Kidney Tumors: The Interplay Between Histopathology and Molecular Studies

Evgeny Yakirevich, MD, DSc

Department of Pathology

Lifespan Academic Medical Center

Alpert Medical School at Brown University

Providence, RI, USA

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Disclosures

- I am not an oncologist
- I am not a nephrologist
- I am a pathologist

Outline

- Definition and classification of renal cell carcinoma (RCC)
- Histology and molecular pathology of main histologic subtypes of RCC:
  - Clear cell RCC
  - Papillary RCC
  - Chromophobe RCC
- New subtypes with distinct morphology and molecular alterations
  - HLRCC-associated RCC
  - SDH-deficient RCC

Estimated New Cancer Cases and Deaths, by Sex, United States, 2017

Estimated New Cases

Males			Females		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**	**All Sites**	**852,630**	**100%**

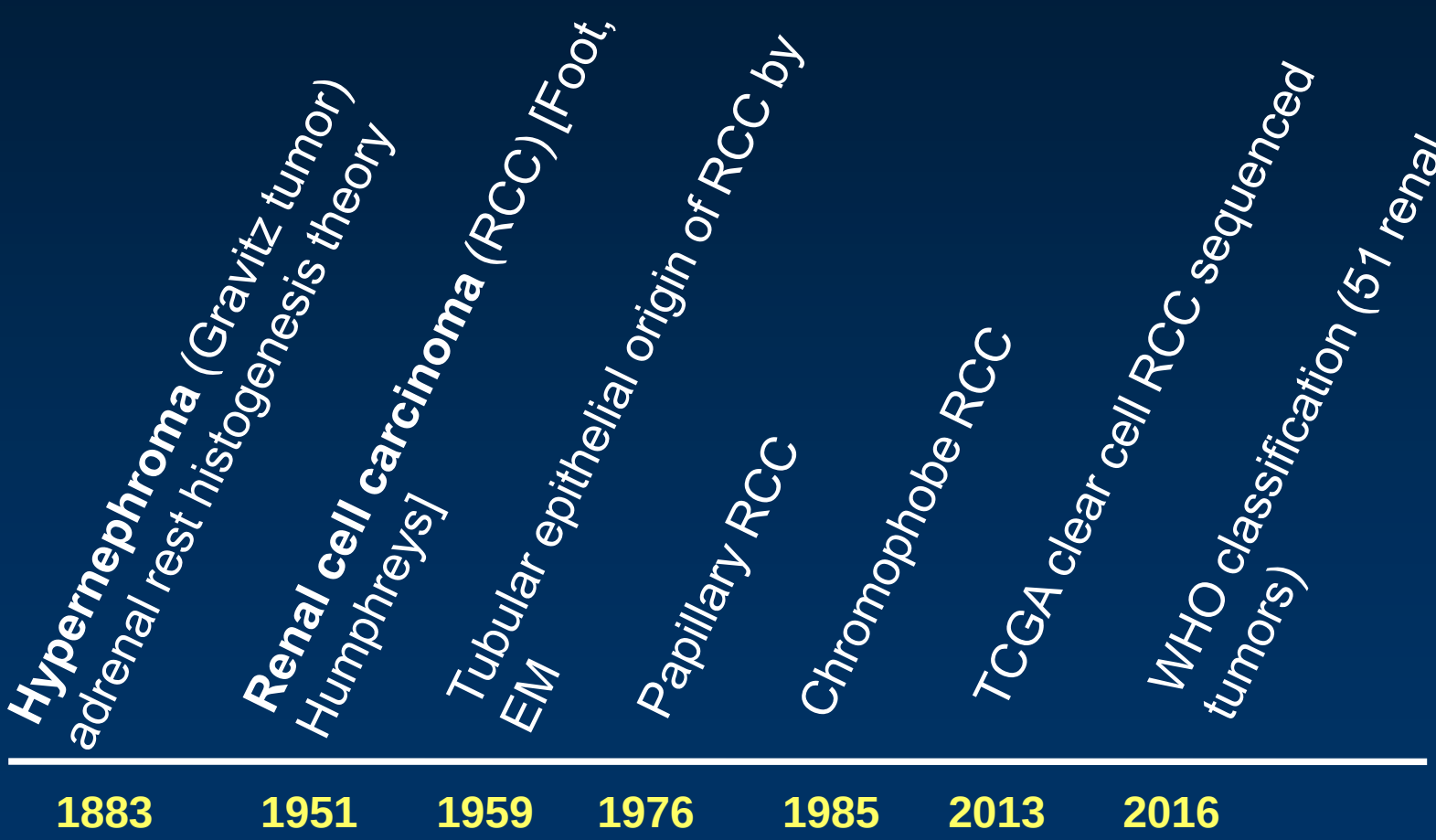
Estimated Deaths

Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**

From Siegel R et al.
CA Cancer J Clin 2017;67:6-30

CA
A Cancer Journal for Clinicians

Classification of Kidney Tumors



16 (85%)

Renal cell tumors – originate from renal tubular epithelium

2016 WHO Classification of Tumours of Kidney

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1*
Papillary renal cell carcinoma	8260/3
Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3*
MiT family translocation renal cell carcinomas	8311/3*
Succinate dehydrogenase–deficient renal carcinoma	8311/3
Mucinous tubular and spindle cell carcinoma	8480/3*
Tubulocystic renal cell carcinoma	8316/3*
Acquired cystic disease–associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0
Metanephric tumours	
Metanephric adenoma	8325/0
Metanephric adenofibroma	9013/0
Metanephric stromal tumour	8935/1
Nephroblastic and cystic tumours occurring mainly in children	
Nephrogenic rests	
Nephroblastoma	8960/3
Cystic partially differentiated nephroblastoma	8959/1
Paediatric cystic nephroma	8959/0
Mesenchymal tumours	
Mesenchymal tumours occurring mainly in children	
Clear cell sarcoma	8964/3
Rhabdoid tumour	8963/3
Congenital mesoblastic nephroma	8960/1
Ossifying renal tumour of infancy	8967/0

Mesenchymal tumours occurring mainly in adults	
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Synovial sarcoma	9040/3
Ewing sarcoma	9364/3
Angiomyolipoma	8860/0
Epithelioid angiomyolipoma	8860/1*
Leiomyoma	8890/0
Haemangioma	9120/0
Lymphangioma	9170/0
Haemangioblastoma	9161/1
Juxtaglomerular cell tumour	8361/0
Renomedullary interstitial cell tumour	8966/0
Schwannoma	9560/0
Solitary fibrous tumour	8815/1
Mixed epithelial and stromal tumour family	
Cystic nephroma	8959/0
Mixed epithelial and stromal tumour	8959/0
Neuroendocrine tumours	
Well-differentiated neuroendocrine tumour	8240/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Phaeochromocytoma	8700/0
Miscellaneous tumours	
Renal haematopoietic neoplasms	
Germ cell tumours	
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (917A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification (756A), taking into account changes in our understanding of these lesions.
*New code approved by the IARC/WHO Committee for ICD-O.

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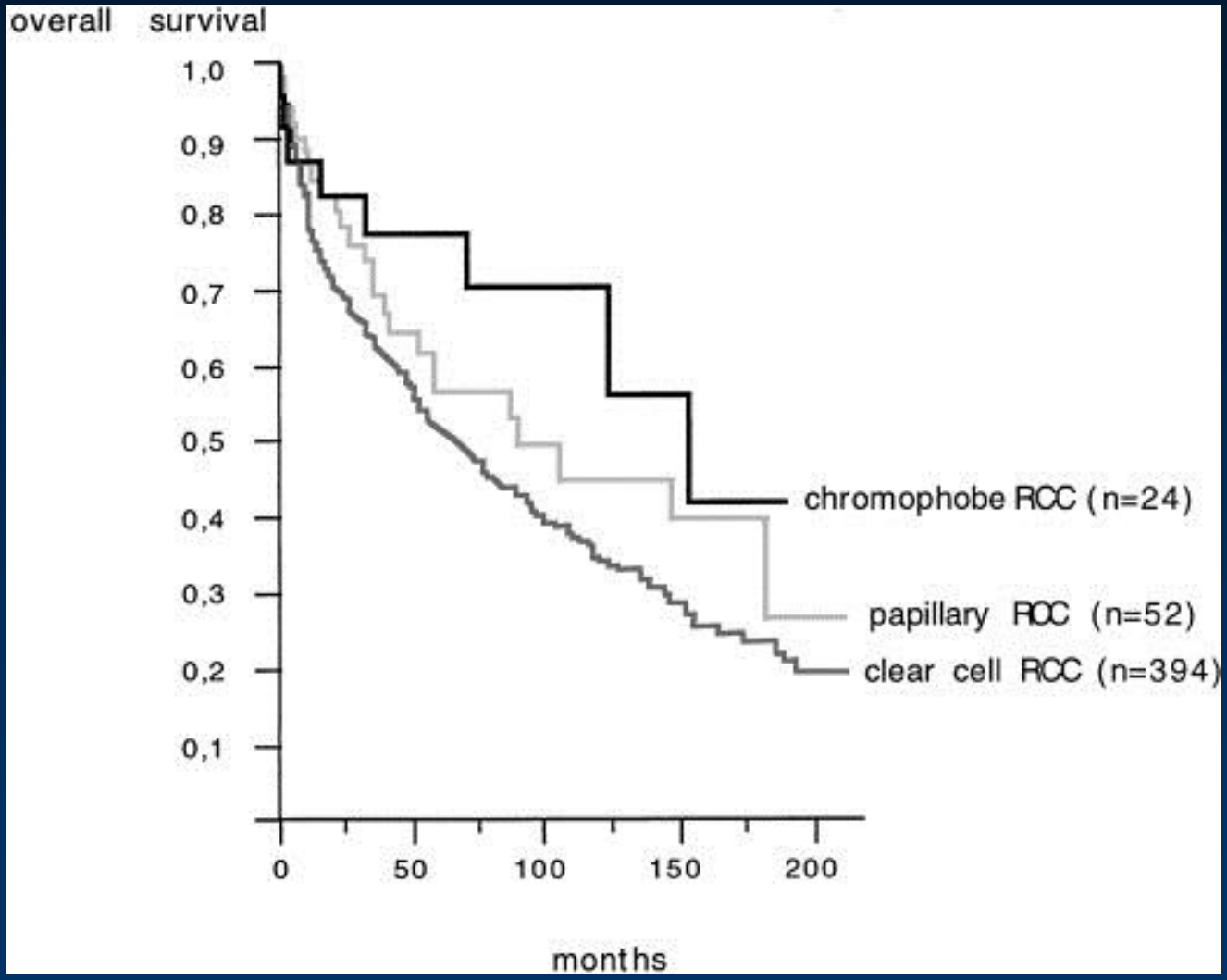
Most Common Histologic Types of RCC

- Clear cell renal cell carcinoma **70%**
- Multilocular cystic renal neoplasm of low malignant potential
- Papillary renal cell carcinoma **15%**
- Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
- Chromophobe renal cell carcinoma **5%**
- Collecting duct carcinoma
- Renal medullary carcinoma
- MiT Family translocation renal cell carcinomas
- Succinate dehydrogenase-deficient renal cell carcinoma
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic renal cell carcinoma
- Acquired cystic disease associated renal cell carcinoma
- Clear cell papillary renal cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

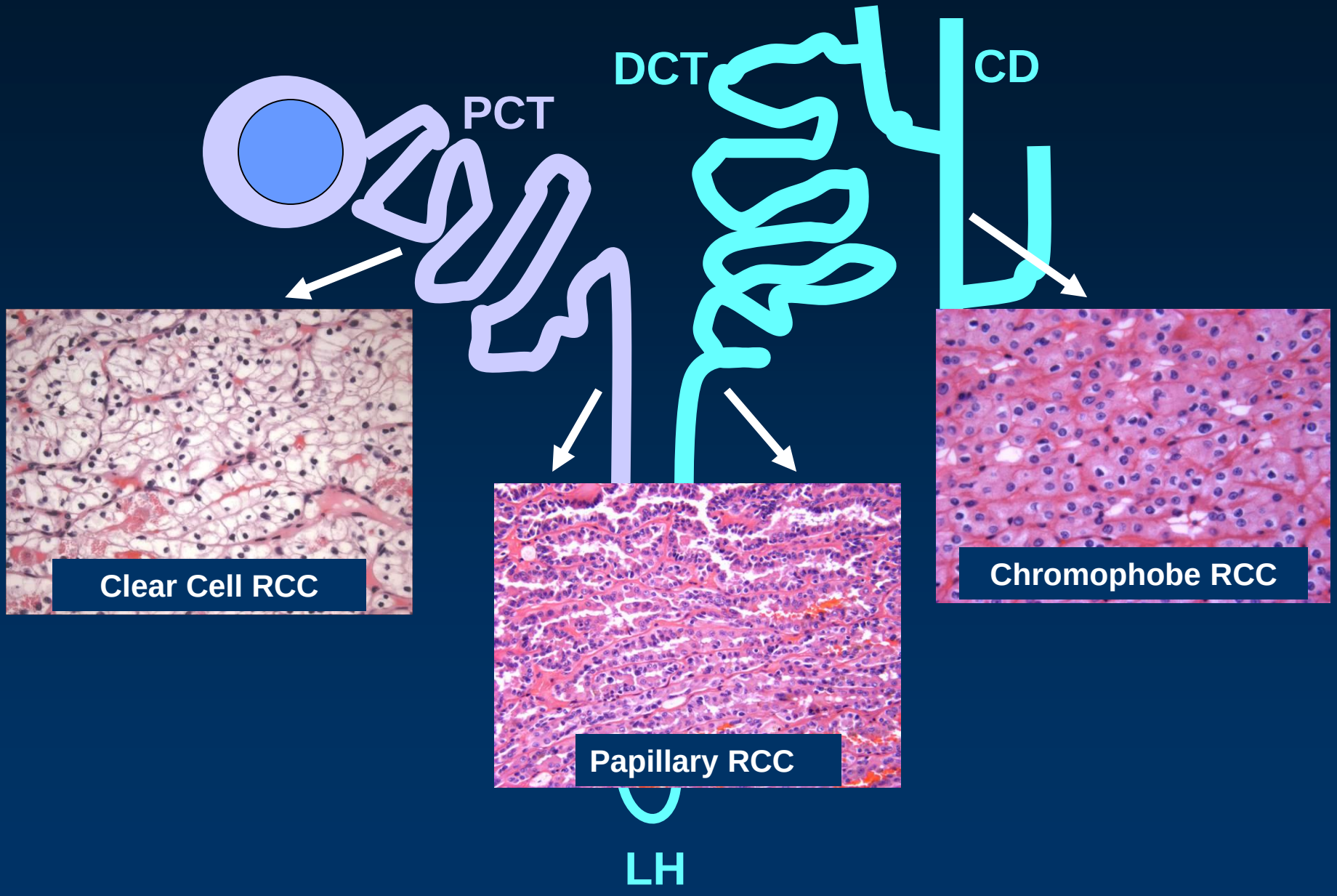
Overall Survival and Histologic Tumor Type in RCC

