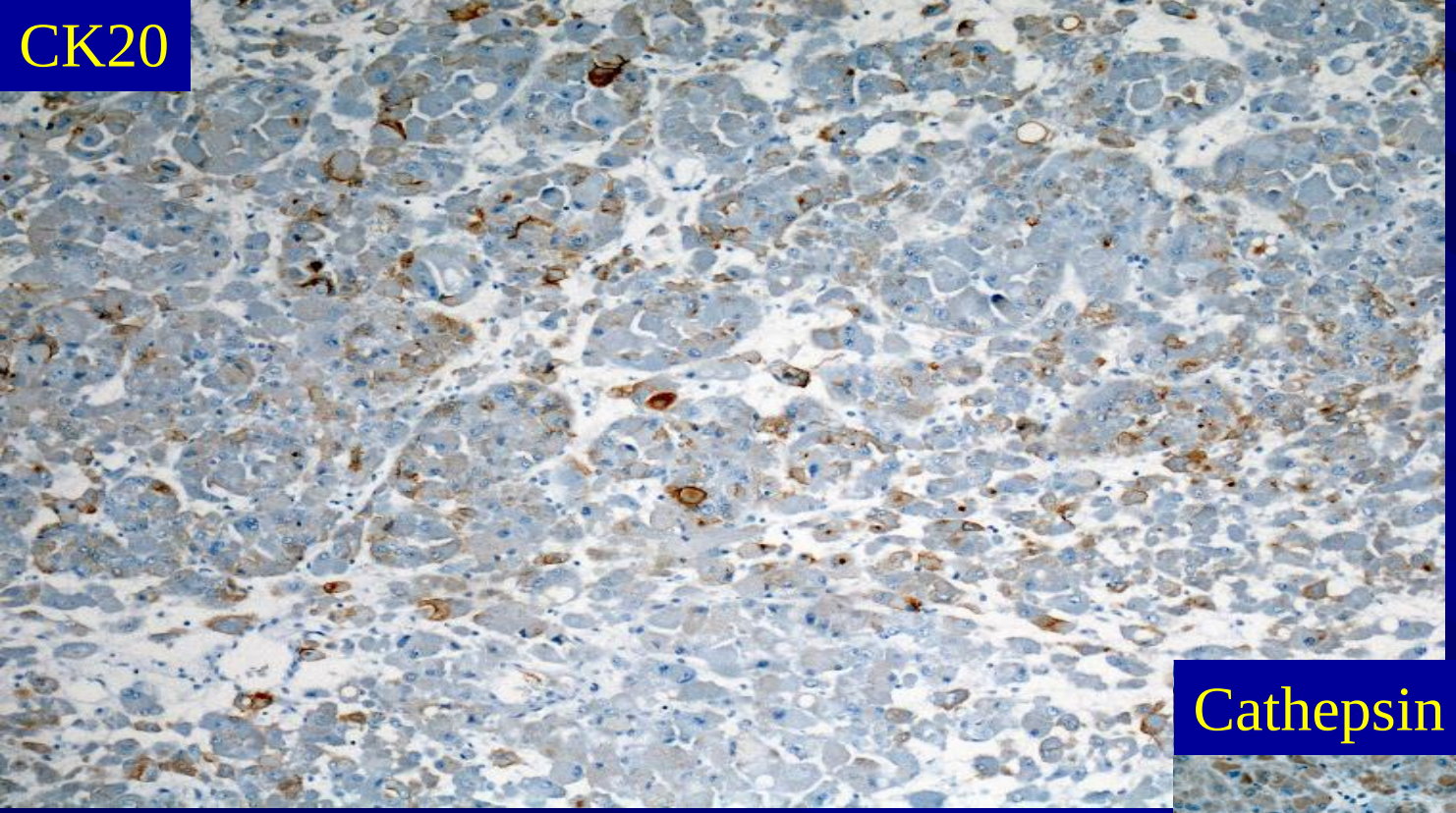
4) Genetic status of *FH* at the time of case sign-out: unknown

