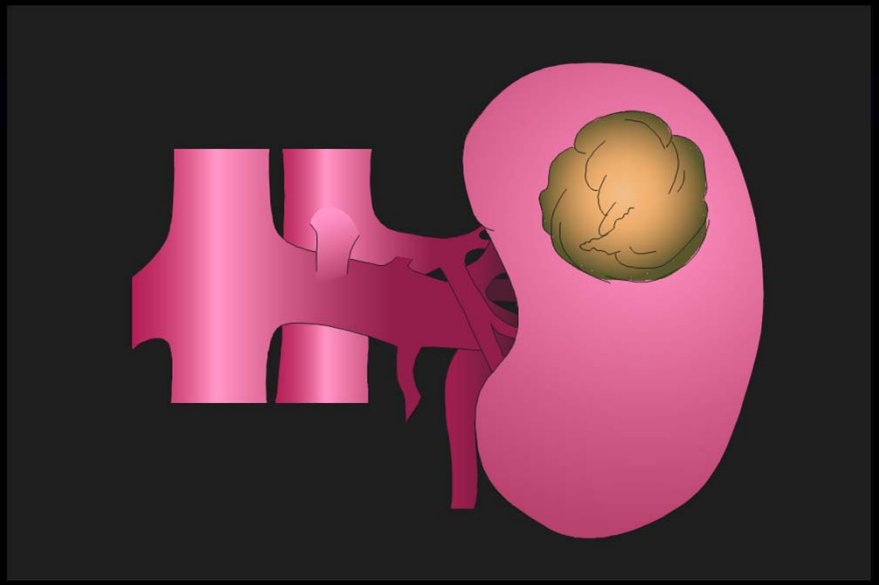
The Genetic Basis of Kidney Cancer: Disease-Specific Approaches to Therapy

W. Marston Linehan, M.D.
Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute

Stage I

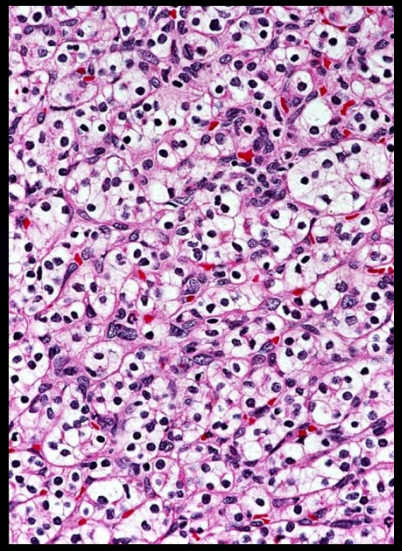
- Tumor within the renal capsule
- T1-2; N0; M0
- 95% 5 year survival



Stage IV

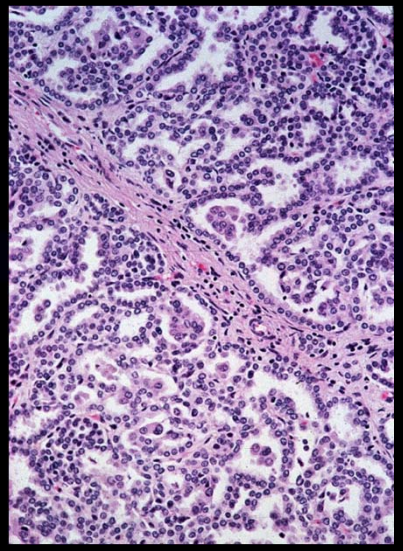
- Adjacent organs or distant metastasis
- T4; M1
- 18% 2 year survival

Human Renal Epithelial Neoplasms



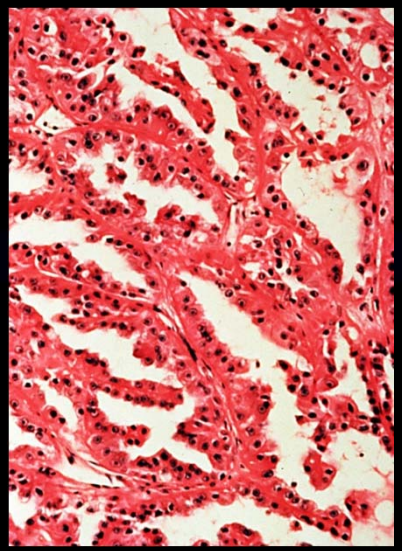
Clear Cell

75%



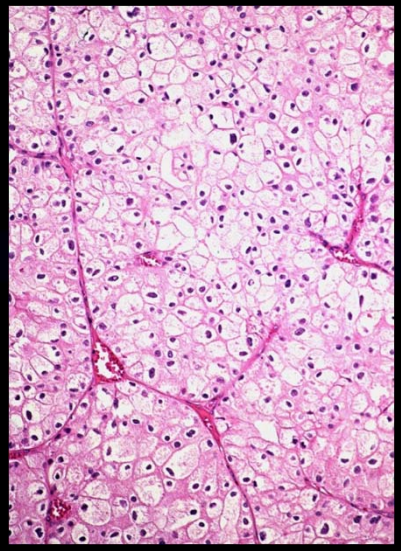
Papillary Type 1

5%



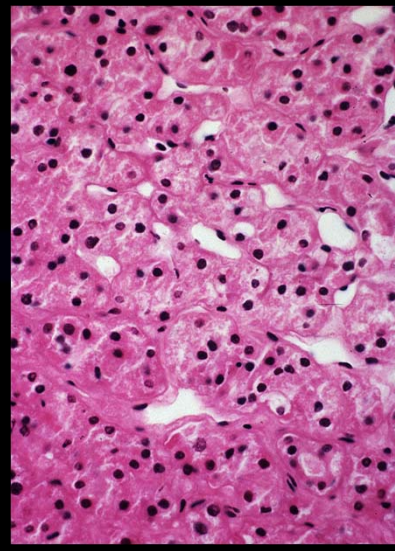
Papillary Type 2

10%



Chromophobe

5%



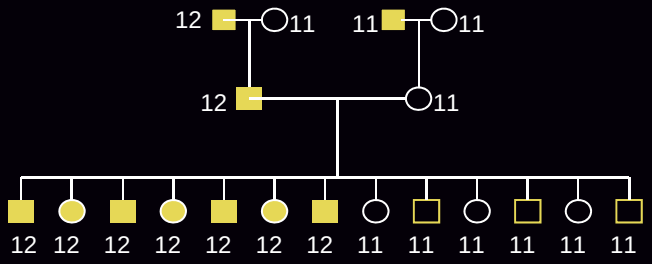
Oncocytoma

5%

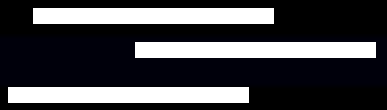
Studying cancer families to identify renal carcinoma genes

Identification of the VHL gene

Collect families



Linkage analysis

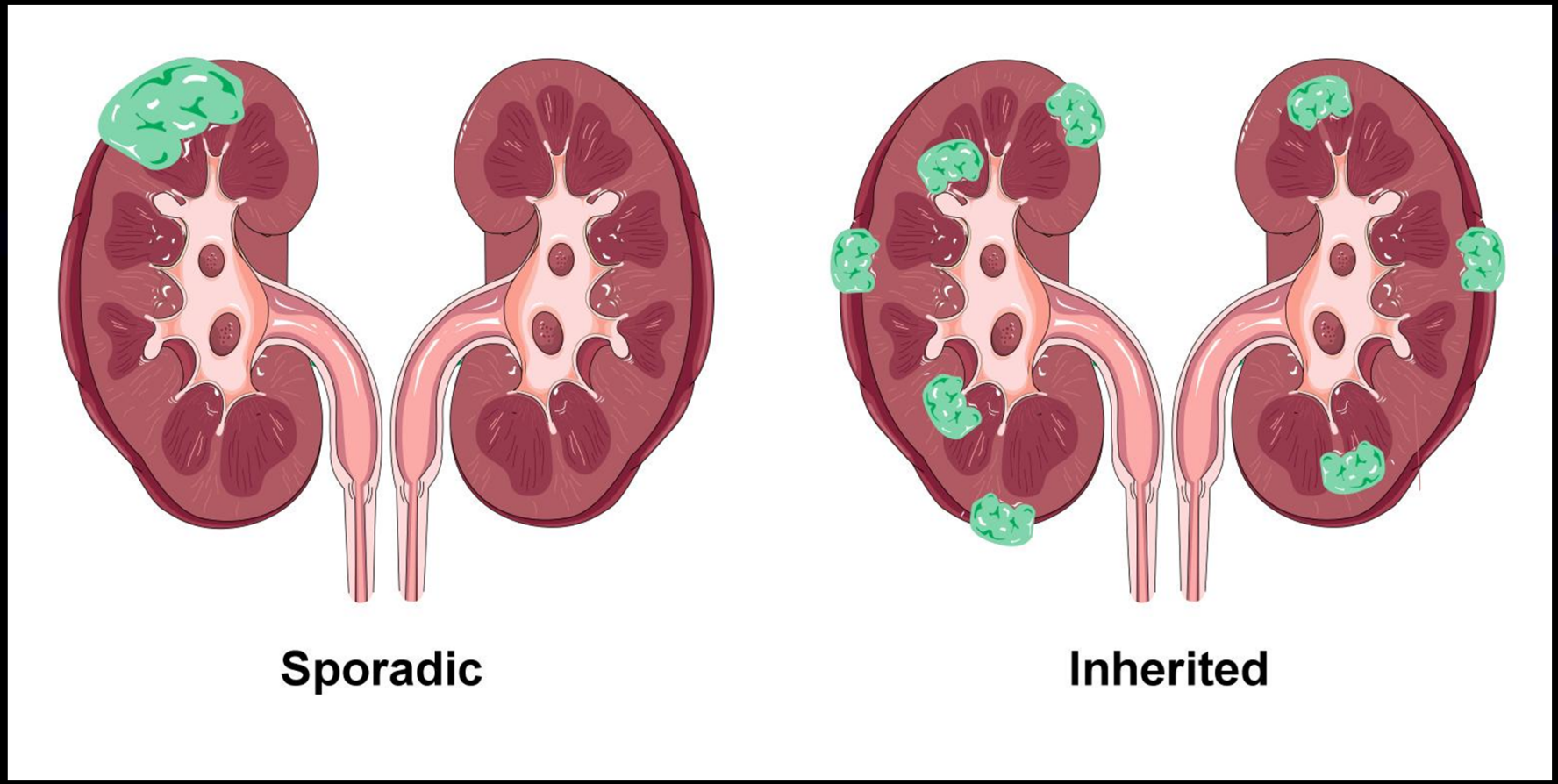


Physical mapping

Inherited Forms of Renal Carcinoma

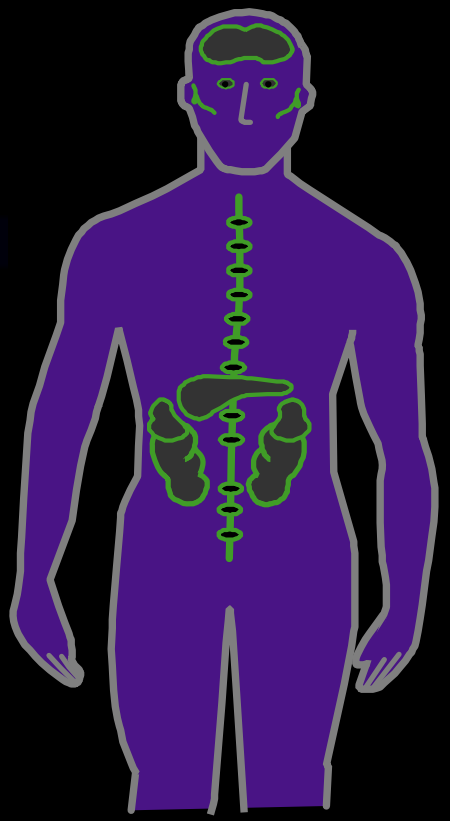
1. **Von Hippel Lindau**
   - Clear Cell
2. **Hereditary Papillary Renal Carcinoma**
   - Papillary Type 1
3. **Birt Hogg Dubé:**
   - Chromophobe/Oncocytoma
4. **Hereditary Leiomyomatosis RCC**
   - Papillary Type 2
5. **Succinate Dehydrogenase Familial Renal Carcinoma**
   - Papillary Type 2

Clear Cell Renal Carcinoma von Hippel Lindau (VHL)



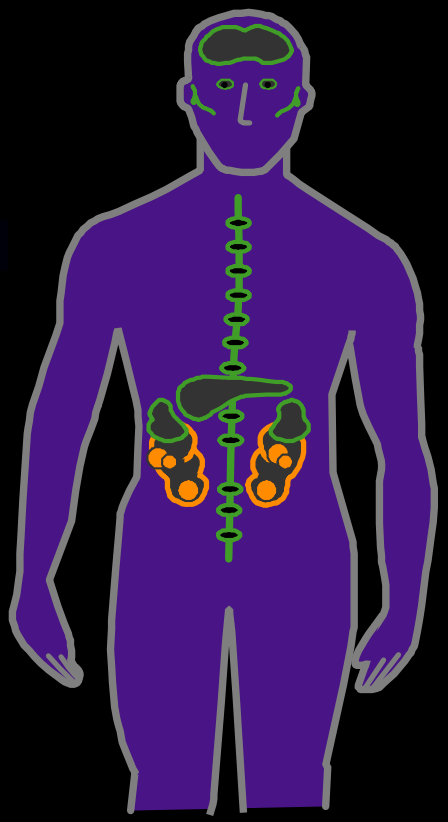
VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears



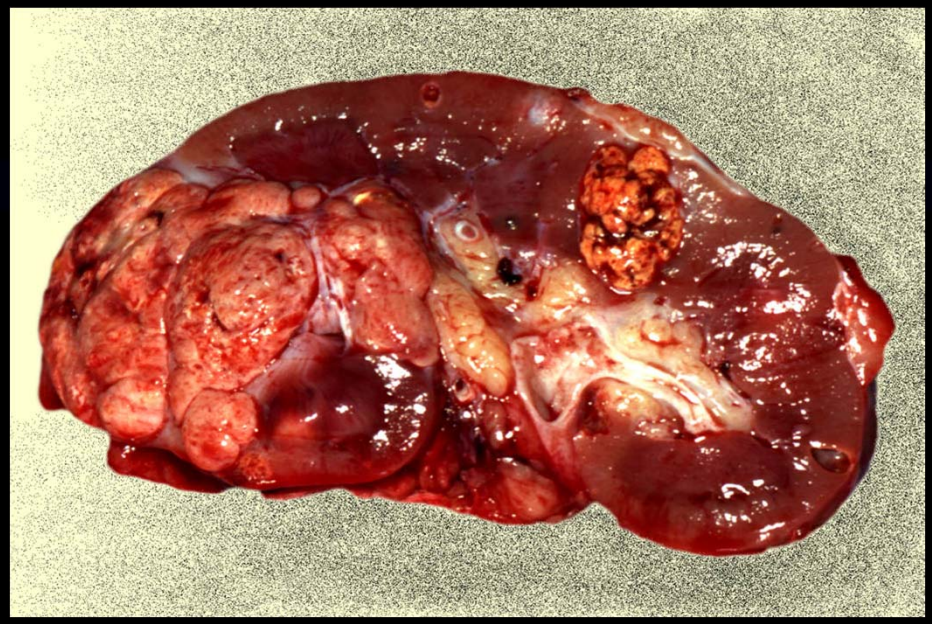
VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears



VHL: Renal Cell Carcinoma

CT Scan: Bilateral,
Multifocal RCC

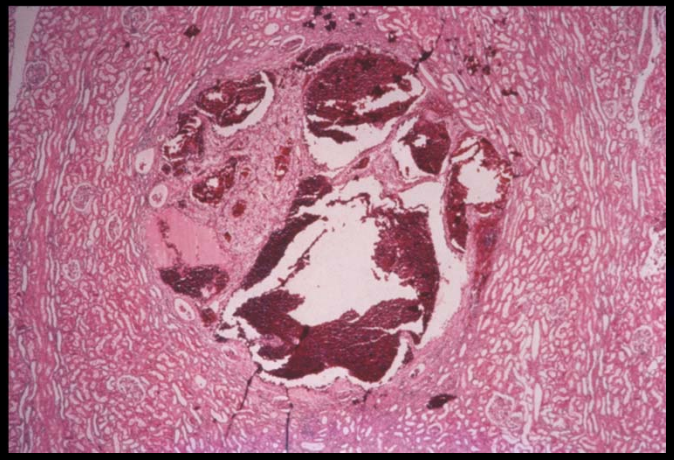


VHL Kidney:
Multifocal RCC

VHL-Associated RCC
High Persistence Rate

Microscopic Tumors

- VHL
  - 600 clear cell RCC/kidney
  - 1300 cysts/kidney



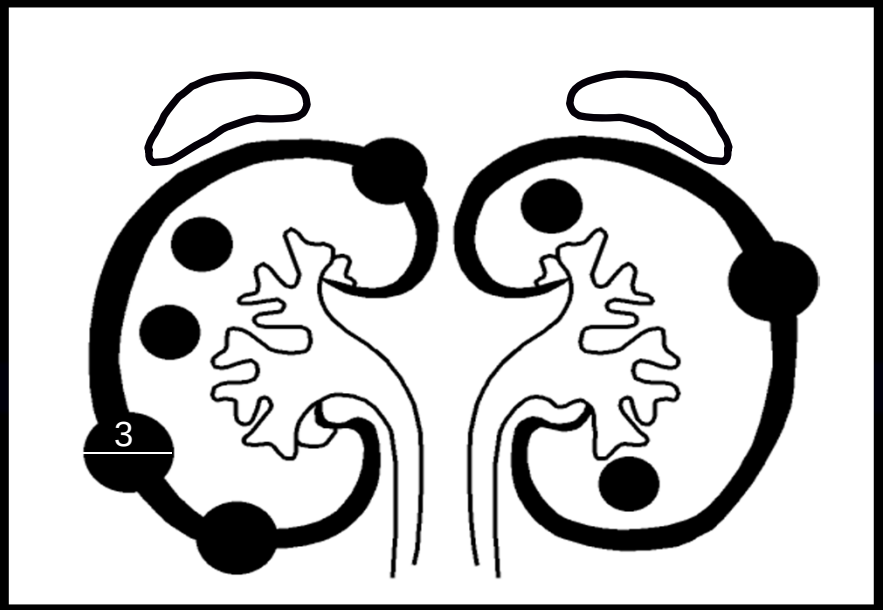
J Urol 154:1995

NCI VHL Kindreds N=367

- 659 patients from 367 VHL families have been evaluated

- 284 nephrectomies/partial nephrectomies

Surgical Management of VHL-Associated Renal Carcinoma

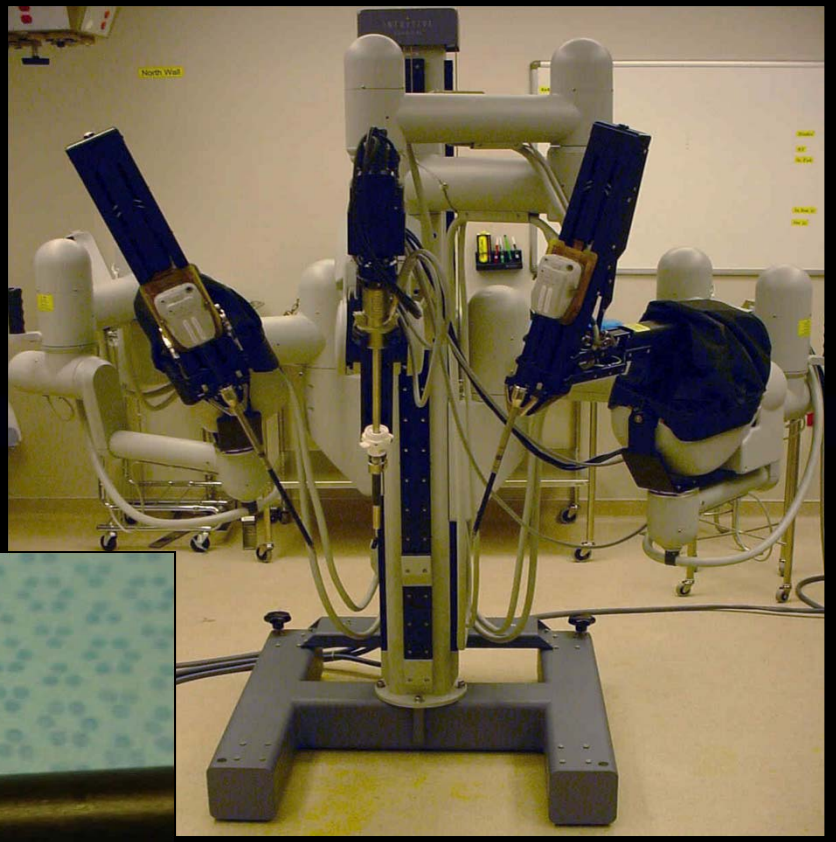


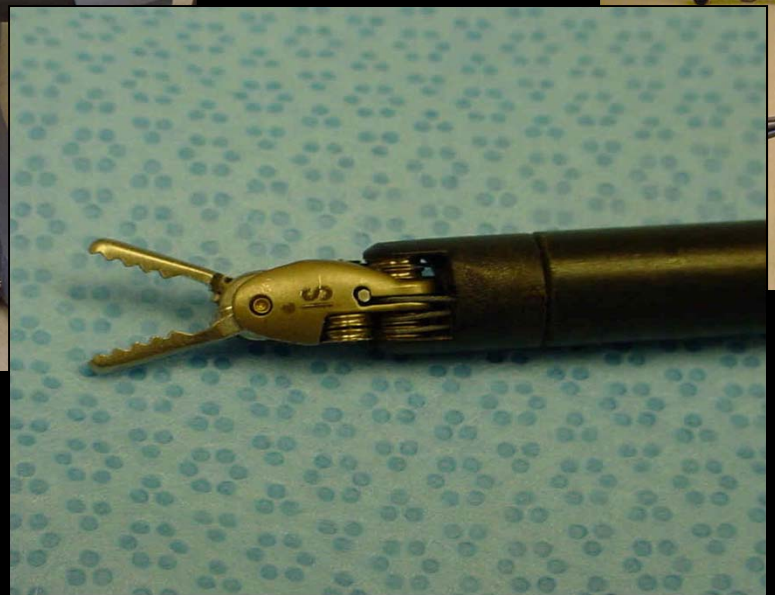
"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

Surgery = nephron sparing enucleation

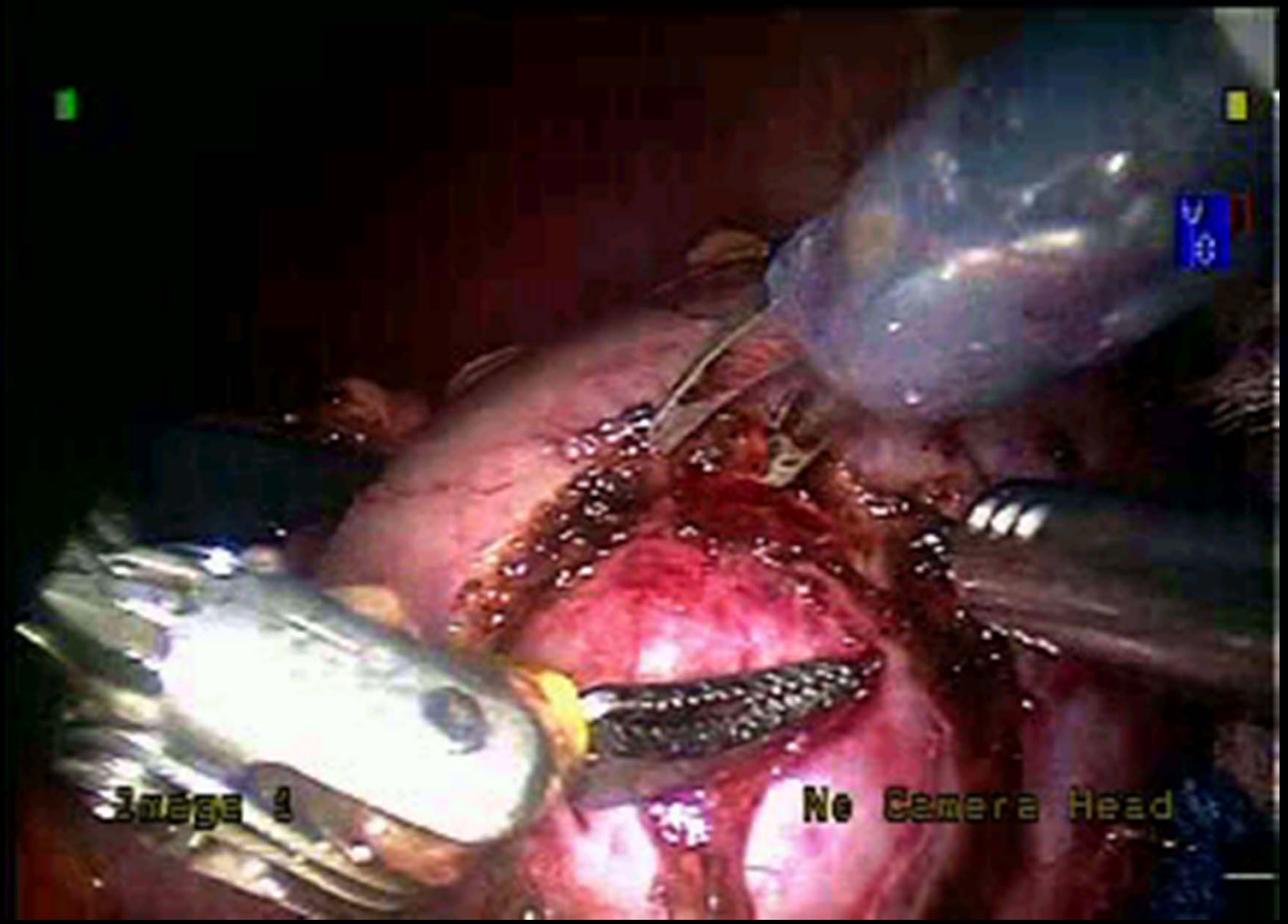
Radiology 174: 1990
J Urol: 153:1995
J Urol 165:2001
J Urol 165:2001
J Urol 172:2004
J Urol 173 2005

Robotic Assisted Partial Nephrectomy

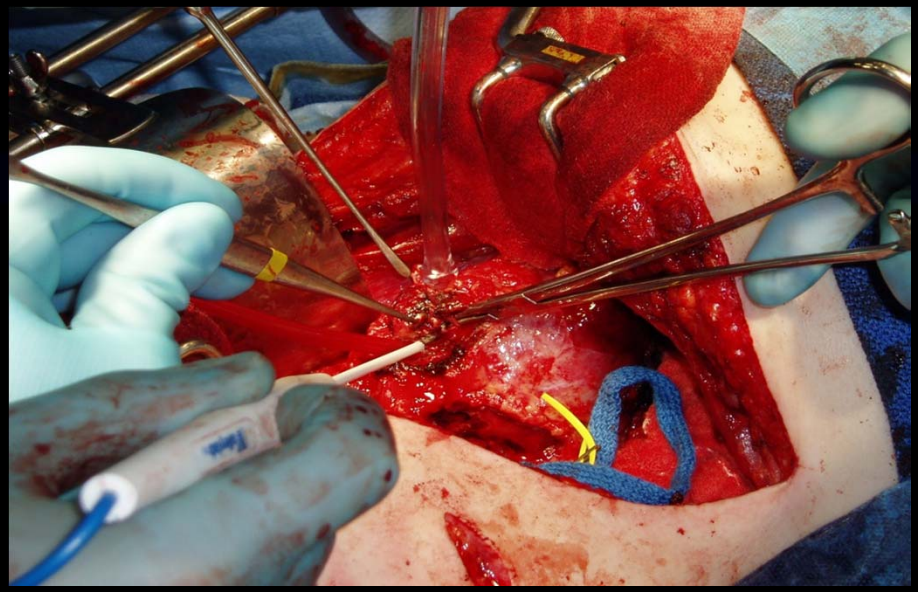




Robotic Assisted Partial Nephrectomy



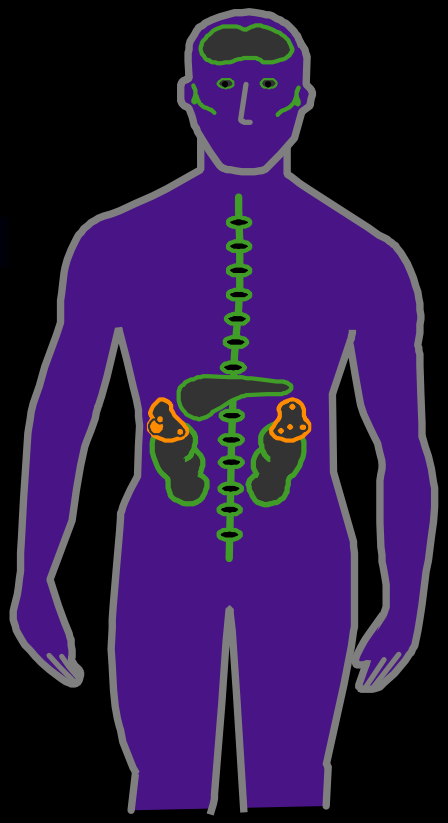
Open Surgery Partial Nephrectomy



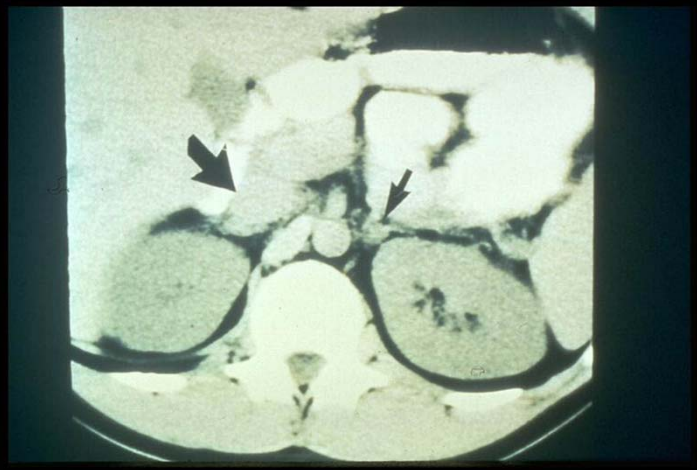
Postoperative

VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears

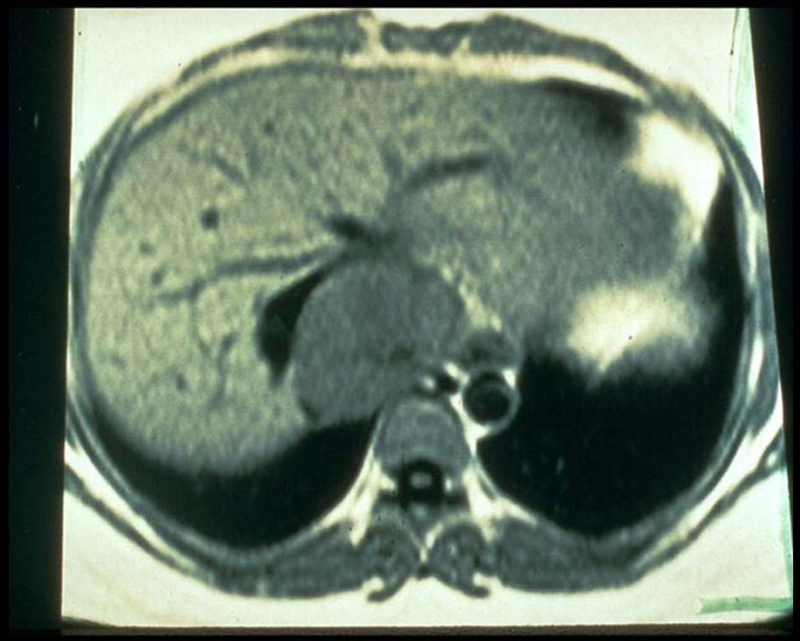


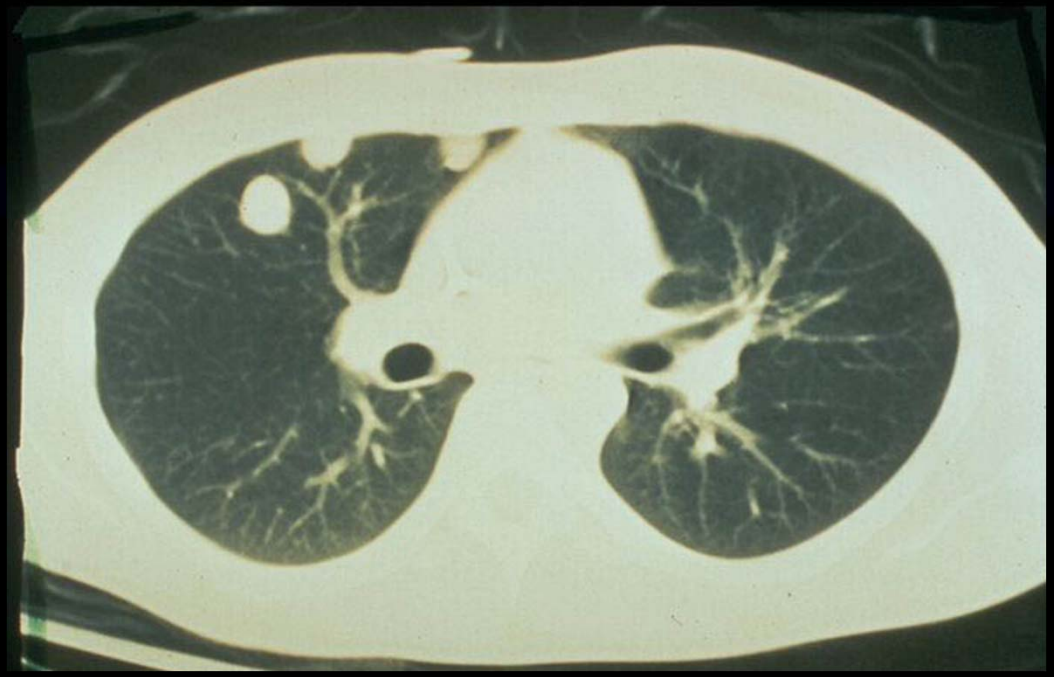
VHL: Bilateral Pheochromocytoma



NEJM 340:1999
Ann Int Med 134:2001
(Of 35 publications)

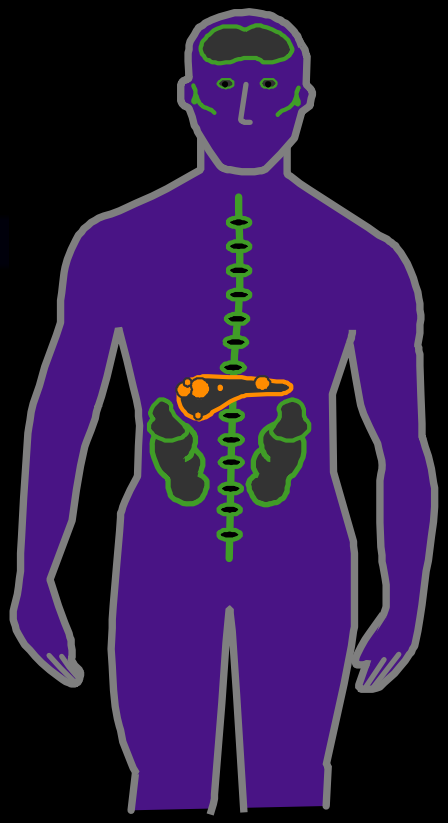
VHL: Pheochromocytoma
Pulmonary Metastases