A Swiss experience with 588 tumors

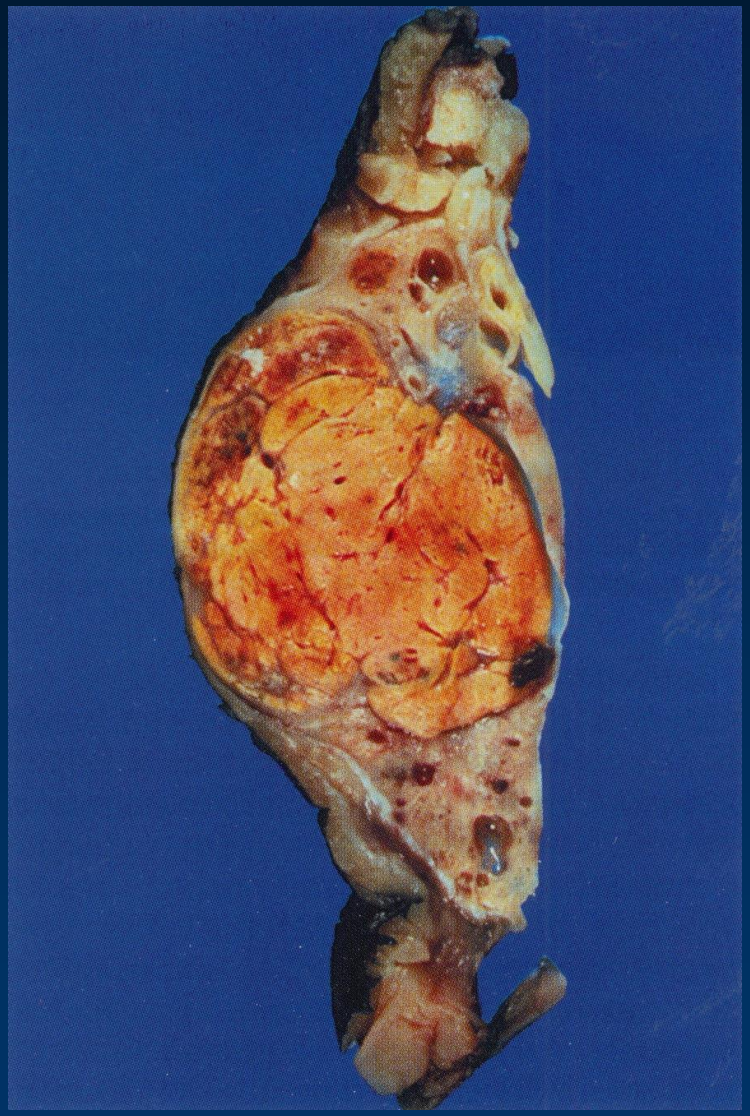


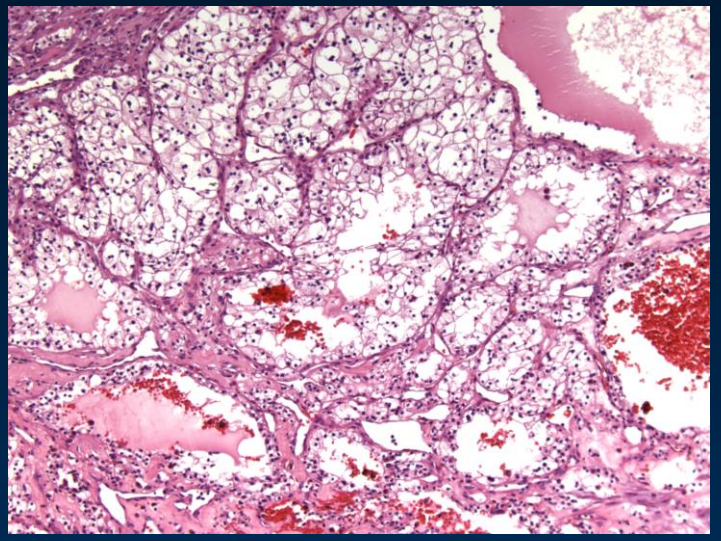
Moch et al, Cancer 2000

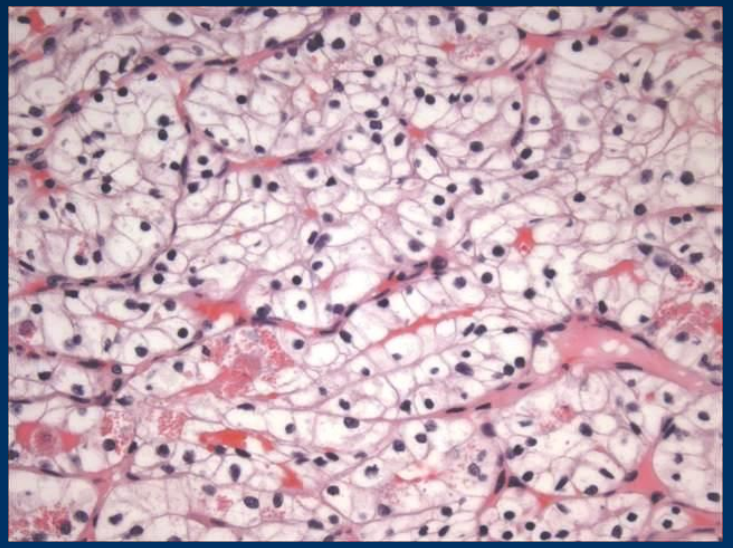
Histogenesis of Renal Cell Carcinoma



Clear Cell RCC

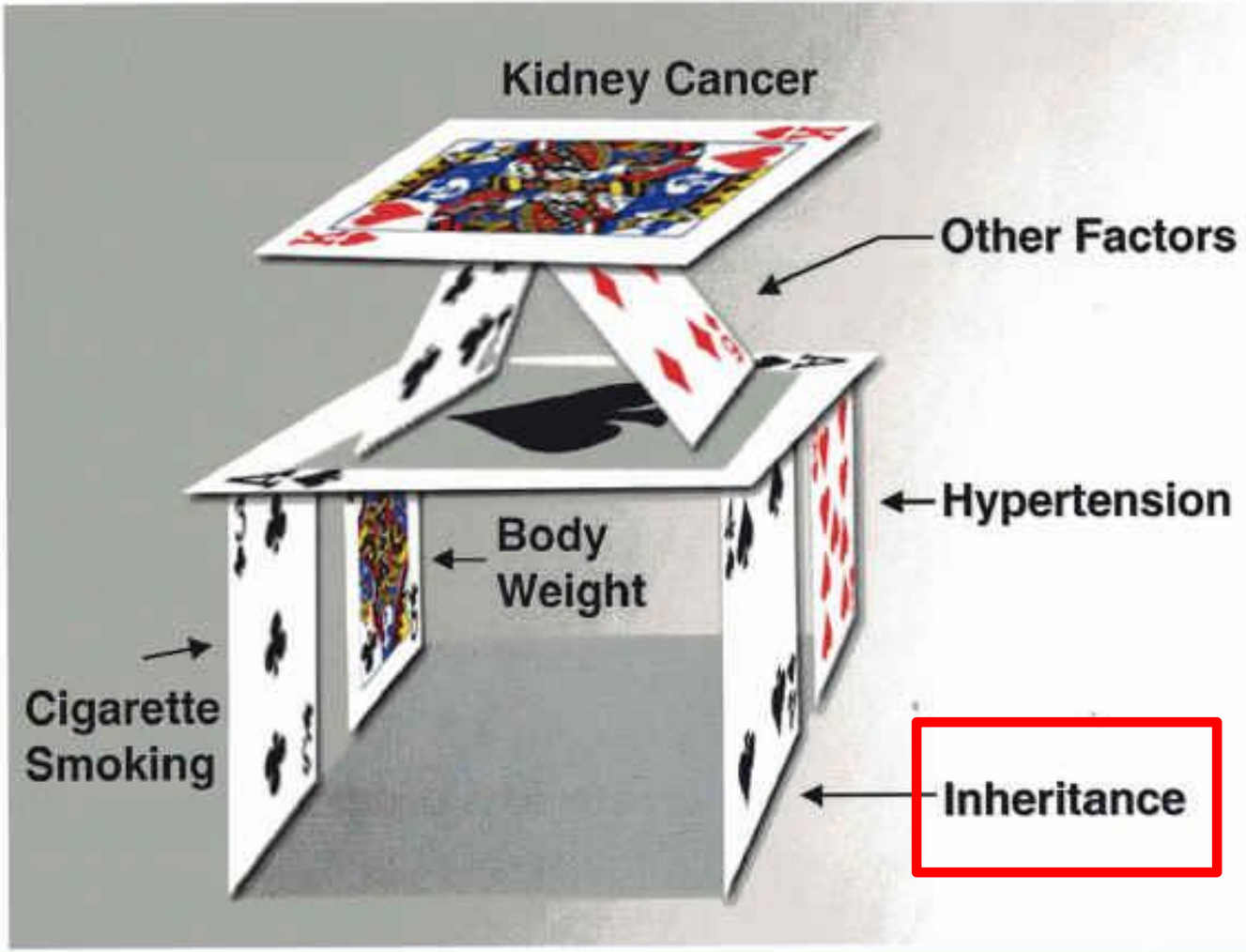






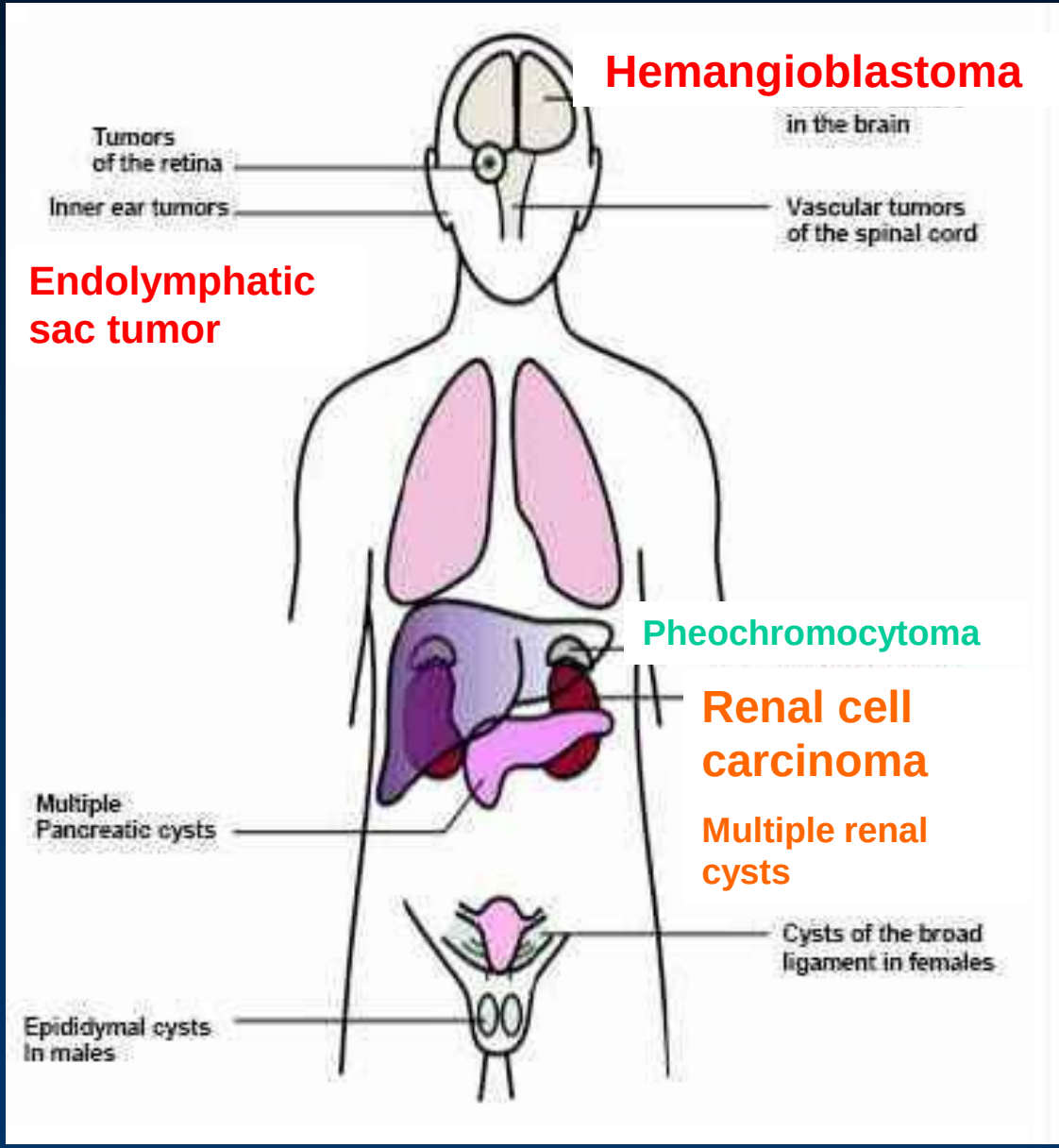
Clear cytoplasm – lipid, glycogen
Prominent blood vessels

