Germline Testing in Hereditary Kidney Cancer Syndromes

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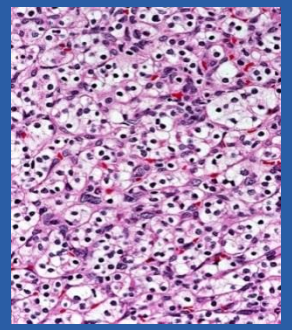
No disclosures.

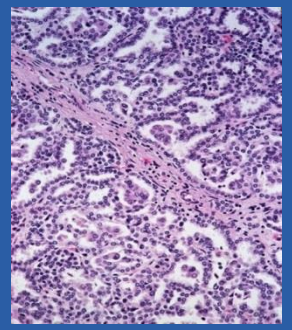
Objectives

- **Why** to perform germline testing?
- **How** to perform germline testing?
- **In whom** to perform germline testing?

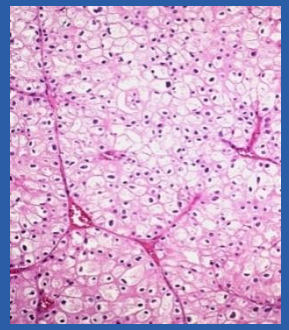
Kidney cancer: Multiple diseases



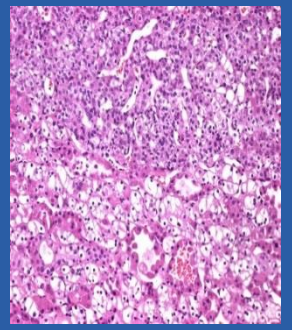
Clear Cell
VHL,TCEB1,BAP1



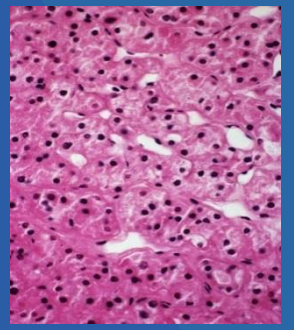
Papillary Type 1
MET



Chromophobe

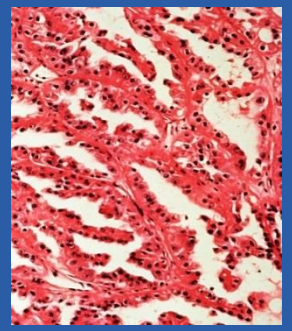


Hybrid

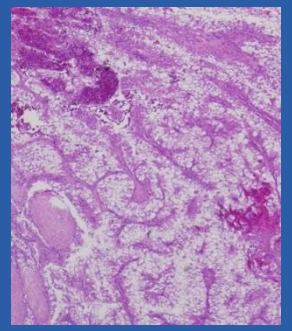


Oncocytoma

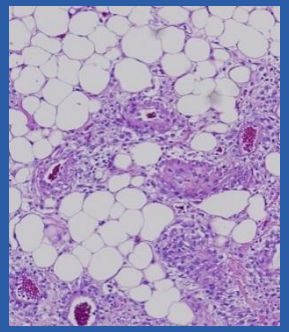
FLCN



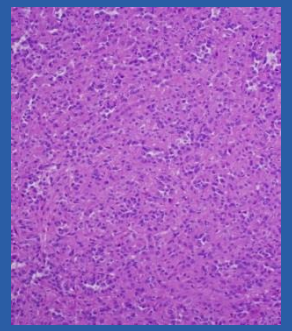
Papillary Type 2
FH



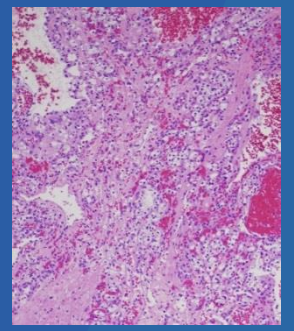
TFE3
TFE3, TFEB, MITF



Angiomyolipoma
TSC1, TSC2



Eosinophilic
SDHA, SDHB, SDHC, SDHD



Clear/Chromophobe
PTEN

Hereditary Kidney Cancer

- Currently 12 known syndromes that confer a predisposition to kidney cancer
- Most series suggest 5-8% of kidney cancers are associated with a known hereditary kidney cancer syndrome.
- But genetic influence likely plays a larger role…

1. Kletscher J Urol. 1995;153(3 Pt 2):904-6.
2. Whang J Urol. 1995;154(3):968-70; discussion 70-1.

Known Inherited Syndromes

1.	von Hippel-Lindau (VHL)	[*VHL]*
2.	Hereditary Papillary Renal Cancer (HPRC)	[MET]
3.	Birt-Hogg-Dube (BHD)	[FLCN]
4.	Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)	[FH]
5.	Succinate Dehydrogenase Deficiency	[SDH-B,C,D]
6.	Microphthalmia-associated Transcription Factor RCC	[MITF]
7.	BAP1-associated kidney cancer	[BAP1]
8.	Tuberous Sclerosis Complex (TSC)	[TSC1,2]
9.	Chromosome 3 Translocation	germline balanced translocation
10.	Hyperparathyroid -Jaw Tumor (HJT)	[CDC73]
11.	Cowden Syndrome	[PTEN]
12.	Familial Renal Oncocytoma (FRO)	mitochondrial genes

How are hereditary cases missed?

- Clinician unfamiliarity with non-renal manifestations
- Variable penetrance
- Poor family history
- Development of *de novo* mutations (~10% of hereditary patients)

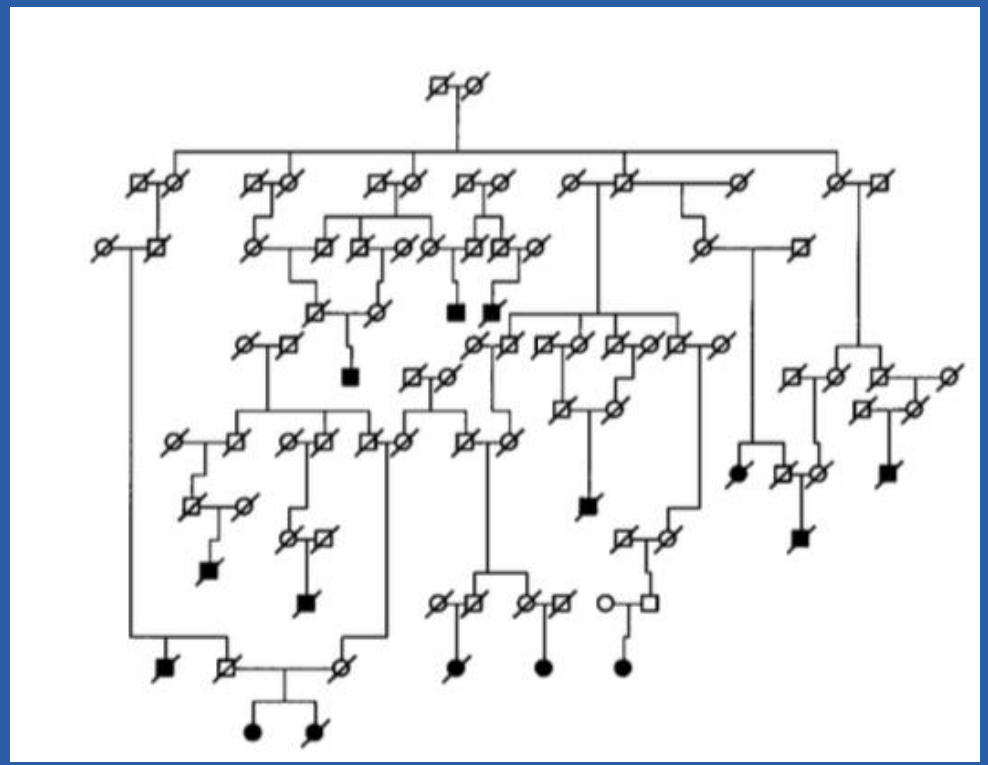
Does it matter?

- Hereditary patients are treated with different paradigms.
- Identify indolent vs aggressive phenotypes
- Emphasis on organ preservation:
  - Active surveillance and partial nephrectomy
- Different pathways for systemic therapy
  - FH-deficient and SDH-deficient tumors
- Screening for the rest of family

A POPULATION-BASED FAMILIAL AGGREGATION ANALYSIS INDICATES GENETIC CONTRIBUTION IN A MAJORITY OF RENAL CELL CARCINOMAS

Tómas Gudbjartsson[1]*, Thora J. Jónasdóttir[2,3], Ásgeir Thoroddsen[1], Gudmundur V. Einarsson[1,4], Gudrún M. Jónsdóttir[2], Kristleifur Kristjánsson[2], Sverrir Hardarson[1,4], Kjartan Magnússon[1], Jeffrey Gulcher[2]*, Kári Stefánsson[2] and Laufey T. Ámundadóttir[2,3]

Int. J. Cancer: **100,** 476–479 (2002)



Iceland – extensive genealogy records for “11 centuries”
1,078 RCC cases
Determine whether patients are more related to each other than controls
58% of all cases were found in families with 2 or more affected members
26% in families with 3 or more affected members.

RR of RCC with 1st degree relative: >2

Original Investigation

Familial Risk and Heritability of Cancer Among Twins in Nordic Countries

JAMA January 5, 2016 Volume 315, Number 1

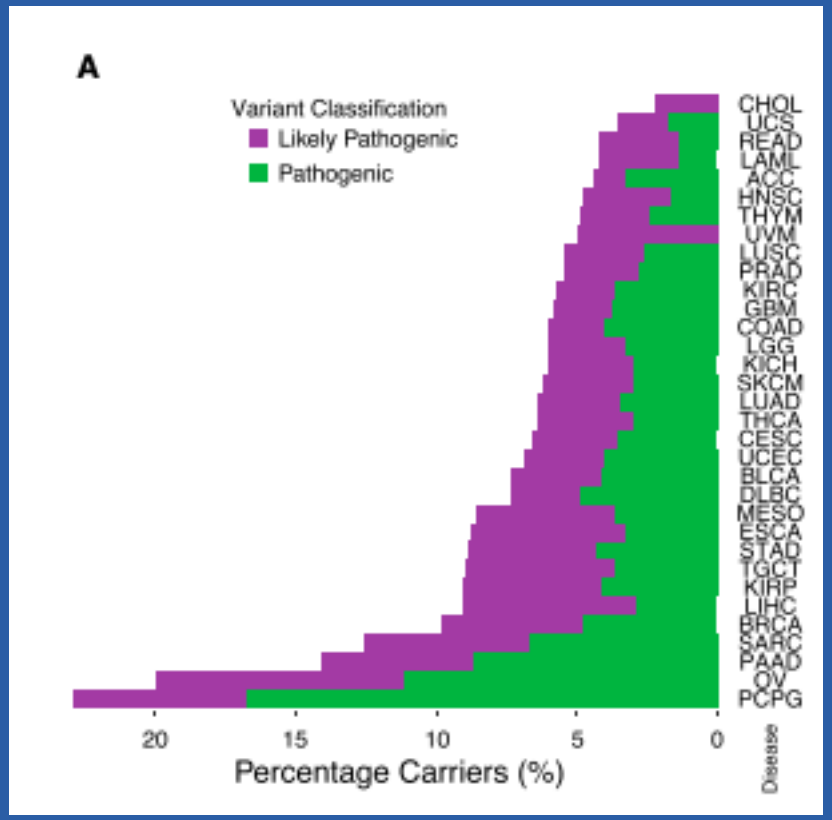
80,309 monozygotic and 123 382 same-sex dizygotic twin individuals within the population-based registers of Denmark, Finland, Norway, and Sweden.
Twins were followed up a median of 32 years