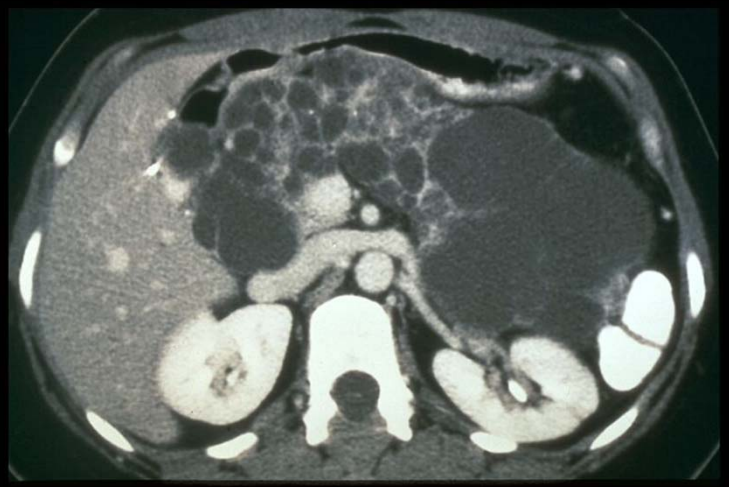


VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears



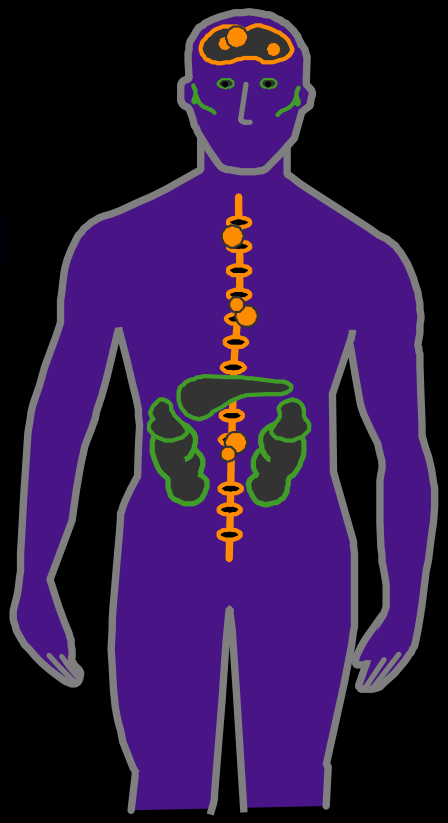
VHL: Islet Cell Carcinoma & Pancreatic Cysts



Am J Surg 124:1998
Lancet 361:2003
(Of 26 publications)

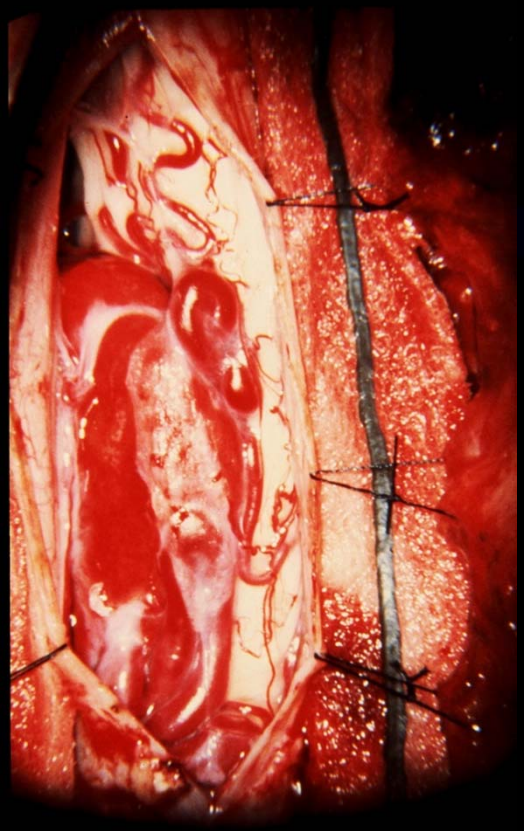
VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears



VHL: Cerebellar Hemangioblastoma

VHL: Spinal Hemangioblastoma



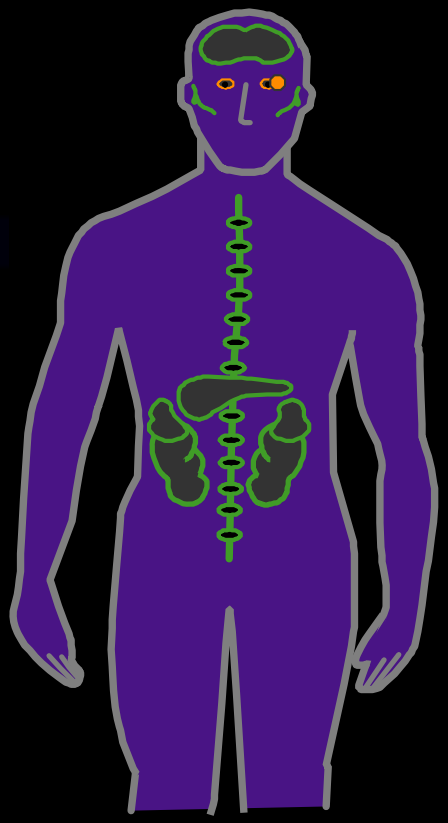
Neurology 41:1998

J Neurosurg 105 200

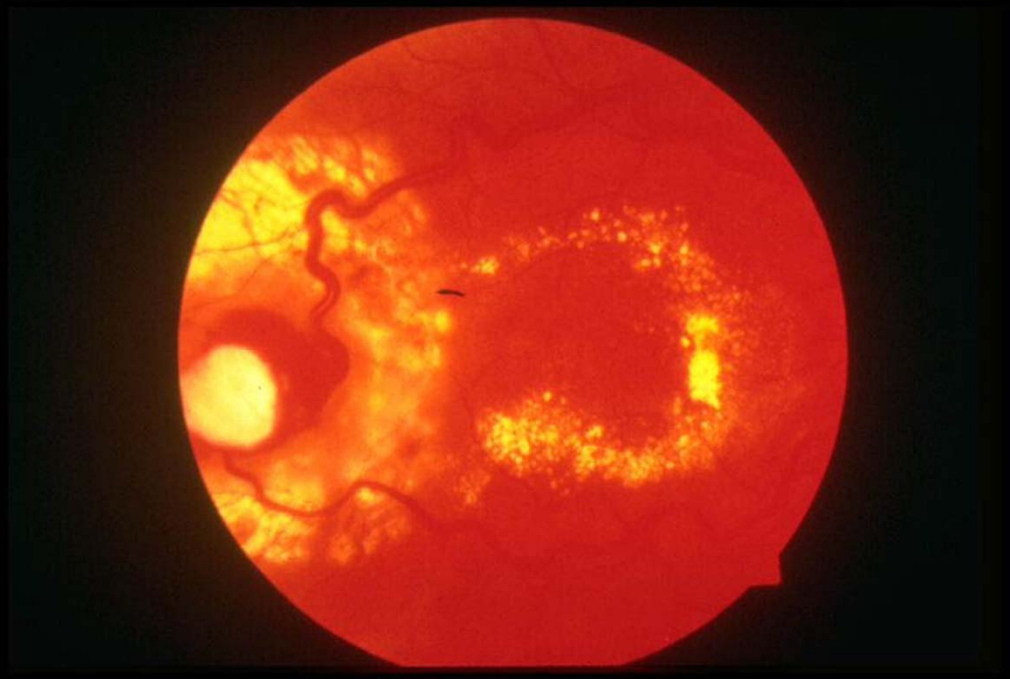
(Of 14 publications)

VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears



VHL: Retinal Angioma



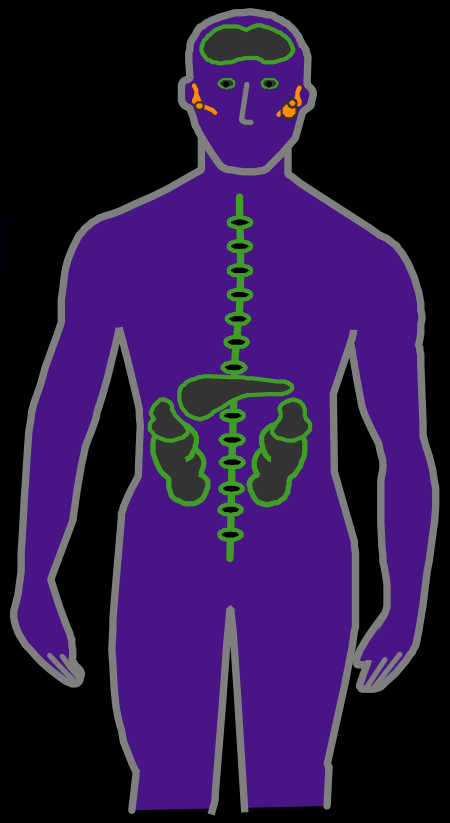
Arch Ophthal 117:1999

Arch Ophthal 125:2007

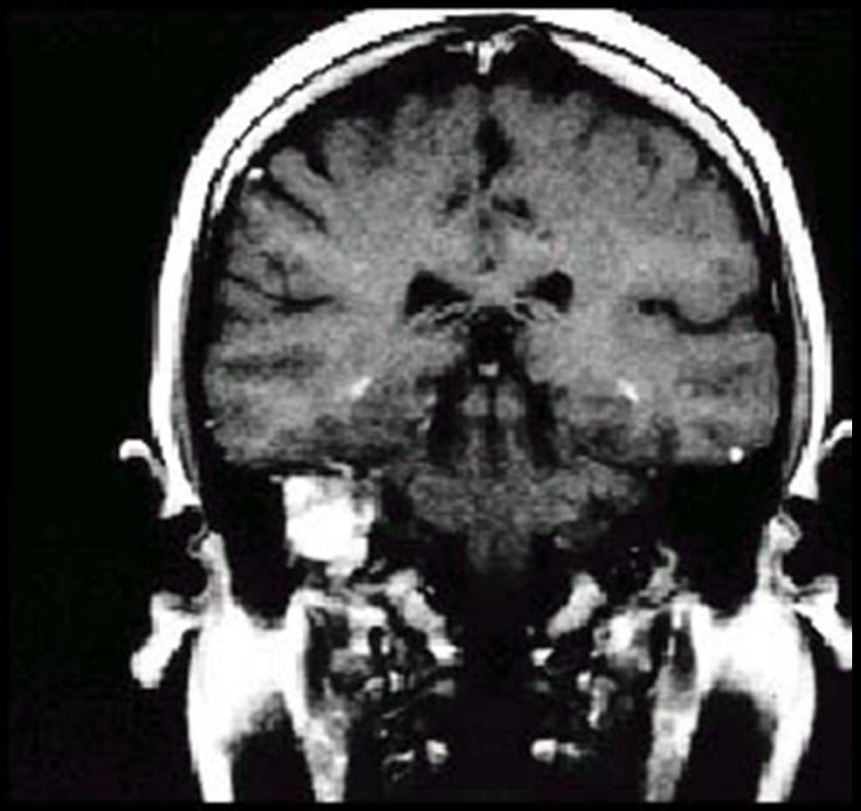
(Of 7 publications)

VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears



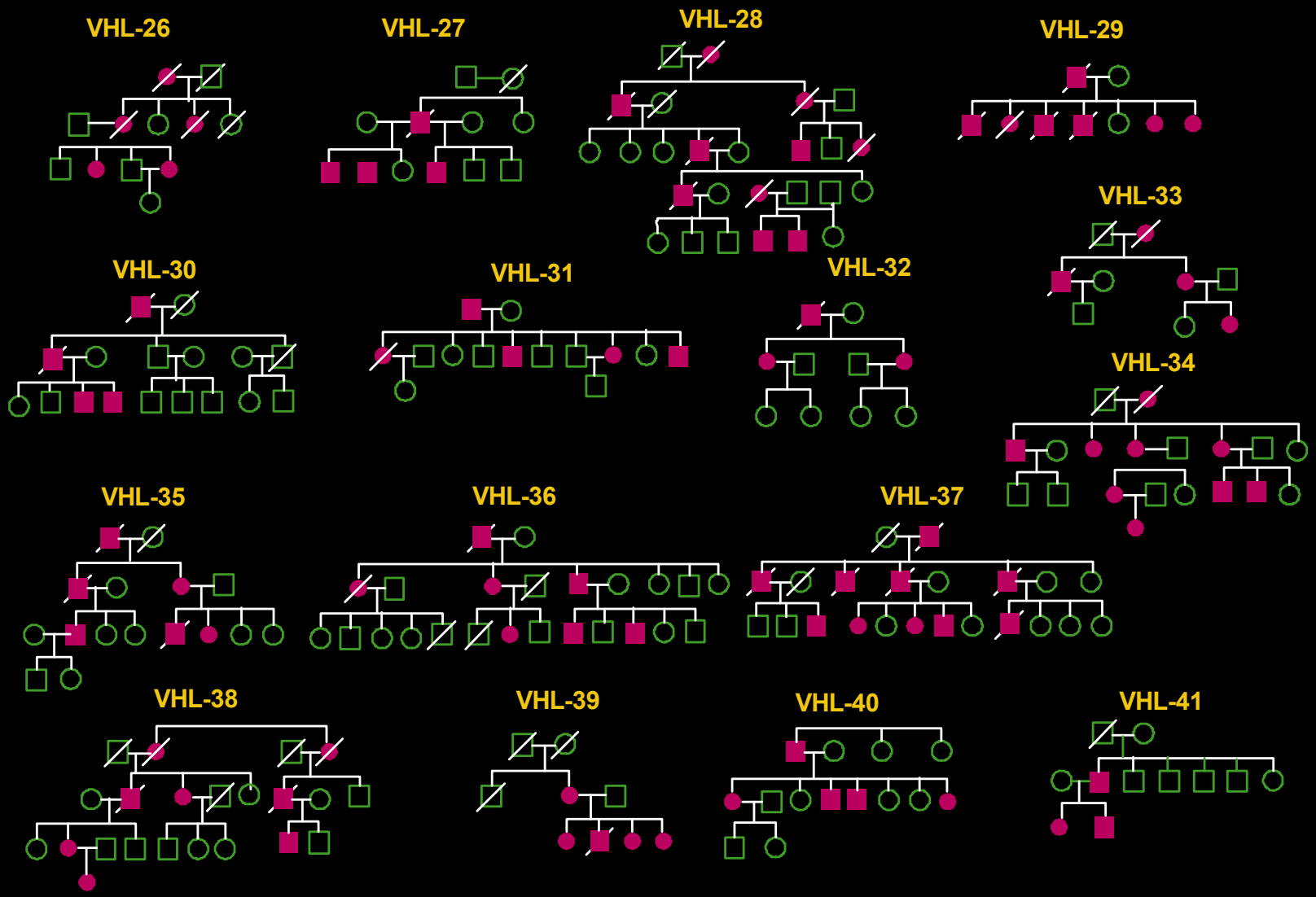
VHL: Endolymphatic Sac Tumor-ELST

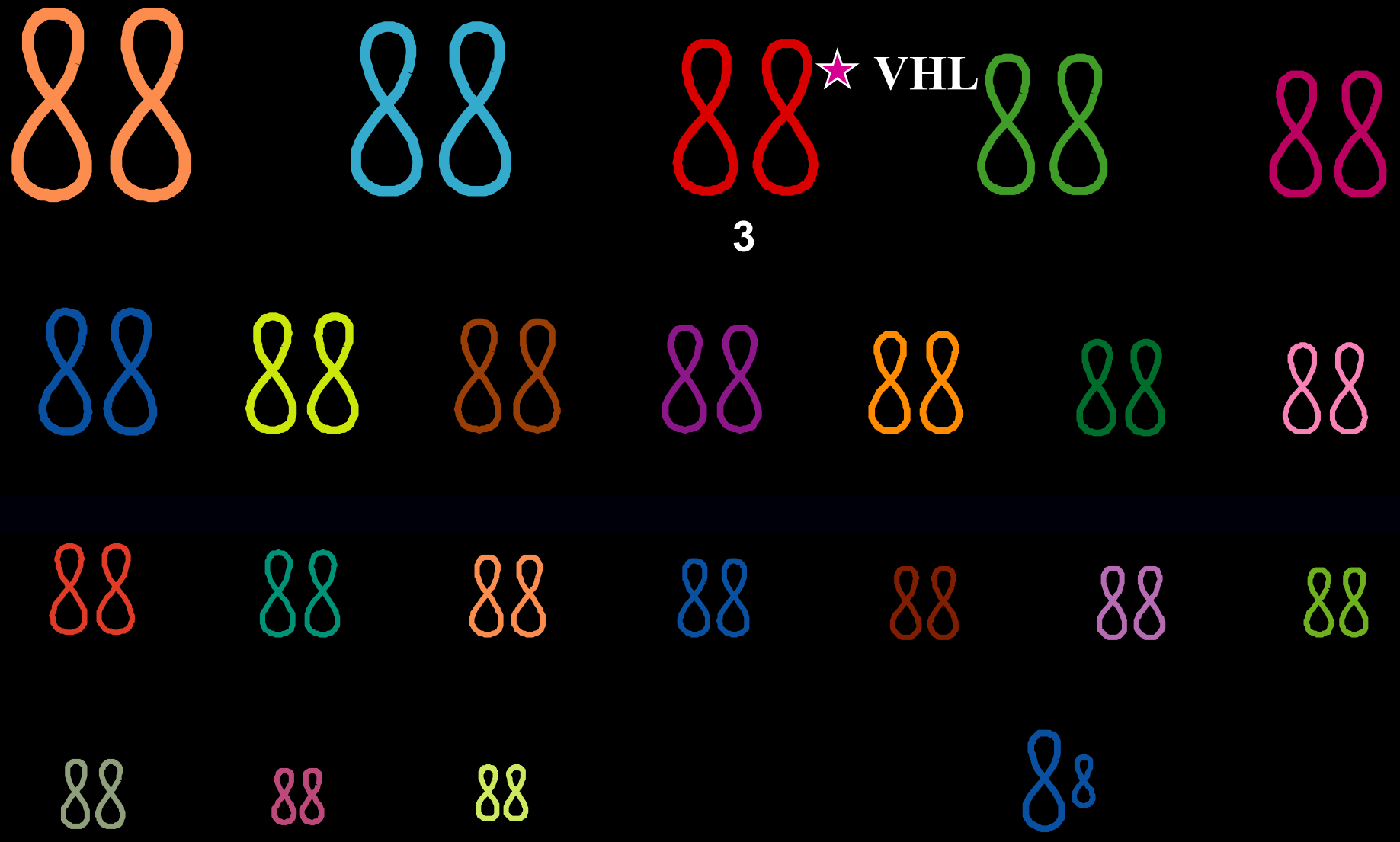


JAMA 277:1997
J Neurosurg 100:2004

NIH Clinical Center

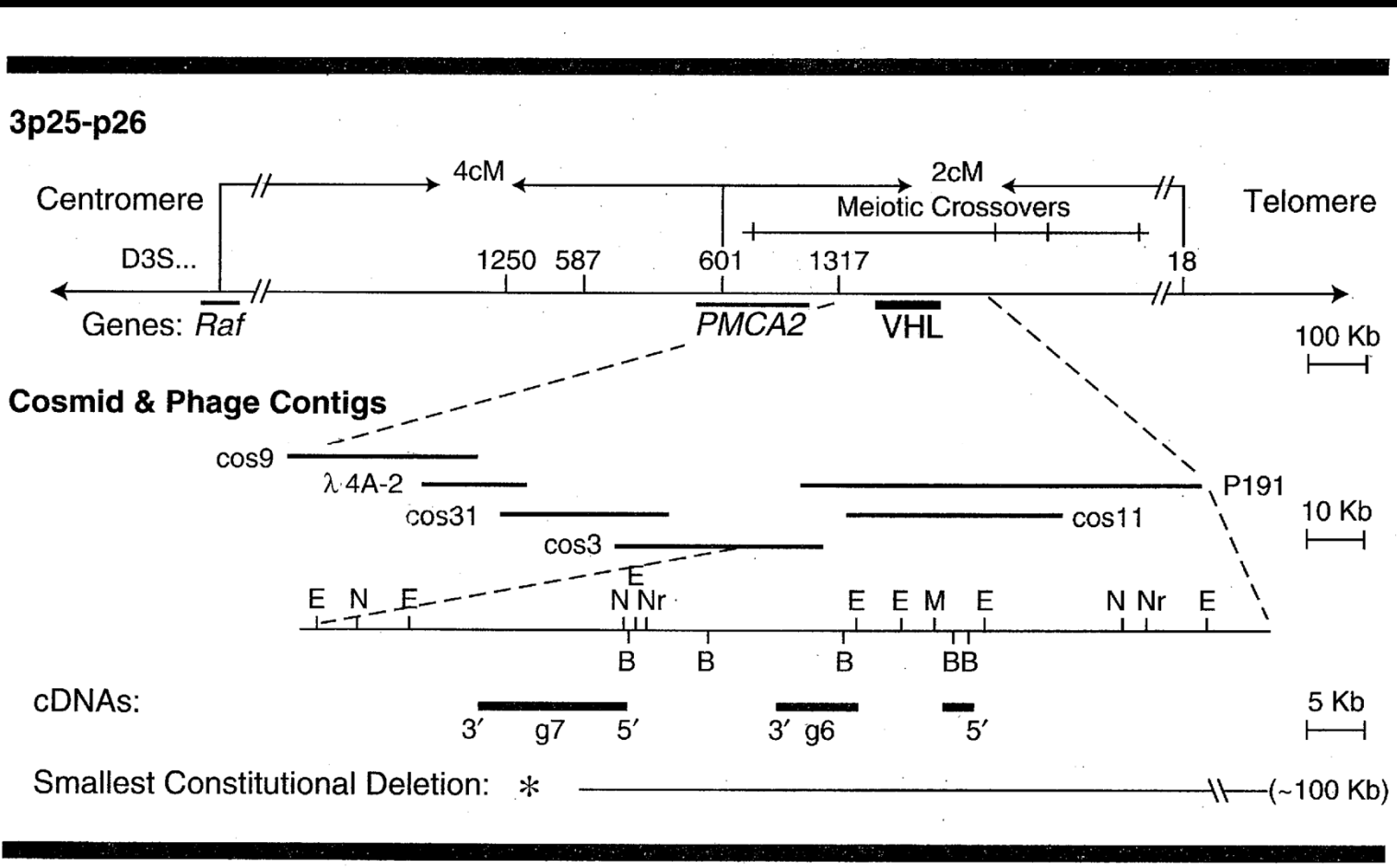
Linkage Analysis: VHL Families





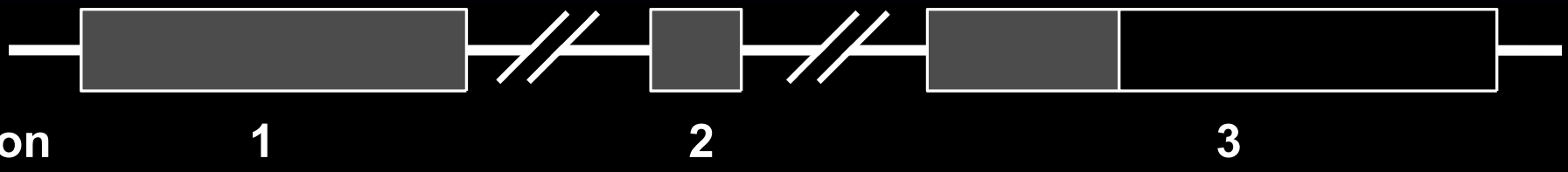
Localization of VHL to short arm of chromosome 3