Genetically Complex Disease-
Kidney Cancer

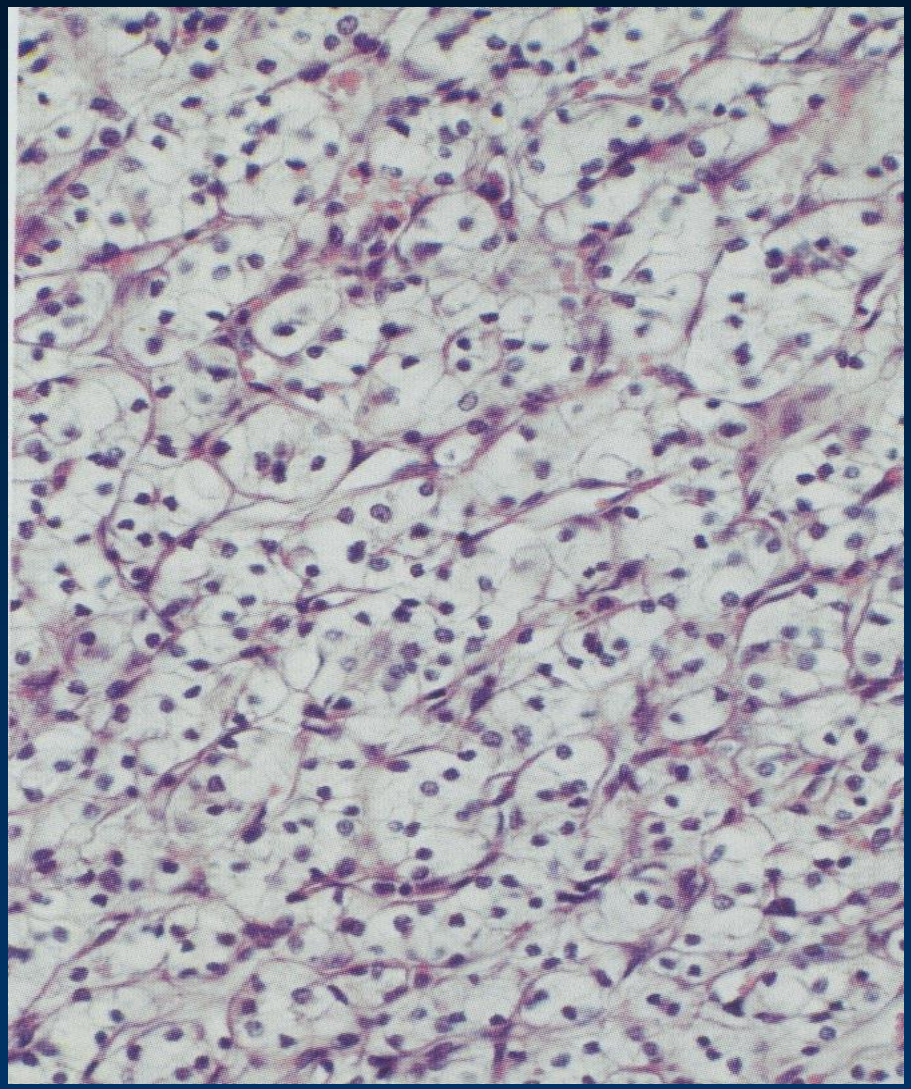


Multiple Clear Cell RCC in Von Hippel-Lindau Disease

- Autosomal dominant heritable neoplasia syndrome
- Multiple tumors and cysts
- Retinal or CNS (cerebellar) **hemangioblastomas**
- Renal cysts (up to 1000)
- **Clear cell RCC** (up to 600) in 40-60%

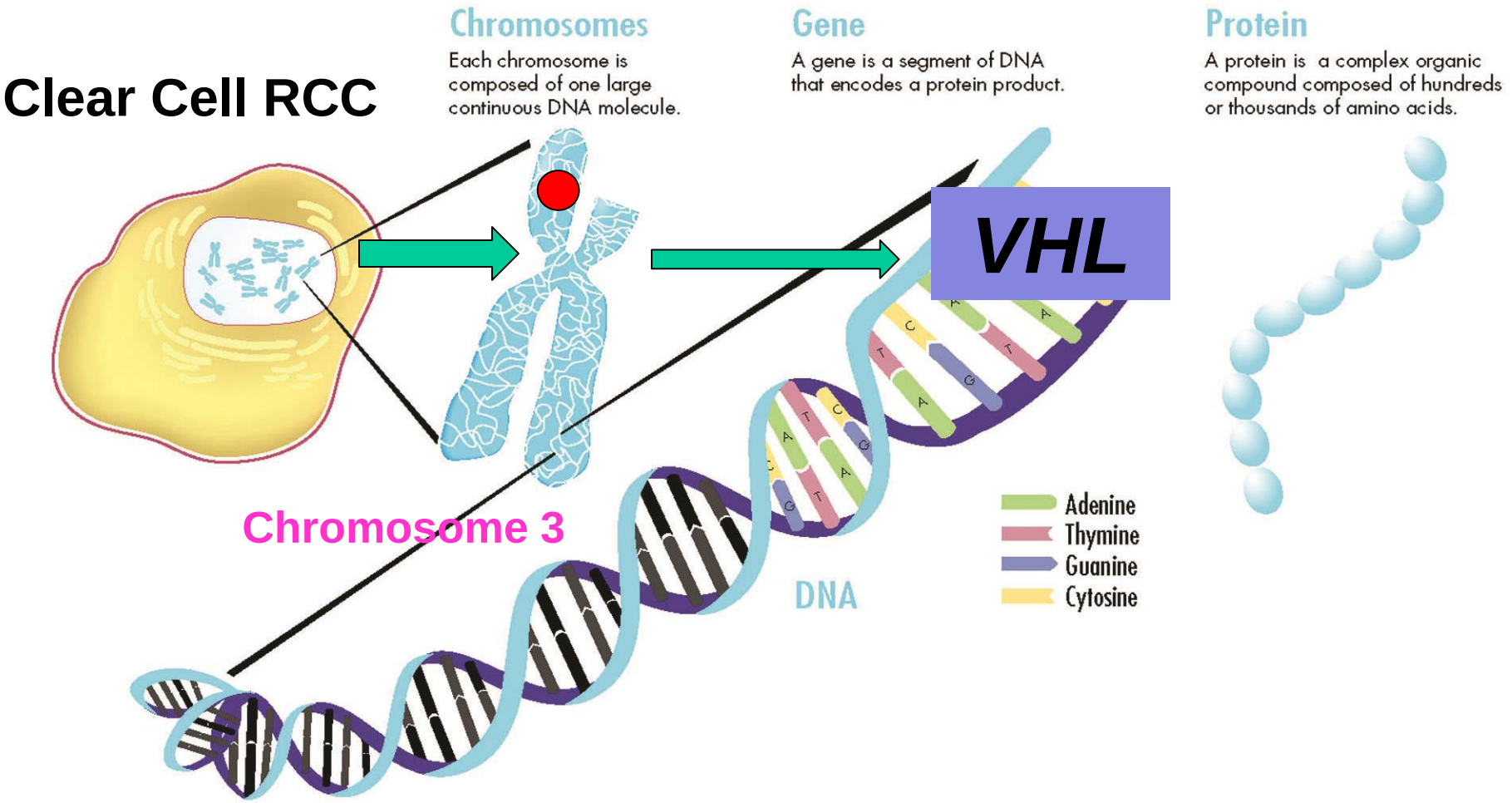


Von Hippel-Lindau Disease

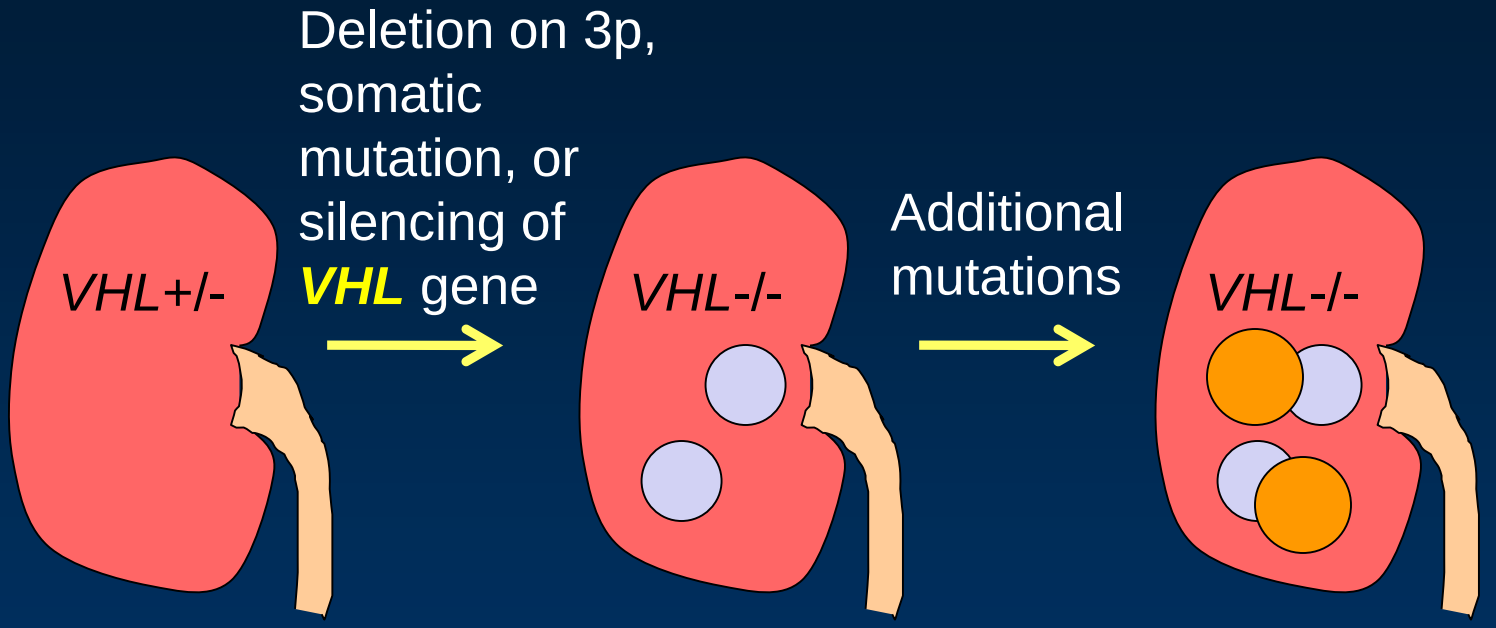


Multiple renal cysts and clear cell RCCs

From Clear Cells to *VHL* Gene



Von Hippel-Lindau Disease is Caused by Germline Mutations in the ***VHL* Gene** (3p25.3)