Table 3. Estimates of Heritability and Shared Environment for Specific Types of Cancer in the NorTwinCan Cohort[a]

	Familial Risk, % (95% CI)	
	Heritability	Shared Environment
Overall cancer	33 (30-37)	0
Head and neck	9 (0-60)	26 (0-65)
Stomach	22 (0-55)	6 (0-31)
Colon	15 (0-45)	16 (0-38)
Rectum and anus	14 (0-50)	10 (0-38)
Lung	18 (0-42)	24 (7-40)
Skin		
Melanoma	58 (43-73)	0
Nonmelanoma	43 (26-59)	0
Breast	31 (11-51)	16 (0-31)
Corpus uteri	27 (11-43)	0
Ovary	39 (23-55)	0
Prostate	57 (51-63)	0
Testis	37 (0-93)	24 (0-70)
Kidney	38 (21-55)	0
Bladder, other urinary organs	30 (0-67)	0
Leukemia, other	57 (0-100)	0

Cell

Pathogenic Germline Variants in 10,389 Adult Cancers



10,000+ adult cancers in the TCGA dataset . TCGA specifically excluded known hereditary cancer syndromes

Pathogenic germline alterations found in:
6% ccRCC
9% pRCC
6% chromophobe RCC

Genome-wide association study identifies multiple risk loci for renal cell carcinoma

Ghislaine Scelo *et al.*#

NATURE COMMUNICATIONS | DOI: 10.1038/ncomms15724

- 13 loci have been identified that confer increased risk of RCC, OR ~1.5 in patients of European ancestry

A Genome-Wide Association Study of Renal Cell Carcinoma among African Americans Cancer Epidemiol Biomarkers Prev; 23(1) 2014

		NCI study		
Race	RCC subtype	N_{Case}/N_{Cont}	OR (95% CI)	*P*
African American				
	Clear cell	127/375	0.69 (0.52–0.93)	0.01
	Other	127/375	1.00 (0.75–1.34)	0.99
			$P_{hom} = 0.03$	
European ancestry				
	Clear cell	544/712	0.79 (0.57–1.09)	0.15
	Other	268/712	1.00 (0.68–1.48)	0.98
			$P_{hom} = 0.18$	

Increasing emphasis in multiple malignancies

- Recent NCCN guideline changes
  - Prostate: germline testing **recommended for all high-risk patients**
  - Pancreatic: germline testing **recommended for** all patients
  - Breast: **strong consider** germline testing

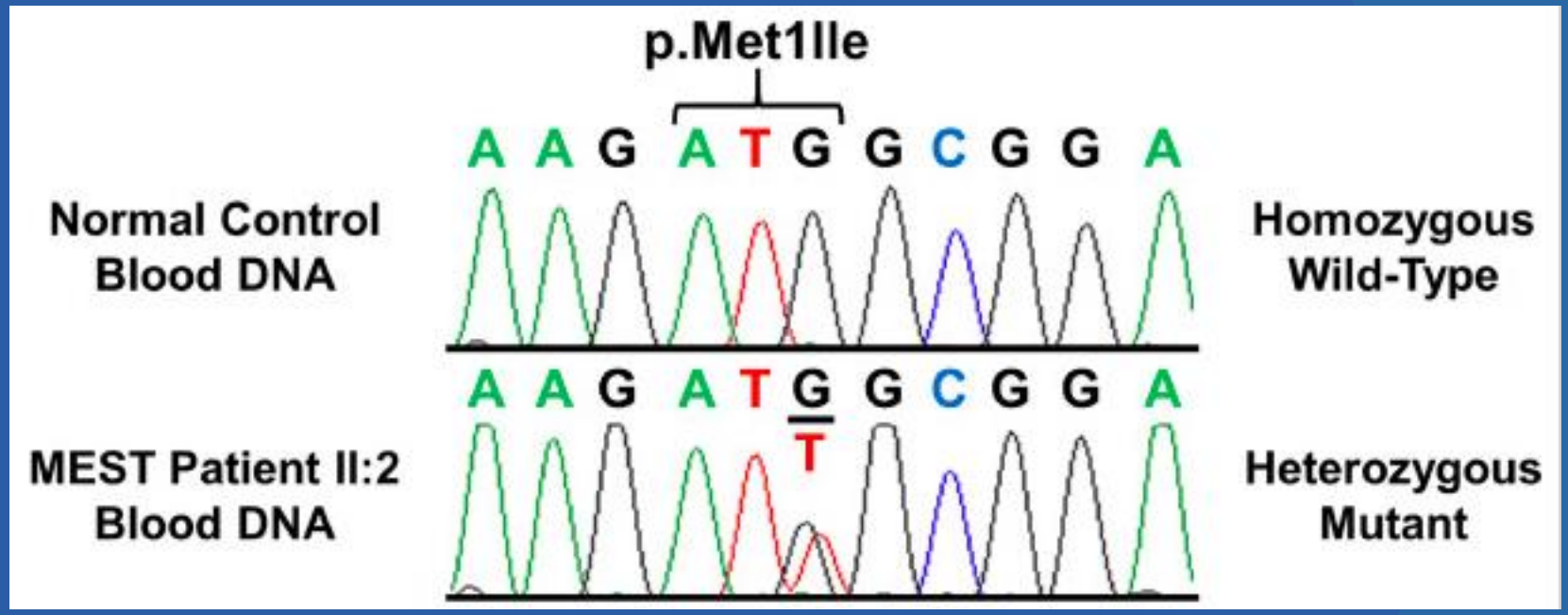
Objectives

- **Why** to perform germline testing?
  - Syndromes are not rare
  - Can affect management
- **How** to test perform germline testing?
- **In whom** to perform germline testing?

How to test

- How many genes?
  - Single gene
    - confirm clinical diagnosis or known family variant
    - lowest cost
  - 15-25 gene renal panels: established germline genes.
    - no clear syndromic features, but suspicious family or person history
  - Expanded panels
    - included non-renal cancer susceptibility genes
    - decreased signal:noise, may find more VUS → increased uncertainty

Sanger sequencing



Genetic Testing

GeneDx an OPKO Health Company

Test Information Sheet

OncoGeneDx: Renal Cancer Panel

Panel Gene List: *BAP1, EPCAM*, FH, FLCN, MET, MITF*, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL*

*Testing includes sequencing and deletion/duplication analysis for all genes except *EPCAM* (del/dup only) and *MITF* (only c.952G>A (p.Glu318Lys) will be analyzed and reported).

INVITAE

○ 01361	Invitae Renal/Urinary Tract Cancers Panel		24	BAP1, CDC73, CDKN1C, DICER1, DIS3L2, EPCAM, FH, FLCN, GPC3, MET, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC, SMARCA4, SMARCB1, TP53, TSC1, TSC2, VHL, WT1
	○ 01361.1	Add-on preliminary-evidence genes	6	BUB1B, CEP57, MITF, PALB2, SDHA, SDHD

Testing considerations

- Genetic counselors: high demand, limited supply – may face wait times
- Cost – in U.S., variable insurance coverage. Need to establish risk – 3 generation pedigrees
- Implications
  - Insurability – health and life insurance
  - Screening for family members
  - Incidental findings

Objectives

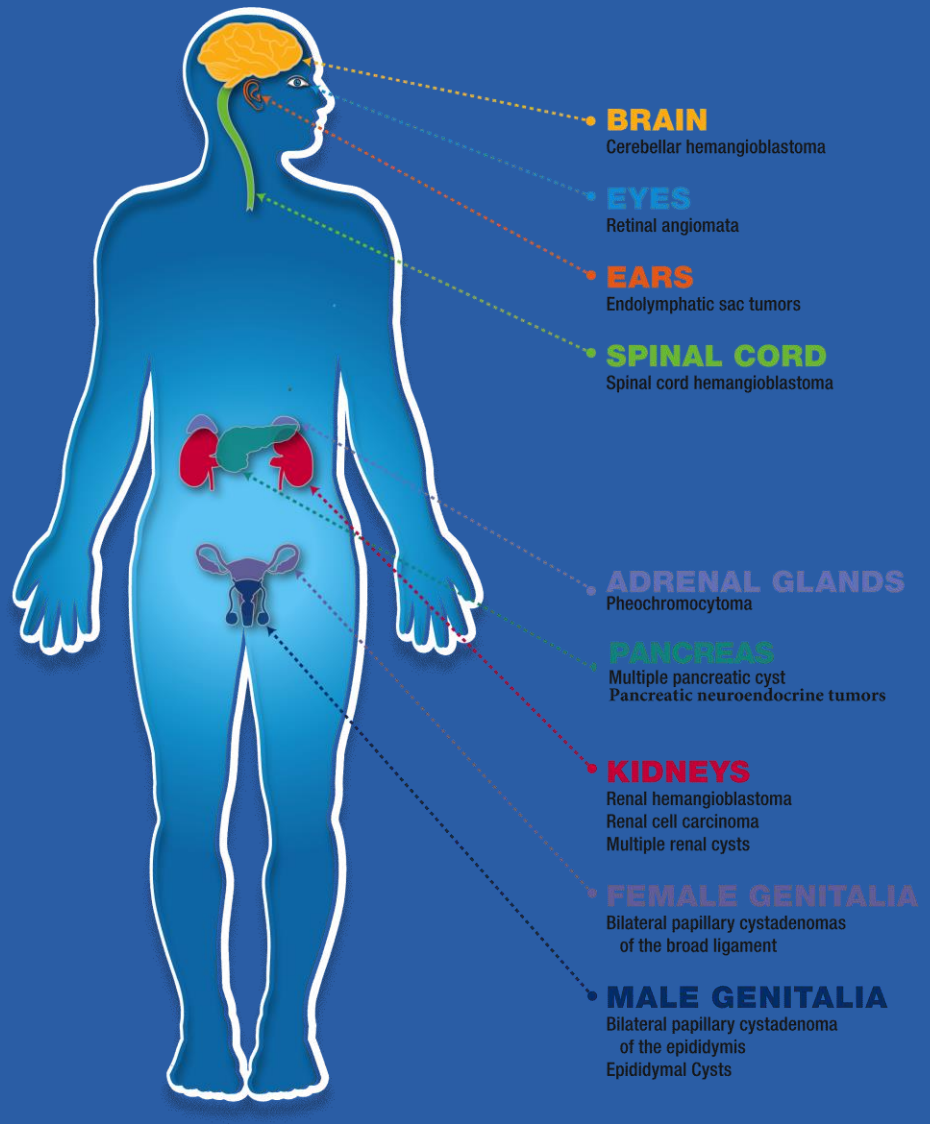
- **Why** to perform germline testing?
- **How** to perform germline testing?
  - In coordination with a genetic counselor
  - Renal panel with known germline-altered genes for most suspected patients

In whom to perform germline testing?

