Identification of VHL Kidney Cancer Gene
Molecular Diagnosis, Oxygen Sensing, Precision Therapy

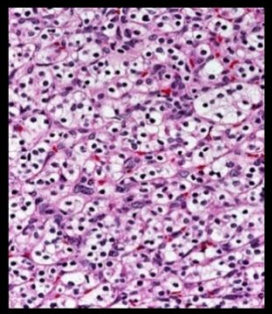
W. Marston Linehan, M.D.

Chief, Urologic Oncology Branch

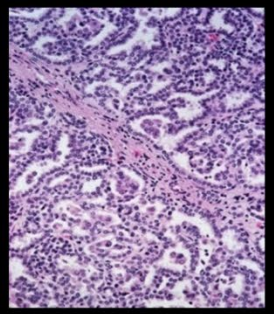
National Cancer Institute

National Institutes of Health

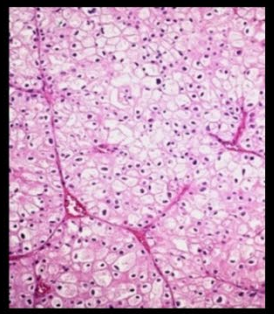
Renal Cell Carcinoma



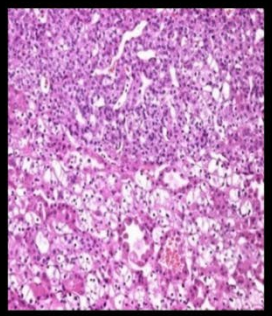
Clear Cell
VHL,TCEB1,BAP1



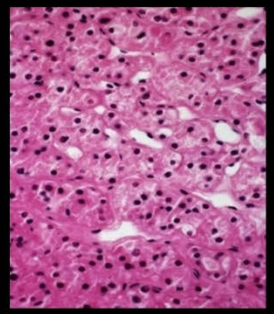
Papillary Type 1
MET



Chromophobe

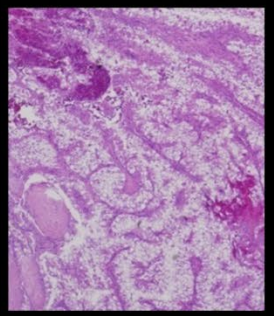


Hybrid

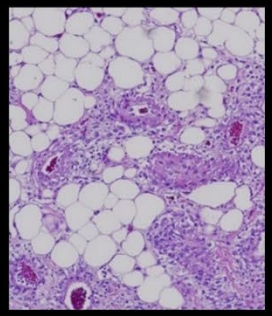


Oncocytoma

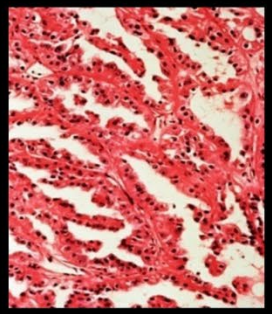
FLCN



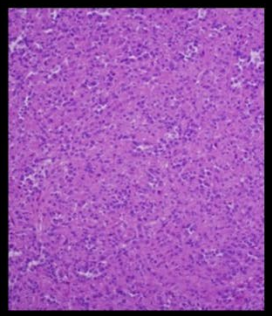
Papillary Epitheloid
TFE3, TFEB, MITF



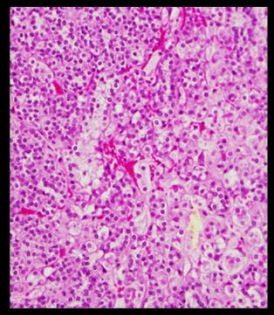
Angiomyolipoma
TSC1, TSC2



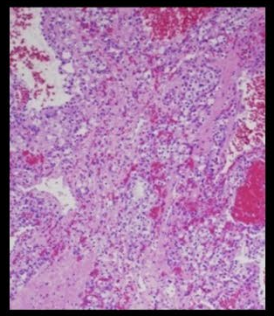
Papillary Type 2
Fumarate Hydratase (FH)



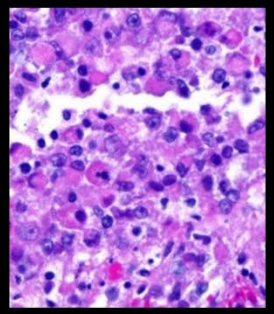
Eosinophilic
SDHB, SDHC, SDHD



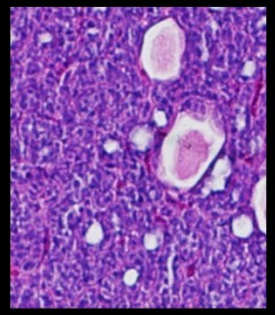
Tubular Eosinophilic
IDH2



Clear/Chromophobe
PTEN



Medullary
SMARCB1



MEST
CDC73

Cancer Discovery 9:2019

Inherited Forms of Renal Carcinoma

Histology	Syndrome	Affected	Families
Clear Cell	VHL	1148	443
	Chr 3 Trans	11	5
	BAP1	16	9
Papillary	HPRC	60	16
	HLRCC	715	338
	MITF	2	1
Chromophobe	BHD	702	308
	TSC	13	13
	Cowden	24	24
Oncocytic	SDHRCC	21	18
	FRO	49	11
	FRC	220	167
		3006	1416

Described 8 Novel Diseases at CCRH

Year	Gene	Disease
1994	*MET*	Hereditary Papillary Renal Cell Carcinoma
1995	*FH*	Hereditary Leiomyoma and Renal Cell Carcinoma
1996	*TFE3*	TFE3 Renal Cell Carcinoma
1998	*TBD*	Familial Renal Oncocytoma
1999	*FLCN*	Birt-Hogg-Dube Familial Renal Cell Carcinoma
2012	*SDHC*	SDHC Renal Cell Carcinoma
2013	*BAP1*	BAP1 Familial Renal Cell Carcinoma
2021	*IDH2*	IDH2 Renal Cell Carcinoma

Discovered 9 Disease Genes at Clinical Center Research Hospital

Year	Gene	Disease
1993	*VHL**	von Hippel-Lindau
		Clear Cell Renal Cell Carcinoma
		Chuvash Polycythemia
1995	*TCEB1**	Clear Papillary Renal Cell Carcinoma
1996	*TFE3*	TFE3 Renal Cell Carcinoma
1997	*MET*	Hereditary Papillary Renal Cell Carcinoma
		Type 1 Papillary Renal Cell Carcinoma
2002	*FLCN**	Birt-Hogg-Dube
2003	*FH*	Hereditary Leiomyoma and Renal Cell Carcinoma
2012	*SDHC*	SDHC Renal Cell Carcinoma
2013	*BAP1*	BAP1 Familial Renal Cell Carcinoma
2021	*IDH2*	IDH2 Renal Cell Carcinoma

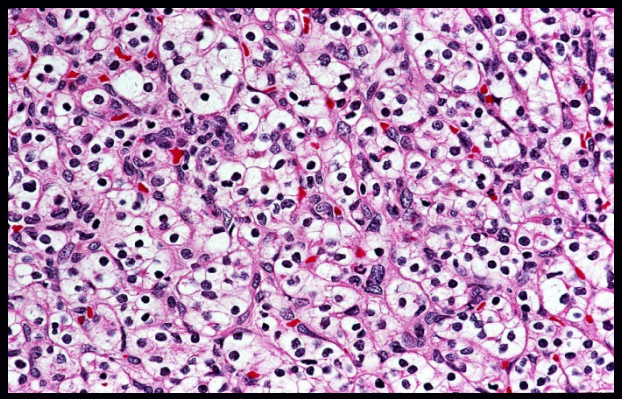
***novel gene**

Nature
Vol. 327, No. 6124, pp 721-727, 25 June 1987

Loss of alleles of loci on the short arm of chromosome 3 in renal cell carcinoma

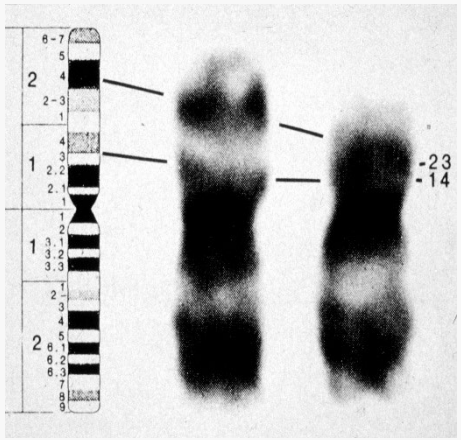
B. Zbar*, H. Brauch*, C. Talmadge*, & W. M. Linehan†

*Laboratory of Immunobiology, National Cancer Institute- Frederick Cancer Research Facility, Frederick Maryland 21701, USA
†Surgery Branch, National Cancer Institute, Bethesda, Maryland 20892, USA



