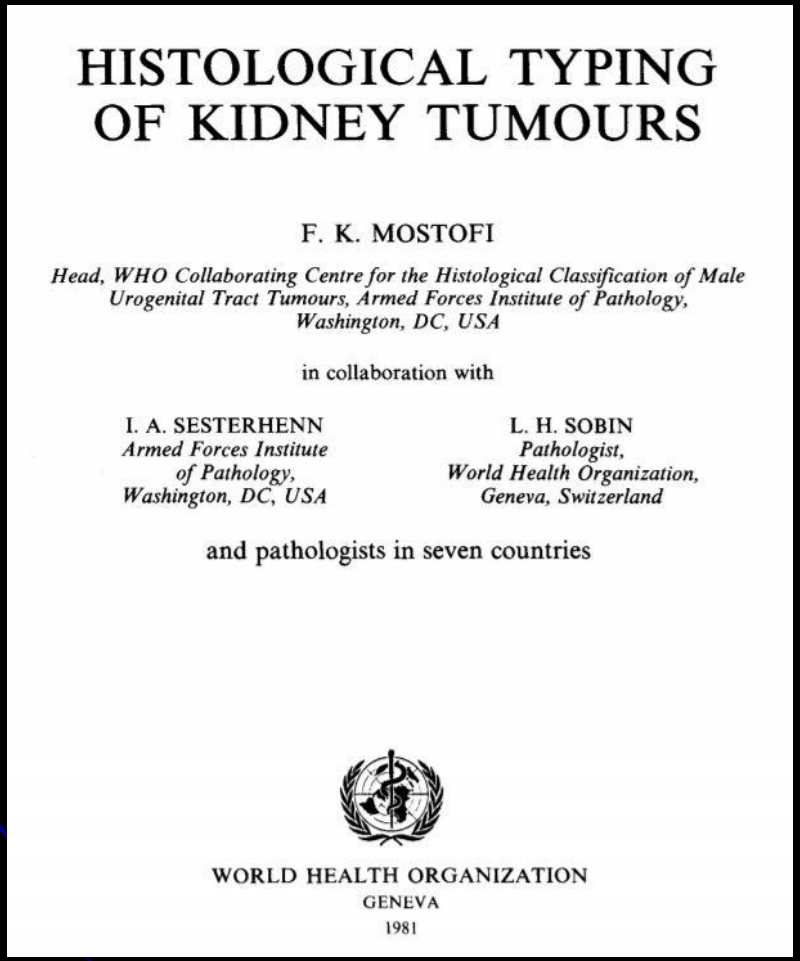
Eosinophilic Renal Tumors: Current Concepts

Sara M Falzarano, MD, PhD
University of Florida College of Medicine
Gainesville, Florida

Objectives

- Discuss renal cell tumor classification with emphasis on renal neoplasms exhibiting predominantly eosinophilic cytoplasm
- Provide an algorithmic approach to differential diagnosis of eosinophilic renal tumors
- Review salient characteristics of select eosinophilic renal tumors including novel and emerging entities with potential clinical implications

World Health Organization (WHO) First Classification of Renal Tumors: The Good Old Days…



HISTOLOGICAL TYPING OF KIDNEY TUMOURS

F. K. MOSTOFI

Head, WHO Collaborating Centre for the Histological Classification of Male Urogenital Tract Tumours, Armed Forces Institute of Pathology, Washington, DC, USA

in collaboration with

I. A. SESTERHENN
Armed Forces Institute of Pathology, Washington, DC, USA

L. H. SOBIN
Pathologist, World Health Organization, Geneva, Switzerland

and pathologists in seven countries

WORLD HEALTH ORGANIZATION
GENEVA
1981

…When They All Fit in One Column…

HISTOLOGICAL CLASSIFICATION OF KIDNEY TUMOURS

I. EPITHELIAL TUMOURS OF RENAL PARENCHYMA

A.	Adenoma	8140/0*
B.	Carcinoma	
	1. Renal cell carcinoma	8312/3
	2. Others	

II. EPITHELIAL TUMOURS OF RENAL PELVIS

A.	Transitional cell papilloma	8120/0
B.	Transitional cell carcinoma	8120/3
C.	Squamous cell carcinoma	8070/3
D.	Adenocarcinoma of renal pelvis	8140/3
E.	Undifferentiated carcinoma of renal pelvis	8020/3

III. NEPHROBLASTIC TUMOURS

A.	Nephroblastoma [Wilms' tumour]	8960/3
B.	Mesoblastic nephroma	8960/1
C.	Multilocular cystic nephroma	[a]

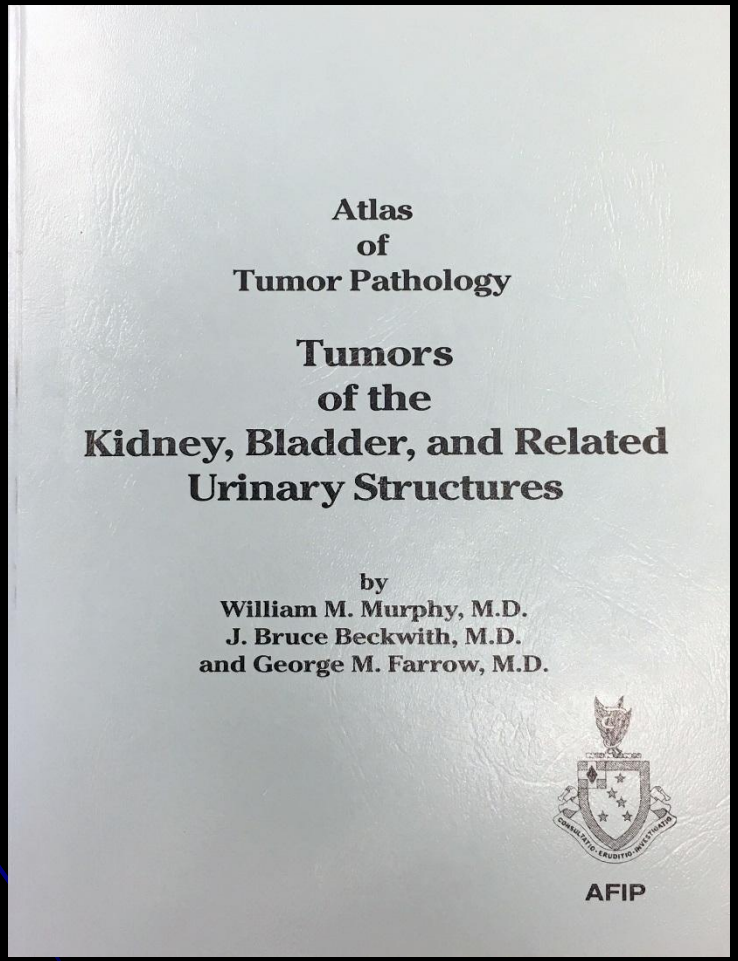
IV. NON-EPITHELIAL TUMOURS

A.	Benign	
	1. Angiomyolipoma	8860/0
	2. Fibroma	8810/0
	3. Haemangioma	9120/0
	4. Others	
B.	Malignant	

V. MISCELLANEOUS TUMOURS

A.	Juxtaglomerular cell tumour	8361/1
B.	Others	

A Classification Based on Age, Cell Type and Growth Pattern



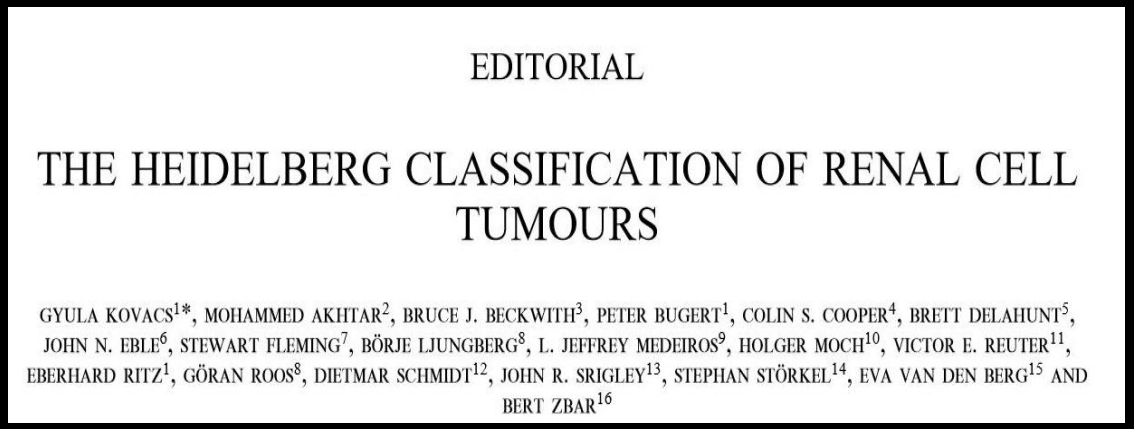
A Classification Based on Age, Cell Type and Growth Pattern

Epithelial Tumors of Adults 1994

- Renal cell carcinoma (RCC)
  - ✓ Clear cell (hypernephroid) type
  - ✓ Papillary type
  - ✓ Granular cell type
  - ✓ Chromophobe cell type
  - ✓ Sarcomatoid type
  - ✓ Collecting duct type
- Renal cortical adenoma
- Oncocytoma

Murphy WM et al. 1994 Atlas of Tumor Pathology (third series)

1997 Update on Renal Cell Tumors: A classification based on genetic knowledge



EDITORIAL

THE HEIDELBERG CLASSIFICATION OF RENAL CELL TUMOURS

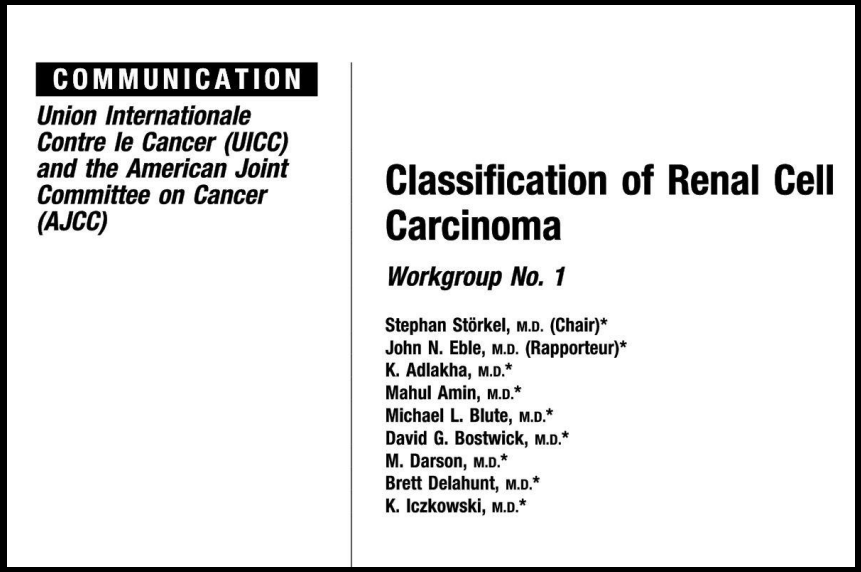
GYULA KOVACS[1]*, MOHAMMED AKHTAR[2], BRUCE J. BECKWITH[3], PETER BUGERT[1], COLIN S. COOPER[4], BRETT DELAHUNT[5], JOHN N. EBLE[6], STEWART FLEMING[7], BÖRJE LJUNGBERG[8], L. JEFFREY MEDEIROS[9], HOLGER MOCH[10], VICTOR E. REUTER[11], EBERHARD RITZ[1], GÖRAN ROOS[8], DIETMAR SCHMIDT[12], JOHN R. SRIGLEY[13], STEPHAN STÖRKEL[14], EVA VAN DEN BERG[15] AND BERT ZBAR[16]

- Conclusions of a workshop entitled 'Impact of Molecular Genetics on the Classification of Renal Cell Tumours', held in Heidelberg in October 1996

Kovacs G et al. Journal of Pathology 1997; 183:131-133

Renal Cell Tumors: 1997 Update
The “principles” of Heidelberg Classification

1. Based on morphology yet in line with the “genetic facts”
2. Simple, unambiguous terms reflecting a salient morphologic feature of the neoplasm
3. Consistent with historic usage when possible
   - ✓ new term if “meaning” significantly changed
4. Terms not descriptions



COMMUNICATION

Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC)

Classification of Renal Cell Carcinoma

Workgroup No. 1

Stephan Störkel, M.D. (Chair)*
John N. Eble, M.D. (Rapporteur)*
K. Adlakha, M.D.*
Mahul Amin, M.D.*
Michael L. Blute, M.D.*
David G. Bostwick, M.D.*
M. Darson, M.D.*
Brett Delahunt, M.D.*
K. Iczkowski, M.D.*

Storkel S et al. Cancer 1997; 80:987-989

“With these principles and classification in mind, the diagnosis of ‘granular cell renal carcinoma’ […] is no longer useful”

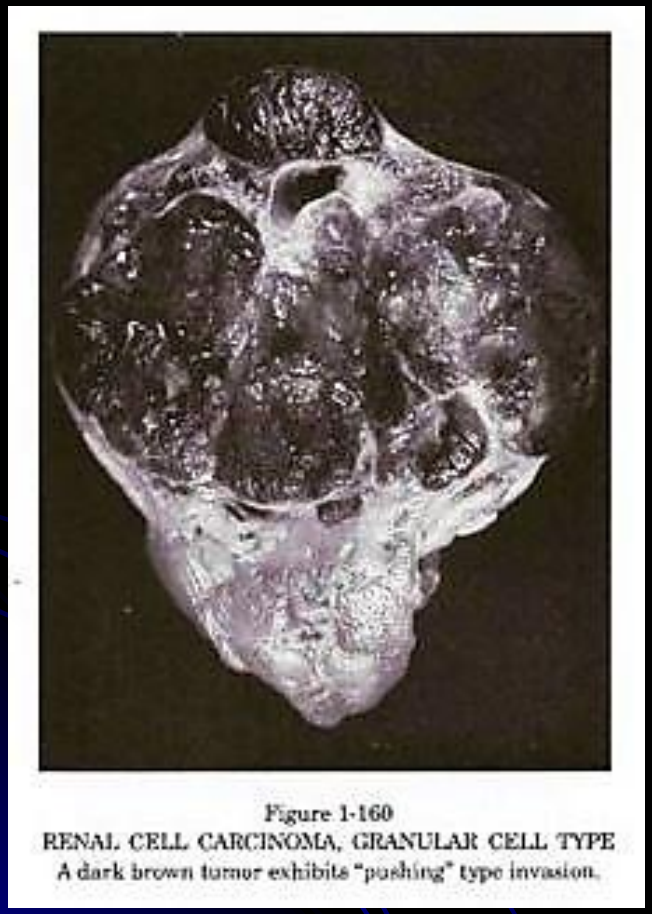


Figure 1-160
RENAL CELL CARCINOMA, GRANULAR CELL TYPE
A dark brown tumor exhibits “pushing” type invasion.

- Oncocytoma
- Chromophobe renal cell carcinoma
- Papillary renal cell carcinoma
- Collecting duct carcinoma
- Epithelioid angiomyolipoma

Reuter V. Seminars in Diagnostic Pathology 1999; 16:135-145
Kovacs G et al. Journal of Pathology 1997; 183:131-133
Storkel S et al. Cancer 1997; 80:987-989

The Pandora box of kidney tumor entities had been opened to generate…

It is very satisfying to know that there is a very tight relationship between the morphological and genetic features of the majority of these tumors. Just as rewarding is the recent evidence that this classification serves to define distinct clinical entities as well.[15]

Reuter V. Seminars in Diagnostic Pathology 1999; 16:135-145

…the ever expanding [double-column] list…

- Renal cell tumours
  - 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
  - Other renal tumours
    - Clear cell papillary renal cell tumour
    - Mucinous tubular and spindle cell carcinoma
    - Tubulocystic renal cell 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 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
- Metanephric tumours
  - Metanephric adenoma
  - Metanephric adenofibroma
  - Metanephric stromal tumour
- Mixed epithelial and stromal renal tumours
  - Mixed epithelial and stromal tumour of the kidney
  - Paediatric cystic nephroma
- Renal mesenchymal tumours
  - Adult renal mesenchymal tumours
    - Classic angiomyolipoma / PEComa of the kidney
    - Epithelioid angiomyolipoma / epithelioid PEComa of the kidney
    - Renal haemangioblastoma
    - Juxtaglomerular cell tumour
    - Renomedullary interstitial cell tumour
  - Paediatric renal mesenchymal tumours
    - Ossifying renal tumour of infancy
    - Congenital mesoblastic nephroma
    - Rhabdoid tumour of the kidney
    - Clear cell sarcoma of the kidney
- Embryonal neoplasms of the kidney
  - Nephroblastic tumours
    - Nephrogenic rests
    - Cystic partially differentiated nephroblastoma
    - Nephroblastoma
- Miscellaneous renal tumours
  - Germ cell tumours of the kidney

Amin MB et al., editors. Chapter 2: Tumours of the kidney. In: WHO Classification of Tumours Editorial Board. Urinary and male genital tumours. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 8). https://publications.iarc.fr.

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Cytoplasmic Eosinophilia is a Common Finding in Renal Neoplasms

In the "Old" entities…

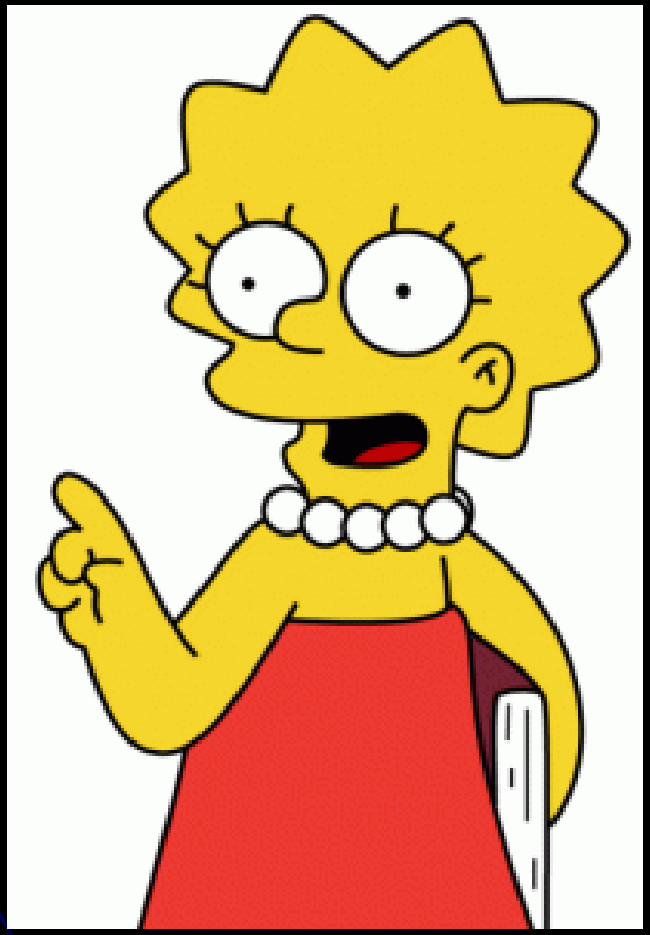
- ✓ Clear cell RCC
- ✓ Papillary RCC
- ✓ Chromophobe RCC
- ✓ Collecting duct/Medullary RCC
- ✓ Unclassified RCC
- ✓ Oncocytoma
- ✓ Angiomyolipoma (PEComa)

…And in Many Other

- ✓ "Other oncocytic tumors"
- ✓ Tubulocystic RCC
- ✓ Acquired cystic disease (ACD)-associated RCC
- ✓ Eosinophilic solid and cystic (ESC) RCC
- ✓ Molecularly defined RCCs
  - SDH-deficient
  - FH-deficient
  - *TFE3/TFEB* rearranged
  - Others

What Do I Do When I Get a Renal Tumor with [Predominant] Eosinophilic Features?