Hereditary Kidney Cancer

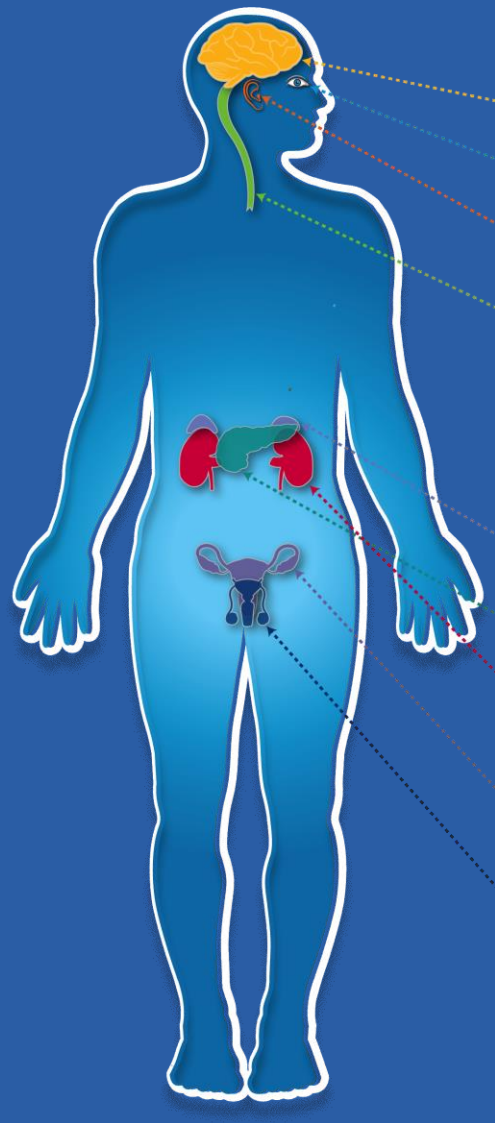
- When to evaluate:
  - Feature of genetic syndrome
  - Early onset (before age 46)
  - Family history, especially first-degree relative
  - Bilateral and/or multifocal
  - Advanced disease
  - Rare histology

von Hippel-Lindau Disease



- VHL is a hereditary, multi-organ cancer syndrome
- Germline alterations of *VHL*
- AD inheritance
- 1:36,000

von Hippel-Lindau Disease



BRAIN
Cerebellar hemangioblastoma

EYES
Retinal angiomata

EARS
Endolymphatic sac tumors

SPINAL CORD
Spinal cord hemangioblastoma

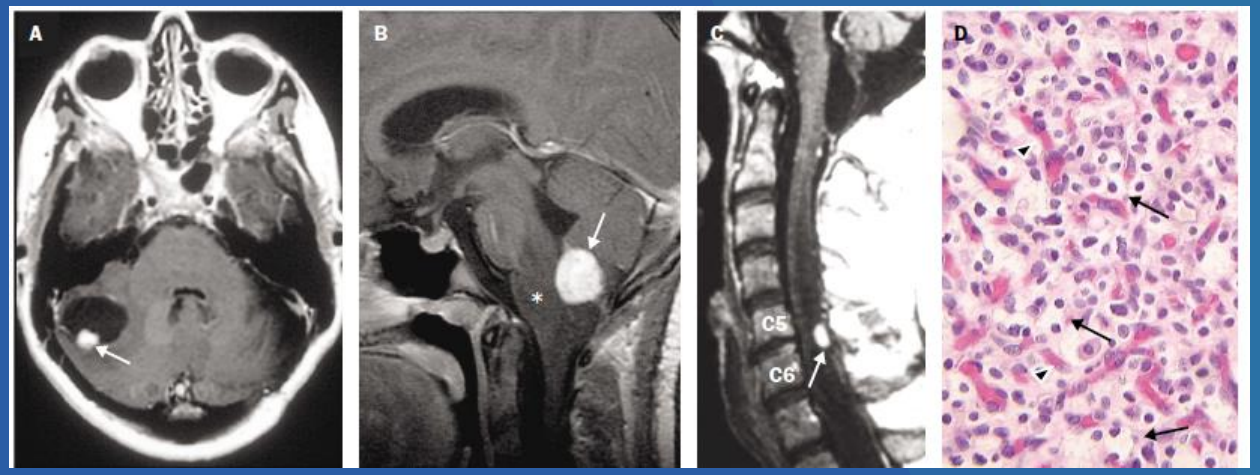
ADRENAL GLANDS
Pheochromocytoma

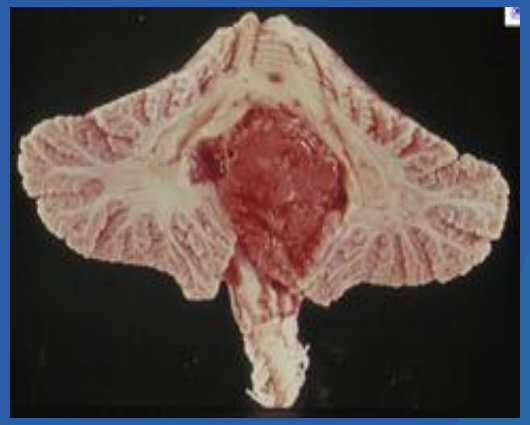
PANCREAS
Multiple pancreatic cyst
Pancreatic neuroendocrine tumors

KIDNEYS
Renal hemangioblastoma
Renal cell carcinoma
Multiple renal cysts

FEMALE GENITALIA
Bilateral papillary cystadenomas of the broad ligament

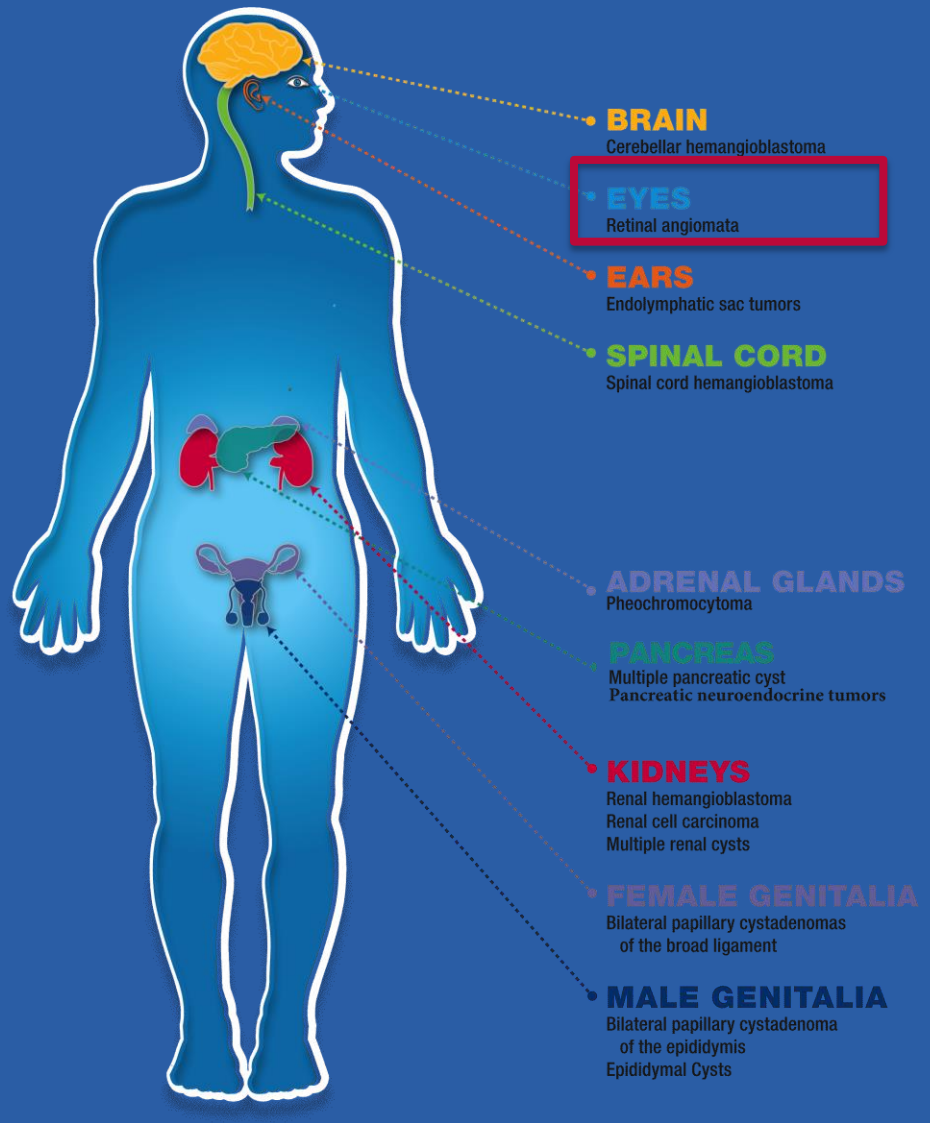
MALE GENITALIA
Bilateral papillary cystadenoma of the epididymis
Epididymal Cysts