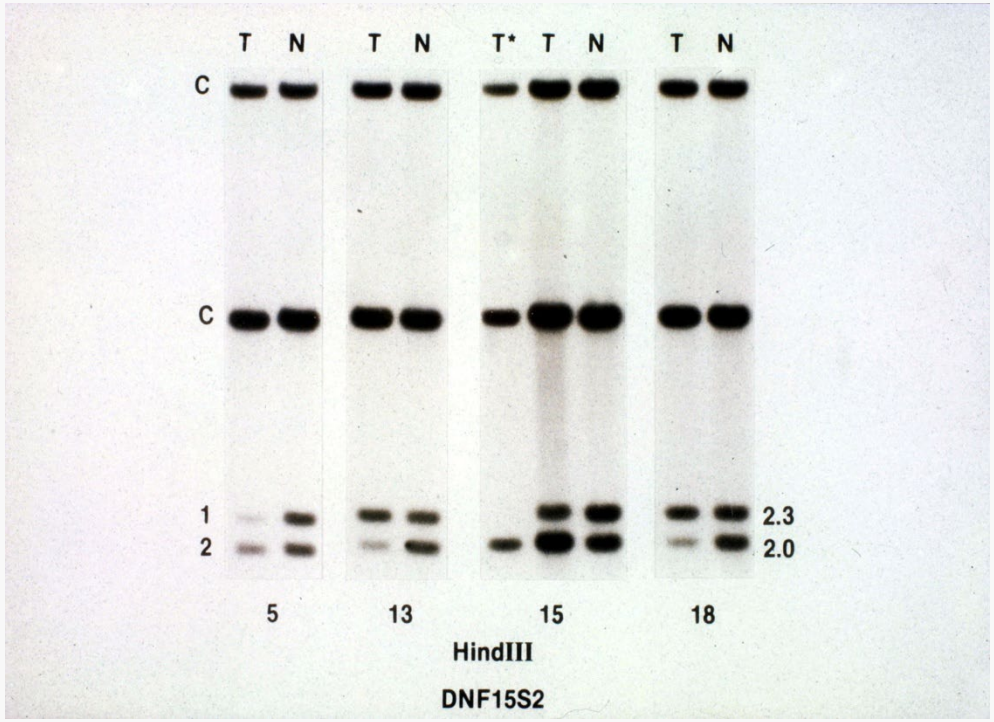
ccRCC

3p-Deletion



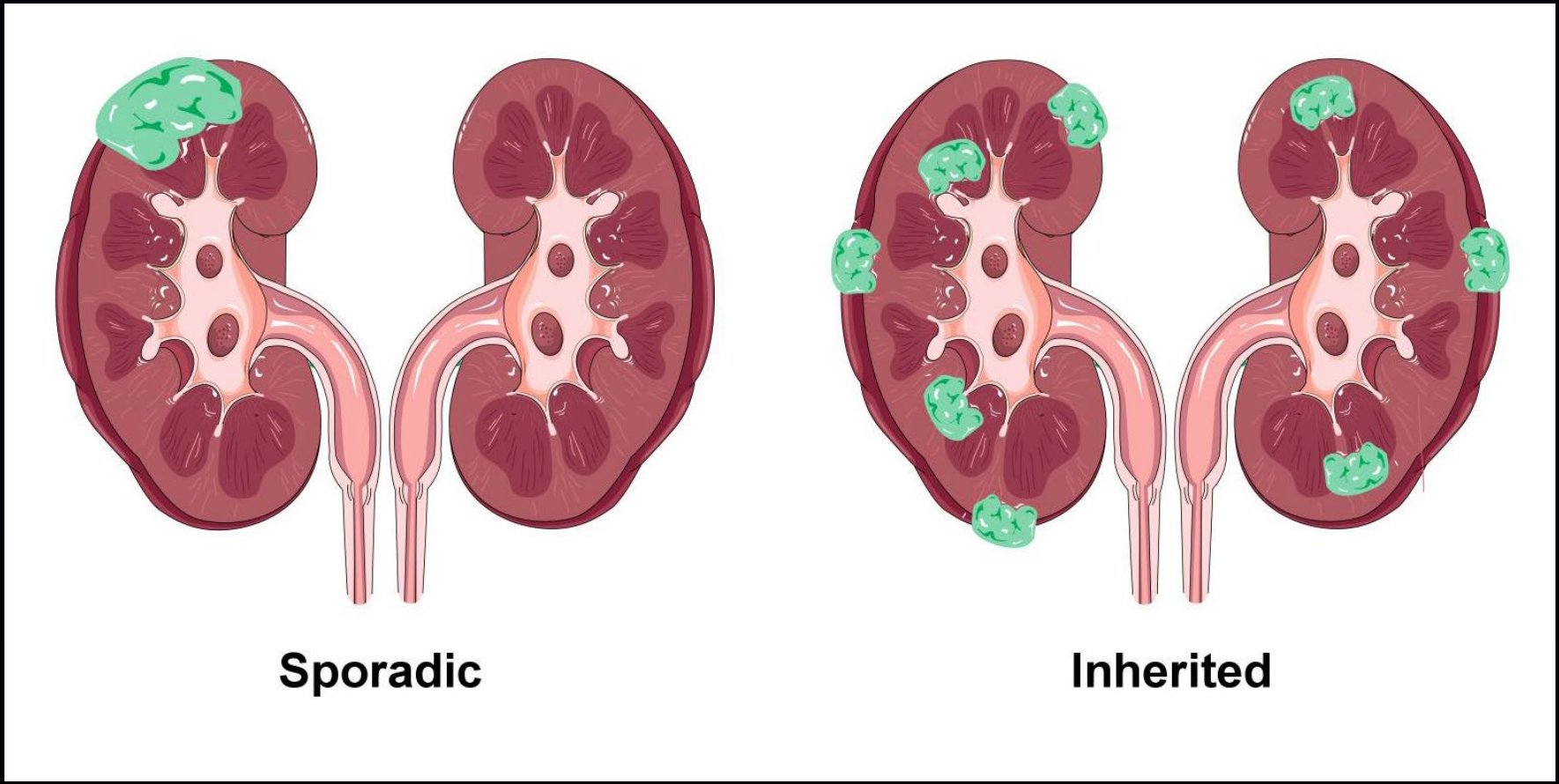
Chromosome 3

LOH

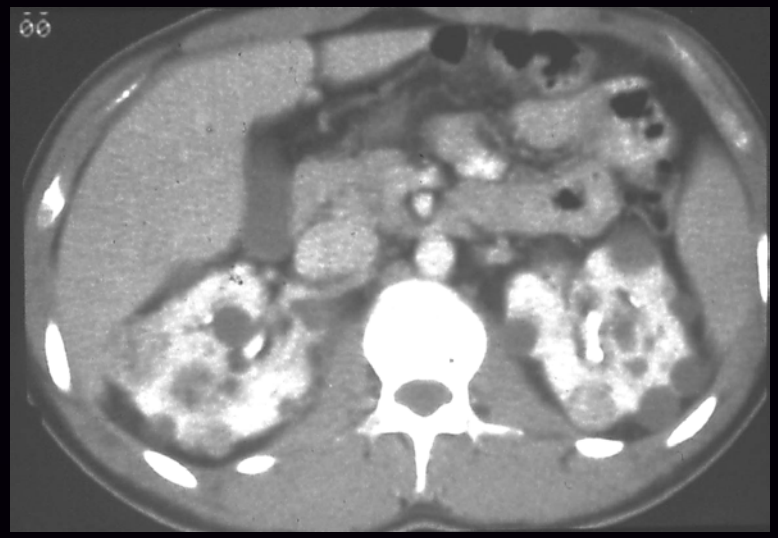


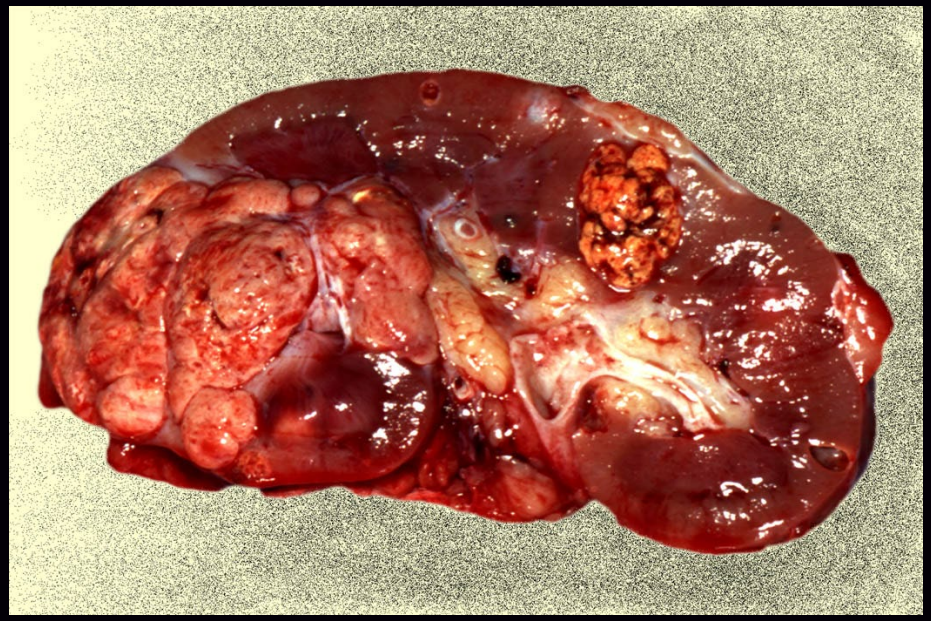
Locus DNF15S2

Clear Cell Renal Carcinoma von Hippel-Lindau (VHL)



