THE CLINICAL AND PATHOLOGIC BASIS OF CLASSIFICATION OF RENAL CELL CARCINOMA

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WHY DO WE CLASSIFY

Uniform nomenclature used by all physicians, scientists, public health policy makers, registry & surveillance community & patients to understand, manage, record and study disease

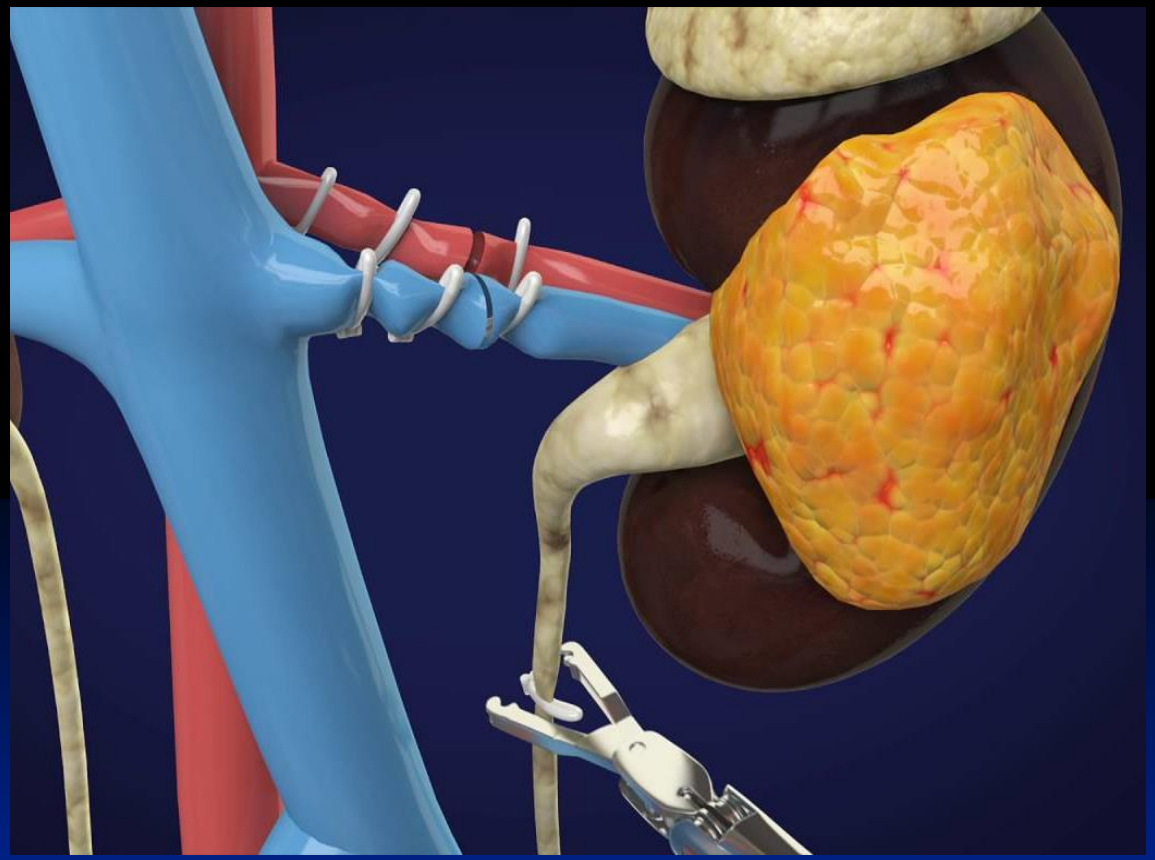
- *ESTABLISH PATIENT MANAGEMENT PARADIGMS*
- *ENABLE BIDIRECTIONAL TRANSLATIONAL RESEARCH BETWEEN LABORATORY DISCOVERY AND CLINICAL PRACTICE*
- *FOSTER MEANINGFUL COMPARABLE RESEARCH*
- *FORMULATE HEALTH POLICY - CANCER REGISTRY & CLINICAL OUTCOME DATA*

CLASSIFICATION OF RENAL TUMORS

Rayer (1841) – Clinical classification based on 13 tumors

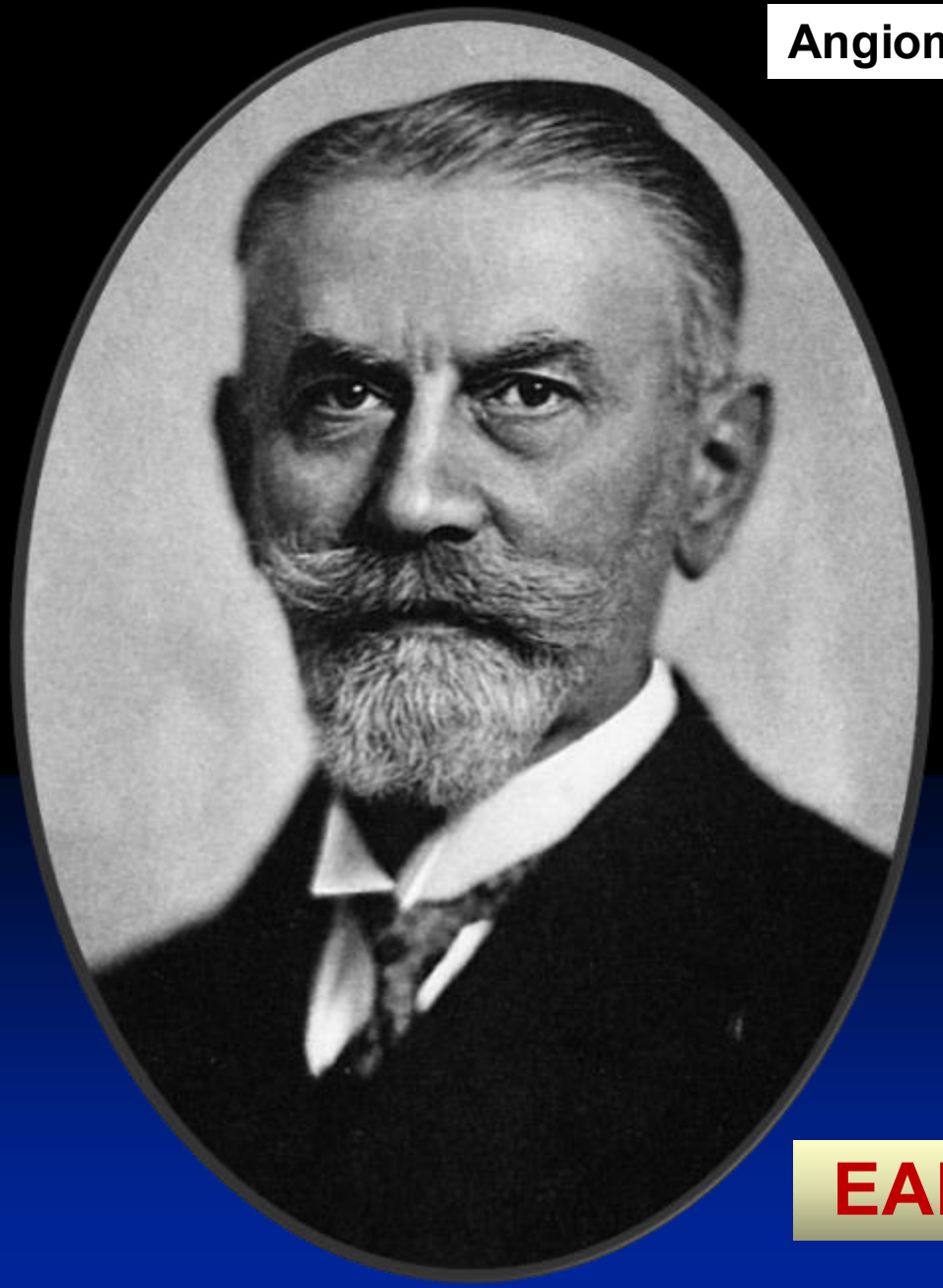
- ***Encephaloid form:***
  - No increase in renal volume…(cortical)
  - No hematuria
- ***Cancers of renal calyx:***
  Hematuria
- ***Hard tumors:***
  - Easily palpable
  - Usually associated

DECEMBER 7, 1875



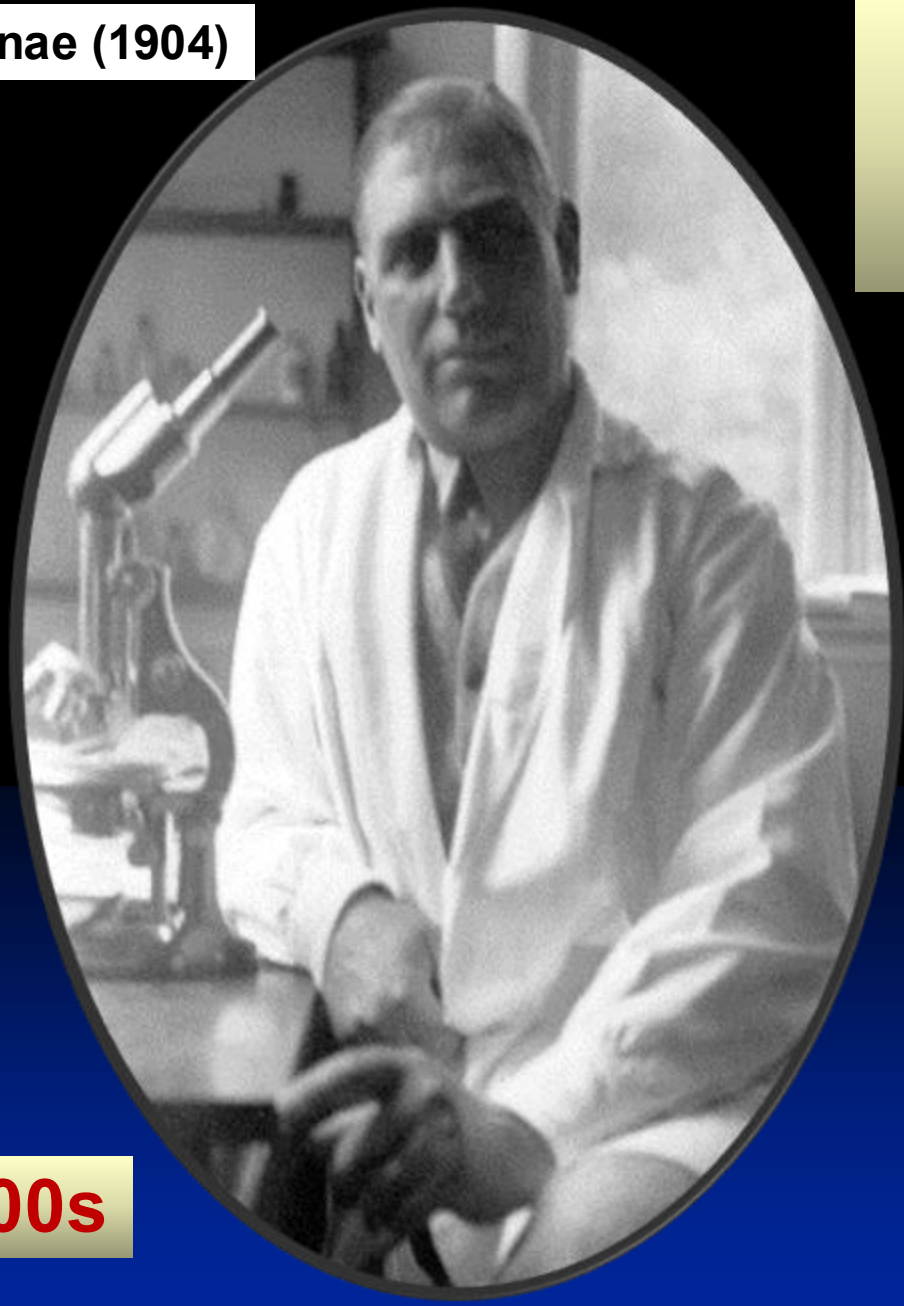
- **Lagenbuch, first nephrectomy for a renal tumor**
- **3 prior nephrectomies (1861, 1867, 1868): post-operative deaths**
  - **Successful post-operative course**
  - **Tumor never diagnosed - *"accidentally disposed prior to examination"***

Angiomatosis retinae (1904)



Eugen Von Hippel, German Ophthalmologist

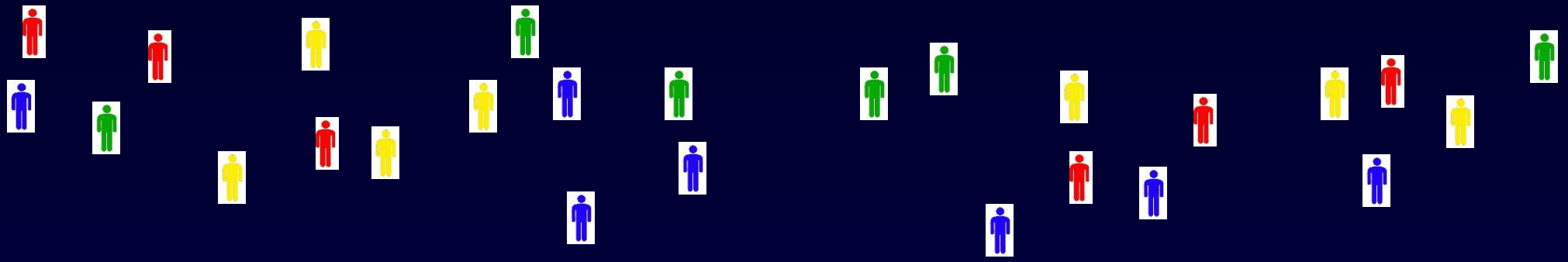
EARLY 1900s

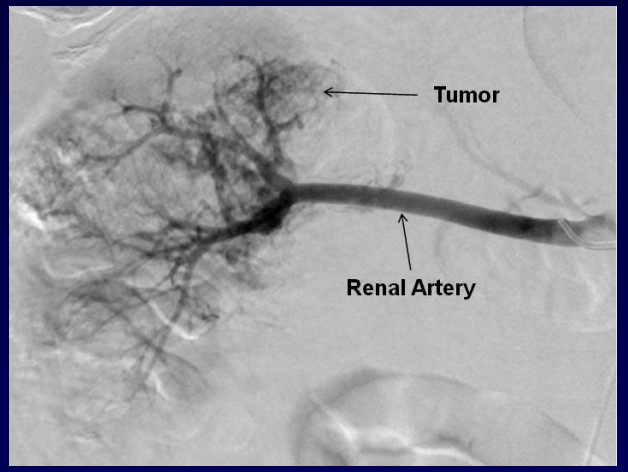


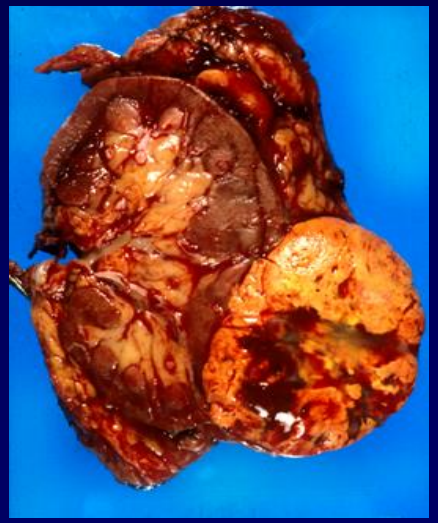
Arvid Lindau. Swedish Pathologist

1936
VHL disease

Cerebellar hemangiomas
renal, pancreatic and epididymal cysts &
renal tumors associated with retinal lesions (1926)





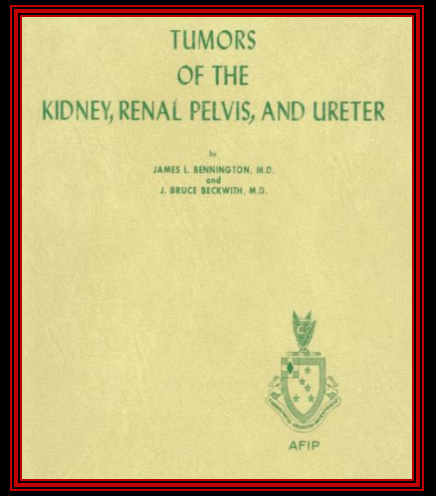


Surgery

1970s

1975: CLASSIFICATION OF RENAL TUMORS

- "Tumors of kidney, renal pelvis & ureter"
  - 2nd series AFIP fascicle
  - *"Renal carcinoma has many faces"*