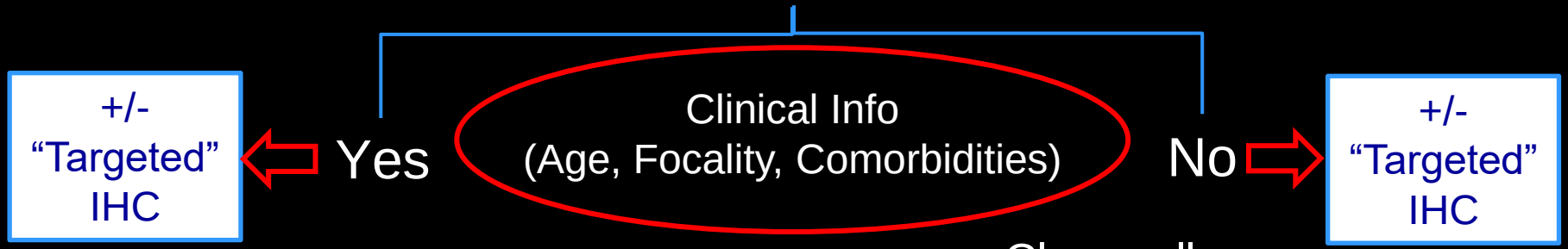
What Do I Do When I Get a Renal Tumor with [Predominant] Eosinophilic Features?



What is the Overarching Architecture?

Non-Papillary

- Could it fit in “Chromophobe/Oncocytoma spectrum”?



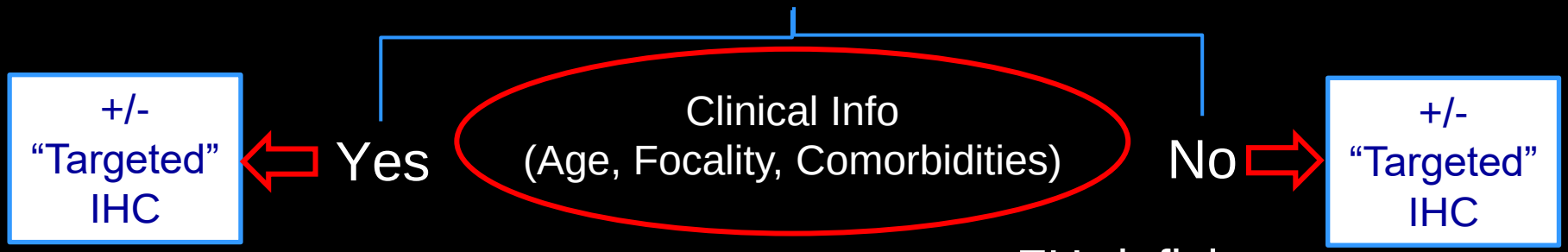
- Chromophobe
- Oncocytoma
- Others
  - ✓ “Hybrid”
  - ✓ EVT
  - ✓ LOT
  - ✓ “ORNLMP”

- Clear cell
- Molecularly defined (SDH,FH,*TFE3/TFEB,etc.*)
- ESC
- (ACD-associated)
- Medullary (+/-SMARCB1)
- “Unclassified” (molecular)
- Non-RCC (PEComas, mets)

What is the Overarching Architecture?

Papillary

- Does otherwise fit criteria for “papillary type”?



- Papillary
  - ✓ Warthin-like
  - ✓ Papillary Renal Neoplasm With Reverse Polarity
  - ✓ Biphasic squamoid alveolar

- FH-deficient
- *TFE3*-rearranged
- (*TFEB*-altered)
- ACD-associated
- Clear cell
- “Unclassified” (molecular)
- Non-RCC

FH = Fumarate Hydratase expression as assessed by immunohistochemistry

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What is the Overarching Architecture?

Papillary

- Does other … pillary type”?

+/- “Targeted” IHC ⇦ Yes

No ⇨ +/- “Targeted” IHC

- Papillary
  - ✓ Warthin-li…
  - ✓ Papillary … Neoplasm … Reverse …
  - ✓ Biphasic … squamoid … alveolar

… deficient
…3-rearranged
…EB-altered)
…D-associated
…ar cell
…classified”
…lecular)
…-RCC

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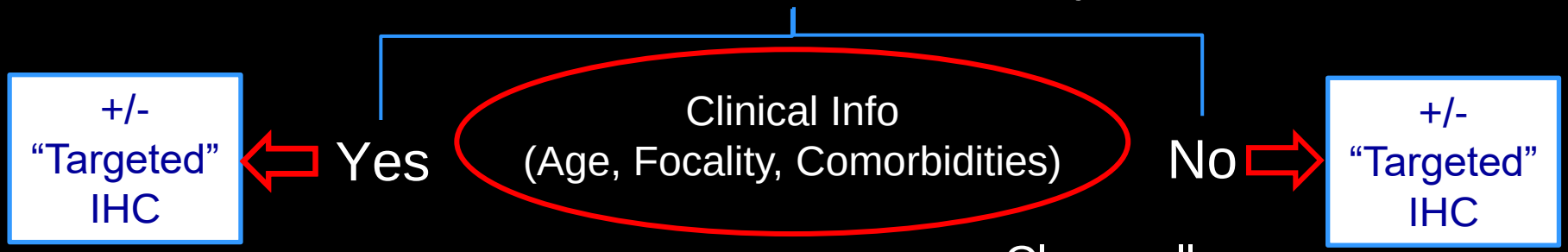

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“Chromophobe/Oncocytoma Spectrum”

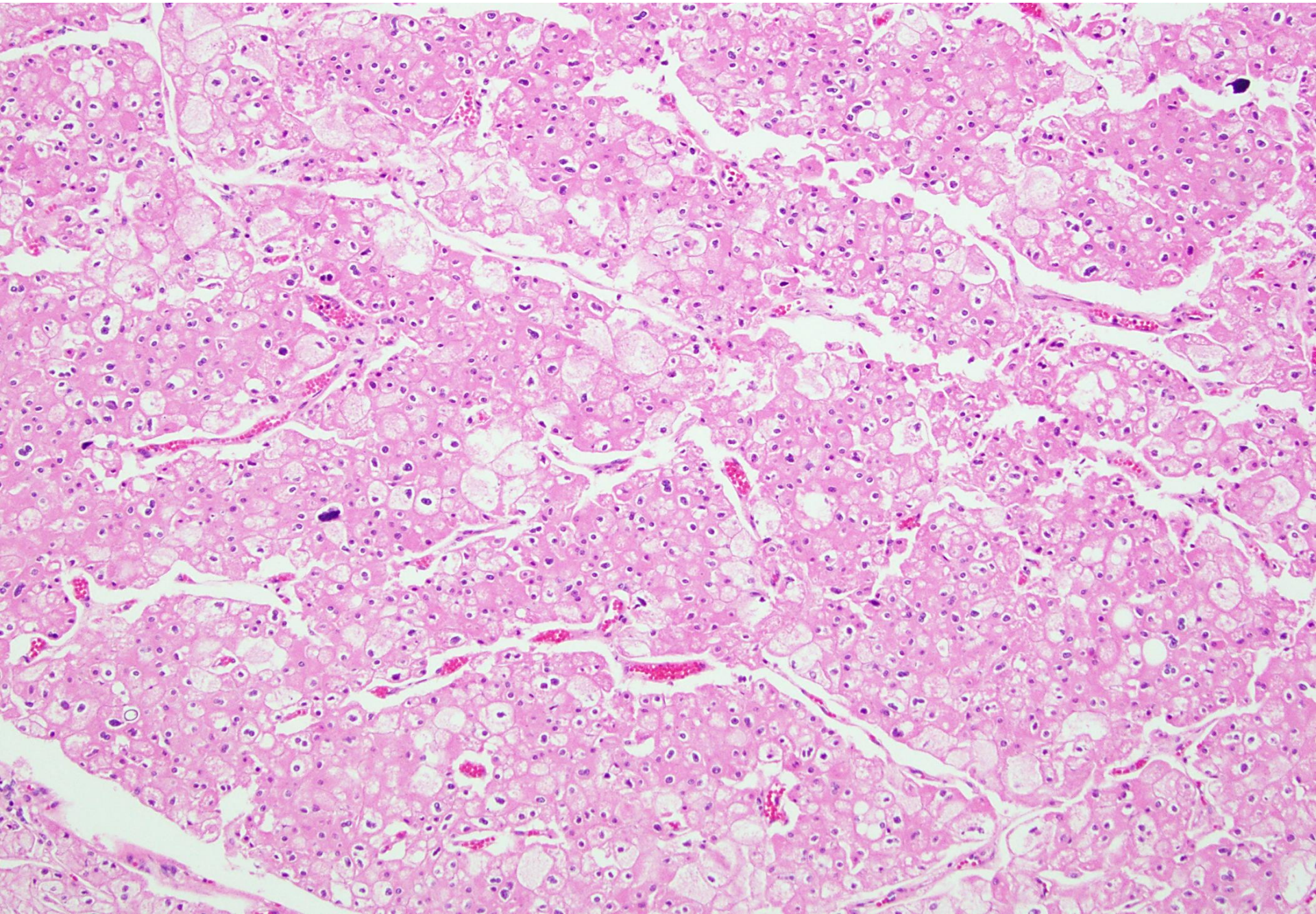
Chromophobe RCC

Chromophobe RCC: Key Points

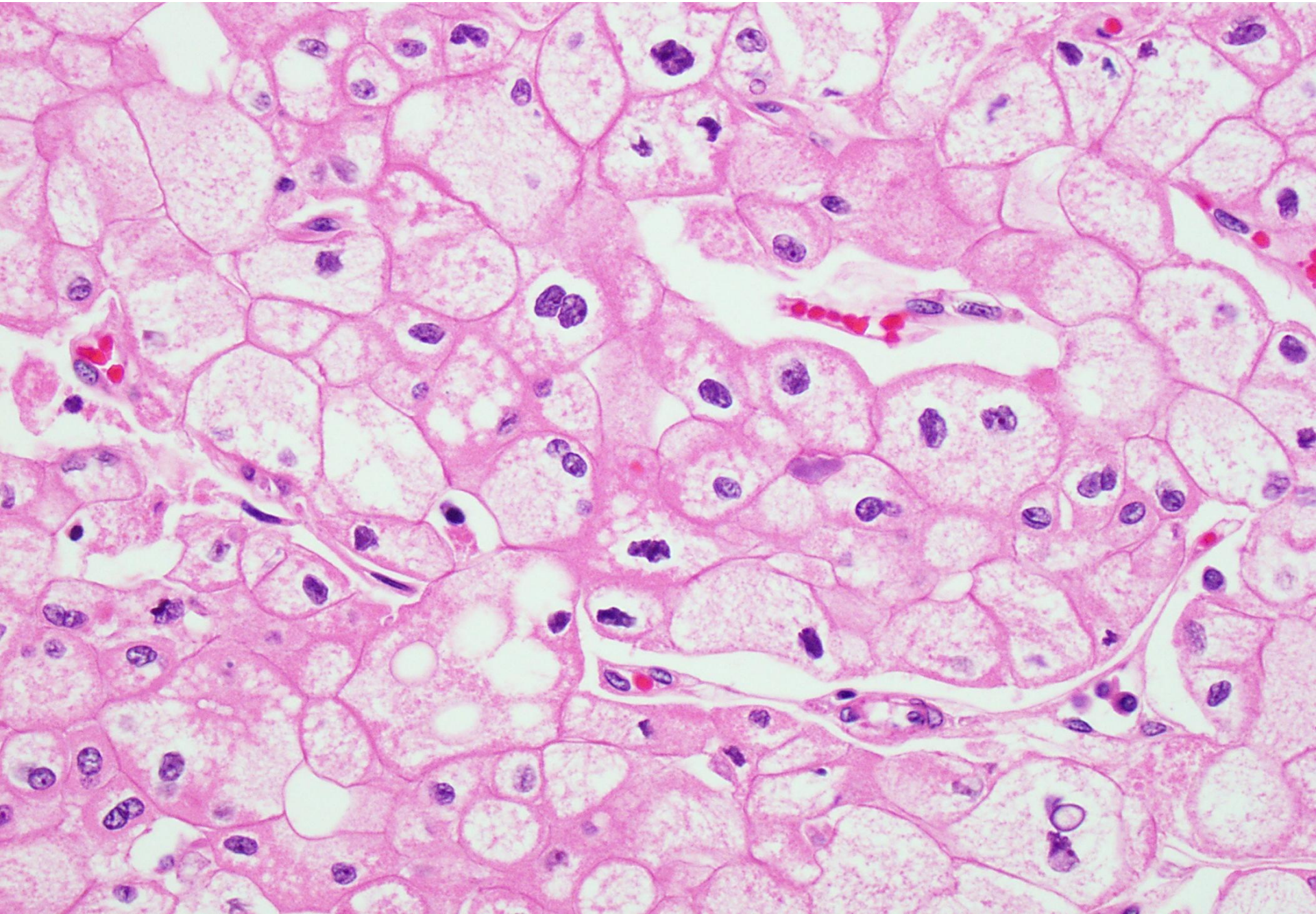
- Age ~6th decade
- Large pale and smaller eosinophilic cells with wrinkled (raisinoid) nuclei, perinuclear halos (‘‘koilocytoid atypia’’), and frequent binucleation
- Chromosome (Ch) 1, 2, 6, 10, 13,17 loss (86%)
- Mitochondrial DNA mutations (~20%)
- Relatively indolent behavior (sarcomatoid features related to aggressiveness)

Amin MB et al. Am J Surg Pathol 2008;32:1822-34
Brunelli M et al. Modern Pathology 2005;18:161–169
Davis CF et al. Cancer Cell. 2014; 26: 319–330