VHL: Renal Cell Carcinoma

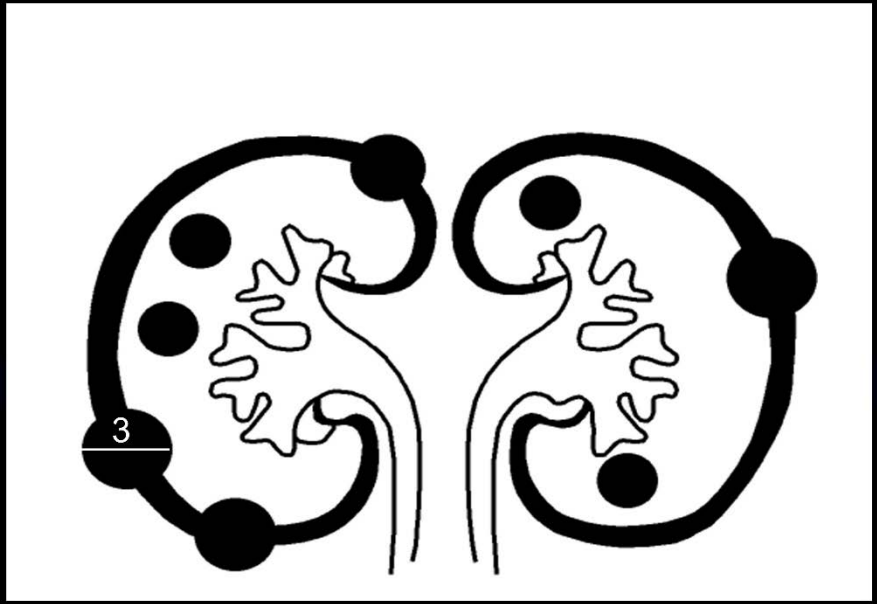




1151 RCC Procedures

<u>810 RCC Procedures at CCRH</u>

Surgical Management of VHL-Associated Renal Carcinoma

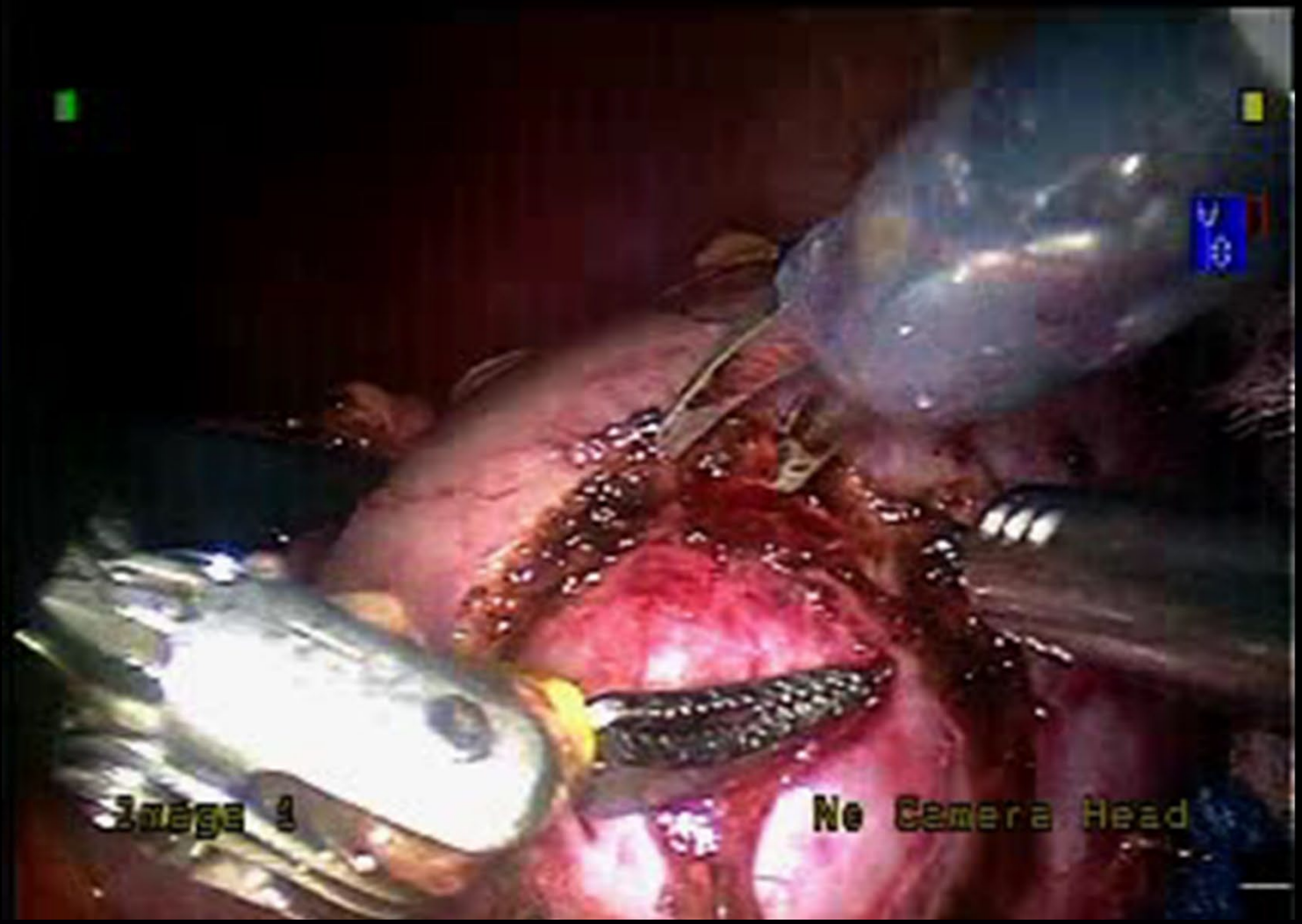


“3 cm rule”

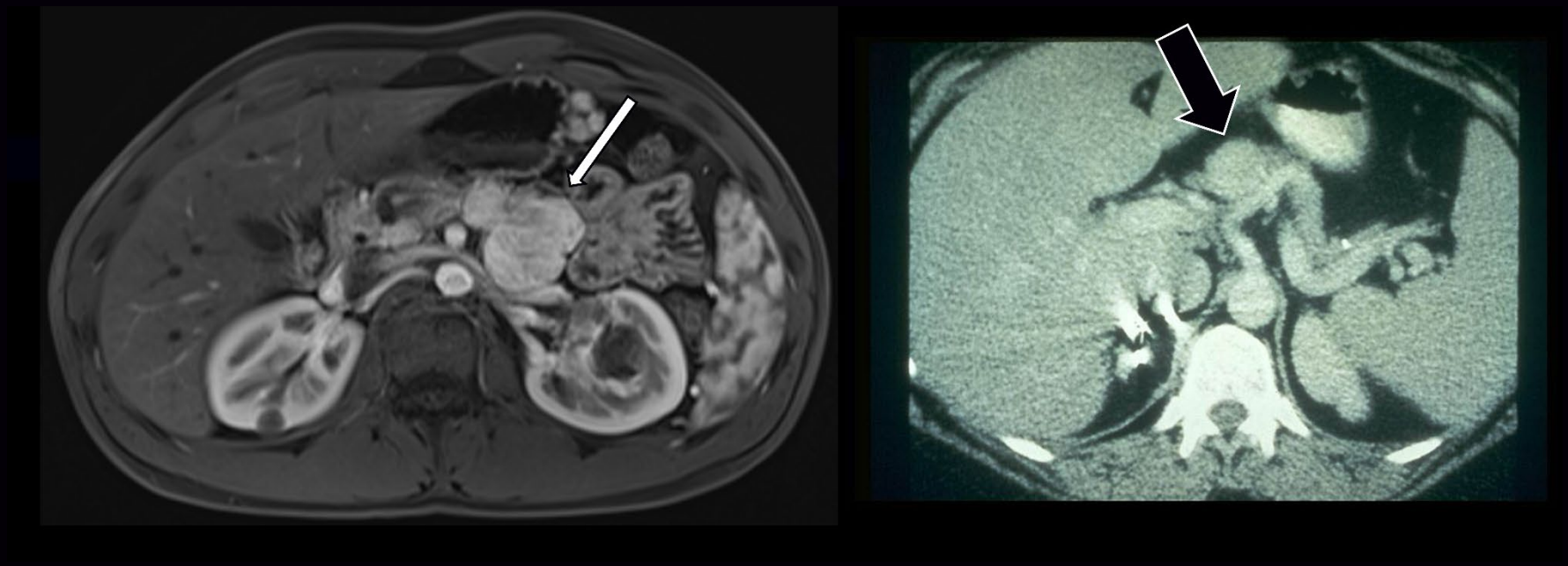
Delay surgery until diameter of largest renal tumor = 3 cm