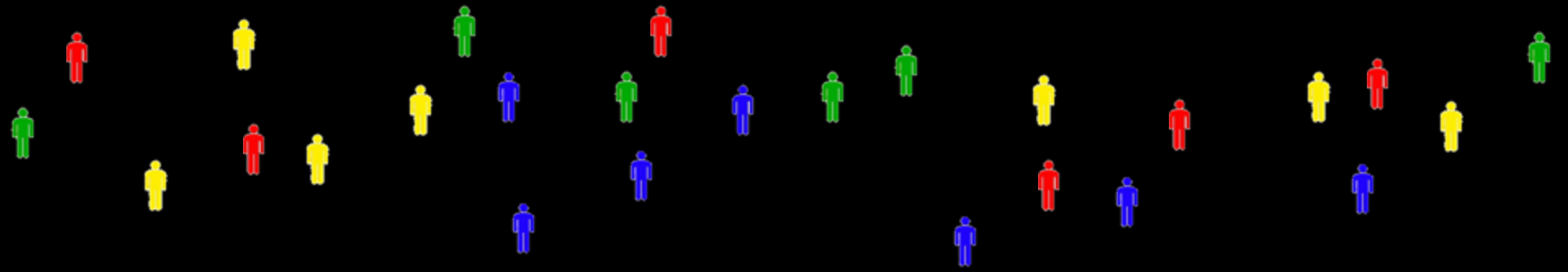
2 types of RCC

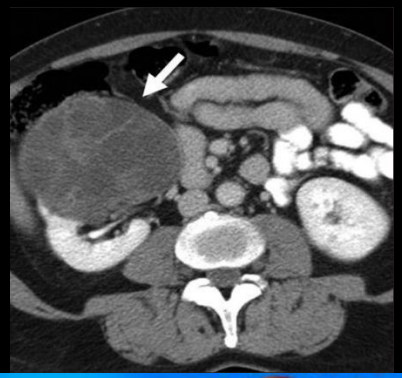
Clear cell carcinoma

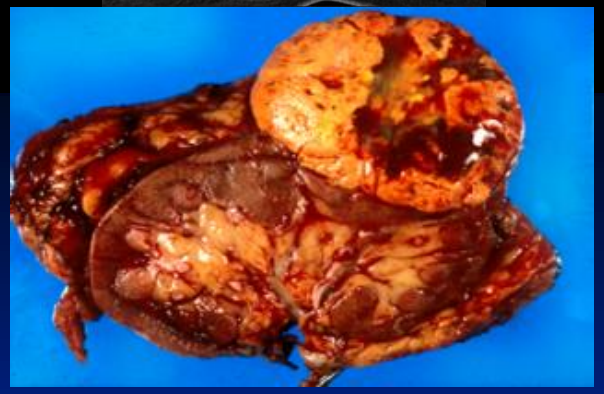
Granular cell carcinoma

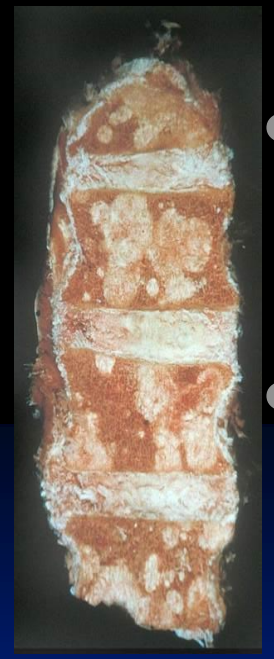
- Outcome studies, conflicting

CLASSIFICATION: DIAGNOSIS









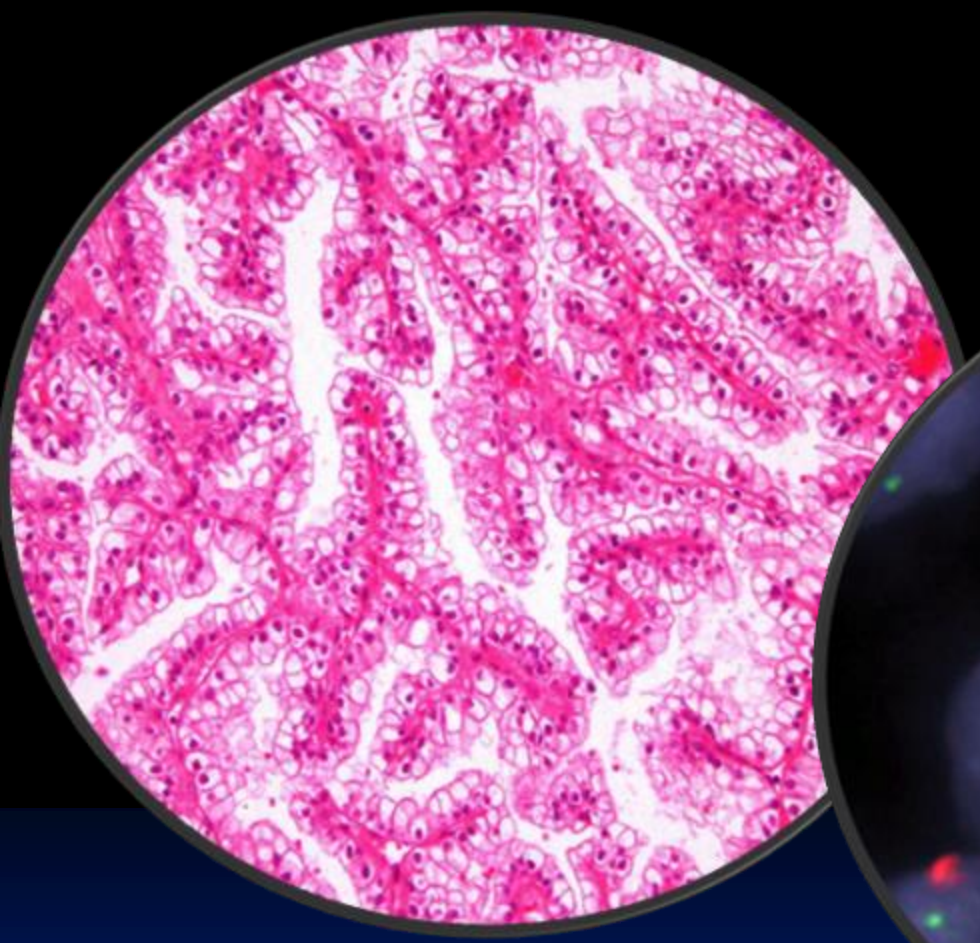
- Enigmatic clinical behavior
- Proclivity for distant metastasis

Surgery

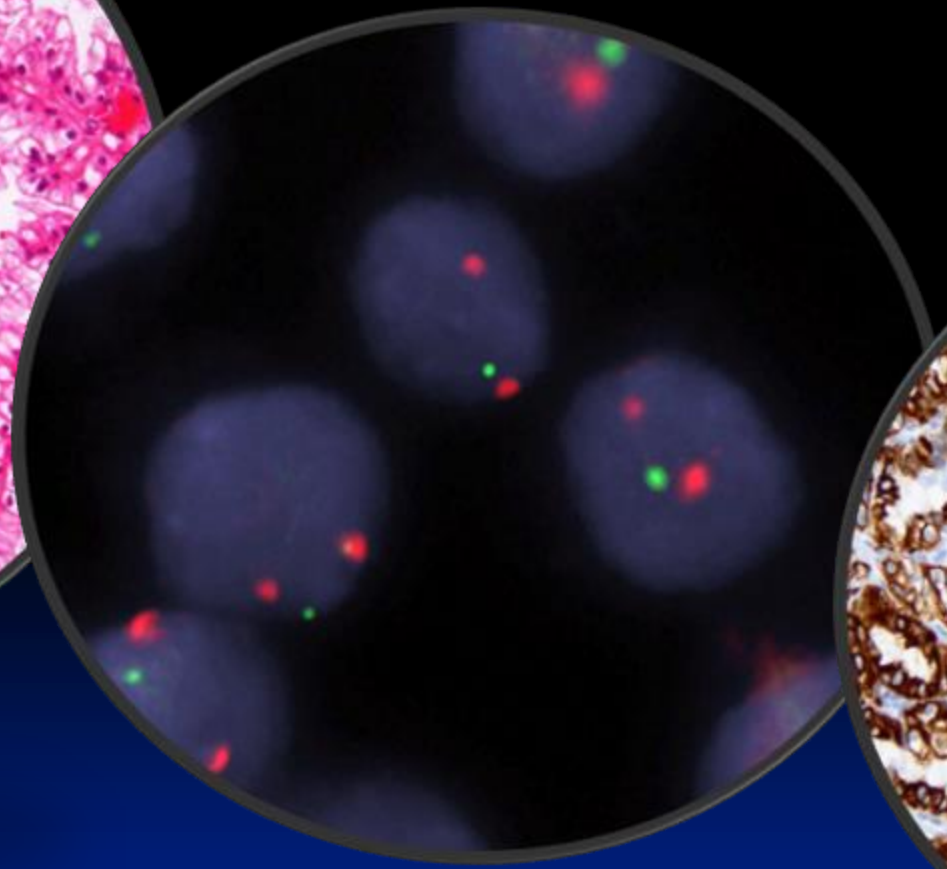
1980s

Immunotherapy

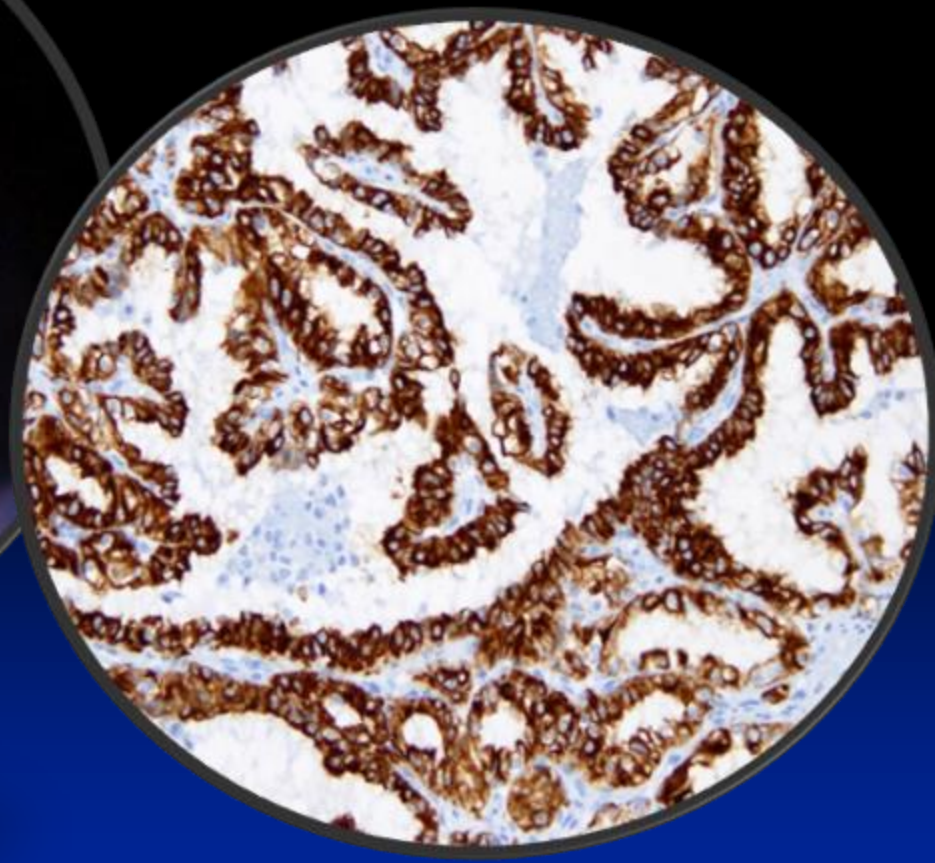
1975-1990s



H&E



FISH



IHC

1990s

Understanding of the VHL disease has been pivotal in the RCC molecular story

- Identification (1988) and its location short arm of Chr. 3 & cloning (1993) of the *vHL* gene (tumor suppressor)

- helped refine histologic classification - vHL "gold standard"

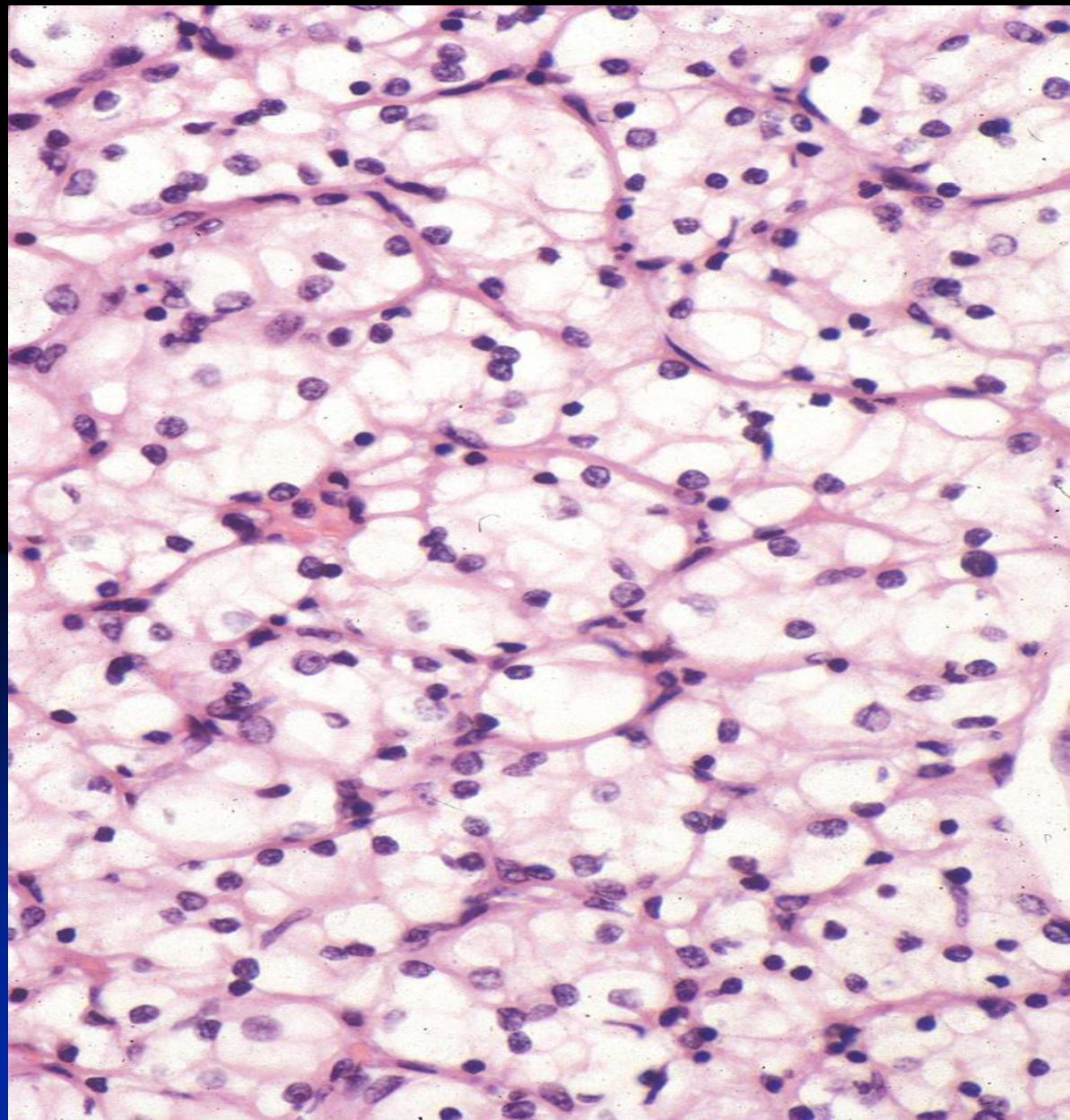
- molecular biology laid the foundation for the paradigm for targeted therapies for RCC

- established the importance of hereditary renal neoplasia (3-8 % of renal cancers)- [2024 estimates in the US: 80,000 at 5% of tumors; 3000-4000 cancers annually possibly hereditary]

THREE BROAD AND MOST IMPORTANT REASONS FOR MOLECULAR TESTING

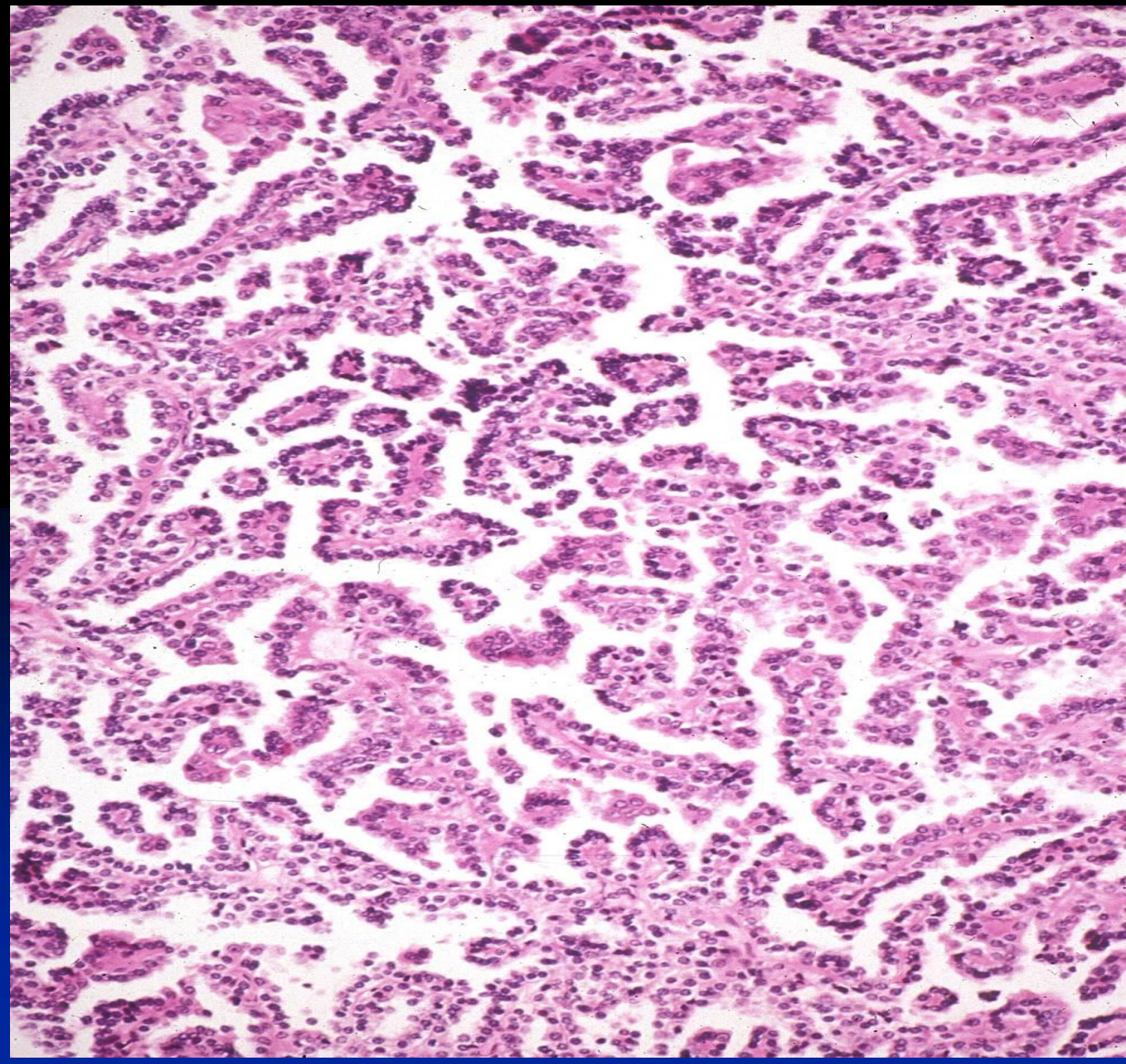
Clear Cell RCC

- Mutations in VHL gene (3p25-26) or loss of chr 3p
  - Virtually all cases of VHL syndrome
  - Somatic mutations, losses, promoter hypermethylation in
  - 80% sporadic cases