VHL Gene Localization Map



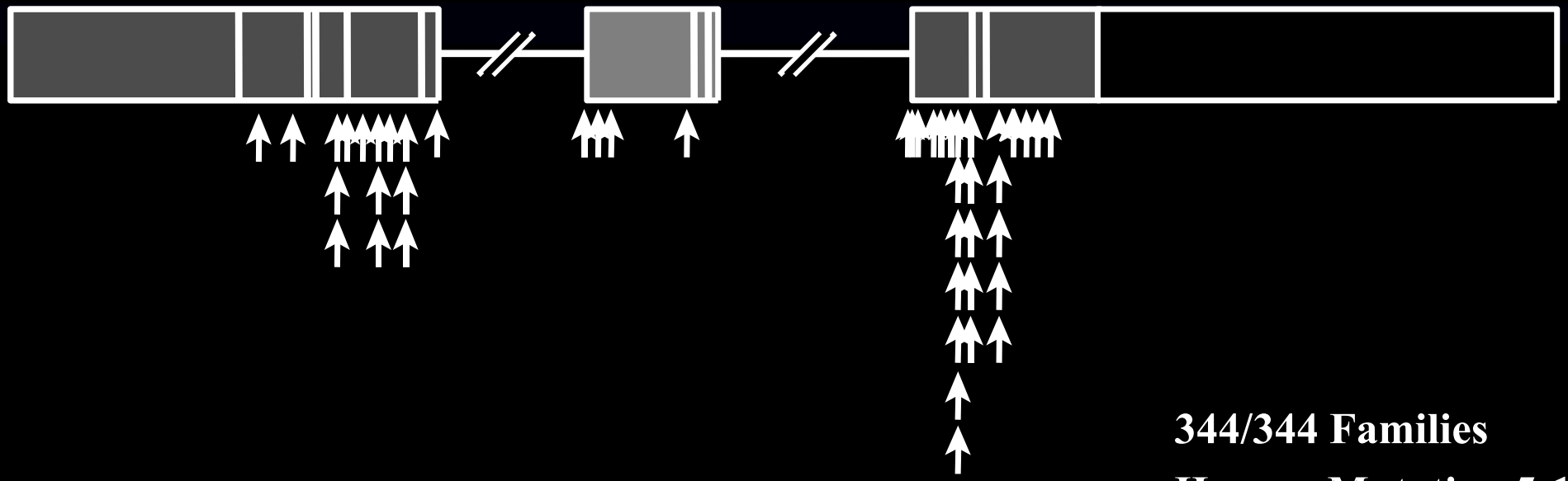
Latif, et al Science 260; 1993

Human VHL Gene



Science 260:1993

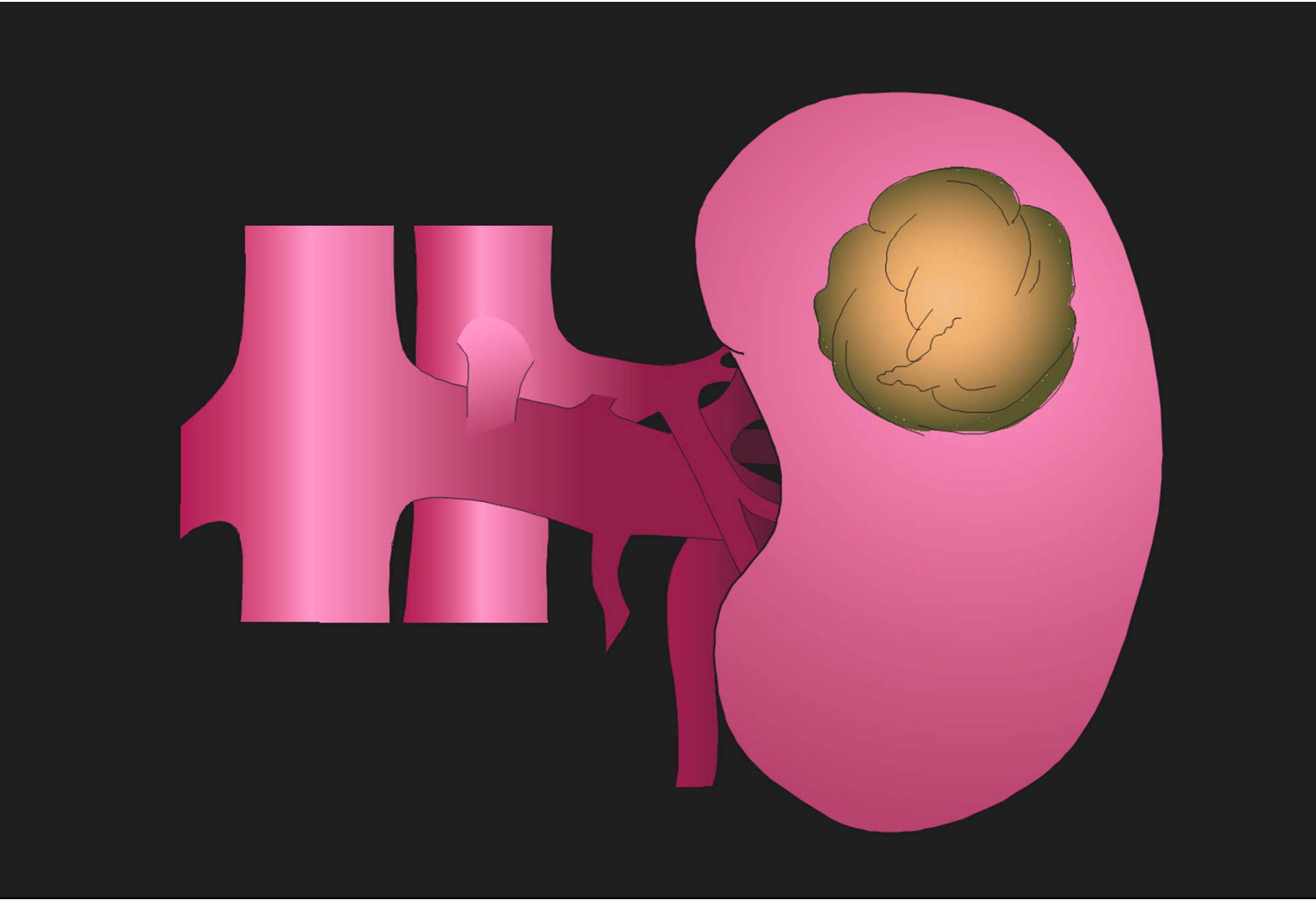
Germline VHL Mutations



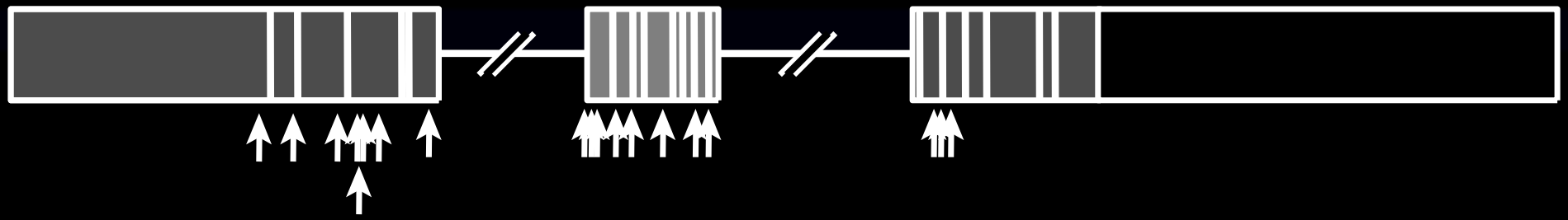
344/344 Families

Human Mutation 5:1995

Corbin et al. In Prep



Sporadic Clear Cell RCC
VHL Gene Mutations

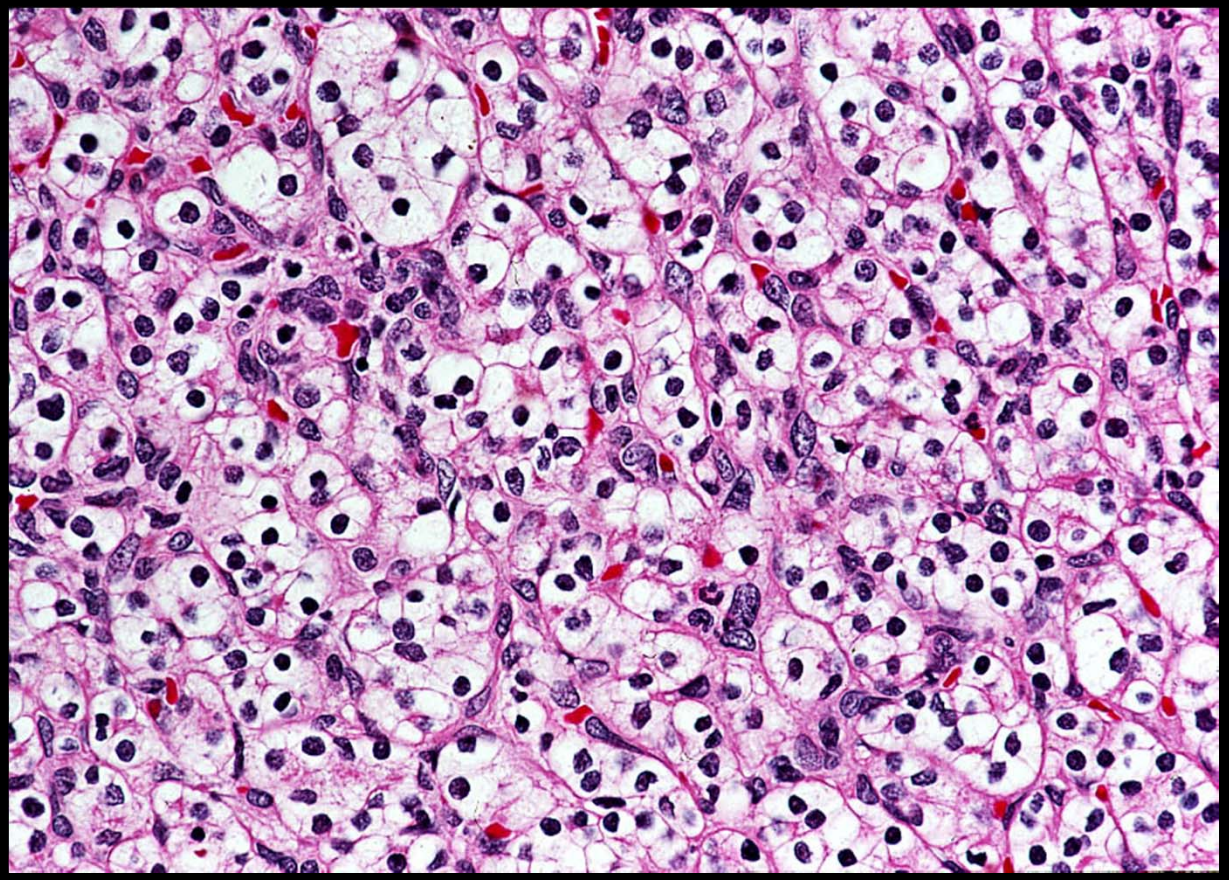


Science 260:1993

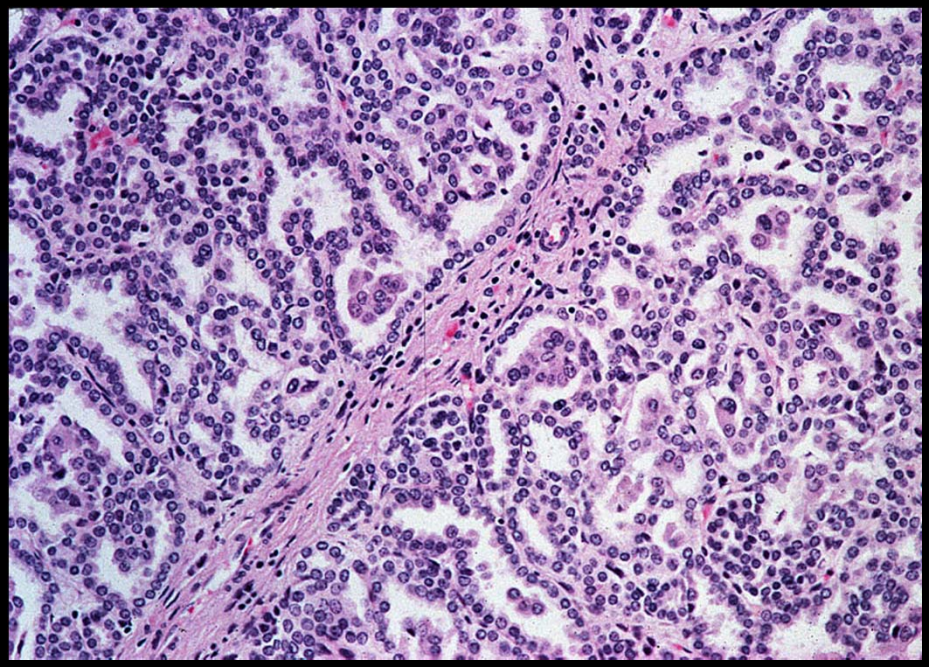
Nature Genetics 7:1994

Clin Cancer Res 14:2008

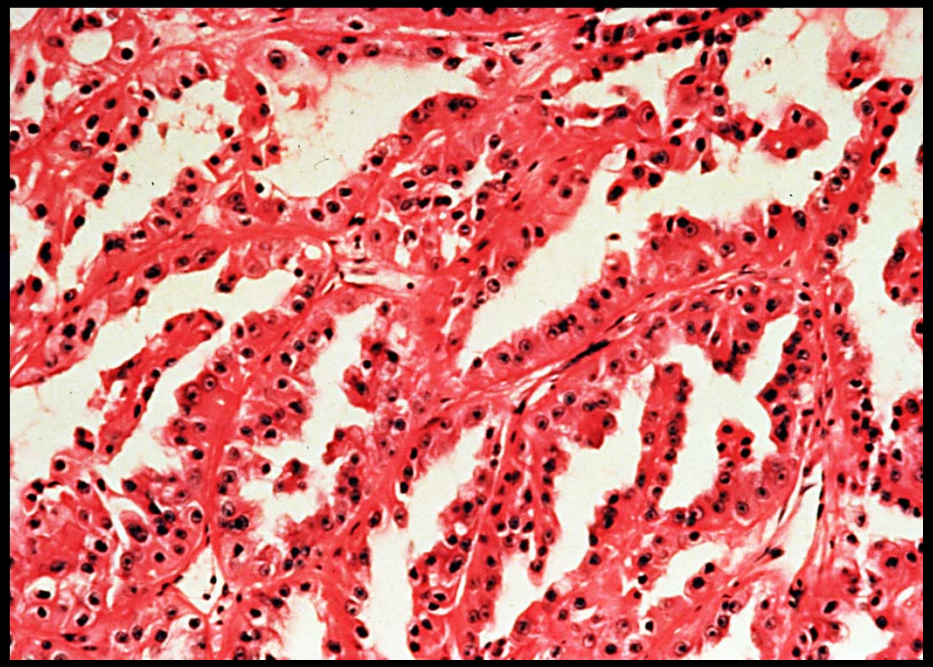
Clear Cell Renal Carcinoma



Papillary Renal Carcinoma

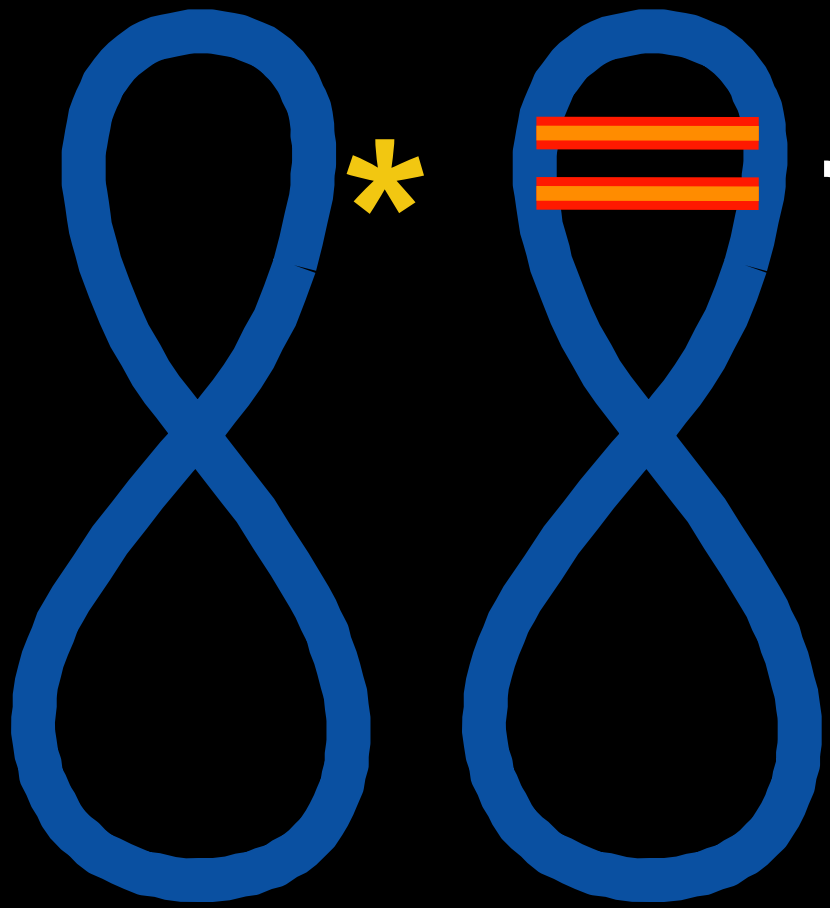


Type 1



Type 2

Mutated



Deleted

Chromosome 3
Clear Cell Kidney Cancer

Athymic Nude Mouse Bearing VHL -/- Clear Cell RCC

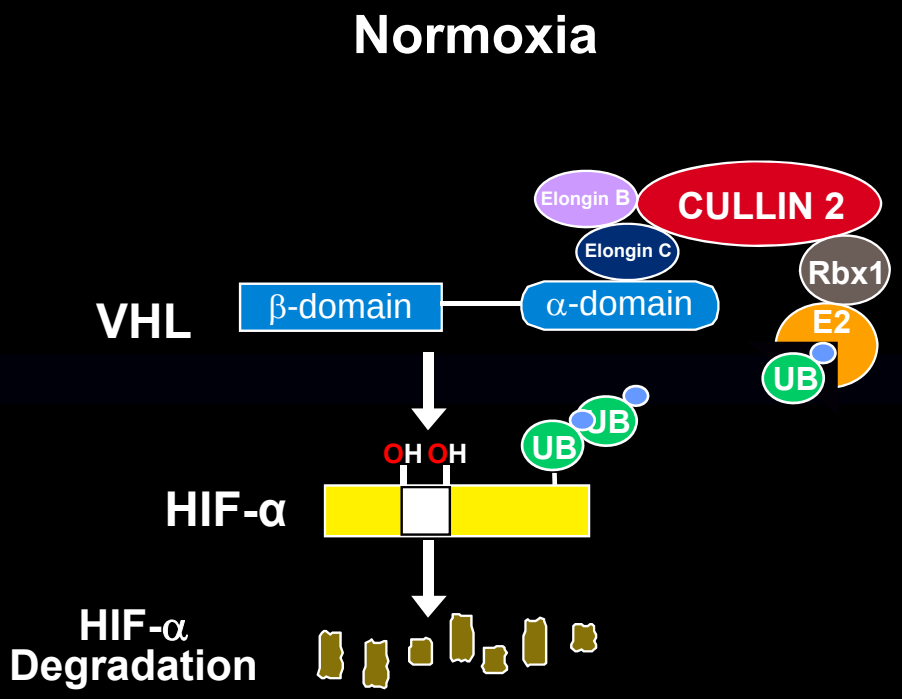
PNAS 93:1996

Addition of wild type *VHL* to *VHL* -/- RCC cell line abrogates tumor formation

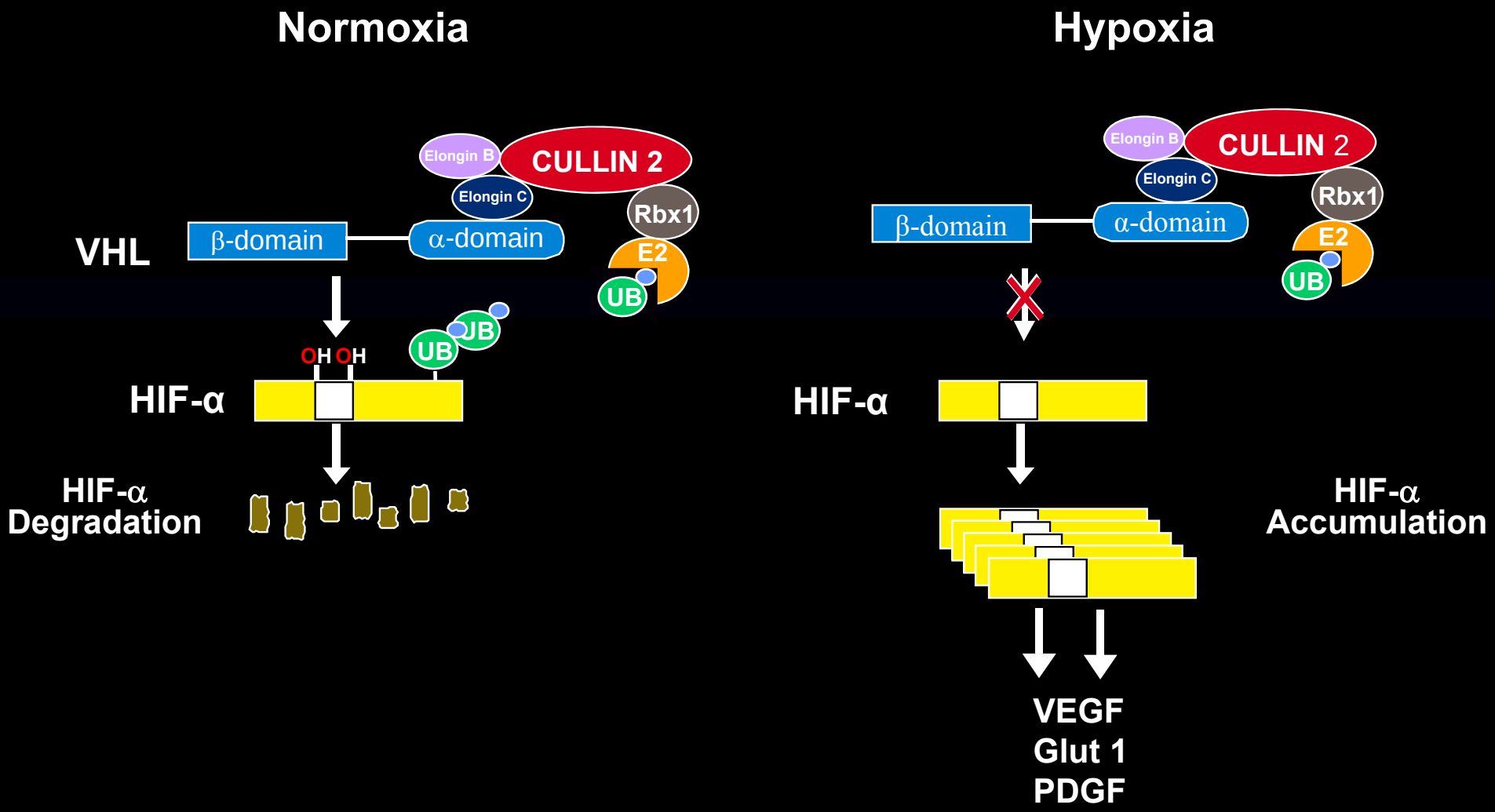
PNAS 93:1996

How Does the VHL Gene Function?

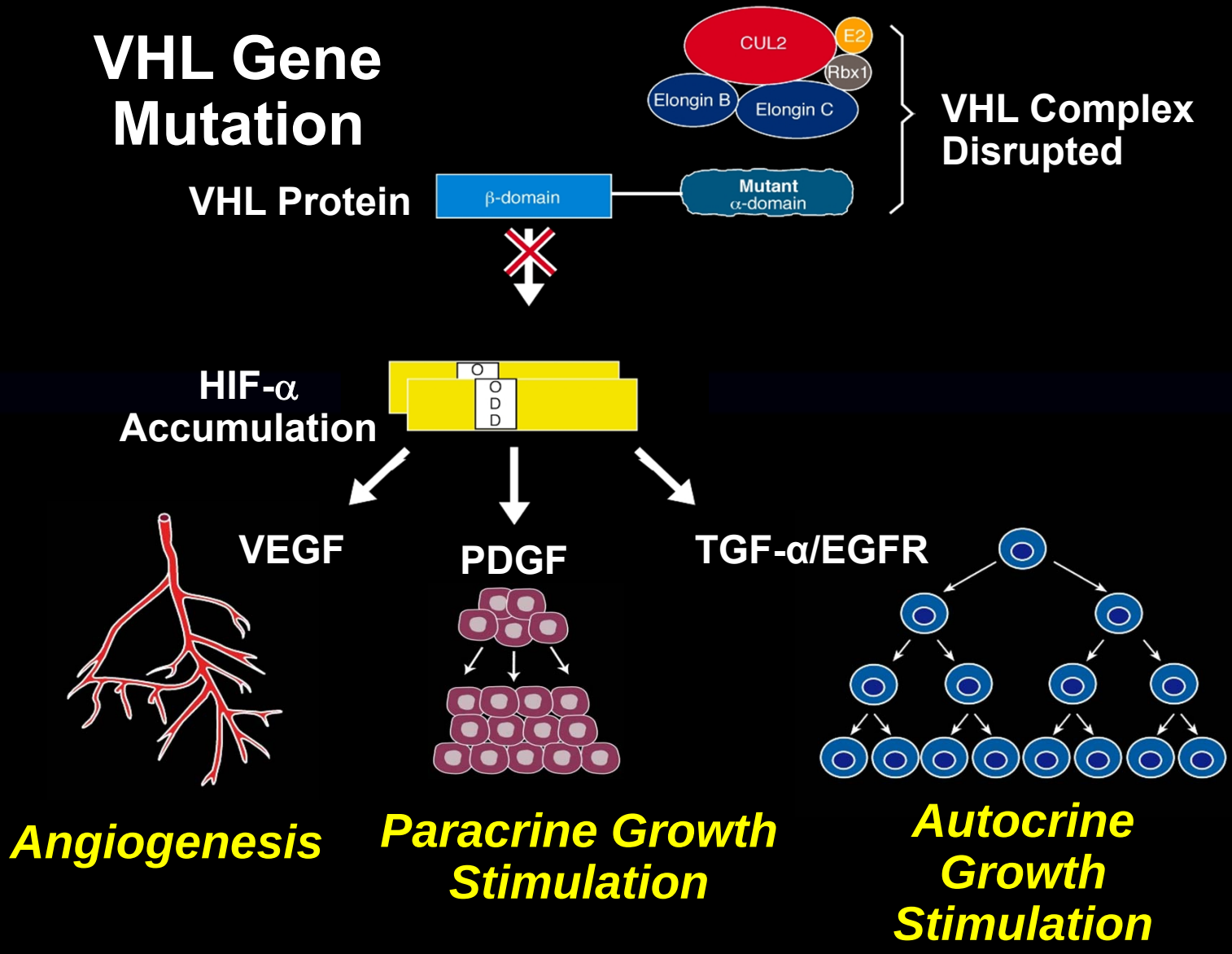
HIFα is targeted for degradation in normoxic,



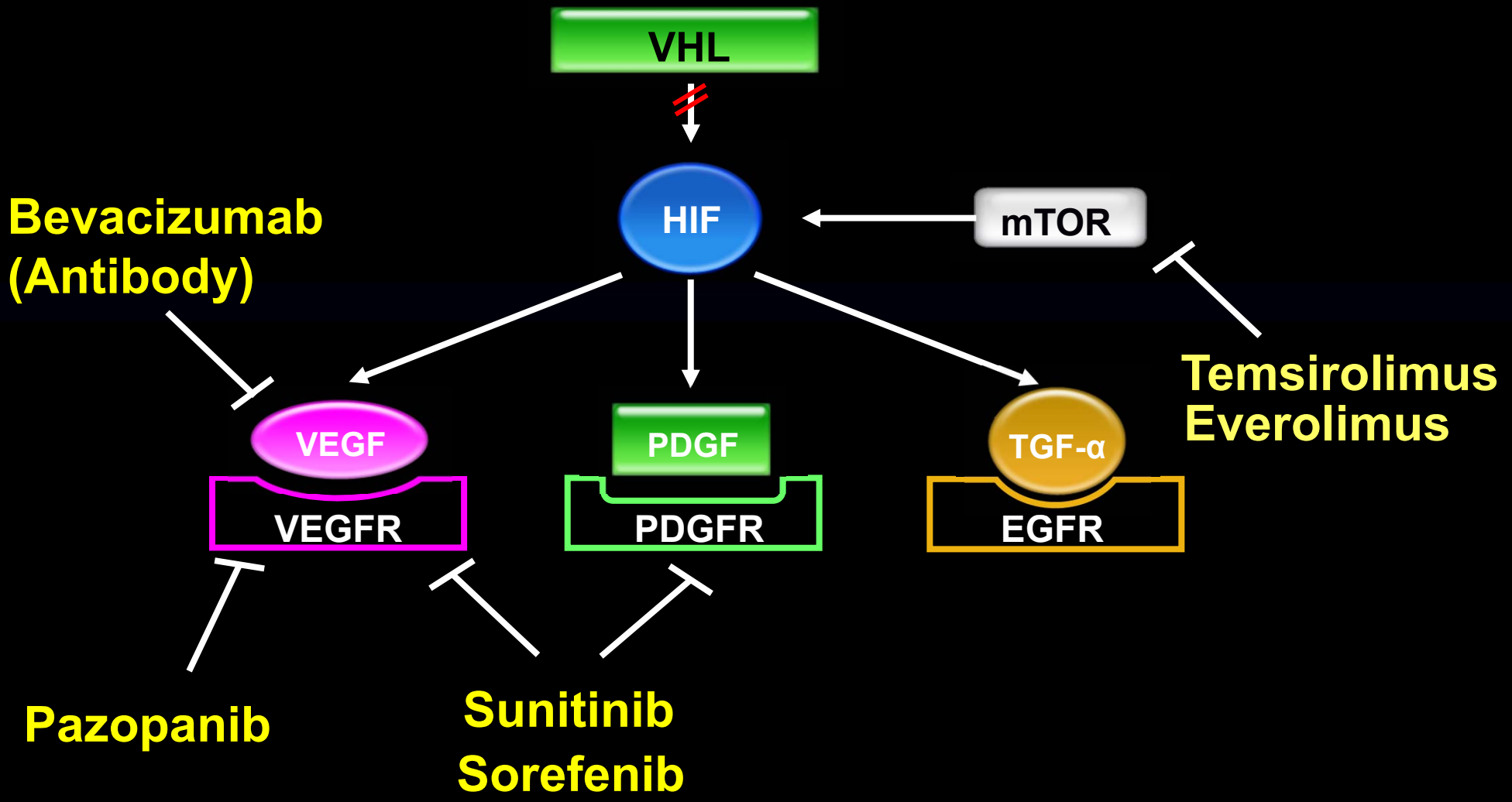
HIFα is targeted for degradation in normoxic, but not hypoxic cells



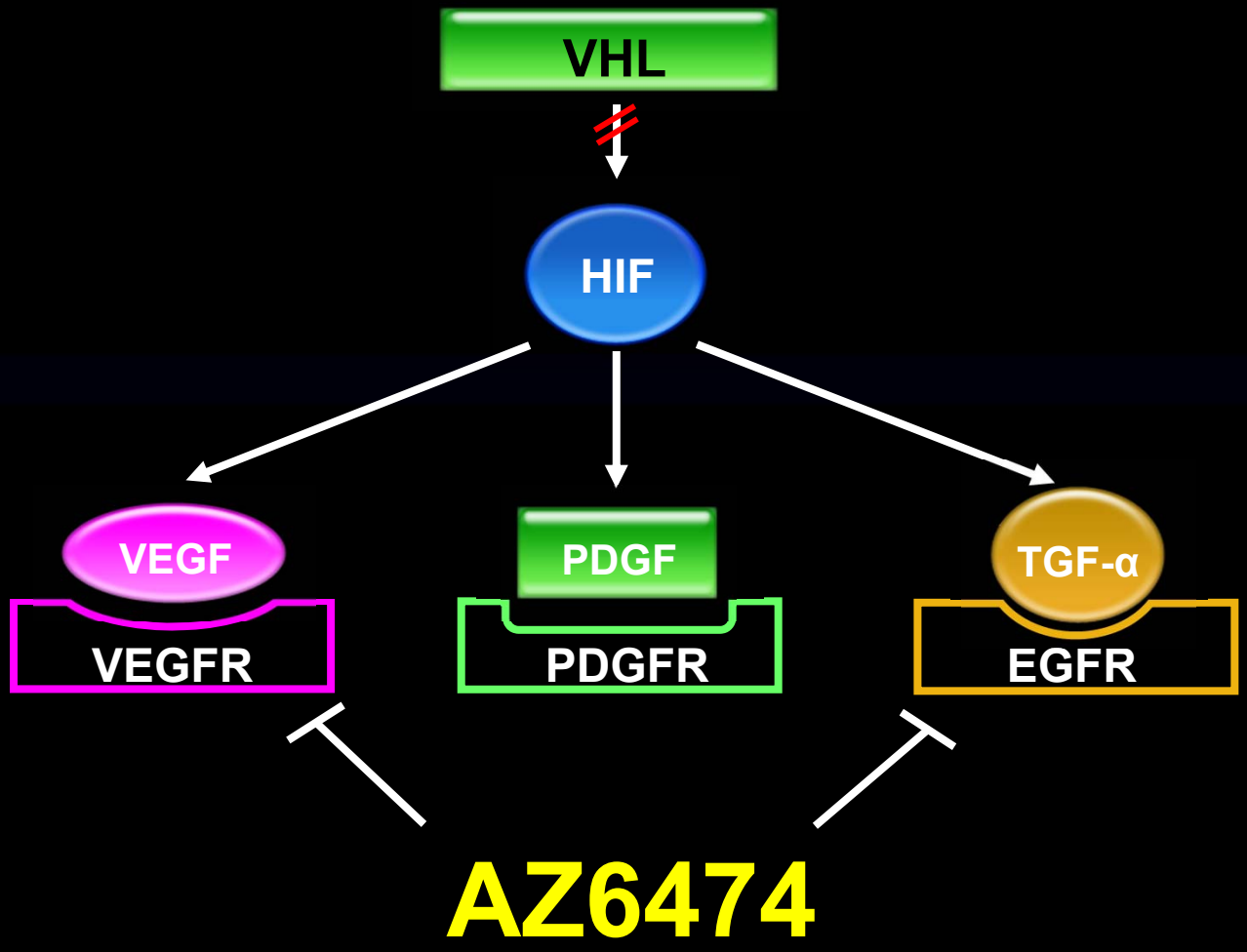
Downstream effects of *VHL* mutation



Targeting VHL/HIF pathway in clear cell RCC



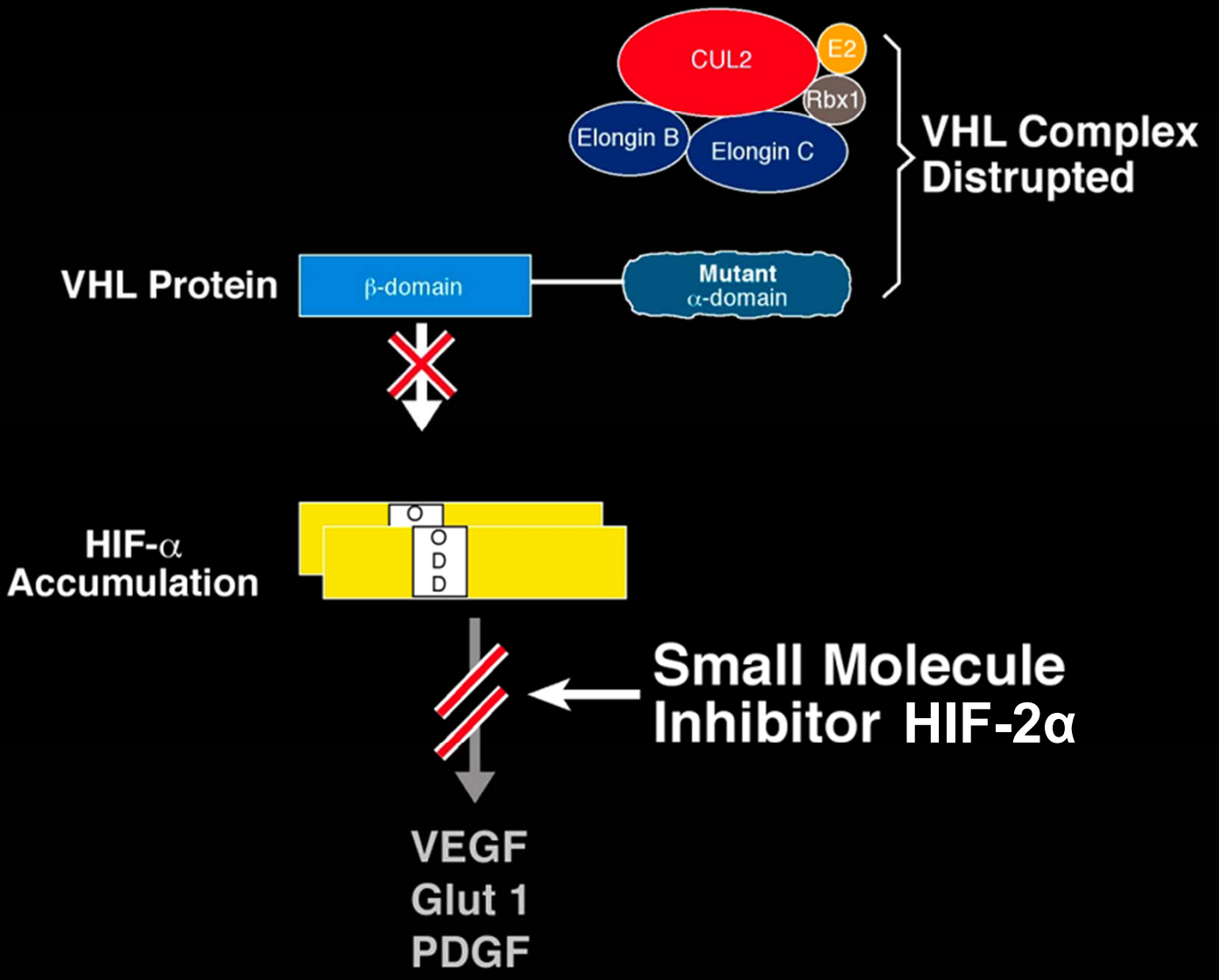
Targeting VHL/HIF pathway in clear cell RCC: AZ6474



Targeting the VHL Pathway

1. Targeting the downstream HIF targets:
   a. VEGFR
   b. PDGFR
   c. EGFR
2. Targeting HIF transcription/translation

Potential Small Molecule Target

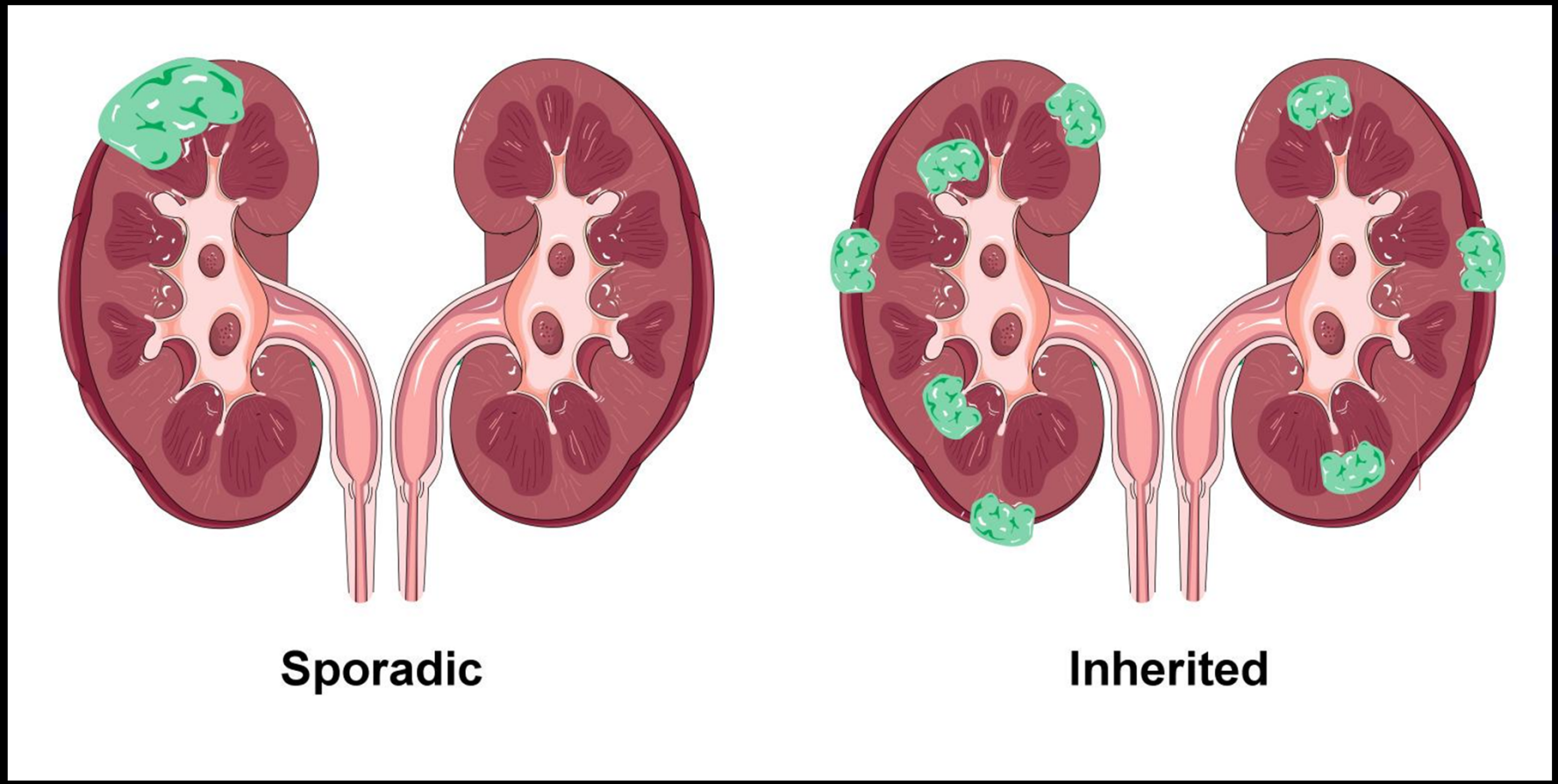


Non-Clear Cell RCC

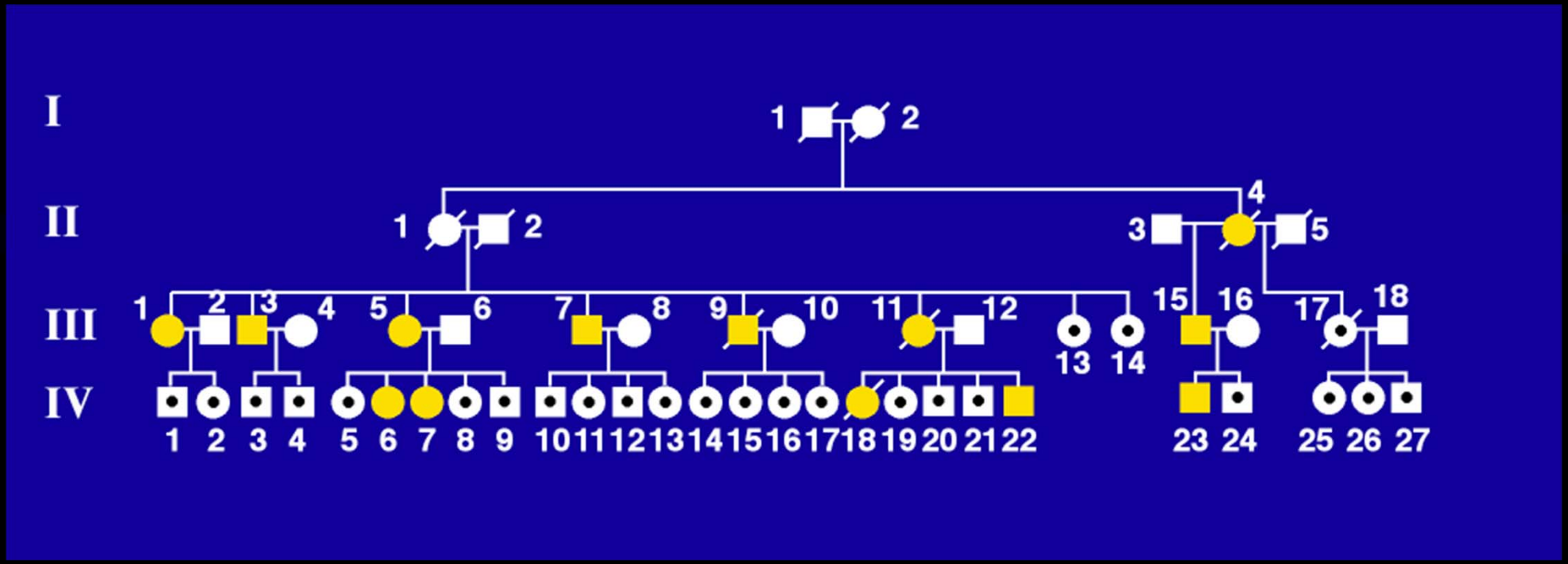
What possible approaches are there for developing therapeutic approaches for patients with:

1. Type 1 Papillary RCC
2. Chromophobe RCC
3. Type 2 Papillary RCC
4. Collecting Duct RCC

Inherited Renal Carcinoma



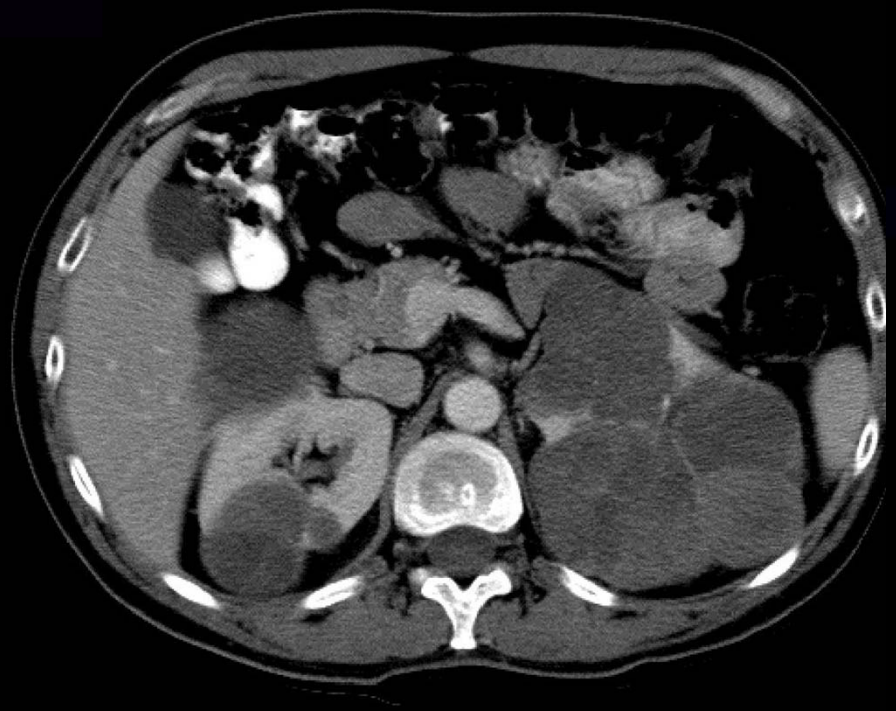
Hereditary Papillary Renal Carcinoma (HPRC)