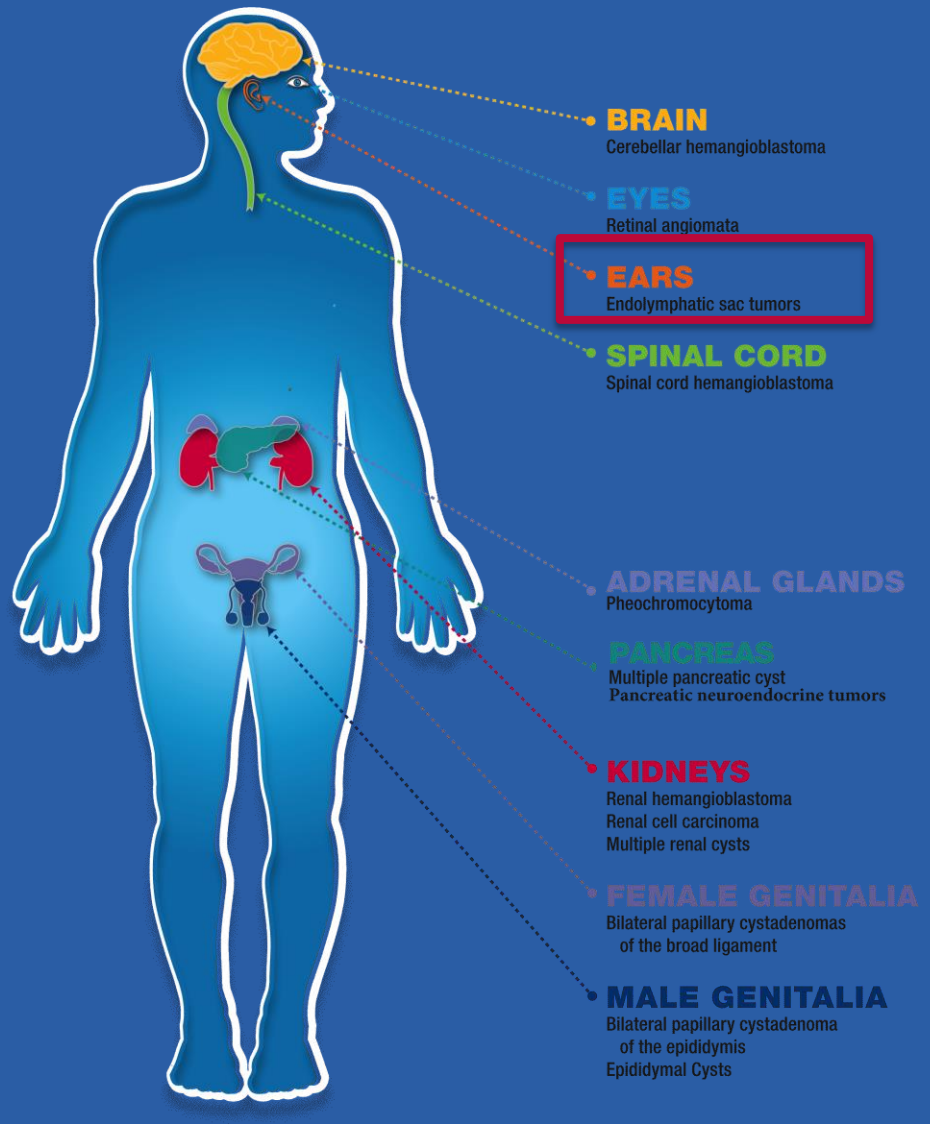
CNS Hemangioblastomas

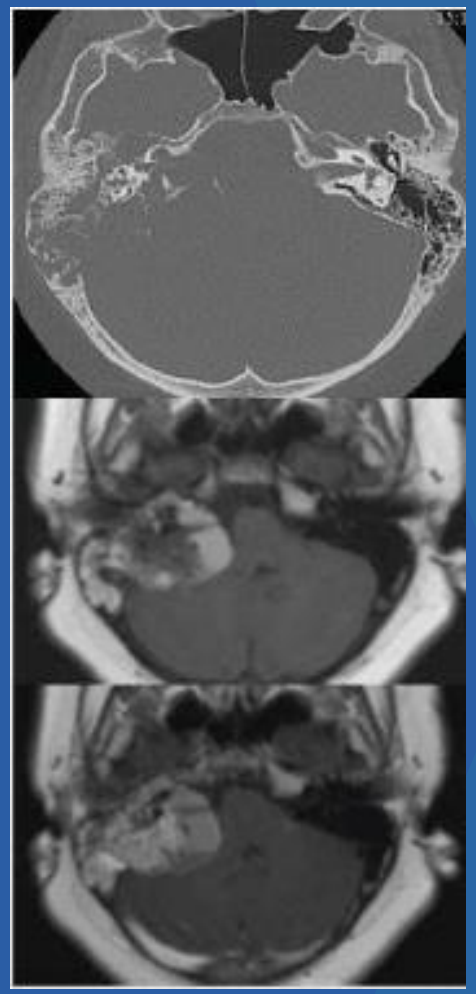
von Hippel-Lindau Disease



Retinal Angiomas

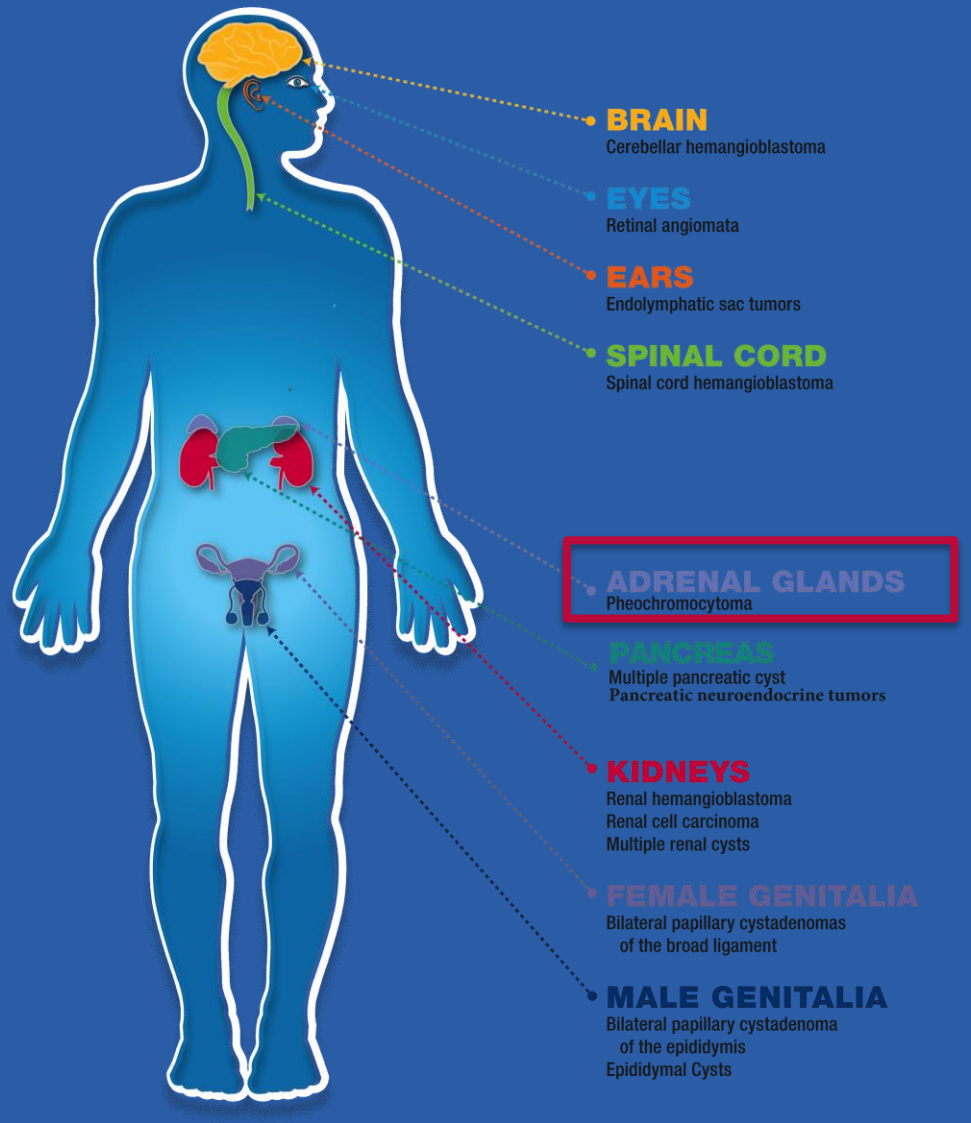
von Hippel-Lindau Disease





Endolymphatic Sac Tumors (ELST)

von Hippel-Lindau Disease



BRAIN
Cerebellar hemangioblastoma

EYES
Retinal angiomata

EARS
Endolymphatic sac tumors

SPINAL CORD
Spinal cord hemangioblastoma

ADRENAL GLANDS
Pheochromocytoma

PANCREAS
Multiple pancreatic cyst
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Renal hemangioblastoma
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FEMALE GENITALIA
Bilateral papillary cystadenomas of the broad ligament