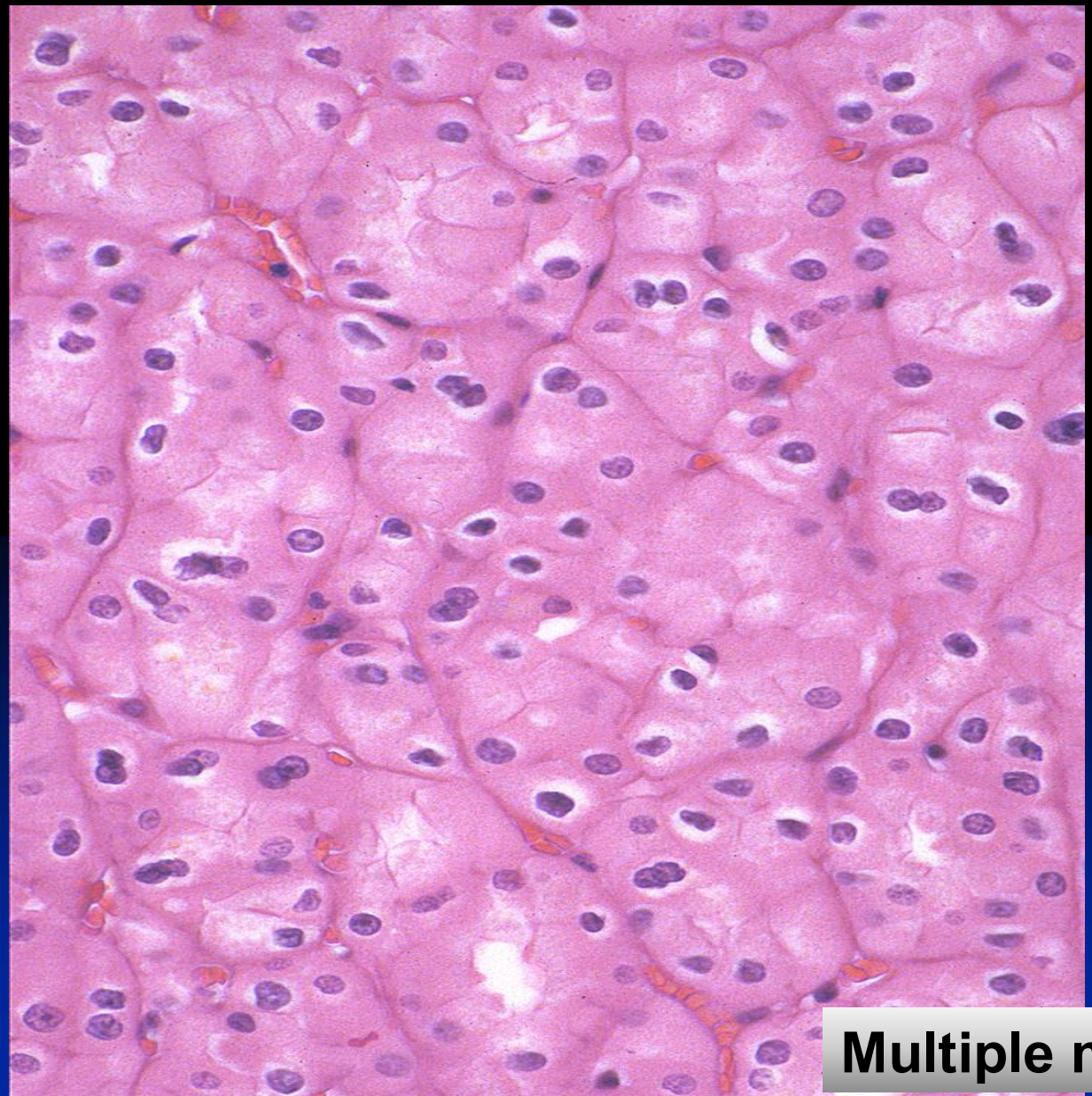


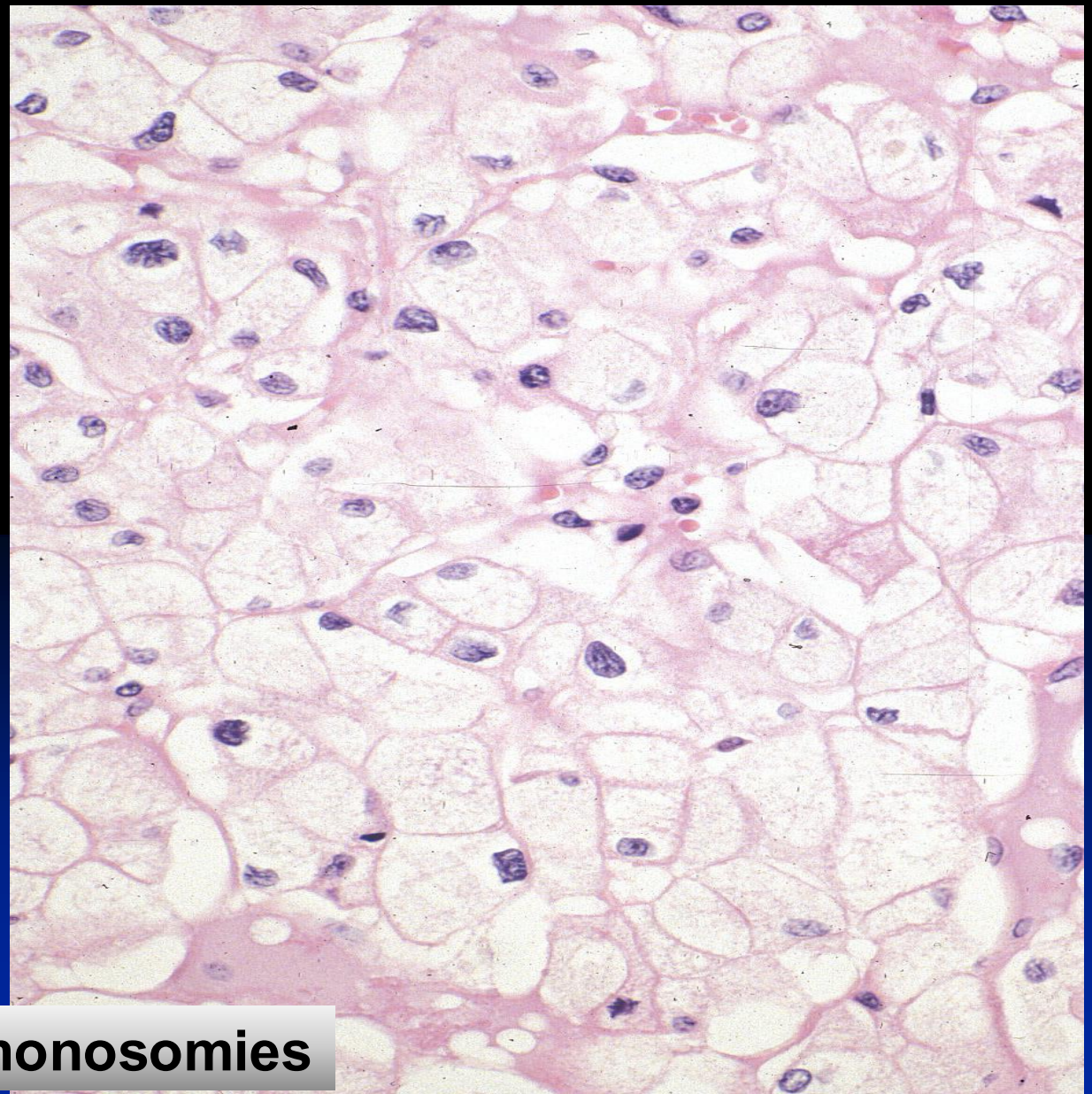
Papillary RCC

- Trisomy 7, 17
- Loss Y
- Trisomies of chromosomes 12, 16, 20
- LOH at 9p13
- Activation of MET oncogene located at 7q31 (all familial papillary RCC cases and 13% sporadic)

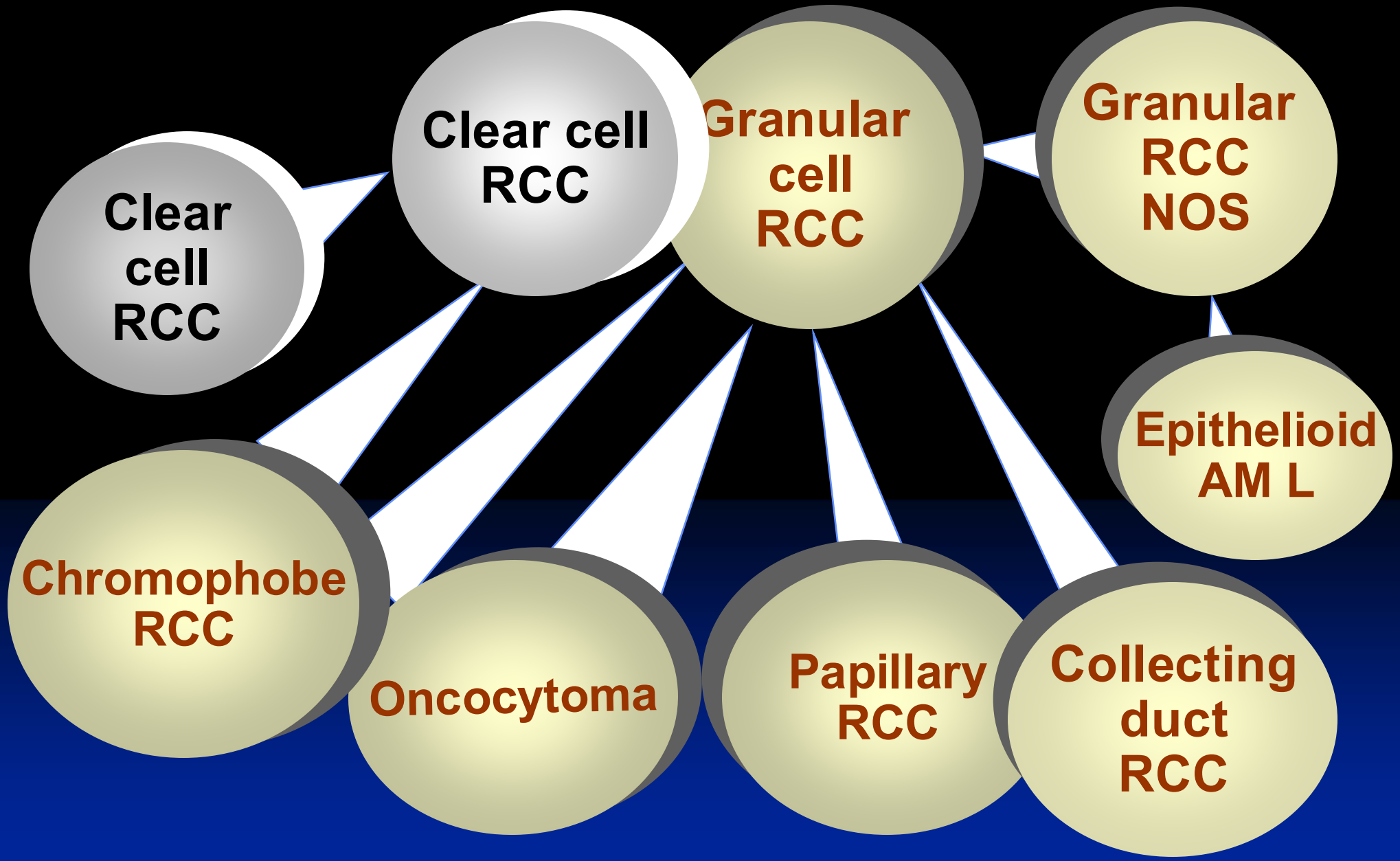


CHROMOPHOBE RCC





Multiple monosomies


Clear cell RCC
Clear cell RCC
Granular cell RCC
Granular RCC NOS
Epithelioid AM L
Chromophobe RCC
Oncocytoma
Papillary RCC
Collecting duct RCC

1997

WHO, AJCC/UICC CONSENSUS CONFERENCE:

"DIAGNOSIS AND PROGNOSIS OF RENAL CELL CARCINOMA"

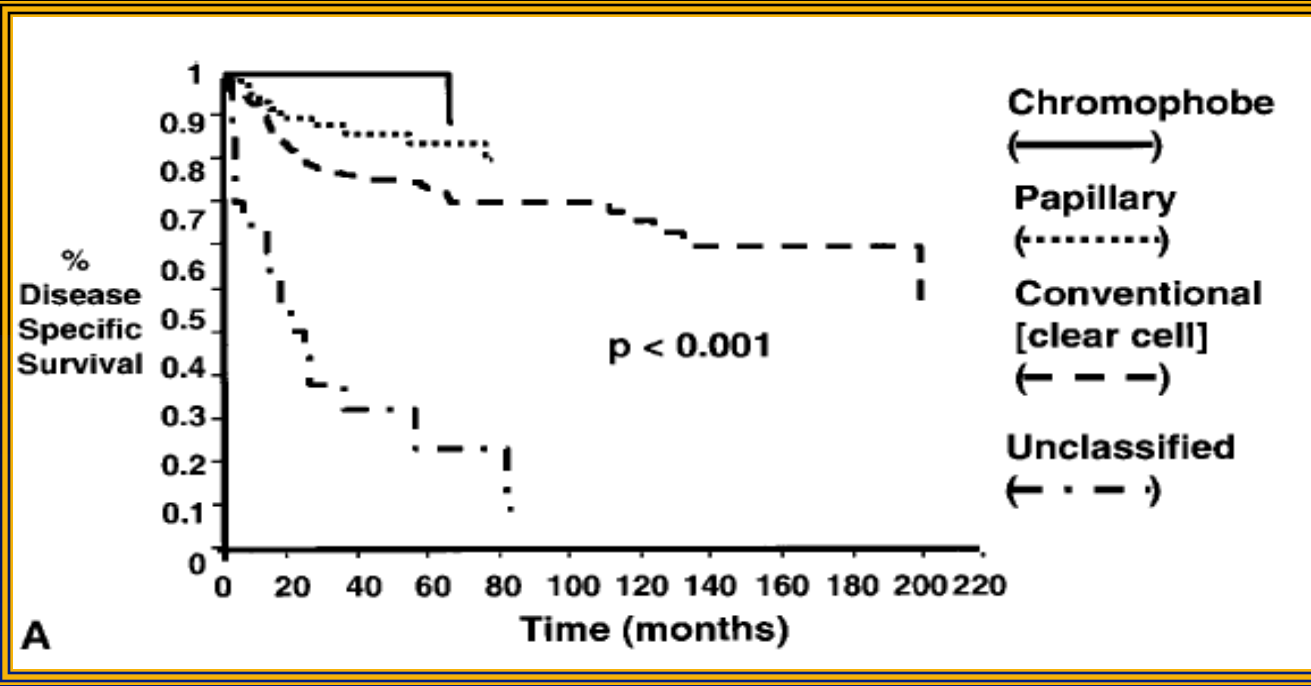
Benign

- Papillary adenoma
- Renal oncocytoma
- Metanephric adenor

5 types of RCC

Malignant

- Conventional (clear cell) renal carcinoma
- Papillary renal cell carcinoma
- Chromophobe renal cell carcinoma
- Collecting duct carcinoma
- Renal cell carcinoma, unclassified