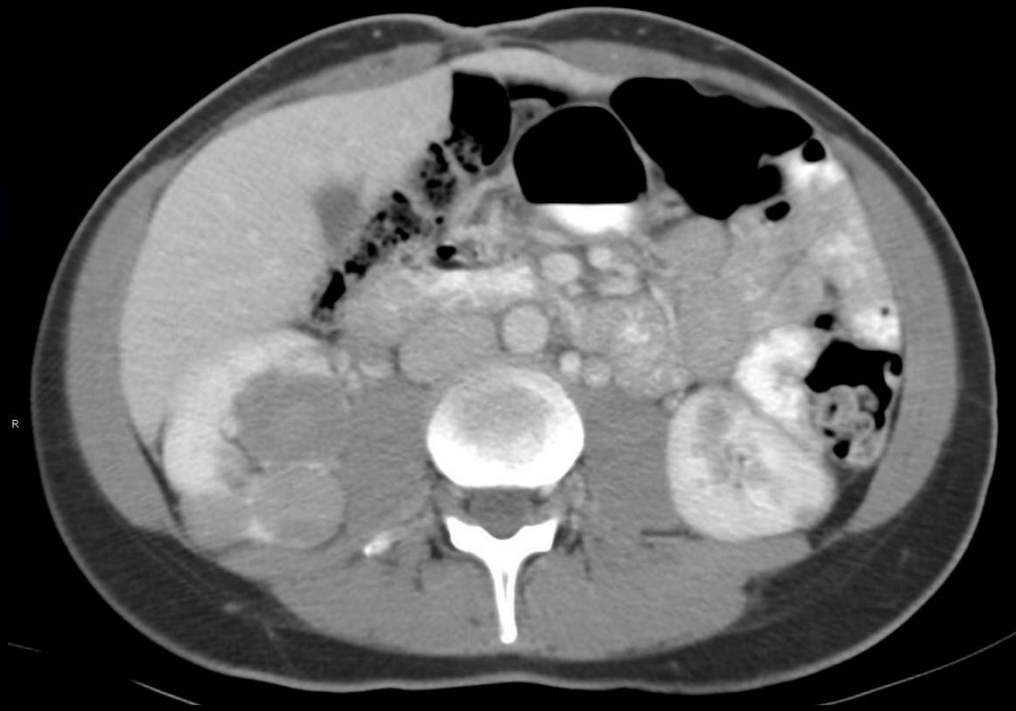
J. Urol 151: 1994

J. Urol 153: 1995

Hereditary Papillary Renal Cancer (HPRC)



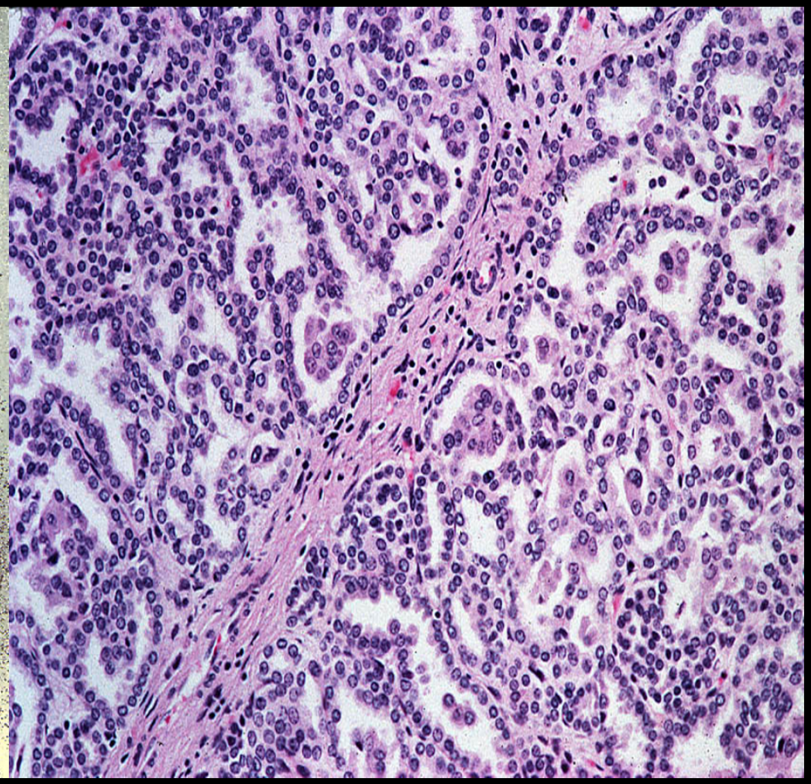
38 year old male



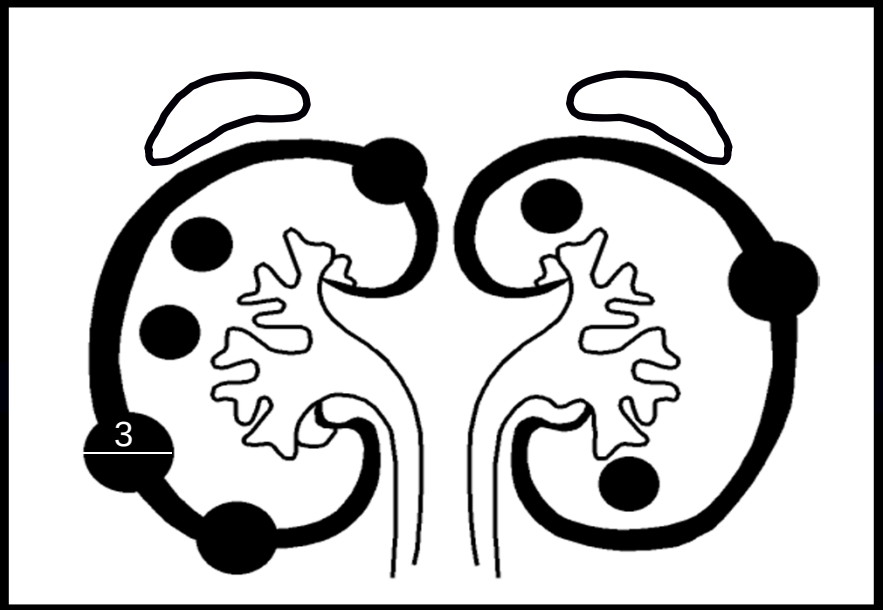
27 year old female

J Urol*: 172, 2004*

Hereditary Papillary Renal Carcinoma
Type 1 papillary renal carcinoma



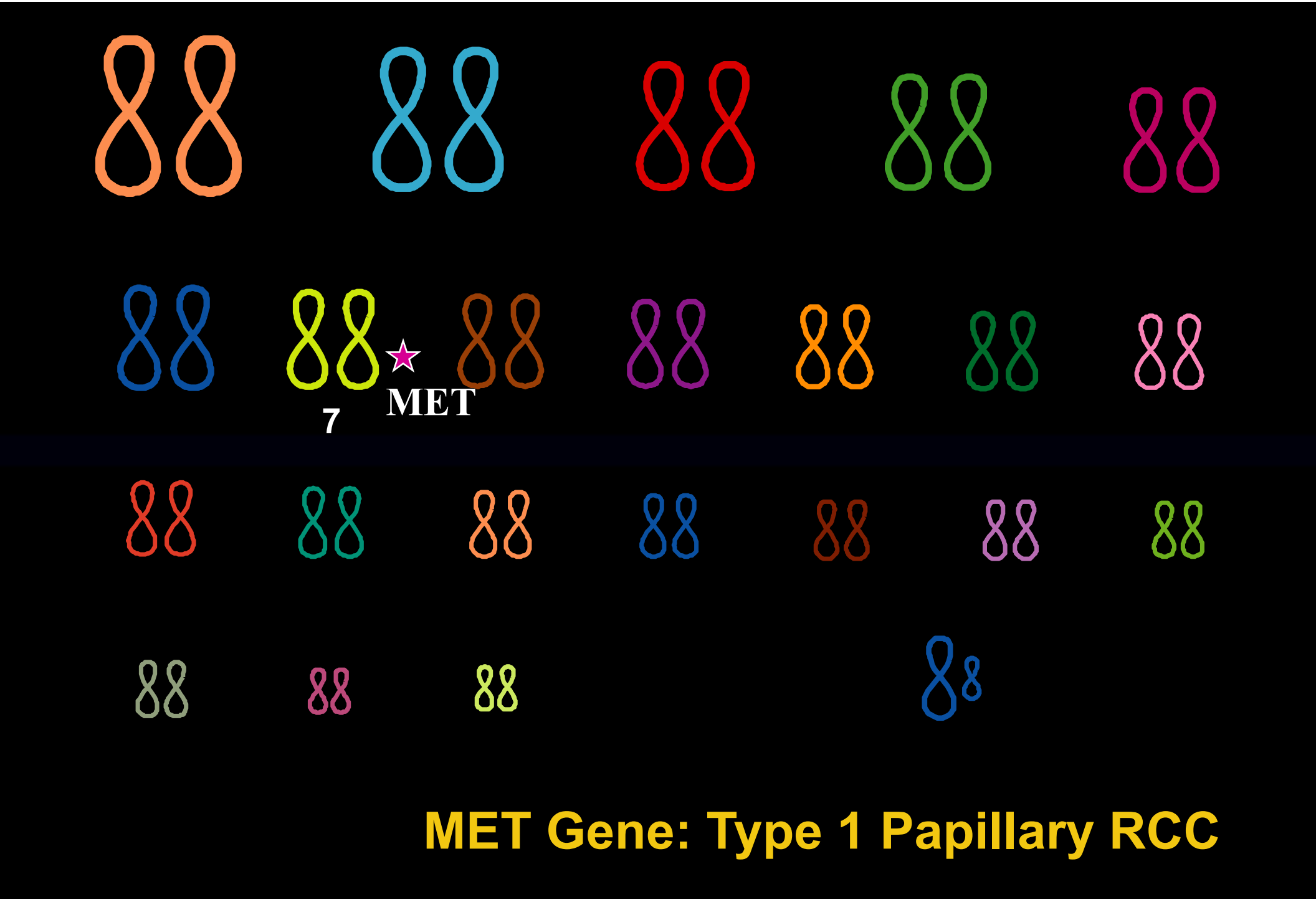
Surgical Management of HPRC-Associated Renal Carcinoma



"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

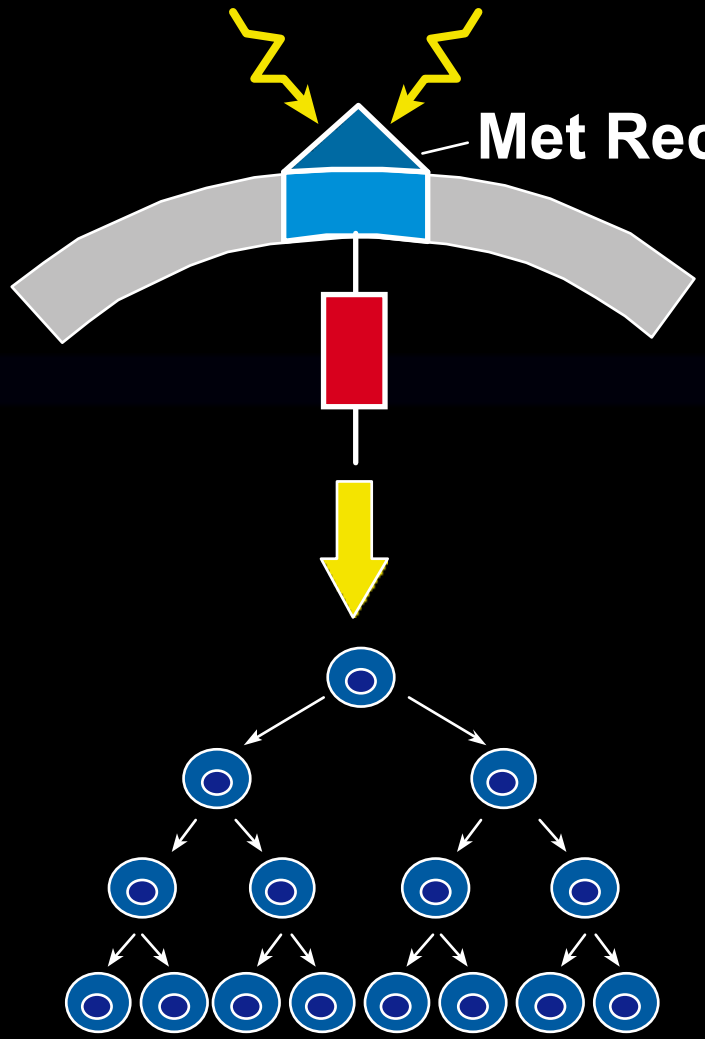
Surgery = nephron sparing enucleation

W J Urol 13: 1995
J Urol: 153:1995
J Urol 165:2001
J Urol 165:2001
J Urol 172:2004
J Urol 173 2005



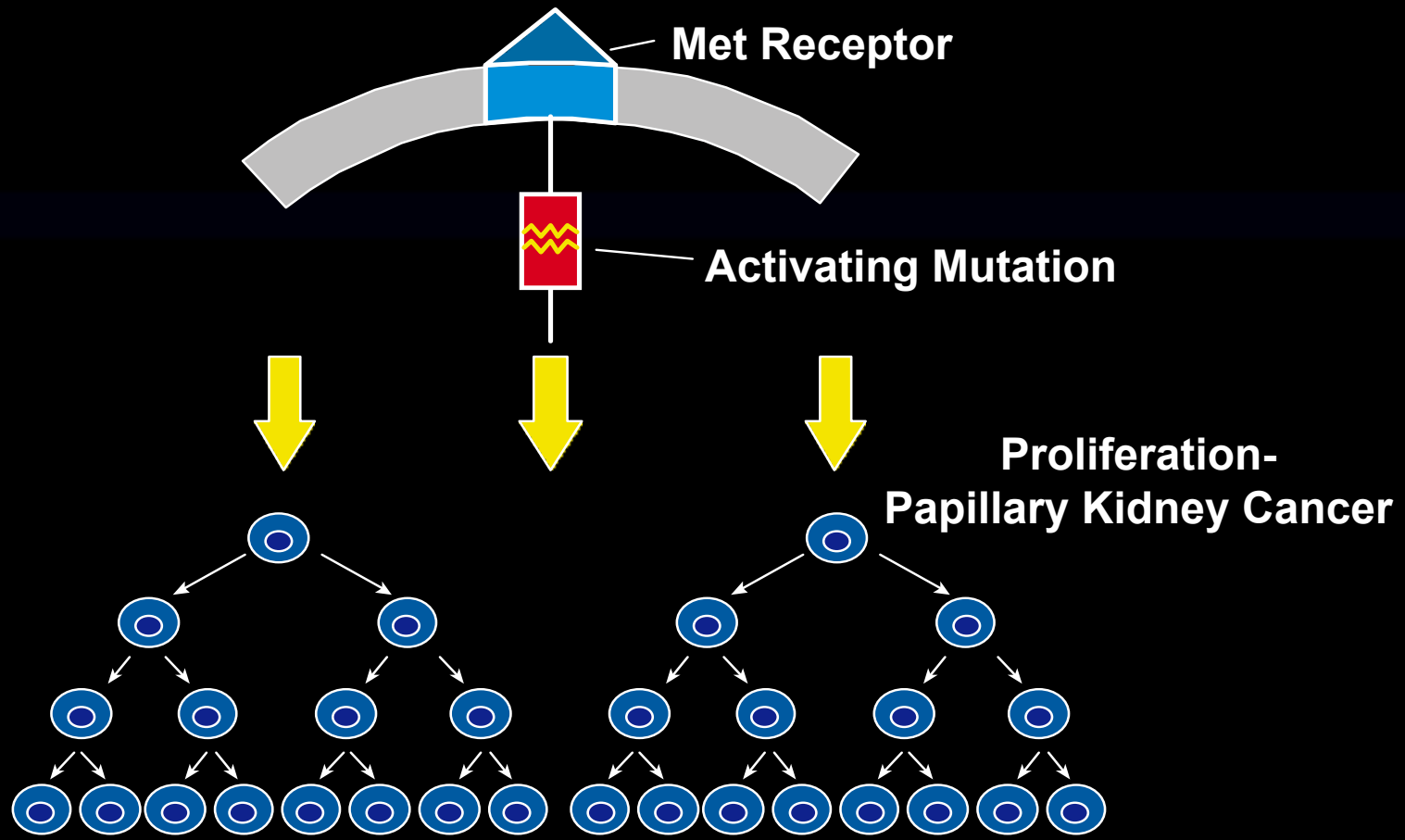
MET Gene: Type 1 Papillary RCC

MET is the HPRC Gene

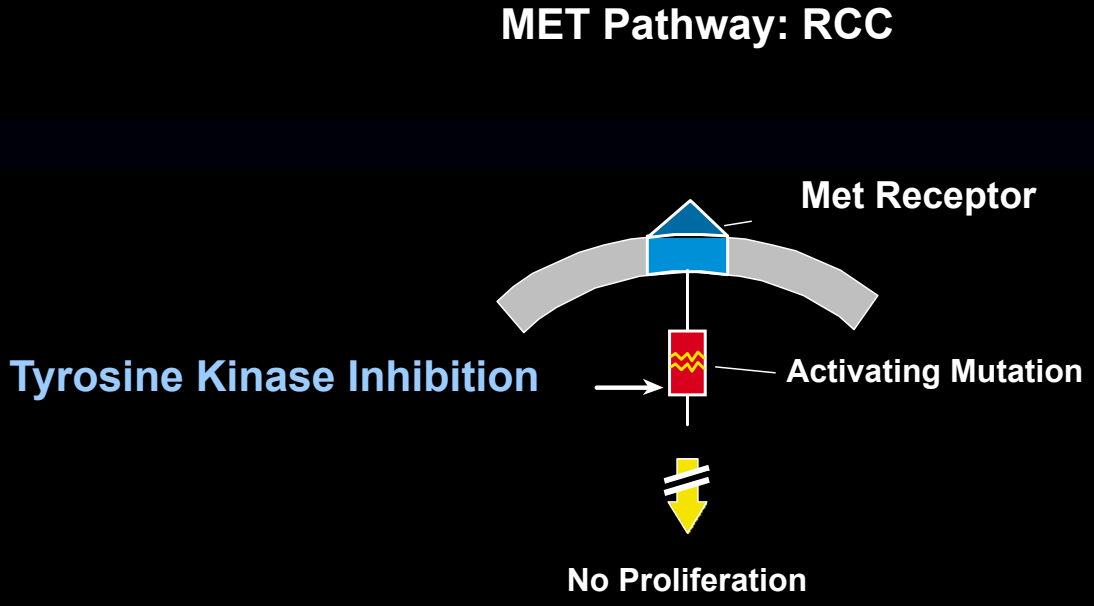


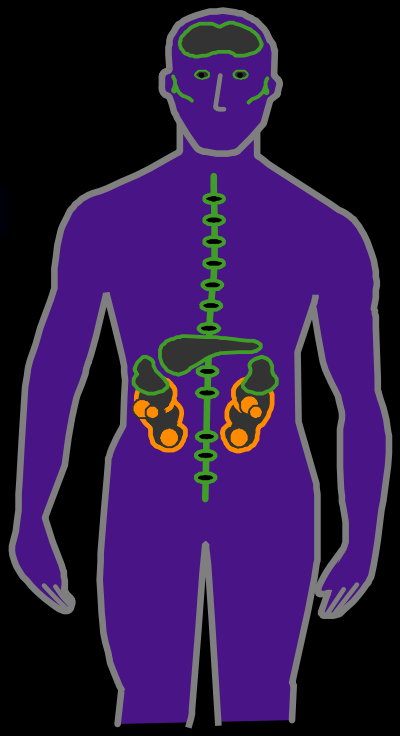
Nature Genetics 16:1997

Activating mutations in the tyrosine kinase domain of MET are found in the germline of HPRC patients



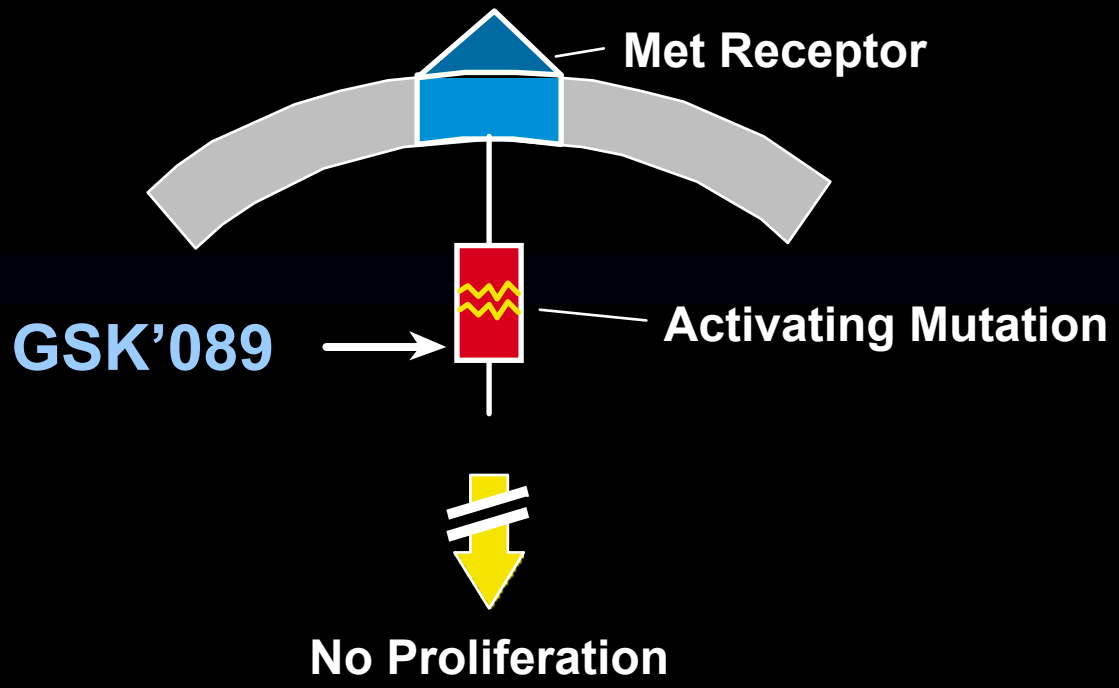
Targeting Met Gene Pathway: Hereditary Papillary Renal Carcinoma



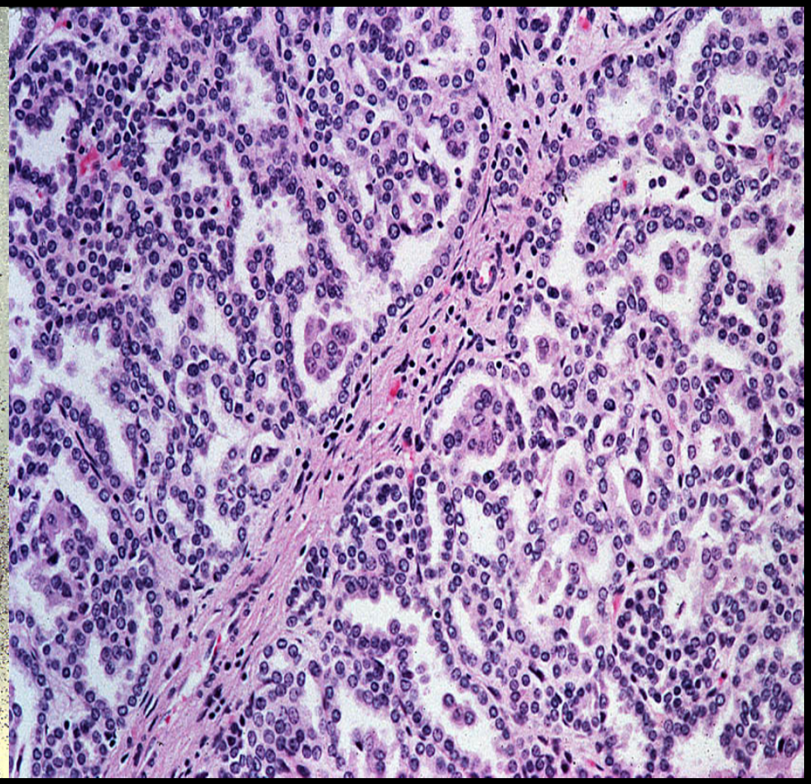


Hereditary Papillary Renal Cell Carcinoma (HPRC)

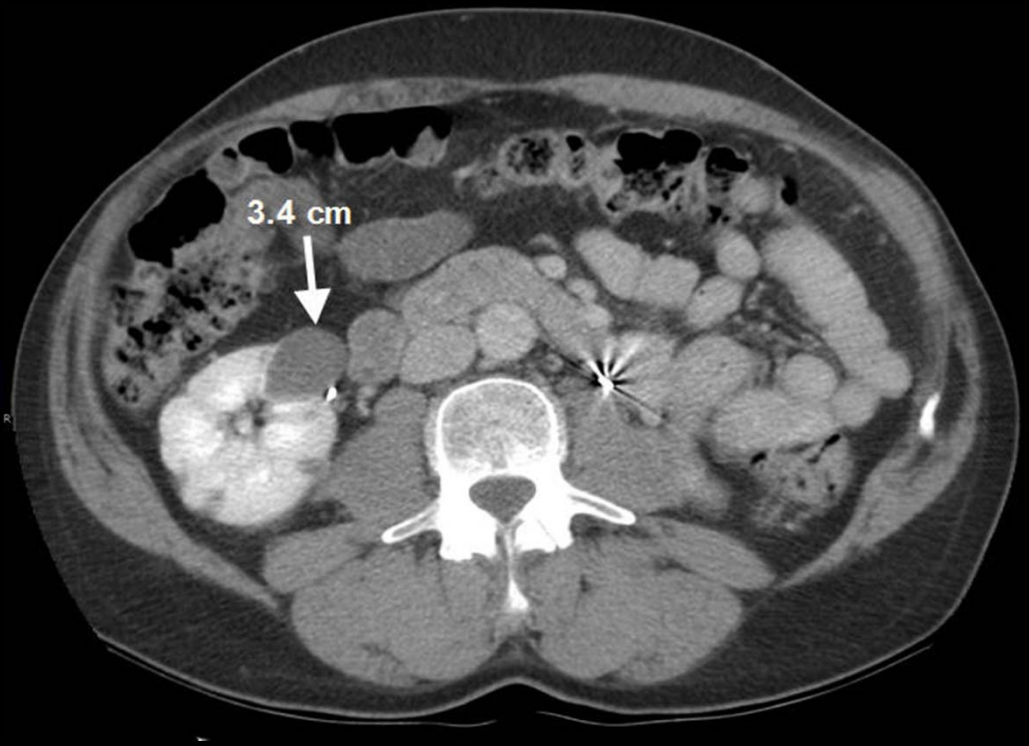
GSK'089:
Dual VEGFR and MET Inhibitor



Hereditary Papillary Renal Carcinoma (HPRC) Type 1



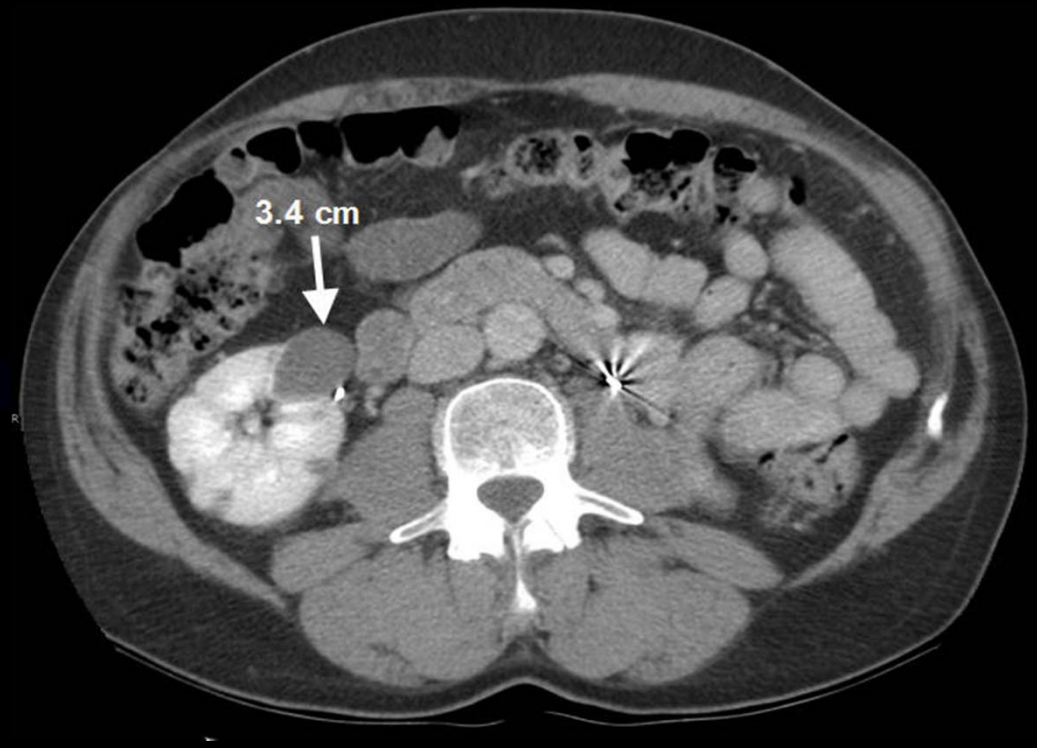
Regression of a renal tumor in a patient with HPRC treated with GSK'089



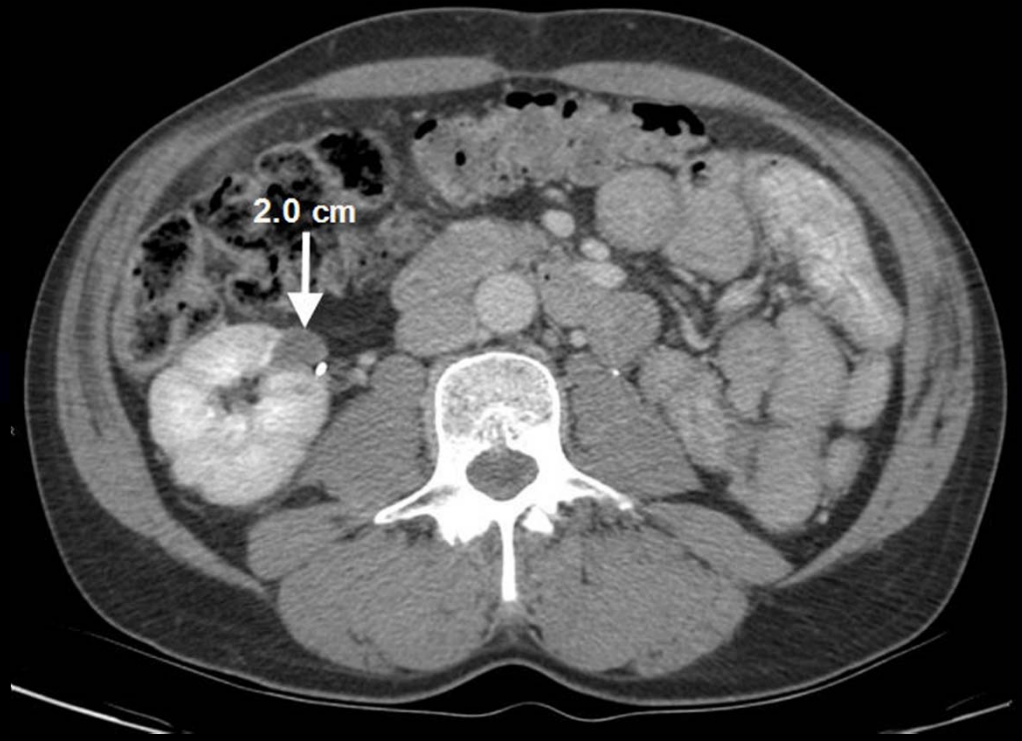
Pre-Treatment

ASCO:2008

Regression of a renal tumor in a patient with HPRC treated with GSK'089



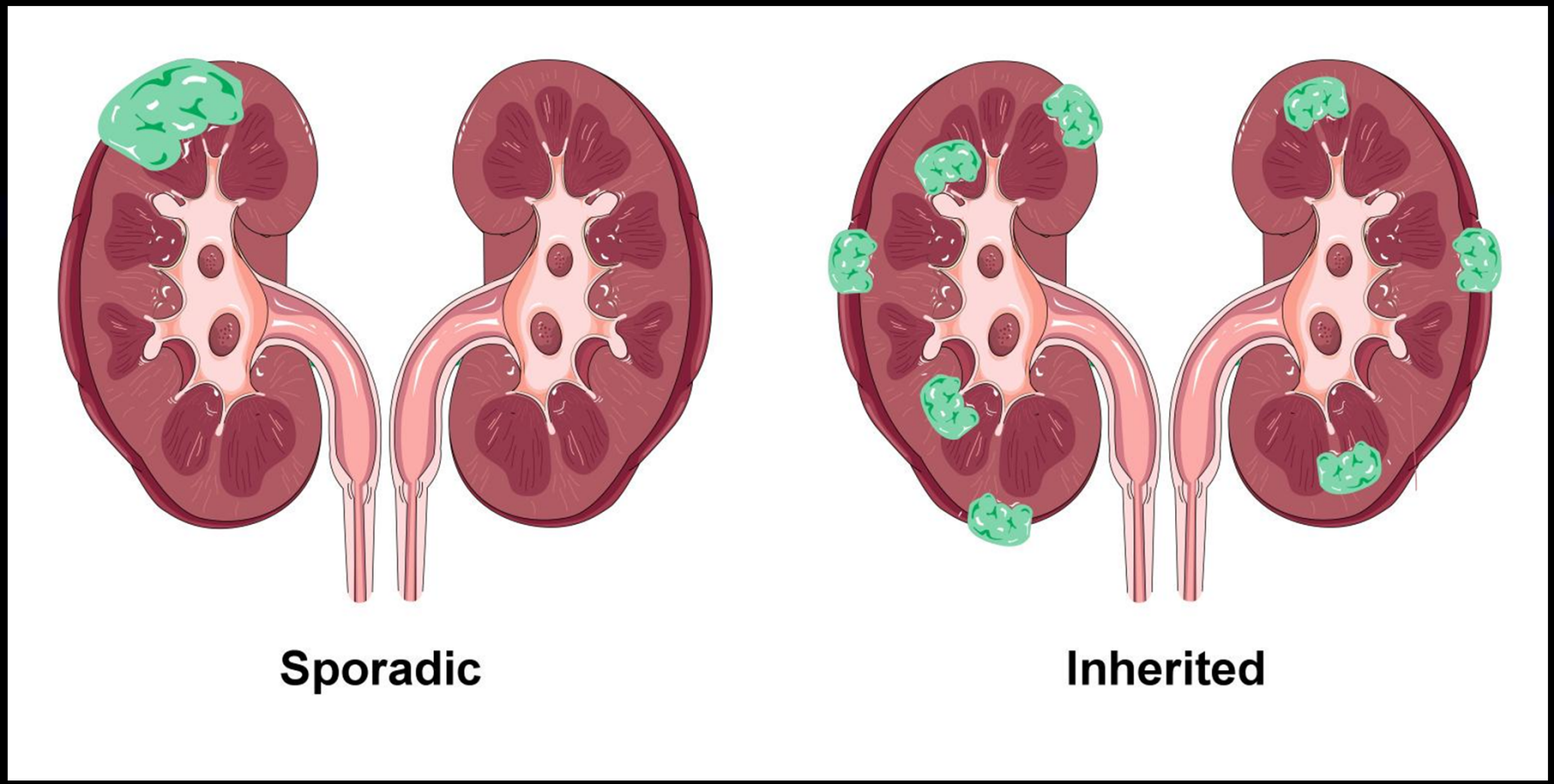
Pre-Treatment



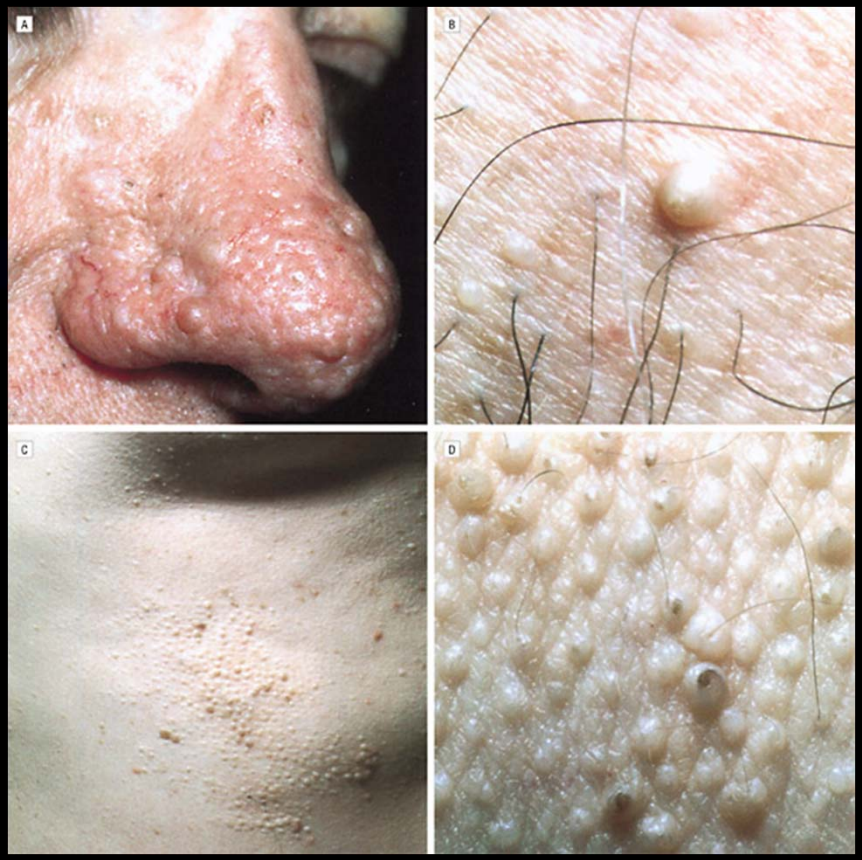
Following 24 cycles of therapy GSK'089

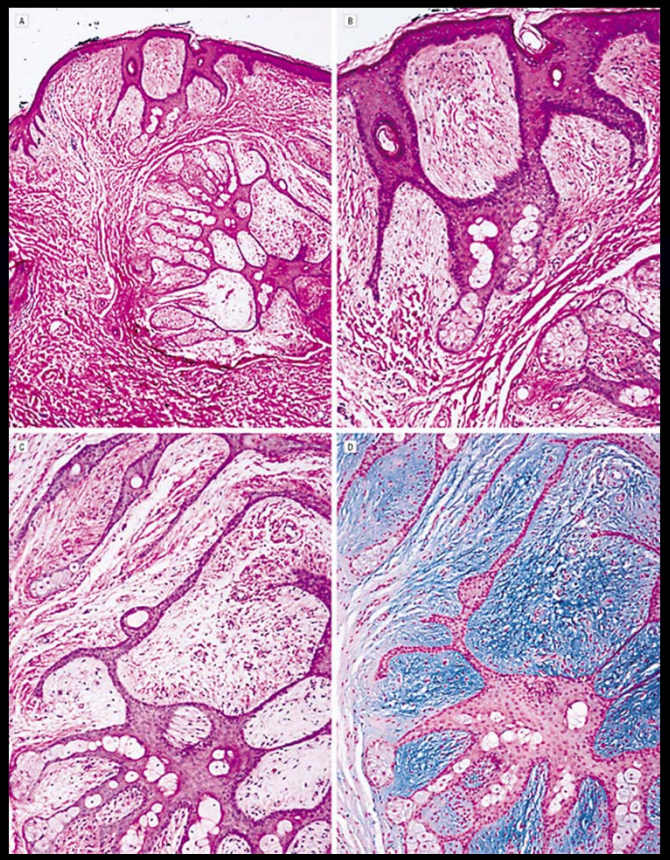
ASCO:2008

Inherited Renal Carcinoma
Birt Hogg Dubé (BHD)