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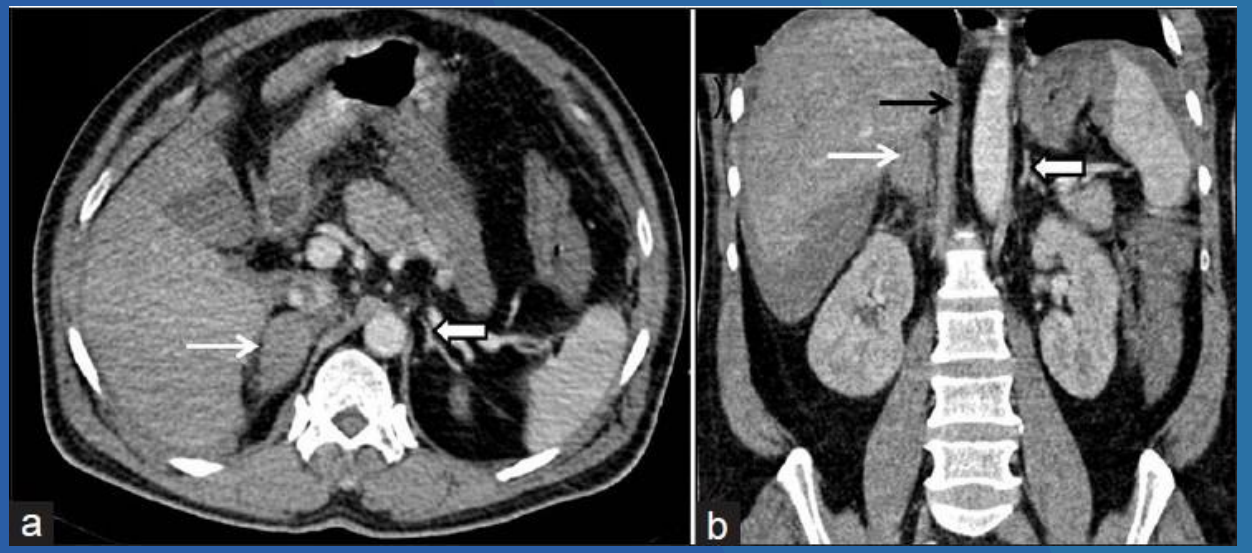
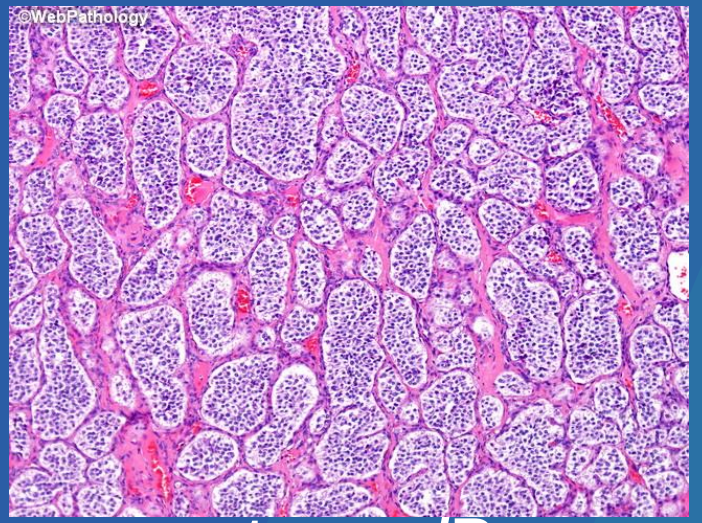
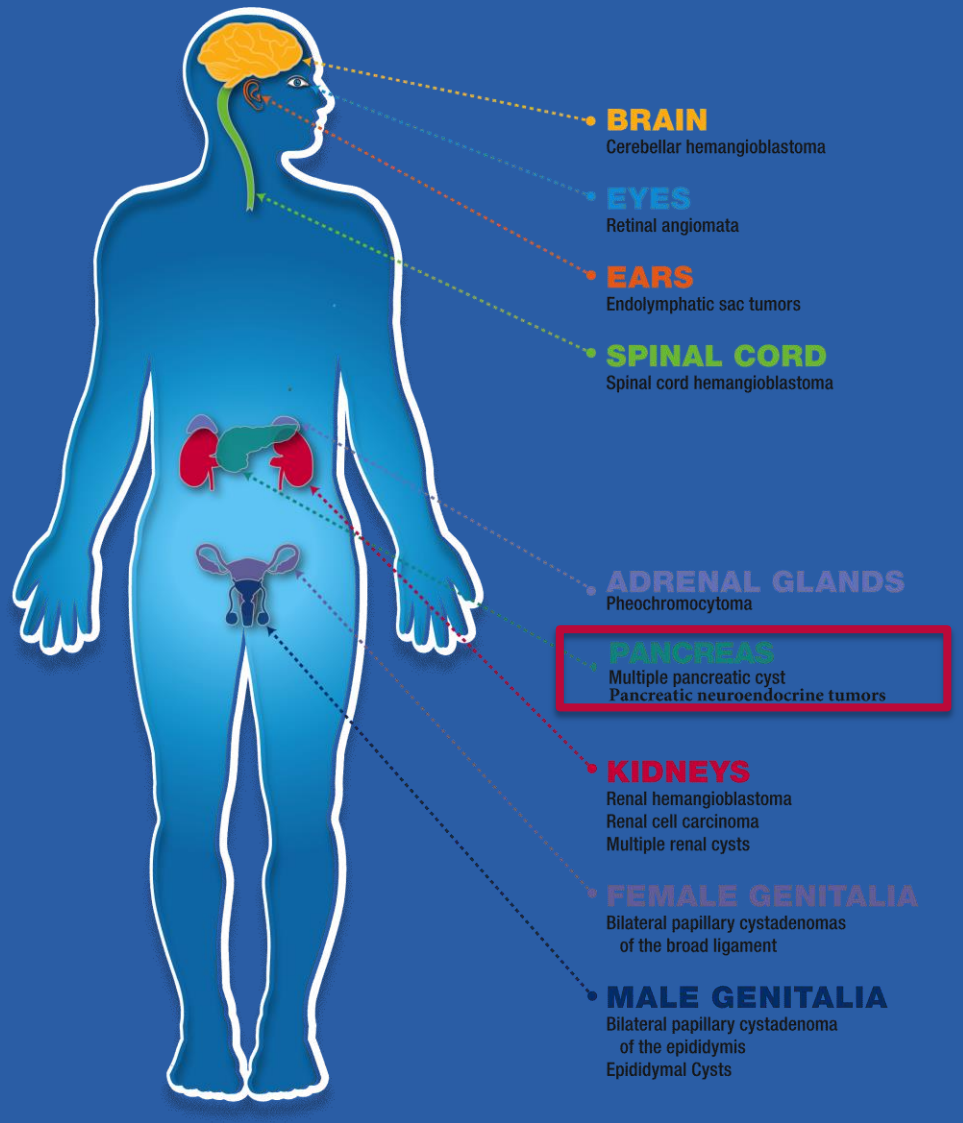
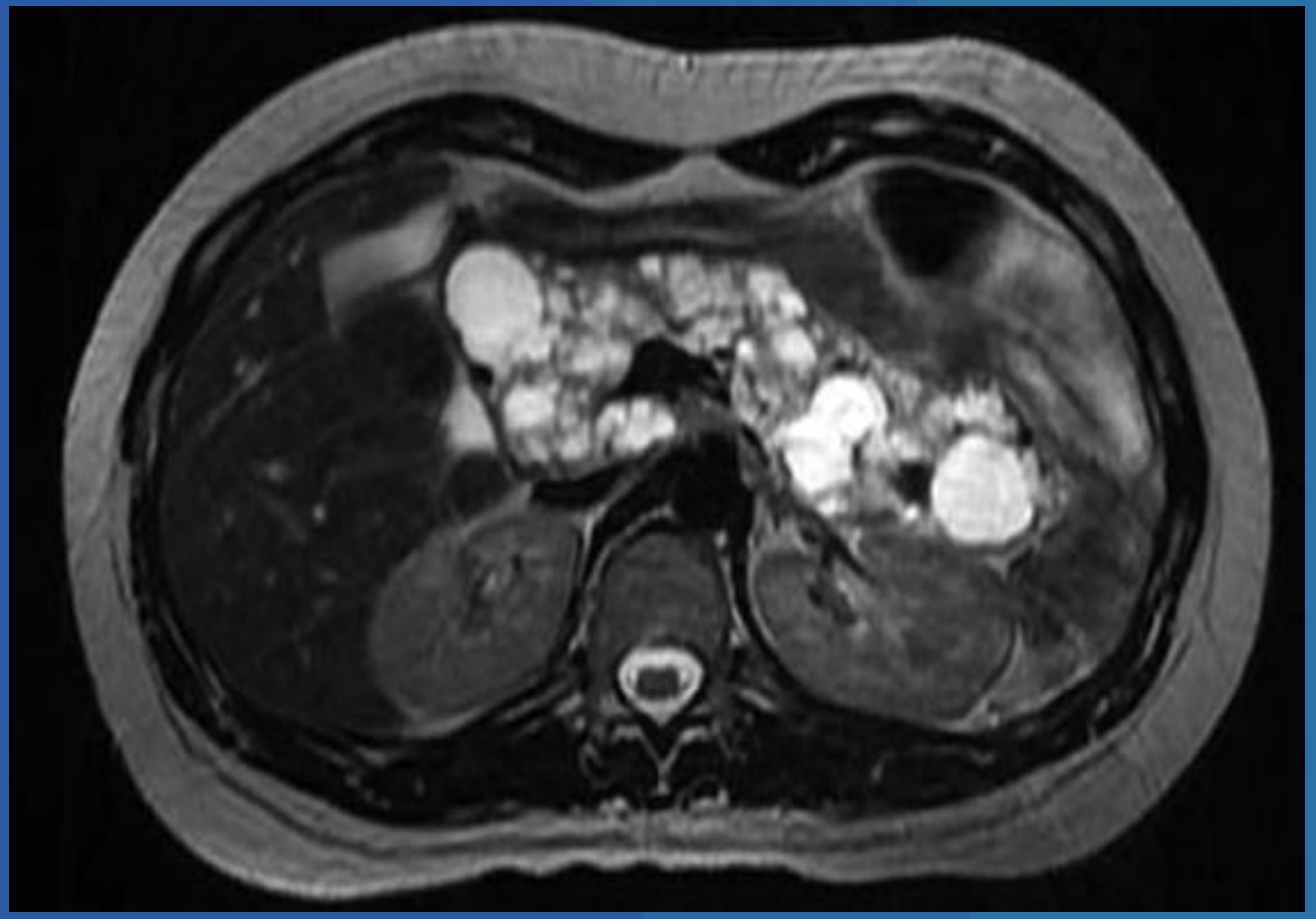




Pheochromocytomas/Paragangliomas