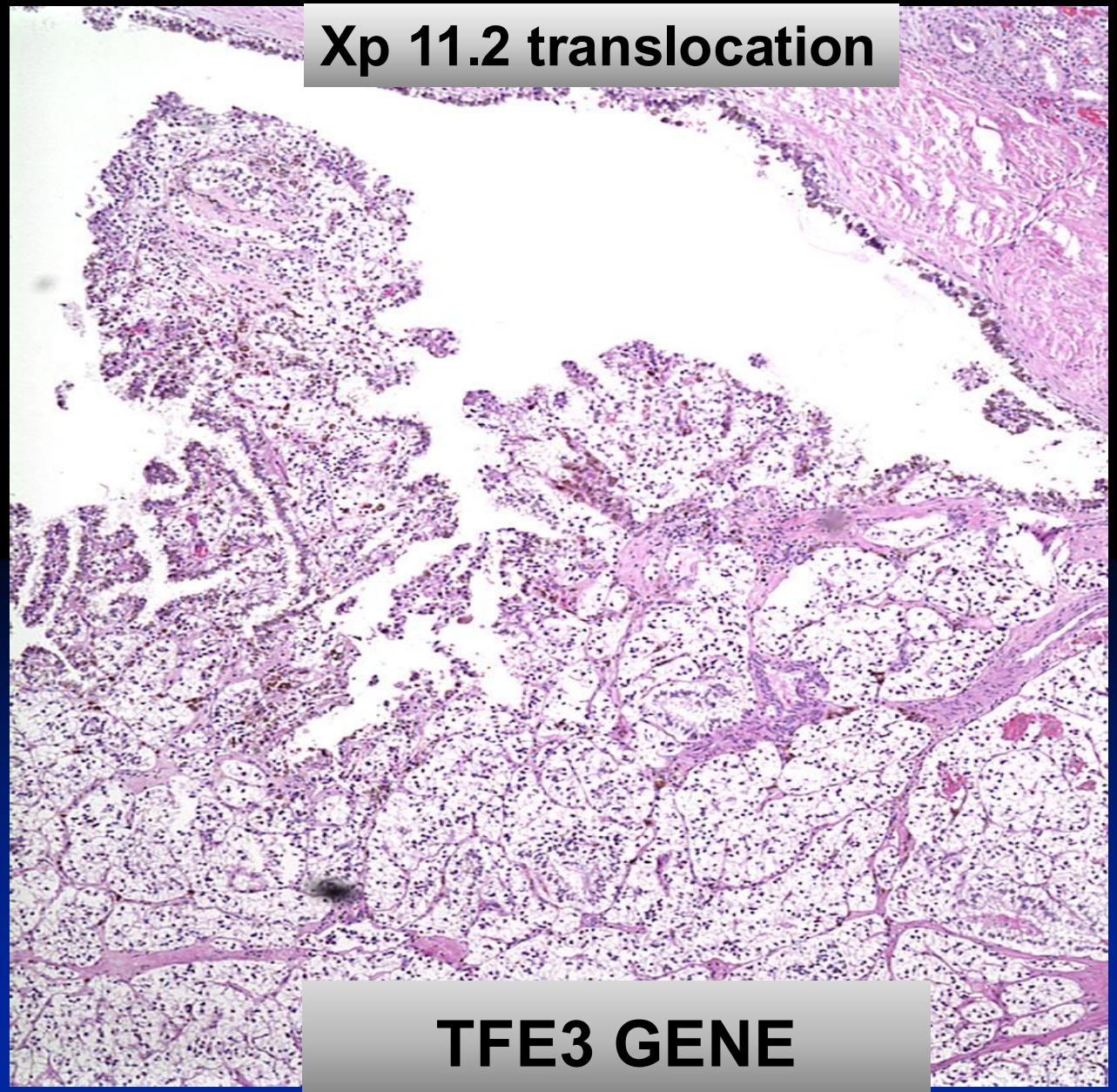
(Störkel, Eble, Adl

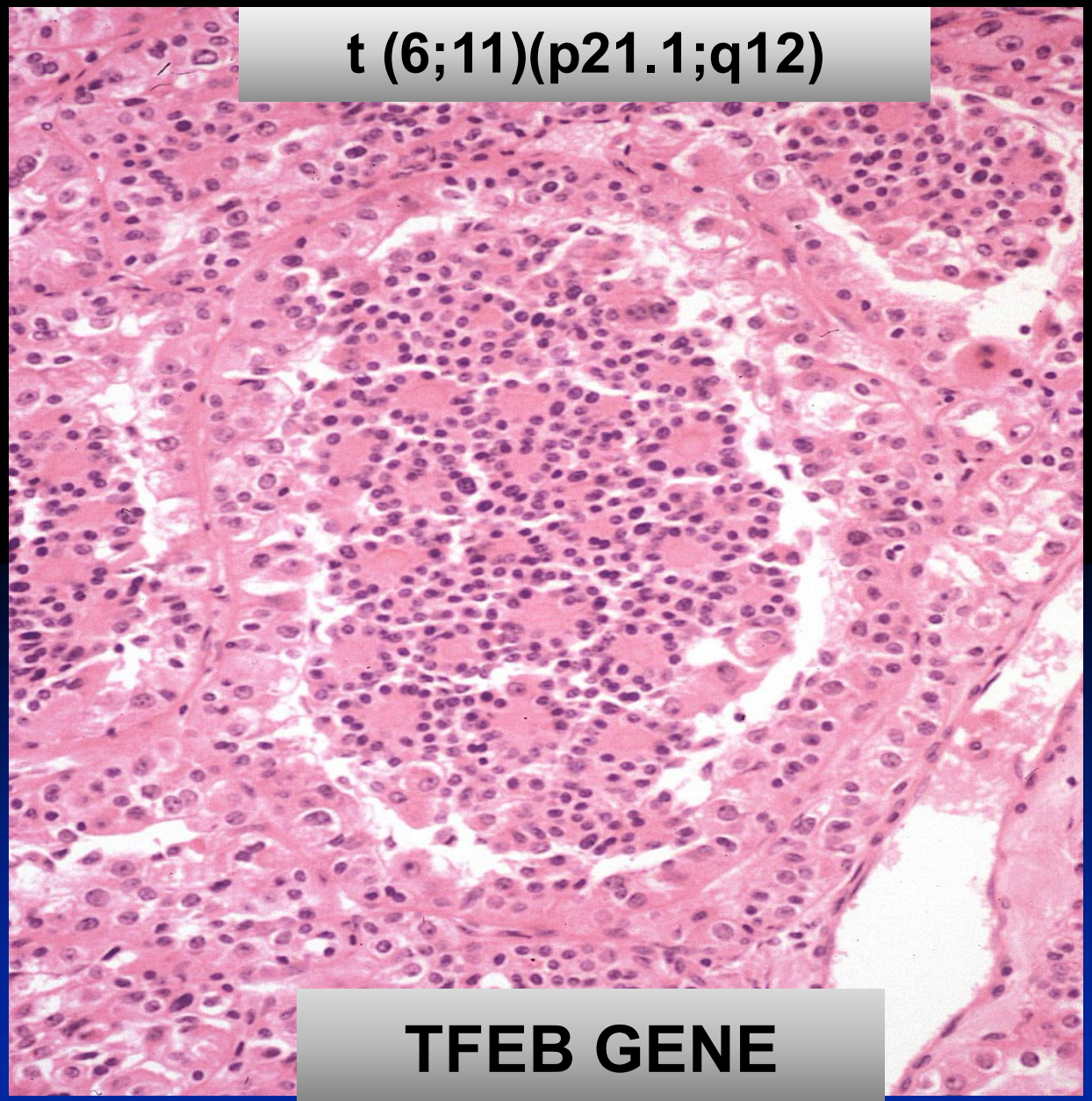
CLASSIFICATION: PROGNOSIS

1998-2001

TRANSLOCATION ASSOCIATED CARCINOMAS

2003



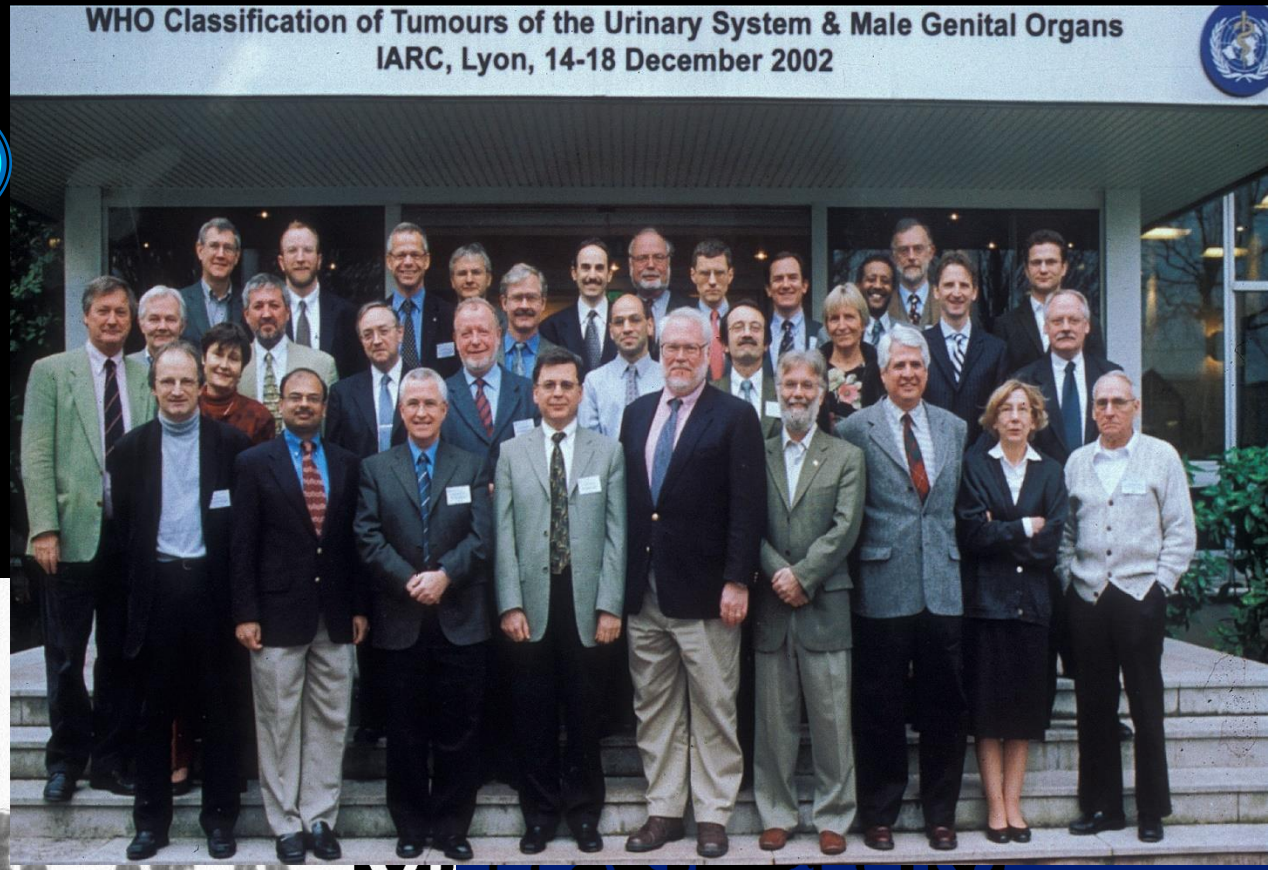


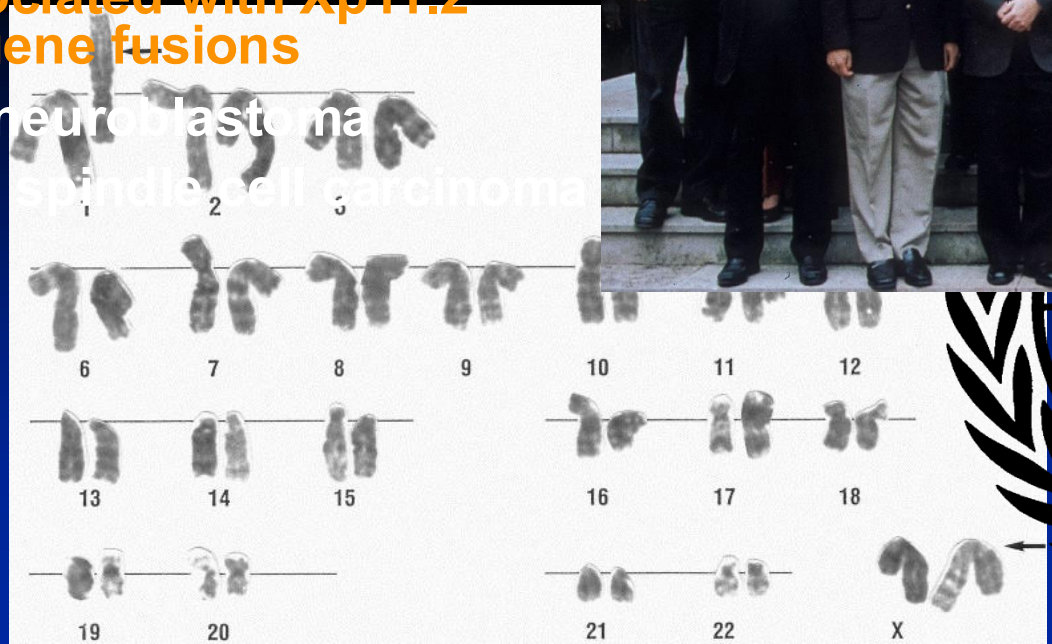
2004

3E WHO CLASSIFICATION OF RENAL TUMORS

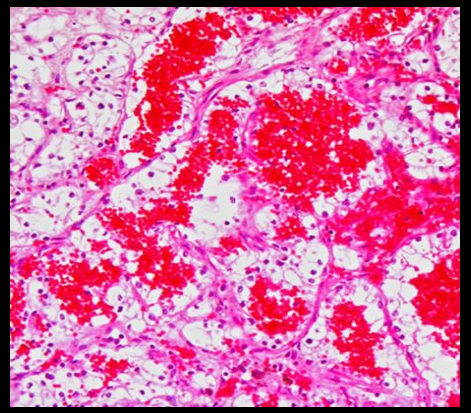
10 types of RCC

- Clear cell RCC
- Multilocular cystic RCC
- Papillary RCC
- Chromophobe RCC
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions
- RCC associated with neuroblastoma
- Mucinous tubular and spindle cell carcinoma
- RCC unclassified

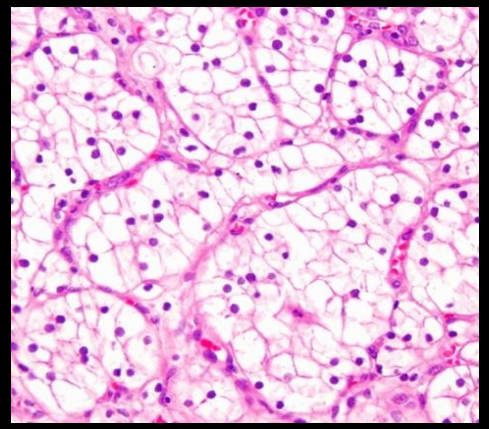




VHL & CLEAR CELL RCC: MOLECULAR BIOLOGY & THERAPY



Late 1990s- 2010



VHL

Growth Factors

HIF1 pathway

PI3 Kinase

Temsirolimus
Everolimus

mTOR

Angiogenesis

Promote Survival/
Inhibit Apoptosis

Growth

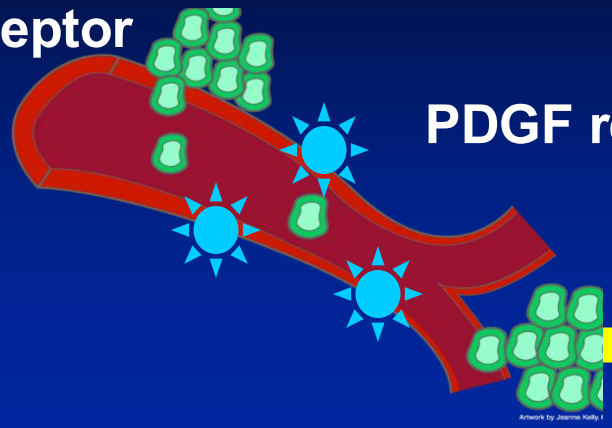
VEGF receptor

Bevacizumab

PDGF receptor

Sunitinib,Sorafenib

Pazopanib, Axitinib



Modified from ASCO cancer.net

TIMELINE: PROGRESS AGAINST KIDNEY CANCER

1983
Humanized monoclonal antibodies
1985
Immunotherapy

2001 Human Genome Project Completed

2000
Combination of Surgical Removal & Immunotherapy

1960 1970 1980 1990 2000 2010 2015

1940s–1960s
First evidence that surgical removal is effective of early-stage cancer

1977
Removing just part of the cancerous kidney is proven safe and effective

1991
Introduction of Laparoscopic Surgery

1995–1997
cryoablation & radiofrequency ablation are introduced for SRM

2005
First FDA Approval of A Targeted Drug for kidney cancer "Sorafenib" (Xple TKI receptors)

2006–2007
Sunitinib (VEGF, PDGFR)
Temsirolimus (mTOR inhibitor)

2009
Everolimus, Bevacizumab, Pazopanib

2011 Axitinib

2015 Nivolumab (PD1) – checkpoint inhibitors

2019 Pembro (or Avelumab) PD1 inhibitors) + Axitinib and/or TKI inhibitors – targeted combination therapy era

2020 Ipilimumab (CTL4 inhibitor)

2021 HIF2 alpha inhibitor VHL tumors (RCC, CNS, pancreatic tumors)

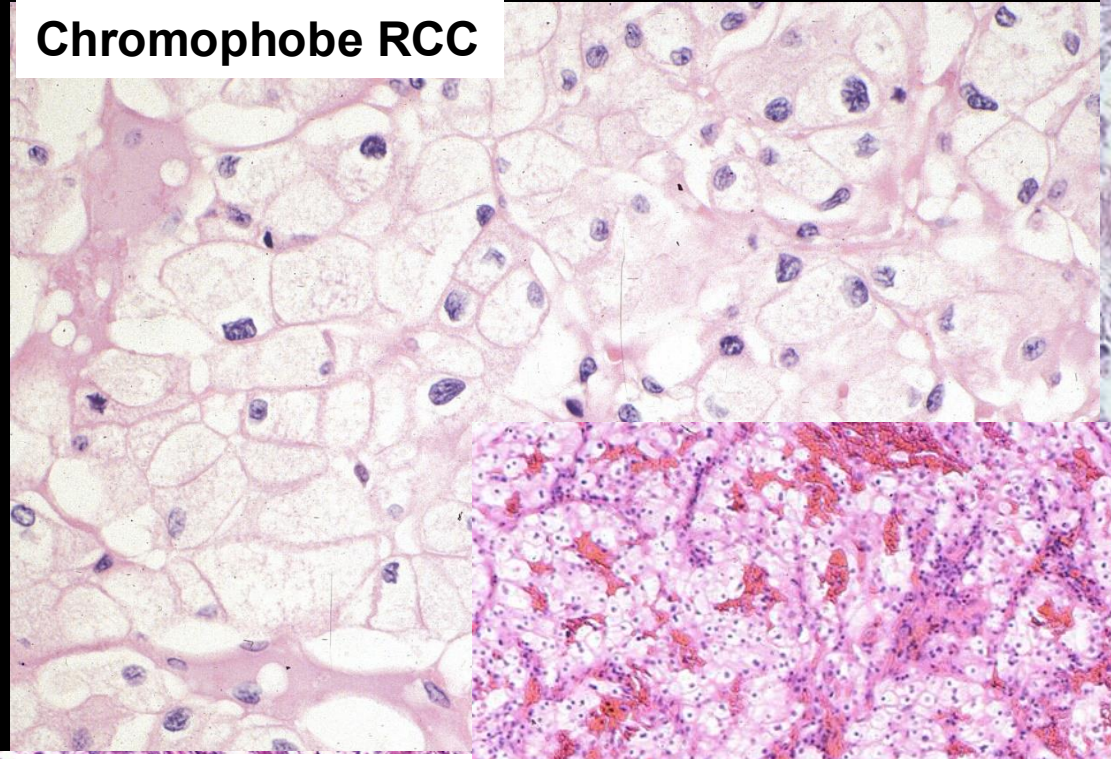
2016

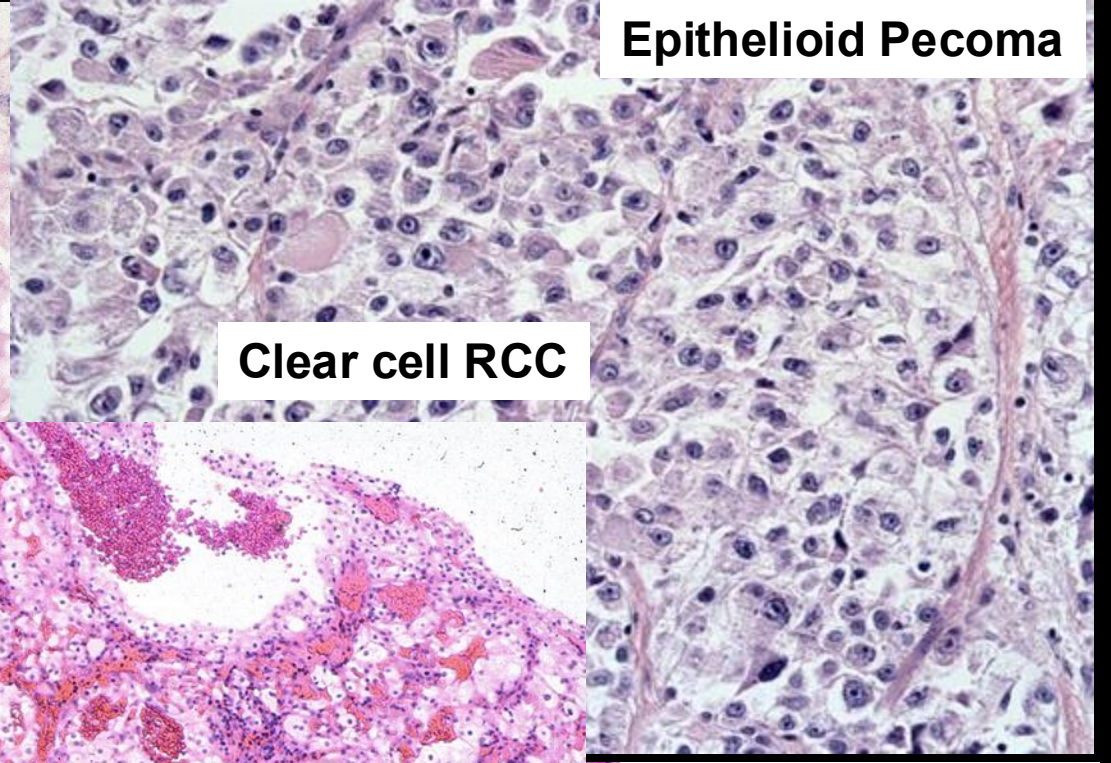
4E WHO CLASSIFICATION OF RENAL TUMORS

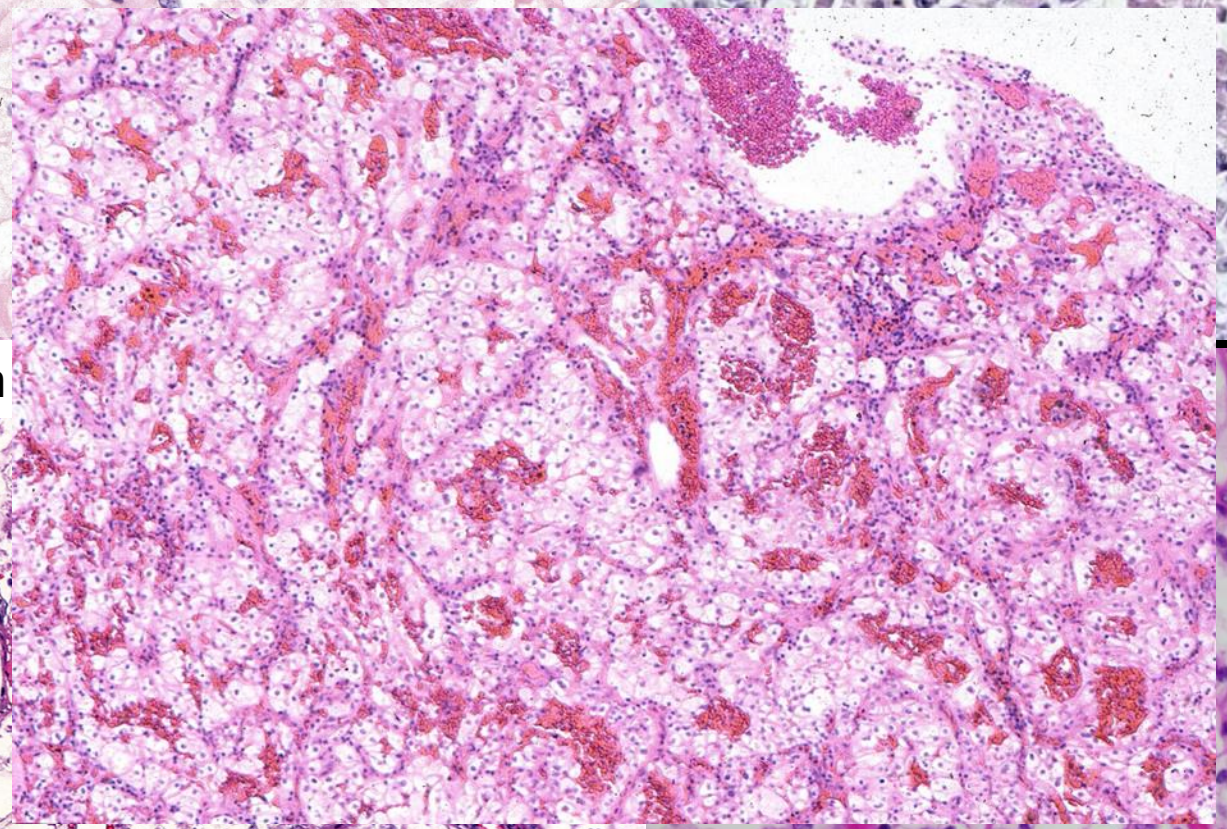
- Clear cell RCC
- Multilocular cystic LMP
- Papillary RCC
- Clear cell- papillary RCC
- Chromophobe RCC
  - Hybrid Oncocytic Chromophobe tumor
- Carcinoma of the collecting ducts
- Renal medullary carcinoma
- MITF family associated RCC
- Mucinous tubular and spindle cell carcinoma
- Acquired cystic disease –associated RCC
- Tubulocystic carcinoma
- Hereditary leiomyomatosis & RCC – associated RCC
- SDHB mutation -associated RCC
- RCC unclassified