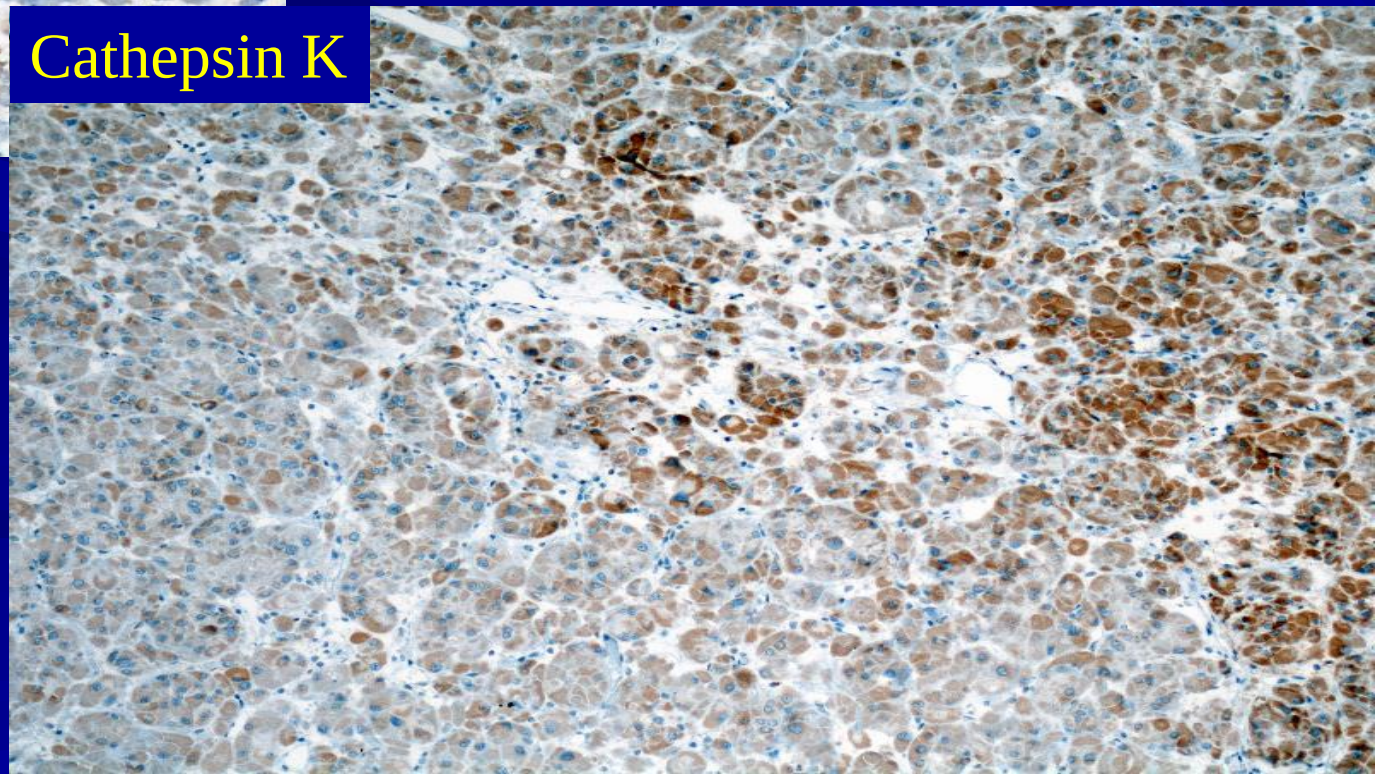
37 y/o female, right renal mass 4.5 cm




Coarse basophilic granules (basophilic stippling)
Eosinophilic solid cystic RCC (ESC RCC)?

Eosinophilic solid cystic RCC (ESC RCC)