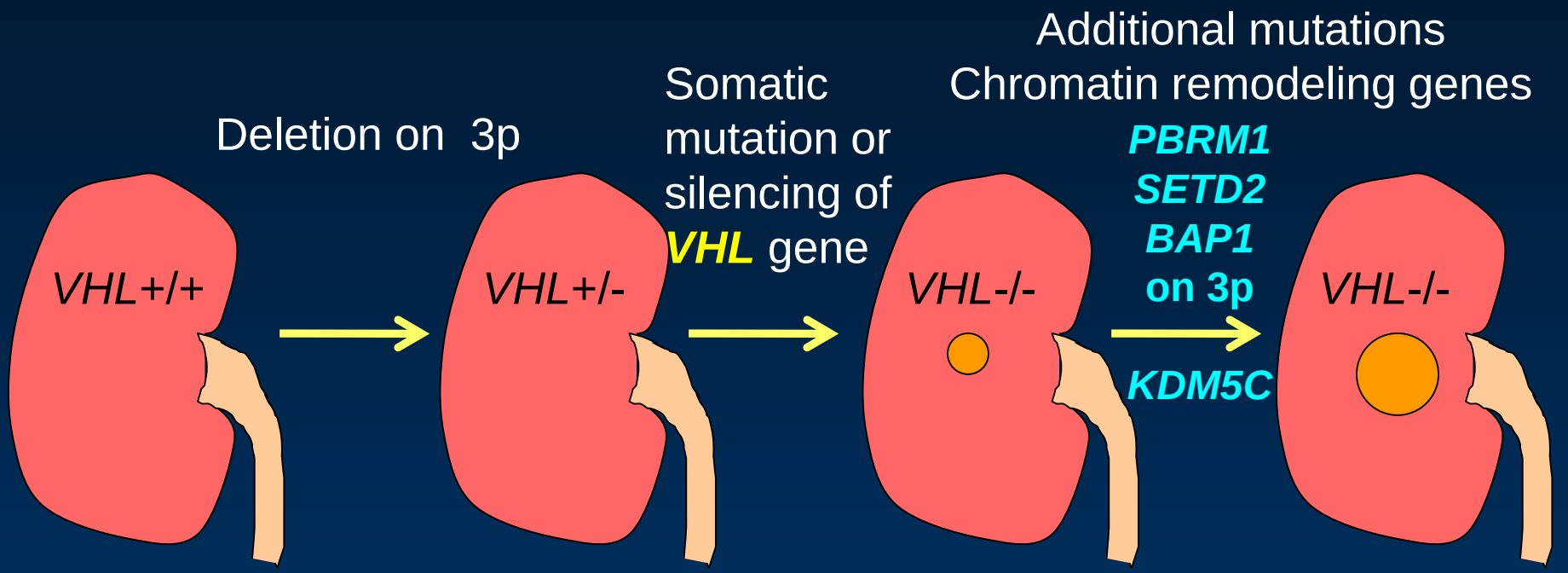


VHL germline mutation

Multiple renal cysts

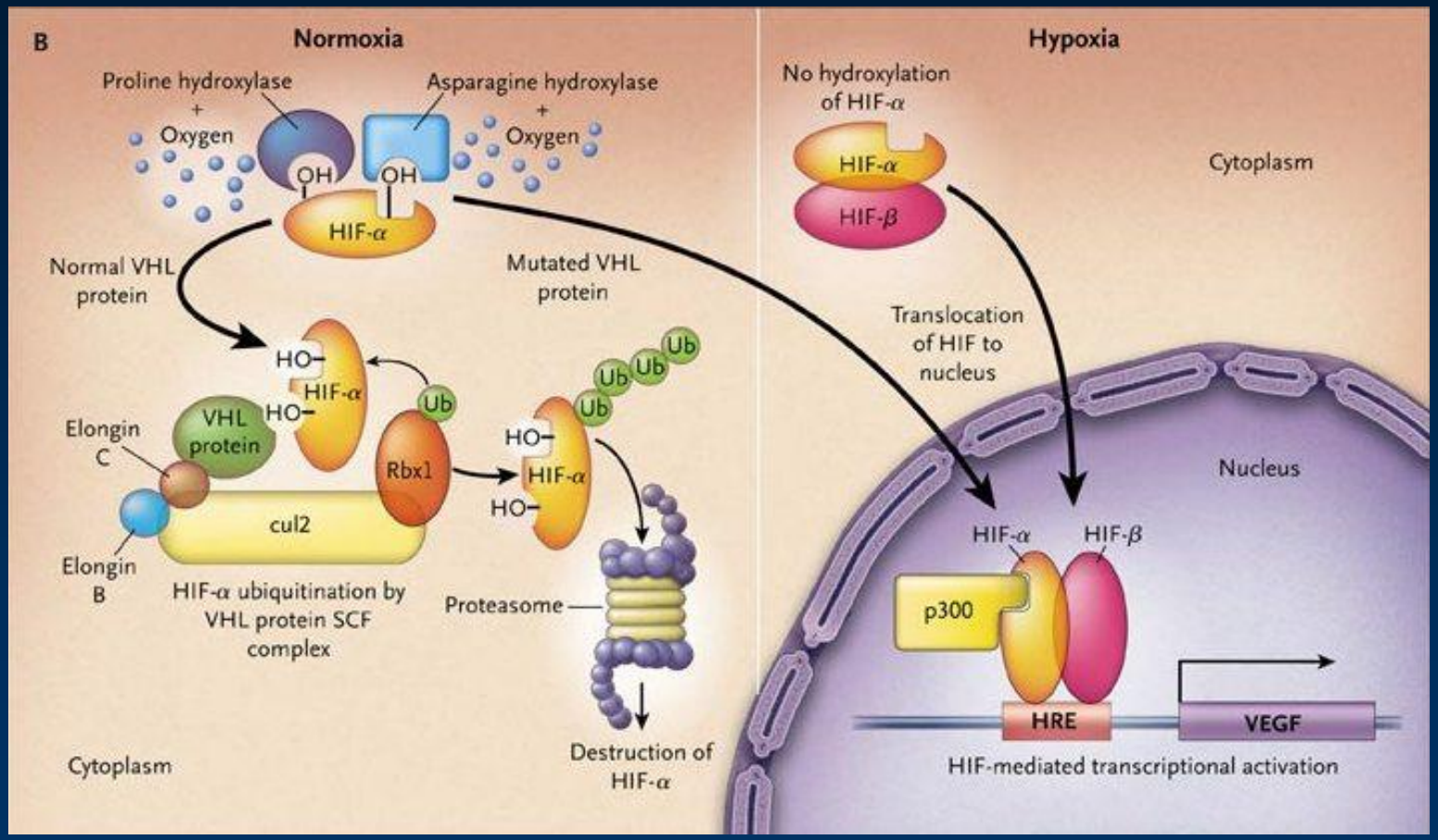
Multiple clear cell RCCs

***VHL* Gene** is Inactivated in Sporadic Clear Cell RCC



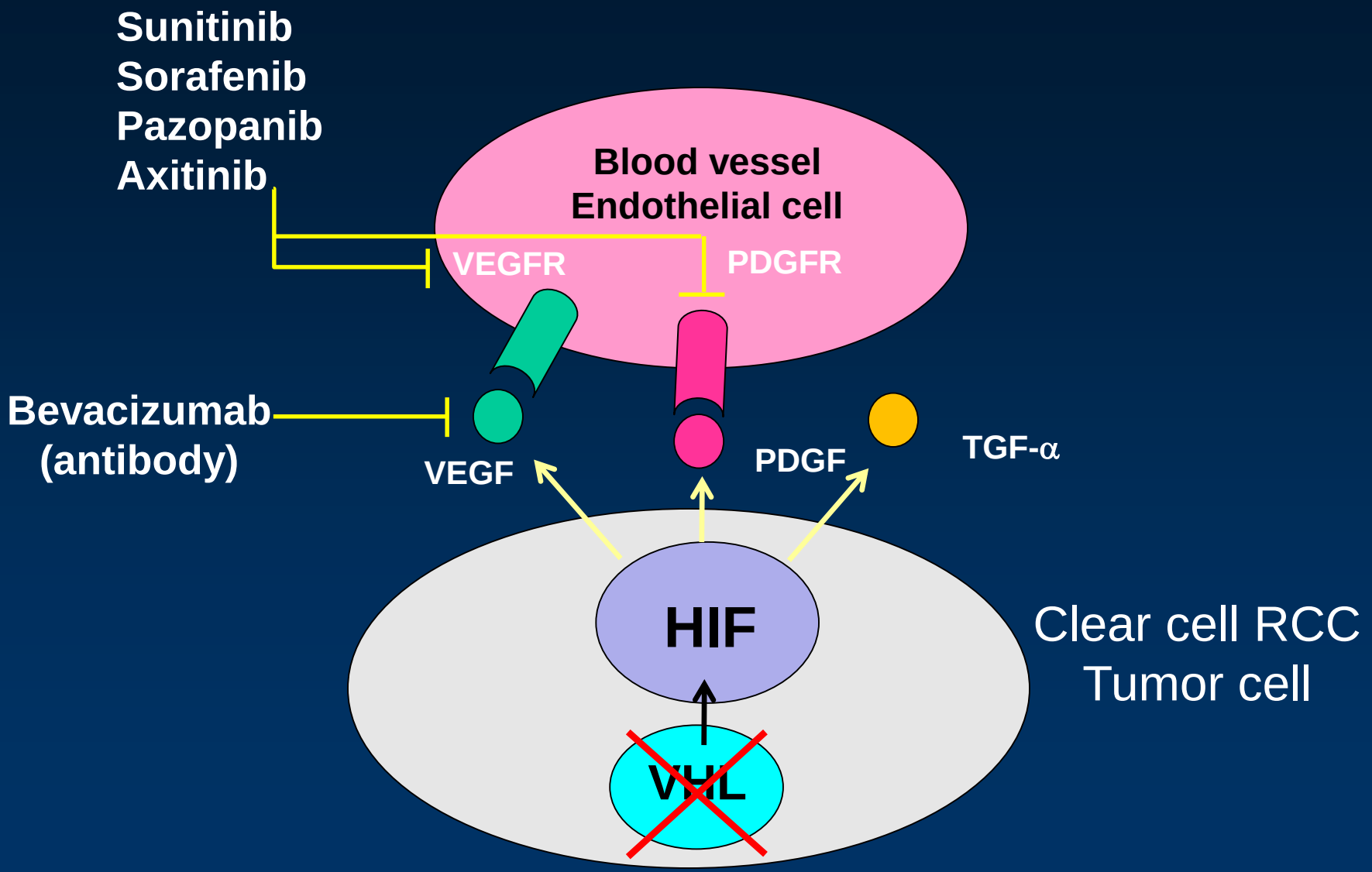
Single clear cell RCC

Abnormal VHL Protein Causes Accumulation of Hypoxia Inducible Factor-α (HIF-α)



HIF-α induces transcription of vascular endothelial growth factor **(VEGF)** involved in angiogenesis , platelet derived growth factor **(PDGF)** and transforming growth factor-α **(TGF-α)** involved in cell growth

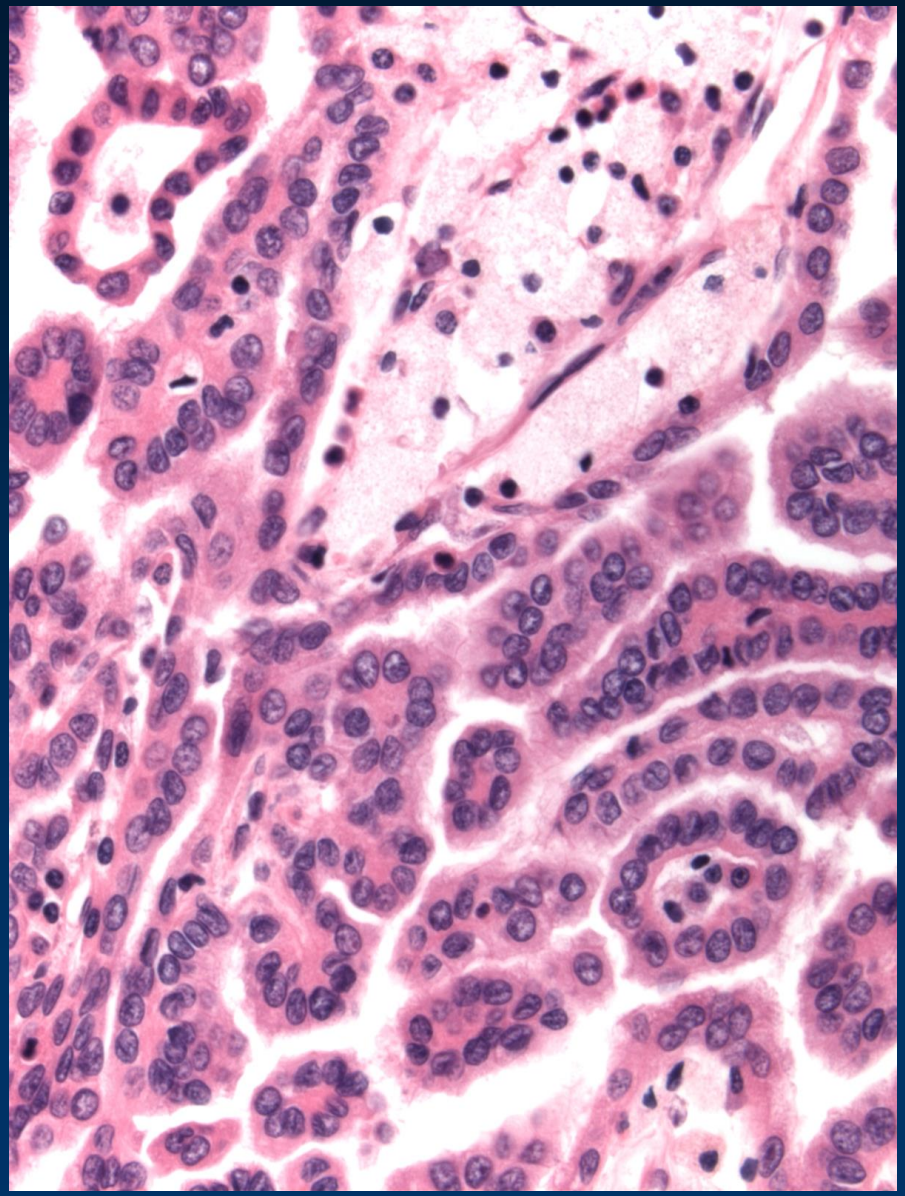
Targeting VHL/HIF in Clear Cell RCC



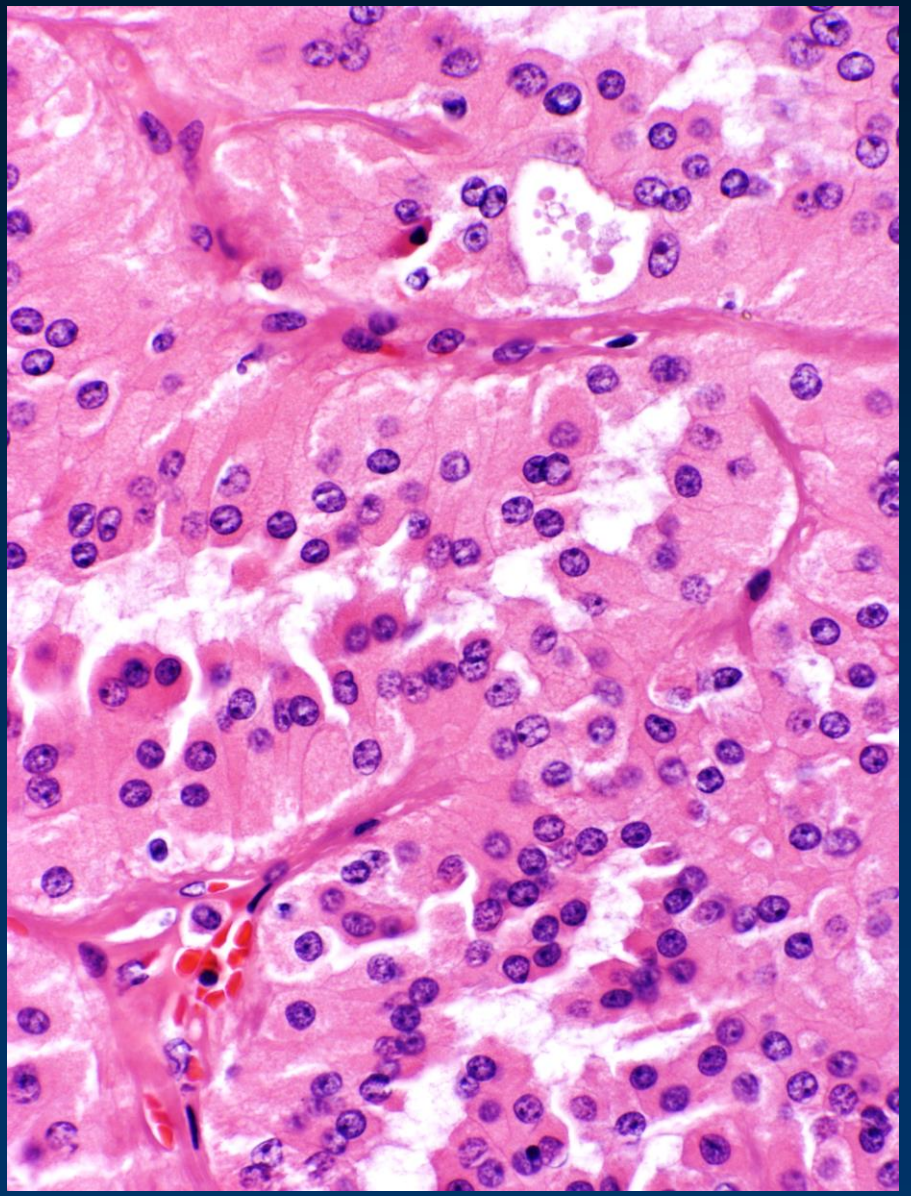
Papillary RCC

- 15% of RCC
- Two histologic subtypes:
  - Type 1
  - Type 2
- Subset with mixed histology