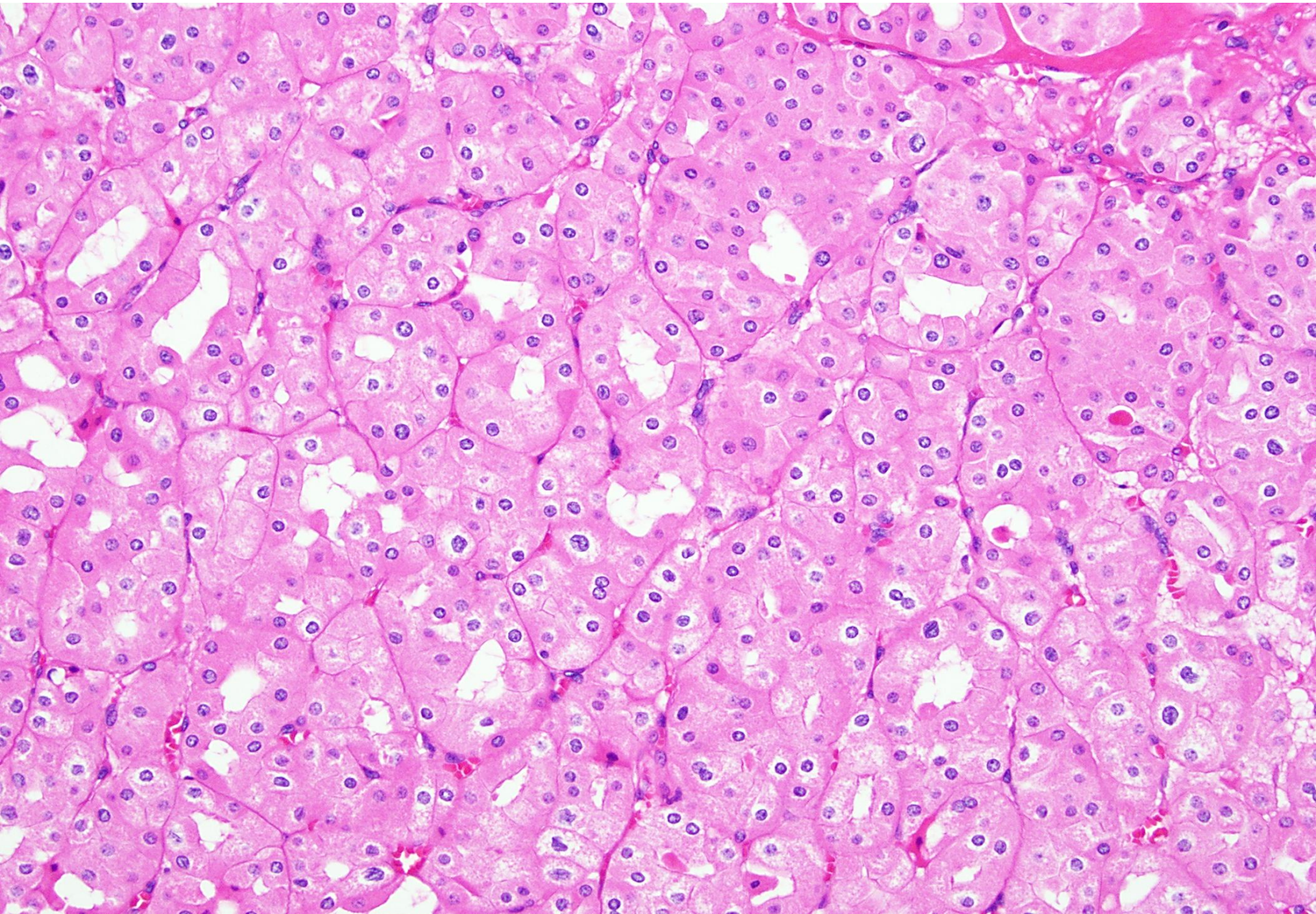
Chromophobe RCC: Classic variant



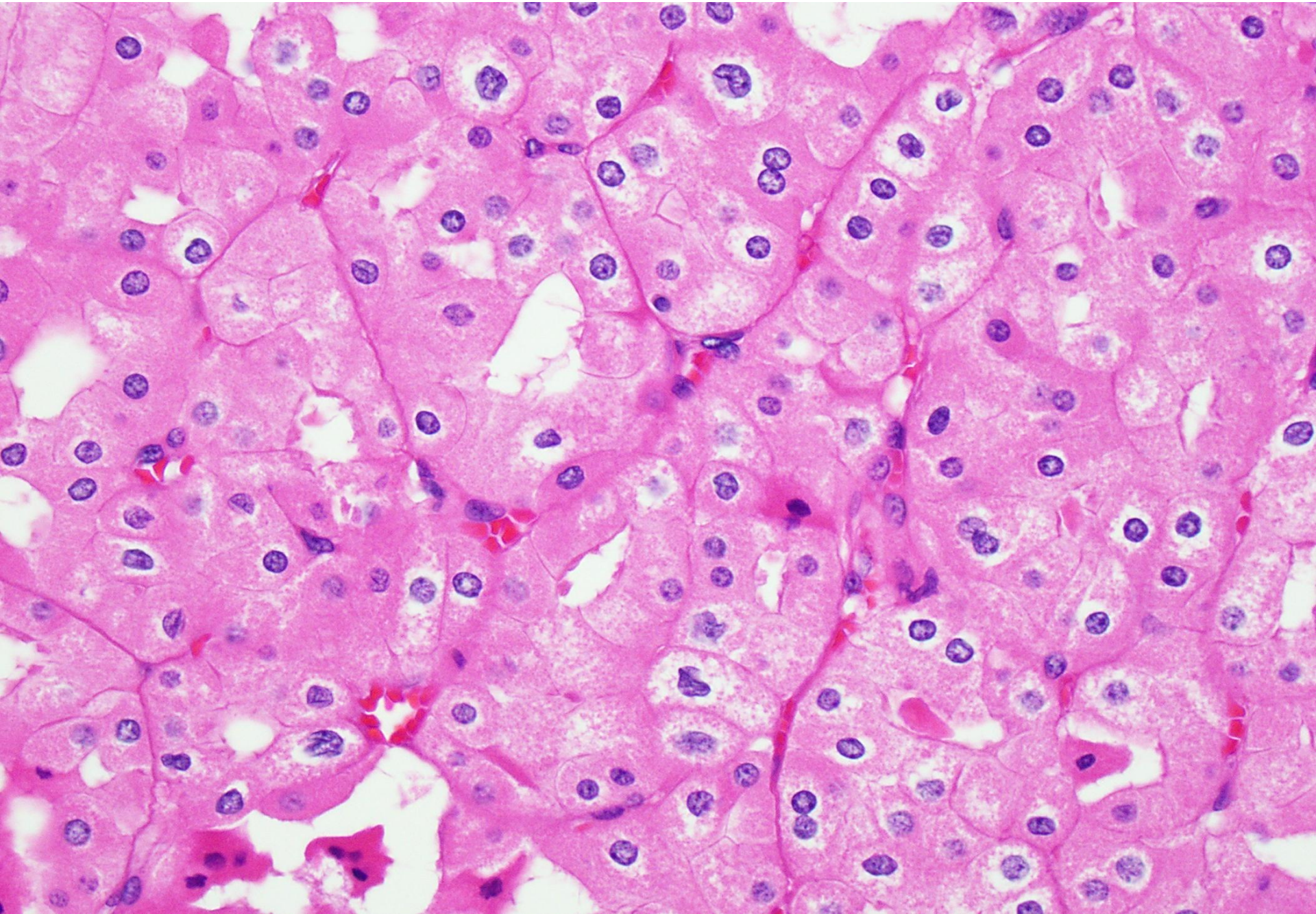
Chromophobe RCC: Raisinoid nuclei



Chromophobe RCC: Eosinophilic variant



Chromophobe RCC: Eosinophilic variant



Chromophobe RCC Ancillary Testing

- (Hale colloidal iron +)
- IHC
  - ✓ Pax-8 +
  - ✓ Cytokeratin 7 +
  - ✓ CD117/C-KIT +
- (Electron Microscopy - Microvesicles)

“Chromophobe/Oncocytoma Spectrum”

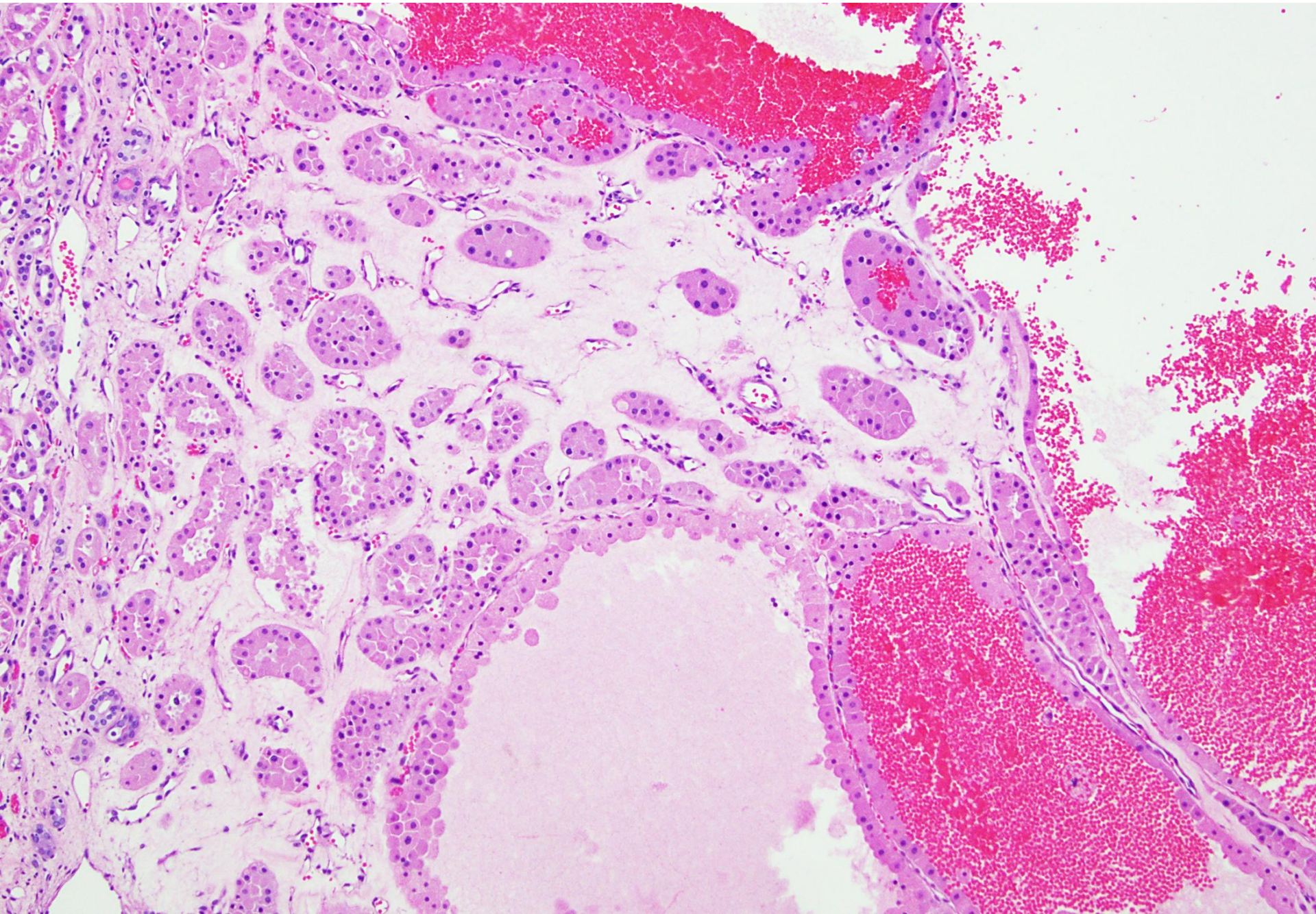
Oncocytoma

Oncocytoma: Key Points

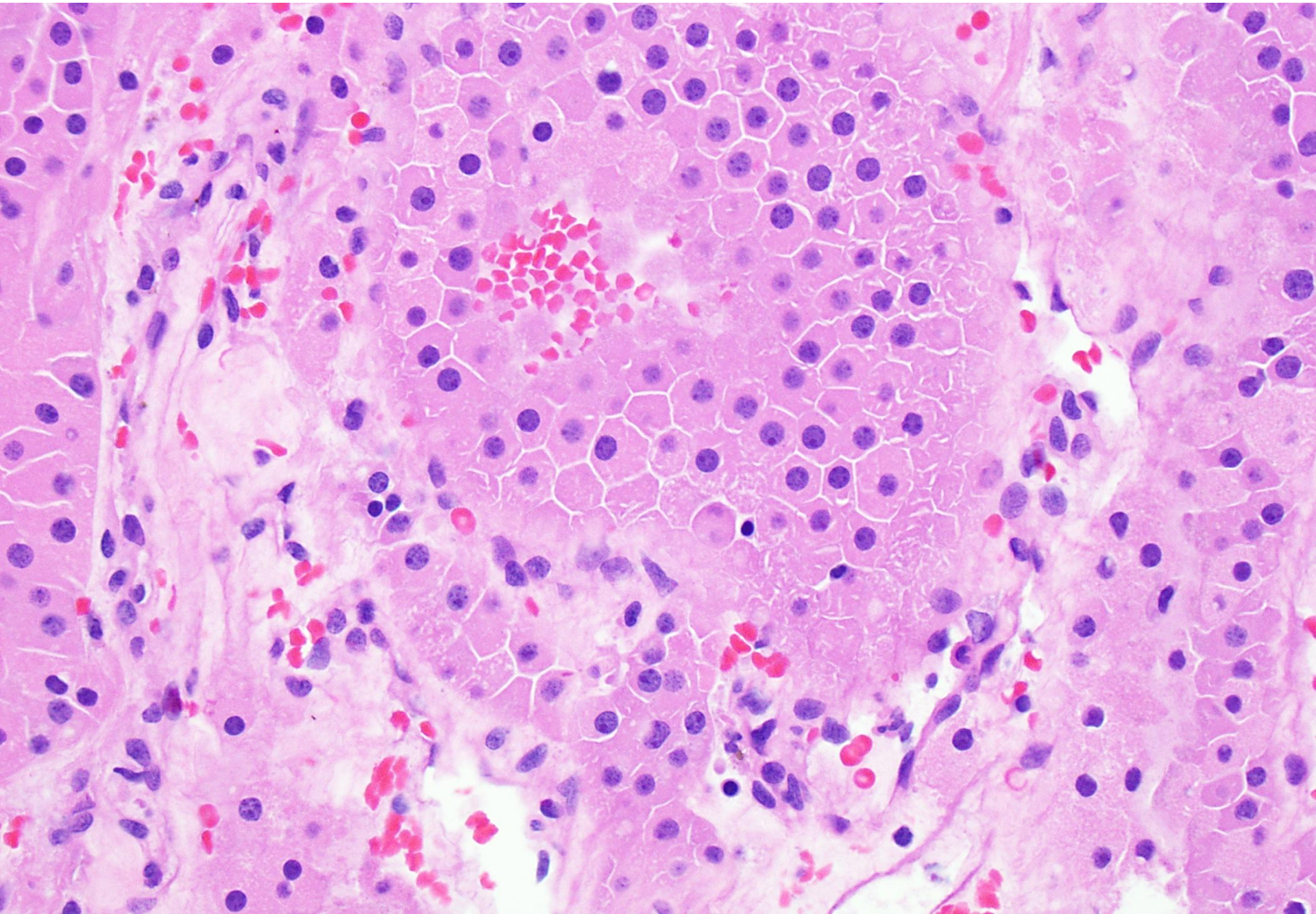
- Age ~6th decade
- Abundant granular eosinophilic cytoplasm, uniform round nuclei with vesicular chromatin and frequently prominent central nucleoli
- Loss of Ch1 and Y
- Translocations of Ch11
- Mitochondrial DNA mutations
- Benign (“atypical” features do not impact prognosis)

Wobker SE and Williamson SR. J Kidney Cancer VHL 2017; 4:1-12
Yusenko M. International Journal of Urology. 2010;17:602-614
Amin MB et al. Am J Surg Pathol. 1997;21:1–12

Oncocytoma



Oncocytoma



Oncocytoma Ancillary Testing

- (Hale colloidal iron -)
- IHC
  - ✓ Pax-8 +
  - ✓ CK7 scattered cell +
  - ✓ CD117/C-KIT +
- (Electron Microscopy – Typical mitochondria)

“Chromophobe/Oncocytoma Spectrum”

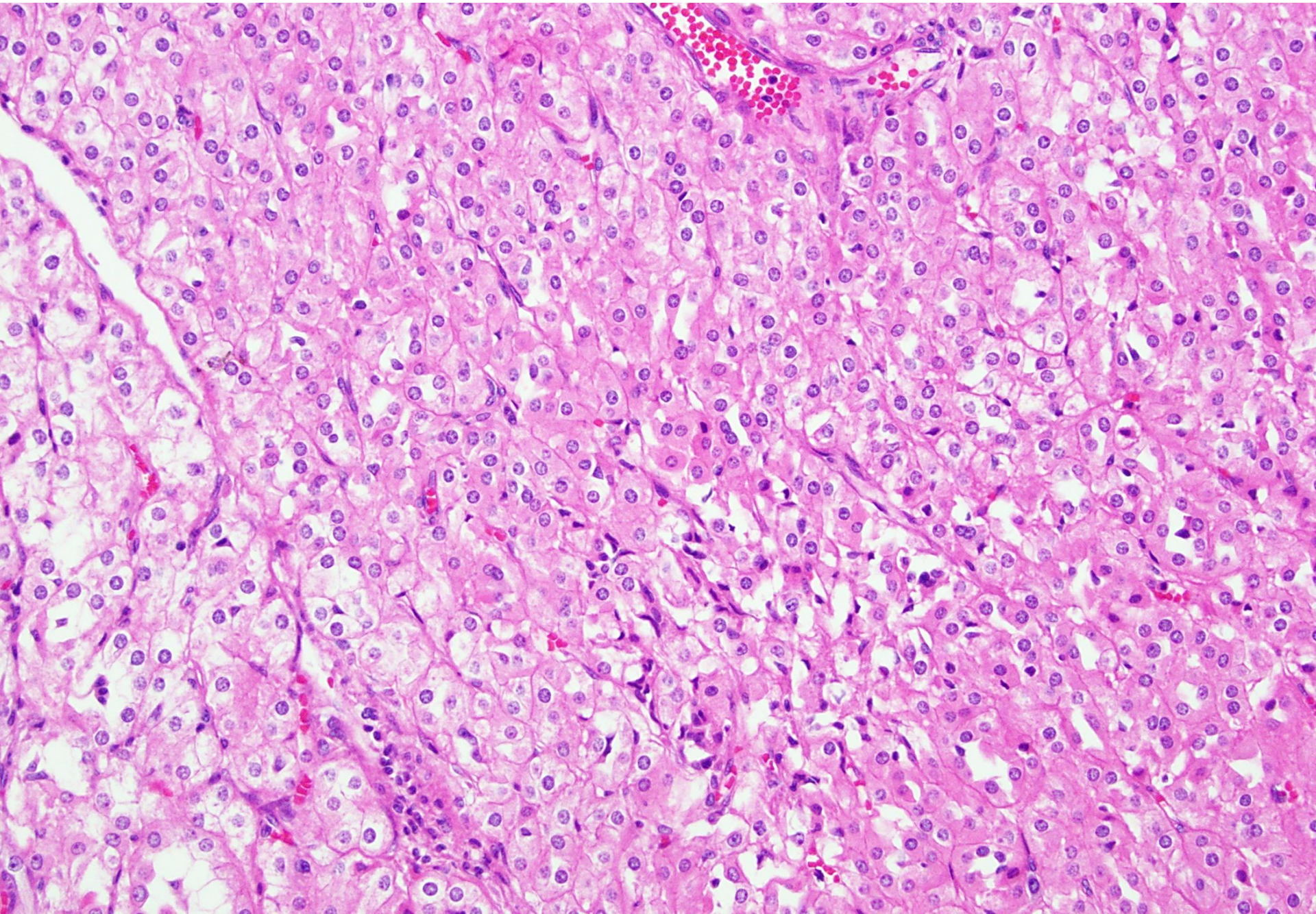
Hybrid Oncocytoma/Chromophobe Tumors (HOCT)

HOCT: Key Points

- Age ~5th decade
- >>> presence of single or clusters of clear cells in an oncocytoma-like background
- Multifocality and background renal oncocytosis
- Germline *FLCN* (folliculin) mutation in Birt-Hogg-Dubé (BHD)
  - ✓ With other clinical features of BHD
- Relatively indolent behavior