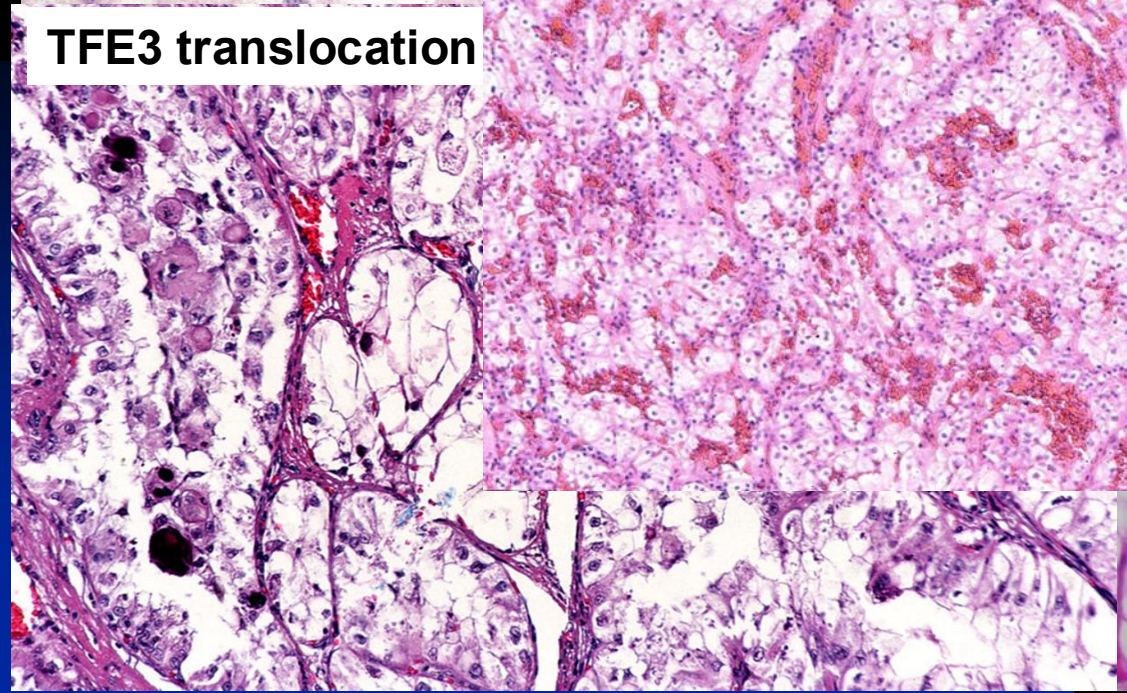
13 types of RCC

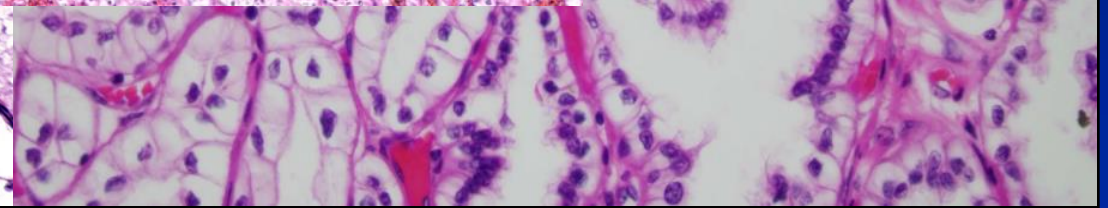
Diagnosis
Prognosis
Prediction
Prevention