Papillary RCC Type 1

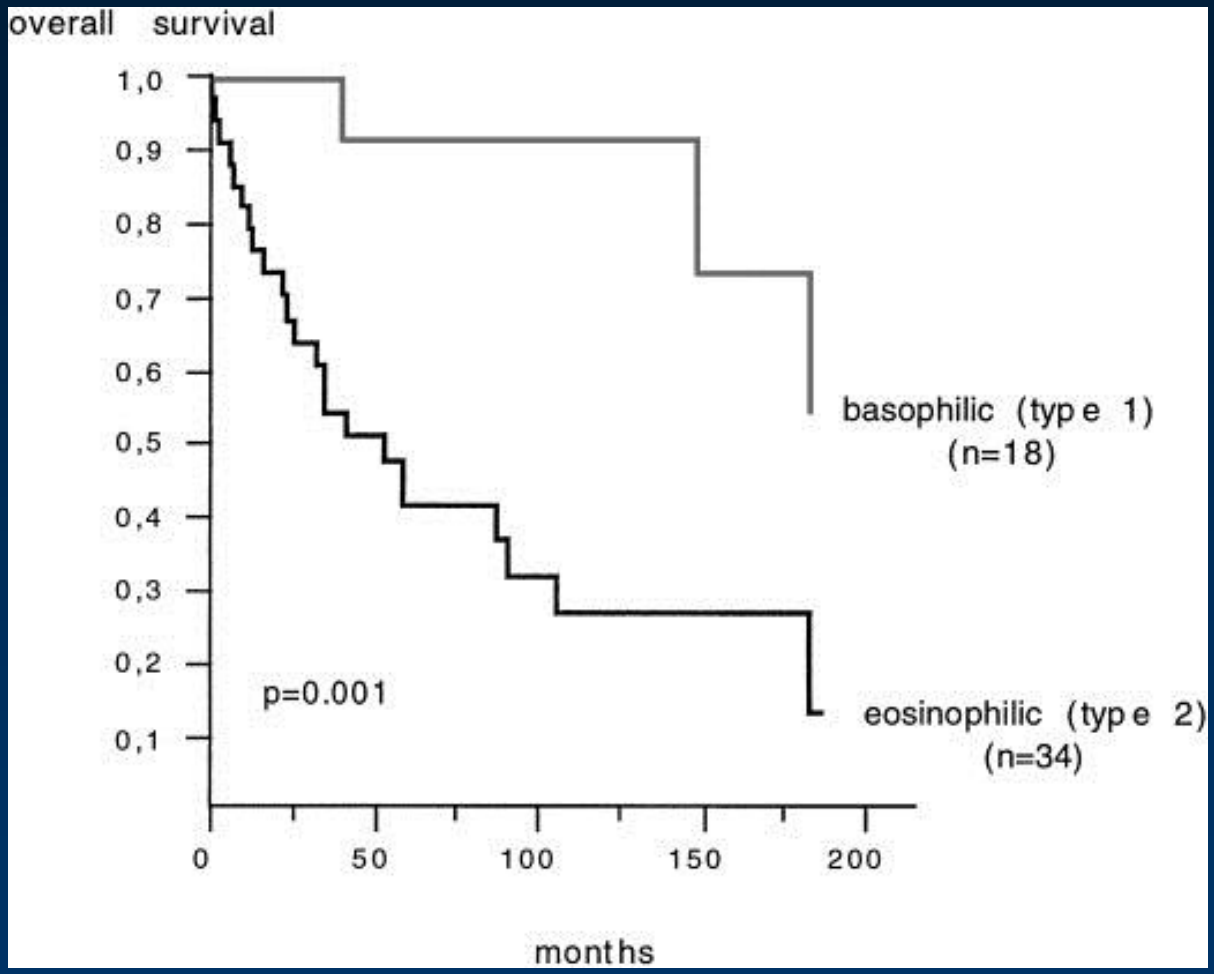


Papillary RCC Type 2



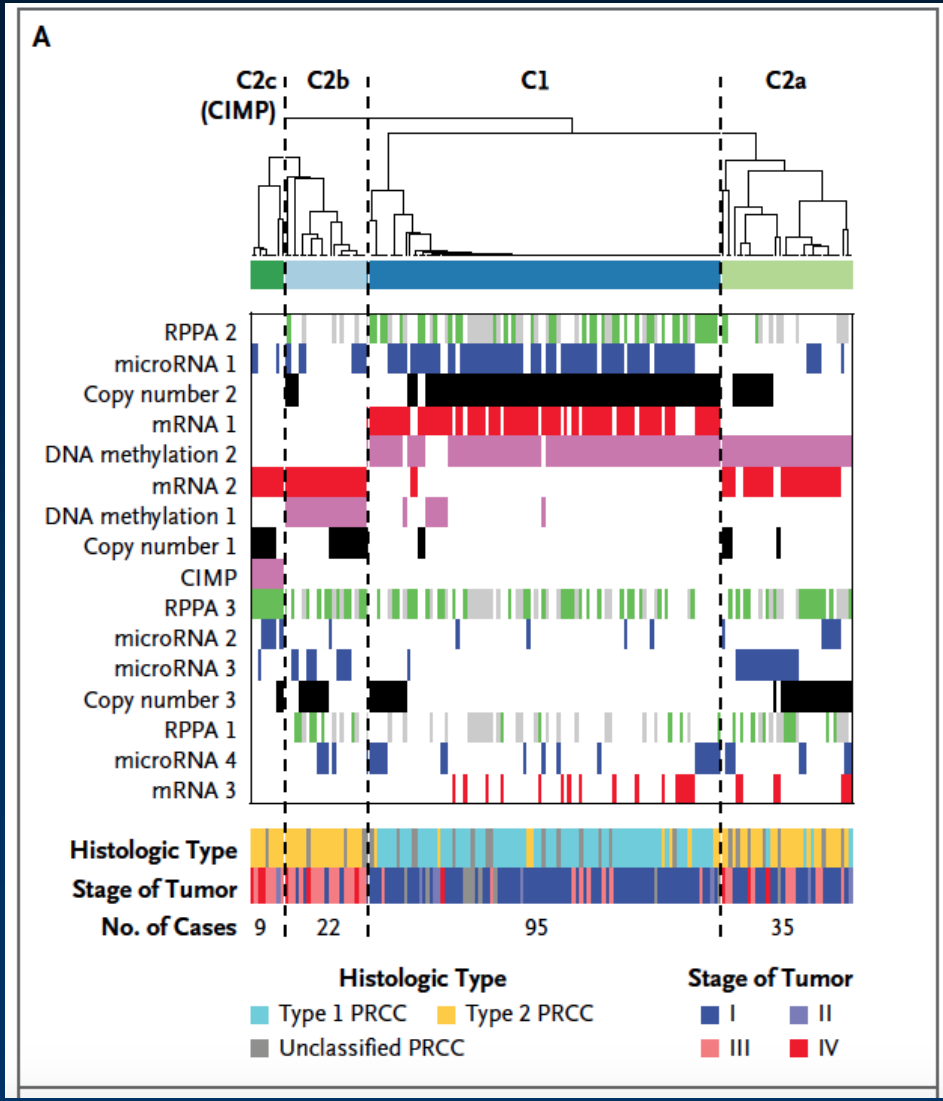
Overall Survival in Papillary RCC According to Papillary Subtype

A Swiss experience with 588 tumors

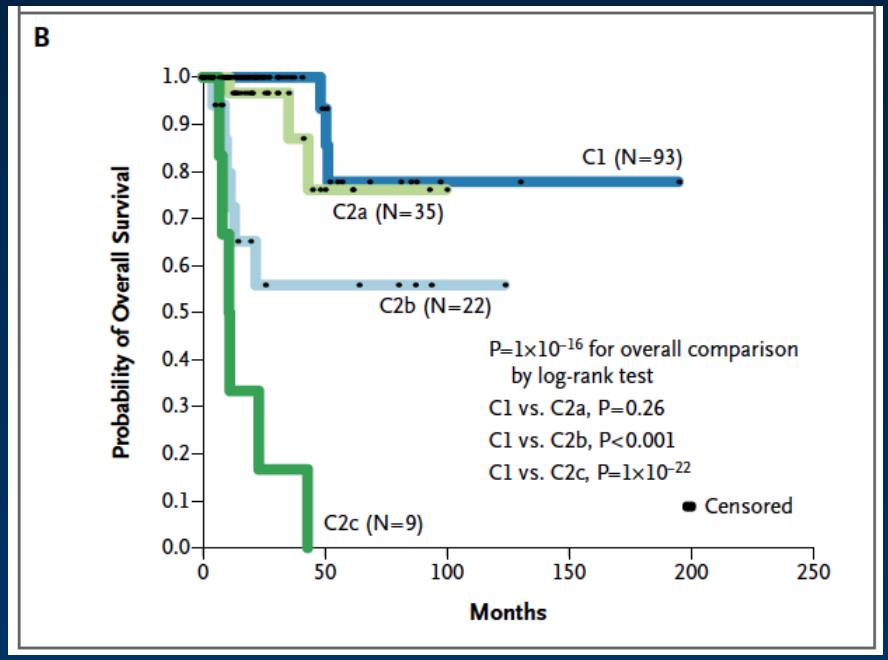


Moch et al, Cancer 2000

Multiplatform-Based Subtype Discovery in 161 Papillary RCC

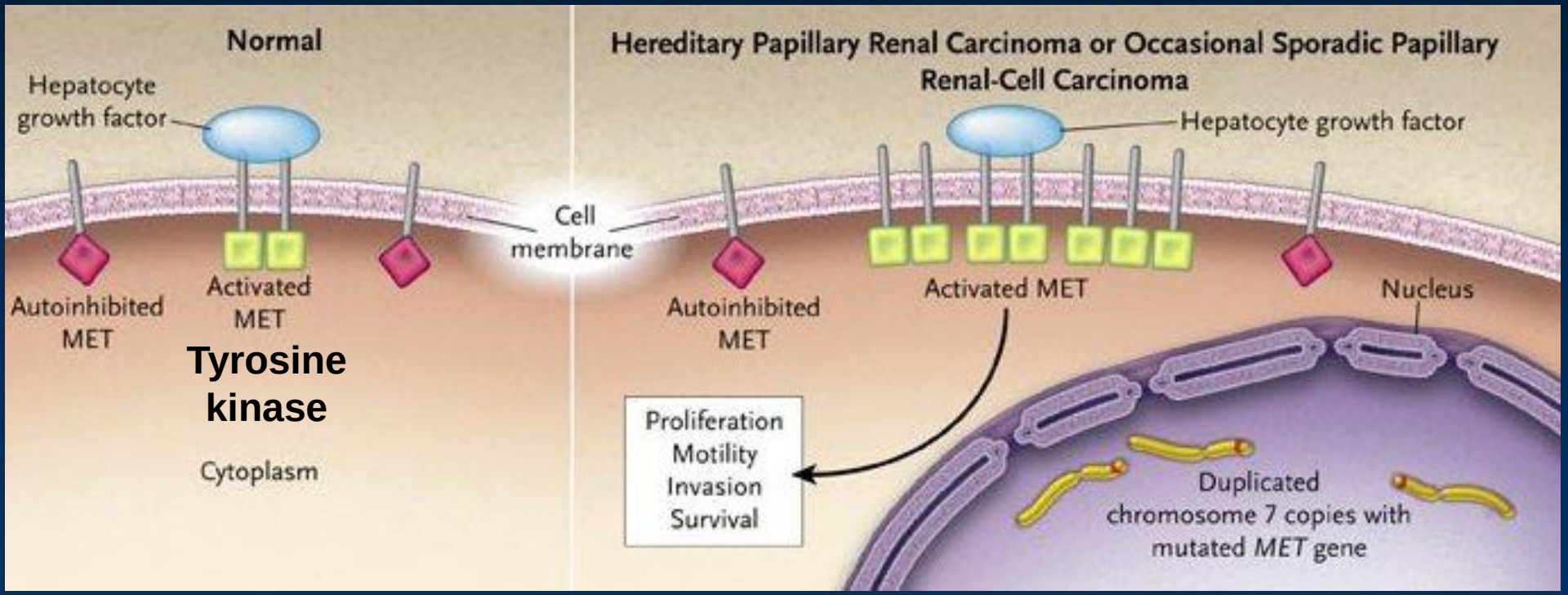


Type 2 papillary RCC – at least 3 different entities genetically

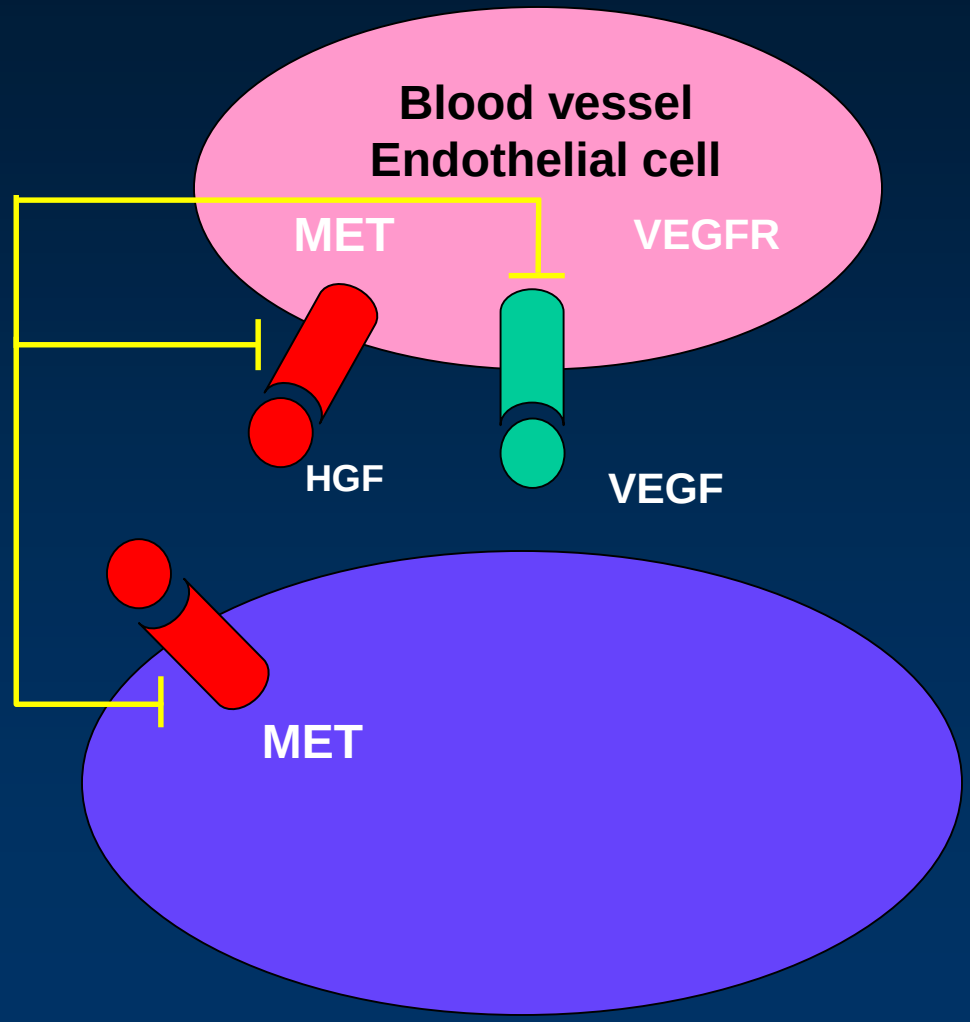


The Cancer Genome Atlas Research Network.
N Engl J Med 2016, 374:135-45.