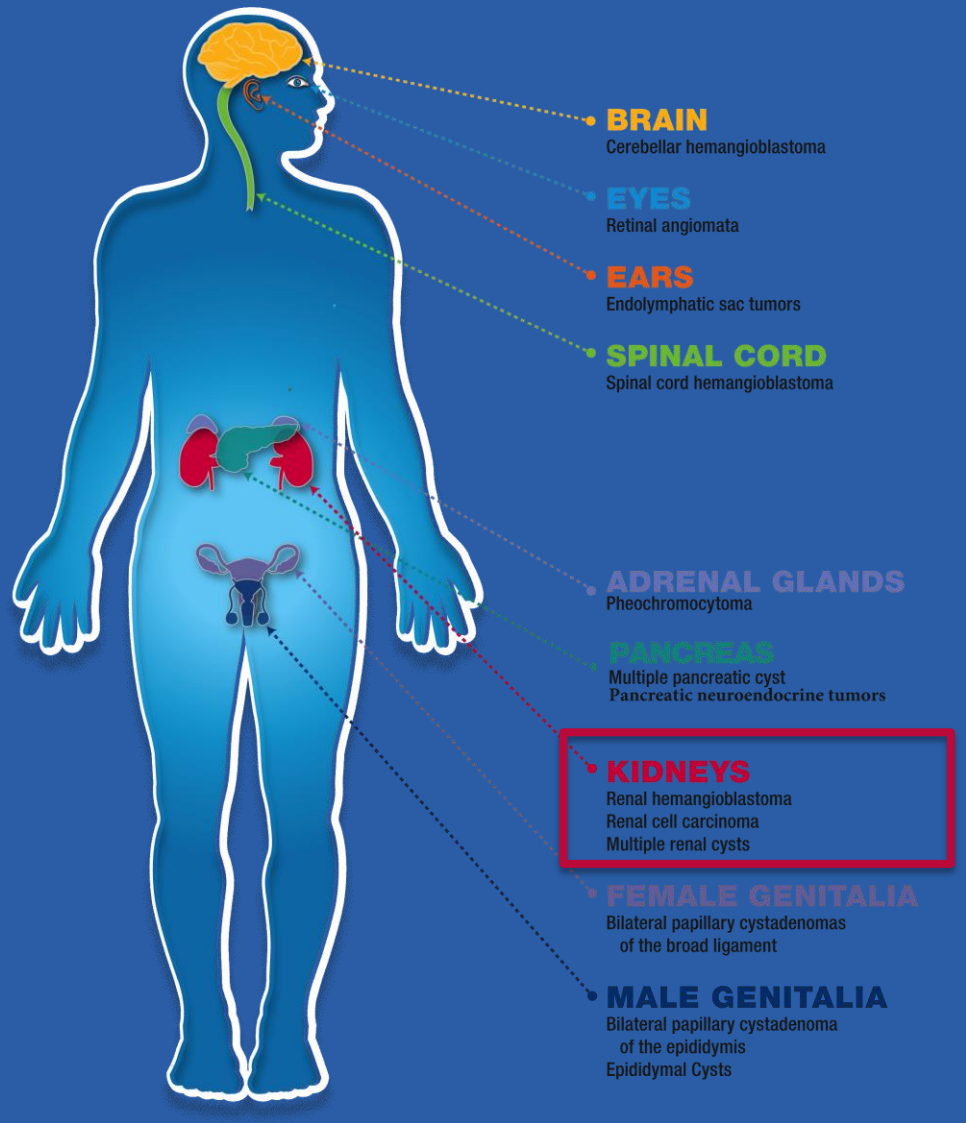
von Hippel-Lindau Disease

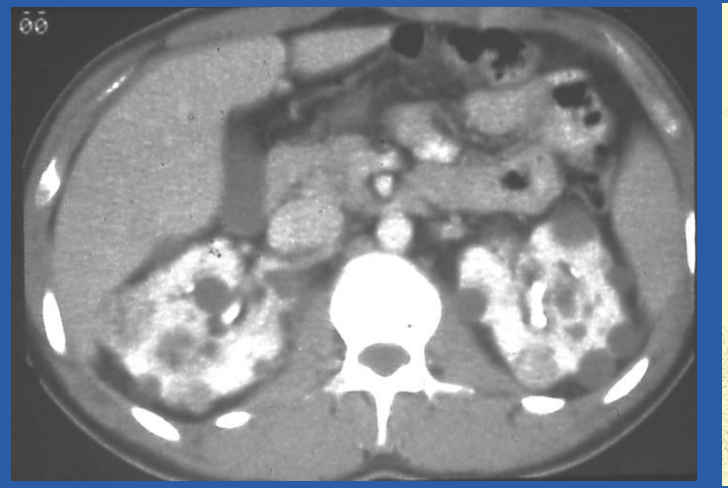


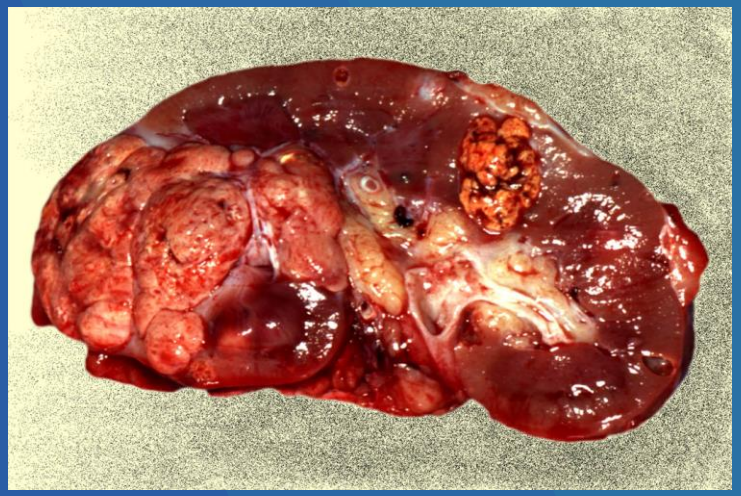


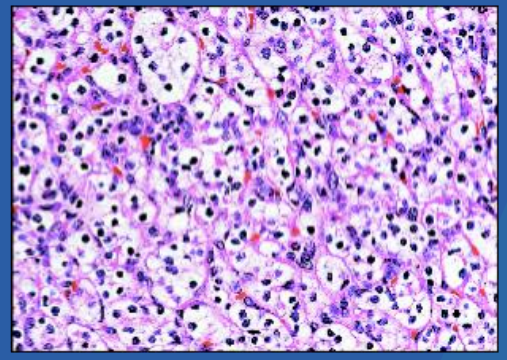
Pancreatic Cyst
Pancreatic Neuroendocrine Tumors