Iribe Y et al. Pathology International 2015; 65: 126–132

HOCT



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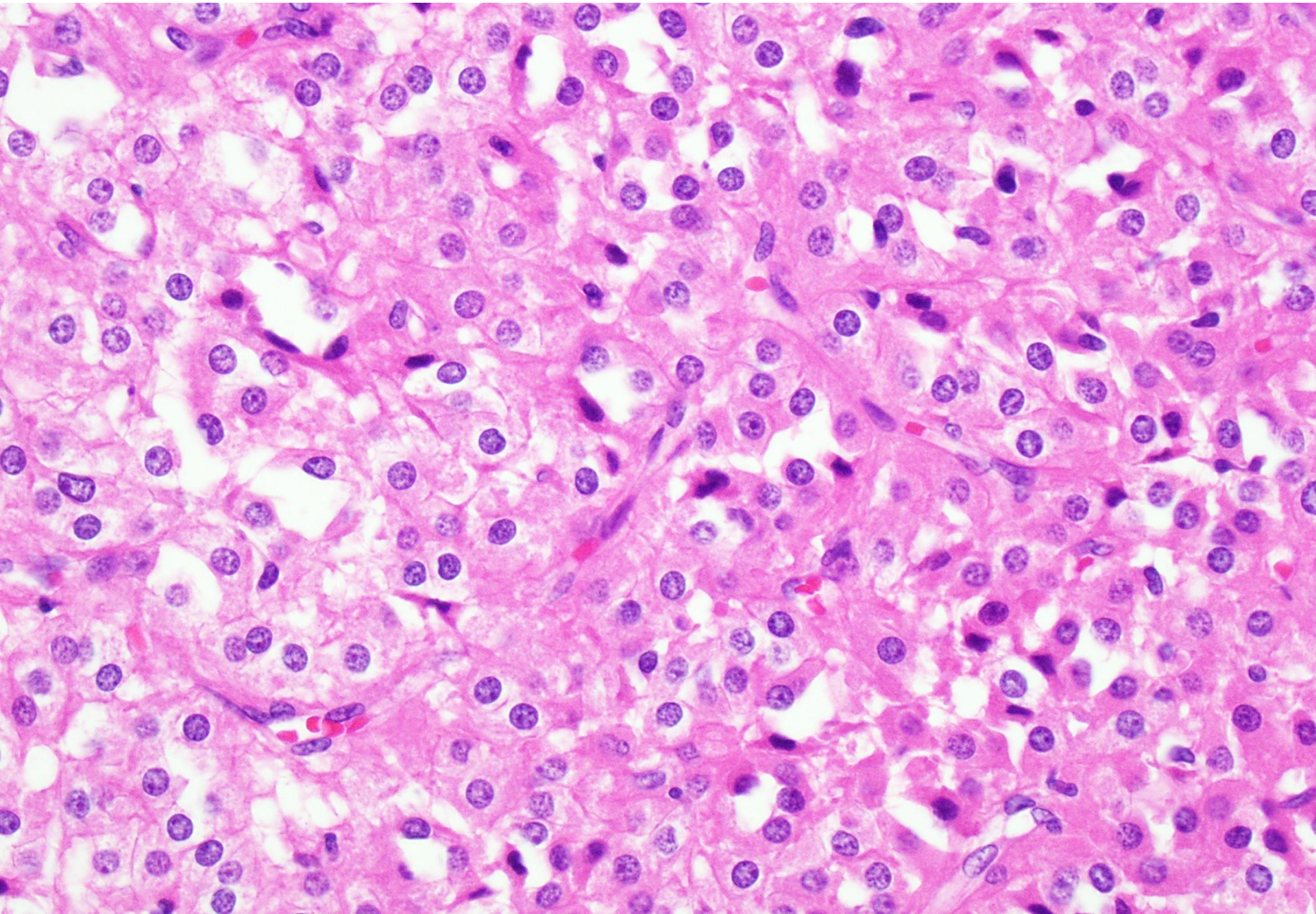
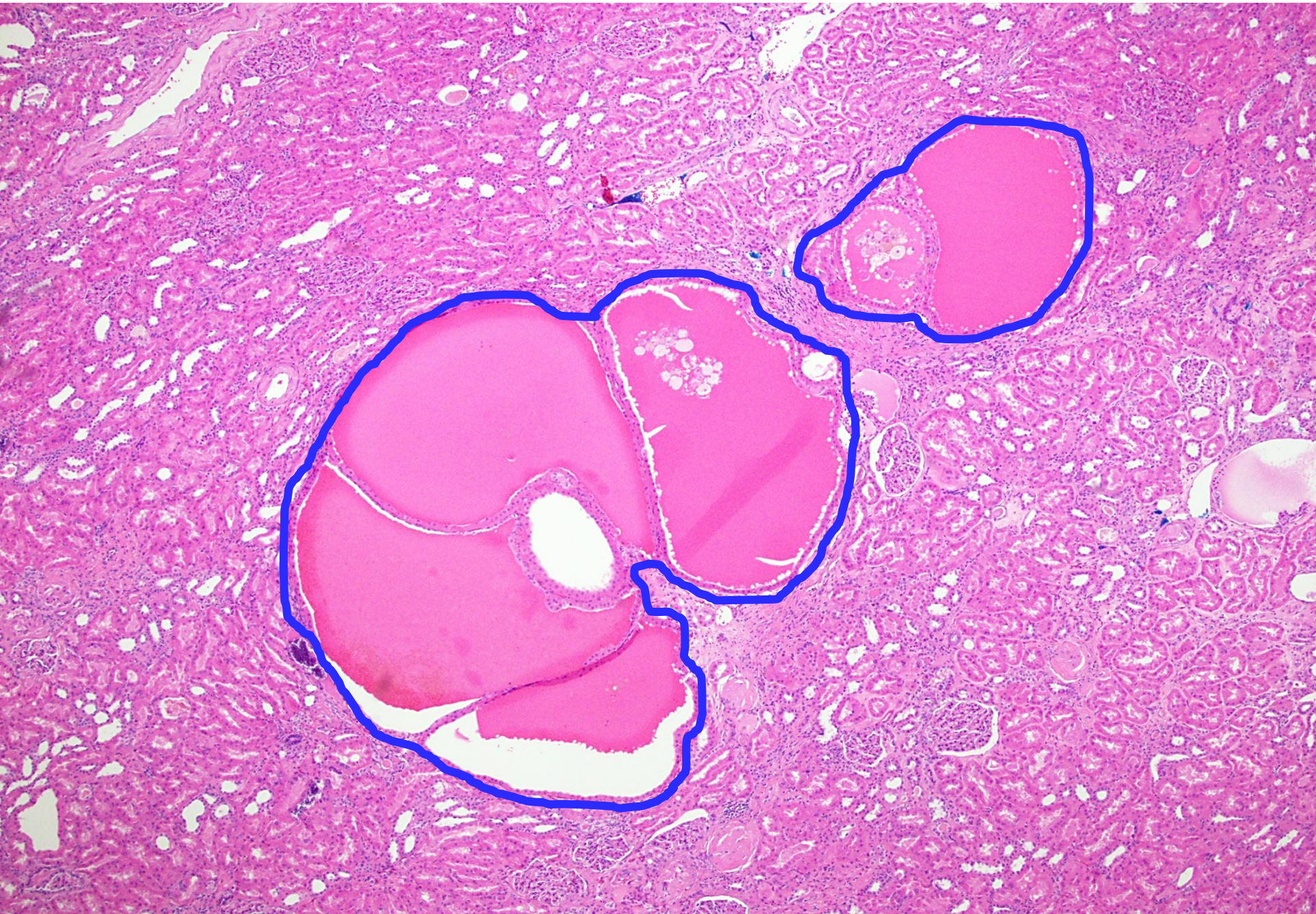


Background kidney



HOCT Ancillary Testing

- Overlapping (“hybrid”) cytochemical and immunohistochemical features with both Chromophobe RCC and oncocytoma

“Chromophobe/Oncocytoma Spectrum”

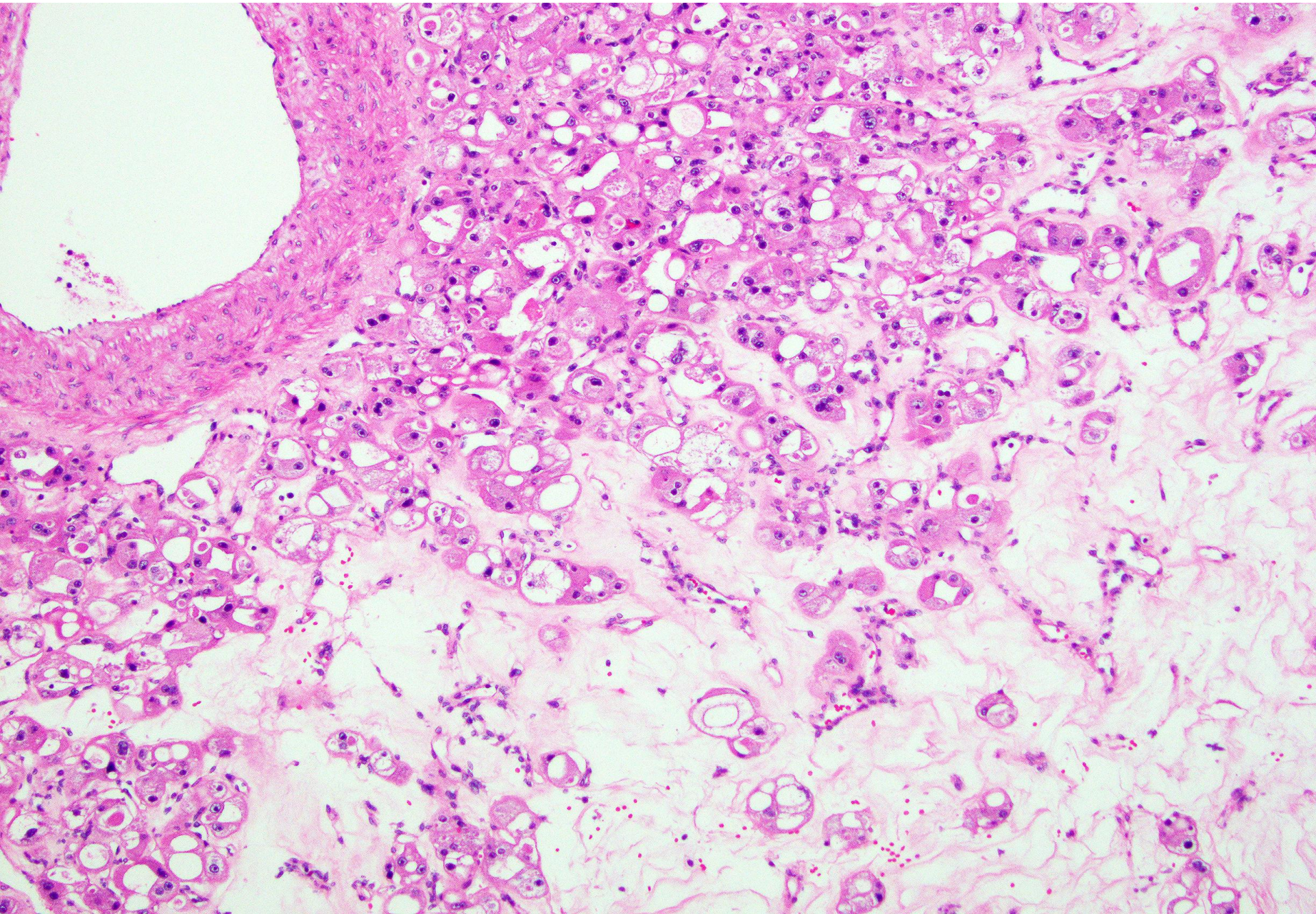
Other Oncocytic Tumors with features of…

Eosinophilic vacuolated tumor (EVT): Key Points

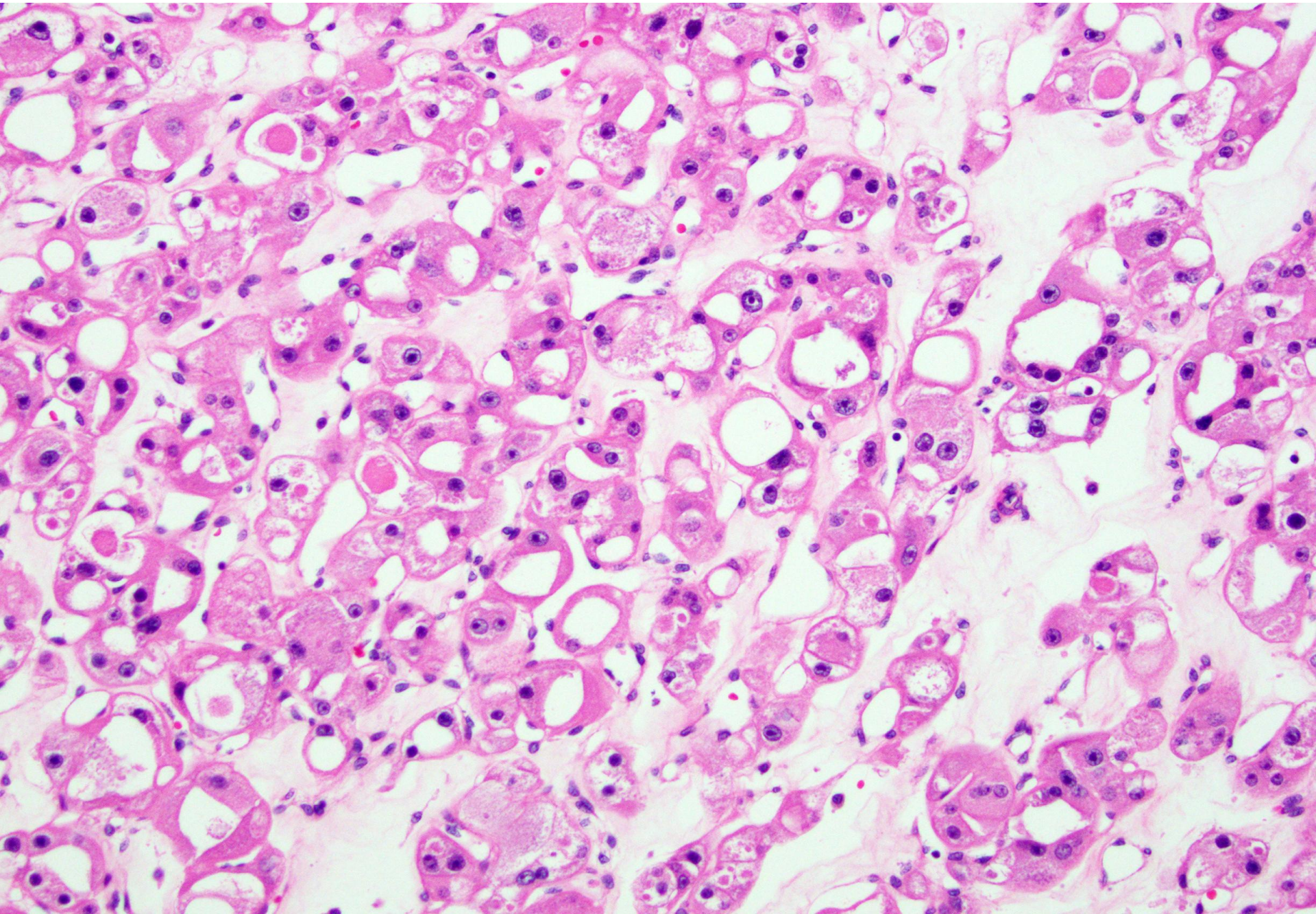
- Also termed “high-grade oncocytic tumour” or “sporadic RCC with eosinophilic and vacuolated cytoplasm”
- Wide age range (median 54 years)
- Solid growth of eosinophilic (oncocytic) cells with frequent large cytoplasmic vacuoles and prominent nucleoli; large vessels at edge
- *TSC1*, *TSC2*, or *MTOR* mutations (limited data)
- Typically indolent behavior (limited data)

Trpkov K et al. Mod Pathol. 2021 Jun;34(6):1167-1184

EVT



EVT



EVT Ancillary Testing

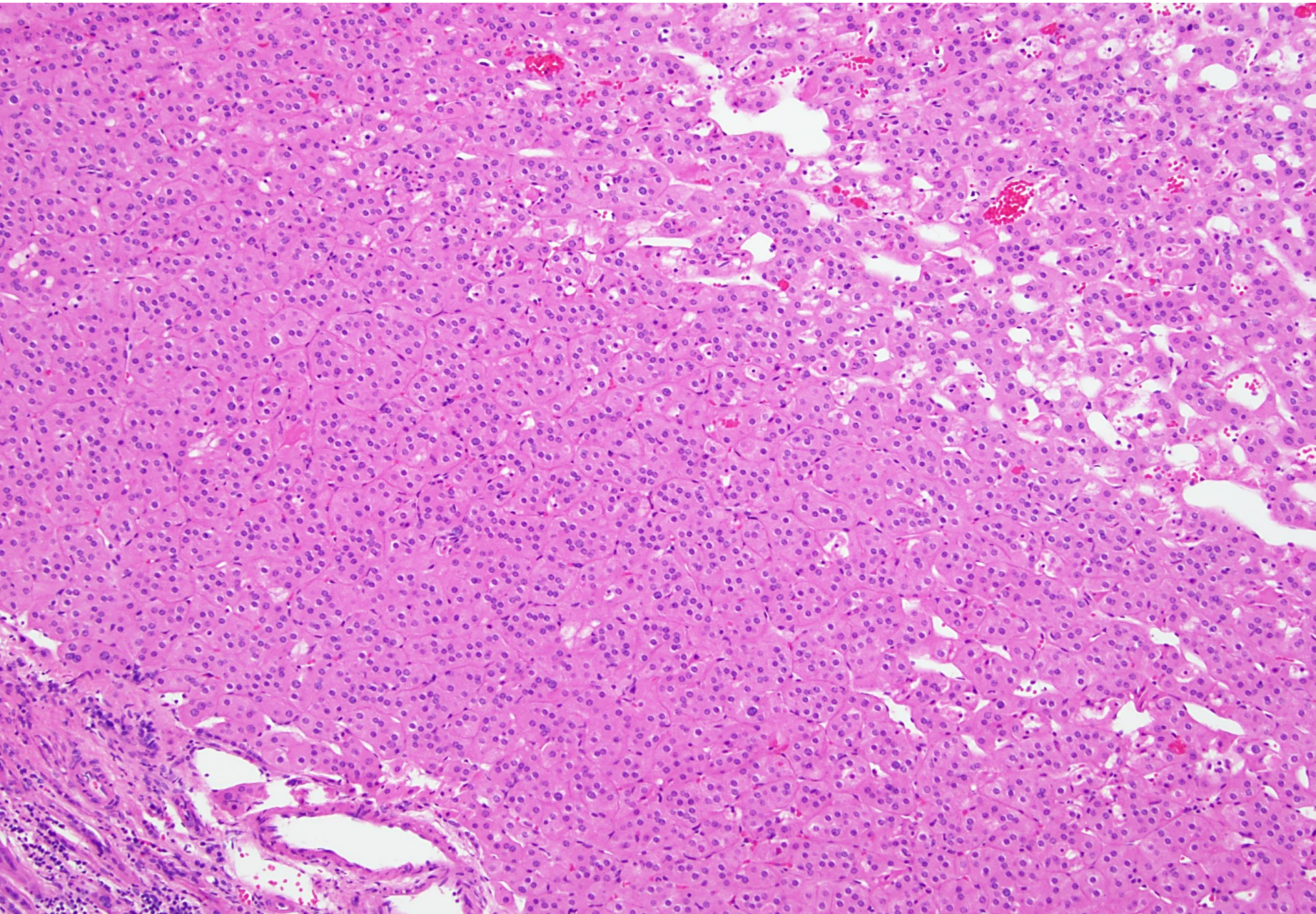
- IHC
  - ✓ Pax-8 +
  - ✓ CD117/C-KIT +
  - ✓ Cathepsin K +
  - ✓ CK7 rare cells
  - ✓ CK20 –
  - ✓ HMB45/melan A -
  - ✓ TFE3 -