Surgery = nephron sparing enucleation

Robotic Assisted Partial Nephrectomy

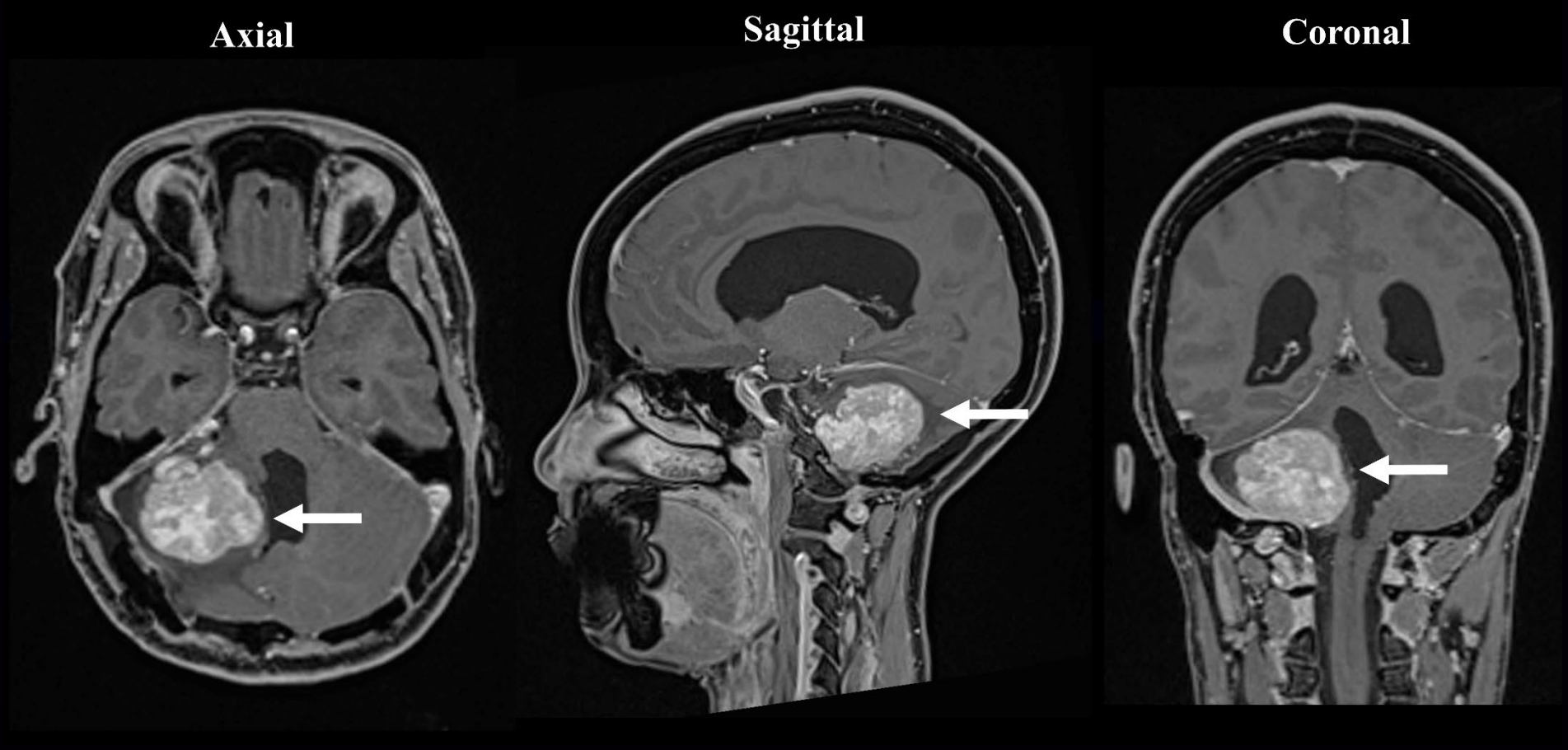


VHL Pancreatic Neuroendocrine Cancer



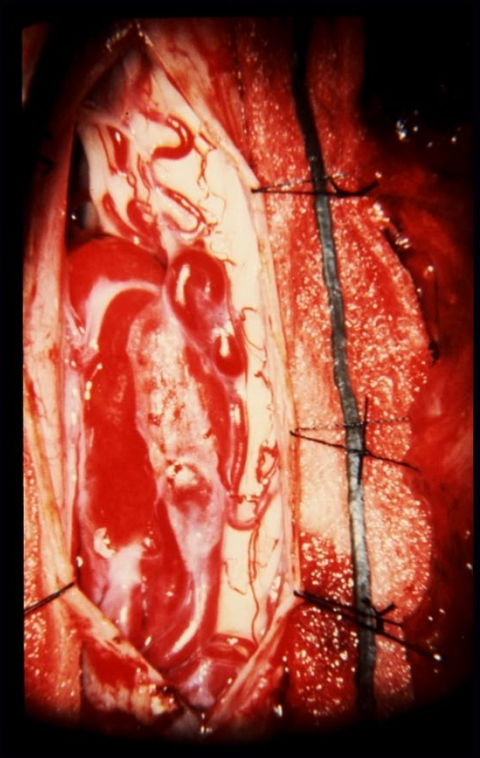
Pancreatic Neuroendocrine Cancer (PNET)
115 Surgical Procedures at CCRH

VHL Cerebellar Hemangioblastoma



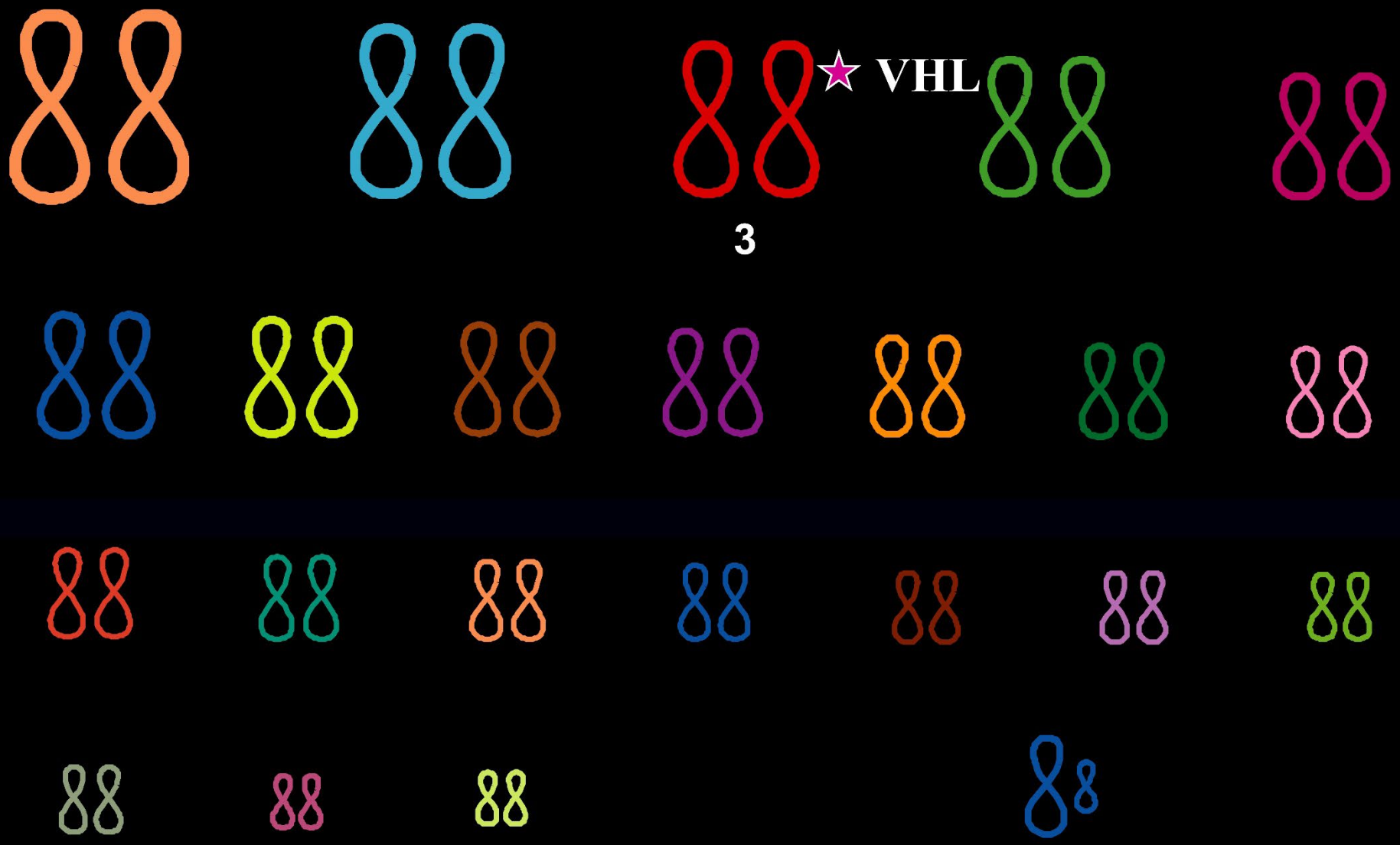
Brain or Spinal Hemangioblastoma
1250 Surgical Procedures at CCRH

VHL Spinal Hemangioblastoma



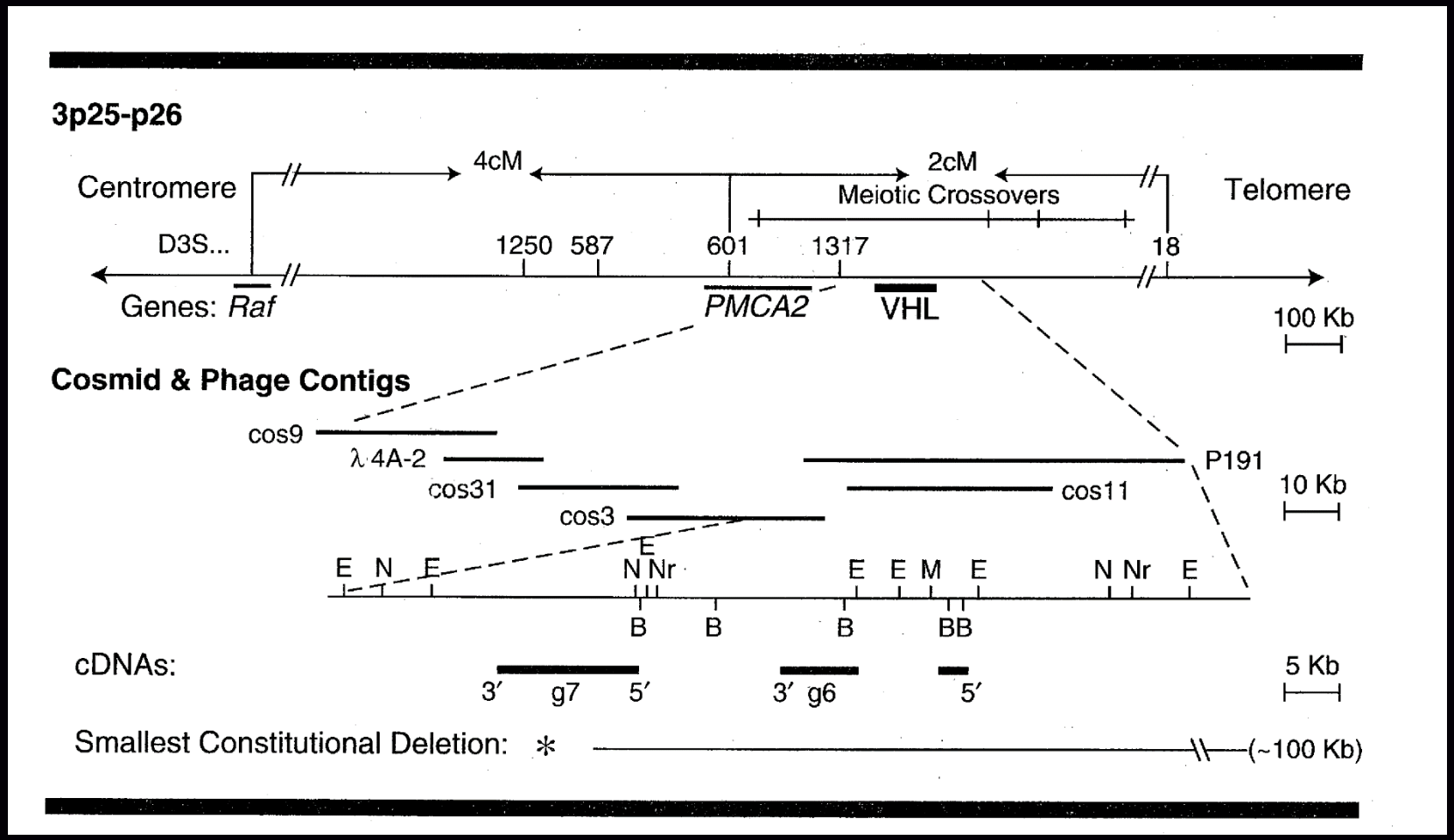
Brain or Spinal Hemangioblastoma
1250 Surgical Procedures at CCRH