von Hippel-Lindau Disease



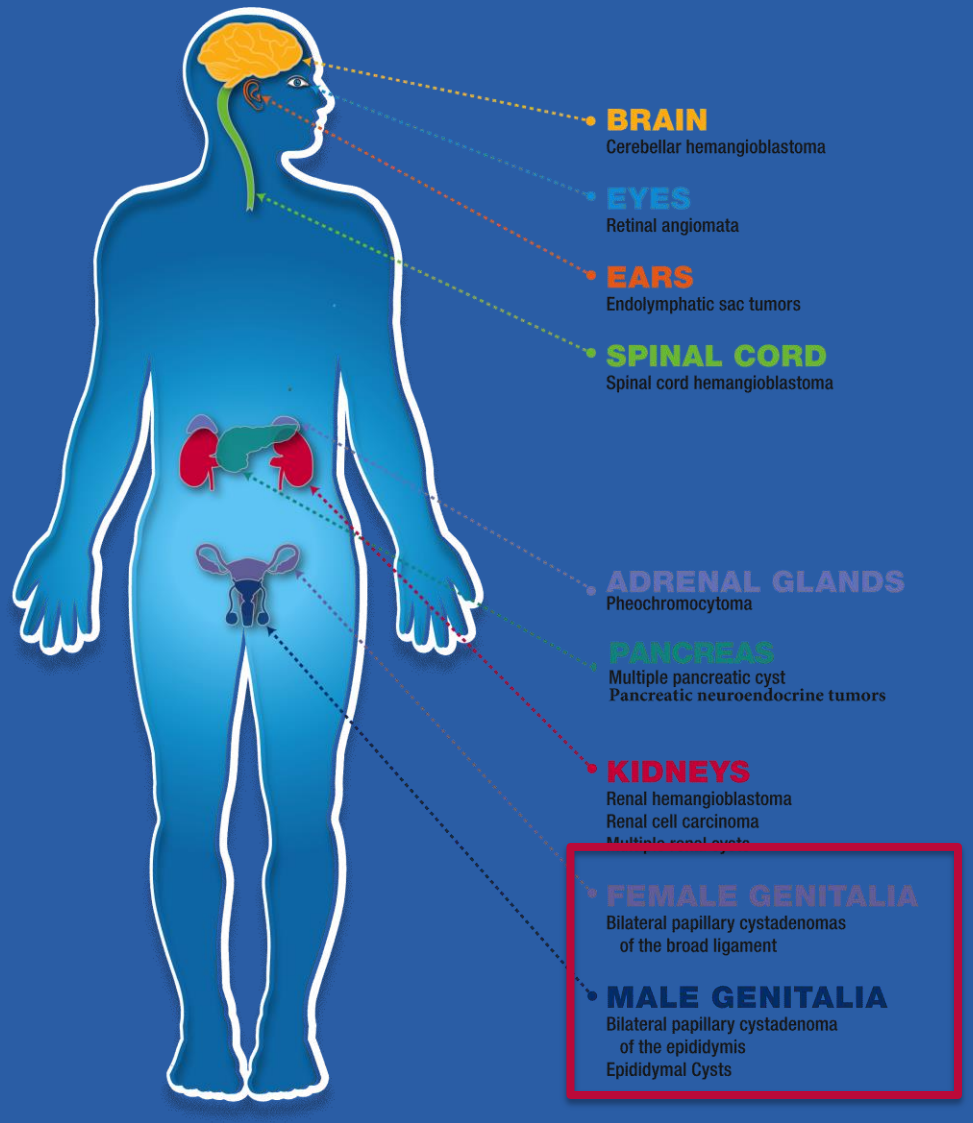


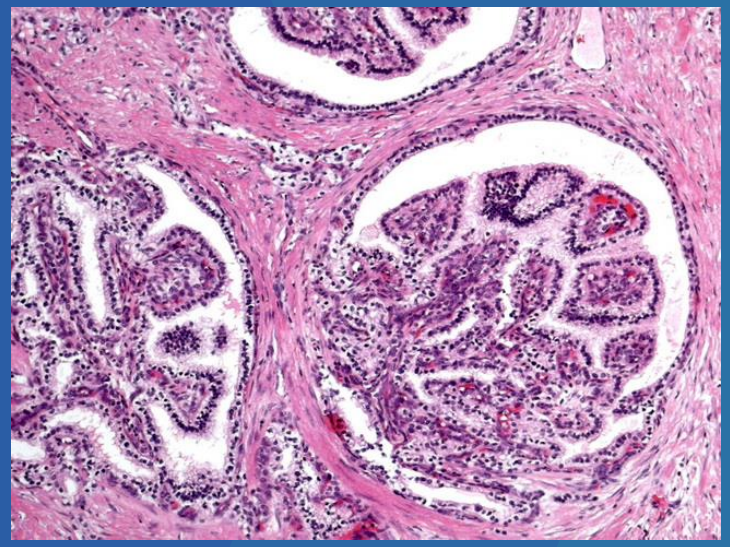




Kidney cysts
Renal cell carcinoma

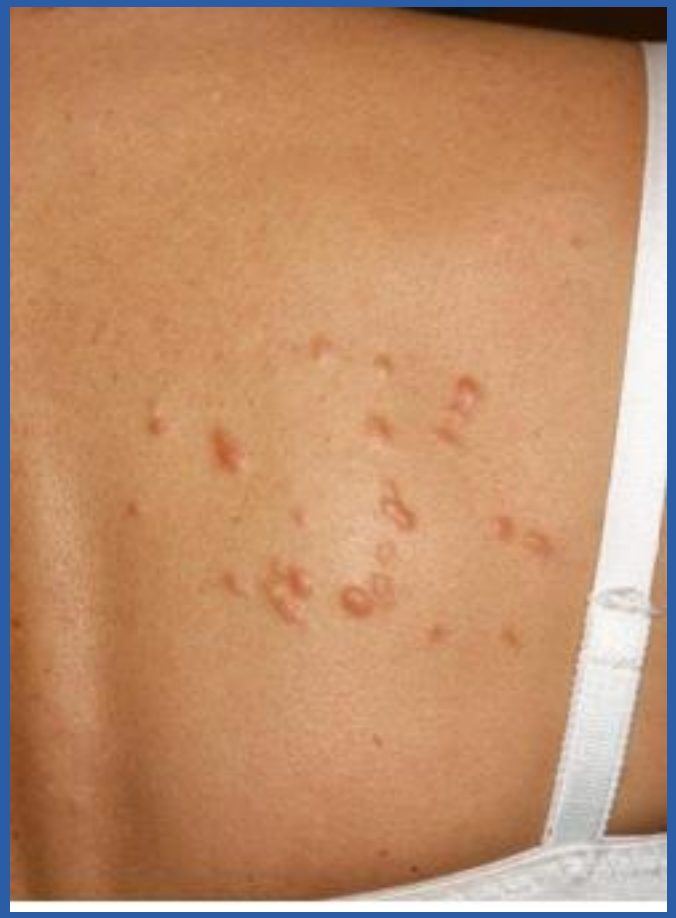
von Hippel-Lindau Disease

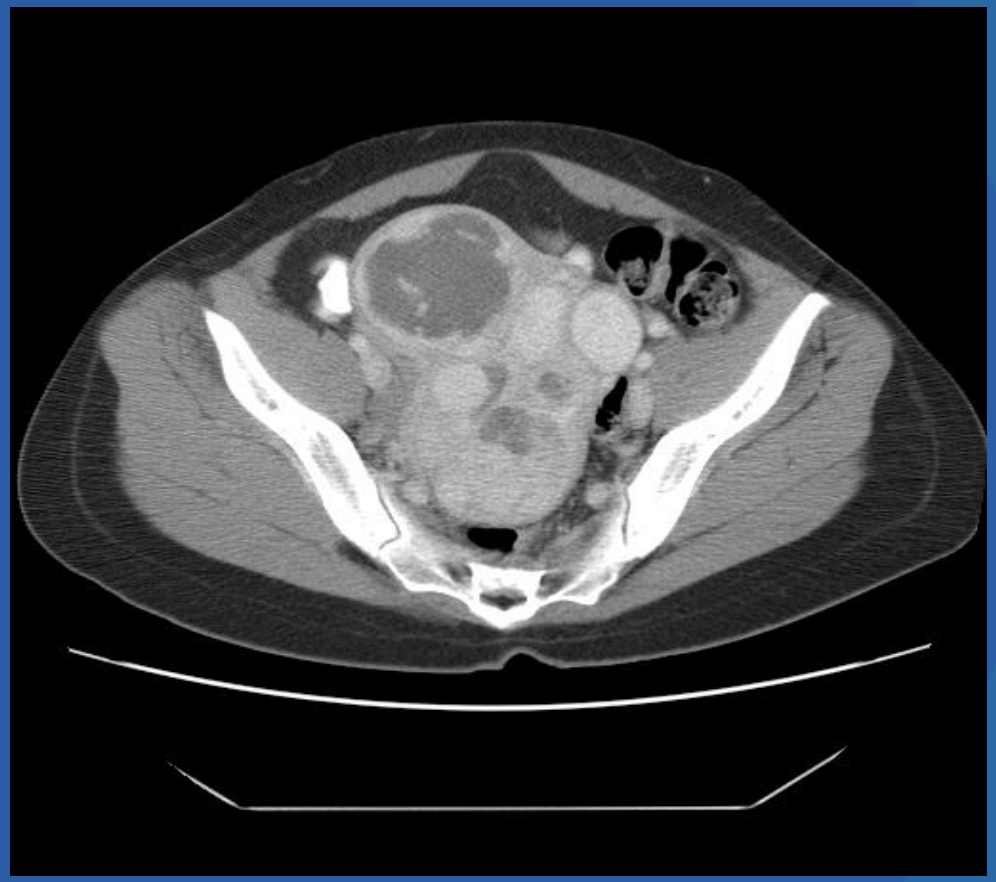




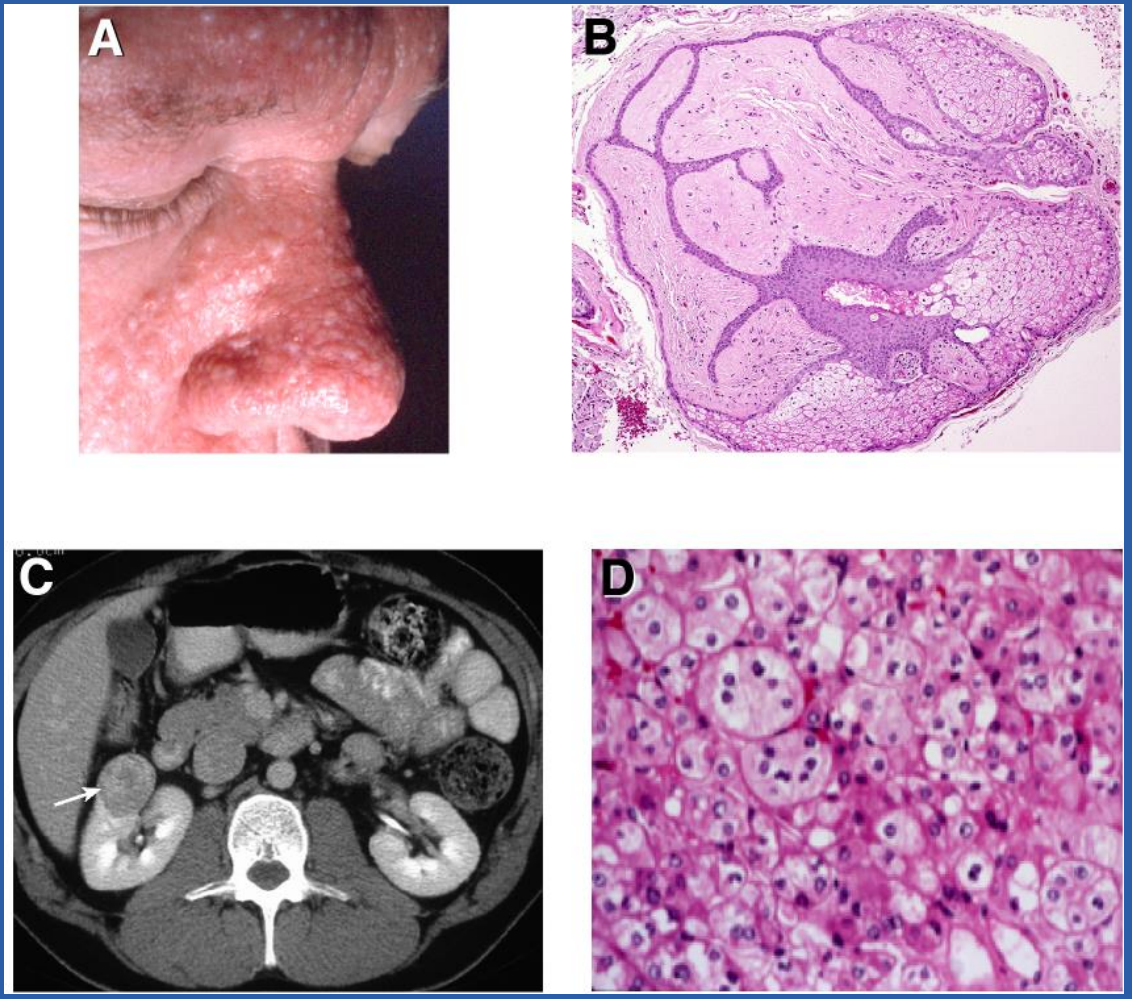
Cystadenomas of the broad ligament
Cystadenomas of the epididymis

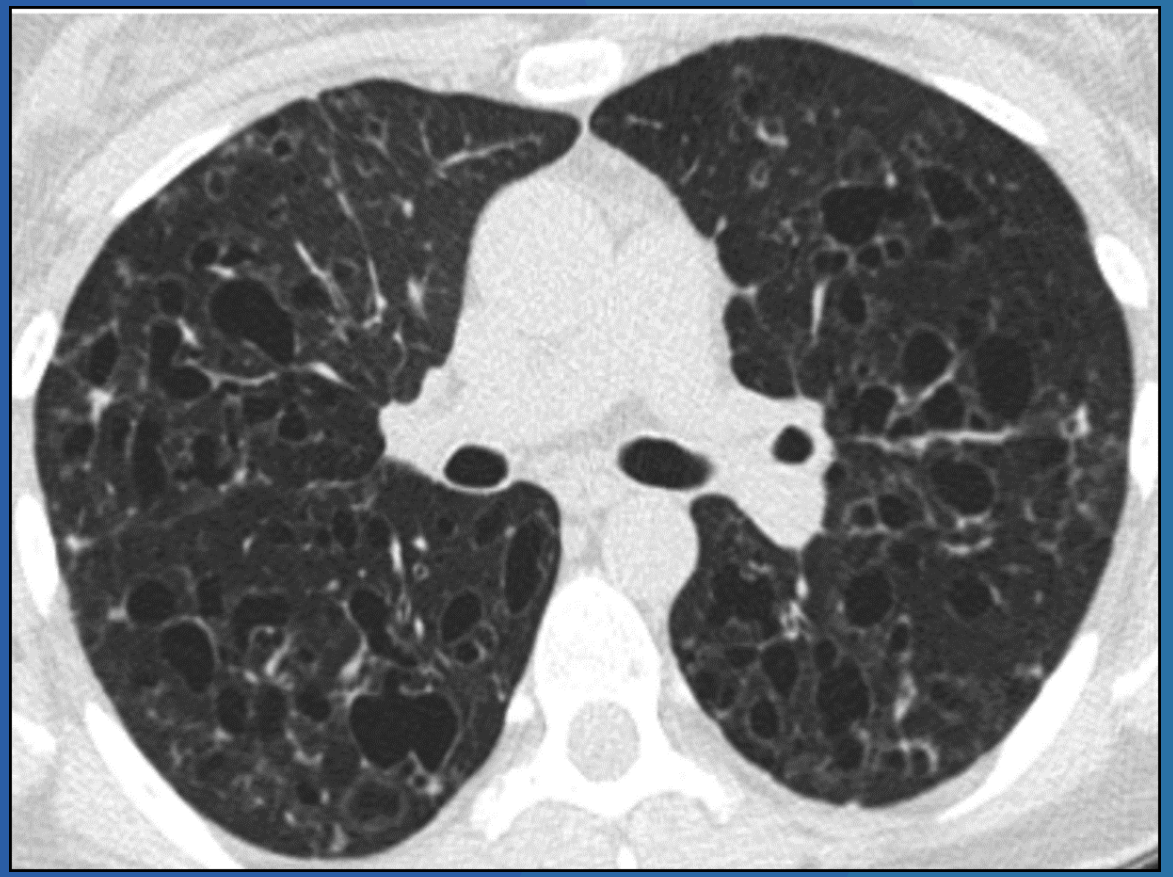
Hereditary Leiomyomatosis and Renal Cell Carcinoma