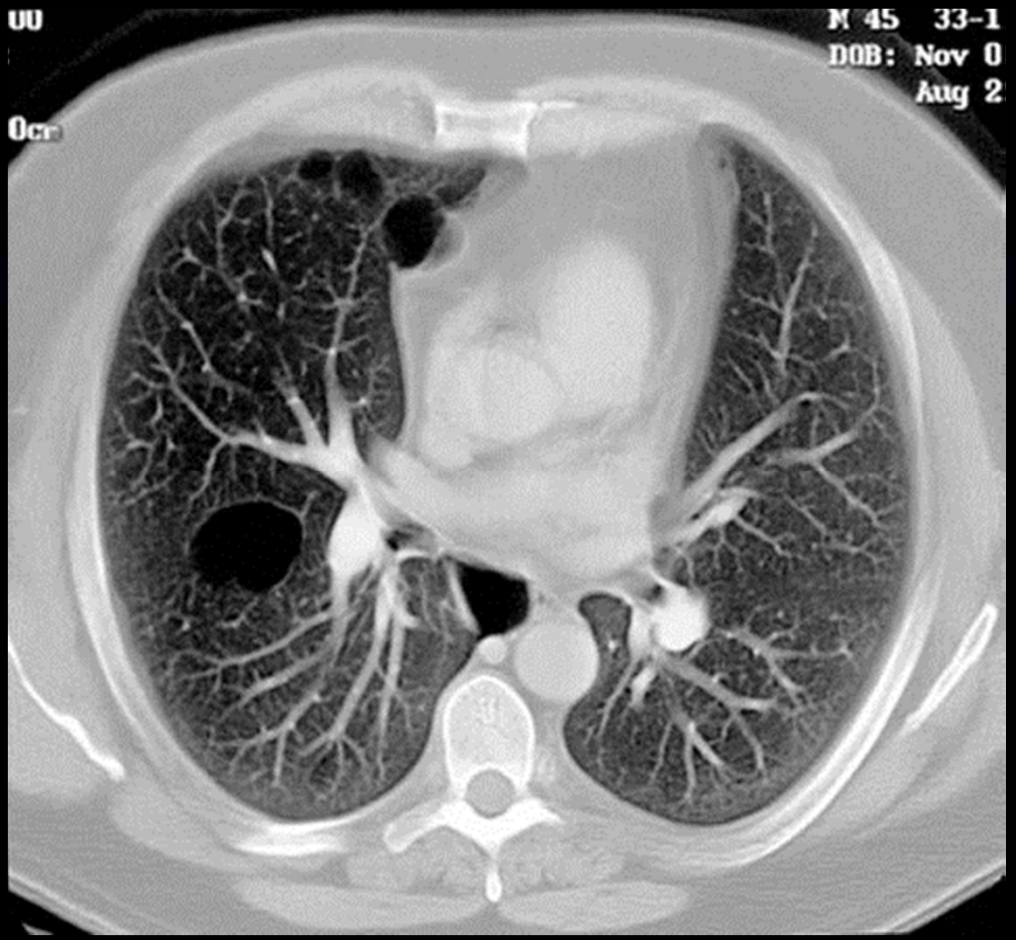


Birt Hogg Dubé
Cutaneous Manifestations

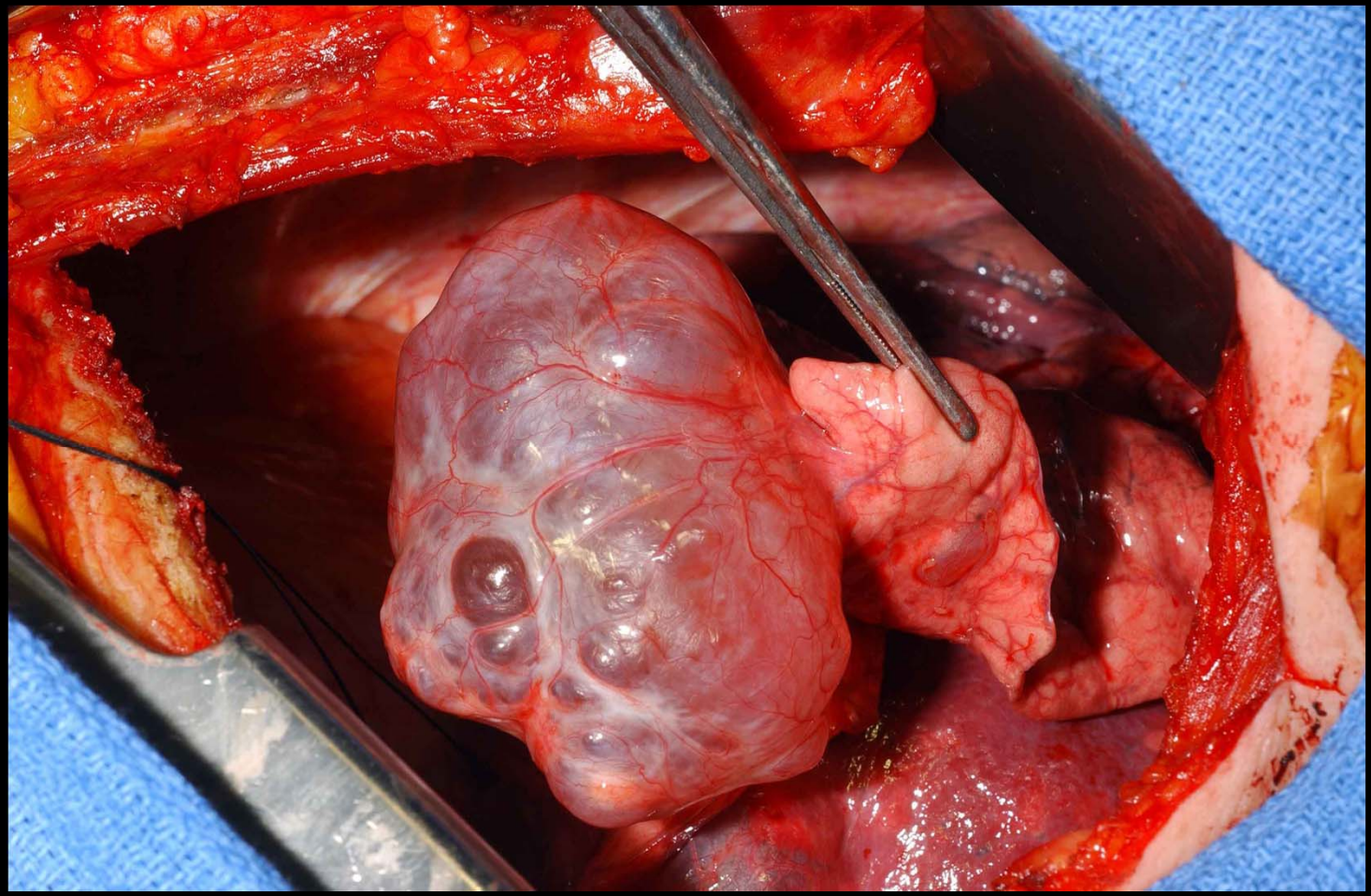




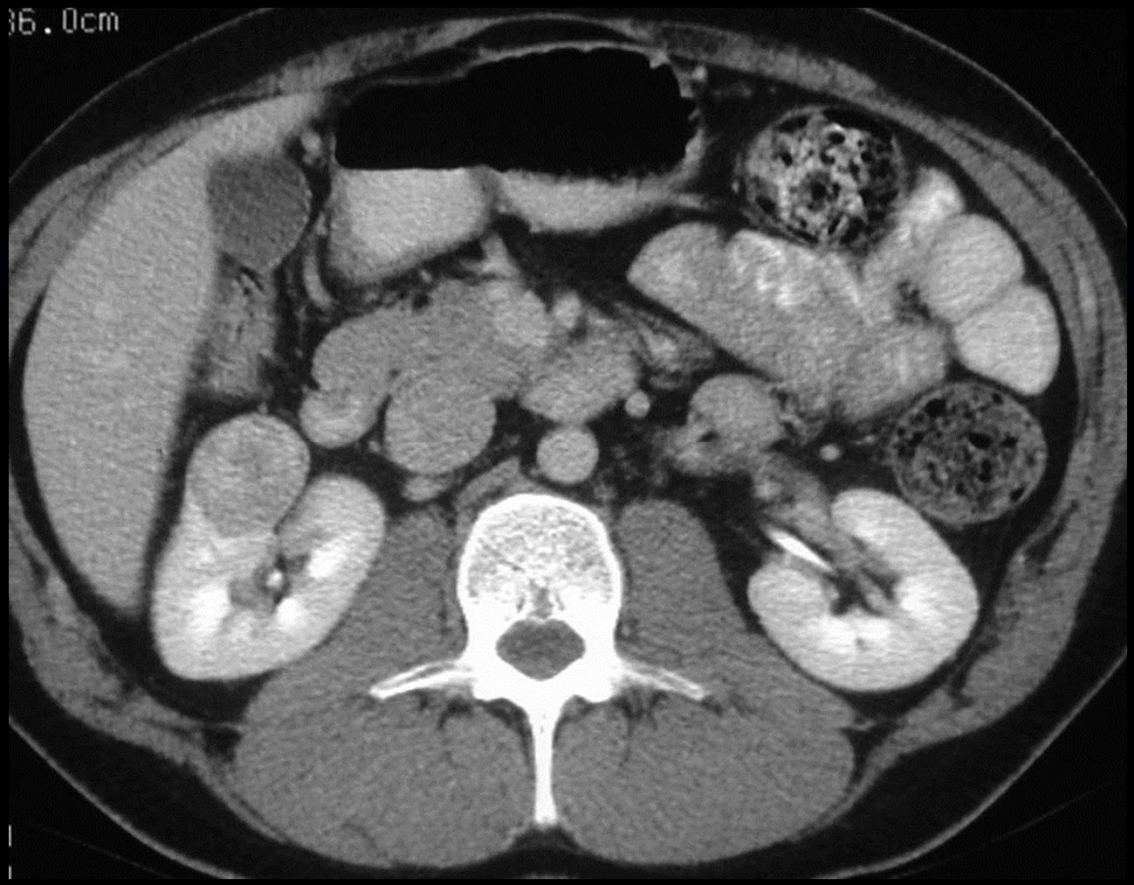
Birt Hogg Dubé Lung Cysts



Birt Hogg Dubé Lung Cysts

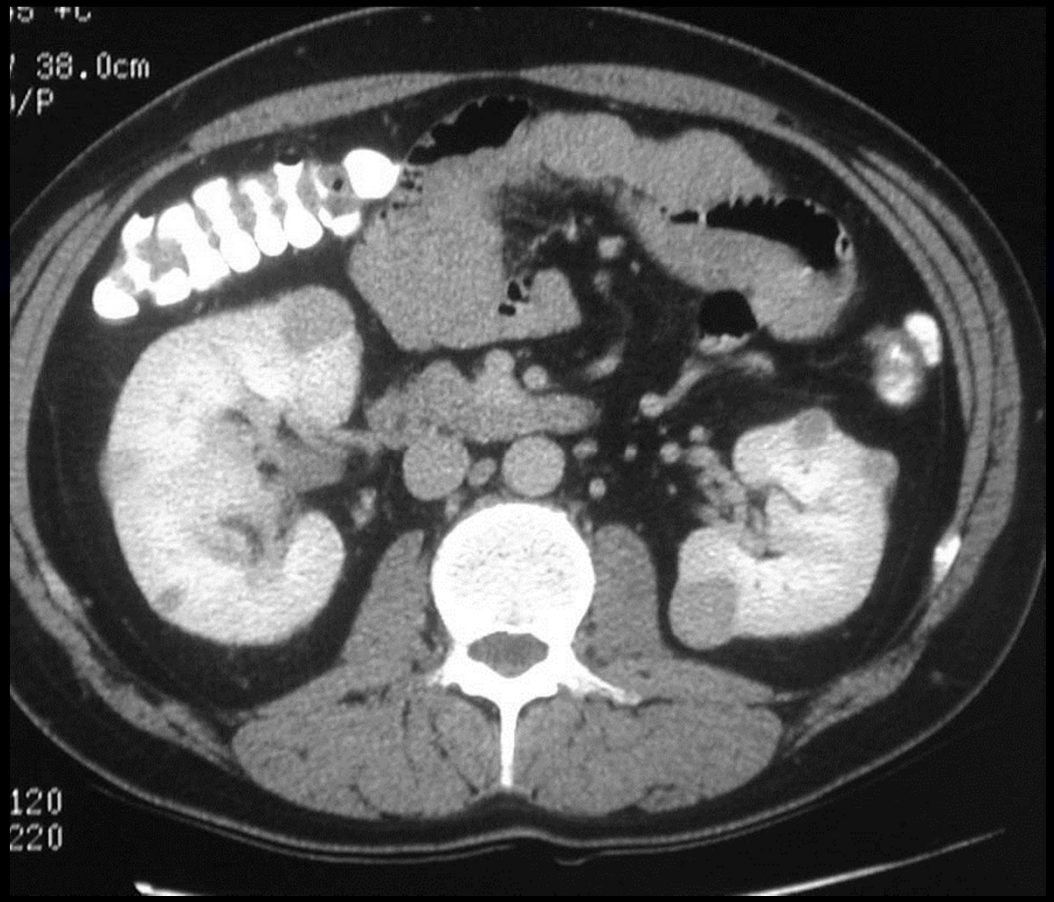


Kidney Tumors in Birt Hogg Dubé



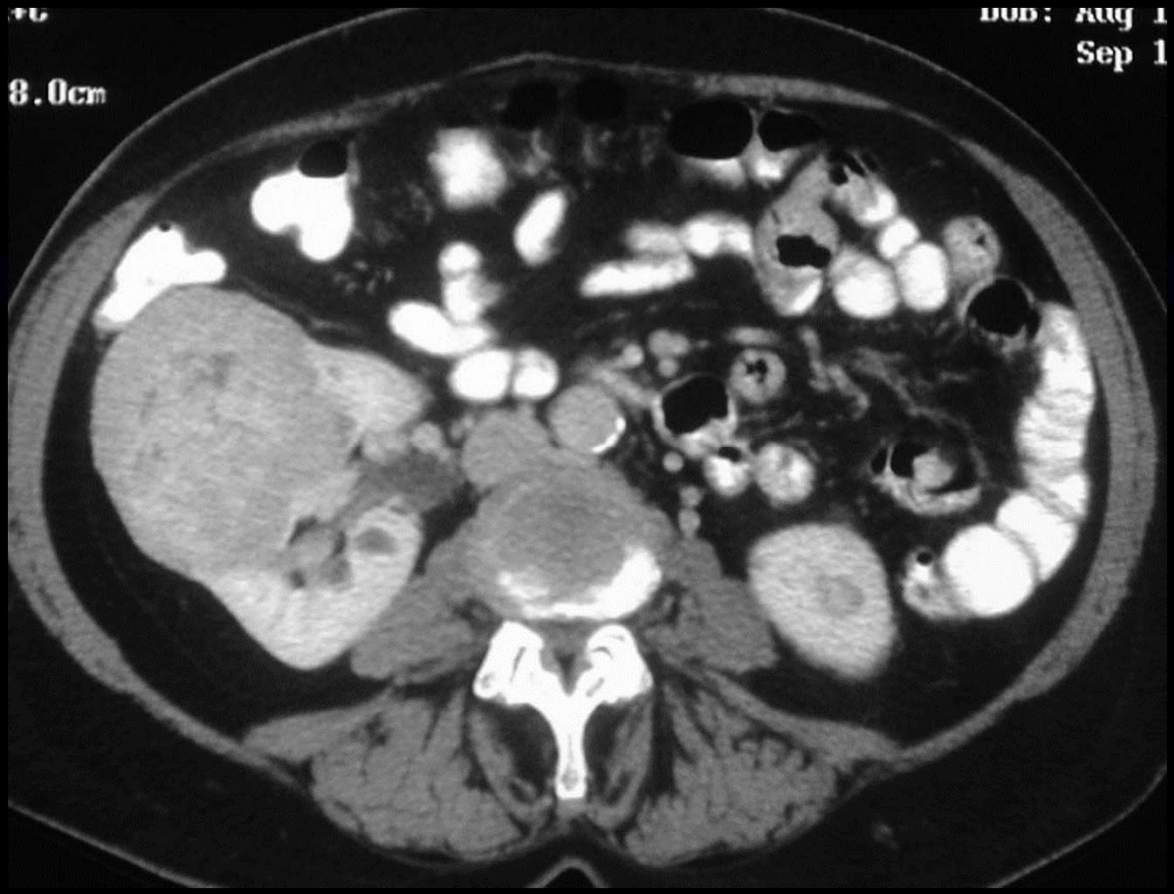
J Urol 173 2005

Kidney Tumors in Birt Hogg Dubé



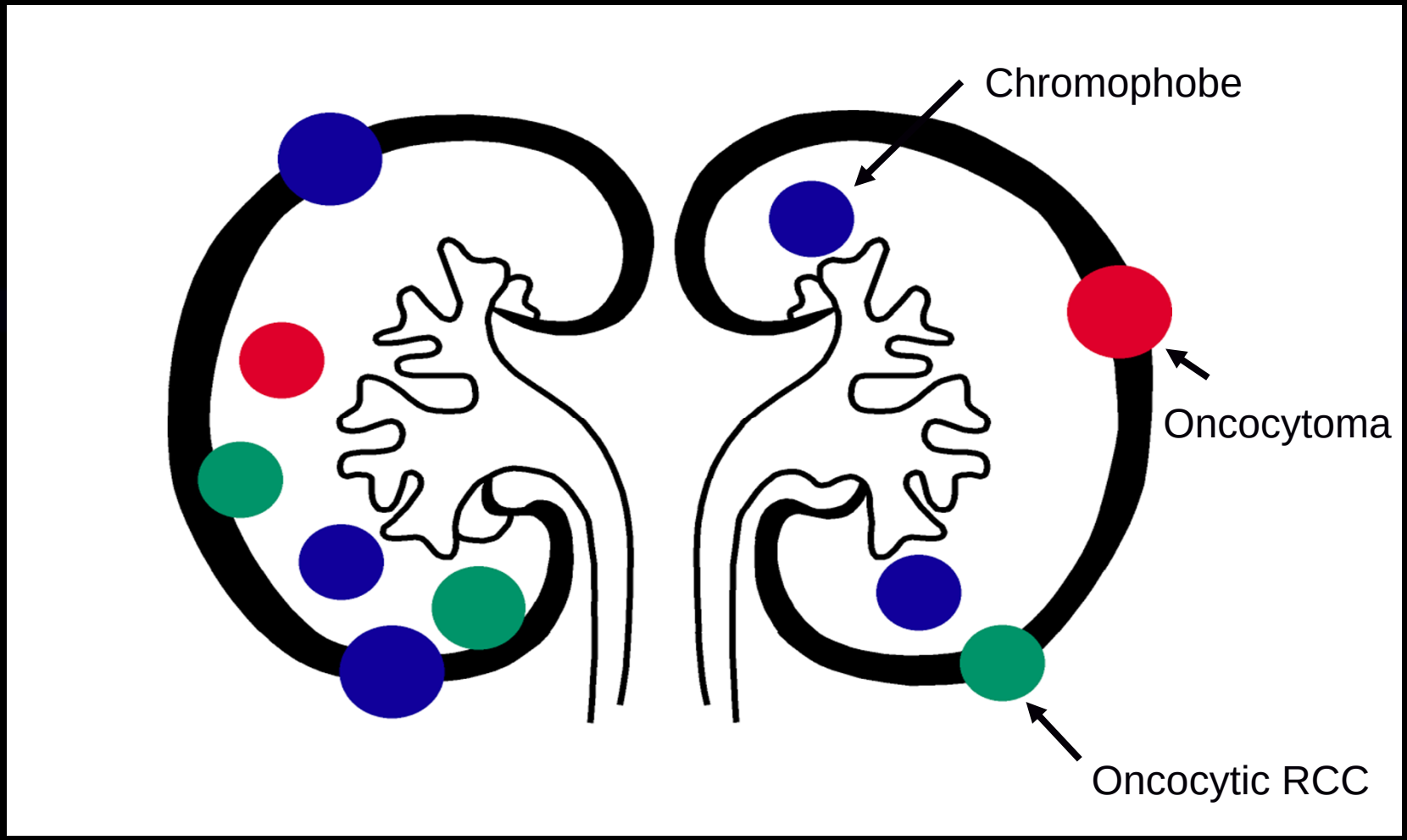
J Urol 173 2005

Kidney Tumors in Birt Hogg Dubé

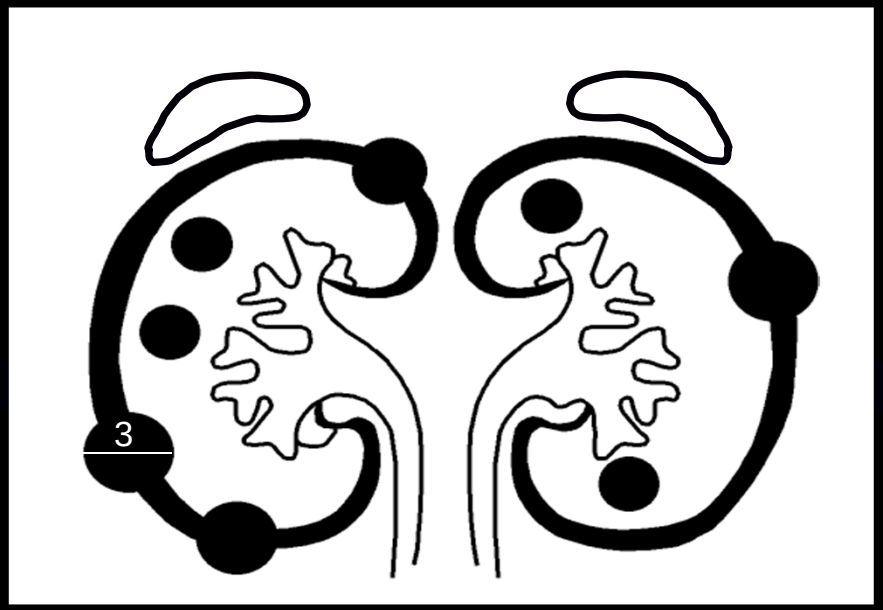


J Urol 173 2005

BHD Renal Tumor Pathology



Surgical Management of BHD-Associated Renal Carcinoma



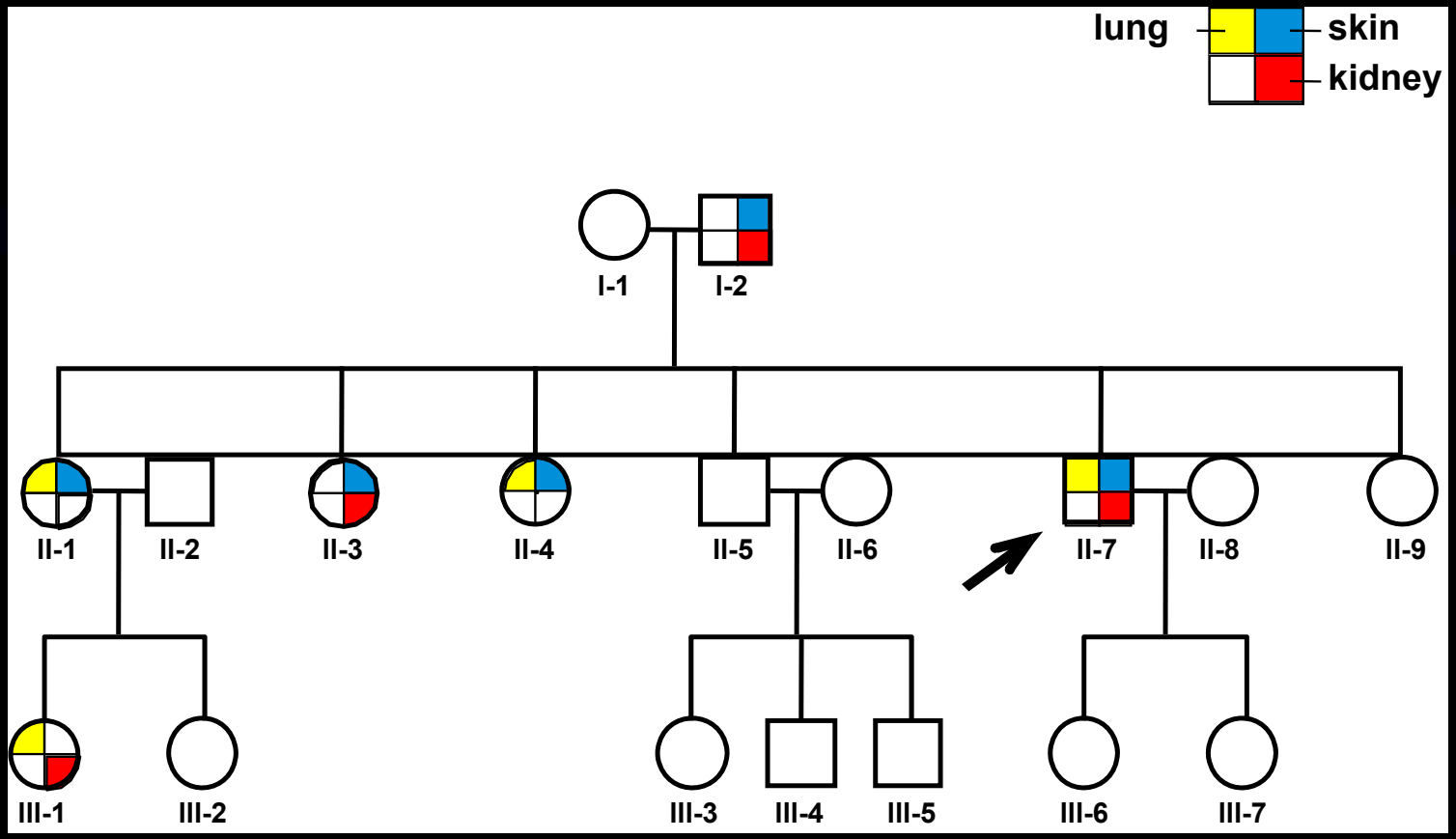
"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