VHL: Retinal Angioma



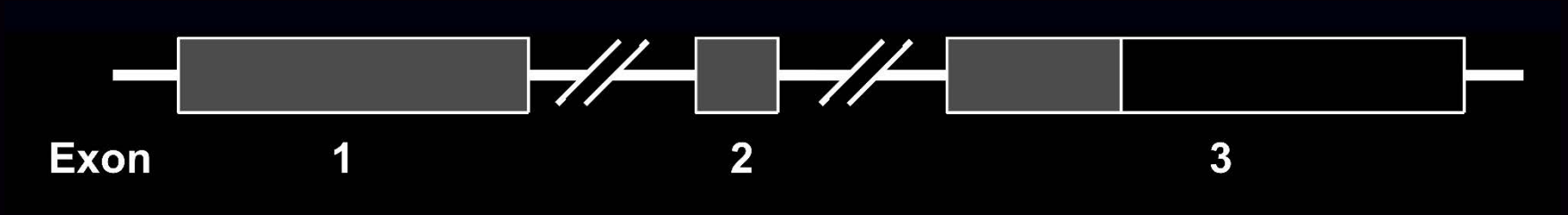
VHL Gene: Clear Cell RCC

VHL Gene Localization Map



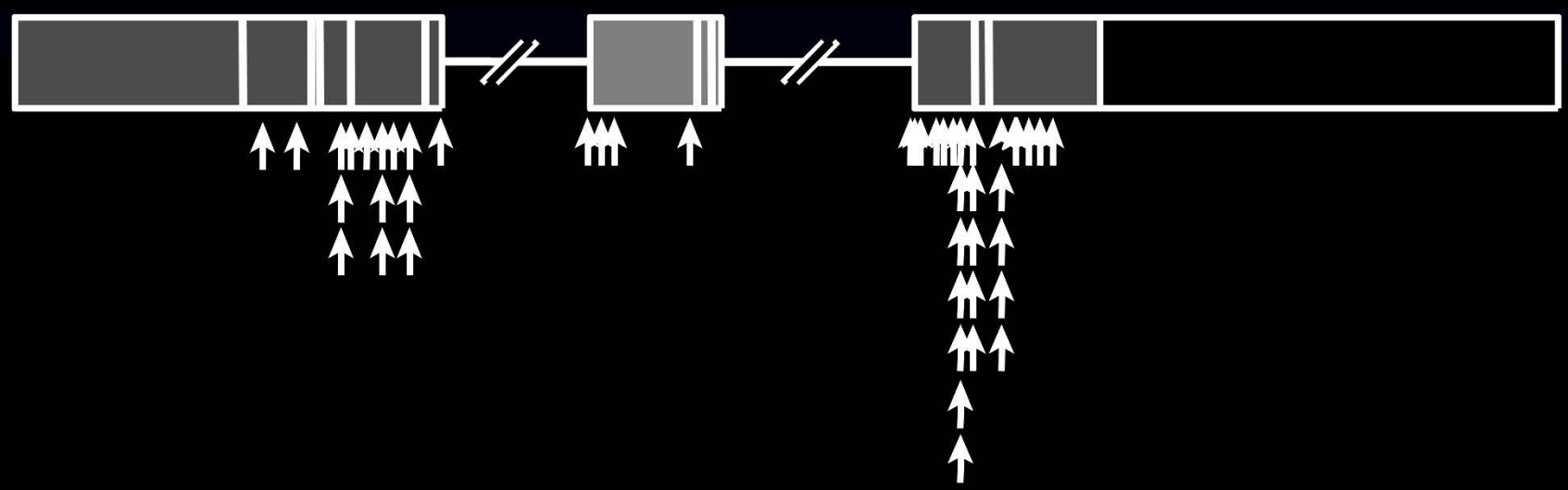
Science 260:1993

VHL Gene



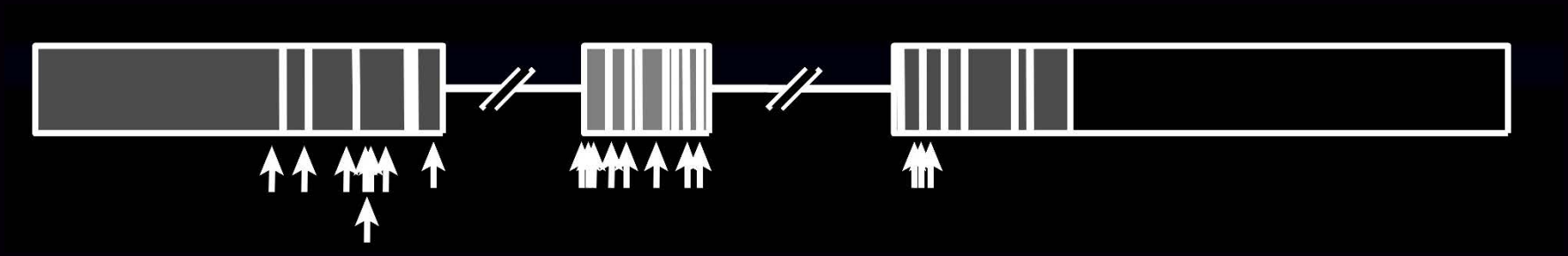
Science 260:1993

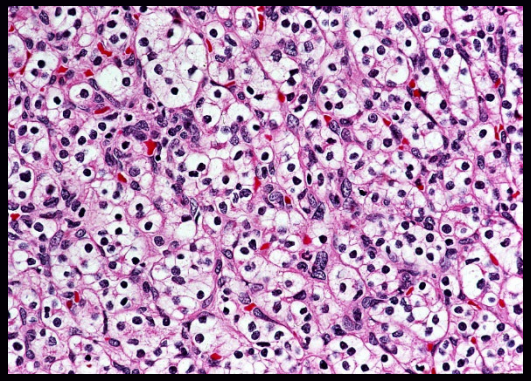
Germline *VHL* Gene Mutations 413/413 Families



Science 260:1993

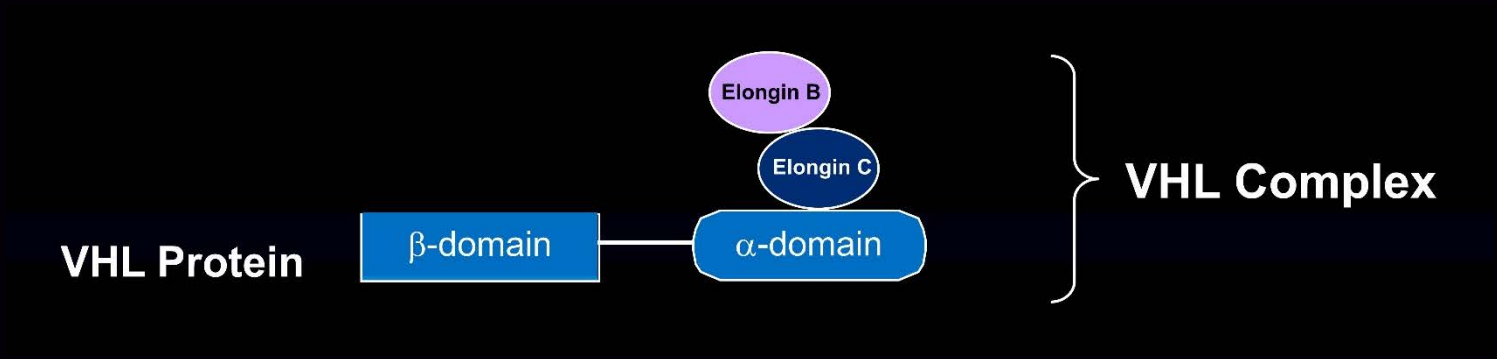
Sporadic Clear Cell RCC
VHL Gene Mutations





Science 260:1993
Nature Genetics 7:1994
Nature 469:2013
N Engl J Med 374:2016

pVHL Forms a Complex with Elongins C/B



Science 260:1995
Kaelin Science 260:1995

pVHL Regulates VEGF in a Post Transcriptional Fashion

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 10589–10594, October 1996
Biochemistry

Post-transcriptional regulation of vascular endothelial growth factor mRNA by the product of the *VHL* tumor suppressor gene