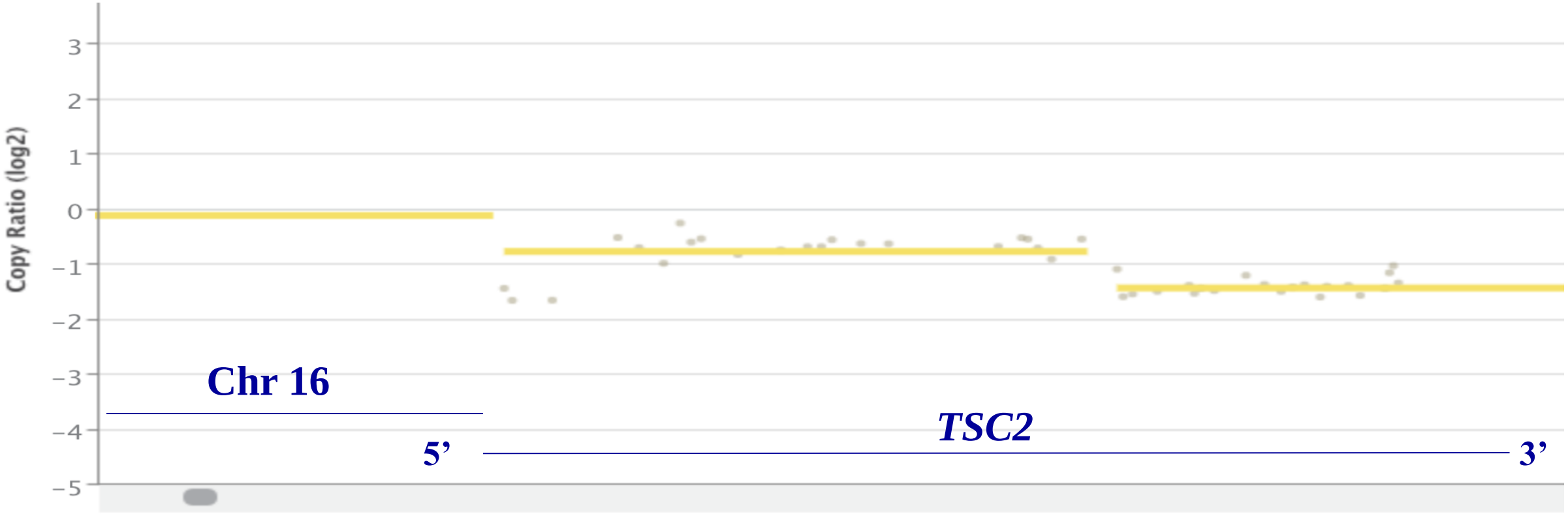




Next Generation Sequencing

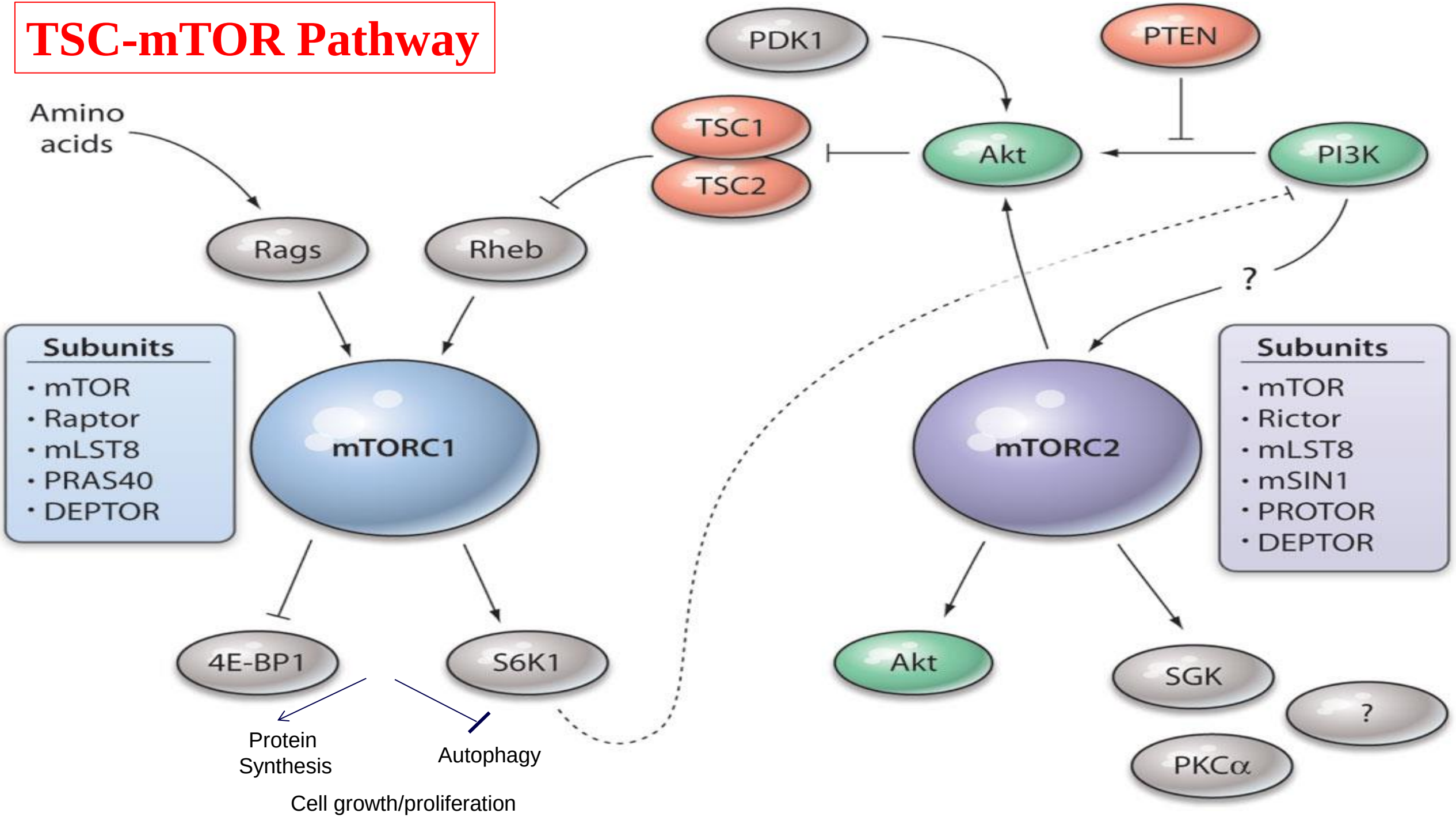
TIER 2 - VARIANTS OF POSSIBLE CLINICAL SIGNIFICANCE

VARIANT	COMMENT
TSC2 **Pos:** chr16:2075770-2229129 **Copy Number:** 0 **Aberration Type:** loss	**Diagnosis:** There are two distinct copy number states within the TSC2 gene. Some sections are at a one copy loss, and others are at a two copy loss. This likely represents biallelic inactivation of the gene. RNA expression analysis also shows that this has lower expression than any case we've previously tested across tumor types.



Eosinophilic solid cystic (ESC) RCC with somatic *TSC2* mutation

TSC-mTOR Pathway



RCC in Tuberous Sclerosis Complex (germline mutations in *TSC1/2*)

	Yang *et al* (AJSP 2014)	Guo *et al* (AJSP 2014)
Patients/ Tumors	19/46	18/57
RCC w/ SM stroma	24 (52%)	17 (30%)
Oncocytic tumors resembling onco/ChRCC	15 (33%)	34 (59%)
Other	Unclassified 7 (15%)	Eosinophilic solid cystic RCC 6 (10%)