Surgery = nephron sparing enucleation

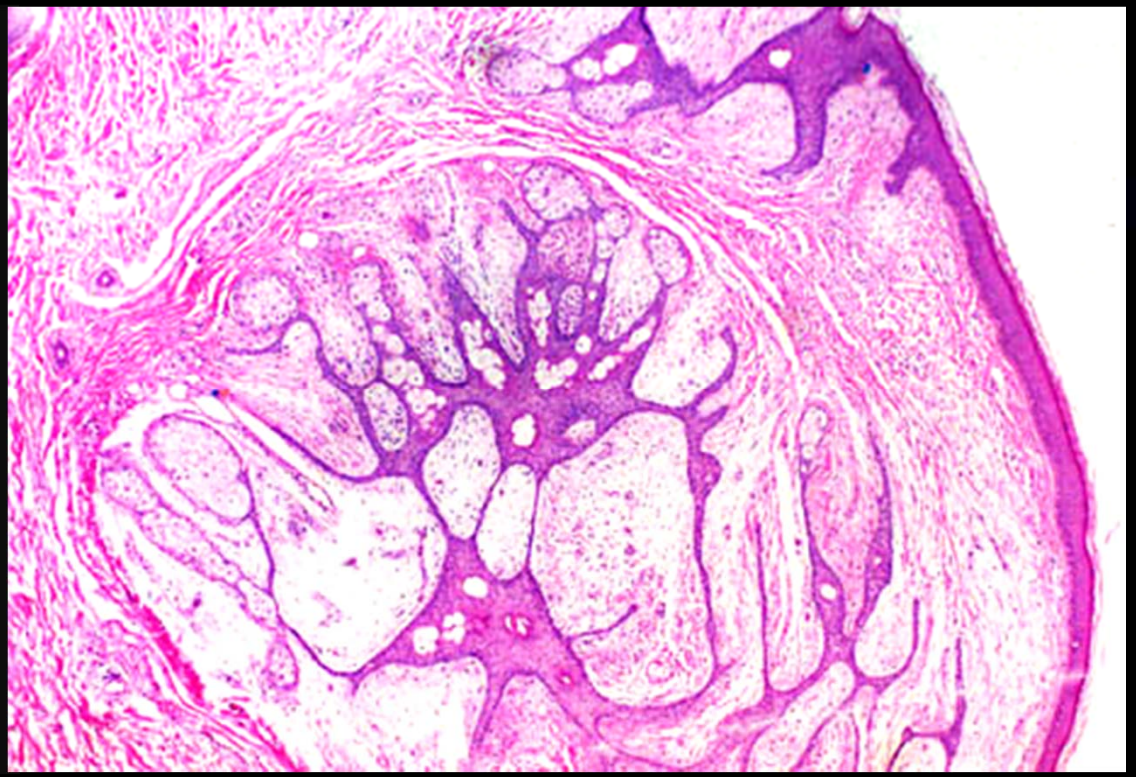
J Urol 173: 2005

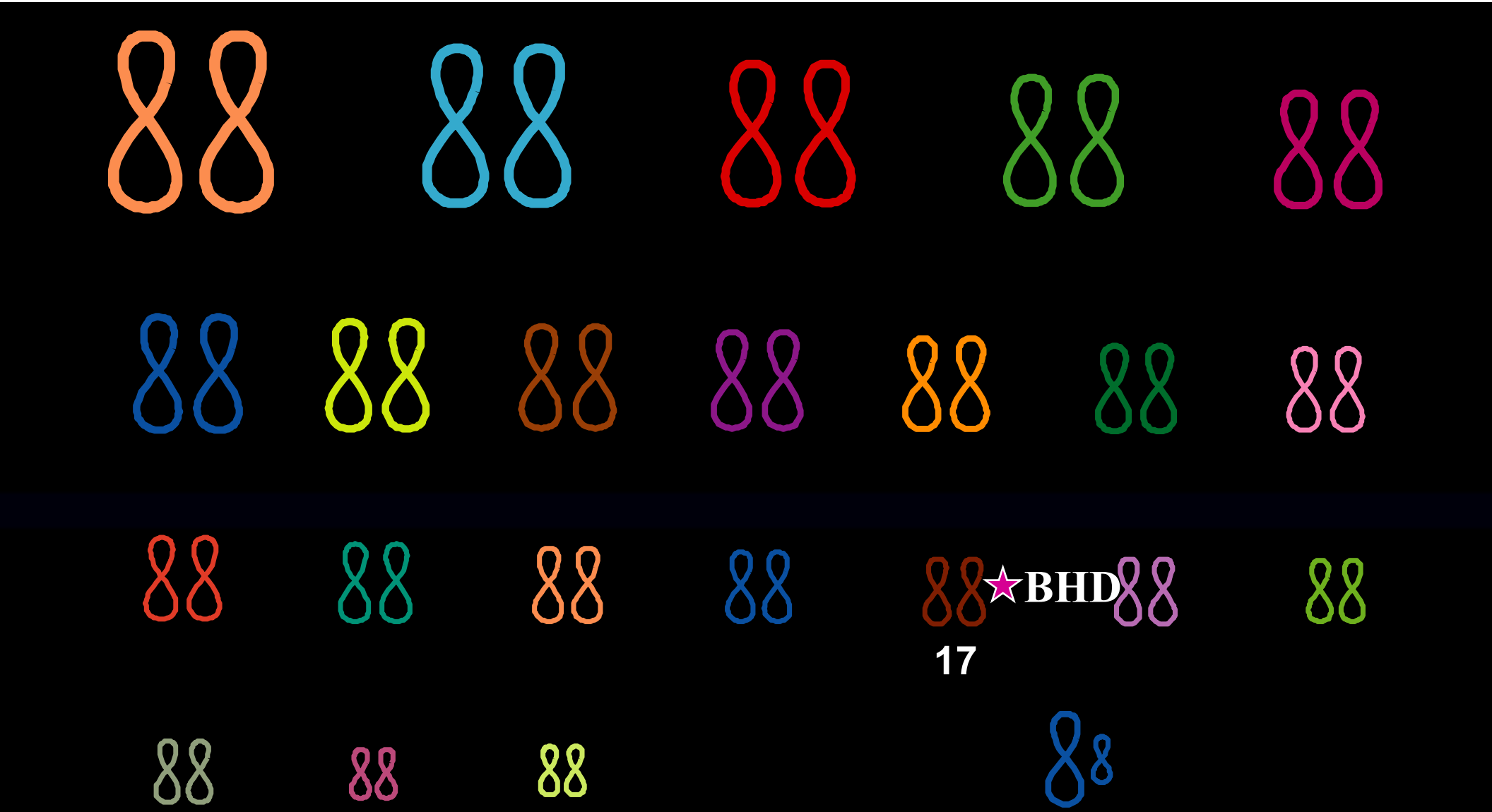
Am J Hum Genet 76: 2005

Identification of the BHD Gene



Cutaneous Fibrofolliculomas





BHD Gene: Chromophobe RCC

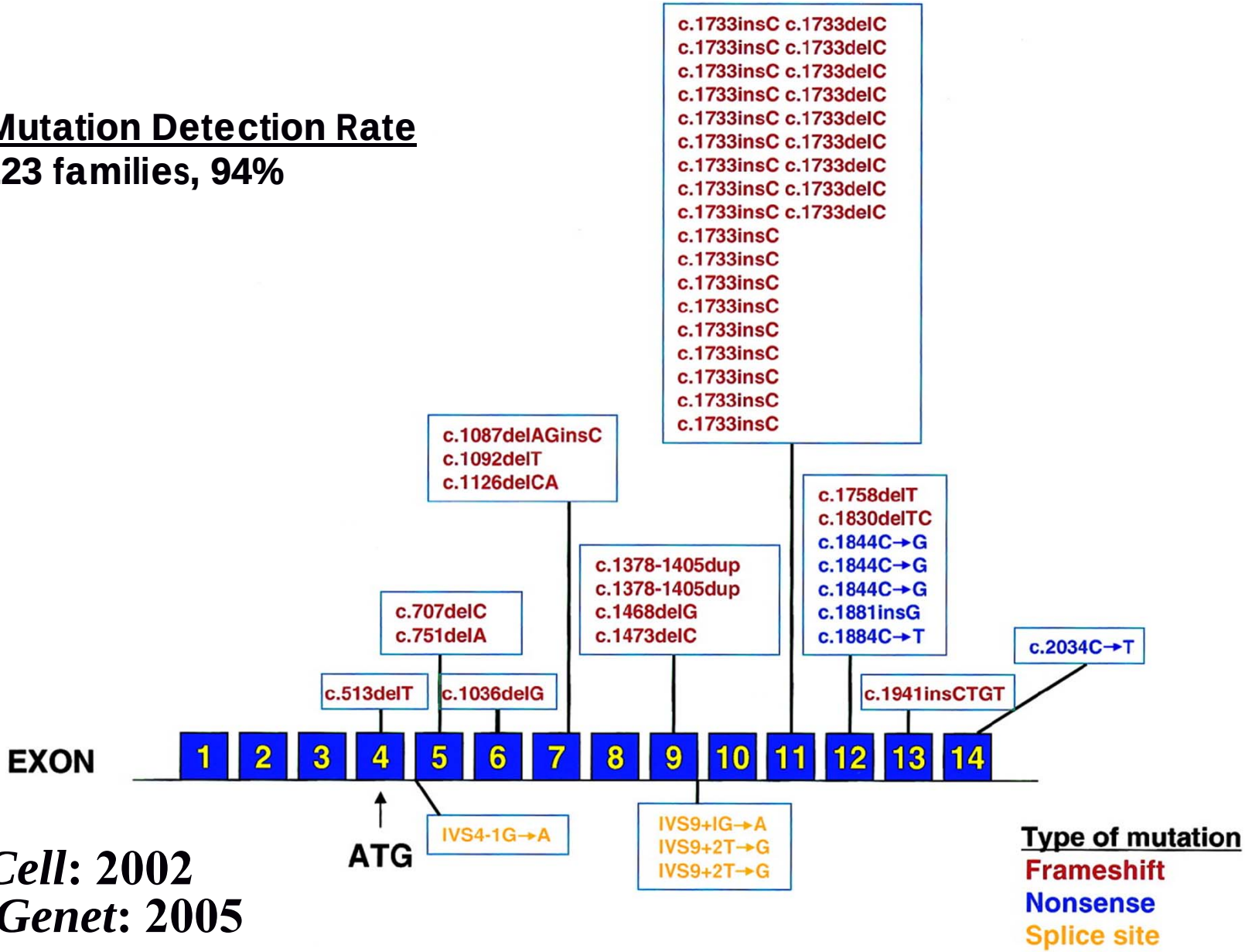
Am J Hum Genetics 69:2001

BHD predicted protein sequence

Cancer Cell: 2002

Germline mutations in BHD families

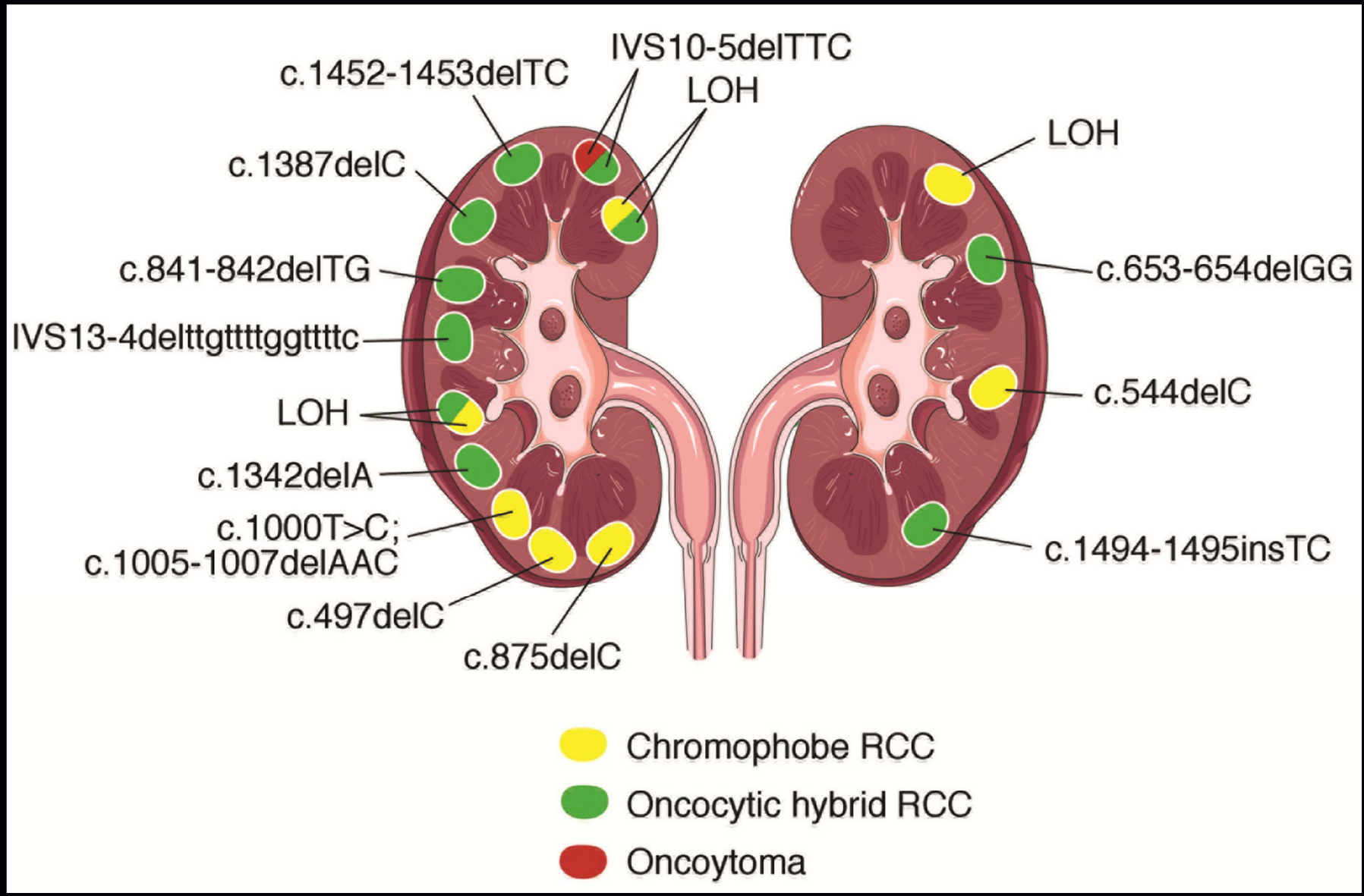
BHD Mutation Detection Rate
116/123 families, 94%



Cancer Cell: 2002
Am J H Genet: 2005

What Kind of Gene is BHD?

Somatic mutations in tumors from a single BHD patient



UOK 257, BHD -/- RCC cell line, is tumorigenic

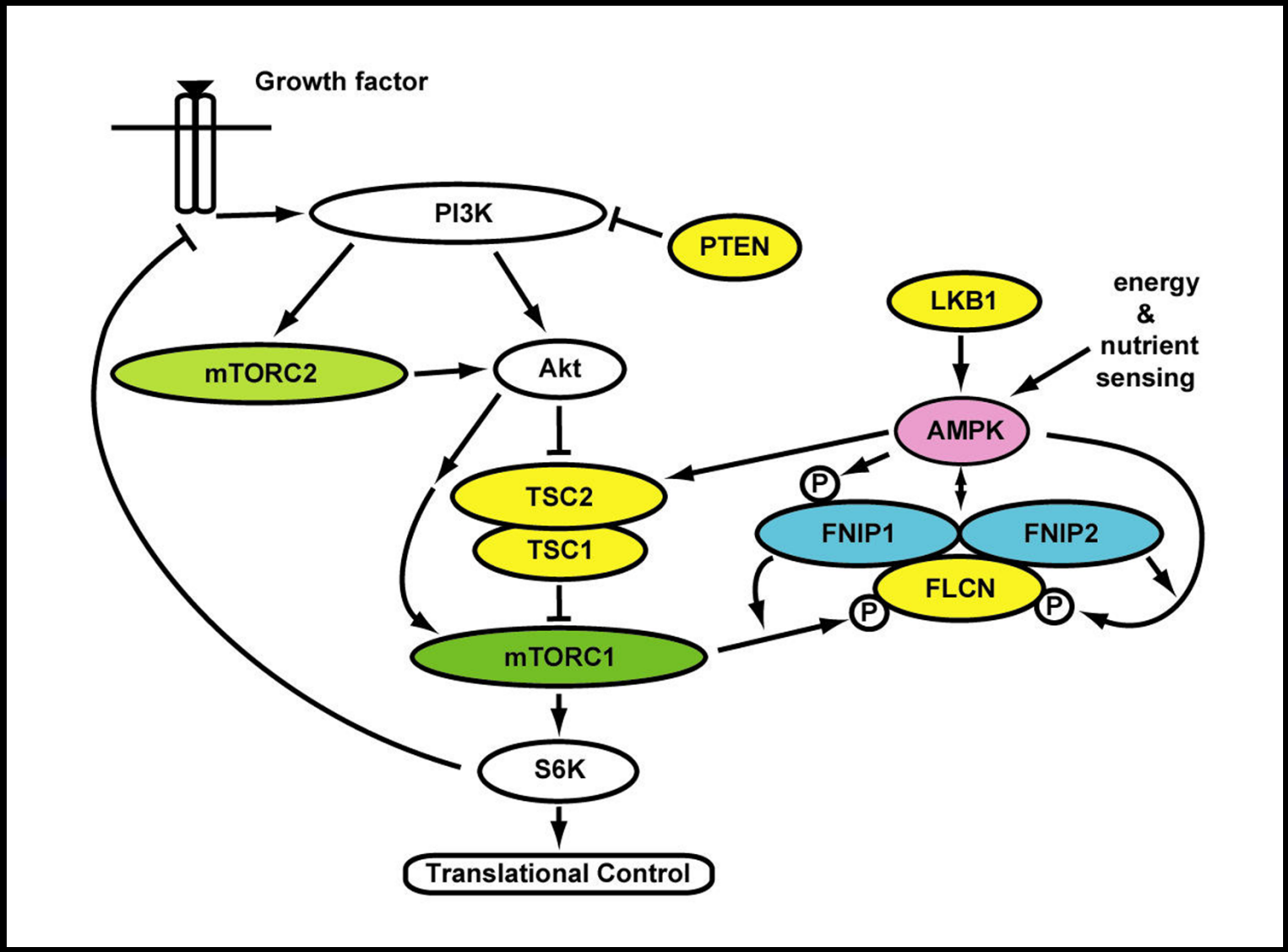
UOK257

UOK 257-2, BHD restored RCC cell line, is not tumorigenic

UOK257-2

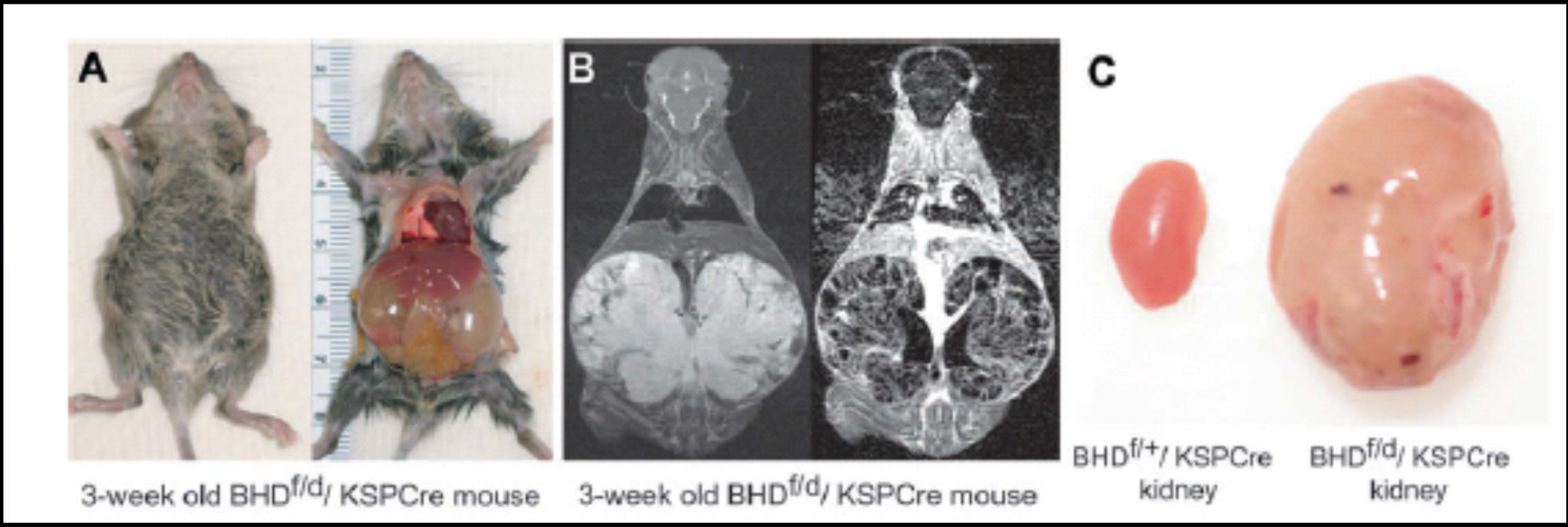
How Does the BHD Gene Function?

Folliculin-FNIP1/2-AMPK Interactions



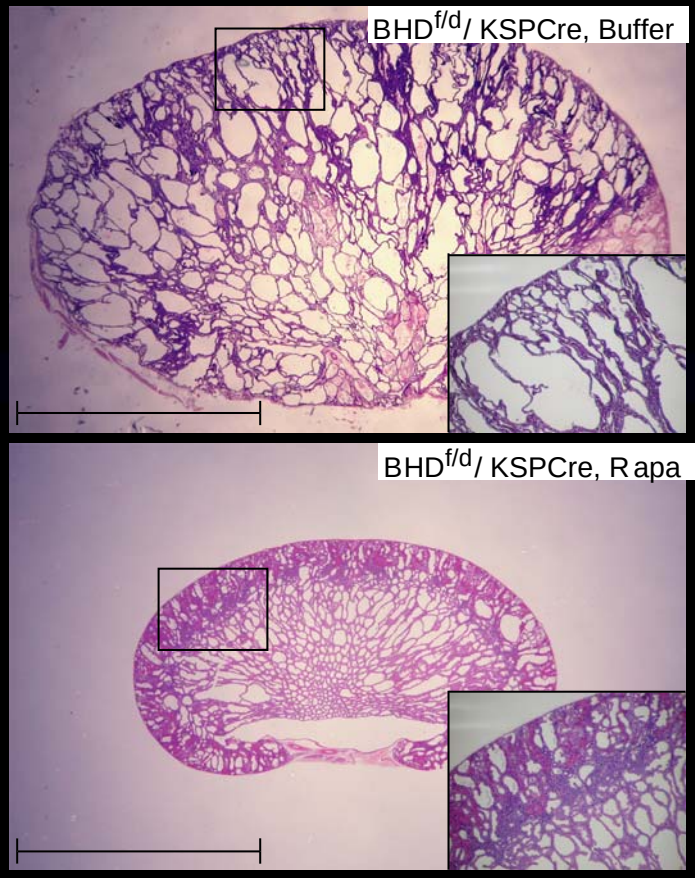
PNAS 103:2006
Gene 415:2008
PNAS 103:2009

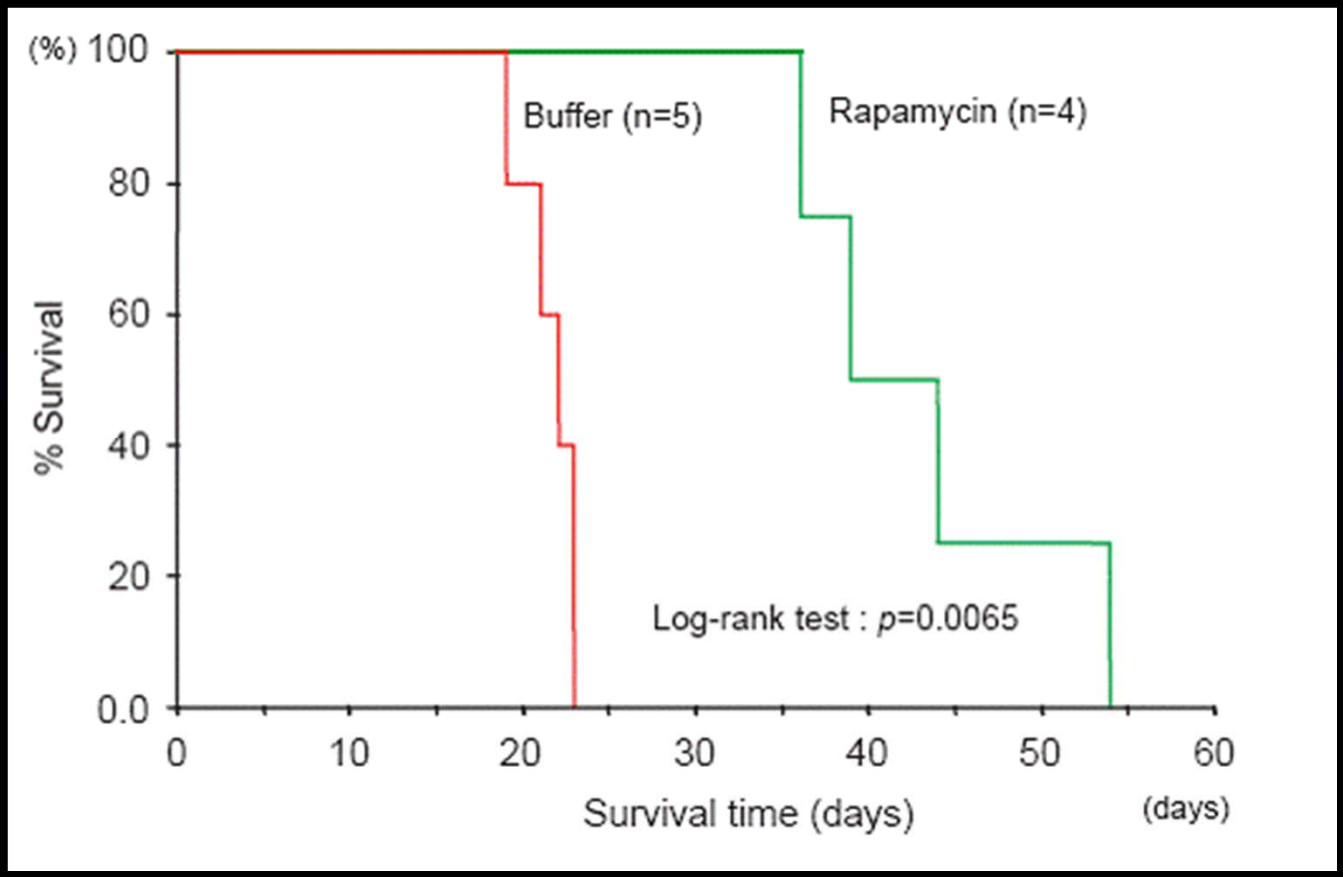
BHD Deletion Specifically in the Kidney



Baba, *JNCI* 100:2008

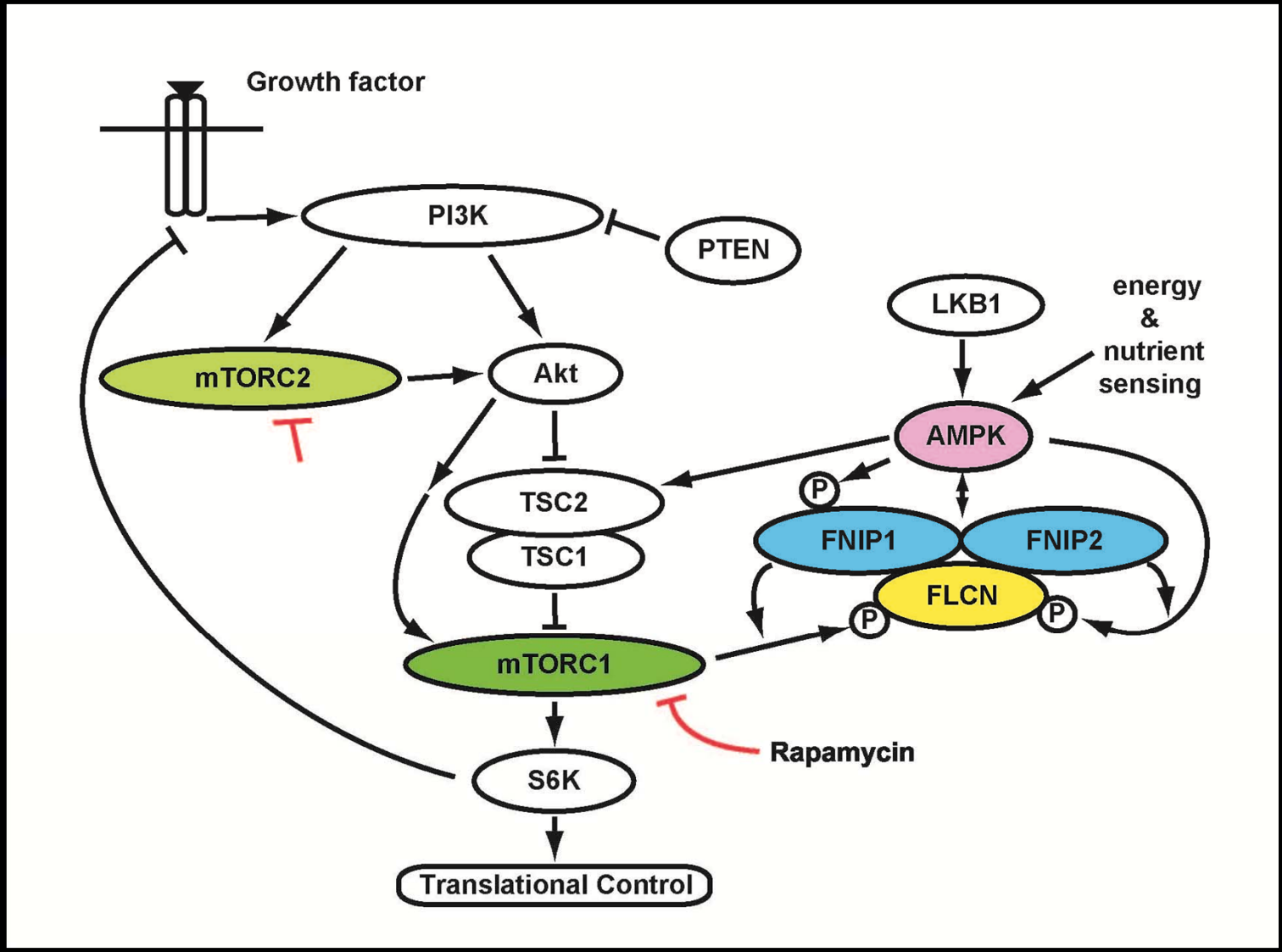
BHD Flox/Delete KspCre
Renal Phenotype & Survival +/- Rapamycin





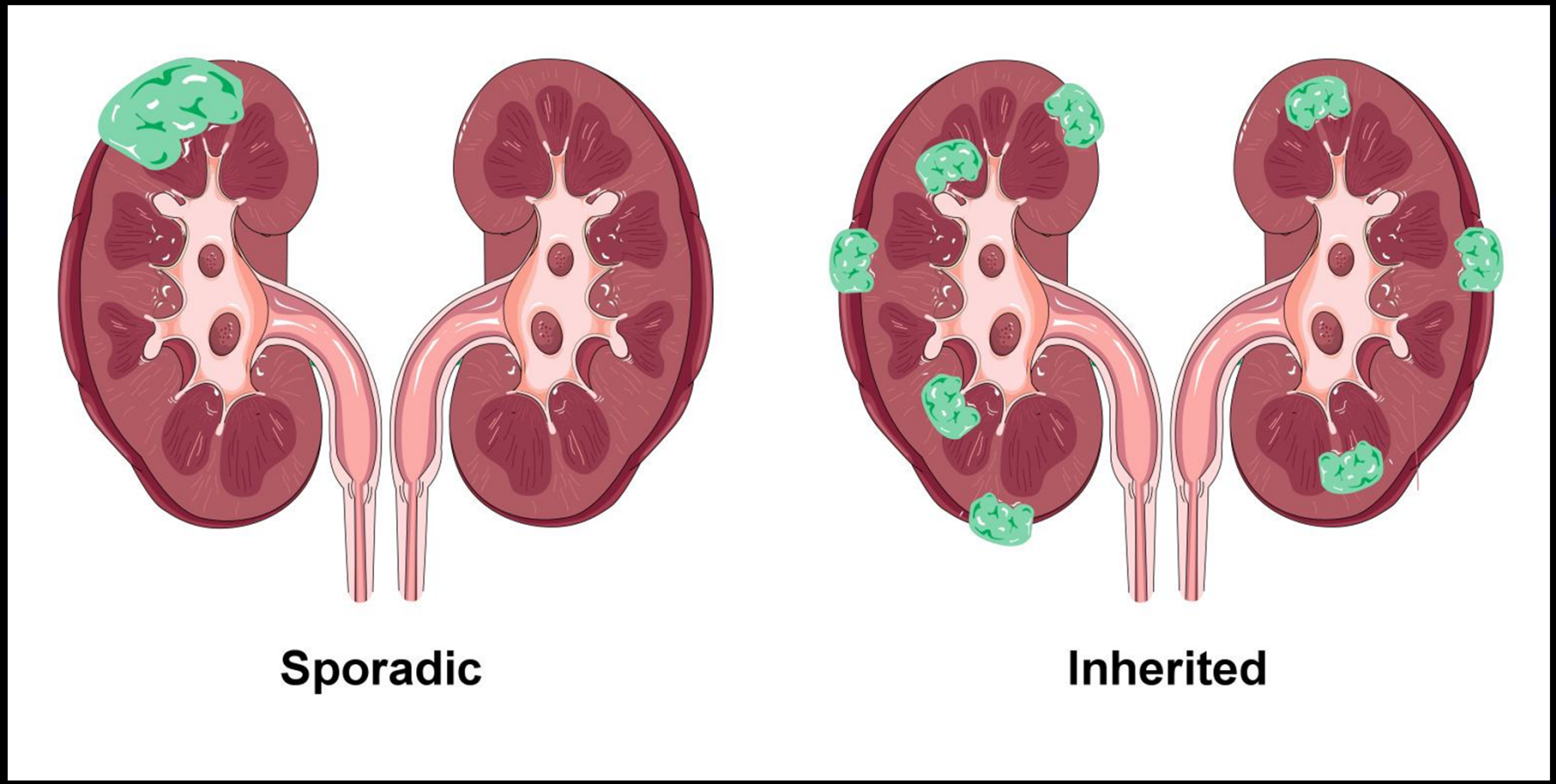
Baba, *JNCI* 100:2008

Targeting the BHD Pathway: mTORC1 + mTORC2



PNAS 103:2009

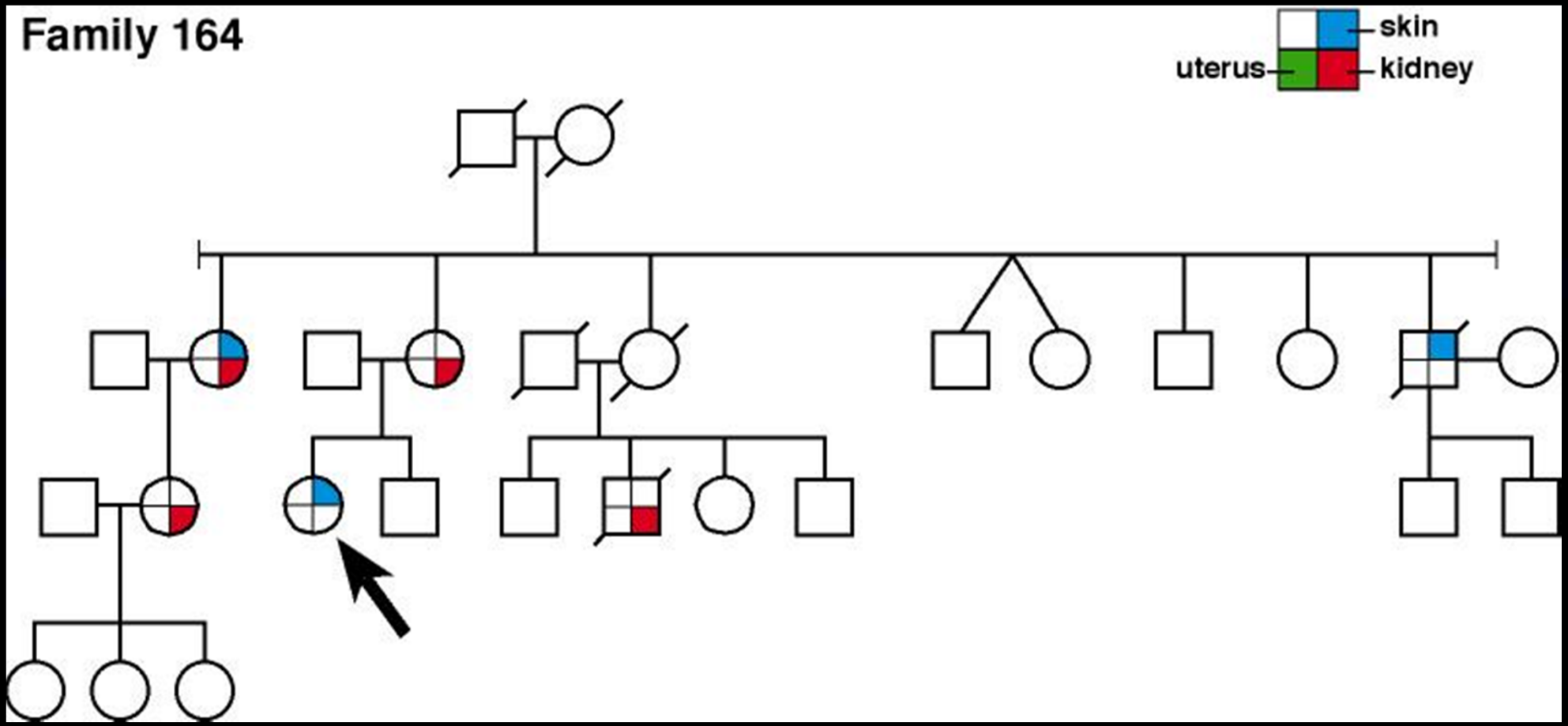
Inherited Renal Carcinoma: Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)



Hereditary Leiomyomatosis Renal Cell Carcinoma: HLRCC

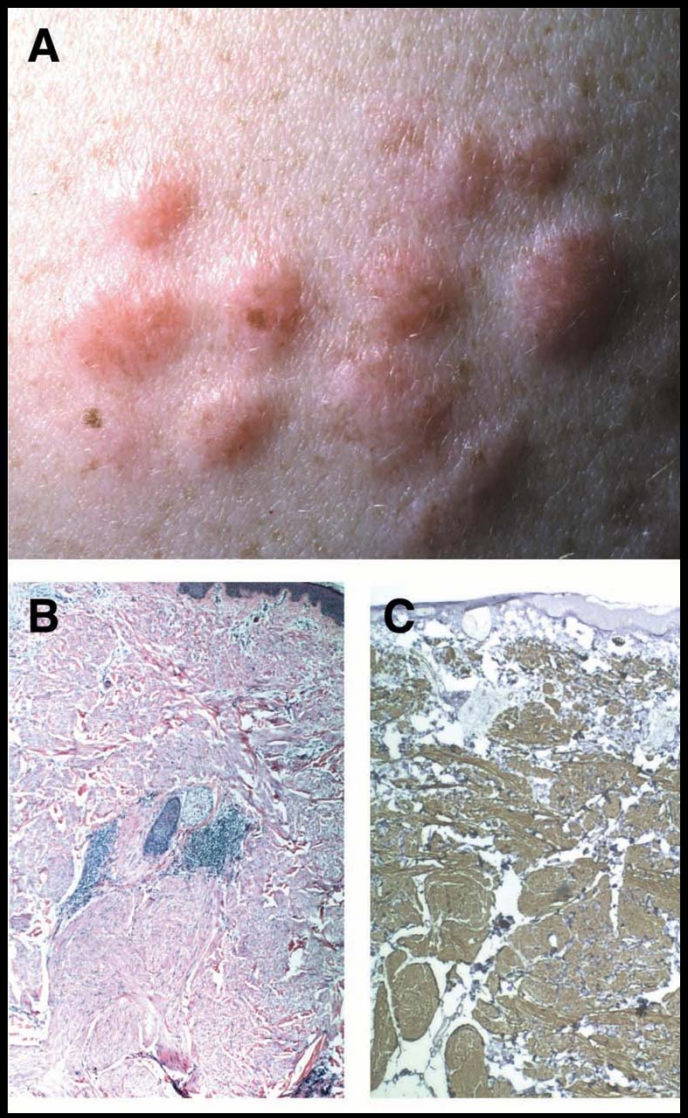
- Cutaneous leiomyomas
- Uterine leiomyomas (fibroids)
- Renal cell carcinoma