Activation Mutations in *MET* Oncogene (7q31) in Type 1 Papillary RCC



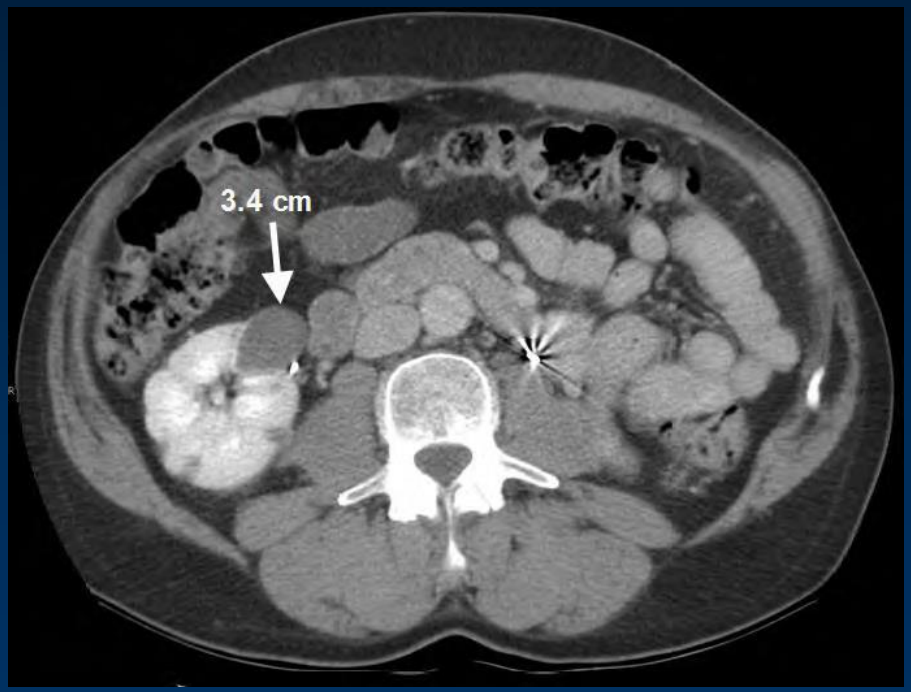
Targeted Therapies in Type 1 Papillary RCC with MET Inhibitors



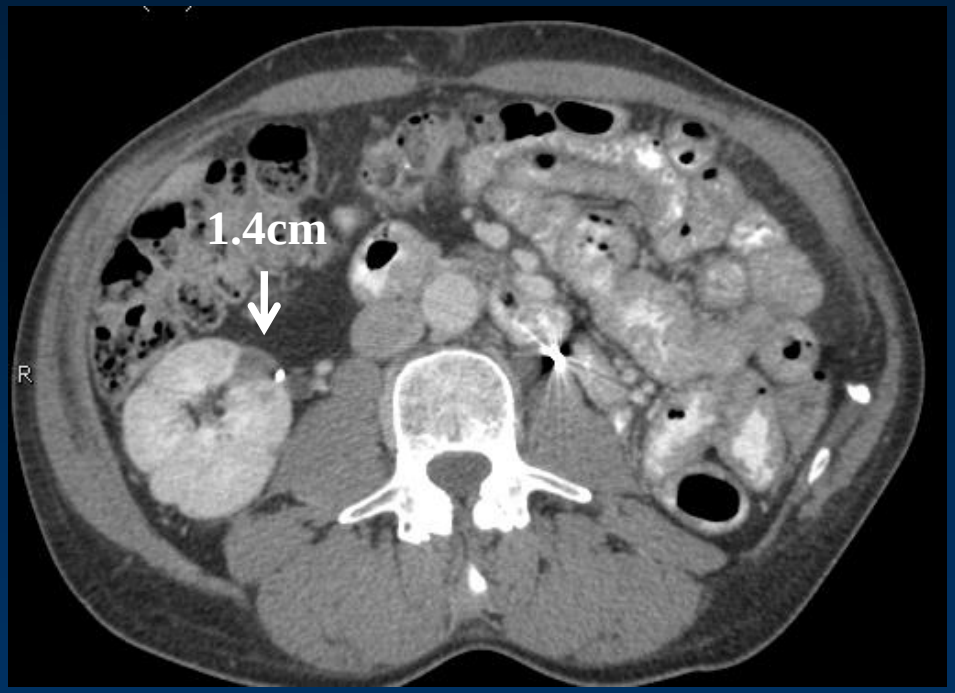
Foretinib
Cabozantinib

Papillary RCC
Tumor cell

Regression of Papillary RCC Treated with MET Inhibitor Foretinib



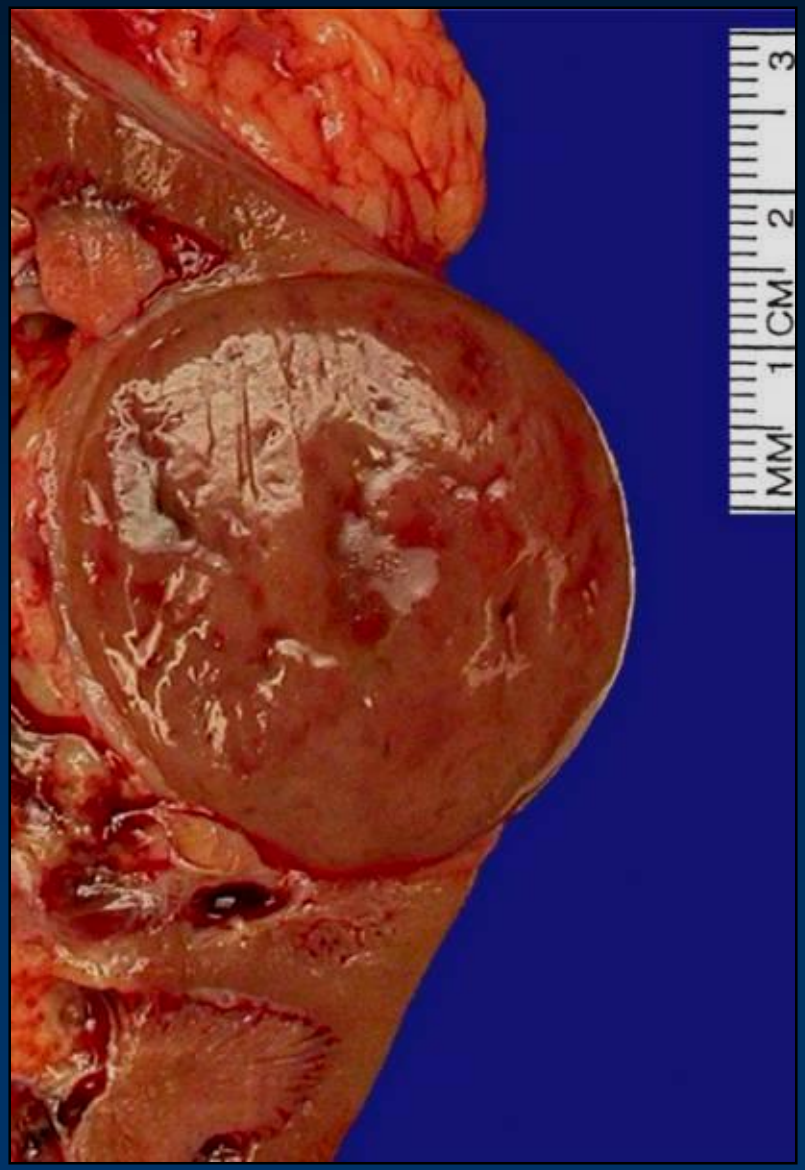
Pre-Treatment

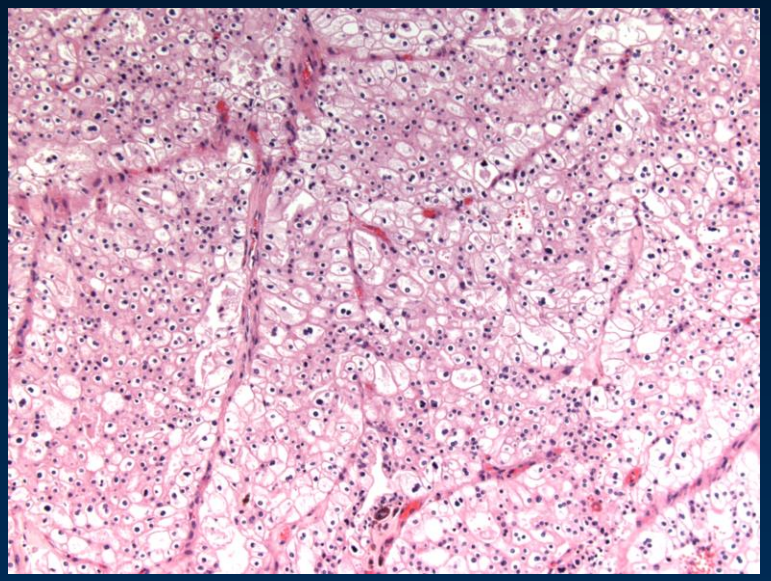


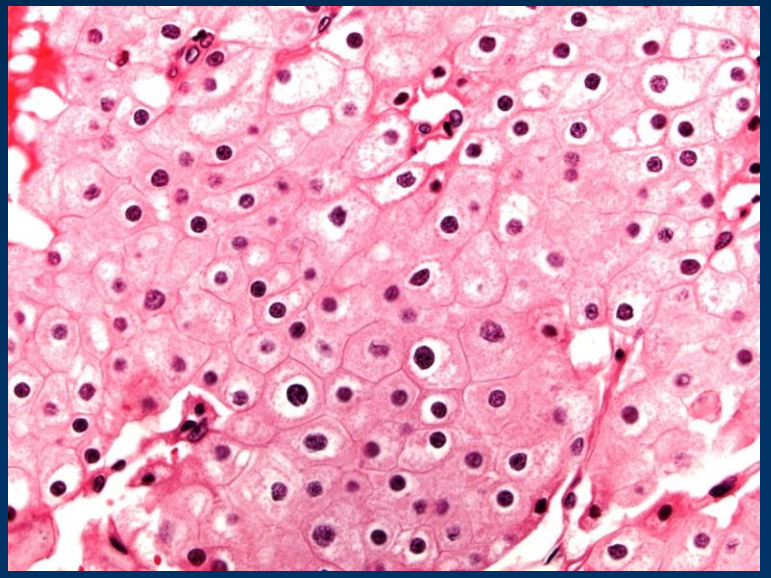
Following 49 cycles of therapy

J Clin Oncol 10:2012

Chromophobe RCC





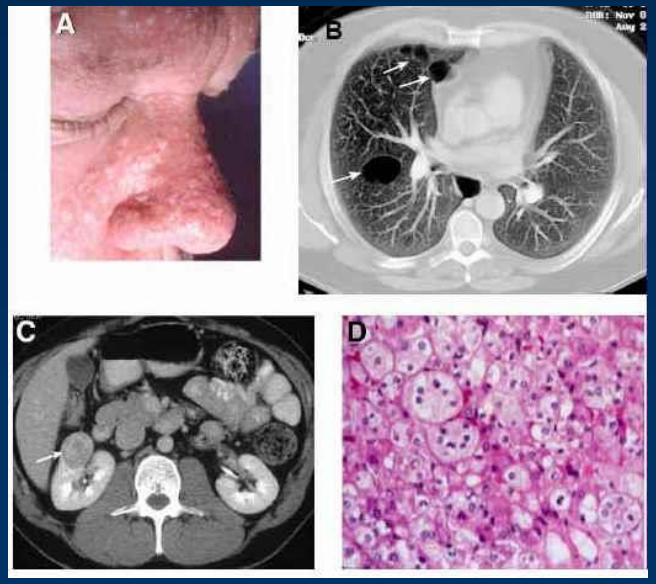


Chromophobe RCC

Inherited

in Birt-Hogg-Dube syndrome

- Folliculin *(FLCN)* mutation



Sporadic

- Folliculin *(FLCN)* mutation rare
- Hypodiploid DNA: -1,-2,-6,-**10**,-13,-**17**,-21
  (Multiple chromosomal losses)
- ***TP53*** mutation (chr **17**)
- ***PTEN*** mutation (chr ***10***)

New RCC Subtypes with Molecular Alterations and Distinct Histology

- Clear cell renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential
- Papillary renal cell carcinoma
- Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
- Chromophobe renal cell carcinoma
- Collecting duct carcinoma
- Renal medullary carcinoma
- MiT Family translocation renal cell carcinomas
- Succinate dehydrogenase-deficient renal cell carcinoma
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic renal cell carcinoma
- Acquired cystic disease associated renal cell carcinoma
- Clear cell papillary renal cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)-associated Renal Cell Carcinoma