ORIGINAL ARTICLE

AJSP 2016

Eosinophilic, Solid, and Cystic Renal Cell Carcinoma

Clinicopathologic Study of 16 Unique, Sporadic Neoplasms Occurring in Women

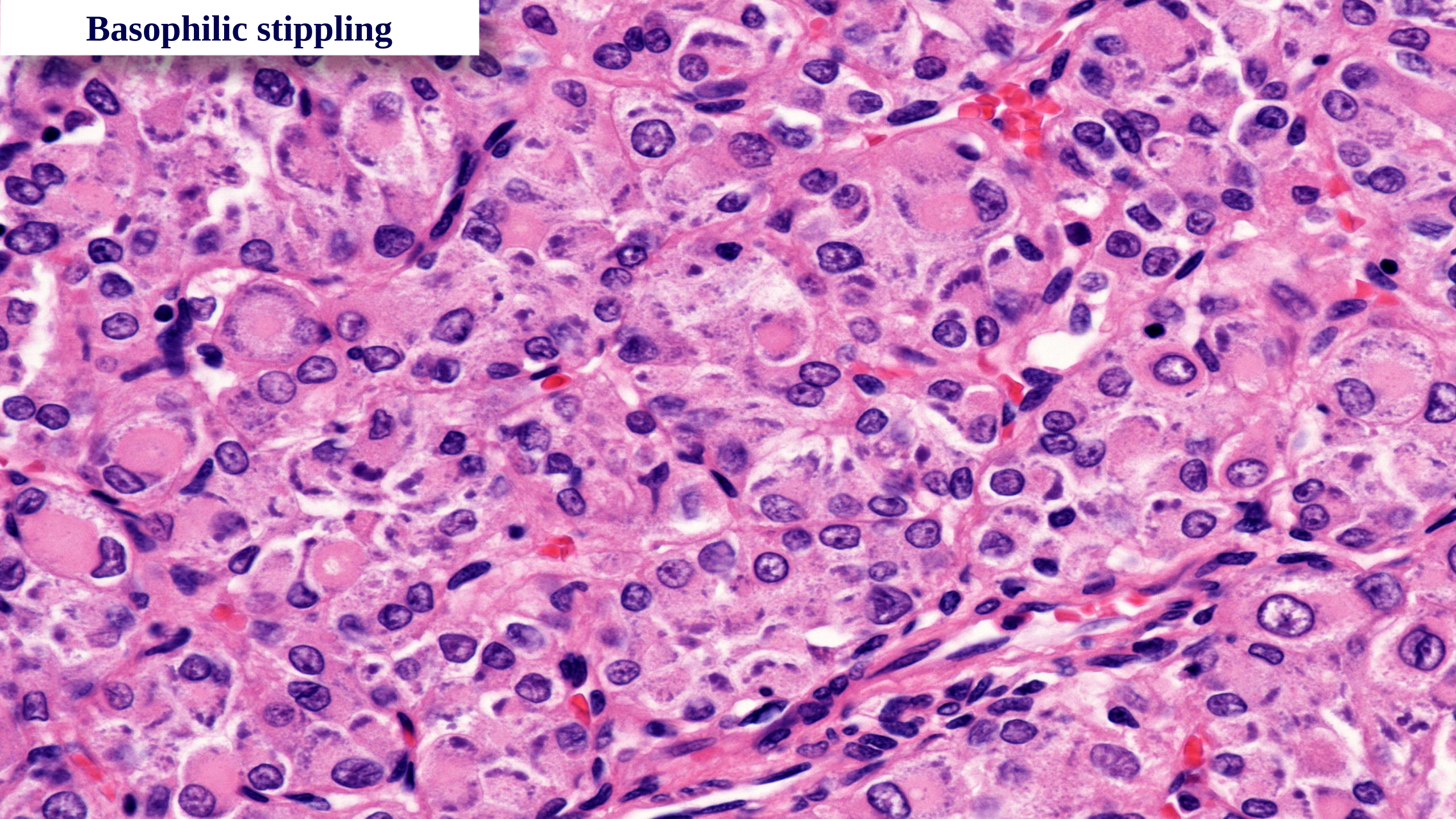
Kiril Trpkov, MD, FRCPC, Ondrej Hes, MD, PhD,† Michael Bonert, MD,* Jose I. Lopez, MD, PhD,‡ Stephen M. Bonsib, MD,§ Gabriella Nesi, MD,‖ Eva Comperat, MD,¶ Mathilde Sibony, MD,# Daniel M. Berney, MD,** Petr Martinek, MSc,† Stela Bulimbasic, MD,†† Saul Suster, MD,‡‡ Ankur Sangoi, MD,§§ Asli Yilmaz, MD,* John P. Higgins, MD,‖‖ Ming Zhou, MD, PhD,¶¶ Anthony J. Gill, MD, PhD,## Christopher G. Przybycin, MD,*** Cristina Magi-Galluzzi, MD, PhD,*** and Jesse K. McKenney, MD****

- **Morphologically very similar to eosinophilic solid cystic RCCs in tuberous sclerosis complex (TSC)**
- **Sporadic; patients without TSC**