HLRCC Kindred



J Urol:153 1995

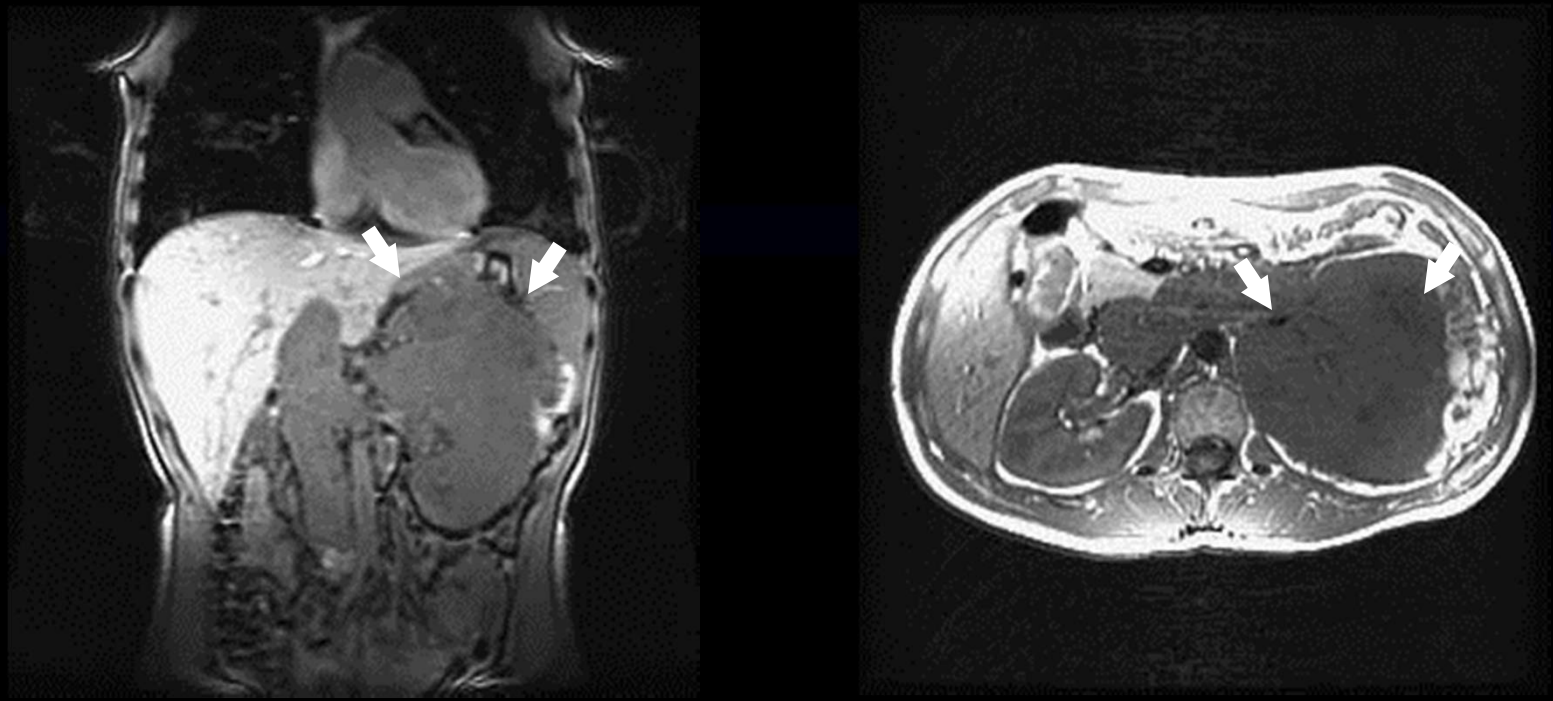
HLRCC: Cutaneous Manifestations



HLRCC: Uterine leiomyomas

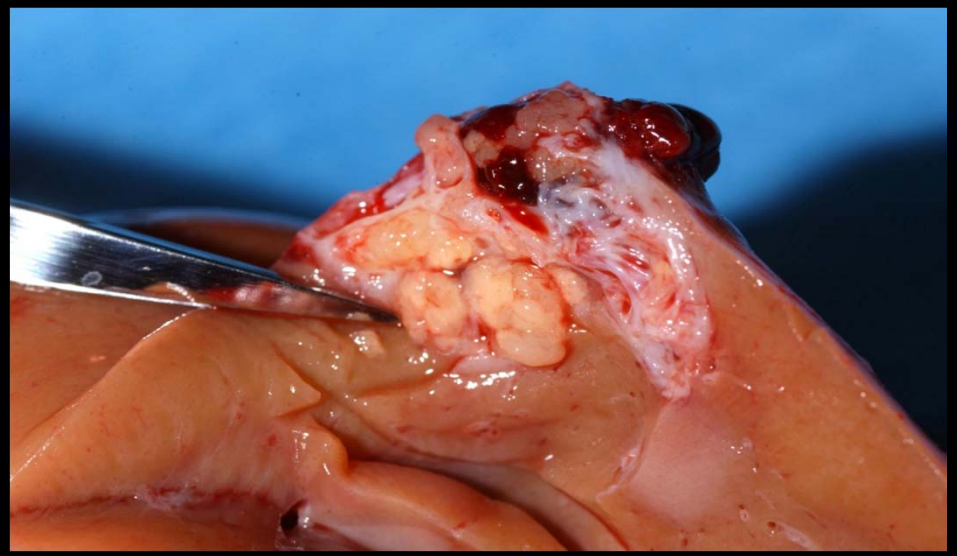
Am J Hum Genet 71:2003

HLRCC Kidney Cancer
19 Year Old Male



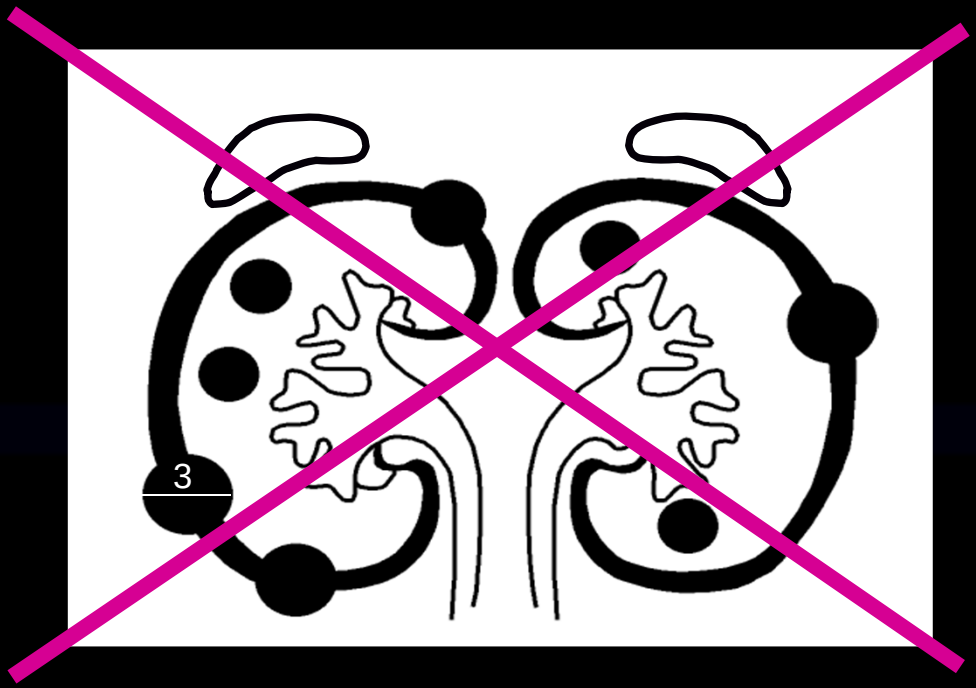
J Urol:177 2007

HLRCC Patient
2/22/02



J Urol:177 2007

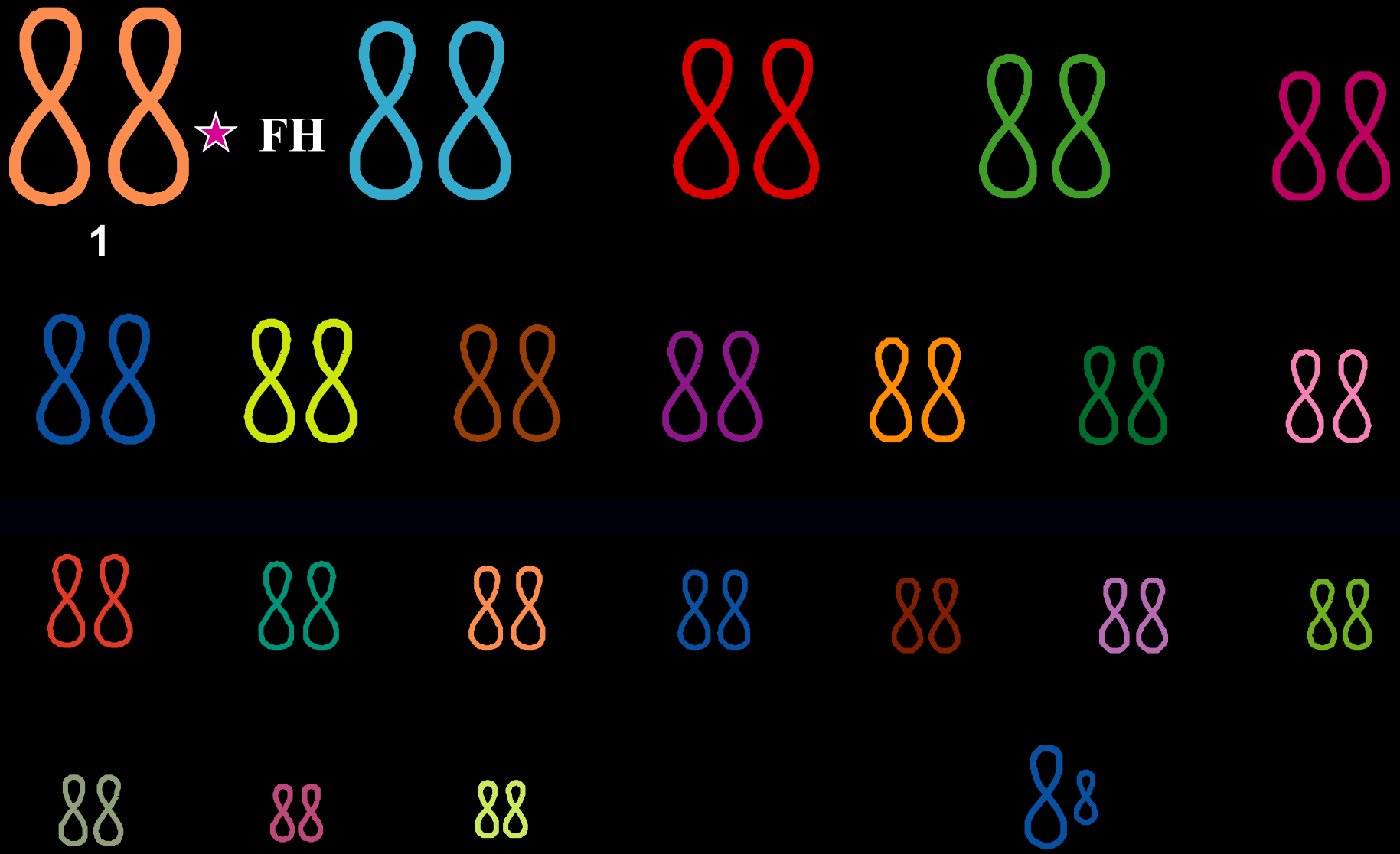
Surgical Management of HLRCC-Associated Renal Carcinoma



"3 cm rule"
Delay surgery until diameter of largest renal tumor = 3 cm

Surgical management should NOT be delayed

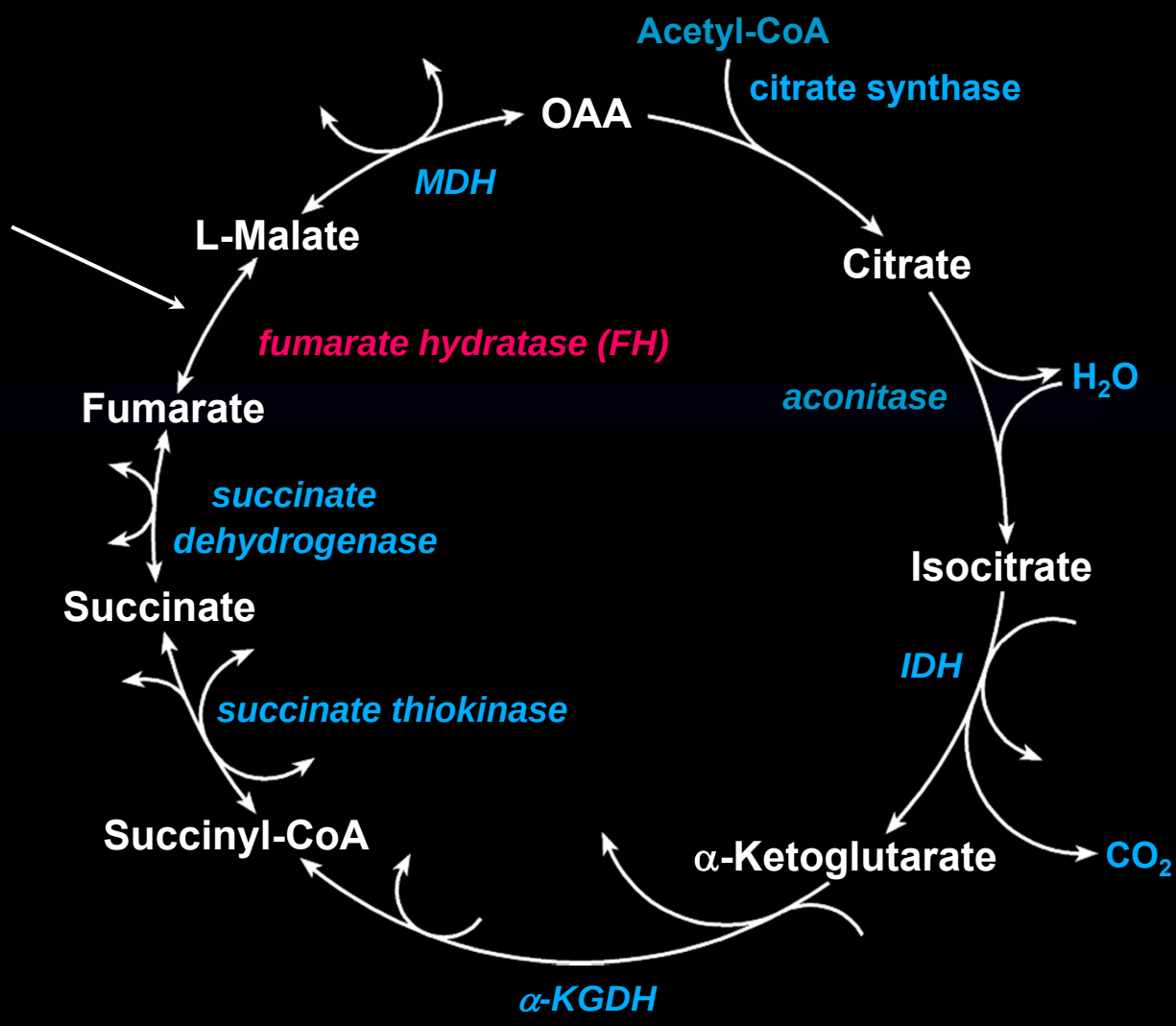
Nature CPU 3:2007
J Urol 177:2007



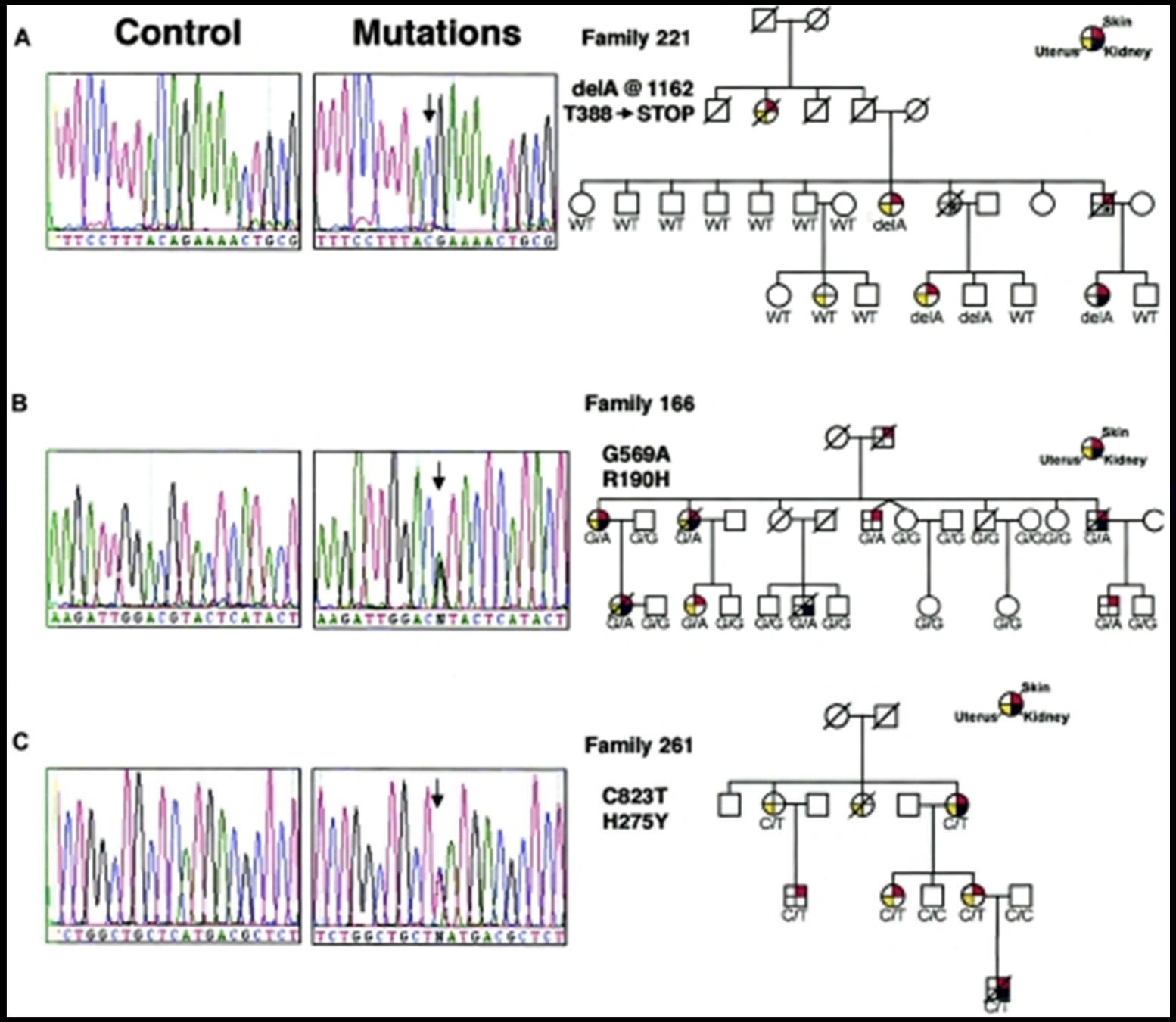
Fumarate Hydratase Gene: HLRCC

Fumarate Hydratase (FH): HLRCC Gene

FH catalyzes the conversion of fumarate to malate

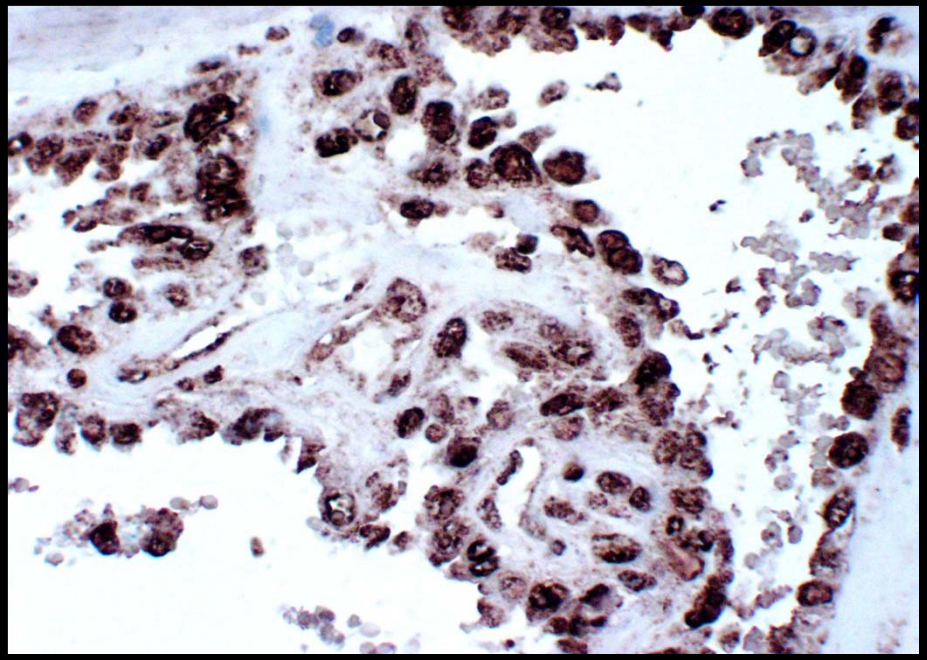


Tomlinson, et al. Nature Genetics:30 2002

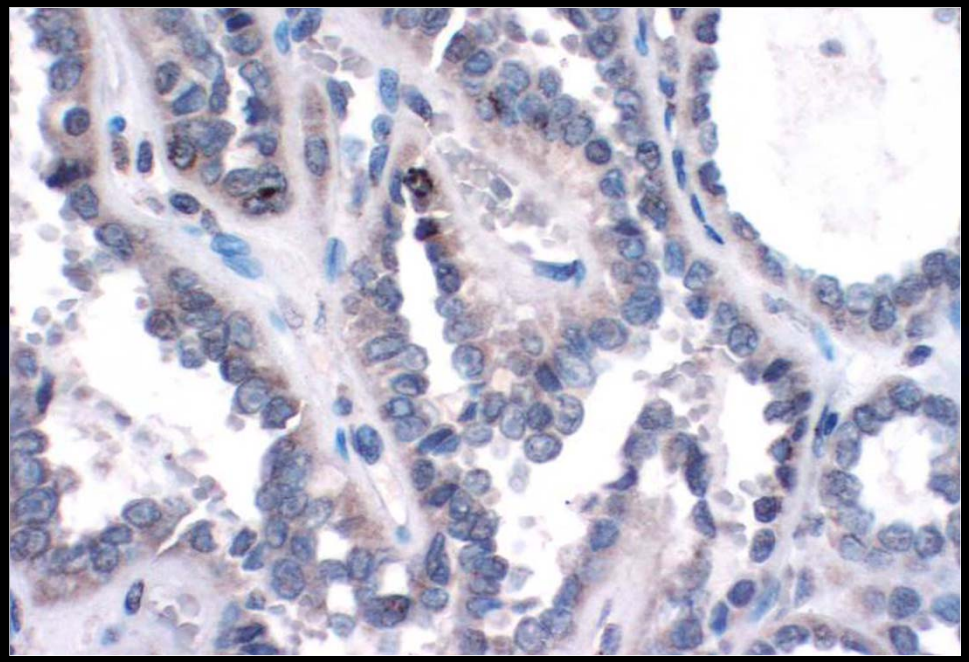

A
Control
Mutations
Family 221
delA @ 1162
T388→STOP
Skin
Uterus
Kidney
WT
delA
B
Family 166
G569A
R190H
G/A
G/G
C
Family 261
C823T
H275Y
C/T
C/C

How Does Loss of a Krebs Cycle Enzyme Lead to Kidney Cancer ?

HLRCC-Renal Cancer: HIF



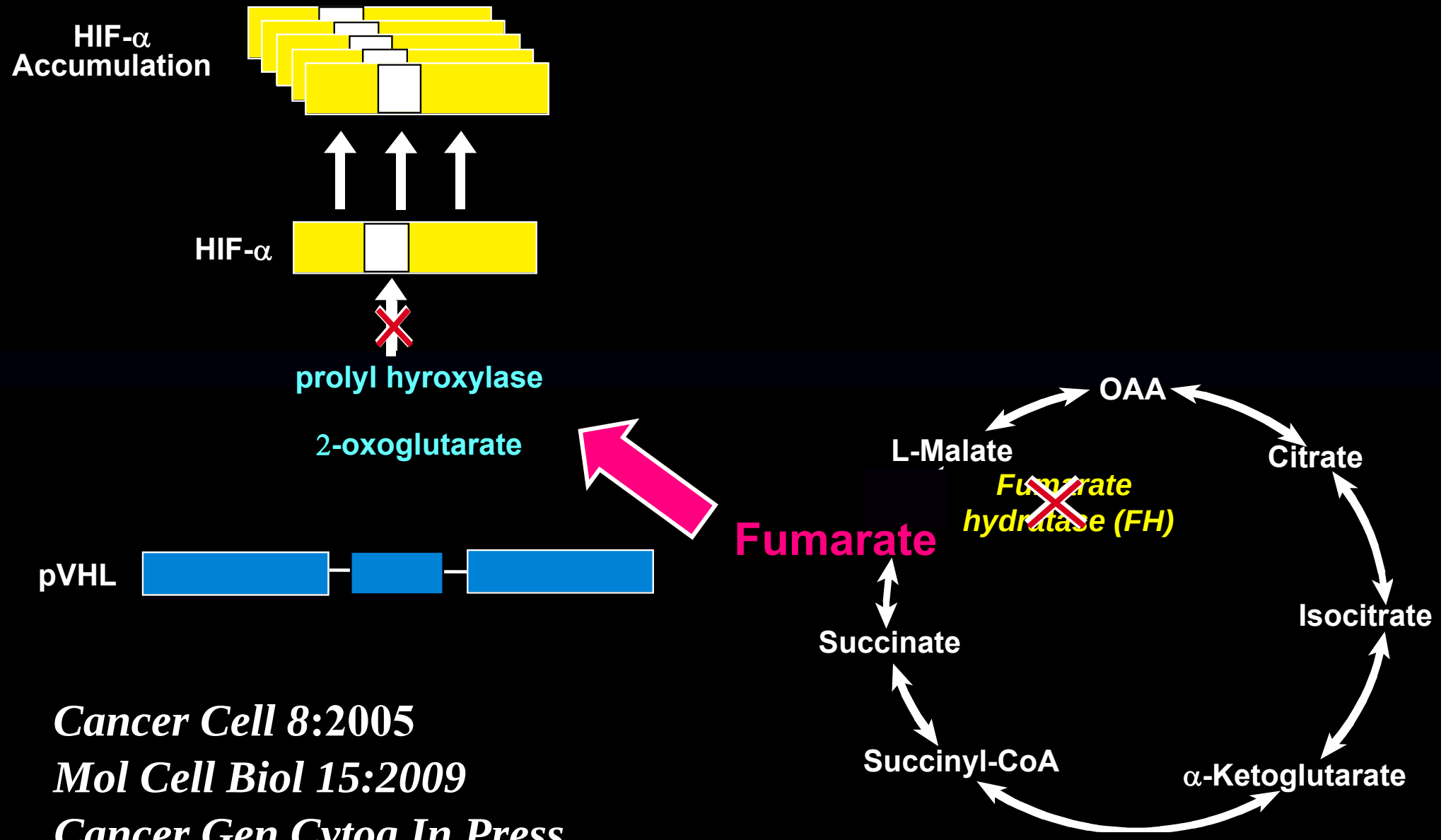
HIF-1α



HIF-2α

Cancer Cell: 2005

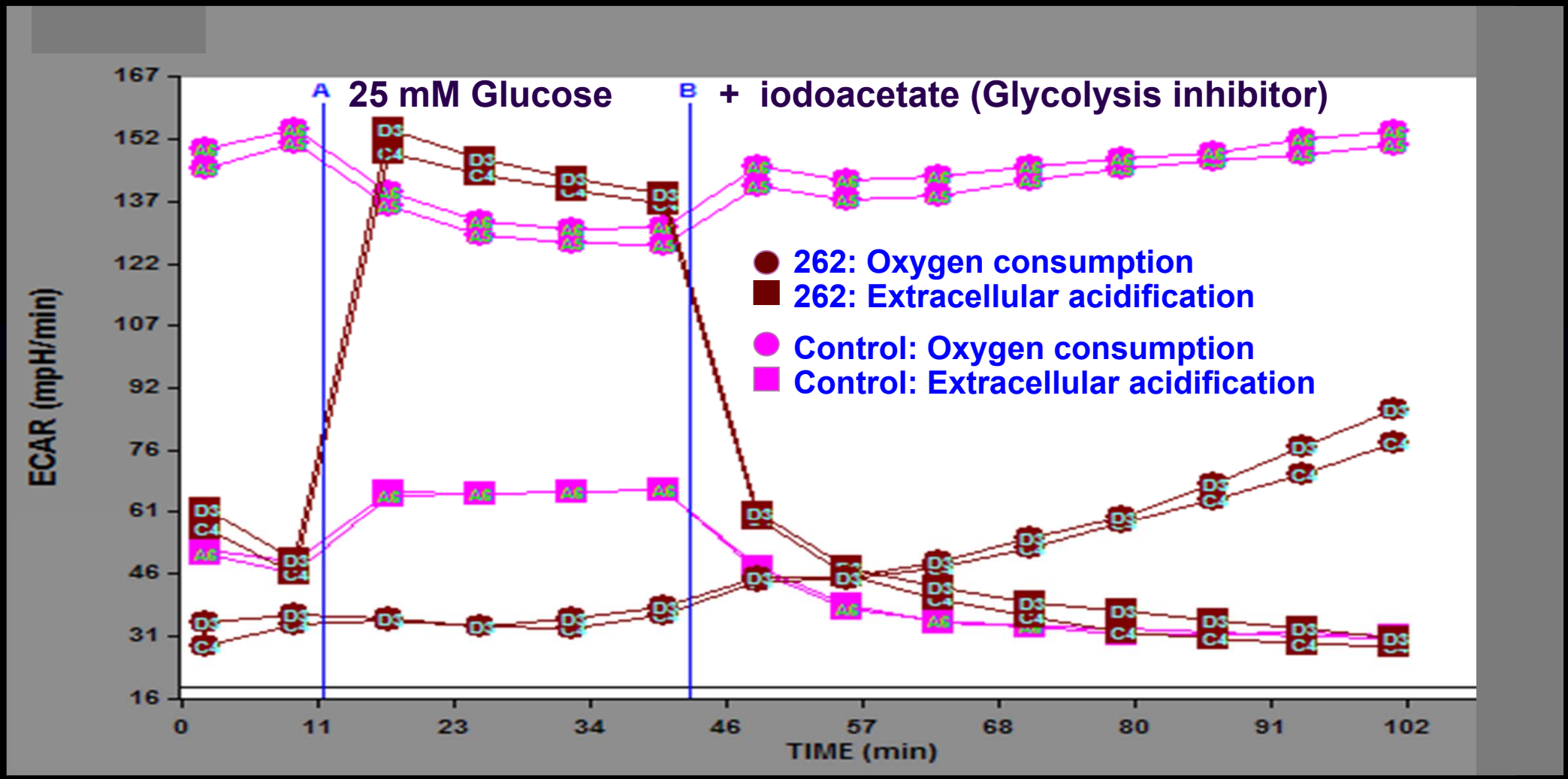
Fumarate blocks HIF Degradation



Cancer Cell 8:2005
Mol Cell Biol 15:2009
Cancer Gen Cytog In Press

Low respiration and high glycolysis rates in UOK262 cells

Seahorse Extracellular Flux Analyzer

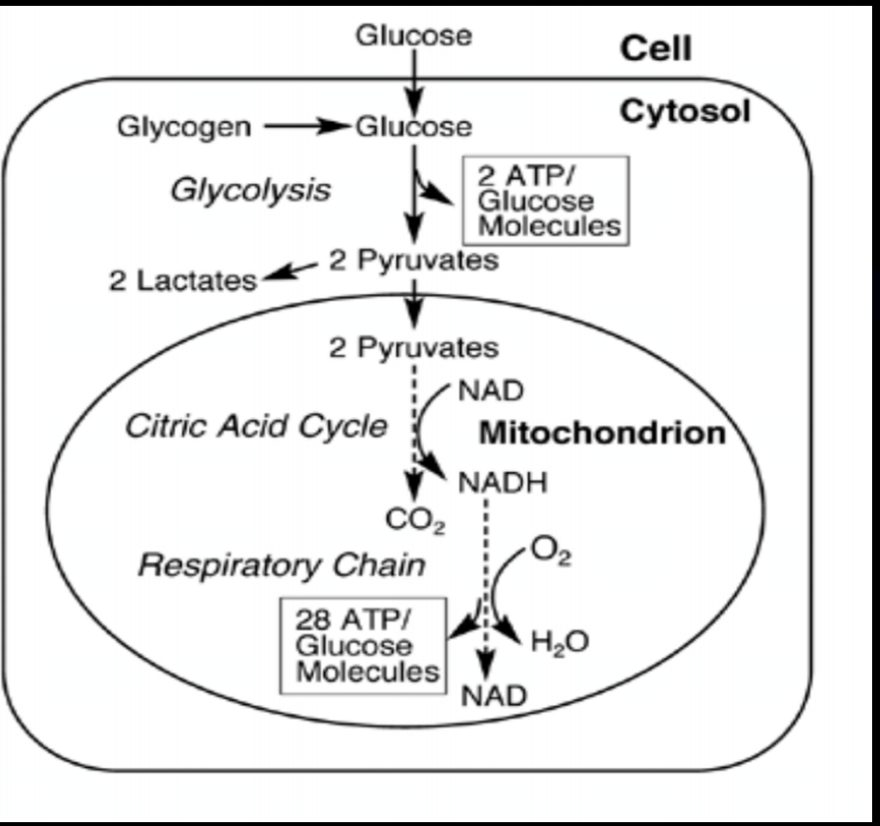


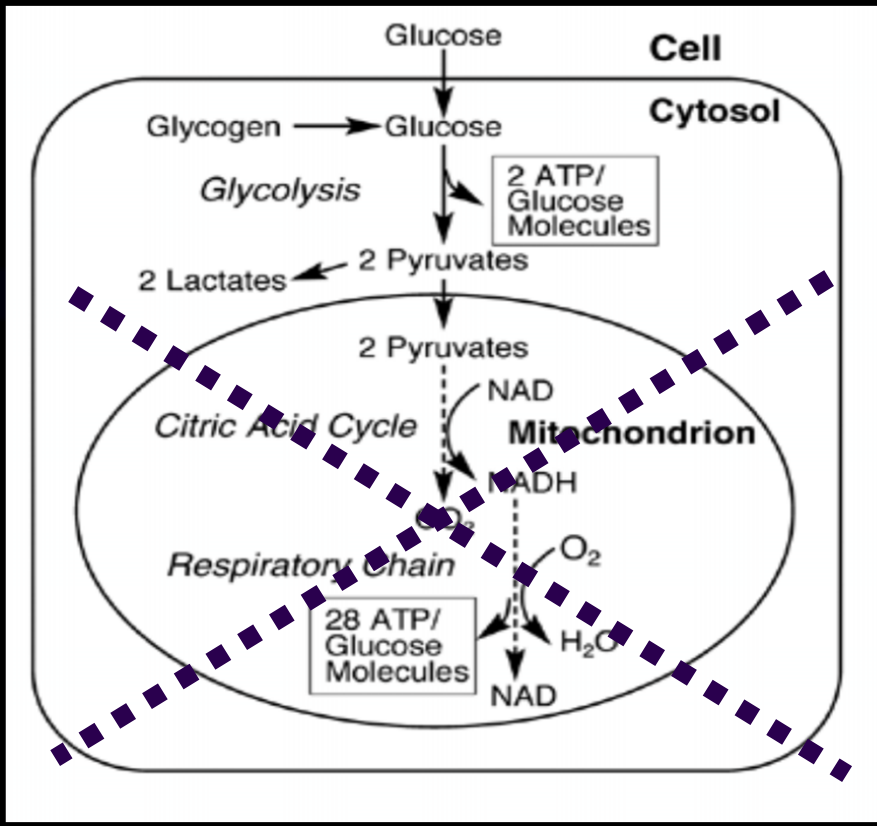
The "Warburg Effect"