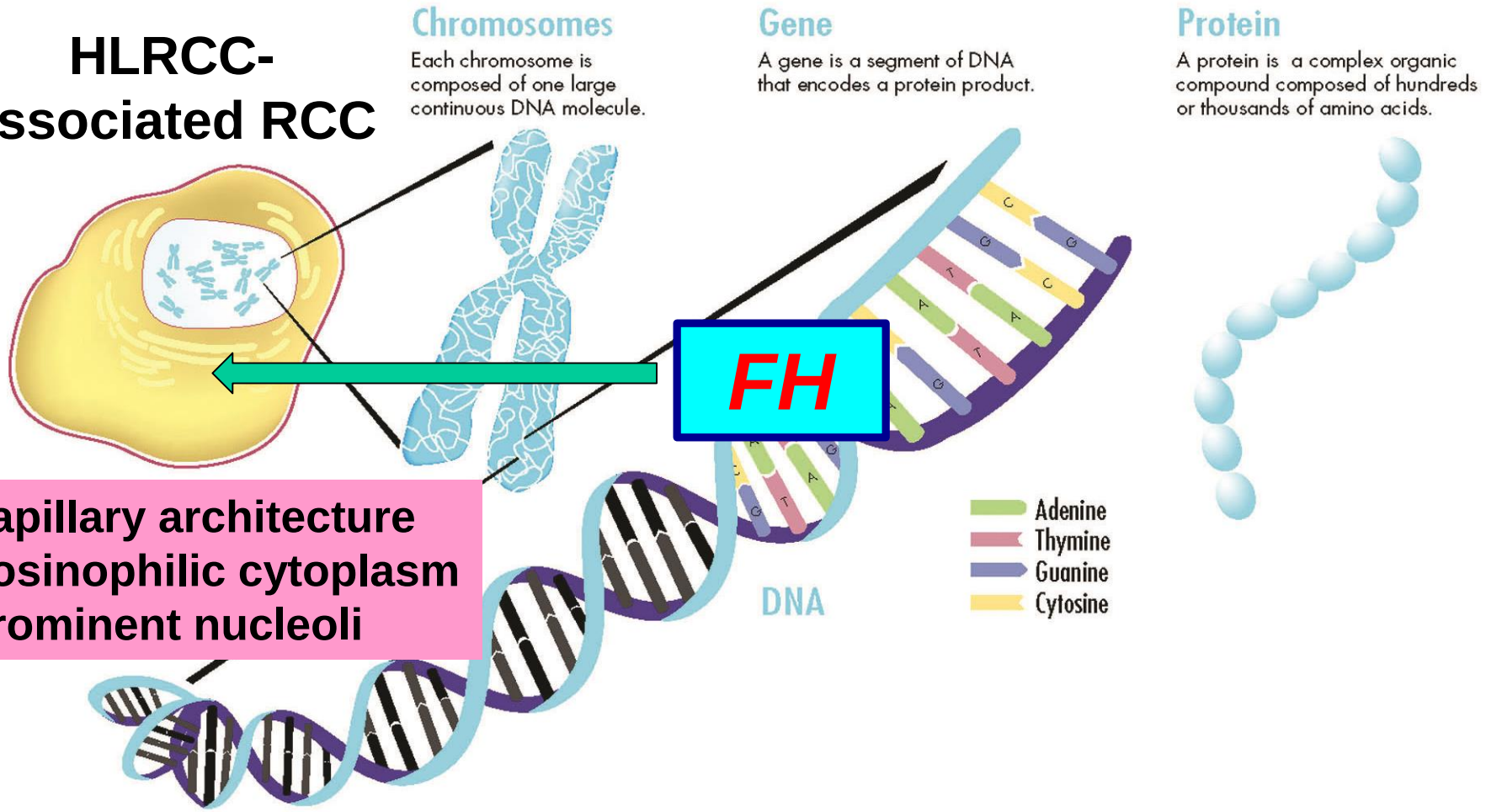
- Multiple cutaneous and uterine leiomyomas

HLRCC-associated RCC

- RCC (1/3 of patients)
  - Solitary
  - **Aggressive**
- Germline mutation in *Fumarate Hydratase* (*FH*) gene on 1q42
- FH is a Krebs cycle enzyme
- Patients should undergo formal genetic testing

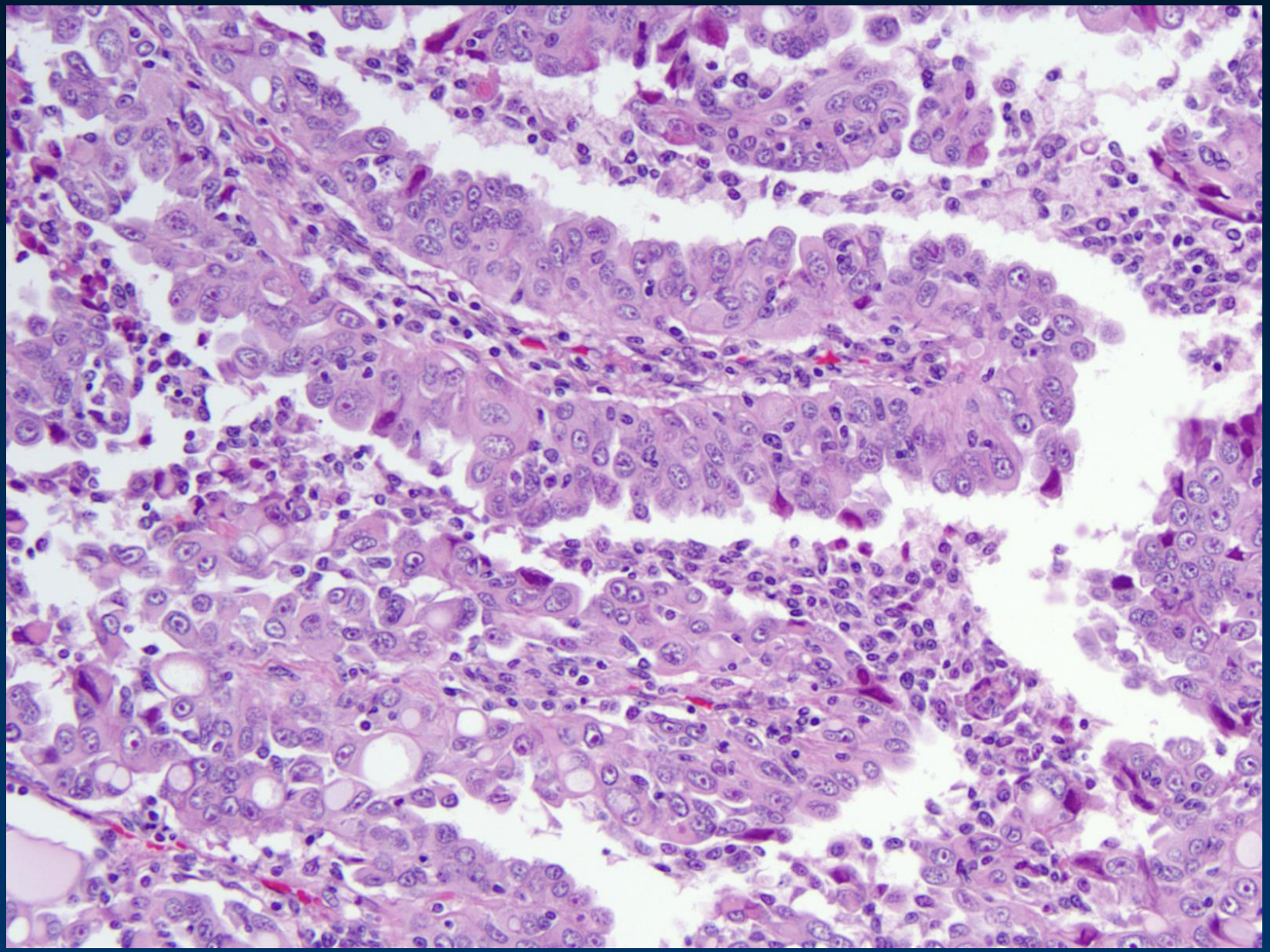
From *FH* Gene to Characteristic Histopathology

HLRCC-associated RCC

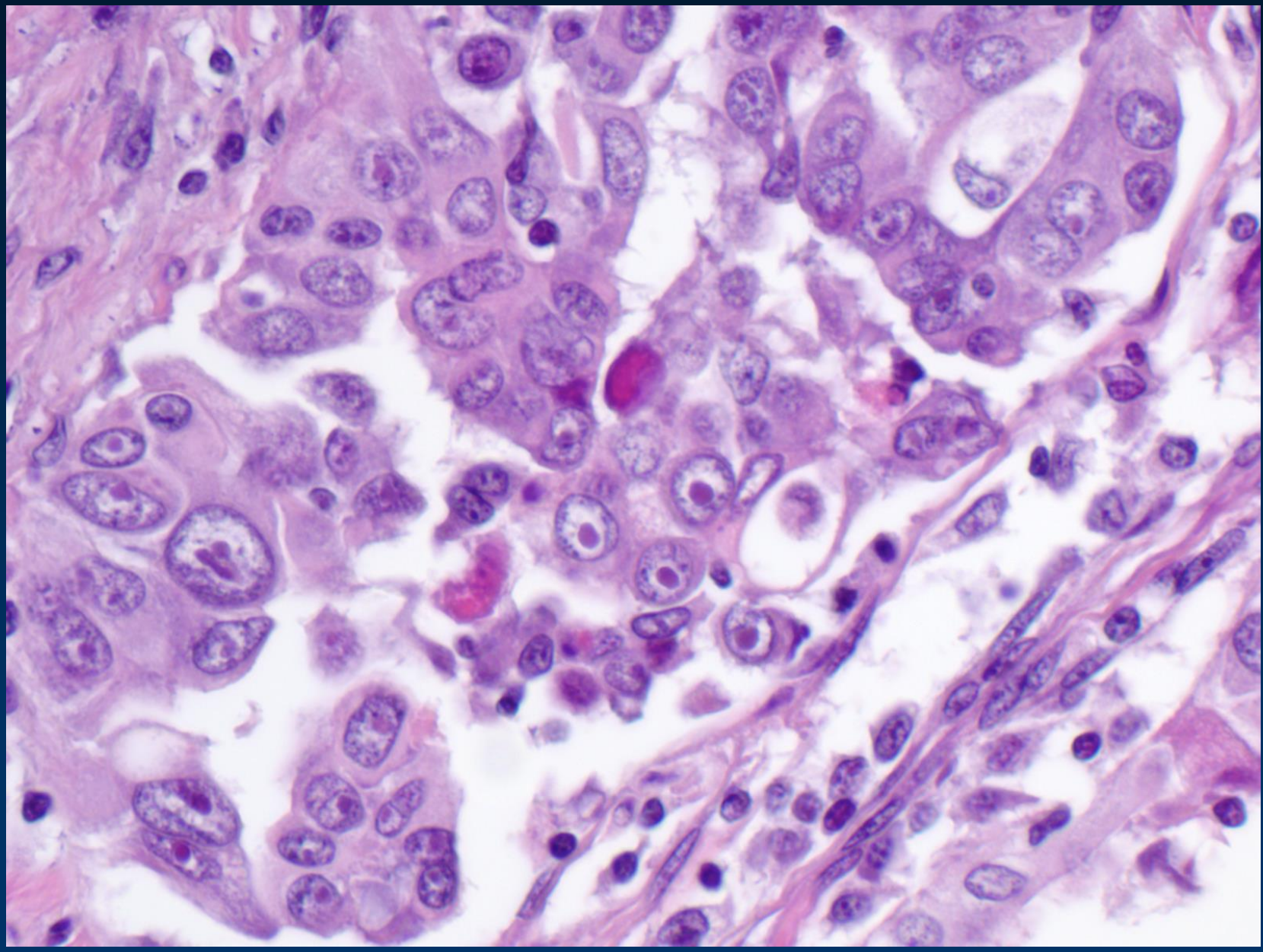


Papillary architecture
Eosinophilic cytoplasm
Prominent nucleoli

HLRCC-associated RCC



HLRCC-associated RCC



Succinate Dehydrogenase (SDH)-deficient RCC

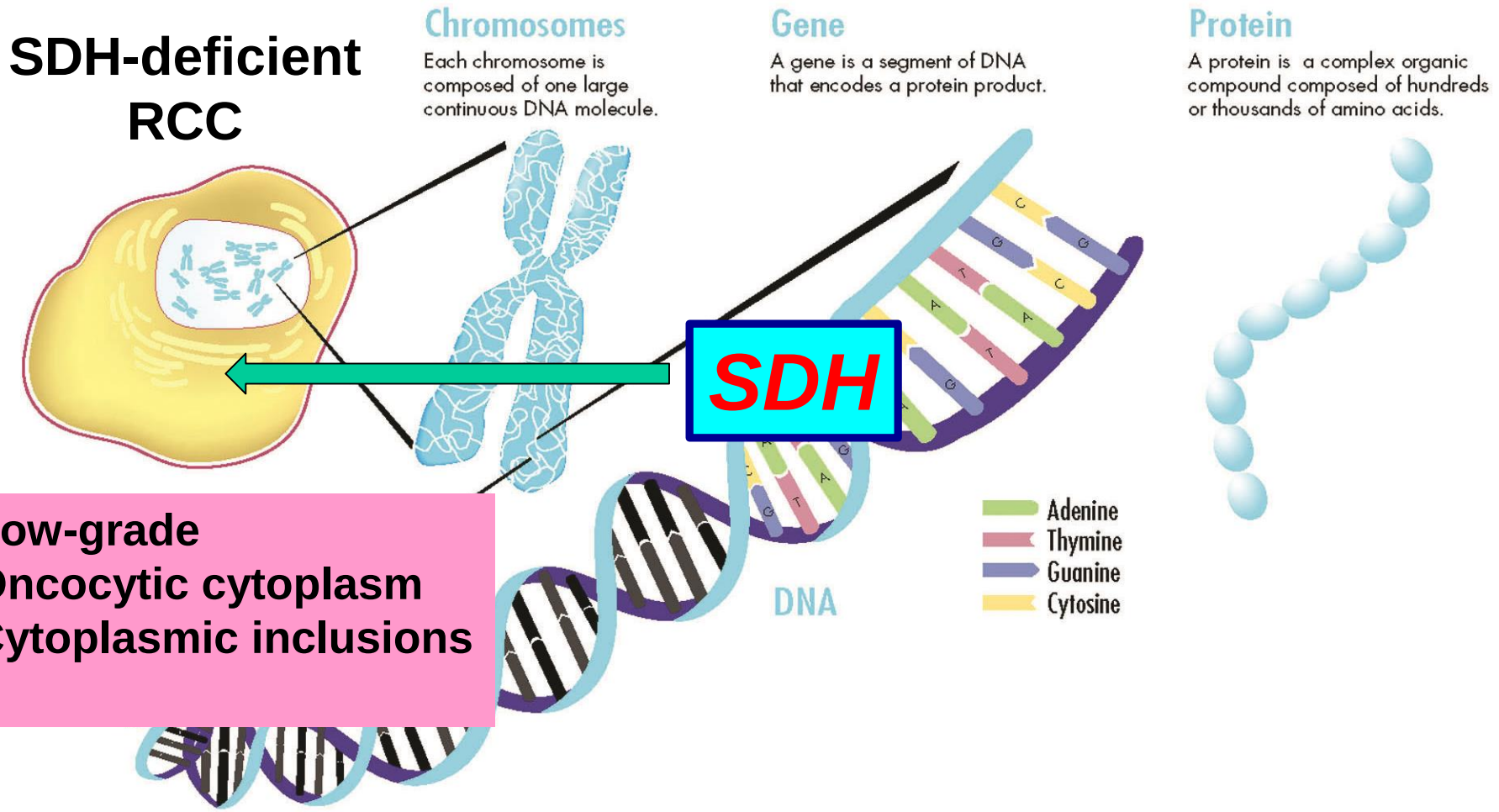
- First described in patients with *SDHB* germline mutations
- SDH is a Krebs cycle enzyme
- Personal/family history of
  - Pheochromocytoma/Paraganglioma
  - Gastrointestinal stromal tumor (GIST)
- Patients with *SDH* mutation have 14% lifetime risk of RCC