Sporadic ESC RCC Morphological Features

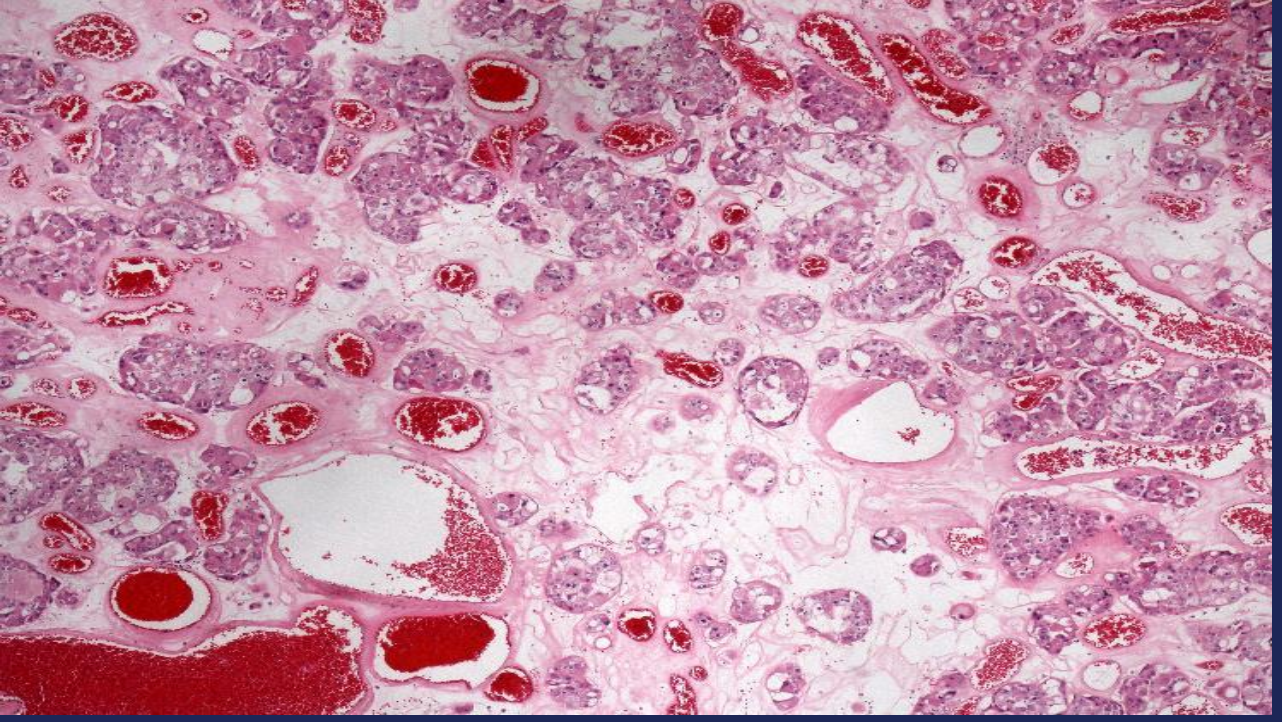
1. Solid and cystic components
2. Voluminous eosinophilic cytoplasm
3. Basophilic granules in the cytoplasm (basophilic stippling)
4. CK20 at least focally +; Cathepsin K +; CK7-

Basophilic stippling



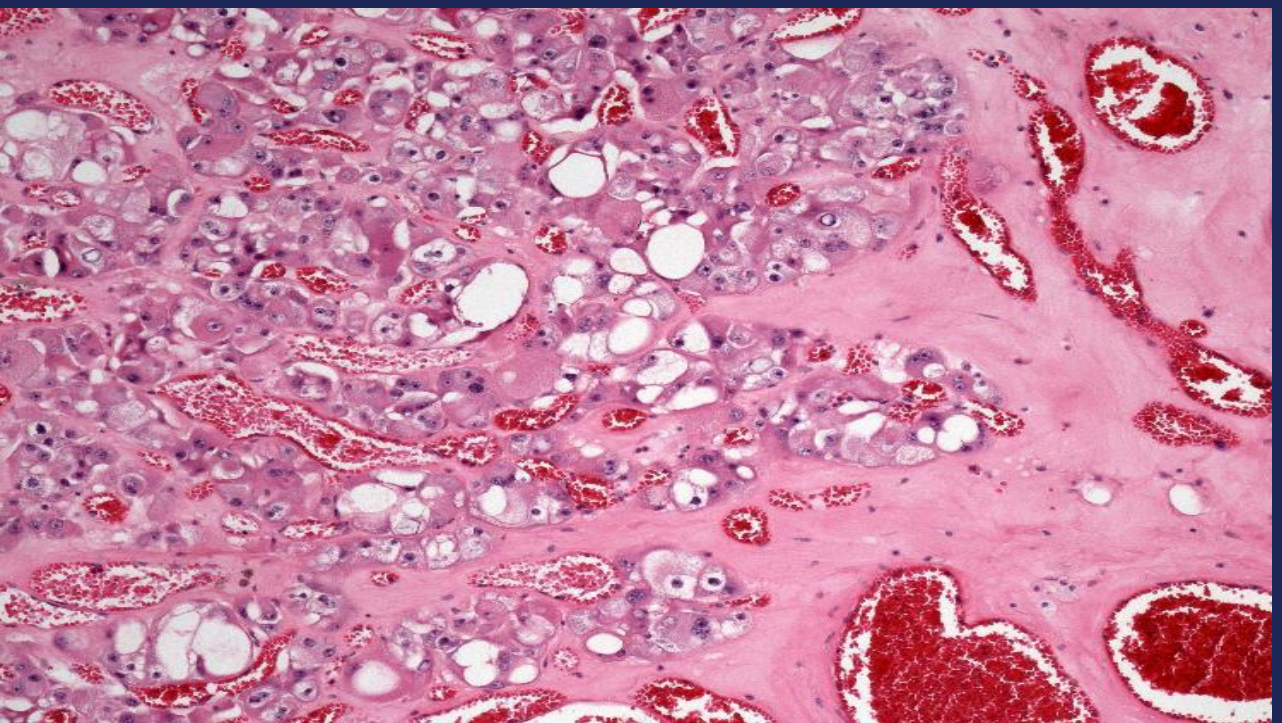
Genetic Characteristics of Sporadic ESC RCC