Low-grade oncocytic tumor (LOT): Key Points

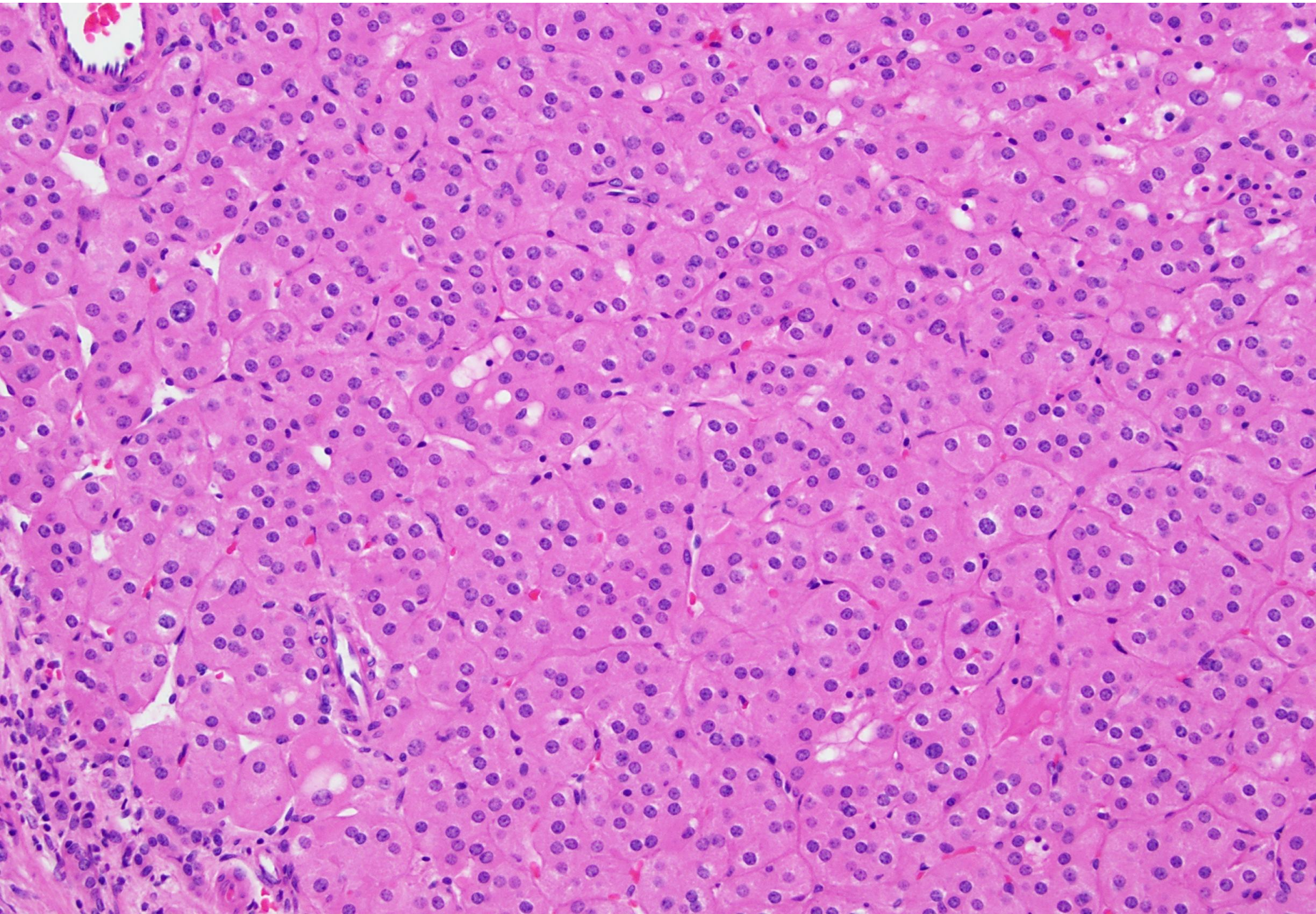
- Older patients
- Solid growth of eosinophilic (oncocytic) cells with bland nuclei lacking prominent nucleoli or nuclear membrane irregularities
- *TSC1*, *TSC2*, or *MTOR* mutations (limited data)
- Typically indolent behavior (limited data)

Trpkov K et al. Mod Pathol. 2021 Jun;34(6):1167-1184

LOT



LOT: bland cytology



LOT Ancillary Testing

- IHC
  - ✓ Pax-8 +
  - ✓ CK7 +
  - ✓ CD117/C-KIT -
  - ✓ CK20 -

All clear so far?

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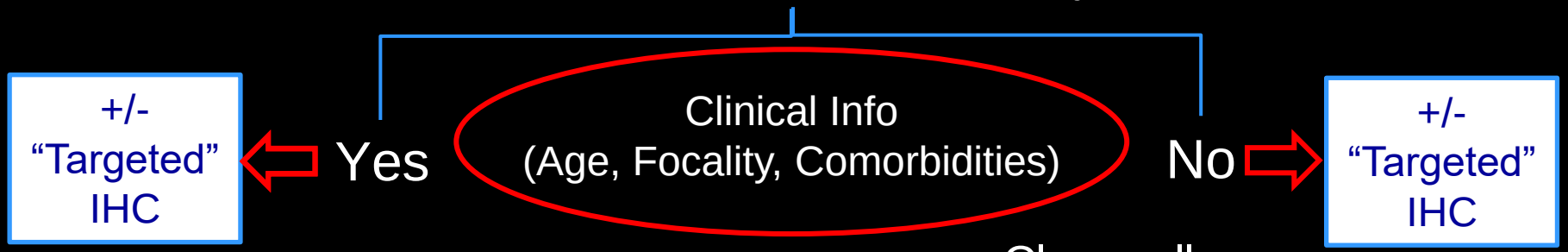

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- ESC
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- Medullary (+/-SMARCB1)
- “Unclassified” (molecular)
- Non-RCC (PEComas, mets)

Distinct Entities Outside of Chromophobe/Oncocytoma Spectrum

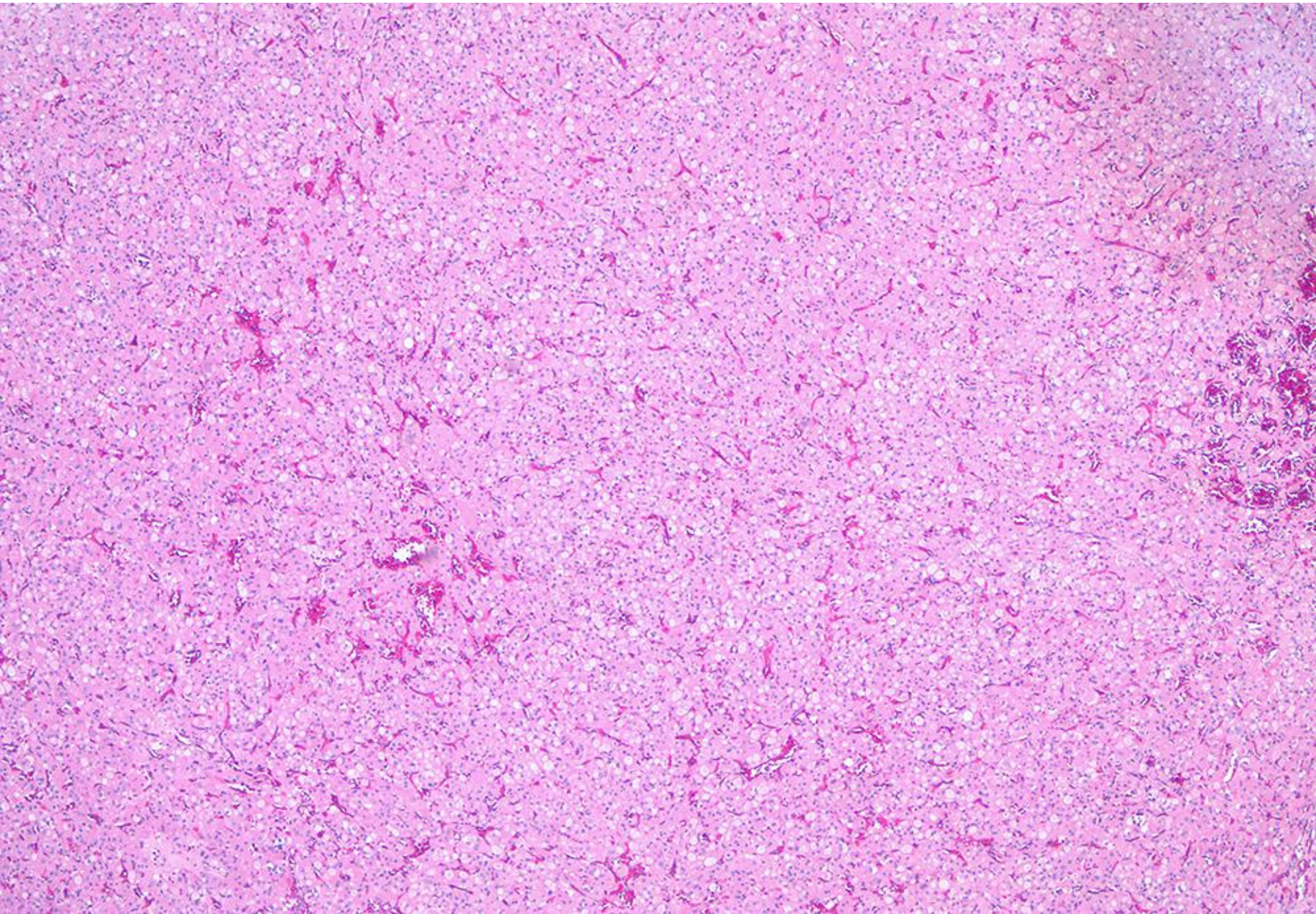
Succinate dehydrogenase (SDH)-deficient RCC

SDH-deficient RCC: Key Points

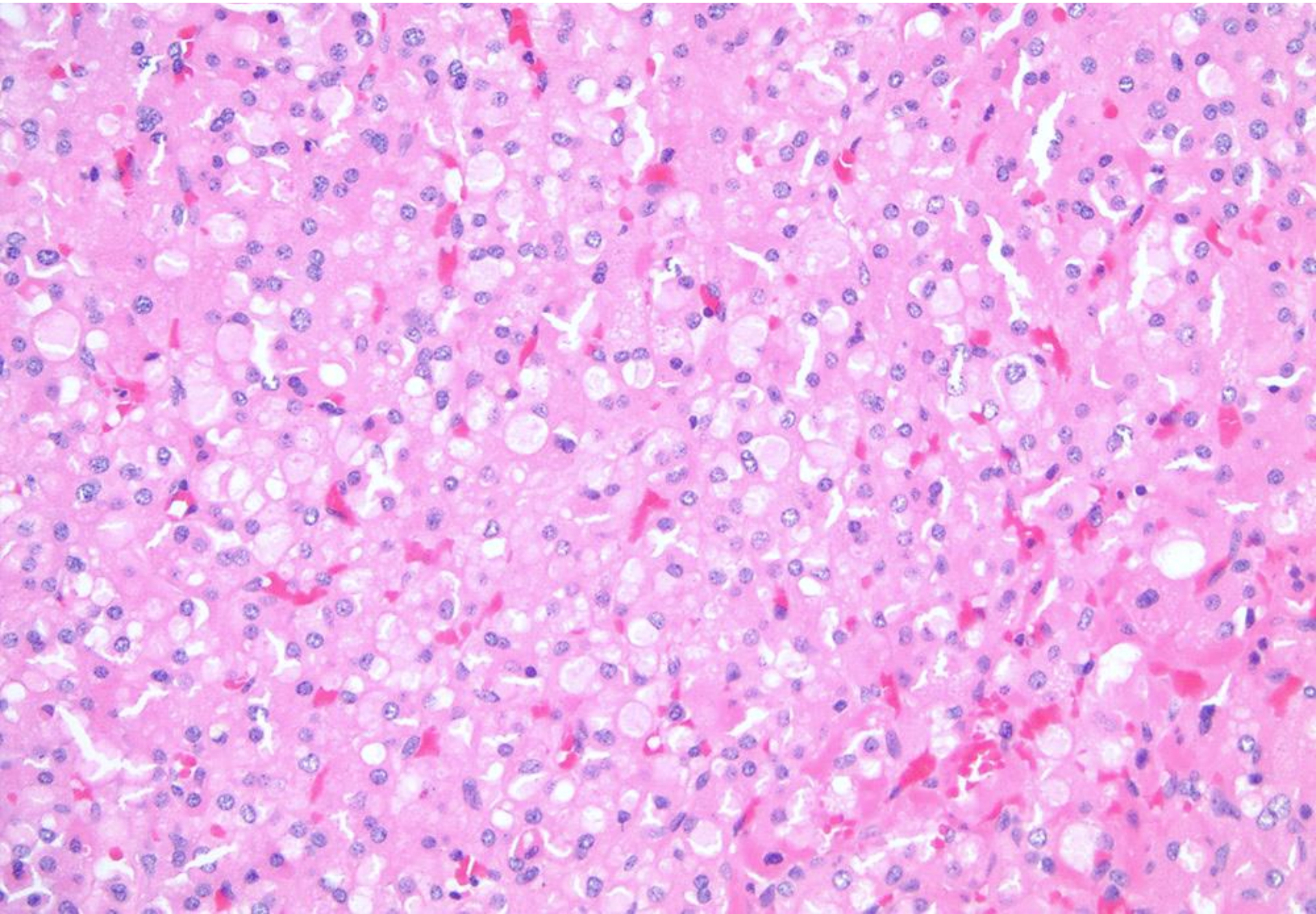
- Age ~4th decade
- Solid growth of uniform cuboidal cells with finely granular eosinophilic cytoplasm, centrally located round nuclei, and characteristic cytoplasmic inclusions
- Germline mutation of one of *SDH* genes (*SDHB*>>>) or SDH assembly factor (*SDHAF*)
- Often multifocal/bilateral
- Can be aggressive

Gill AJ et al. Am J Surg Pathol 2014;38:1588-1602
Gill AJ et al. Am J Surg Pathol 2011;35:1578–1585

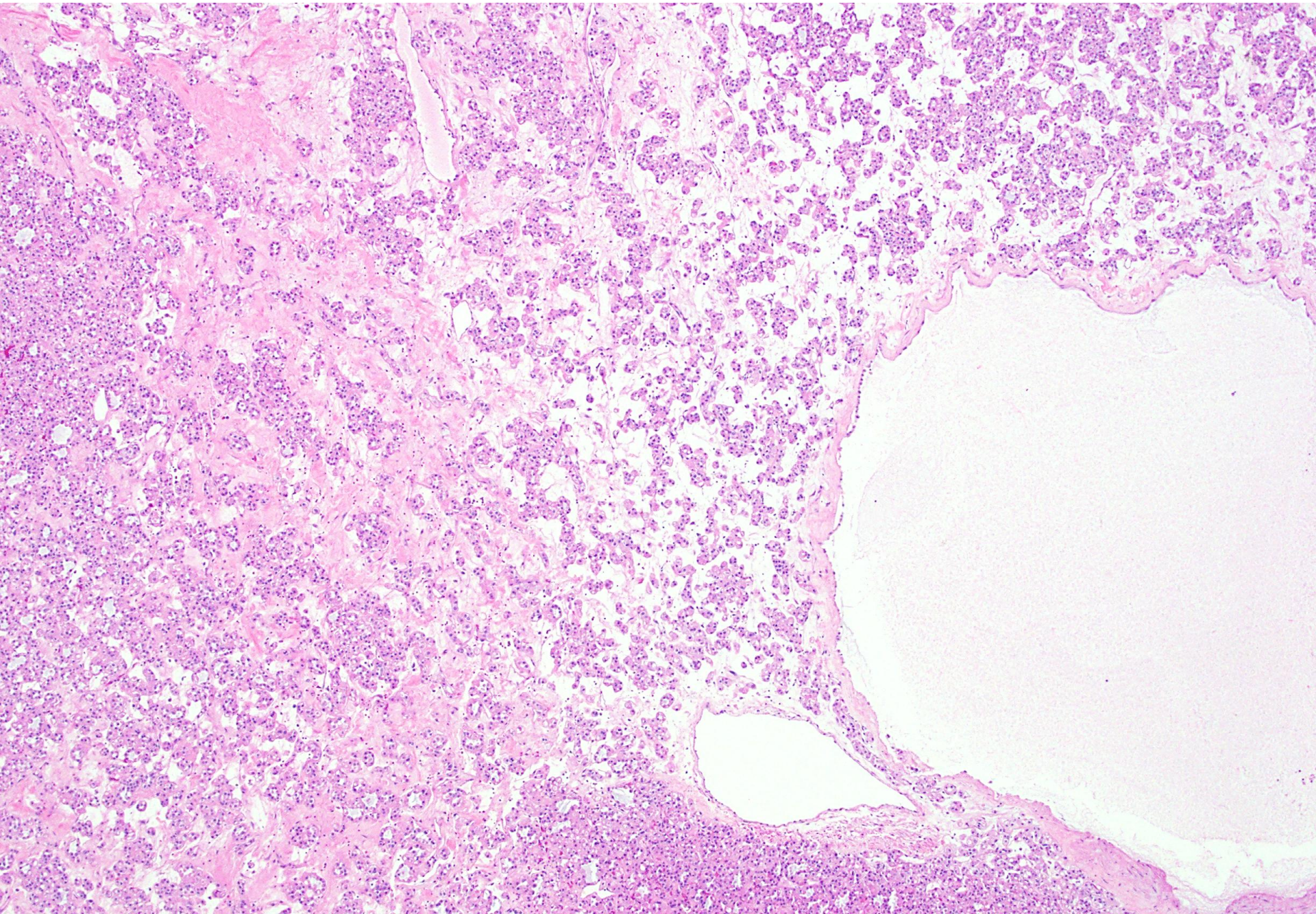
SDH-deficient RCC



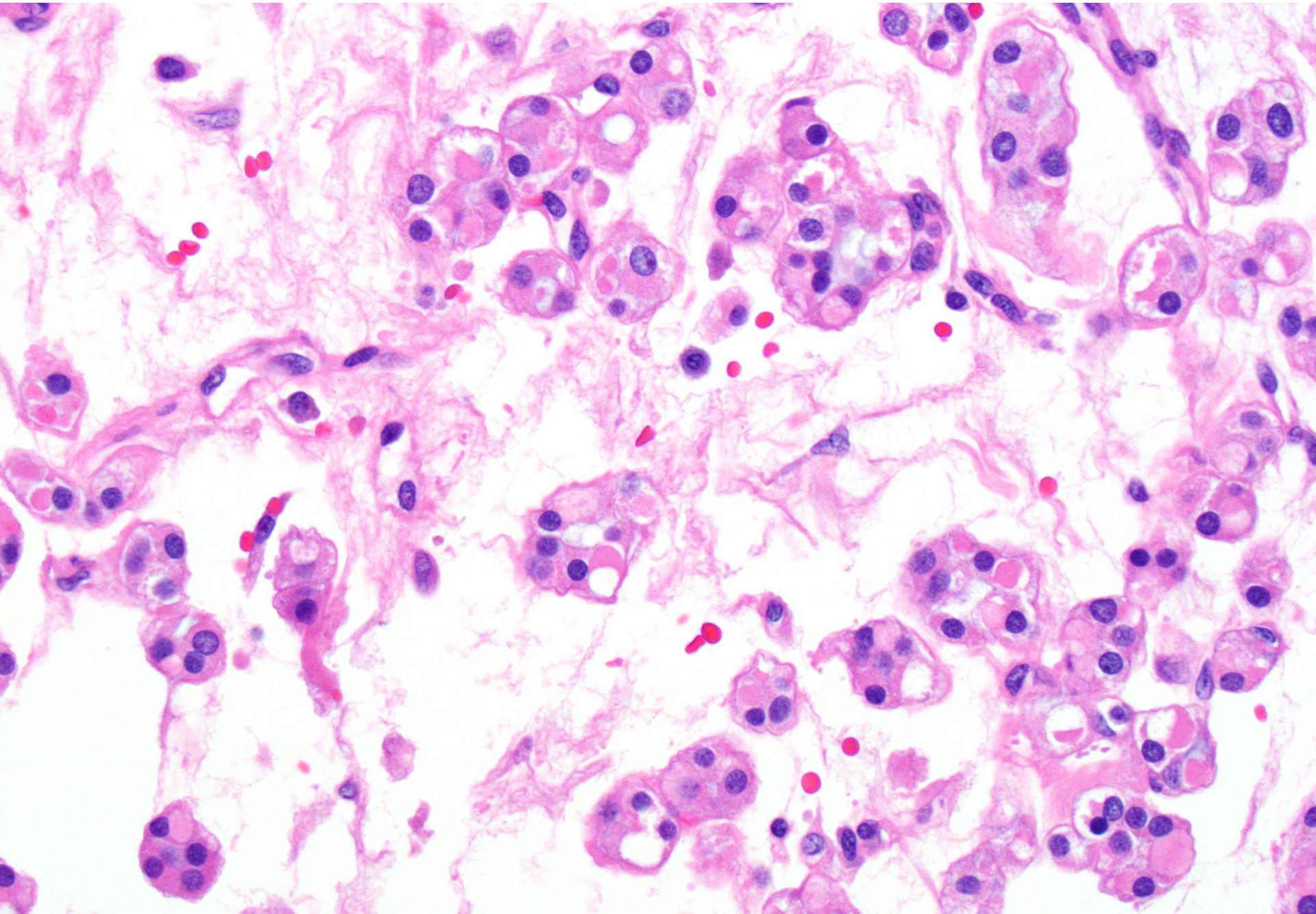
SDH-deficient RCC: Intracytoplasmic Inclusions