Birt Hogg Dubé

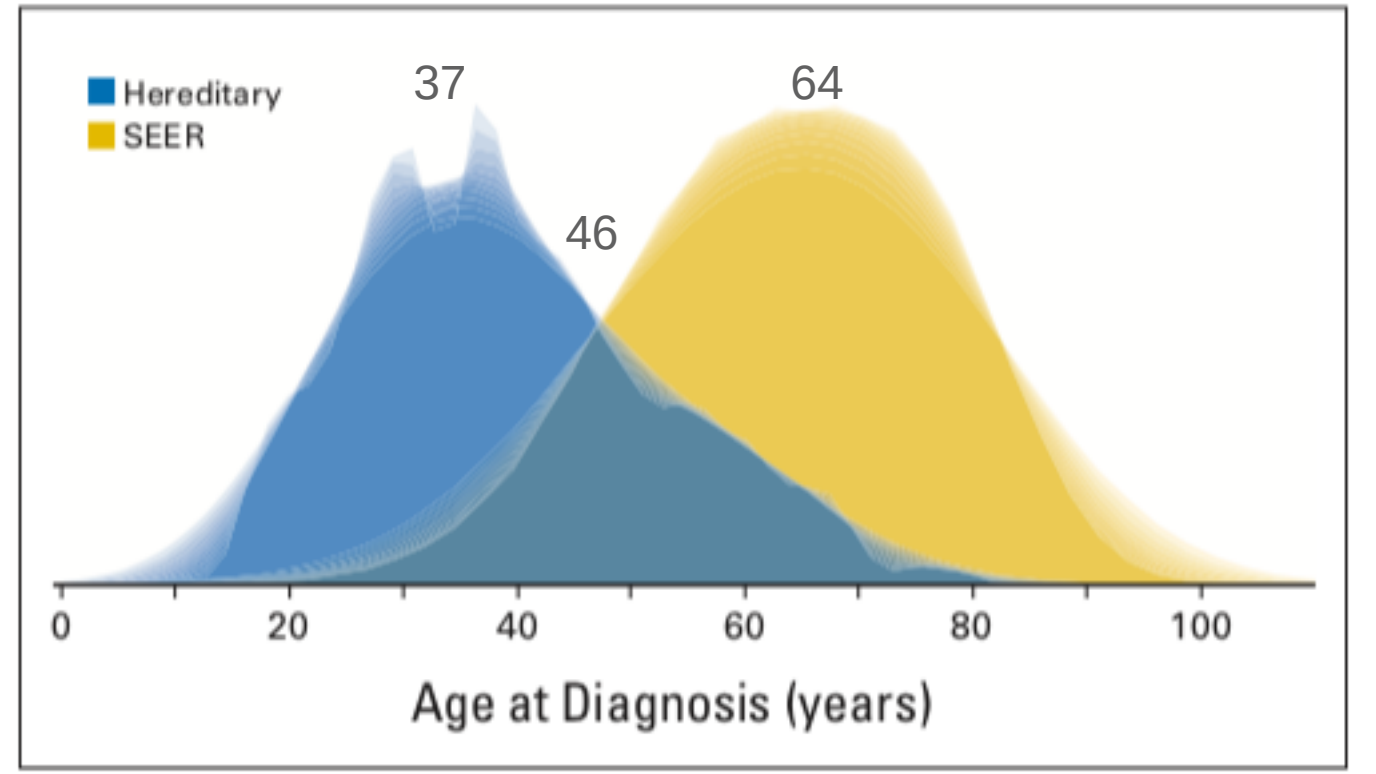




Kidney + other malignancies

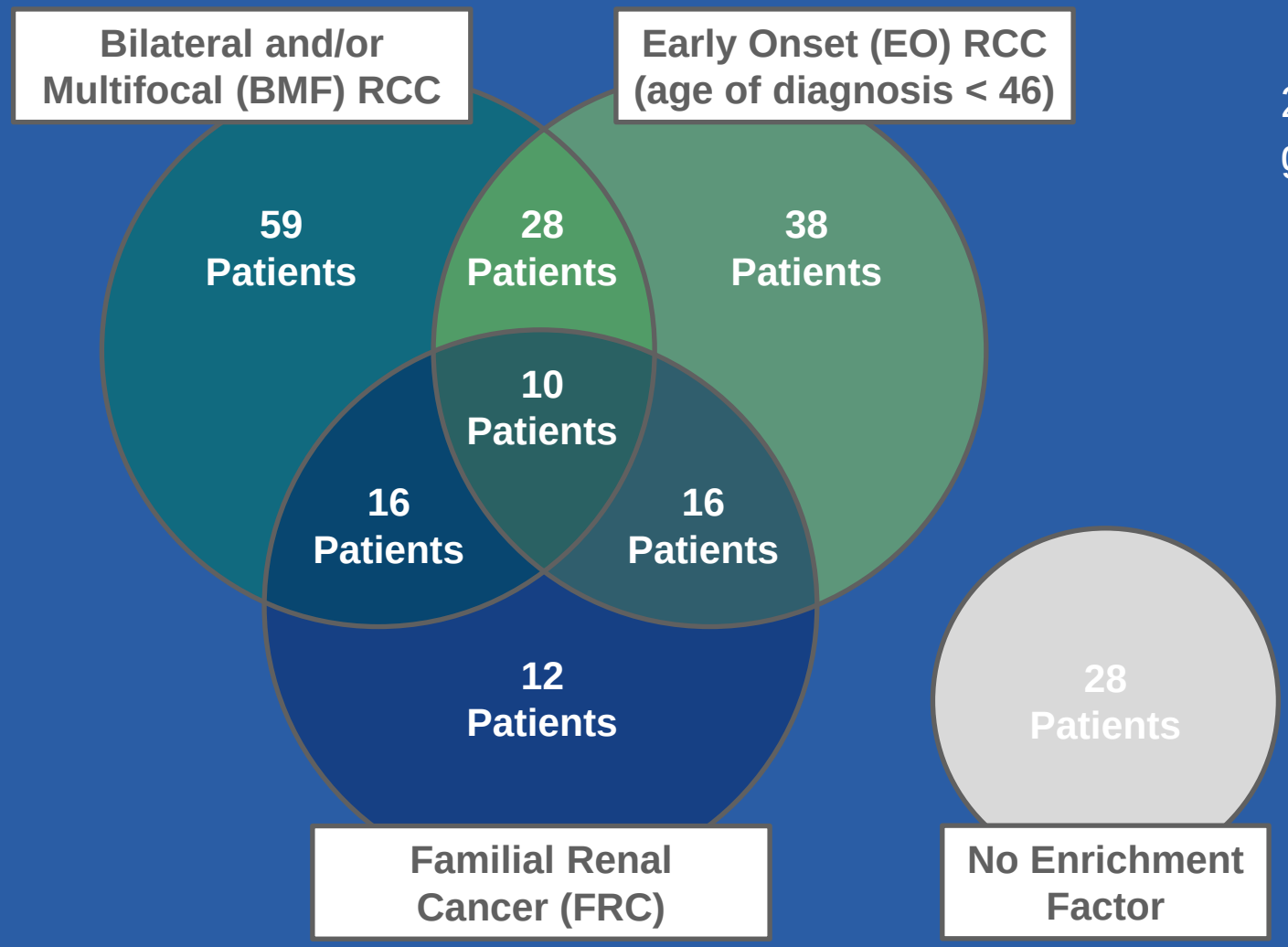
- VHL- pancreas, CNS
- MITF – melanoma
- BAP1 – melanoma, mesothelioma
- Cowden's/PTEN- breast, endometrial, thyroid, colorectal, melanoma

Defining Early-Onset Kidney Cancer: Implications for Germline and Somatic Mutation Testing and Clinical Management



Shuch B, JCO 2014

Enriched population screening

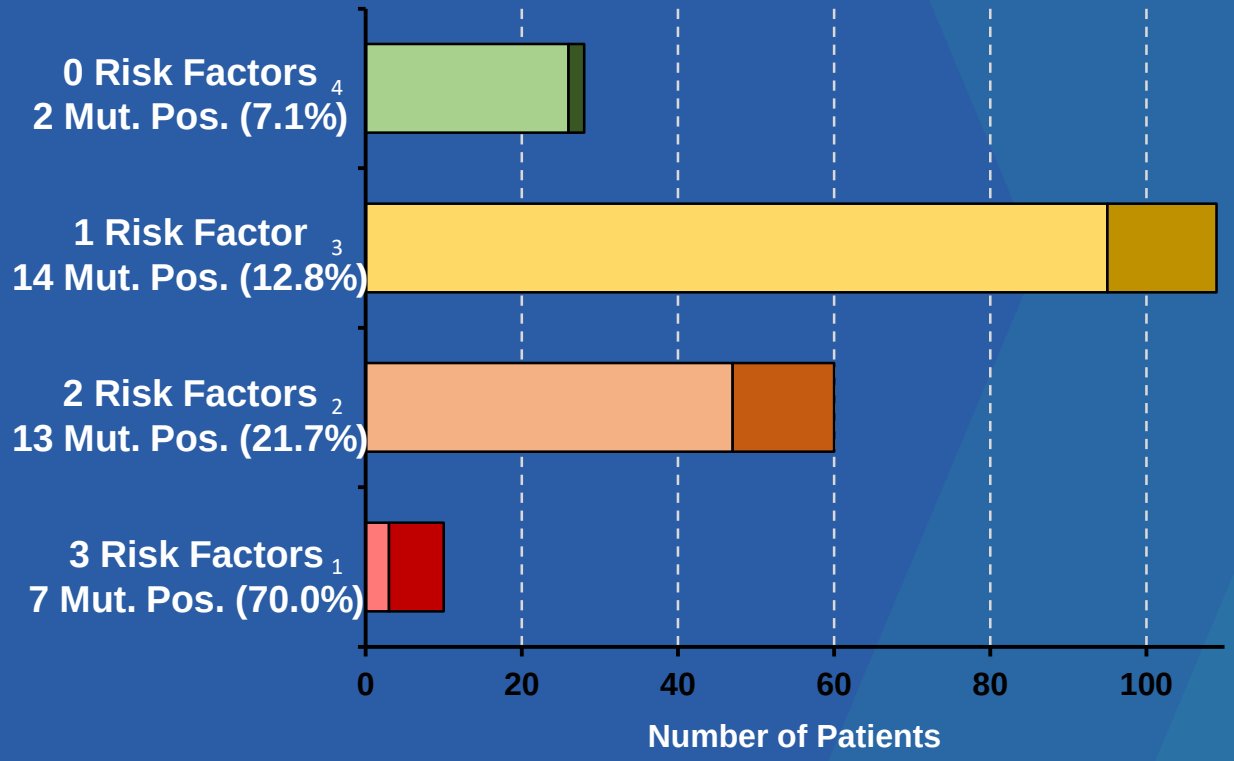


207 patients referred with no clinical or genetic diagnosis of heredity syndrome

Ball MW et al AUA 2019

Results

- Overall positive results (17%)
  - Early onset (19.5%)
  - FRC (35.2%)
  - BMF (21%)
  - 15% has VUS

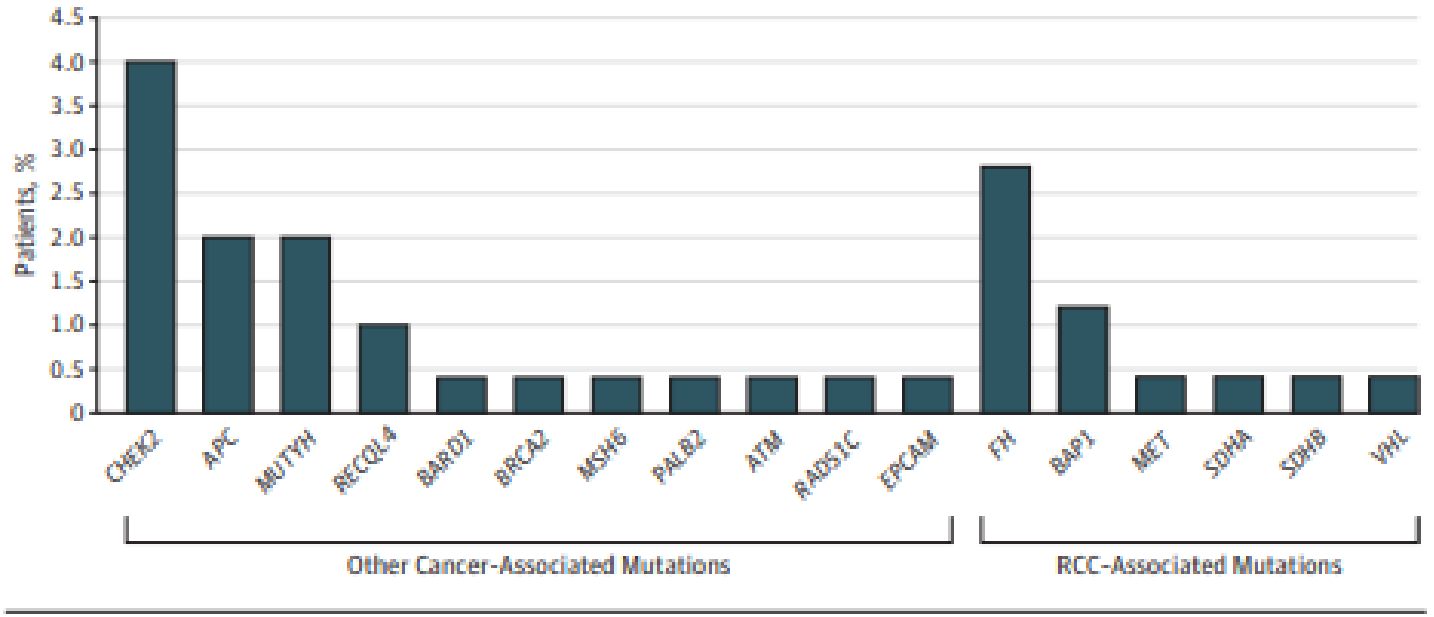


Ball MW et al AUA 2019

Advanced disease

267 unscreened patients presenting with stage III or IV RCC at MSK

Figure 1. Frequency and Distribution of Pathogenic Germline Mutations



Germline mutations were found in 41 patients (16.1%): RCC-associated mutations in 14 (5.5%) and other cancer-associated mutations in 27 (10.6%). Renal cell carcinoma (RCC)–associated germline mutations include mutations in *BAP1*, *FH*, *MET*, *SDHA*, *SDHB*, and *VHL*.

Carlo et al, JAMA Oncology

Objectives

- **Why** to perform germline testing?
- **How** to perform germline testing?

  In whom to perform germline testing?
  - Feature of genetic syndrome
  - Early onset (before age 46)
  - Family history, especially first-degree relative
  - Bilateral and/or multifocal
  - Advanced disease
  - Rare histology

Conclusions

- Clinicians treating kidney cancer will see hereditary syndrome patients (whether you know it or not)
- Early onset, bilateral/multifocal disease, family history should be triggers for genetic counseling.
- Also consider: rare histology, other malignancies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