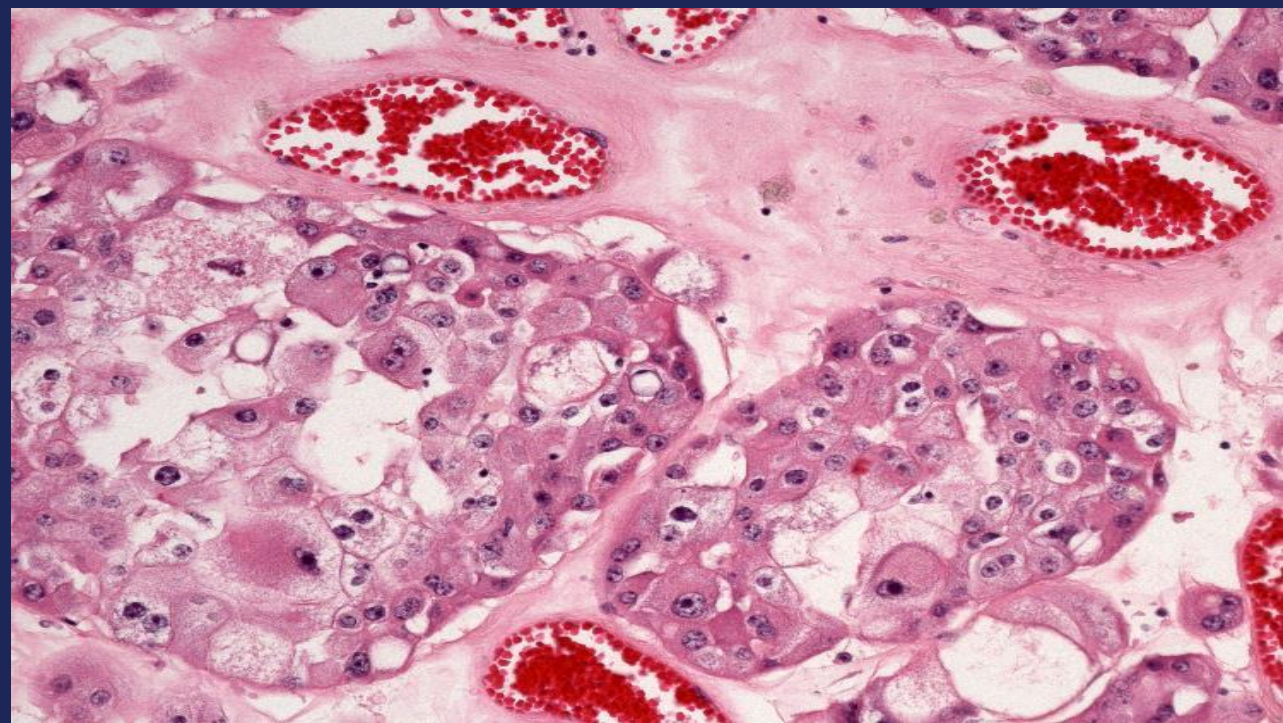
Parilla *et al* (AJSP 2018)	Mehra *et al* (Eur Urol 2018)	Palsgrove *et al* (AJSP 2018)	
2	7	19 (including 3 ESC-like, 1 oncocytoid RCC s/p neuroblastoma)	
TSC2 (2)	*TSC2* (5) *TSC1* (2)	*TSC2* (11) *TSC1* (6)	*TSC2* (18/26) *TSC1* (8/26)
Somatic (2)	Somatic (7)	Somatic ?	Somatic (9/9)
Biallelic?	Biallelic (6)	Biallelic?	Biallelic (6/6)



RCC with Eosinophilic and Vacuolated Cytoplasm Harbors Mutations in TSC/mTORC1 genes (Chen YB et al, AJSP, 2019)

- 7 unclassified oncocytic tumors
- 3/5 somatic inactivating mutations of *TSC2*
- 2/5: activating mutations of *mTORC1*