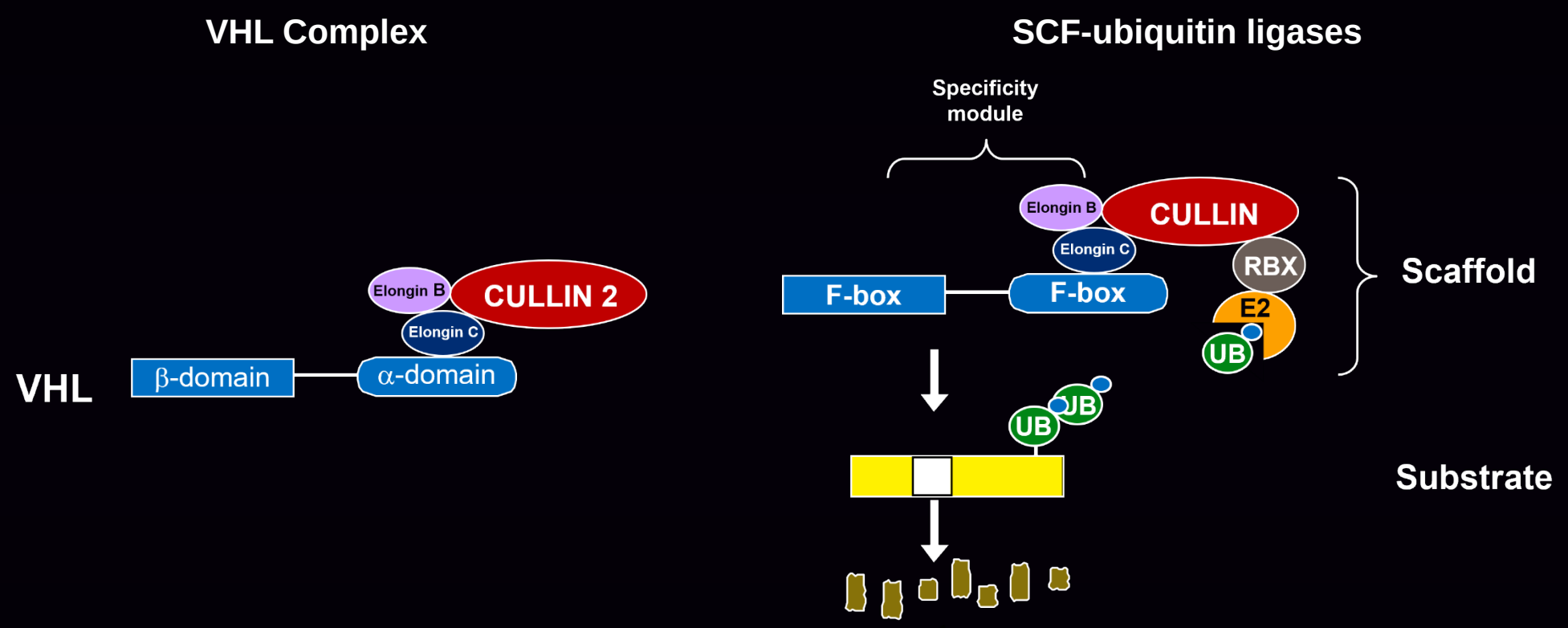
JAMES R. GNARRA*, SHUBO ZHOU*, MARSHA J. MERRILL†, JOSEPH R. WAGNER*, ANTON KRUMM‡, EFSTATHIOS PAPAVASSILIOU†, EDWARD H. OLDFIELD†, RICHARD D. KLAUSNER§, AND W. MARSTON LINEHAN*¶

*Urologic Oncology Section, Surgery Branch, and §Office of the Director, National Cancer Institute, Bethesda, MD 20892; †Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892; and ‡Fred Hutchinson Cancer Research Center, Seattle, WA 98104

Contributed by Richard D. Klausner, July 2, 1996

PNAS 93:1996

pVHL Forms a Complex with Elongins C/B and Cul-2
VHL-Ubiquitin Transferring Enzyme Complex

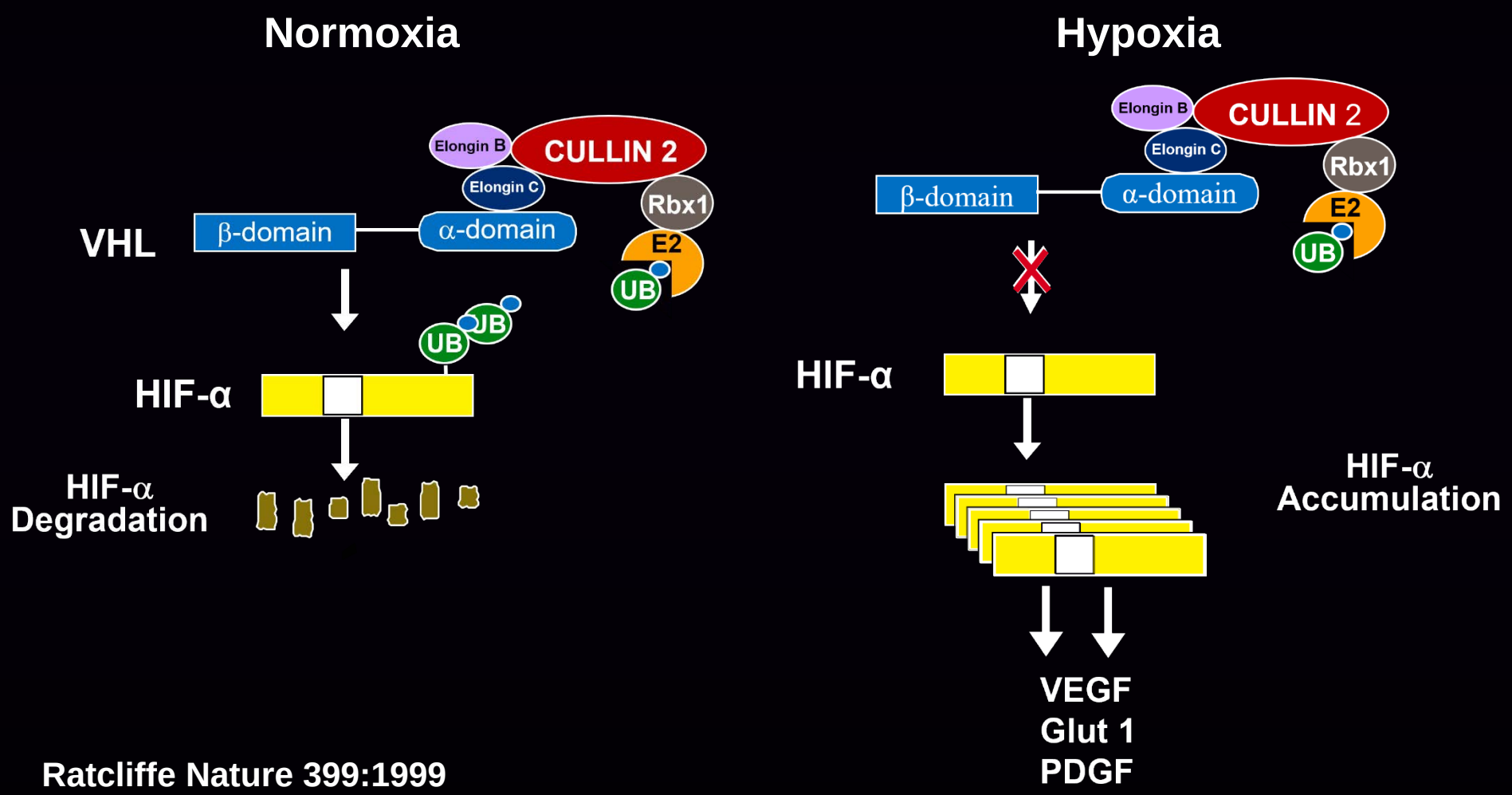


"It is possible that such a proposed degradation complex targets certain transcription factors or factors that regulate the stability of hypoxia-inducible mRNAs, such as VEGF, platelet-derived growth factor-b, and GLUT1."

Science 260:1995

PNAS 94:1997

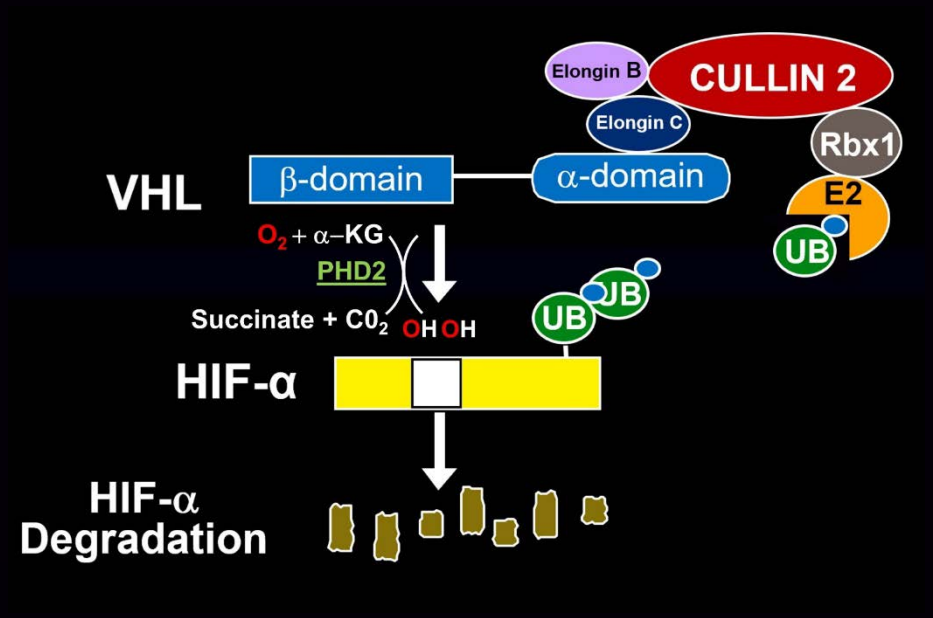
HIFα is targeted for degradation in normoxic but not hypoxic cells