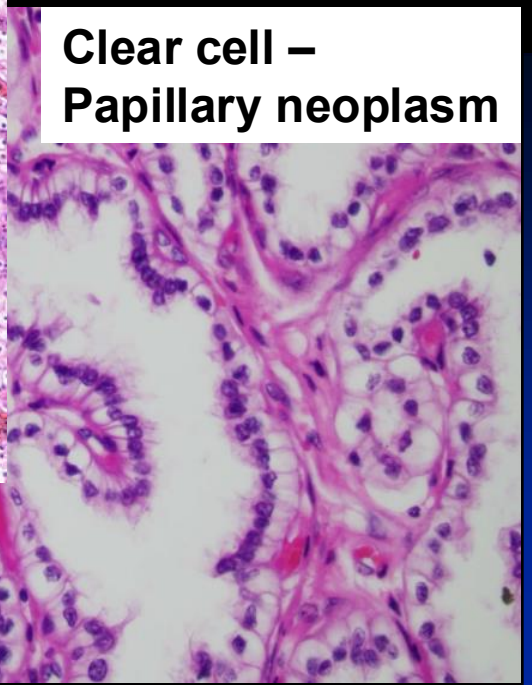

Chromophobe RCC

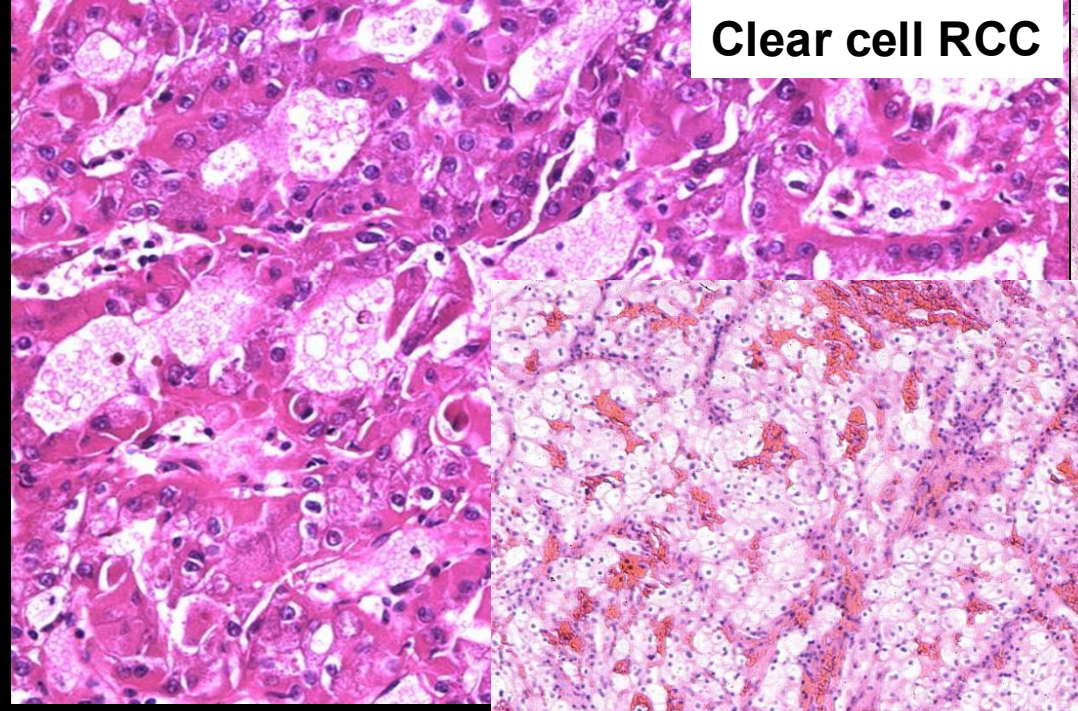

Epithelioid Pecoma

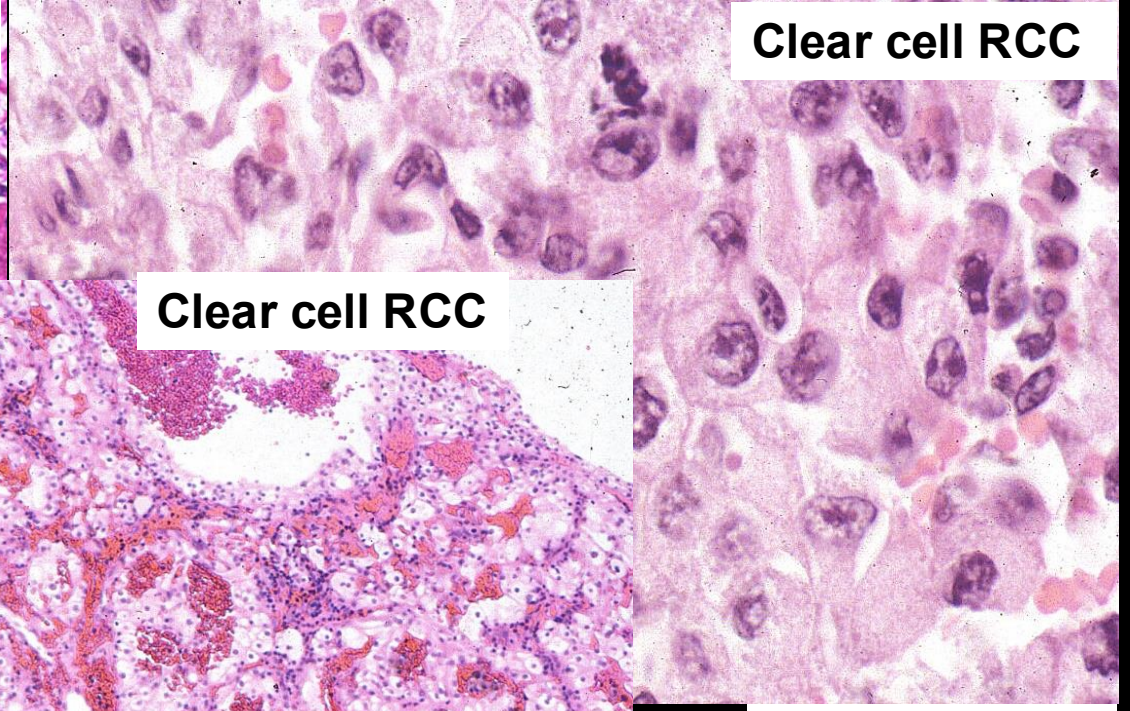

Clear cell RCC

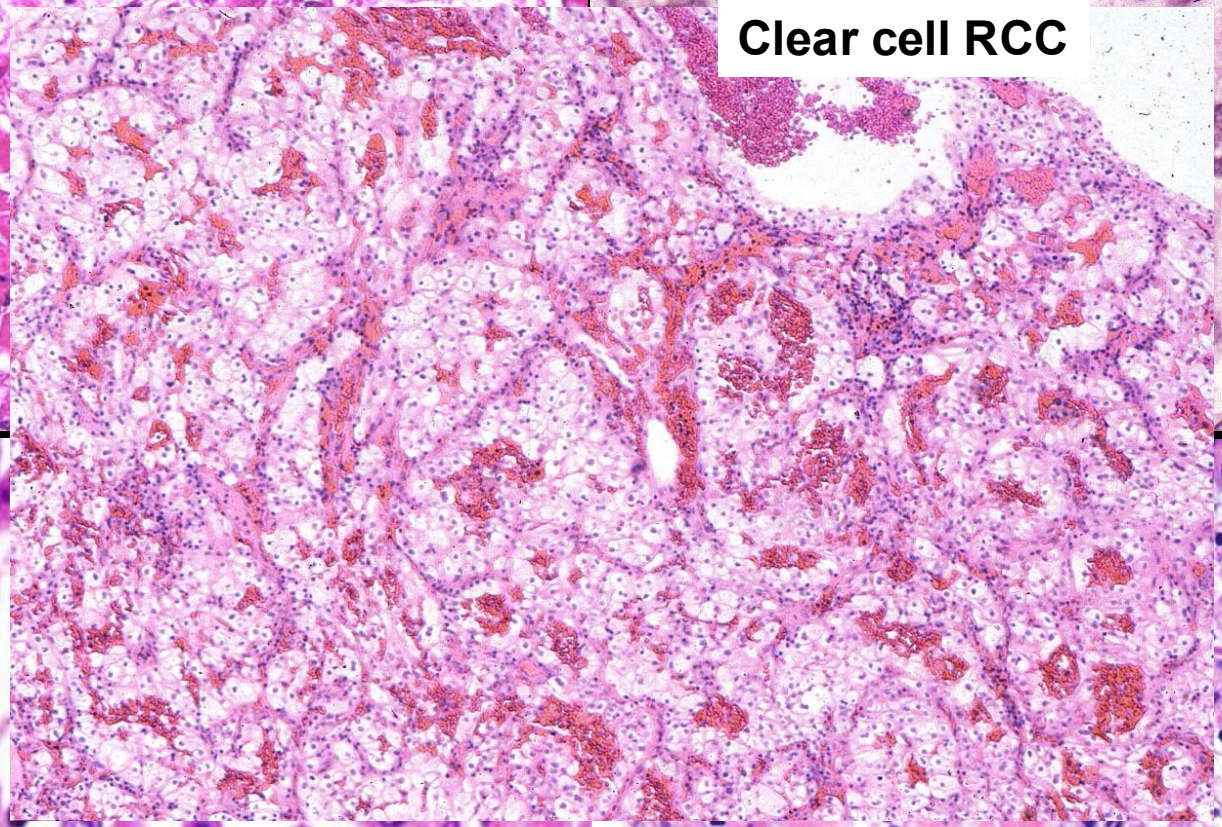

TFE3 translocation

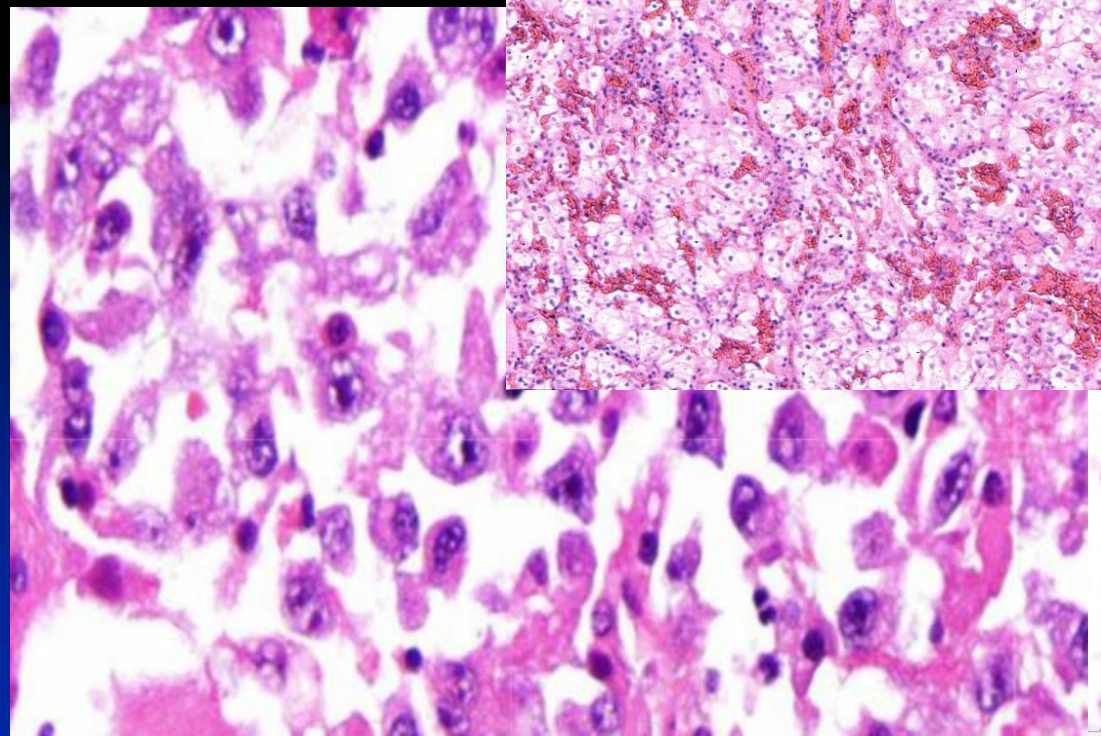


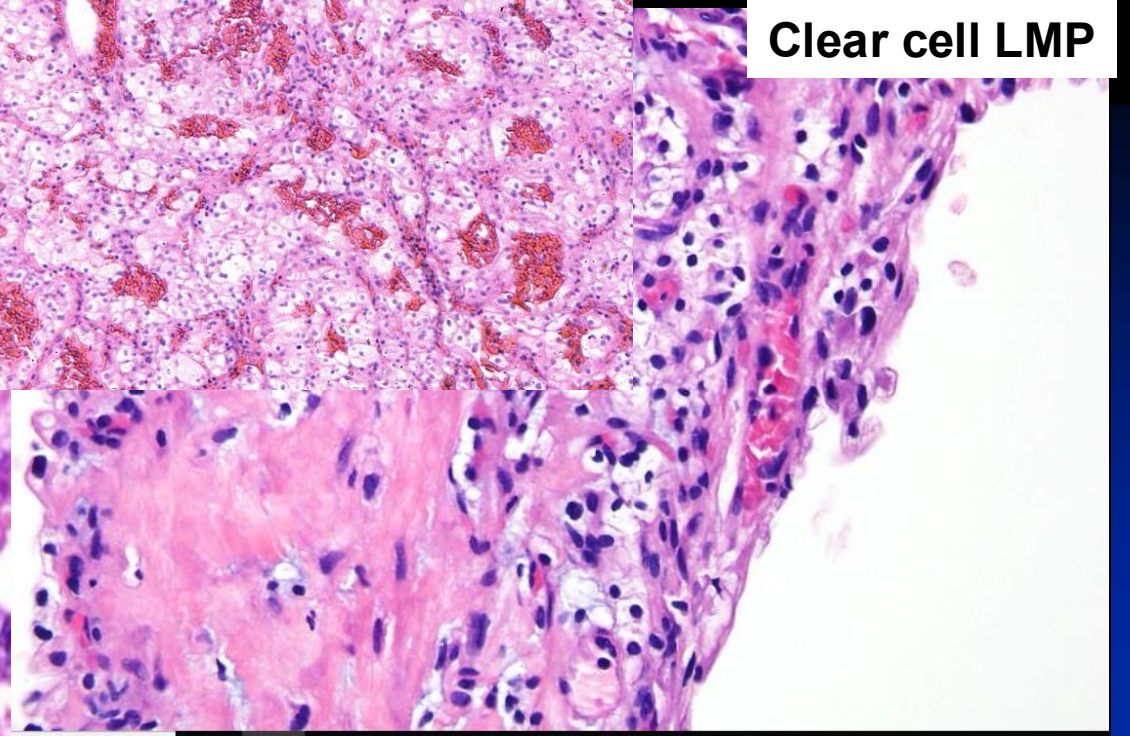

Clear cell –
Papillary neoplasm

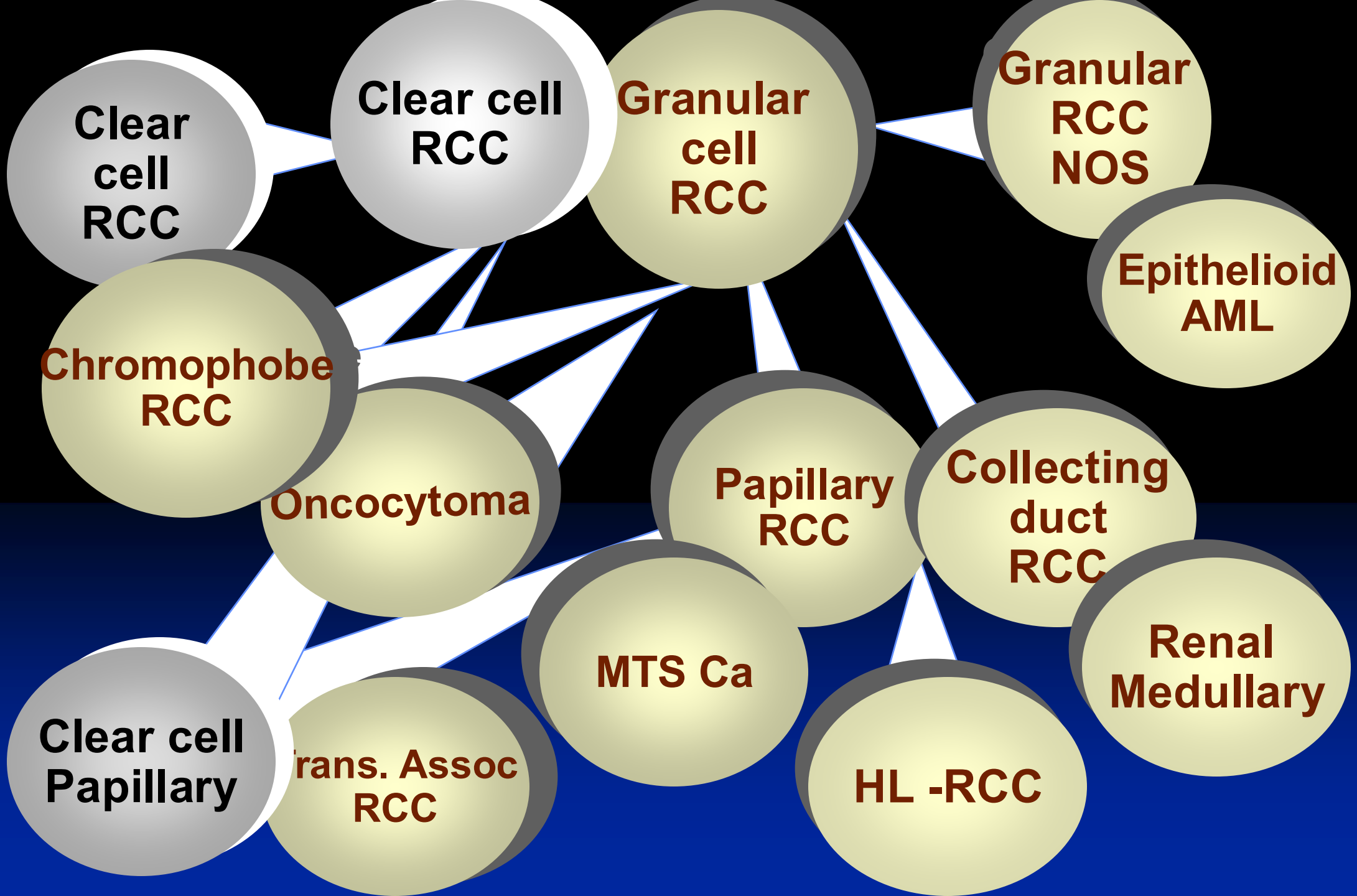

Clear cell RCC

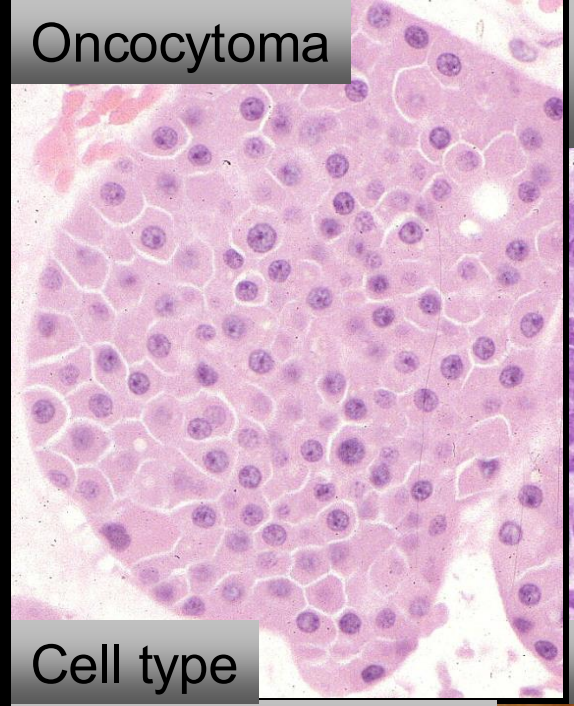

Clear cell RCC

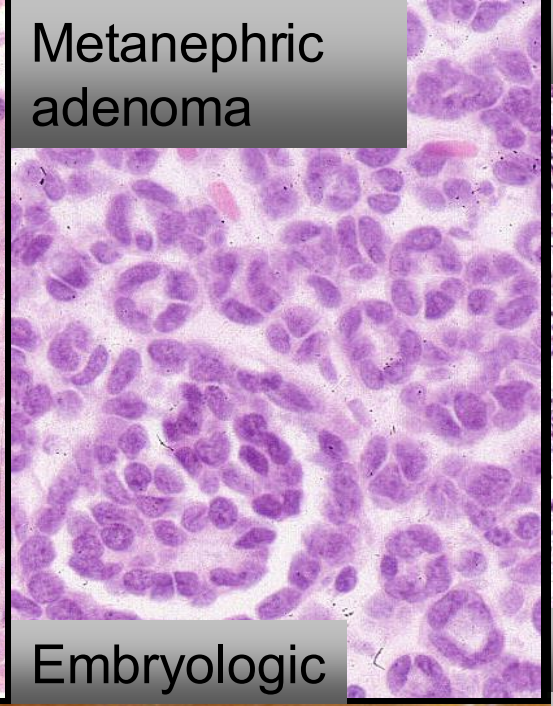

Clear cell RCC

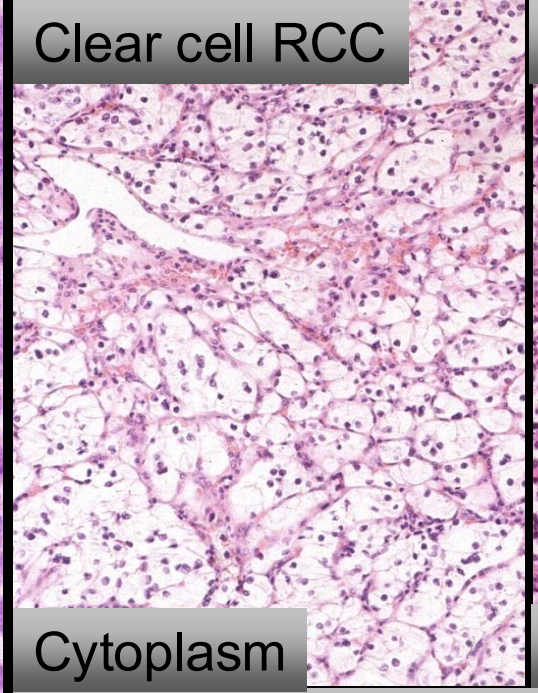


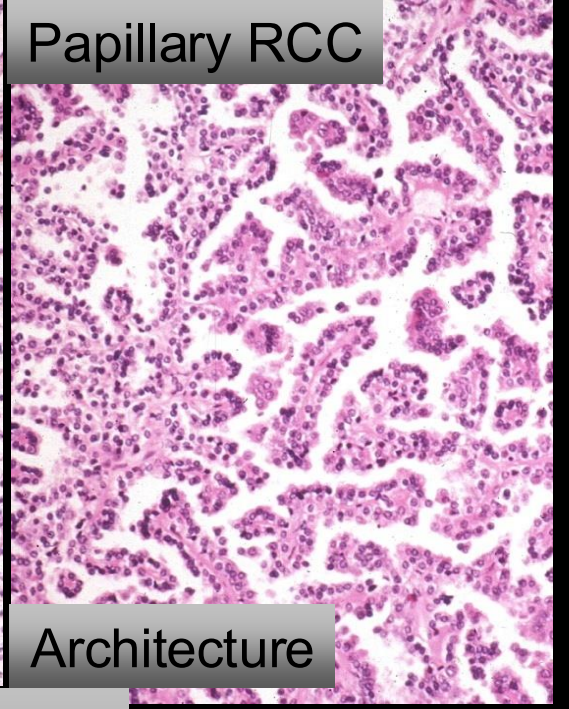

Clear cell LMP

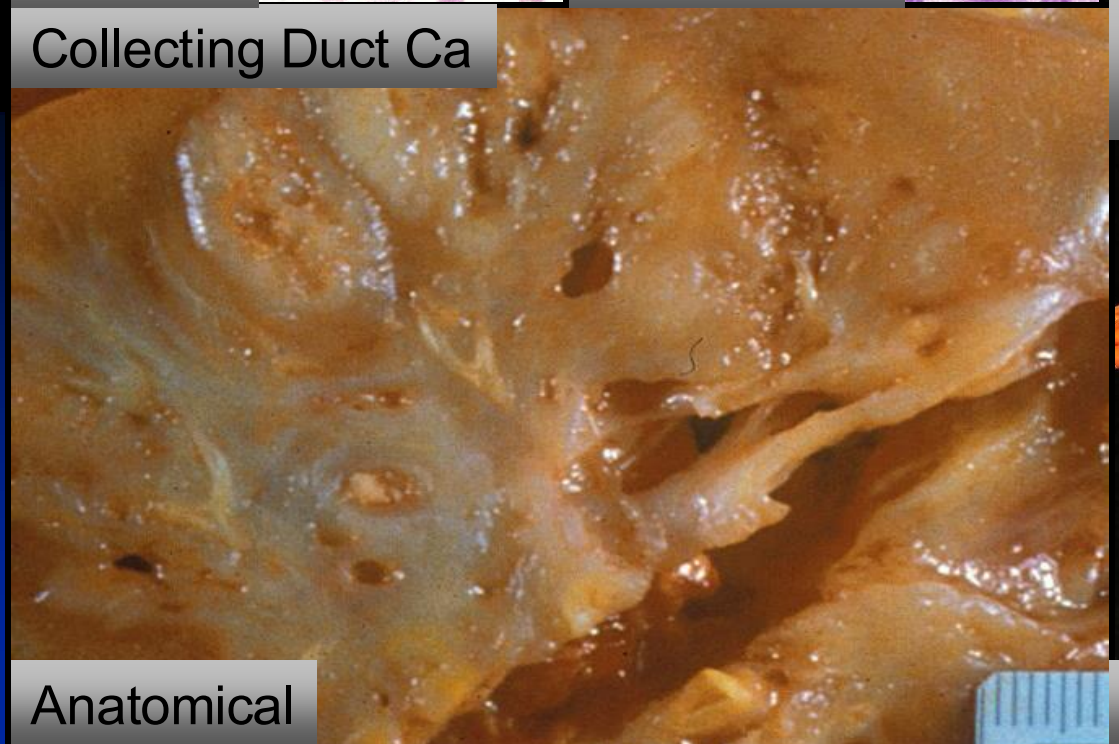

Clear cell RCC
Clear cell RCC
Granular cell RCC
Granular RCC NOS
Epithelioid AML
Chromophobe RCC
Oncocytoma
Papillary RCC
Collecting duct RCC
Renal Medullary
MTS Ca
Clear cell Papillary
rans. Assoc RCC
HL -RCC

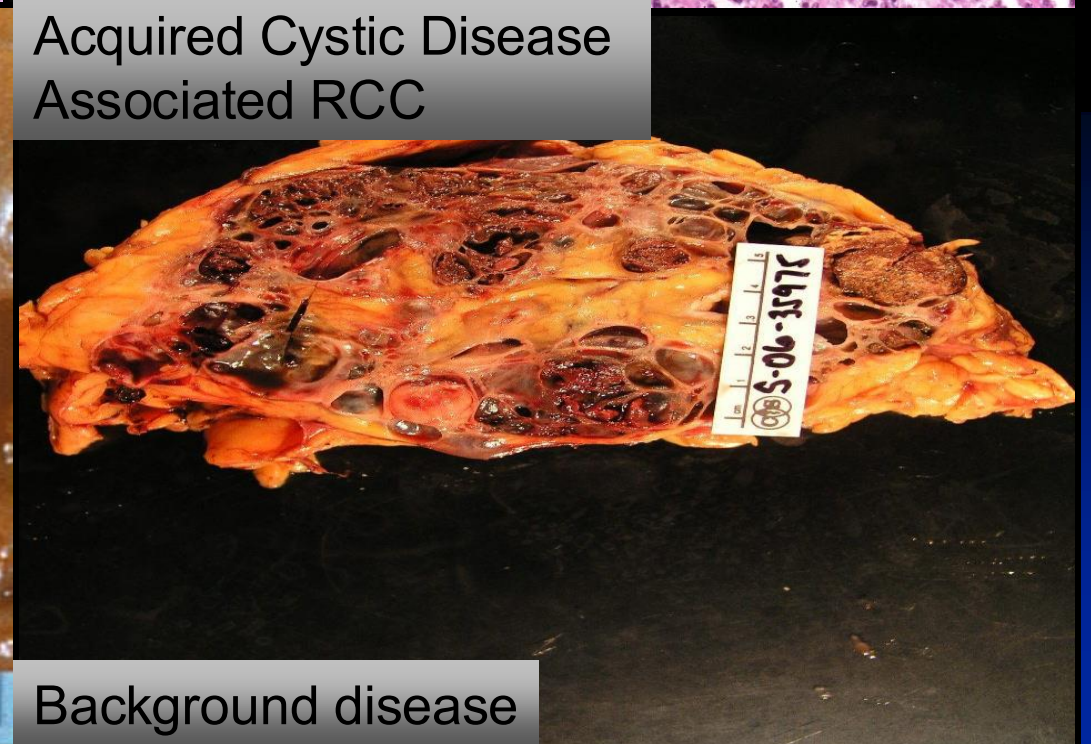

Oncocytoma
Cell type

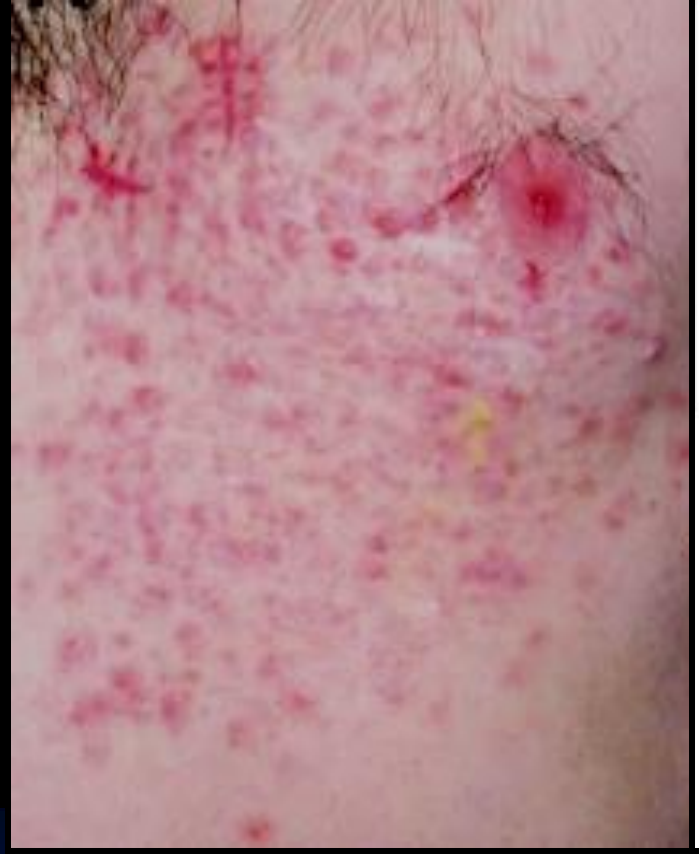

Metanephric adenoma
Embryologic


Clear cell RCC
Cytoplasm


Papillary RCC
Architecture


Collecting Duct Ca
Anatomical


Acquired Cystic Disease Associated RCC
Background disease

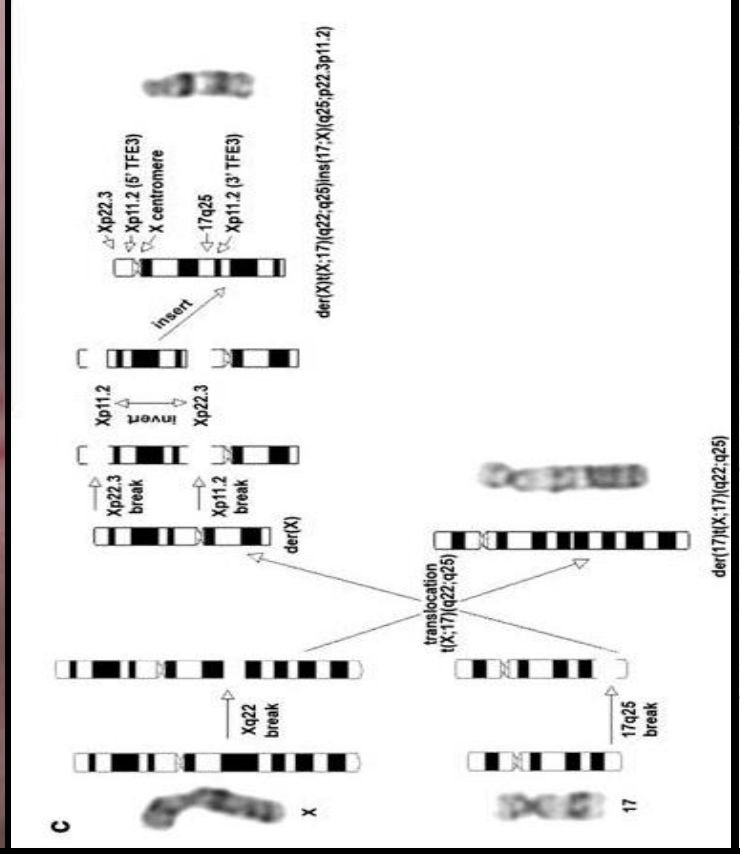


Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (FH Deficient RCC)

AD, germline mutation of fumarate dehydrogenase gene

- Multiple cutaneous and uterine leiomyomas

- Sporadic FY deficient

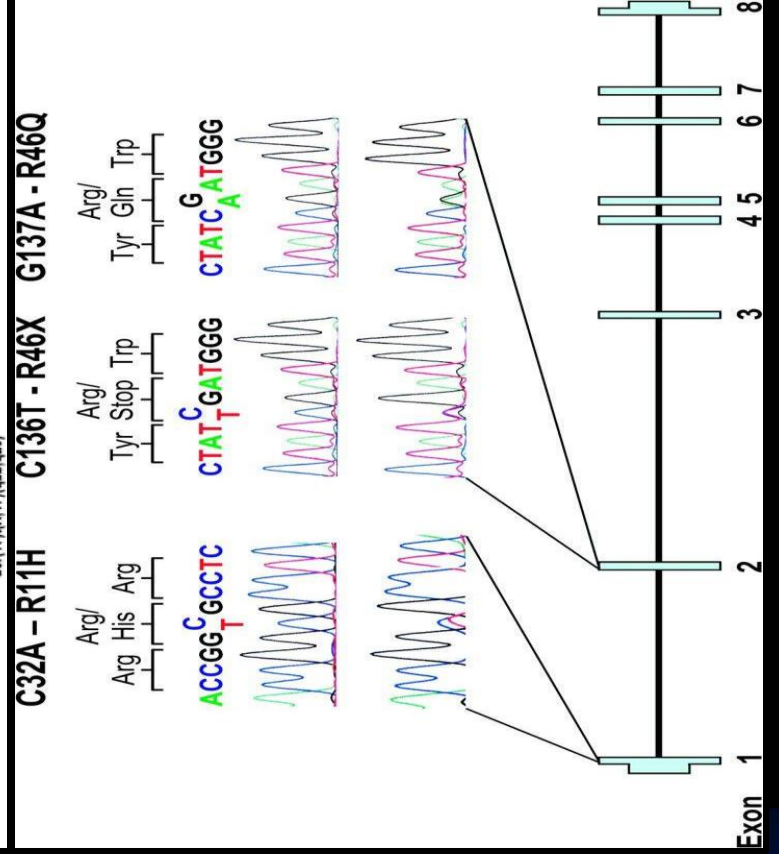


Xp11.2 translocation associated Renal Cell Carcinoma

Younger patients

TFE3 gene fusion abnormalities

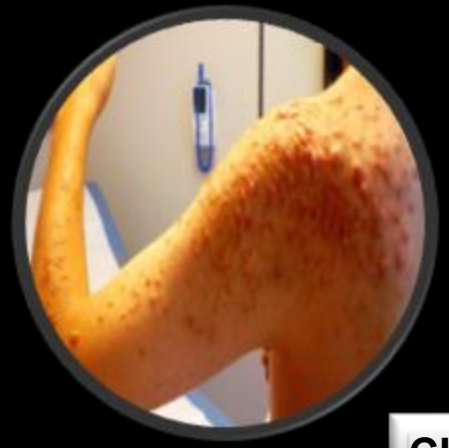
Often metastatic at presentation – "favorable"