SDH-deficient RCC: Oncocytoma-like areas



SDH-deficient RCC: intracytoplasmic inclusions



Ancillary testing

- IHC
  - ✓ Pax-8 +
  - ✓ CK 7 –/focal + (as other keratins!)
  - ✓ CD117/C-KIT -
  - ✓ CK 20 -
  - ✓ SDHB – (loss of expression)

Distinct Entities Outside of Chromophobe/Oncocytoma Spectrum

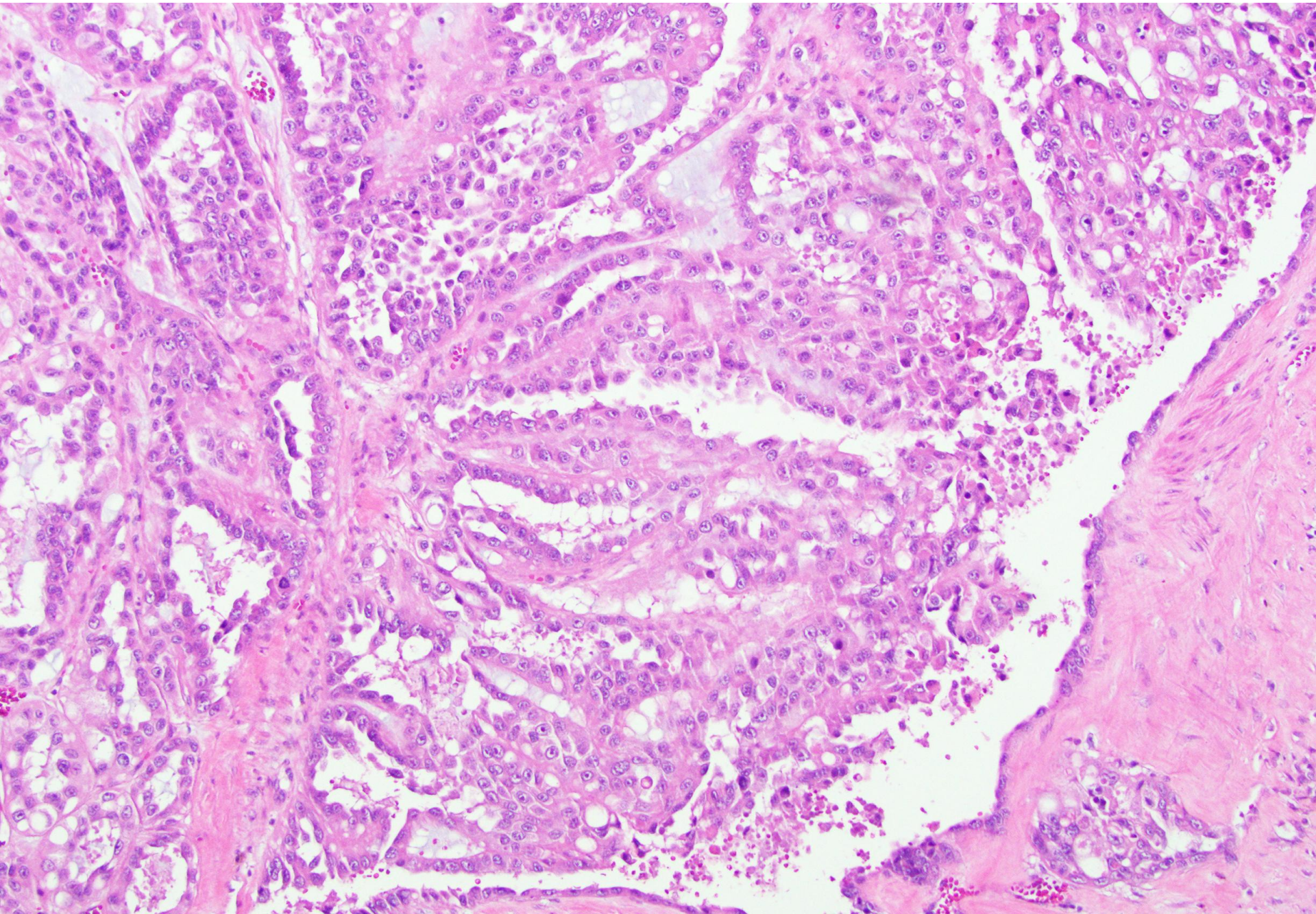
FH-deficient (HLRCC-associated) RCC

FH deficient/HLRCC-associated RCC: Key Points

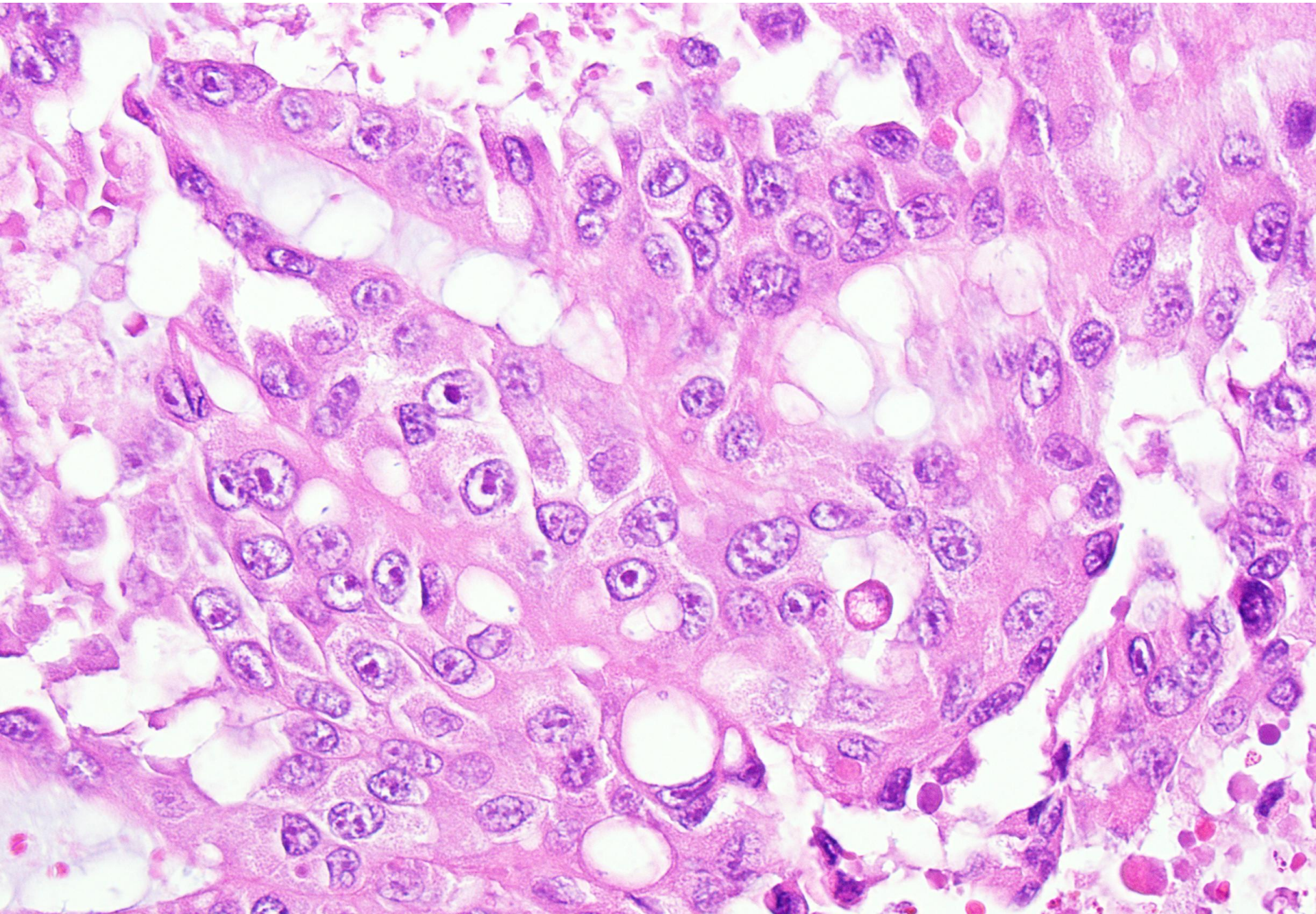
- Age 4th-5th decade
- RCC are occasional manifestation (multiple leiomyomas of skin and uterus)
- Unilateral, variably papillary, solid and tubulocystic growth of eosinophilic cells with abundant cytoplasm and prominent eosinophilic nucleoli with perinucleolar halo (can be focal)
- Germline (in HLRCC) or sporadic *FH* mutation
- Aggressive regardless of stage

Merino MJ. et al. Am J Surg Pathol 2007; 31:1578-85
Chen YB et l. Am J Surg Pathol 2014; 38:627-637

HLRCC-associated RCC



HLRCC-associated RCC



Ancillary testing

- IHC
  - ✓ Pax-8 +
  - ✓ CK 7 -
  - ✓ AMACR (P504S/racemase) -
  - ✓ FH loss of expression
  - ✓ [2-succinocysteine (2SC) +]

Distinct Entities Outside of Chromophobe/Oncocytoma Spectrum

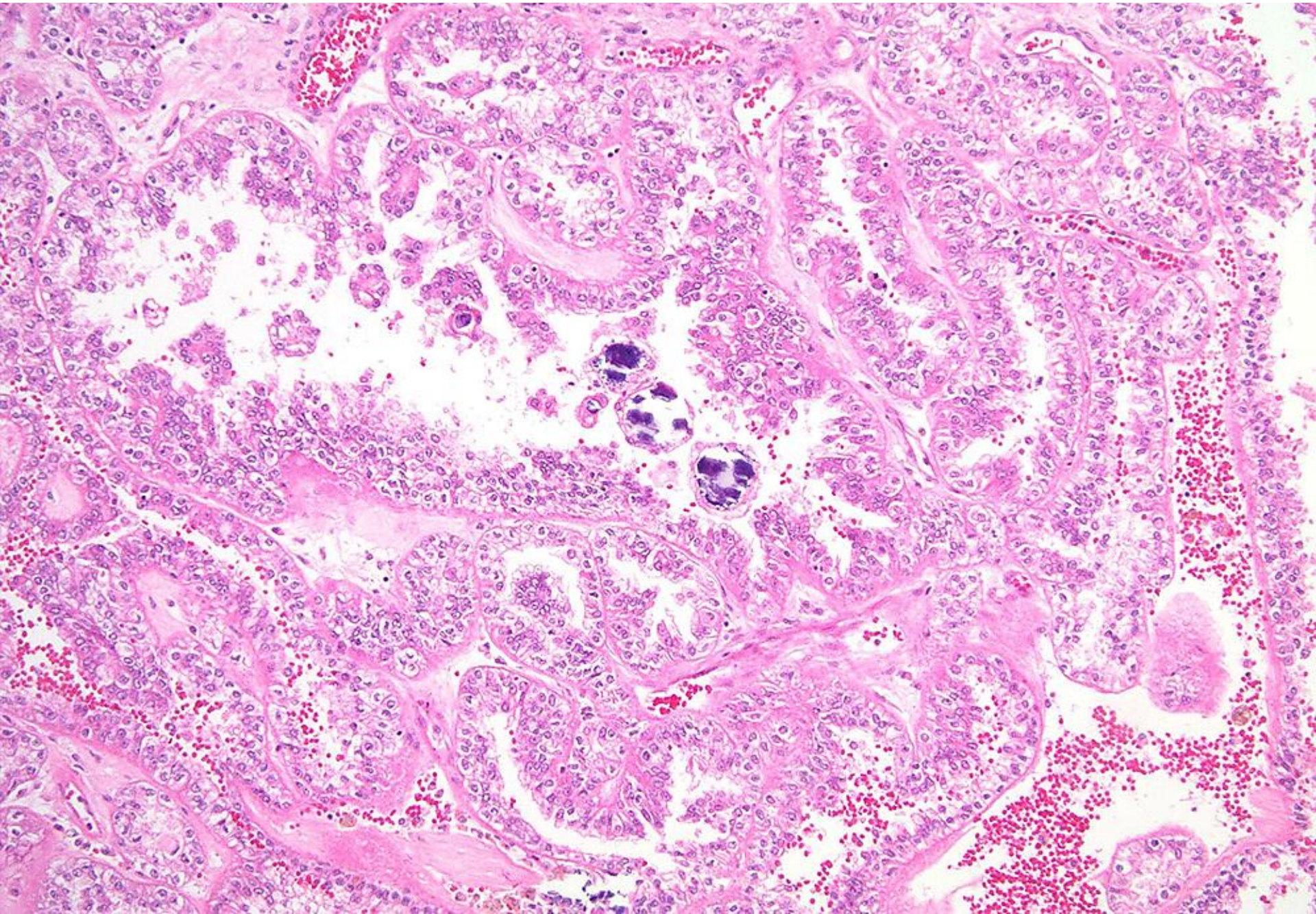
TFE3-rearranged and subset of *TFEB*-altered RCC (formerly “MiT family translocation” RCC)

“MiT family translocation” RCC: Key Points

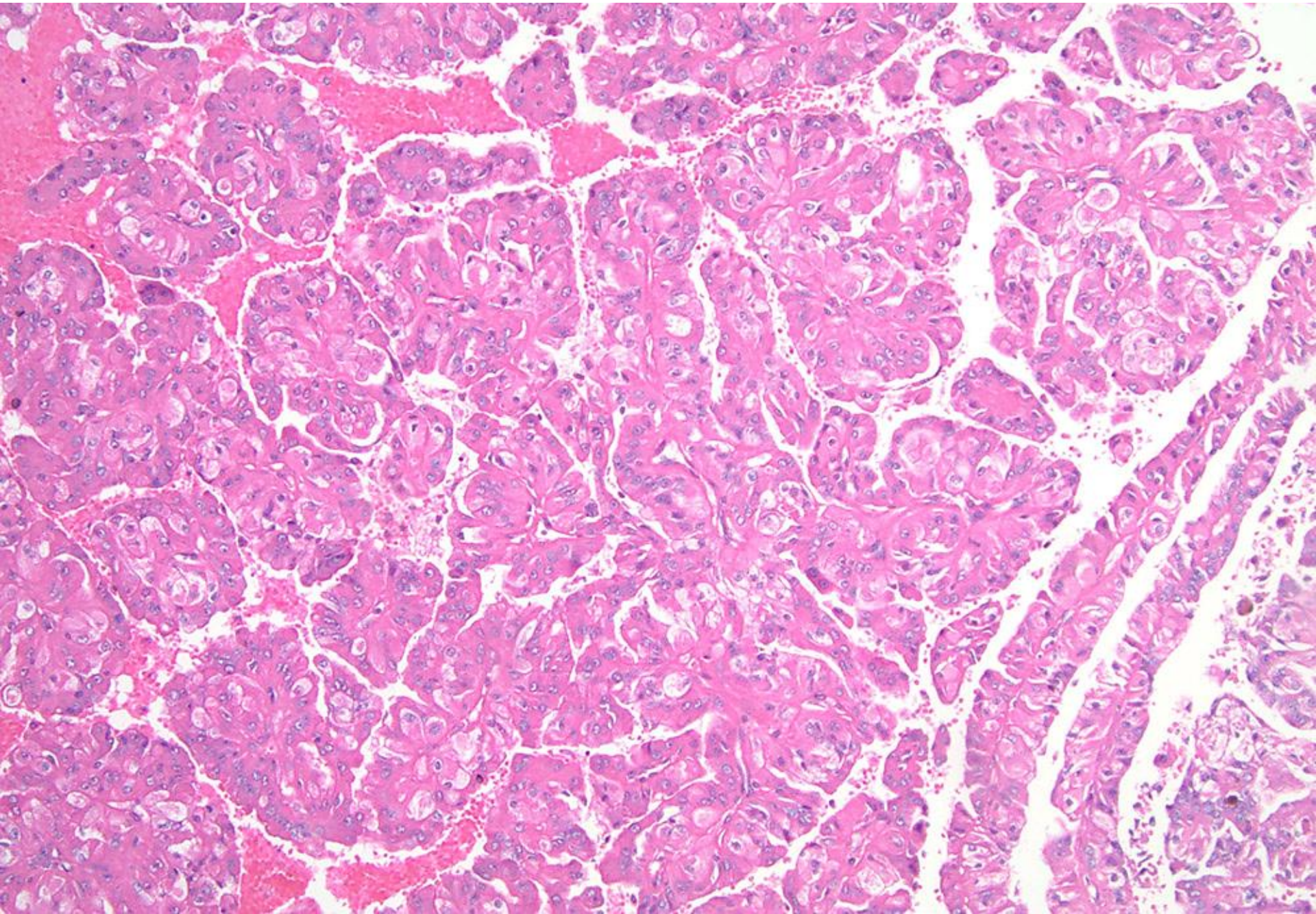
- ~40% of RCC in children; 4% in adults
- Reportedly overlapping histologic patterns
  - ✓ Xp11 (*TFE3*) RCCs >>> clear cells with papillary architecture and abundant psammomatous bodies
  - ✓ t(6:11)(p21;q12) (*TFEB)* >>> solid architecture and biphasic cytology
- Translocations involving *TFE3* (Xp11.2) or *TFEB* (6p21) and a number of recognized partners
- Usually high-stage at presentation
- Clinical behavior age and stage dependent