Succinate Dehydrogenase (SDH)-deficient RCC

- Rare – 0.05%-0.2% of all RCC
- Typically young adults
  - Median age 35 yrs
- Usually indolent
- Patients should undergo formal genetic testing

From *SDH* Gene to Characteristic Histopathology

SDH-deficient RCC



Low-grade
Oncocytic cytoplasm
Cytoplasmic inclusions

Am J Surg Pathol • Volume 38, Number 12, December 2014

ORIGINAL ARTICLE

OPEN

Succinate Dehydrogenase (SDH)-deficient Renal Carcinoma: A Morphologically Distinct Entity

A Clinicopathologic Series of 36 Tumors From 27 Patients

Anthony J. Gill, MD, FRCPA,†‡ Ondrej Hes, MD,§ Thomas Papathomas, MD,‖ Monika Šedivcová, MSc,§ Puay Hoon Tan, MD,¶ Abbas Agaimy, MD,# Per Arne Andresen, MSc,** Andrew Kedziora, FRCPA,† Adele Clarkson, BSc,*† Christopher W. Toon, FRCPA,†‡†† Loretta Sioson, BSc,†‡ Nicole Watson,† Angela Chou, FRCPA,†‡‡ Julie Paik, MBBS,*† Roderick J. Clifton-Bligh, PhD, FRACP,‡§§ Bruce G. Robinson, MD, FRCPA,‡§§ Diana E. Benn, PhD,‡§§ Kirsten Hills, FRCPA,‖‖ Fiona Maclean, FRCPA,¶¶ Nicolasine D. Niemeijer, MD,## Ljiljana Vlatkovic, MD,*** Arndt Hartmann, MD,# Eleonora P.M. Corssmit, MD,## Geert J.L.H. van Leenders, MD,PhD,‖ Christopher Przybycin, MD,††† Jesse K. McKenney, MD,††† Cristina Magi-Galluzzi, MD,PhD,††† Asli Yilmaz, MD,‡‡‡ Darryl Yu, MD,‡‡‡ Katherine D. Nicoll, FRCPA,§§§ Jim L. Yong, FRCPA,§§§ Mathilde Sibony, MD, PhD,‖‖‖ Evgeny Yakirevich, MD, DSc,¶¶¶ Stewart Fleming, MD, FRCPATH,### Chung W. Chow, FRCPA,**** Markku Miettinen, MD,†††† Michal Michal, MD,§ and Kiril Trpkov, MD‡‡‡*

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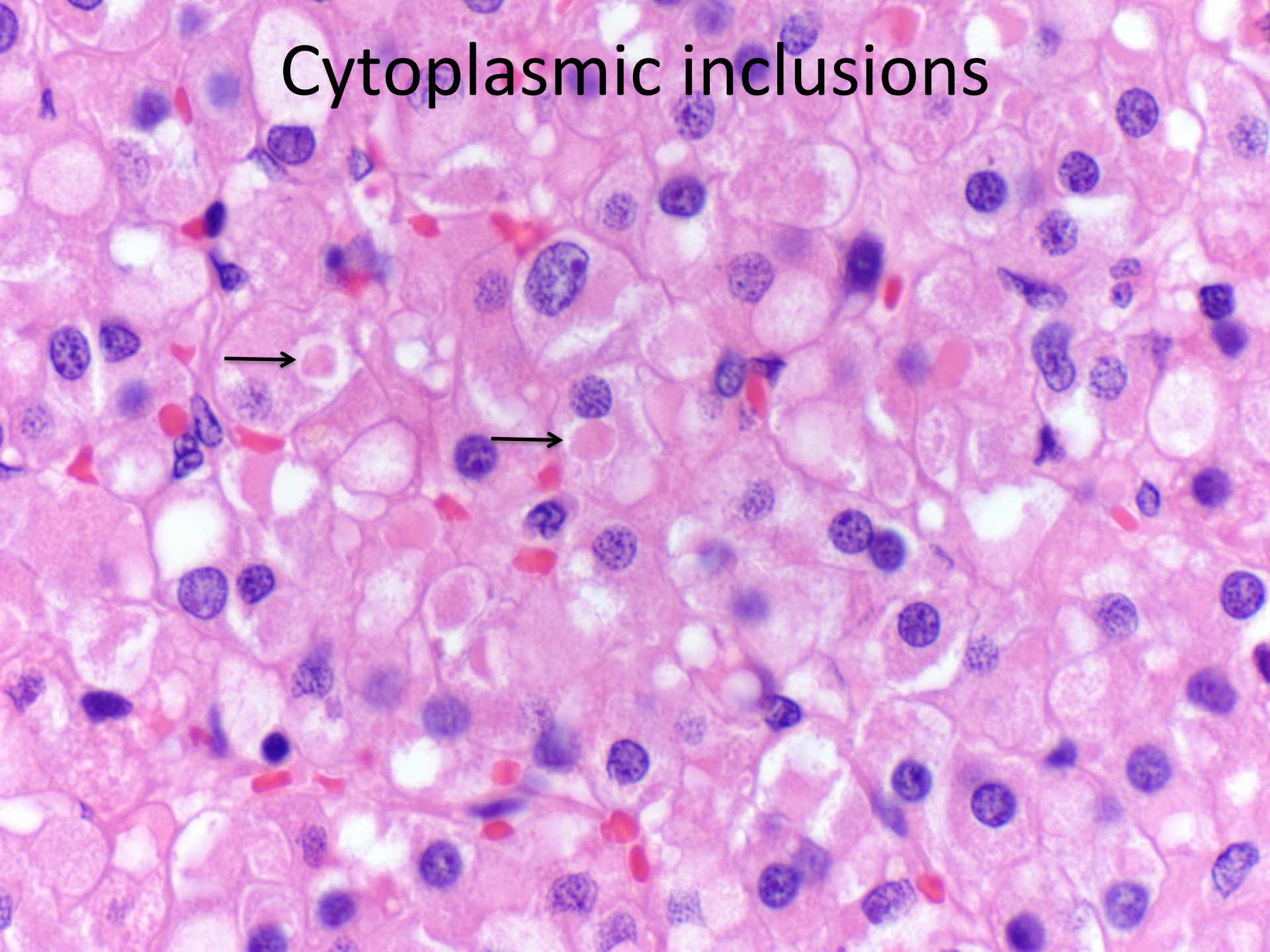
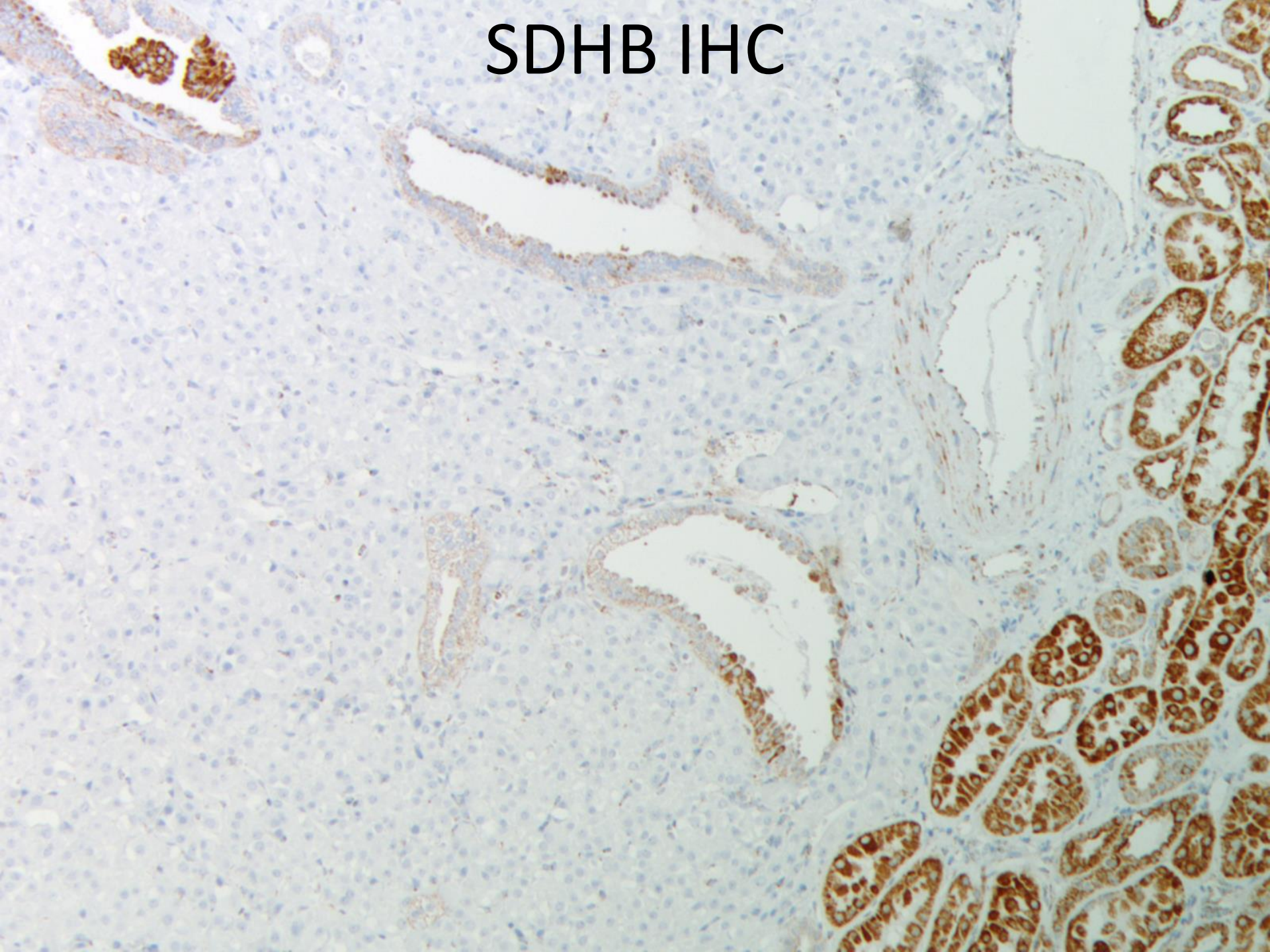
Succinate dehydrogenase-deficient renal cell carcinoma: detailed characterization of 11 tumors defining a unique subtype of renal cell carcinoma

Sean R Williamson[1], John N Eble[2], Mahul B Amin[3], Nilesh S Gupta[1], Steven C Smith[3], Lynette M Sholl[4], Rodolfo Montironi[5], Michelle S Hirsch[4] and Jason L Hornick[4]

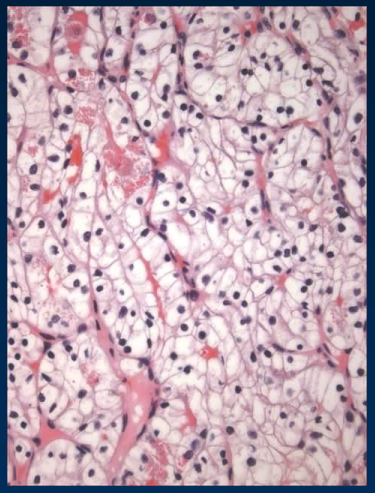
Cytoplasmic inclusions



SDHB IHC



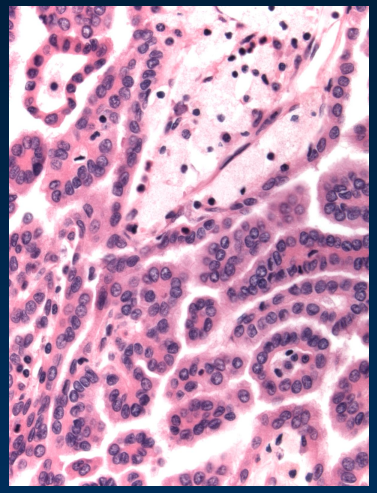
Histologic Types of RCC, Genetics and Targeted Therapies



Clear cell

VHL

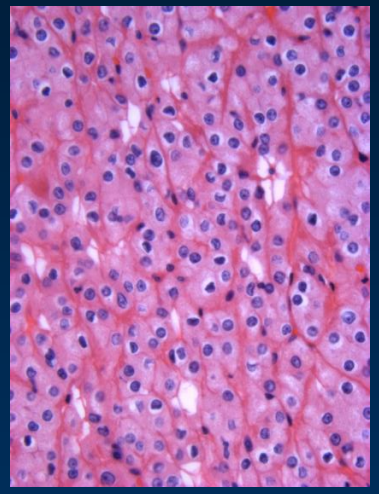
VEGF/VEGFR inhibitors



Papillary type 1

MET

MET inhibitors

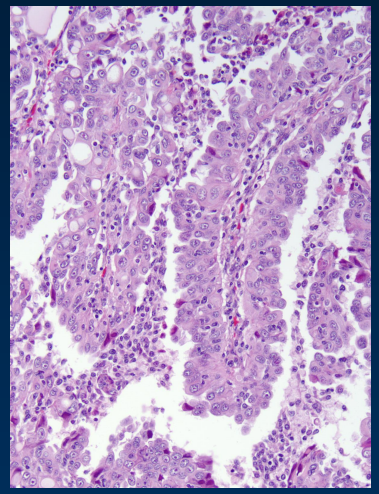


Chromophobe

FLCN

TP53 PTEN

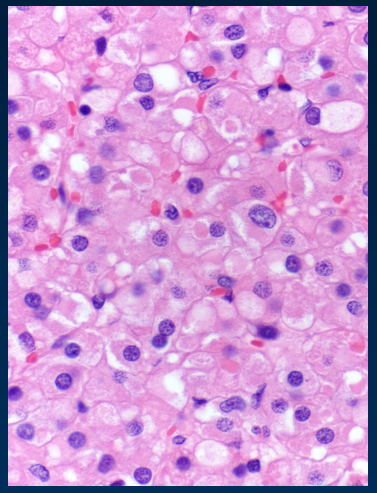
?



HLRCC-RCC

FH

?



SDH-deficient RCC

SDH