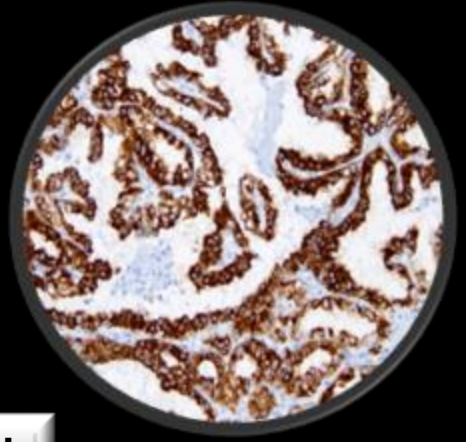
Succinic Dehydrogenase B Mutation Associate RCC

Pheochromocytoma/paraganglioma syndrome type 4; GI Stromal tumors

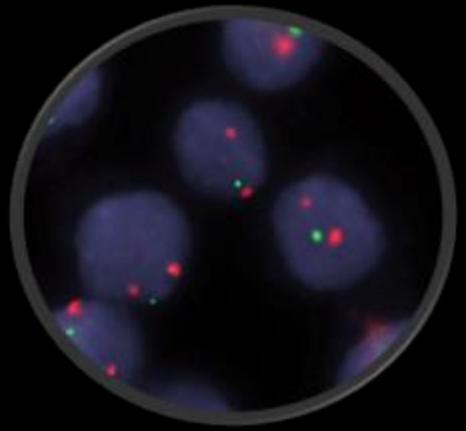
Young pts. indolent



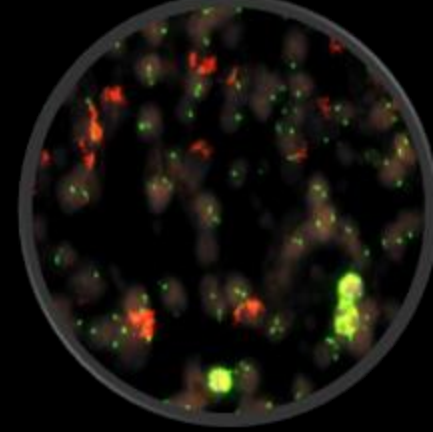
CLINICAL

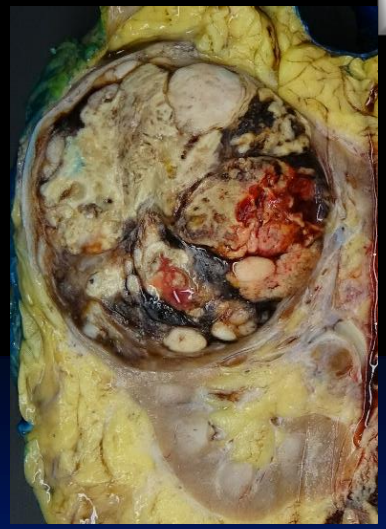


IHC



FISH
COPY NUMBER
CHANGES

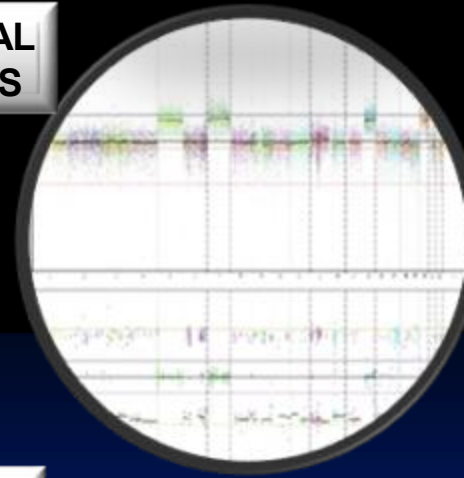




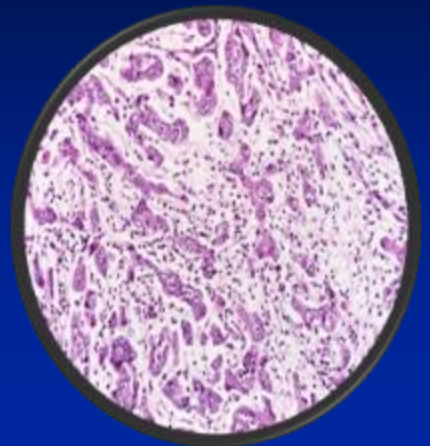
GROSS

FISH
REARRANGEMENTS

CHROMOSOMAL
MICROARRAYS



RENAL CELL CARCINOMA ANALYSIS (2016-2022….)



H&E

NGS MUTATIONAL
ANALYSIS

ABL1	BARD1	CDH1	DCC	ESR1	FLT1	HNF1A	KRAS	MSH3	NTRK3	PRKACA	RIT1	SOS2	TNFRSF14
ABL2	BCL2	CDK12	DDIT3	ESR2	FLT3	HRAS	LIFR	MSH6	NUP93	PRKAR1A	RNF43	SOX9	TOP1
ACVR1	BCL2A1	CDK4	DDR2	ETV6	FLT4	ID3	LRP1B	MTOR	NUTM1	PRKCA	ROBO1	SOX10	TMPRSS2
ACVR1B	BCL2L1	CDK6	DDX3X	ETS1	FOXA1	IDH1	LRRK2	MUTYH	PAK3	PRKDC	ROS1	SOX2	TP53
AJUBA	BCL2L2	CDK8	DICER1	EWSR1	FOXL2	IDH2	LTB	MYB	PALB2	PTCH1	RPL10	SP140	TRAF3
AKT1	BCL2L12	CDKN1A	DIS3	EZH1	FOXO1	IGF1R	LZTR1	MYBL1	PARK2	PTCH2	RPTOR	SPEN	TRAF7
AKT2	BCL6	CDKN1B	DNMT3A	EZH2	FOXP1	IGF2R	MALAT1	MYC	PAX3	PTEN	RRAS	SPOP	TSC1
AKT3	BCOR w/ 3'UTR	CDKN2A	DOT1L	FAM123B (WTX)	FRS2	IKBKE	MAP2K1	MYCL1	PAX5	PTPN1	RRAS2	SPRED1	TSC2
ALK	BCORL1	CDKN2B	DUSP2	FAM46C	FUBP1	IKZF1	MAP2K2	MYCN	PAXB	PTPN11	RUNX1	SPTA1	TSHR
APC	BLM	CDKN2C	DUSP4	FANCA	FUS	IL7R	MAP2K4	MYD88	PBRM1	PTPRB	RUNX1T1	SPRY1	TSHZ2
APOBEC3G	BMPR1A	CEBPA	DUSP6	FANCC	GAB2	INHBA	MAP3K1	MYH9	PDCD1LG2	PTPRD	SDHB	SPRY2	TSHZ3
AR	BRAF	CHD2	DYNC1I1	FANCE	GATA1	INPP4B	MAP3K2	NAV3	PDGFB	PTPRK	SDHD	SPRY4	U2AF1
ARAF	BRCA1	CHD4	EDNRB	FANCF	GATA2	IRF4	MAP3K5	NBN	PDGFRA	PTPRT	SETBP1	SRC	USP7
ARFRP1	BRCA2	CHD5	EIF1AX	FANCG	GATA3	IRS2	MAP3K7	NCAPS	PDGFRB	RAC1	SETD2	SS18	VHL
ARHGAP35	BRD4	CHEK1	EGFR	FANCL	GLI1	JAK1	MAP3K9	NCOA3	PDK1	RAD21	SF3B1	STAG2	WISP3
ARID1A	BRIP1	CHEK2	EGR1	FAT1	GLI2	JAK2	MAPK1	NCOR1	PHF6	RAD50	SH2B3	STAT3	WRN
ARID1B	BTG1	CIC	ELF3	FAT3	GNA11	JAK3	MCL1	NF1	PIK3CA	RAD51	SHH	STAT4	WT1
ARID2	BTK	CLDN18	EMSY (C11orf30)	FBXW7	GNA13	JAZF1	MDM2	NF2	PIK3CG	RAD51C	SIN3A	STAT6	XBP1
ARID5B	CALR	CNOT3	EP300	FGF10	GNAQ	KAT6A	MDM4	NFE2L2	PIK3R1	RAD51D	SUFI2	STK11	XPO1
ASXL1	CARD11	COL1A1	EPCAM	FGF14	GNAS	KDM5A	MED12	NFKBIA	PIK3R2	RAF1	SLITRK6	SUFU	YAP1
ASXL2	CBFB	COL2A1	EPHA3	FGF19	GPC3	KDM5C	MEF2B	NFKBIE	PMS1	RARA	SMAD2	SYNE1	YWHAE
ATF1	CBL	CREBBP	EPHA5	FGF23	GPR124	KDM6A	MEN1	NIPBL	POLD1	RASA1	SMAD3	TADA1	ZMYM3
ATM	CCND1	CRKL	EPHA7	FGF3	GRIN2A	KDR	MET	NKX2-1	POLE	RASA2	SMAD4	TBX3	ZNF217

NGS GENE
FUSION ASSAYS

2022

WHO CLASSIFICATION OF RENAL CELL TUMORS

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

AT LEAST 22 DISTINCTIVE TYPES OF RENAL EPITHELIAL TUMORS

2022

WHO CLASSIFICATION OF RENAL CELL TUMORS

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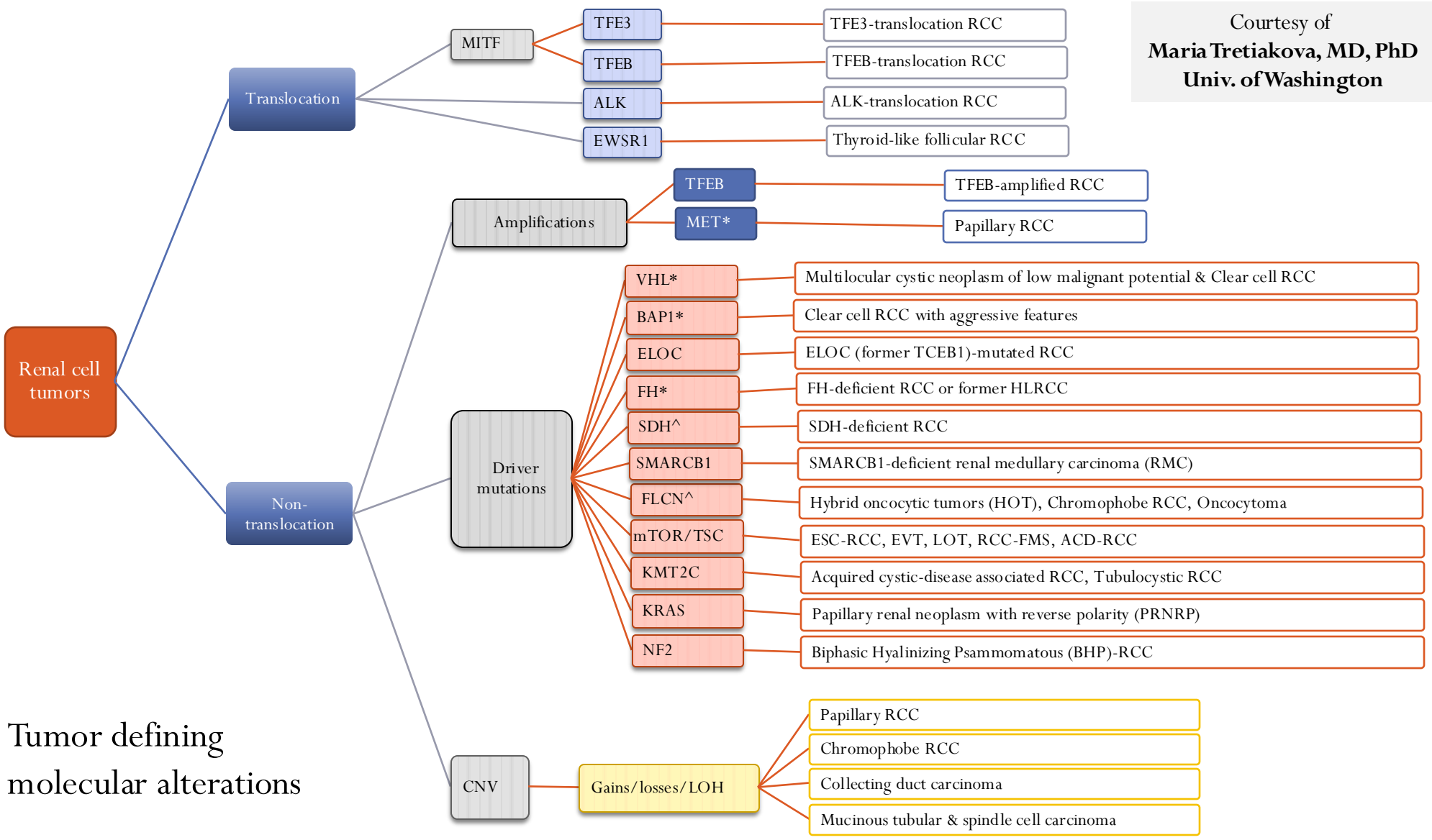
PRIMARY EXPERIMENTAL MODEL INTEREST

WHAT IS NEW & WHO IS WHO IN KIDNEY CANCER - WHO 2022

Concept 1: Molecularly defined renal carcinomas

Tumors with broad morphologic spectrum without complete genotypic-phenotypic-classification correlation – not synonymous with molecular classification

- 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



Courtesy of
Maria Tretiakova, MD, PhD
Univ. of Washington

Tumor defining molecular alterations

WHAT IS NEW & WHO IS WHO IN KIDNEY CANCER - WHO 2022

Concept 2: HEREDITARY KIDNEY CANCERS

Hereditary Renal Cell Carcinoma Syndromes

Separate chapter:

"Genetic syndromes of the urinary & male genital tracts "

– NO LONGER A CHAPTER BUT AN ENTIRE SECTION WITH INDIVDIDUAL WRITE UPS

- Von Hippel-Lindau (VHL) Syndrome
- Hereditary Papillary Renal Carcinoma (HPRC) Syndrome
- Birt-Hogg-Dubé (BHD) Syndrome
- Tuberous Sclerosis (TS) Syndrome
- Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Syndrome
- Succinate dehydrogenase deficient tumor syndromes
- BAP-1 tumor predisposition syndrome
- Hereditary pheochromocytoma-paraganglioma syndromes (incl SDH and VHL germline mutations)
- Lynch syndrome –HNPCC (Hereditary Nonpolyposis Colorectal Cancer syndrome)

WHAT IS NEW & WHO IS WHO IN KIDNEY CANCER - WHO 2022

Concept 3: ***The journey of classification of tumors never really ends - it's a process of continuing refinement*** **- Emerging tumor types**

WHO URO 5: EMERGING RENAL TUMORS AND THEIR ASSOCIATED GENE ALTERATIONS

Proposed entity	Location in current classification	Mutations identified
Thyroid-like follicular carcinoma	Not present	*EWSR1-PATZ1* fusions
Eosinophilic vacuolated tumour (EVT)	Other oncocytic Tumours	somatic *TSC2* inactivating mutations or *MTOR* activating mutation
Low grade oncocytic tumour (LOT)	Other oncocytic Tumours	*MTOR* mutation
Biphasic hyalinizing psammomatous renal cell carcinoma	Not present	*NF2* mutations
Papillary neoplasm with reverse polarity	Subtype of papillary RCC	recurrent mutations of *KRAS*

RCC Development Pathways

Sporadic RCC

- Clear cell RCC
- Chromophobe RCC
- Papillary RCC
- Collecting Duct Ca

2-4% of tumors

Familial

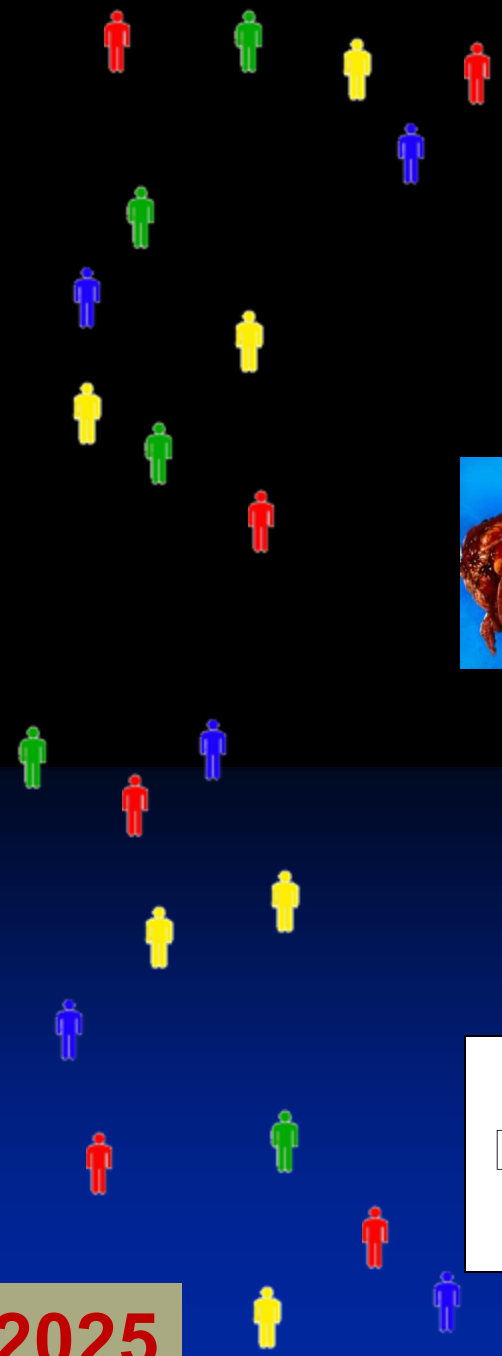
- VHL
- Birt-Hogg-Dube
- HPRCC
- HLRCC-RCC
- Renal medullary

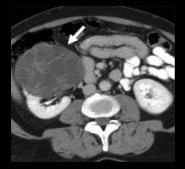
Post treatment RCC

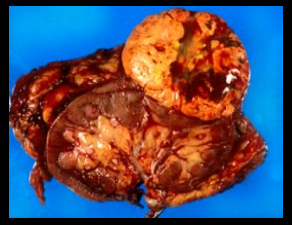
- Post chemotherapy RCC
- Post neuroblastoma RCC