Argani P. Semin Diagn Pathol. 2015;32:103-13
Damayanti NP et al. Clin Cancer Res. 2018;24:5977-5989

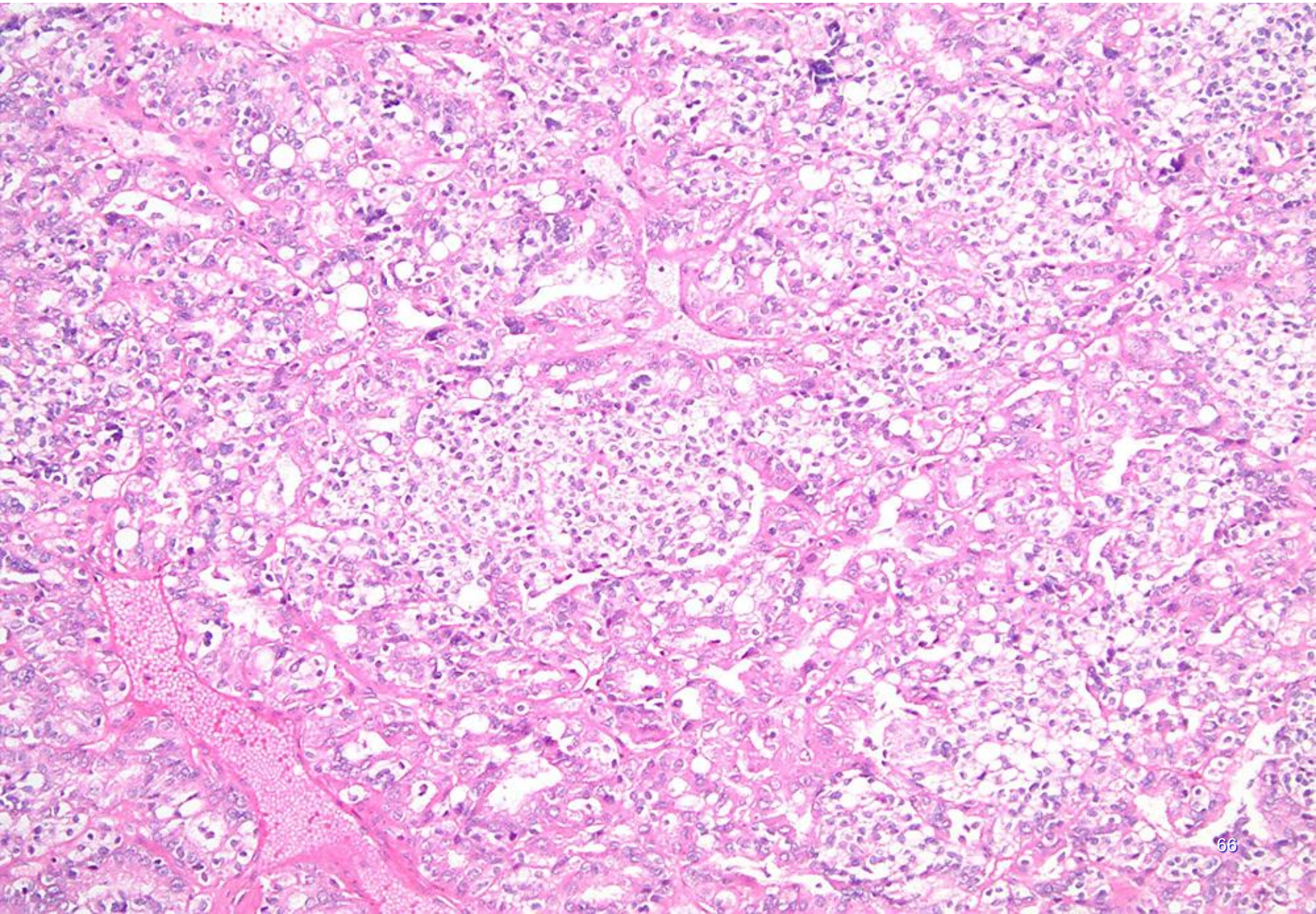
Xp11 (*TFE3)* translocation RCC



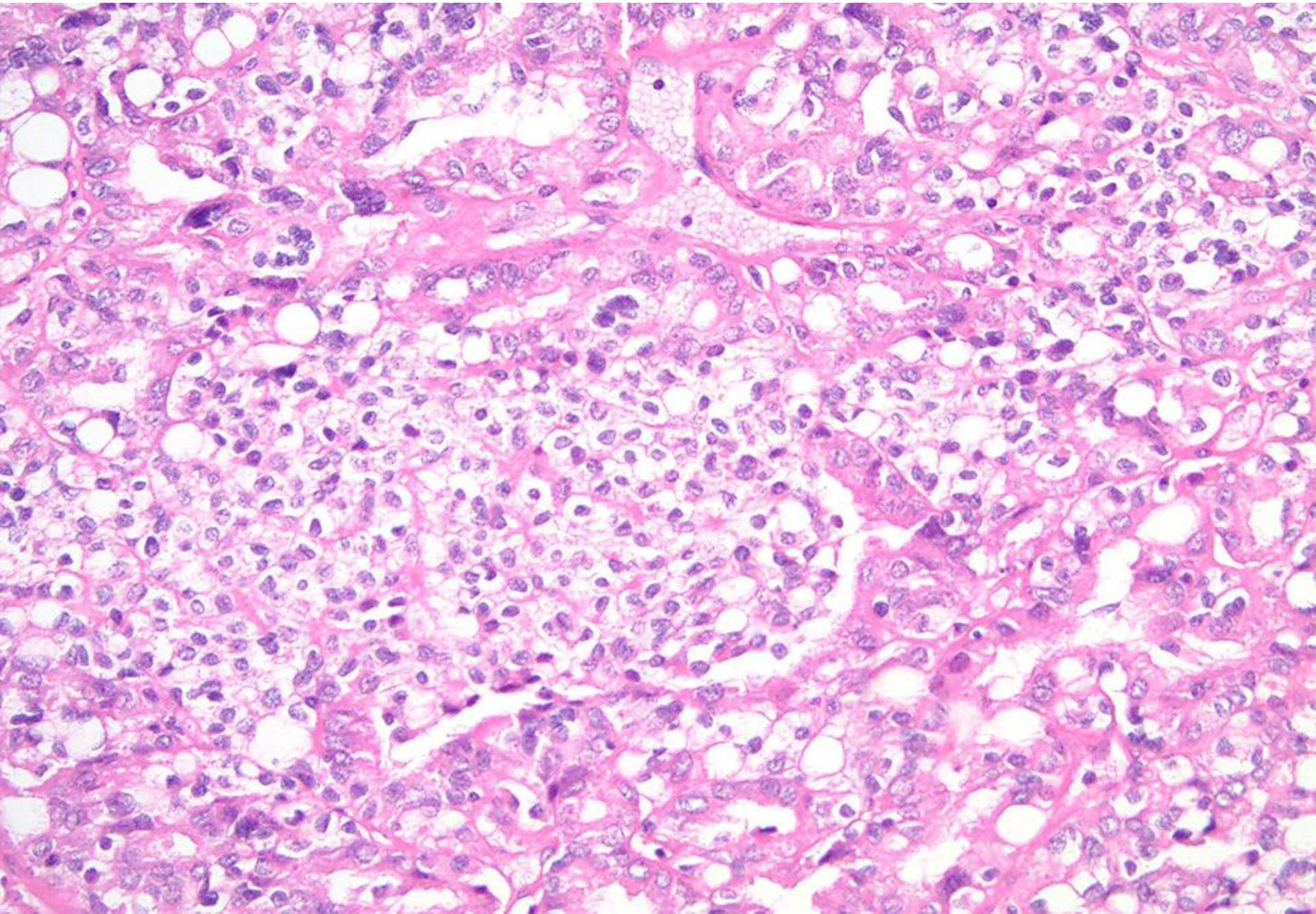
Xp11 (*TFE3)* translocation RCC



t(6:11) (*TFEB)* translocation RCC



t(6:11) (*TFEB)* translocation RCC



TFE3/TFEB-tumors Ancillary testing

- IHC
  - ✓ Pax-8 +
  - ✓ CK 7 - (as other keratins and EMA!)
  - ✓ AMACR (P504S/racemase) + (*TFE3*)
  - ✓ HMB45 and Melan A foc + (*TFEB*>>>*TFE3*)
  - ✓ Cathepsin K + (*TFEB*>>*TFE3*)
  - ✓ TFE3/TFEB protein overexpression
  - ✓ Fumarate hydratase(FH) and SDHB retained
- *TFE3*/*TFEB* fluorescence in situ hybridization

Newly recognized entity

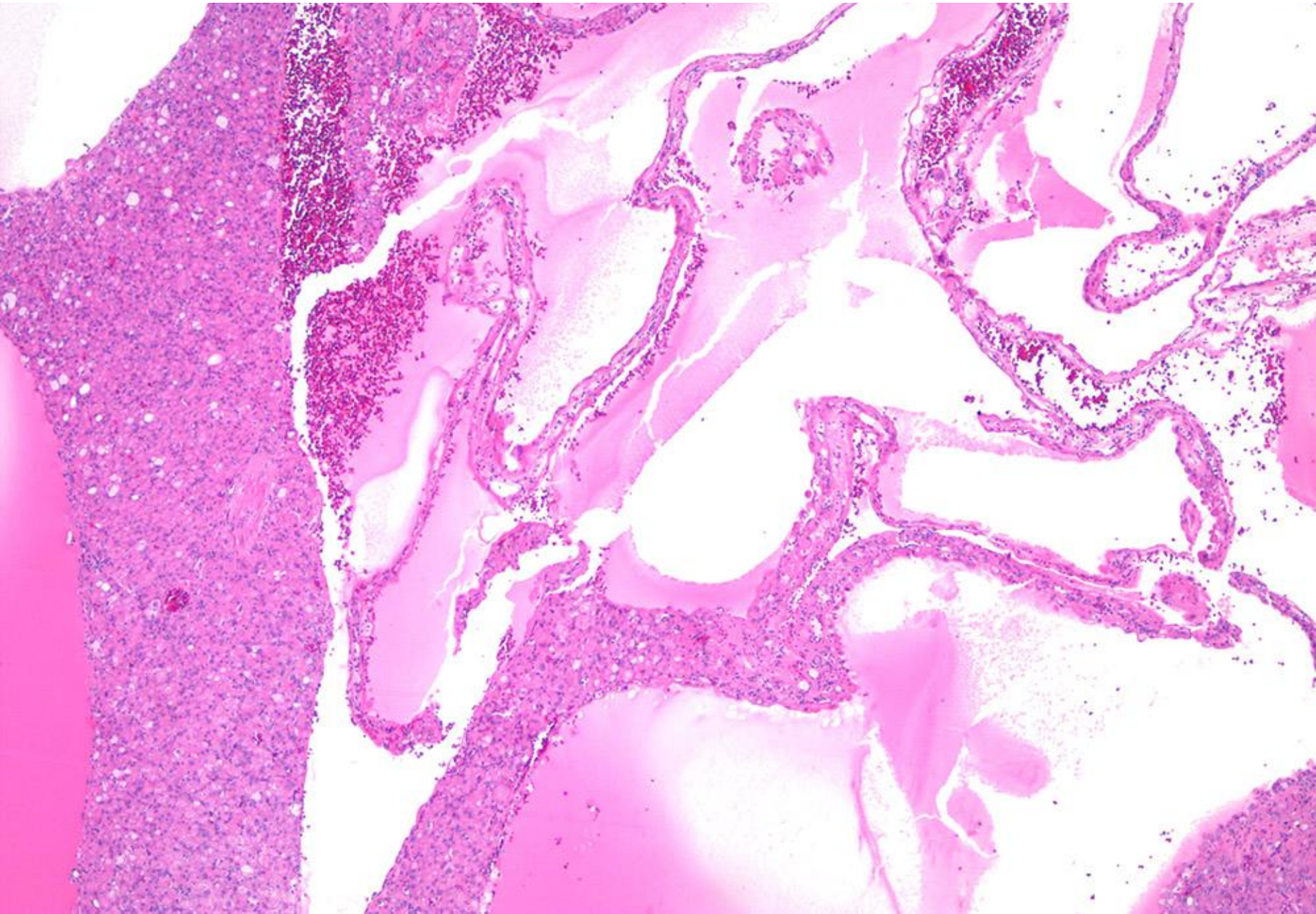
"Eosinophilic Solid and Cystic" (ESC) RCC

ESC RCC: Key Points

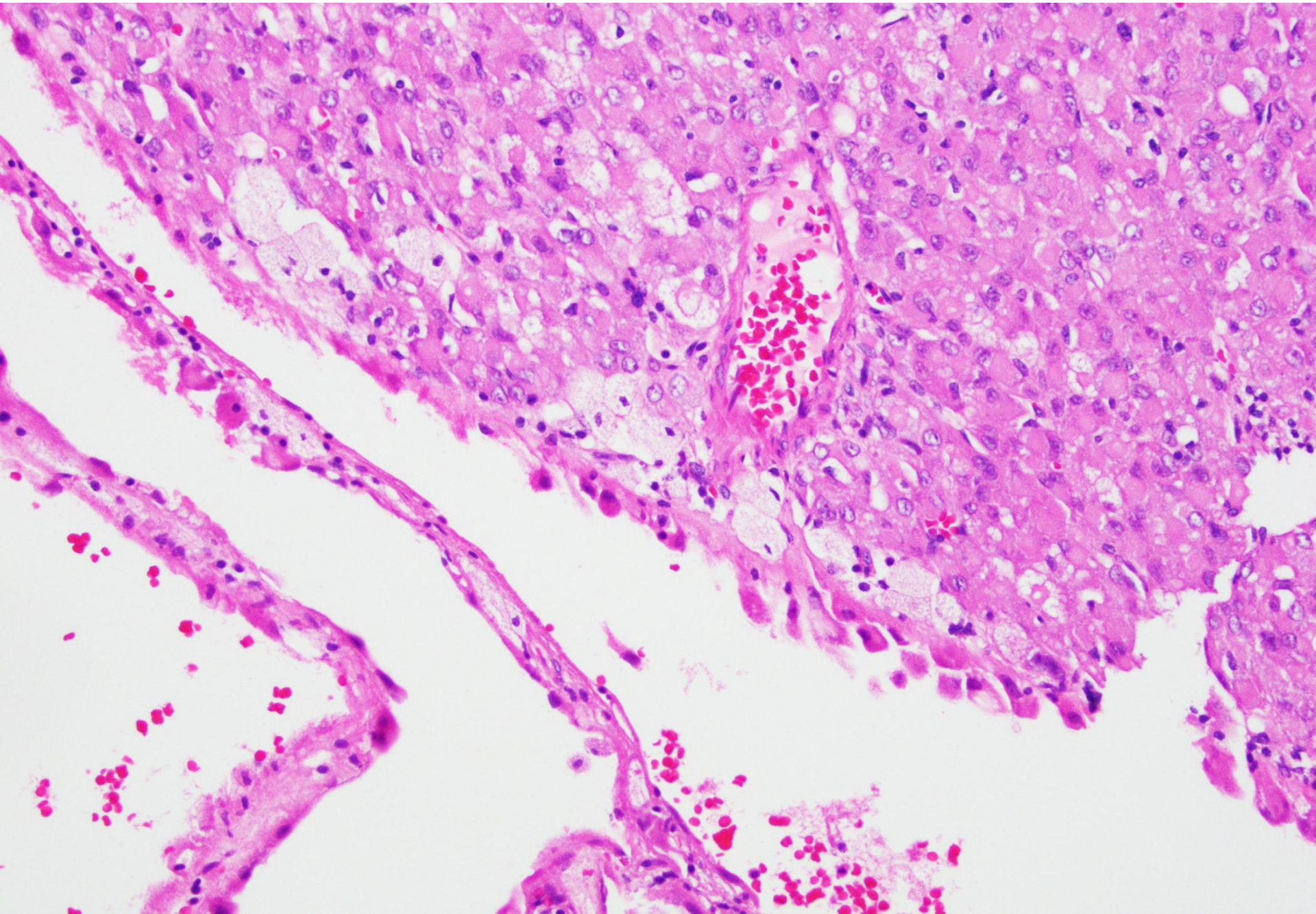
- Described as a morphologic variant of RCCs seen in tuberous sclerosis complex (TSC)
- Sporadic counterpart also reported [predominantly] in women
- Solid and cystic arrangement of eosinophilic cells with abundant, often coarsely granular cytoplasm
- *TSC1* and *TSC2* mutations
- Mostly indolent behavior with a handful of metastatic case reported up to date

Palsgrove DN et al. Am J Surg Pathol. 2018 Sep;42(9):1166-1181
Trpkov K et al. Am J Surg Pathol 2016;40:60
Guo J et al Am J Surg Pathol. 2014;38:1457