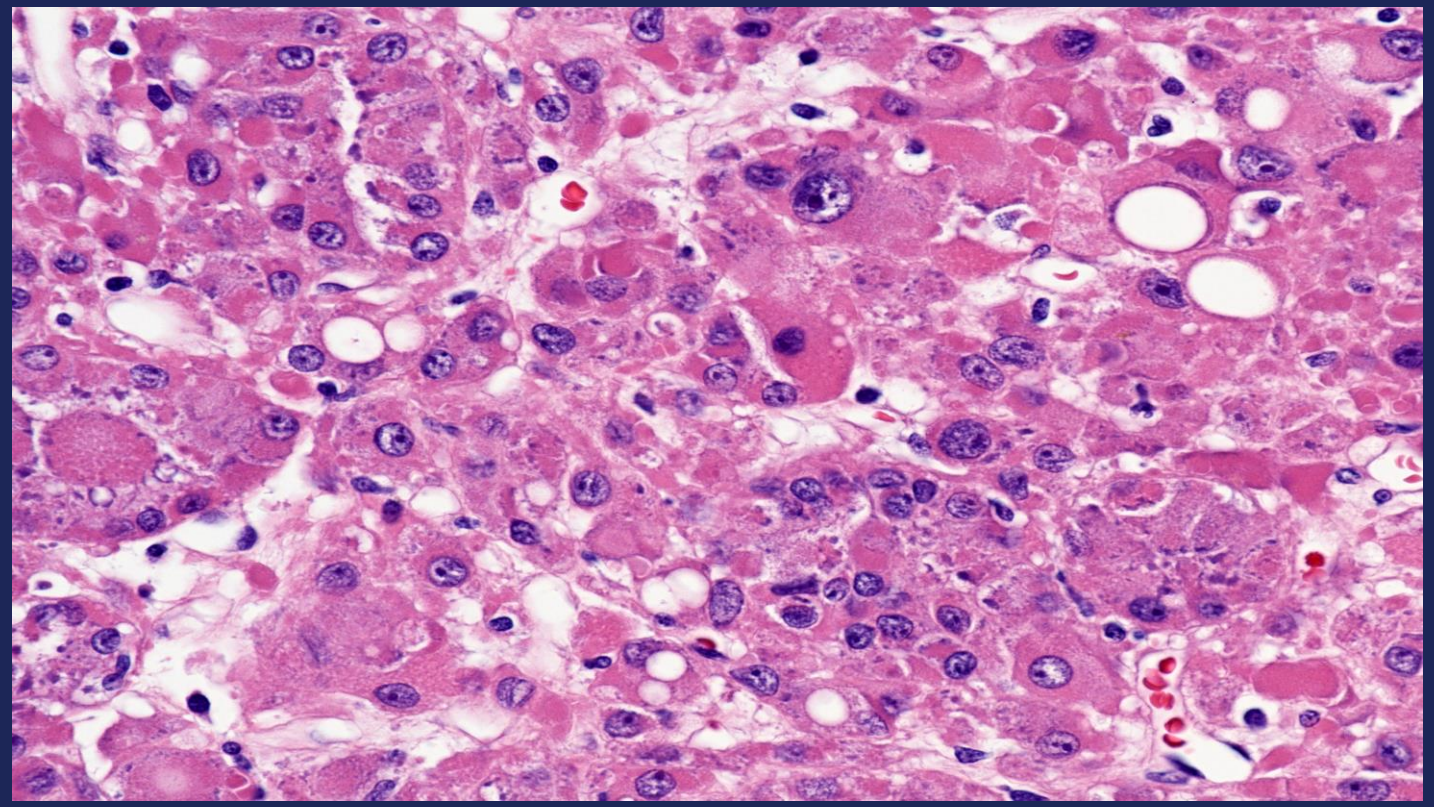


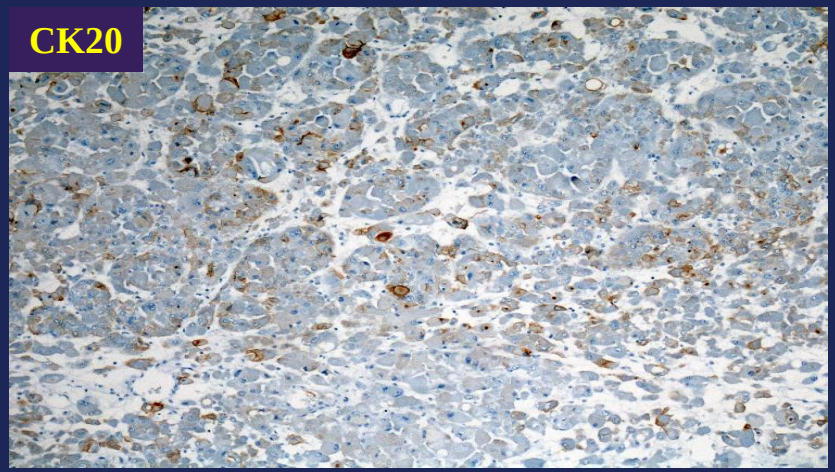


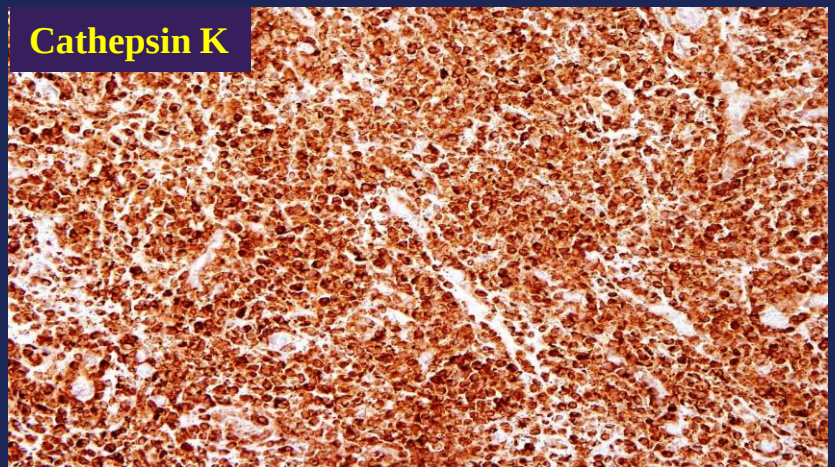
RCC with Somatic *TSC/mTORC1* Mutations: A Distinct Entity