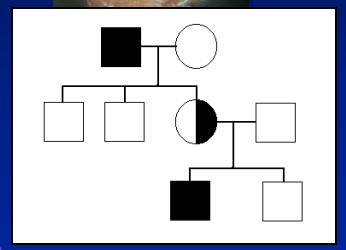
ESRD

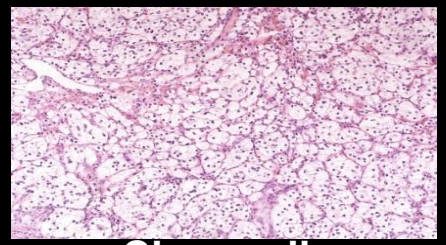
- ACD-assoc RCC
- Clear-papillary tumor







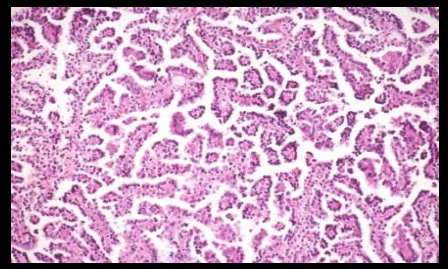




Clear cell

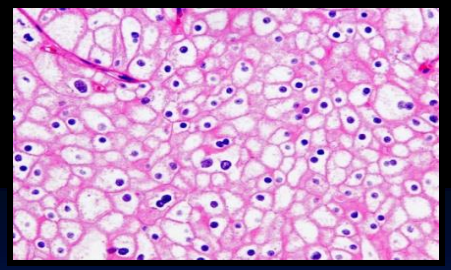
TKI/mTOR inhibitors

Check Point Inhibitors



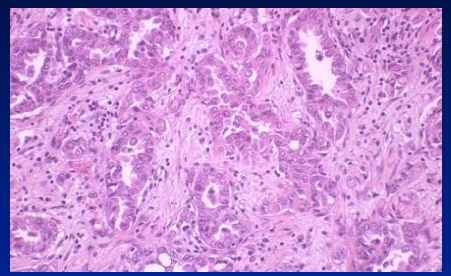
Papillary

MET, Checkpoint inhibitors



Chromophobe

mTOR,TKI checkpoint, inhibitors



Collecting duct

Cytotoxic Chemo

Histology and its implied molecular underpinning served primarily as a biomarker for therapy selection

2005-2025

Sarcomatoid and RCC NOS ⇄ Check point inhibitors

RENAL CELL CARCINOMA SUBTYPES

Subtype	Key Mechanisms	Key Alterations	Therapies
Clear cell RCC	VHL–HIF axis, angiogenesis, metabolism, chromatin remodeling	VHL, PBRM1, BAP1, SETD2	HIF-2α inhibitor, VEGF TKIs, IO–TKI combos
Papillary RCC	MET activation (type 1), metabolic/NRF2 stress (type 2)	MET mutations/amplifications; chr 7/17 gains; FH loss in subsets	MET inhibitors, cabozantinib, bevacizumab+erlotinib
Chromophobe RCC	Mitochondrial/OXPHOS, FLCN–mTOR/AMPK signaling	Multiple monosomies; FLCN mutations (BHD)	Limited VEGF TKI; some mTOR inhibitor benefit
Translocation associated RCC	MiT (TFE3/TFEB) fusion-driven, lysosome/autophagy, OXPHOS dependence	TFE3/TFEB fusions ± amplifications	VEGFR/MET TKIs (cabozantinib), IO–TKI regimens
FH-deficient RCC	Oncometabolite fumarate → pseudohypoxia, NRF2, redox stress	FH germline + somatic loss	Bevacizumab+erlotinib; IO–TKI; metabolic trials
Collecting duct carcinoma/Renal Medullary Carcinoma	CDC: EMT, RTK/MAPK. RMC: SMARCB1 loss, SWI/SNF deficiency, MYC	CDC: CDKN2A/NF2 loss. RMC: SMARCB1 loss	Platinum chemo; cabozantinib, IO, early trials

Pathologic Classification of RCC: WHO 2022 Perspectives

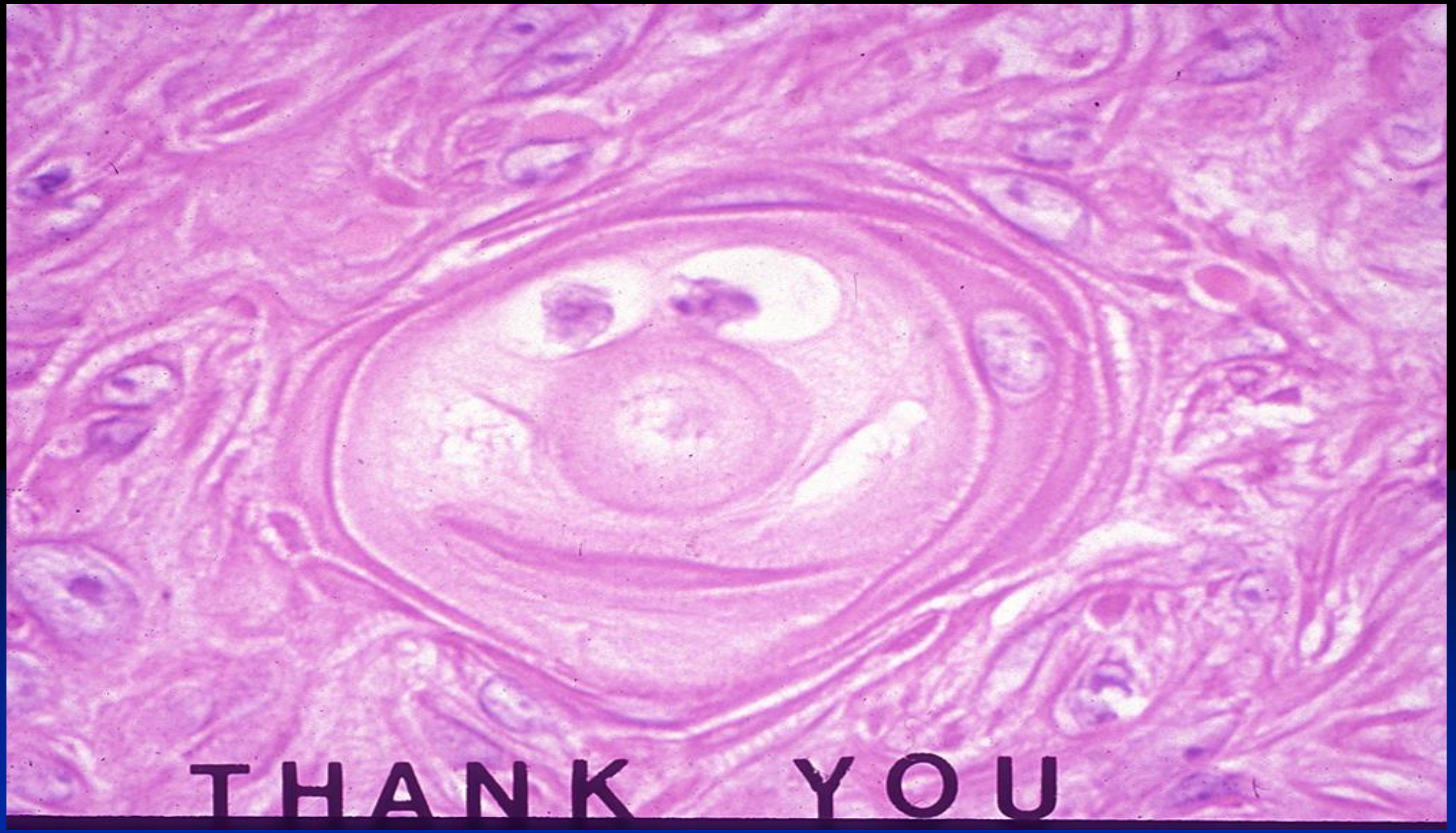
- **Clinico-patho-genomic** multidimensional integrated classification
- The different subtypes of RCC have unique
  - *histology*
  - *IHC*
  - *molecular signature*
  - *clinical aspects (age, prognosis, familial, response to therapies)*
- Morphology alone is not sufficient to provide management relevant individualized patient information necessitating complementary molecular testing in distinct situations
- WHO nomenclature is incorporated in CAP, AJCC and NCCN guidelines

ADULT RENAL EPITHELIAL TUMORS

Clinico-pathologic entities:

- **Organ confined disease:** Prognostically distinctive - *Clear cell-papillary, Chromophobe, Papillary, Clear Cell, Unclassified HG, CDC and FH deficient*
- **Metastatic disease:** Targeted therapies. Clear cell vs. non clear cell
- **Marker for Familial/Genetic Disorders:** VHL, tuberous sclerosis, Birt Hogg Dube, HLRCC-RCC; *SDH* mutation (SDH deficient gastrointestinal stromal tumor (GIST), paraganglioma/phaeochromocytoma)

Accurate subtying of renal epithelial tumors is a clinically important exercise !!


THANK YOU

Targeted therapy in Renal Cell Carcinoma

Tumor type	Known somatic alterations	Involved pathway	Targeted therapy
Clear cell	*VHL, PBRM1,SETD2, BAP1, mTOR, PI3K*	VEGF pathway mTOR pathway	Tyrosine kinase inhibitor; TKI (sorafenib, sunitinib) Newer TKI (pazopanib, axitinib) mTOR inhibitors (everolimus & temsirolimus)
Papillary RCC	*MET*	MET/HGF pathway	TKI, mTOR inhibitors, dual MET/ VEGFR inhibitor (foretinib)
Chromophobe RCC ESC-RCC	*TP53*	Upregulation of the mTOR pathway	mTOR inhibitors (everolimus & temsirolimus)

Targeted therapy in Renal Cell Carcinoma

Tumor type	Known somatic alterations	Involved pathway	Targeted therapy
FH deficient RCC	FH loss		Early phase studies using erlotinib and bevacizumab
MiT family RCC TFEB amplified RCC	Xp11.2 and t(6;11) translocations	MET signals as a down stream consequence of aberrant TFE3 activity	MET inhibitor (tivantinib) (in small cohort) VEGFA amplification
Alk-rearranged RCC			ALK-inhibitors
SMARB1- deficient RCC	SMARB1 (INI-1 loss)		Protesosome targeting therapies
Collecting duct carcinoma	Unknown	Unknown	Unknown (cytotoxic chemotherapy is common)

MiT Family RCC Subtypes

Subtype	Clinical Features	Pathology	Molecular	Prognosis
TFE3-rearranged	Children & adults; more aggressive in adults	Papillary/clear cell patterns; psammoma bodies; TFE3+, cathepsin K+	Xp11.2 TFE3 fusions (PRCC, ASPSCR1, SFPQ, etc.)	Aggressive in adults; variable in pediatrics
TFEB-rearranged	Younger patients; often localized, can metastasize	Biphasic: large eosinophilic + small rosette-forming cells; TFEB+, melanocytic+	6p21 TFEB fusions (MALAT1, ACTB, KHDRBS2, CLTC)	Usually indolent but metastasis/late recurrences occur
TFEB-amplified	Older adults; advanced stage at diagnosis	High-grade eosinophilic tumors; solid/alveolar; TFEB strong nuclear staining	6p21 high-level TFEB amplification ± VEGFA, CCND3	Consistently poor prognosis, aggressive clinical course

RENAL CELL CARCINOMA SUBTYPES

Subtype	Molecular Mechanisms	Molecular / Cytogenetic Alterations	Known Targeted Therapies
ccRCC	VHL loss → HIF stabilization → VEGF, glycolysis, lipid metabolism; 3p suppressor loss; mTOR–HIF cross-talk	3p loss; VHL, PBRM1, BAP1, SETD2 mutations; chr 5q gain; MTOR/TSC1/TSC2	HIF-2α inhibitor (belzutifan); VEGFR TKIs; IO–TKI regimens; mTOR inhibitors
pRCC	Type 1: MET activation. Type 2: metabolic/NRF2 stress, MYC programs	Type 1: MET mutations/amplifications, chr 7/17 gains. Type 2: CDKN2A loss, FH loss	MET inhibitors (savolitinib, crizotinib), cabozantinib, bevacizumab+erlotinib
chRCC	Mitochondrial/OXPHOS programs; FLCN–mTOR/AMPK signaling	Multiple monosomies; FLCN germline mutations (BHD)	mTOR inhibitors; limited VEGFR TKIs; cabozantinib in case reports

RENAL CELL CARCINOMA SUBTYPES

Subtype	Molecular Mechanisms	Molecular / Cytogenetic Alterations	Known Targeted Therapies
tRCC	TFE3/TFEB fusion-driven; lysosome/autophagy, OXPHOS dependence; MAPK/PI3K/MET cross-talk	TFE3/TFEB fusions; TFEB amplification (6p21); diverse partners	VEGFR/MET TKIs (cabozantinib); IO–TKI regimens; trials for MiT/lysosome and OXPHOS targets
FH-deficient RCC	FH loss → fumarate accumulation; protein succination; NRF2/HIF1 activation; glycolysis and redox stress	Germline + somatic FH loss; 2-SC accumulation; hypermethylation phenotype	Bevacizumab+erlotinib; IO–TKI regimens; metabolic synthetic lethal trials
CDC / RMC	CDC: EMT, RTK/MAPK. RMC: SMARCB1 loss → SWI/SNF deficiency, MYC activation, interferon/hypoxia response	CDC: CDKN2A/NF2 loss. RMC: SMARCB1 loss; structural variants; sickle trait context	CDC: platinum chemo, cabozantinib, IO/IO–TKI. RMC: platinum chemo, proteasome inhibitors, IO, EZH2/BRD9 trials

Era	Milestones in RCC Classification
Pre-1980s	‘Grawitz tumor’ concept (late 1800s) Clear cell RCC recognized as dominant type Collecting duct carcinoma described (1949)
1980s	Chromophobe RCC defined (Thoenes, 1985) Papillary RCC recognized as distinct entity (1976 → consolidated)
1990s	Renal medullary carcinoma (1995) Mucinous tubular & spindle cell carcinoma (1997) Xp11/TFE3 translocation RCC (late 1990s)
2000s	TFEB-rearranged RCC (2001) Hereditary leiomyomatosis & RCC (FH-deficient, 2002) Acquired cystic disease–associated RCC (2005) Clear cell papillary RCC (~2006)
2010s	SDH-deficient RCC (~2011) ALK-rearranged RCC (~2011) Tubulocystic RCC (~2016 WHO) Eosinophilic solid & cystic RCC (~2016)
2020s	WHO 2022: major expansion – TFEB-amplified RCC – Low-grade oncocytic tumor (LOT) – Eosinophilic vacuolated tumor (EVT) – Papillary neoplasm with reverse polarity

CONTEMPORARY APPROACH TO DX OF RENAL EPITHELIAL TUMORS

CLINICAL FEATURES:
- Age
- Other specific: family history, ESRD, polycythemia etc.

NUCLEAR FEATURES:
- Round, regular
- Raisinoid
- Elongated

GROSS FEATURES:
- Staging
- Sampling to capture histologic diversity
- Specific features

SPECIFIC OTHER FEATURES:
- Psammomatous calcification
- Sickle cells
- Other

ARCHITECTURAL FEATURES:
- Solid
- Papillary
- Nested etc.

IMMUNOHISTOCHEMICAL PROFILE:
- Age
- Other specific: family history, polycythemia

CYTOPLASMIC FEATURES:
- Clear
- Eosinophilic
- Both

MOLECULAR ALTERATIONS:
- Diagnostic
- Prognostic
- Predictive
- Germline

ALL TUMORS WITH CLEAR CYTOPLASM ARE NOT CLEAR CELL CARCINOMAS

- **Renal tumors with clear cytoplasm:**
  - Clear cell (conventional) RCC
  - Chromophobe RCC
  - Clear-Cell Papillary RCC (tumor)
  - MiTF family translocation associated RCC, typically t(x;1)
  - ELOC/TCEB mutated RCC
  - *Hemangioblastoma*
  - *Epithelioid PEComa (very rarely predominantly clear)*
  - *Papillary RCC (usually focal)*
  - *Oncocytoma (rare;areas of scarring)*
  - *Unclassified RCC*
  - *"Xanthogranulomatous pyelonephritis"*

Virtually any renal tumor can have focal to prominent 'clear cell" areas

RENAL TUMORS WITH EOSINOPHILIC CYTOPLASM

Eosinophilic renal tumors with nested, tubular to solid architecture :

- Renal Oncocytoma
- Chromophobe RCC
- Hybrid Oncocytic chromophobe tumor
- Clear Cell RCC (so called eosinophilic variant)
- t (6:11) translocation associated RCC
- Eosinophilic Solid and Cystic RCC
- SDH deficient RCC
- Low grade FH Deficient RCC
- Eosinophilic vacuolated tumor (EVT)
- Low grade oncocytic tumor (LOT)
- Epithelioid PEComa
- TFEB amplified RCC
- Primary thyroid follicular carcinoma-like RCC

Tubular, tubulocystic and papillary architecture:

- Papillary RCC ('type 2' & 'oncocytic' type)
- TFEB amplified RCC
- Primary thyroid follicular carcinoma-like RCC
- Tubulocystic RCC
- Acquired cystic disease associated RCC
- FH deficient RCC (high grade)

Other:

Invasive urothelial carcinoma
Metastasis
Ext. of adrenocortical neoplasm

Virtually any renal tumor can have focal to prominent 'eosinophilic" areas

RENAL TUMORS WITH PREDOMINANT PAPILLARY ARCHITECTURE

Overall circumscribed tumor

- Papillary RCC
- Clear cell-papillary RCC
- Metanephric adenoma
- Acquired cystic disease - associated RCC
- Mucinous tubular and spindle cell carcinoma

Mixed: Solid, papillary/variable

- MITF family translocation associated RCC (predominantly xp11.2
- TFEB amplified RCC
- FH deficient RCC (high grade)

DIFFERENTIAL DIAGNOSIS OF HIGH GRADE INFILTRATIVE ADENOCARCINOMA OF KIDNEY

- FH deficient and HLRCC- RCC
- Collecting Duct carcinoma (CDC)
- Renal medullary carcinoma (RMC) & related SMARCB1 deficient tumors
- Anaplastic lymphoma kinase (Alk)- rearrangement associated RCC
- Invasive urothelial carcinoma of pelvicalyceal system involving renal parenchyma
- Metastatic carcinoma involving kidney
- Unclassified RCC

- **ccRCC now has multiple credentialed autochthonous mouse models** that reproduce hallmark histology and 3p tumor suppressor biology; they're the most mature RCC animal systems for mechanism + therapy. PMC+1
- **Papillary RCC** is best modeled by **MYC** activation in mice, with **PDX/PDO** filling translational gaps and enabling subtype-specific drug screens. Nature+1
- **Chromophobe/oncocytic tumors** are mechanistically accessible through **FLCN/BHD** and **TSC/mTOR** models, though none is a perfect histologic facsimile of sporadic chRCC. PMC+1
- **MiT family tRCC** finally has credible **TFEB/TFE3** mouse and engineered organoid systems; these are unlocking fusion-specific dependencies. PMC+1
- **FH-deficient RCC**: GEMMs are outstanding for **oncometabolite** biology; for invasive disease and drug testing, lean on **PDX/PDO**. Nature+1
- **CDC/RMC** remain modeling orphans for GEMMs; use **PDX/xenografts** and human multi-omics when you need signal. Oncotarget+1

FINANCIAL DISCLOSURES

- Advanced Clinical: Research and AI consultancy for Google Health
- Ibex: Digital Pathology. Scientific advisory Board member
- Cell Max: Scientific advisory Board member
- Precipio Diagnostics: Scientific advisory Board member
- Karkinos Health: Scientific advisory Board member
- Labcorp: Divisional Medical Director, West Division

I will not be promoting any products directly