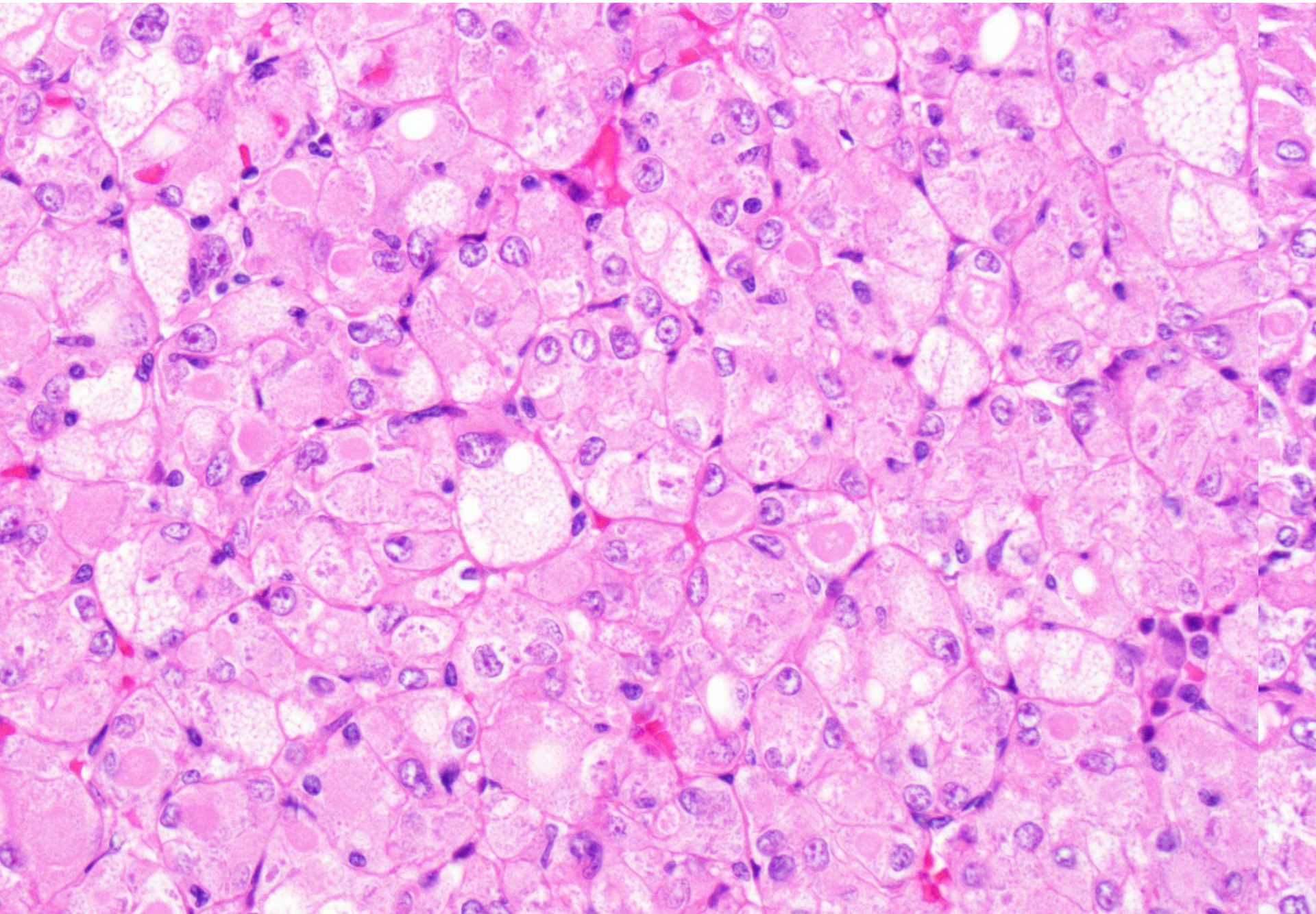
ESC RCC



ESC RCC



ESC RCC: typical cytoplasmic inclusions



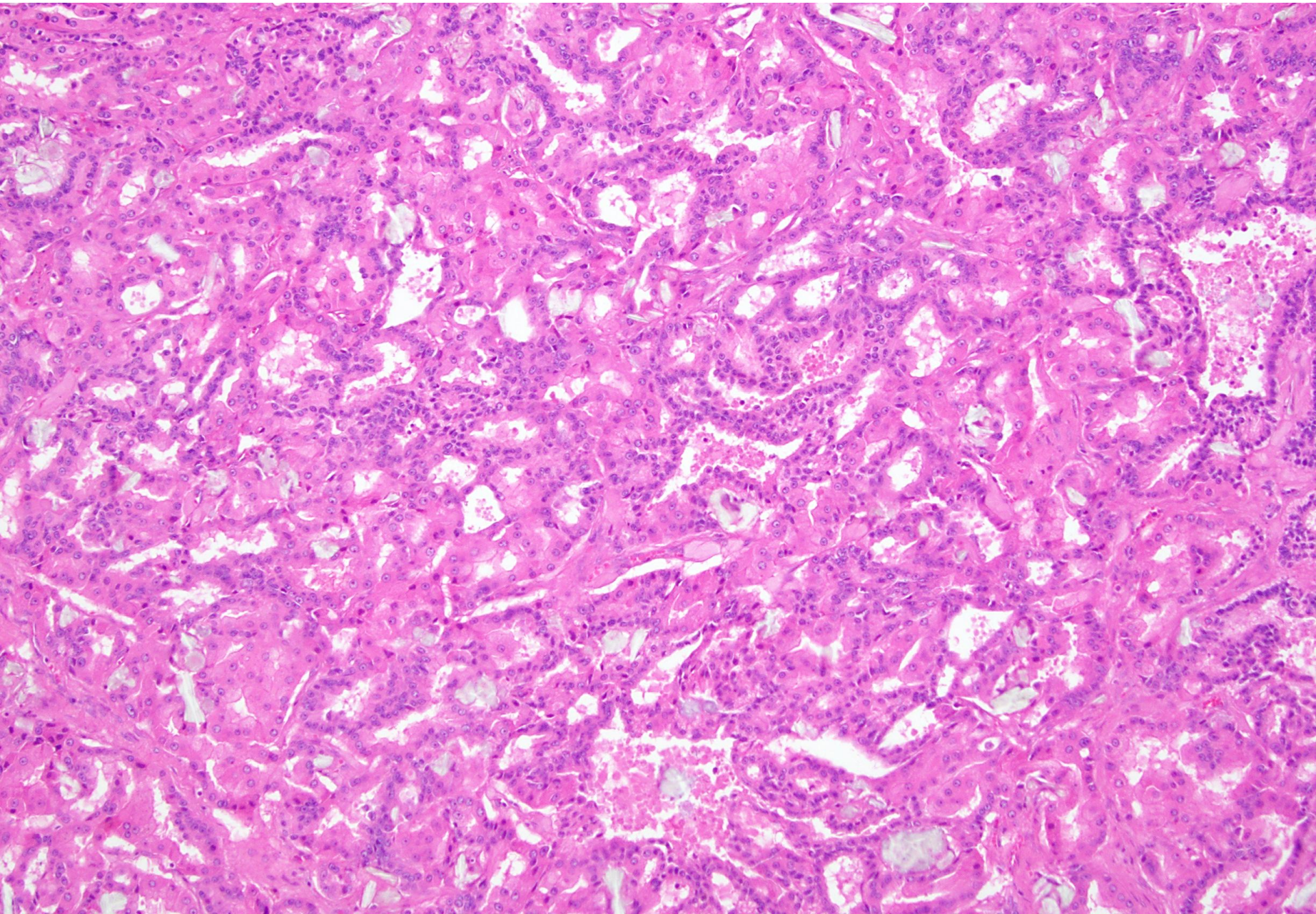
ESC Ancillary Testing

- IHC
  - ✓ PAX-8 +
  - ✓ CK 7 – (rare/focal)
  - ✓ CK 20 + (diffuse to focal)
  - ✓ CD117 –
  - ✓ AMACR variable
  - ✓ CA IX –
  - ✓ SDHB and FH retained

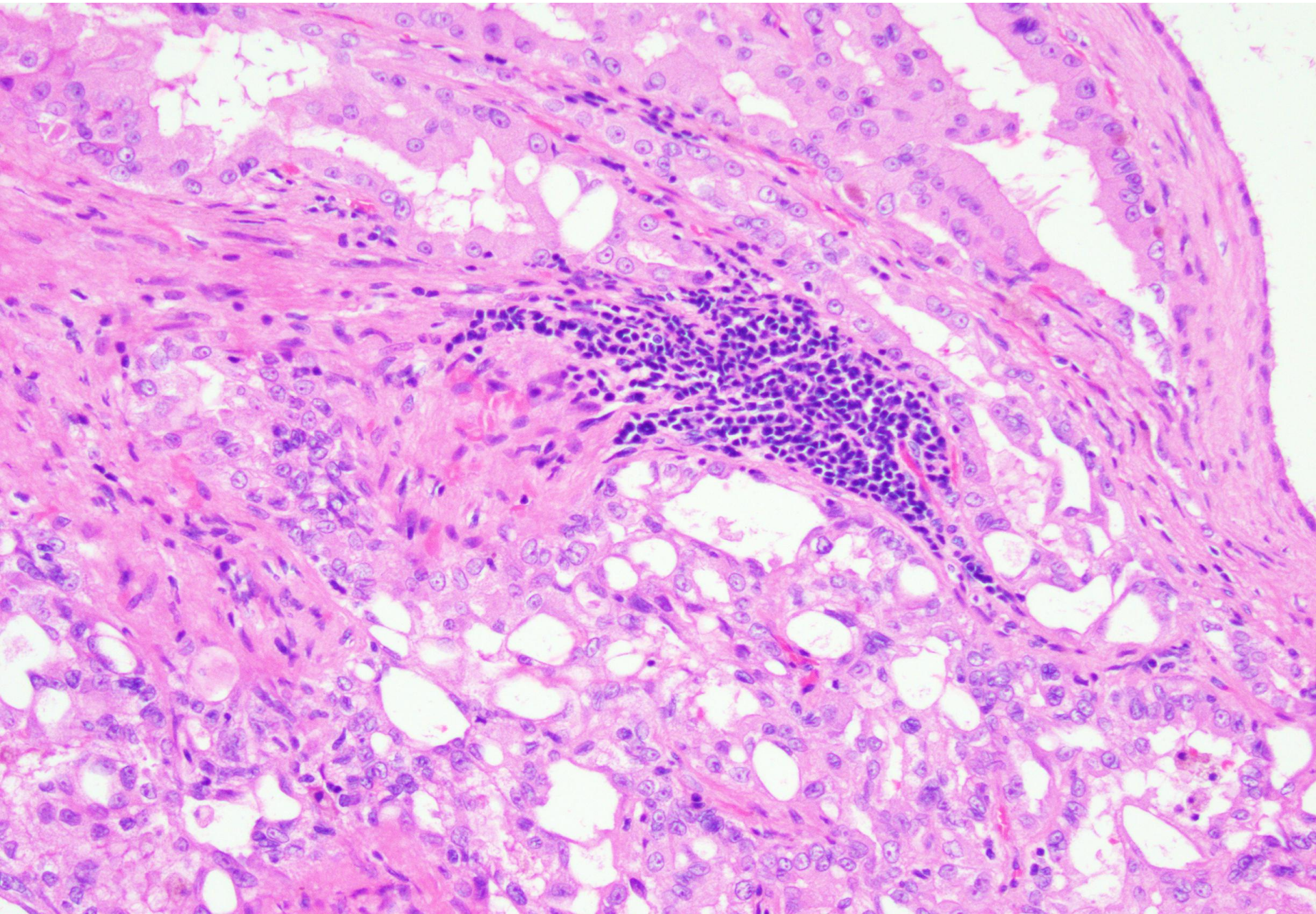
Acquired cystic disease (ACD)-associated RCC

- Patients with acquired cystic disease, usually after long-term dialysis
- M>F
- Architectural variability is common
- Intracytoplasmic or intercytoplasmic lumina or holes, imparting a cribriform (sieve-like) appearance
- Intratumoral oxalate crystal deposition is common

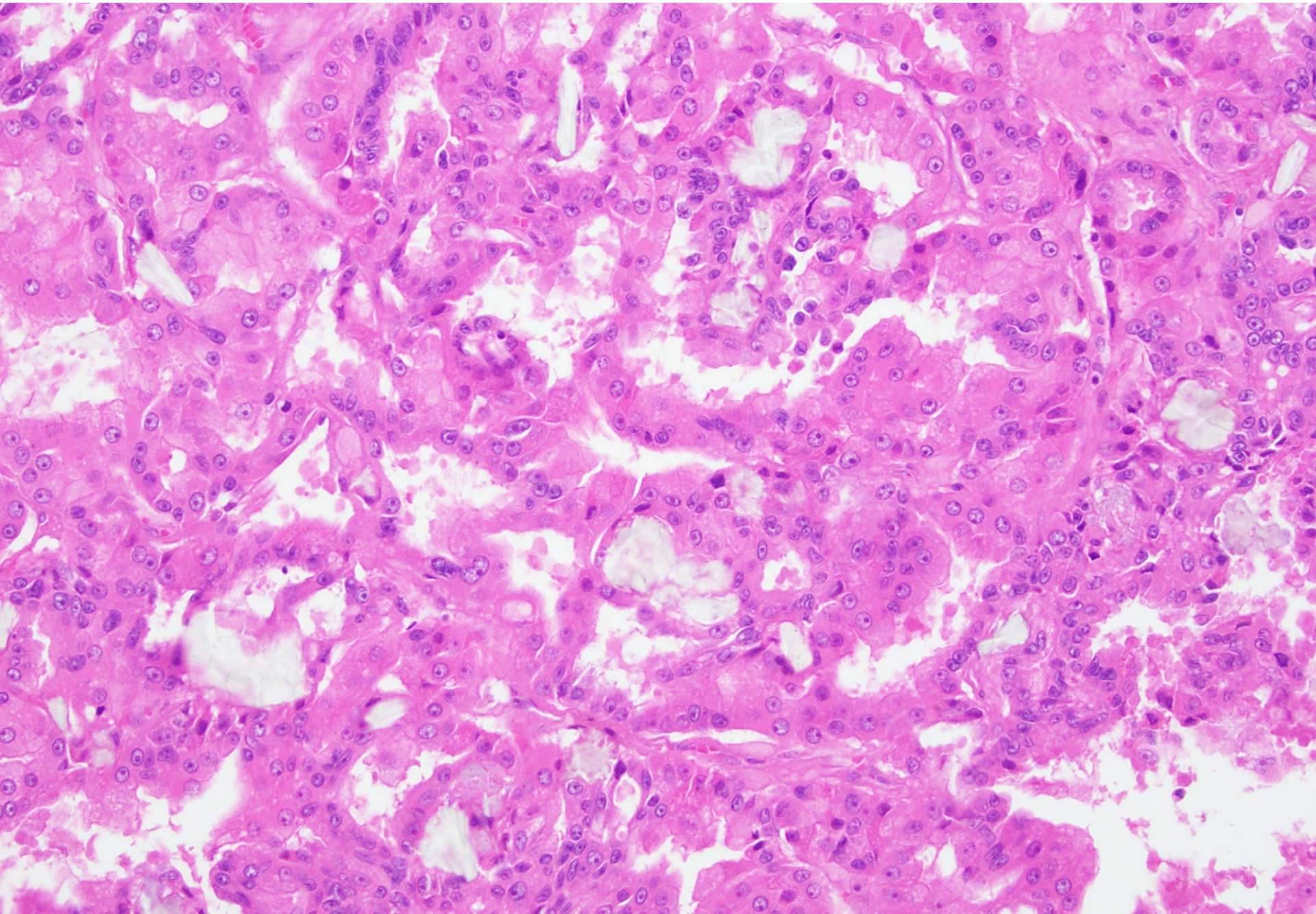
ACD-RCC



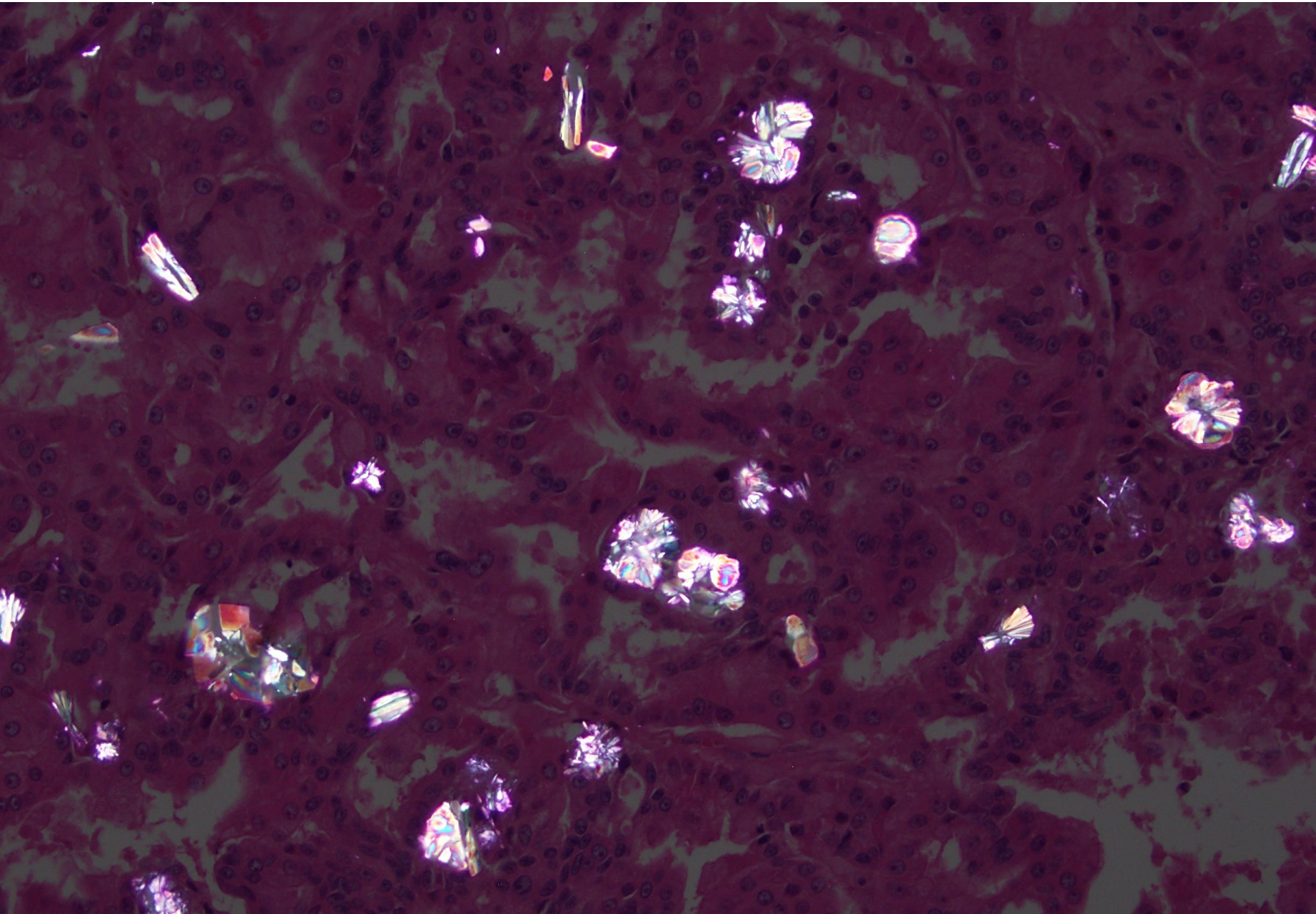
ACD-RCC: sieve-like pattern



ACD-RCC: High-grade cytology and oxalate crystals



ACD-RCC: oxalate crystals, polarized light



ACD-RCC Ancillary Testing

- IHC
  - ✓ PAX8+
  - ✓ AMACR+
  - ✓ CD10+
  - ✓ CK7- (can be positive in cystic areas)
  - ✓ C-KIT-
  - ✓ GATA3-
  - ✓ FH retained

Conclusions

- Renal cell carcinoma classification has dramatically evolved over the past two decades
- Cytoplasmic eosinophilia is a common finding in renal cell tumors that may often pose a challenge to pure morphologic classification
- Molecular characterization of eosinophilic tumors has lead to discovery of and keeps unraveling molecularly distinct entities with potential clinical implications

Take-home message

- Immunohistochemistry testing for SDHB and FH are increasingly important tools in the workup of eosinophilic renal cell tumors
- Cytokeratin expression evaluation may serve as a screening test for translocation-associated renal cell carcinomas
- A constellation of features and markers expression, mandatorily including PAX-8, together with select molecular testing can be helpful in characterizing difficult cases

Is it only 10 o'clock???

Questions any…yawn?