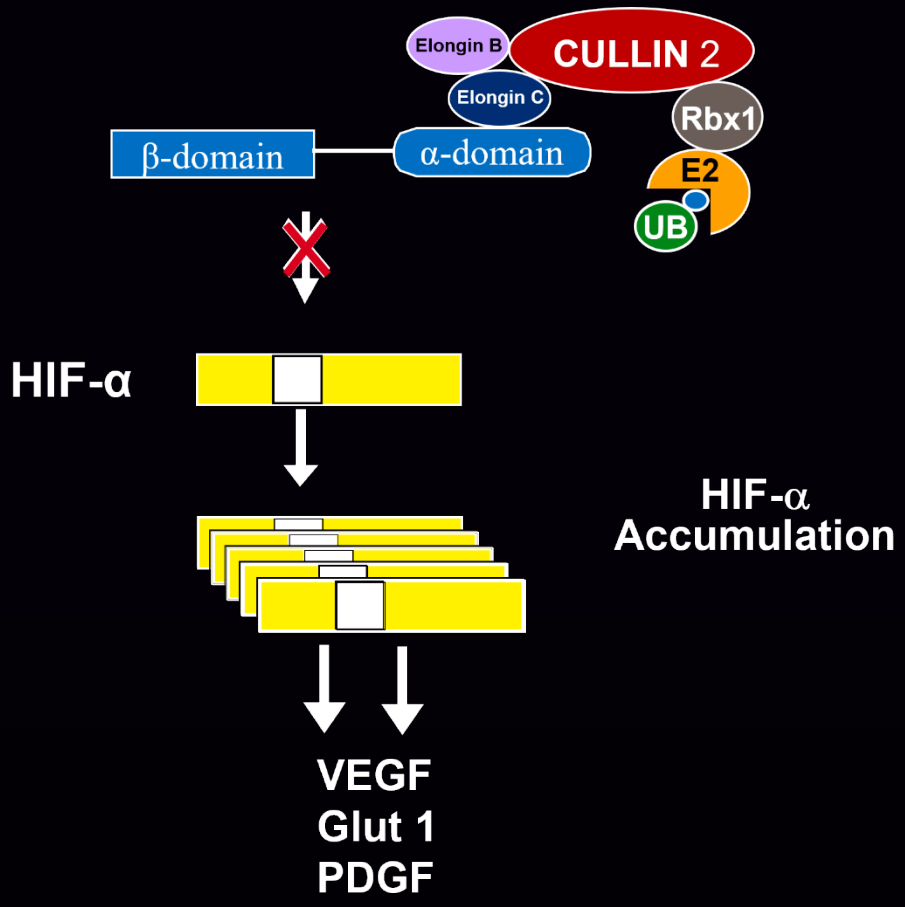
Ratcliffe Nature 399:1999

HIFα is targeted for degradation by prolyl hydroxylation

Normoxia



Hypoxia



Ratcliffe Science 292:2001
Kaelin Science 292:2001

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

2019 Nobel Prize in Physiology or Medicine

“How Cells Sense and Adapt to Oxygen Availability”

William G. Kaelin
Peter J. Ratcliffe
Gregg L. Semenza

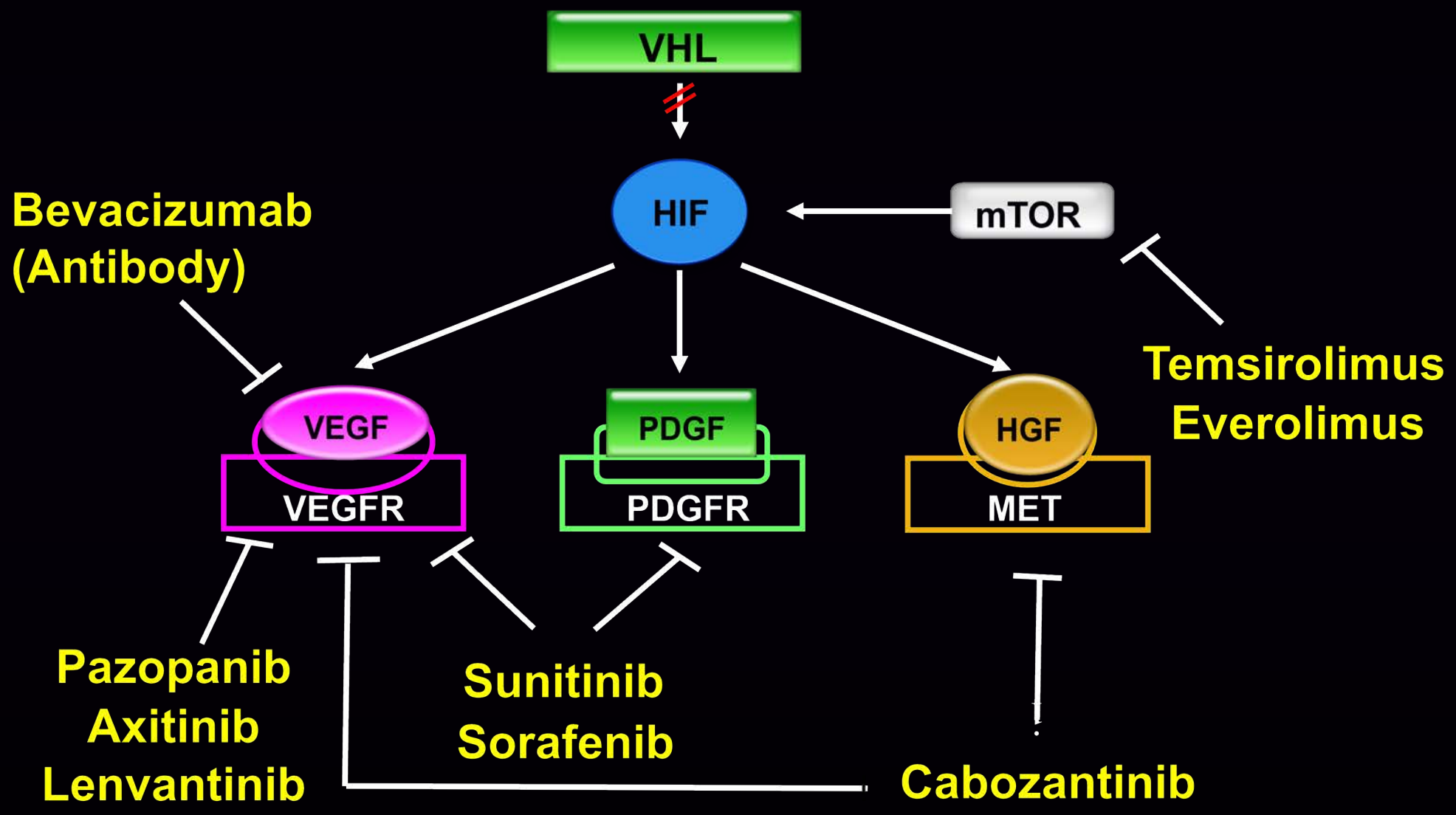
VHL/HIF Pathway

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

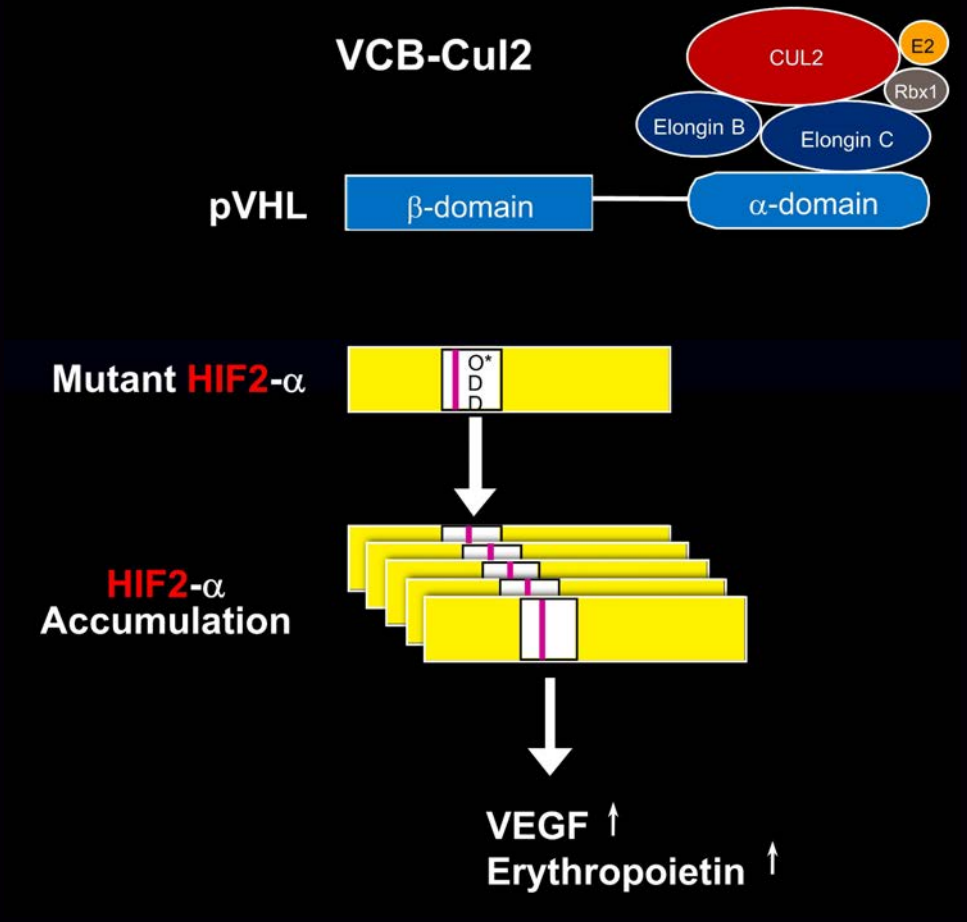
2019 Nobel Prize in Physiology or Medicine
Scientific Background

"…as well as Kaelin and his group had found that VHL associates with …..elongins B and C (Duan et al 1995…) and, in 1997, Klausner, W. Marston Linehan and colleagues showed that VHL is found in a complex with the Cul-2 protein (Pause 1997) …these observations revealed a potential link between VHL and protein degradation."