Similar morphology

- ✓ Pink cell tumor with abundant eosinophilic cytoplasm
- ✓ Basophilic stippling +/-, and/or vacuolation
- ✓ CK20 f+, cathepsin K+







Working up “pink cell tumors”…

Common RCC types

- Clear cell RCC with granular cytoplasm
- Papillary RCC, type 2
- Chromophobe RCC, eosinophilic variant
- Oncocytoma

Looking for well-differentiated areas to classify

Immunohistochemistry

Markers / Diagnosis	CK7	CAIX	AMACR	CD117
CCRCC with granular cytoplasm	-	+	-/+	-
PRCC, type 2	-/+	-	+	-
ChRCC, eosinophilic type	+	-	-/+	+
Oncocytoma	+	-	-	+

Working up “pink cell tumors”…

New RCC entities

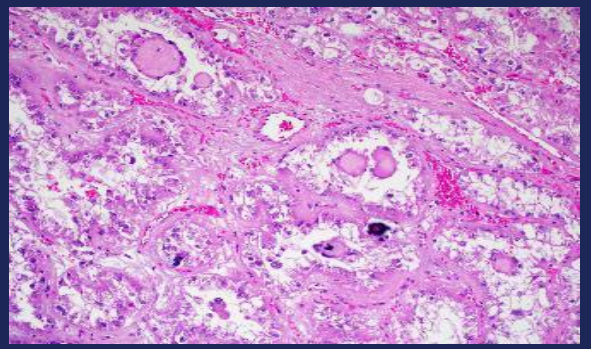
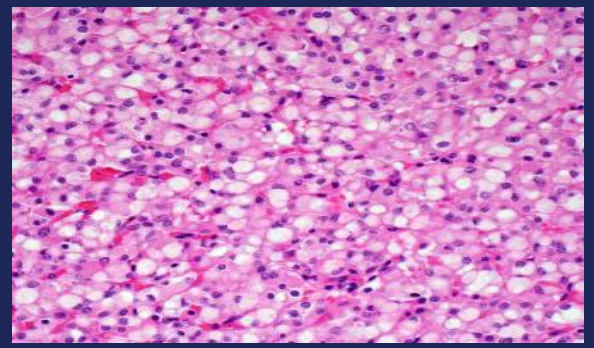
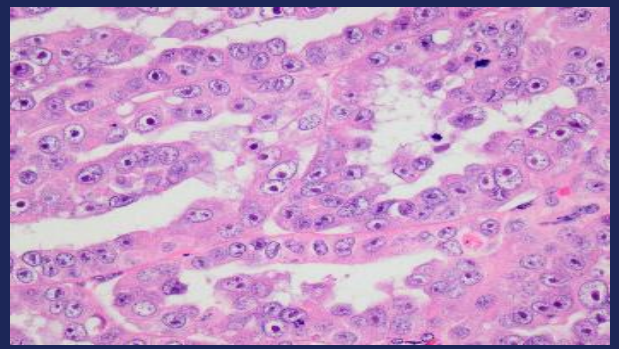
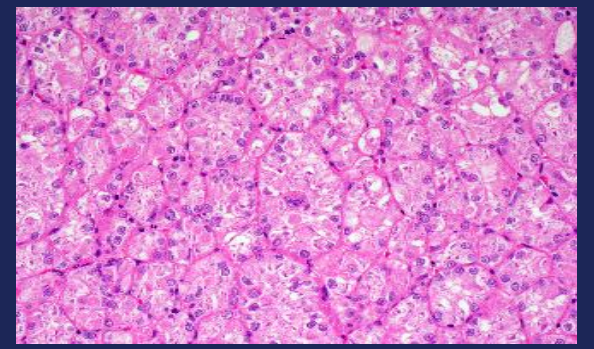
- **Translocation RCC**
- **Acquired cystic disease associated RCC**
- **Succinic dehydrogenase (SDH)-deficient RCC**
- **Fumarate hydratase (FH)-deficient RCC, including HLRCC/RCC**
- ***TSC/mTORC* mutated RCC, including eosinophilic solid cystic RCC**
- **Hybrid oncocytic tumor (HOT) in Birt-Hogg-Dube syndrome (BHD)**

“Odd” Oncocytic Tumors

↓

Characteristic Morphology

Translocation RCC
SDH-deficient RCC
FH-deficient RCC
***TSC/mTORC* 1 RCC**

YES

NO

Confirm with IHC/FISH/sequencing

YES

IHC panel
SDHB
FH
CK20/Cathepsin K
TFE3/TFEB

↓

Translocation RCC
SDH-deficient RCC
FH-deficient RCC
TSC/mTORC RCC

NO

RCC, unclassified type

Mzhou3@Tuftsmedicalcenter.org