Targeting VHL/HIF in Clear Cell RCC

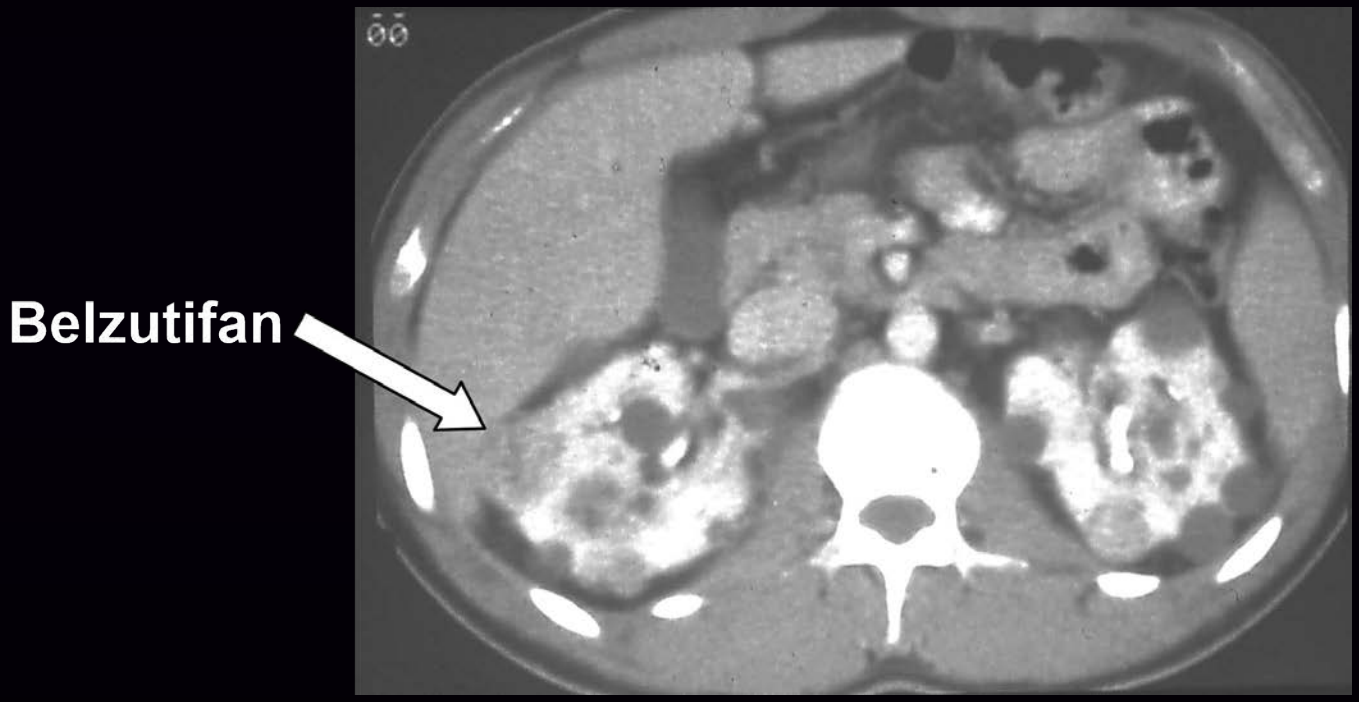


Abrogation of HIF2α degradation is sufficient for tumorigenesis



Kondo *et al*, *Cancer Cell* 1: 2002

VHL Clinical Trial* Belzutifan Targeting HIF2α in Clear Cell RCC

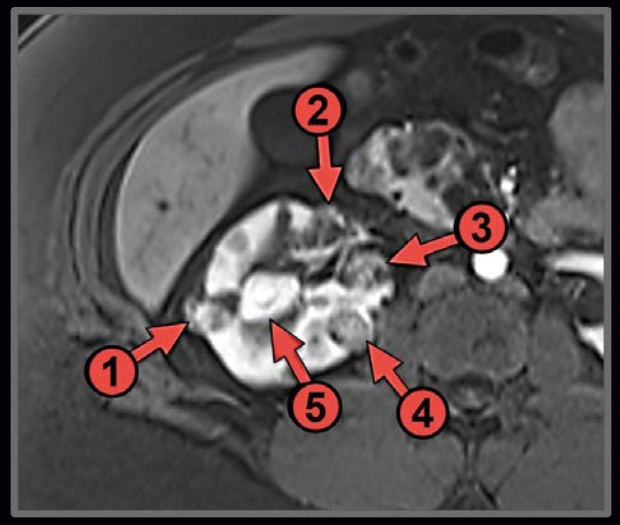


VHL Kidneys
Multifocal Renal Cell Carcinoma

NIH CCRH Lead*

VHL Renal Cell Carcinoma (N=61)

- 49.2% Objective response rate
- 98.2% Partial Response or SD
- 92% Decrease of target lesions
- 85% Remain on study
- NR Median duration of response



N Engl J Med 385:2021

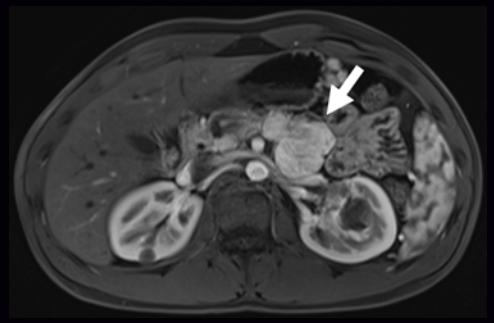
VHL CNS Hemangioblastomas (N=50)

- 30% Objective Response Rate (ORR)
- 6% Complete Response (CR)
- 24% Partial Response (PR)
- 62% Stable
- 4% Progression
- Median duration of response: NR

N Engl J Med 385:2021

Pancreatic Neuroendocrine Tumors (N=22)

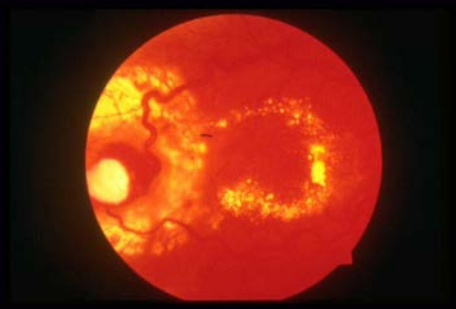
- 91% Objective Response Rate (ORR)
- 14% Complete Response (CR)
- 77% Partial Response (PR)
- 9% Stable
- NR Median duration of response



N Engl J Med 385:2021

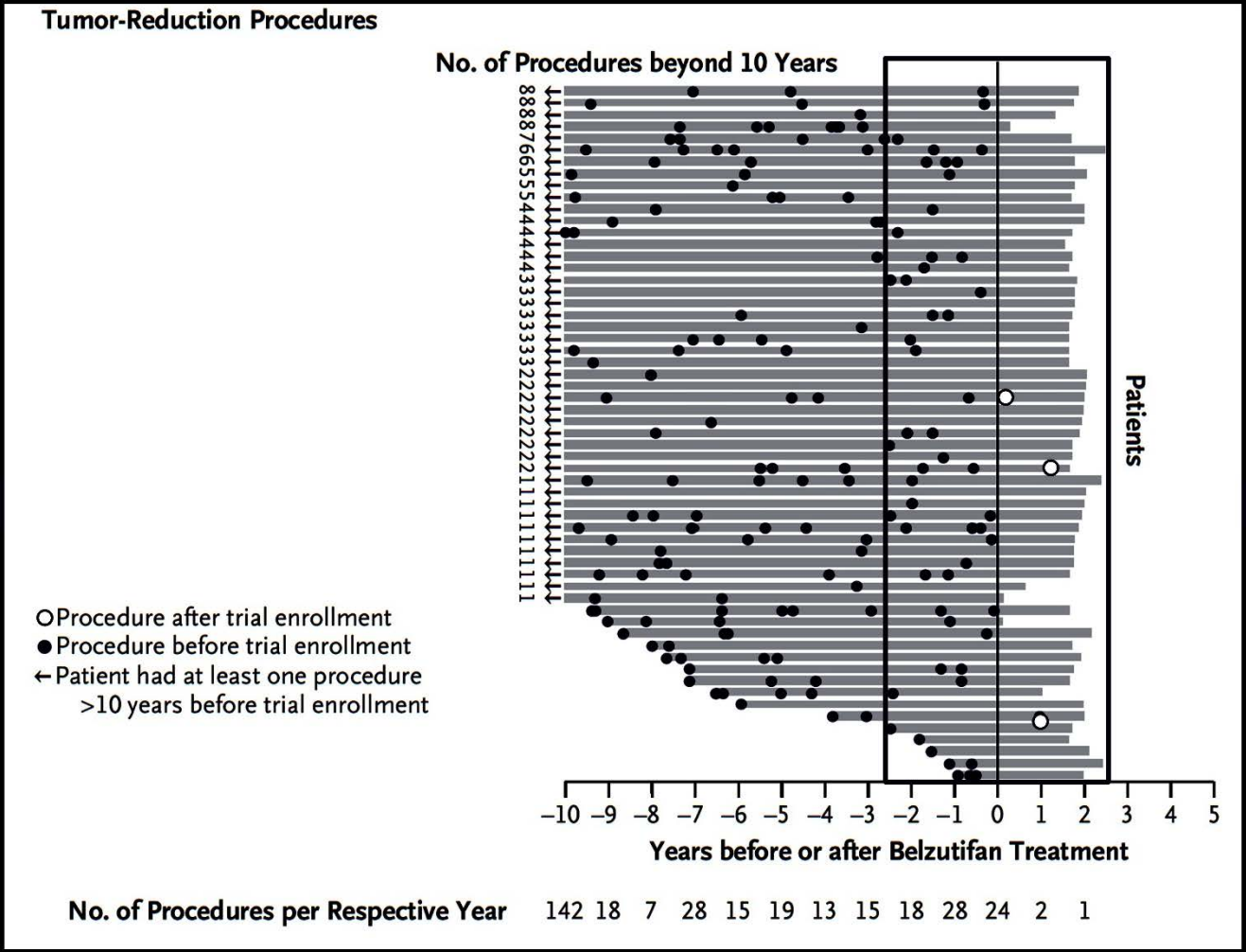
VHL Retinal Angiomas (N=16)

- 100 % Improved + Stable
- 68.8% Improved
- 31.3% Stable
- 0% Progressed
- NR Median duration of response



N Engl J Med 385:2021

Tumor Reduction Procedures



2 ½ years <u>before</u> therapy started: <u>53</u> Surgical Procedures

2 ½ years <u>after</u> therapy started: <u>3</u> Surgical Procedures

N Engl J Med 385:2021