- Tumor cells (unlike their normal counterparts) utilize glycolysis instead of mitochondrial oxidative phosphorylation for glucose metabolism
- Even when in oxygen-rich conditions

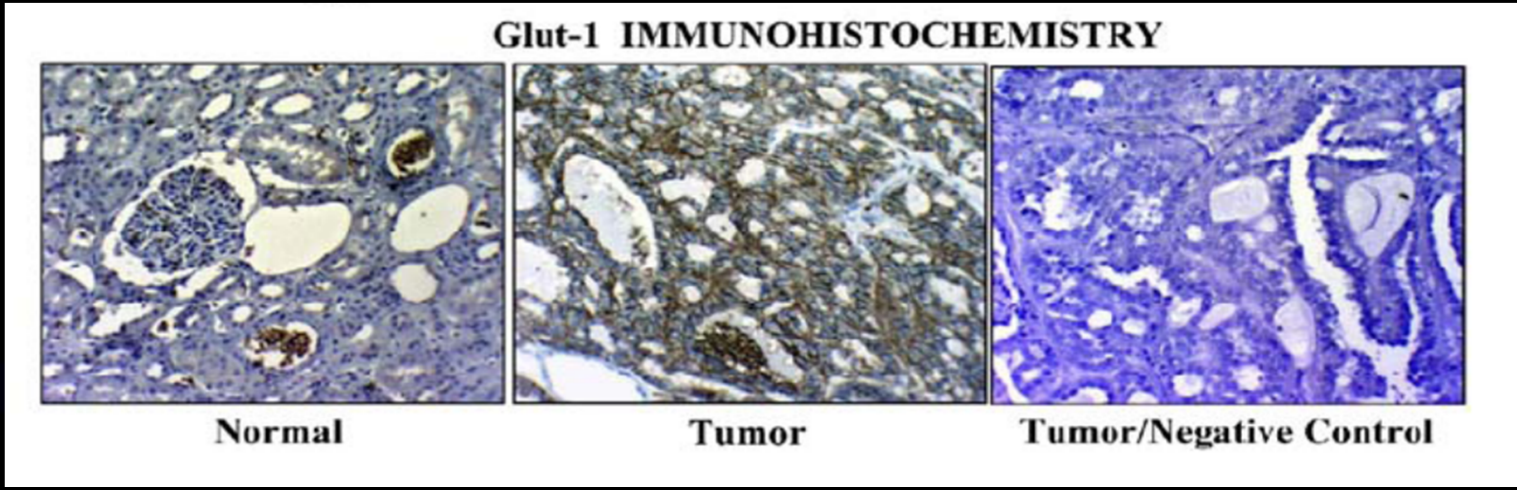
Warburg O: *Biochem Z 152* 1924
Warburg O: *Science* 124 1956

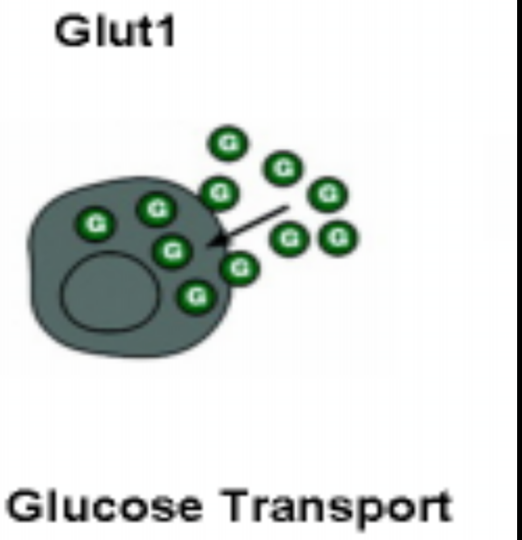
HLRCC: FH Inactivation



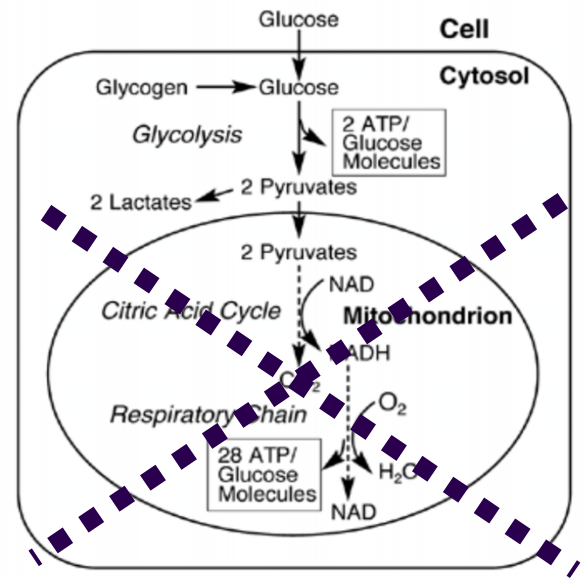


HIF Targets are Upregulated in HLRCC Kidney Tumors

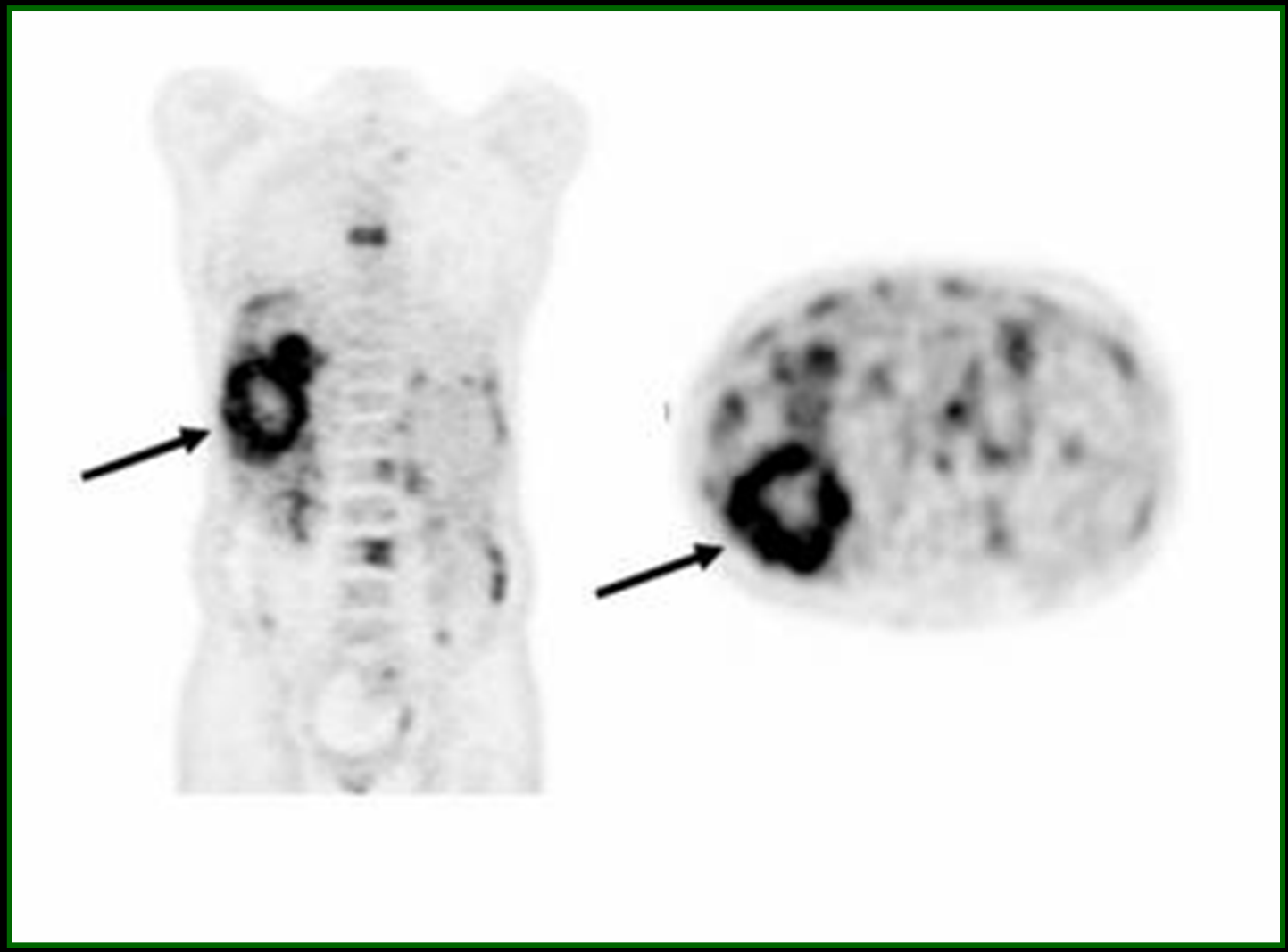




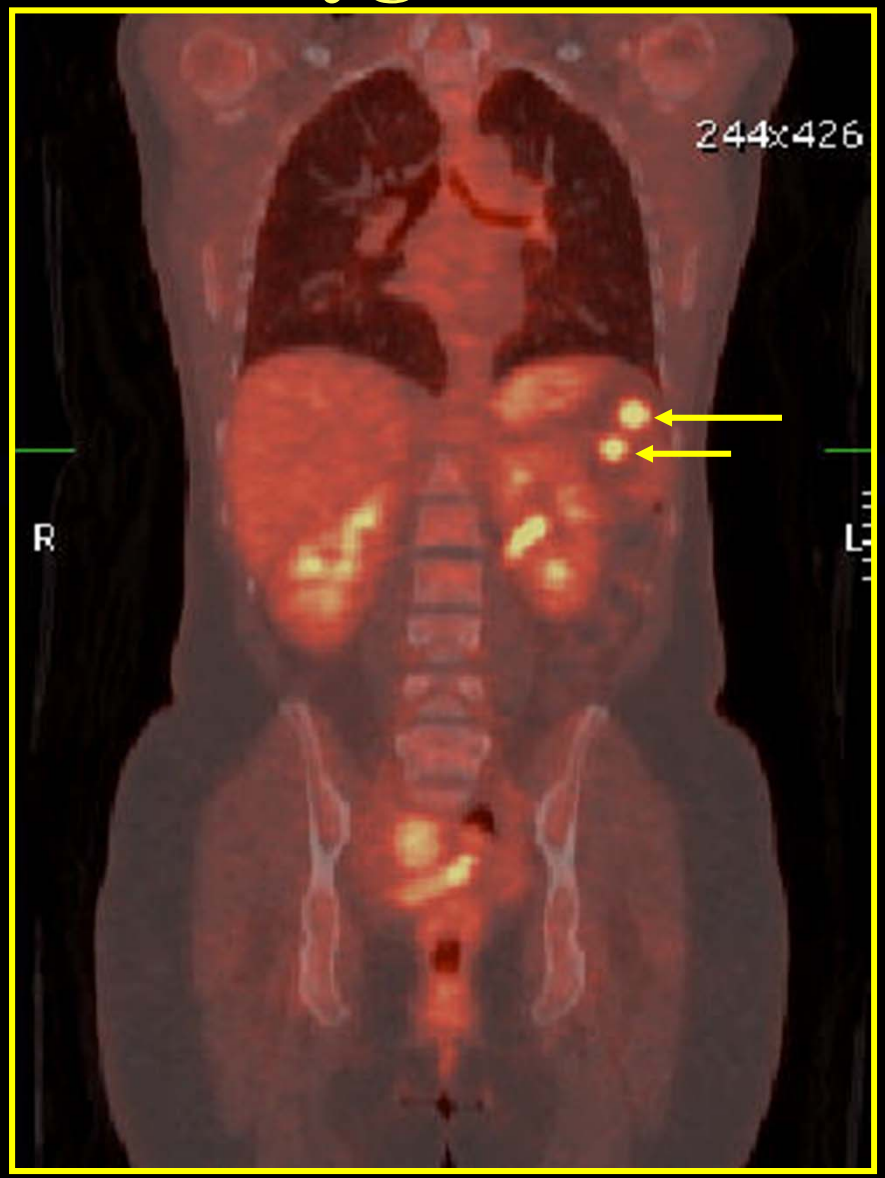
Isaacs Cancer Cell 8: 2005



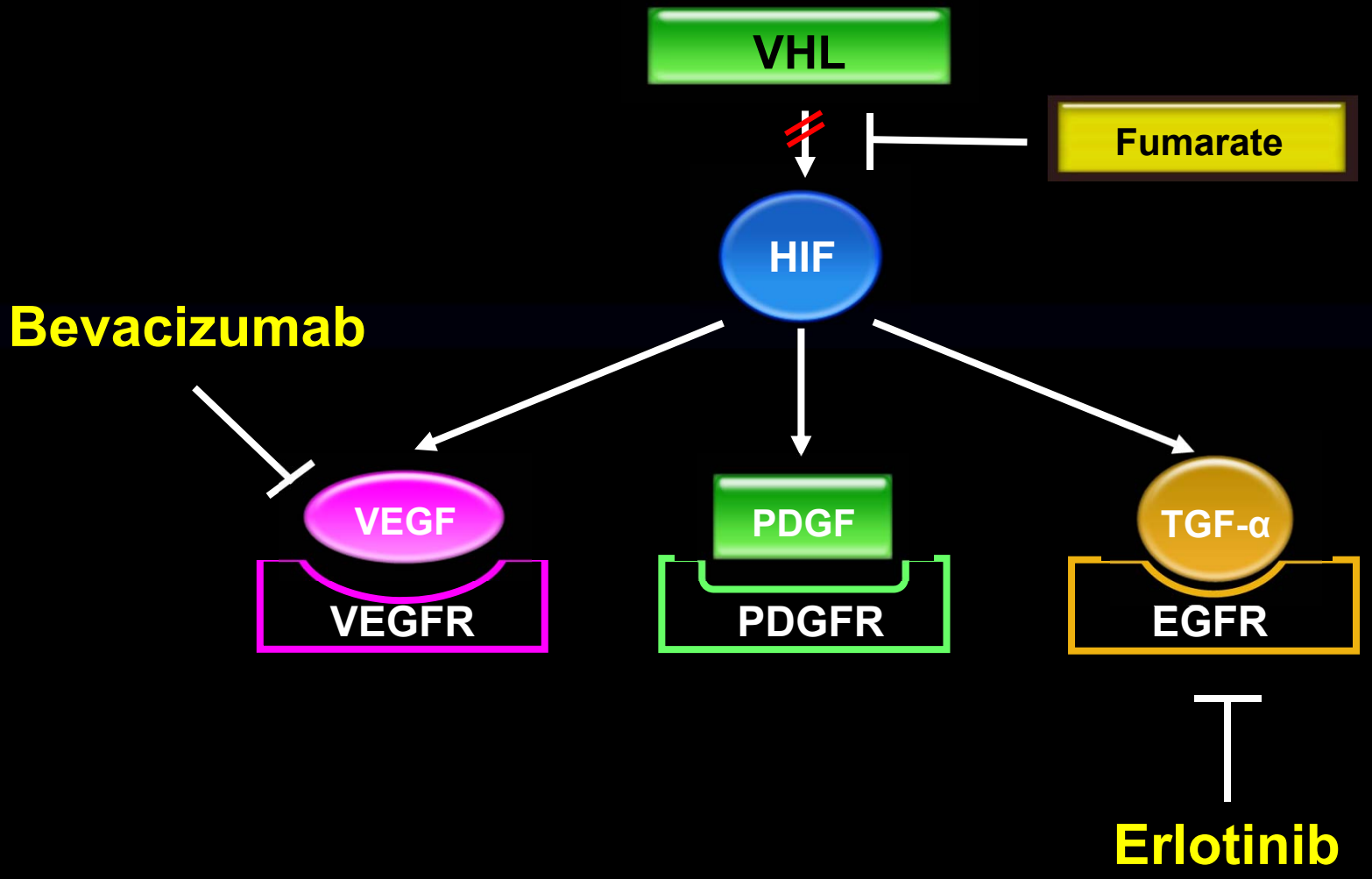
HLRCC tumors *in vivo* are readily detected by [18]fluoro-deoxyglucose-based PET scan



HLRCC tumors *in vivo* are readily detected by [18]fluoro-deoxyglucose-based PET scan



Targeting VEGF/EGFR in advanced HLRCC kidney cancer



Targeting VEGF/EGFR in advanced HLRCC kidney cancer

Patient 1

- Mediastinal, cervical, retroperitoneal lymphadenopathy and pulmonary metastases
- Treated with: bevacizumab and gefitinib
- Partial Response for 18 months

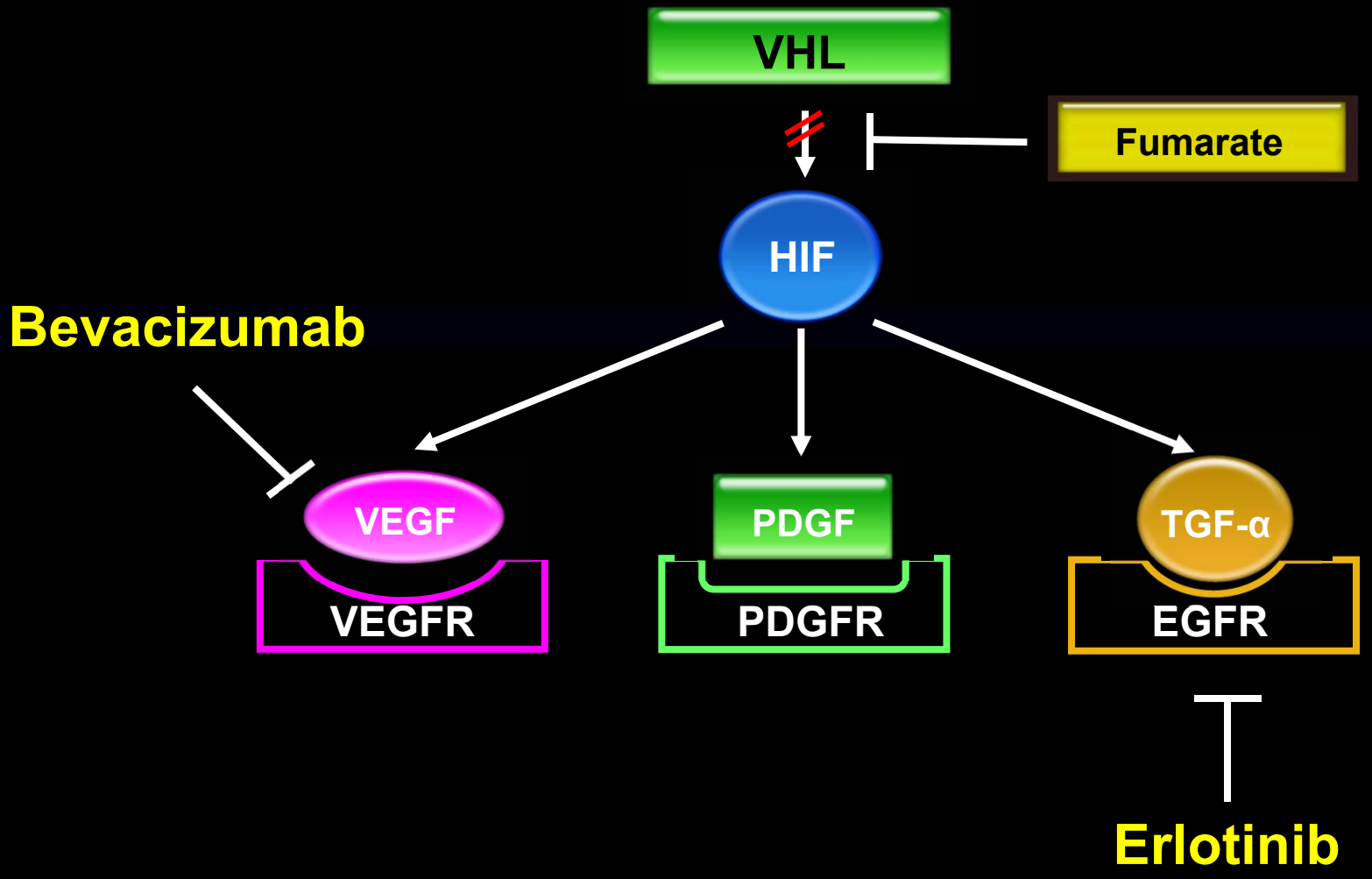
Patient 2

- Abdominal wall/peritoneal metastases
- Treated with: bevacizumab and erlotinib
- CR at 3 months. Remained NED for 36 months

Patient 3

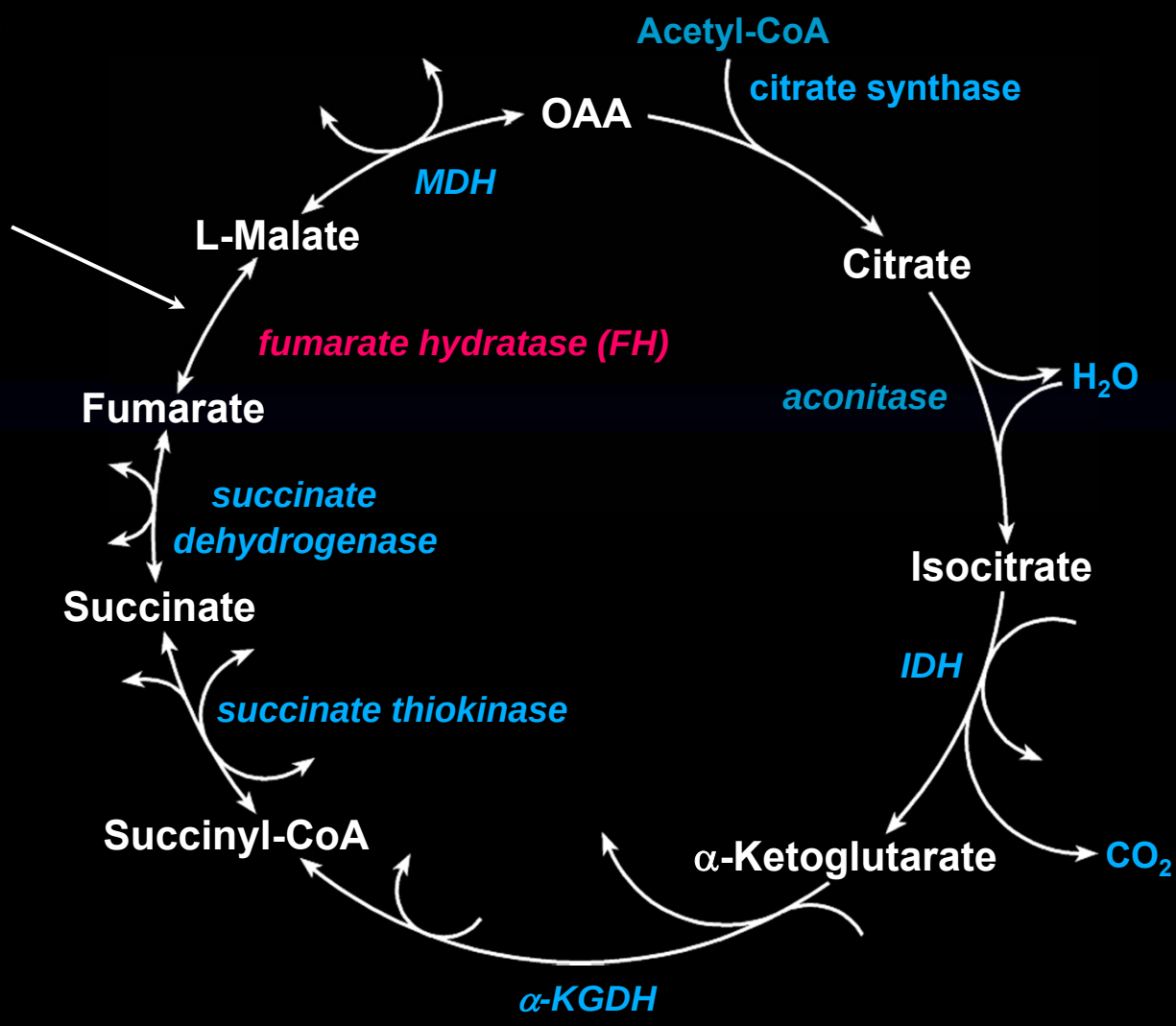
- Hepatic metastases, retroperitoneal lymphadenopathy, ascites
- Treated with: bevacizumab and erlotinib
- PR for 21 months

Targeting VEGF/EGFR in advanced HLRCC kidney cancer



Fumarate Hydratase (FH): HLRCC Gene

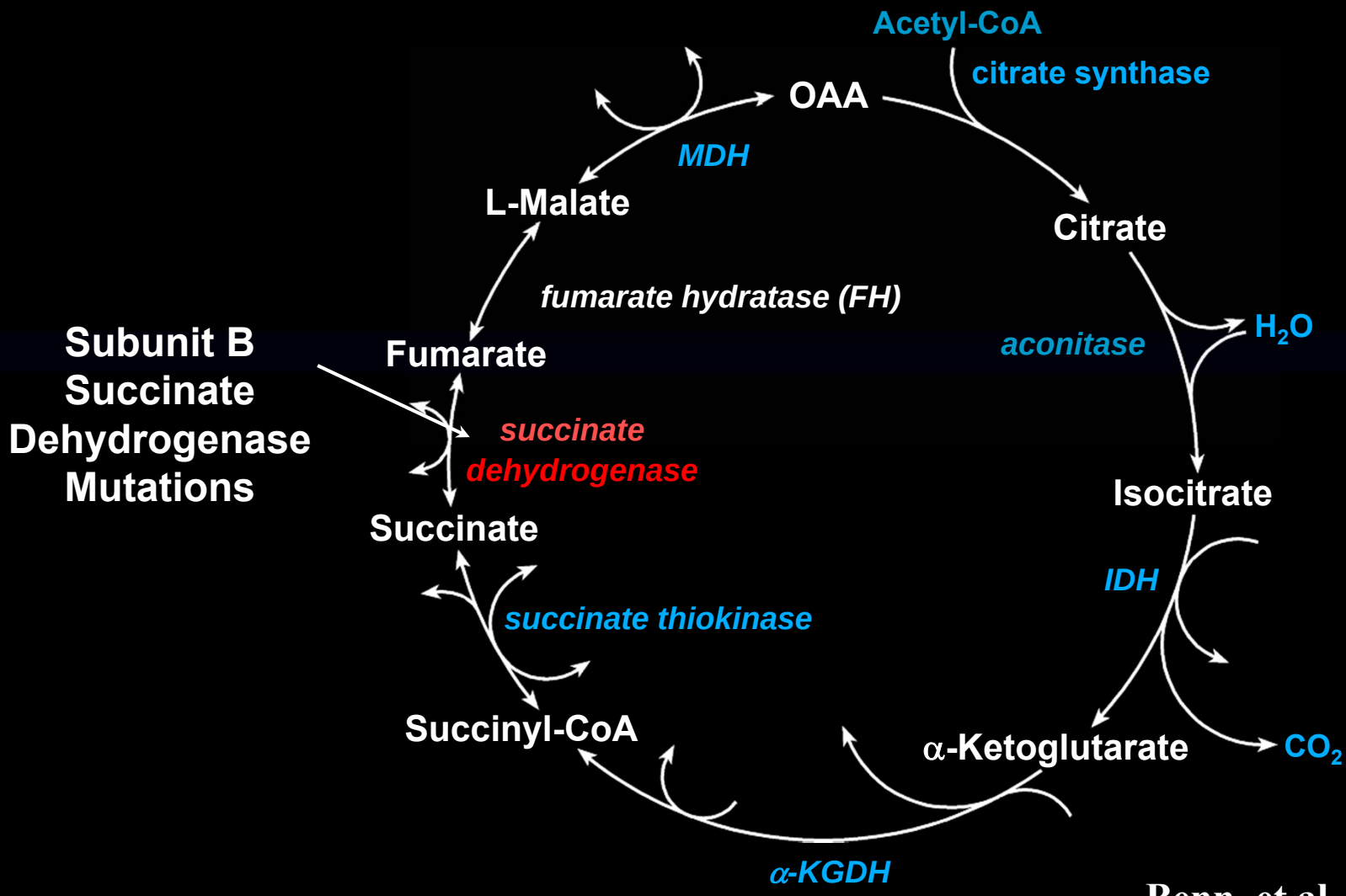
FH catalyzes the conversion of fumarate to malate



Tomlinson, et al. Nature Genetics:30 2002

Succinate Dehydrogenase:

Familial Pheochromocytoma/Kidney Cancer

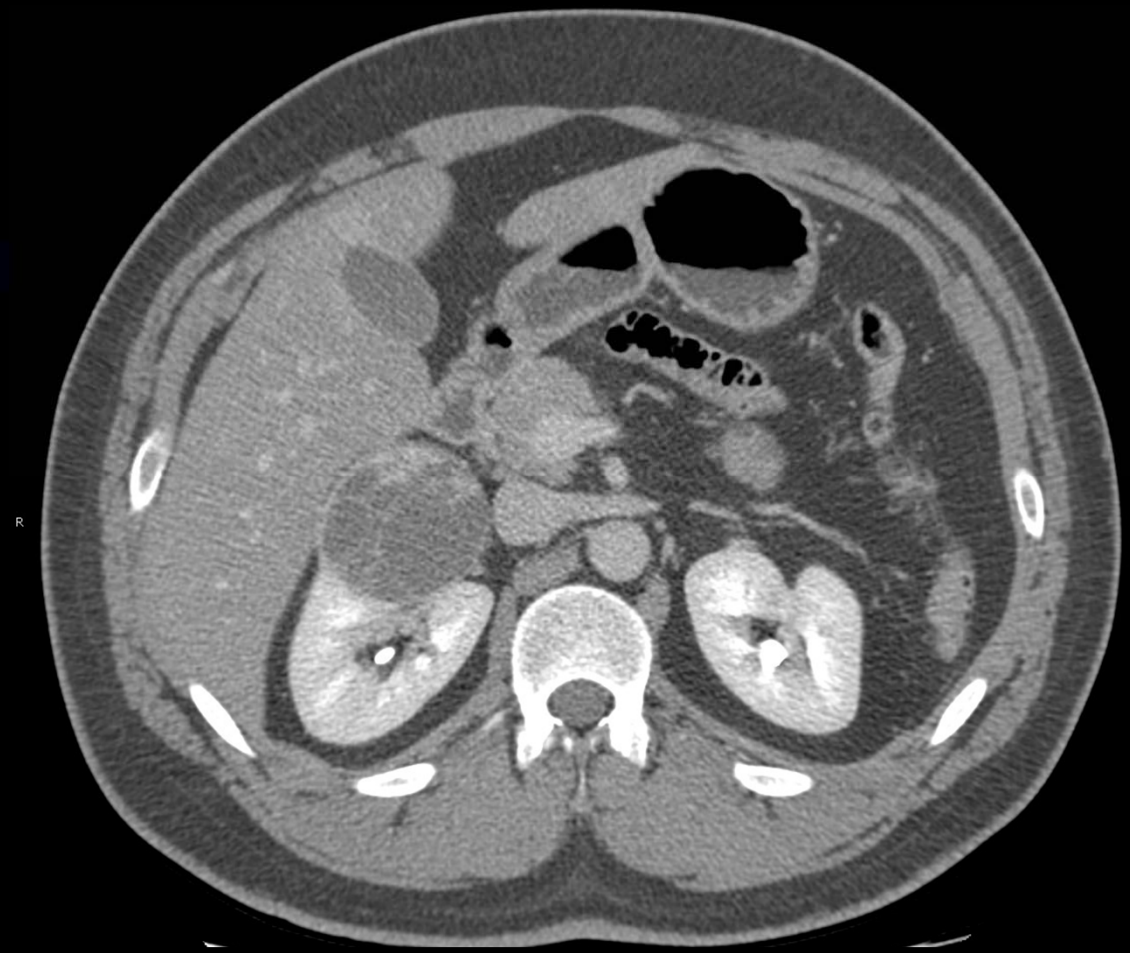


Benn, et al. Oncogene 22:2003

Familial Renal Carcinoma Succinate Dehydrogenase B

- 28 year old male
- Right sided, upper pole cystic mass

Familial Renal Carcinoma
Succinate Dehydrogenase B

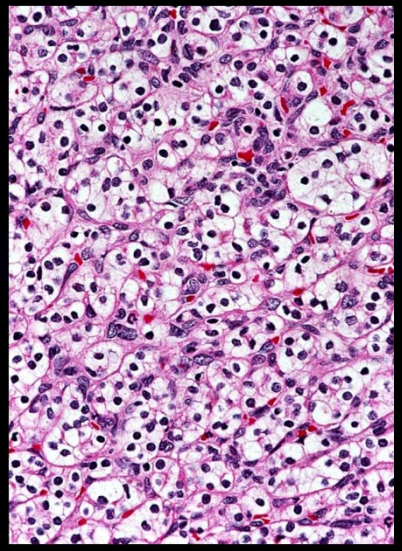


Familial Renal Carcinoma Succinate Dehydrogenase B

- 33 year old female
- Presented with three month history of back pain
- Bone marrow biopsy revealed “metastatic cancer consistent with renal primary”

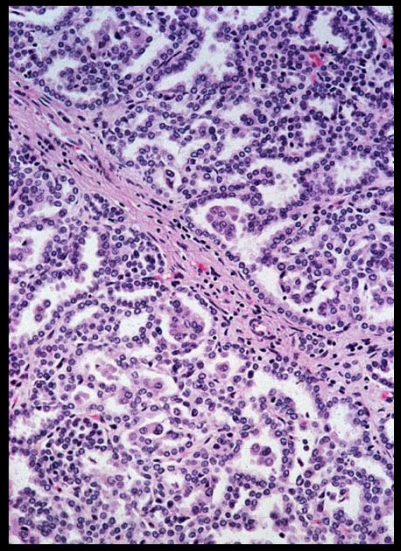
Familial Renal Carcinoma
Succinate Dehydrogenase B

Human Renal Epithelial Neoplasms



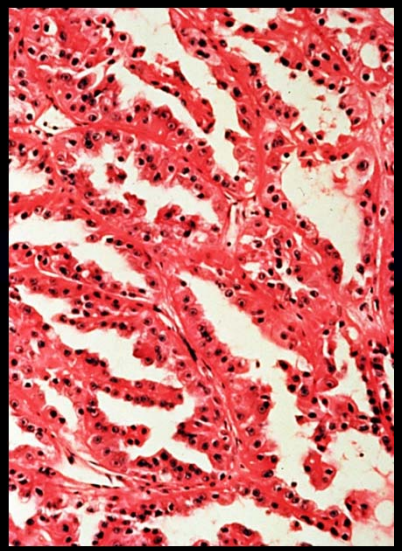
Clear Cell

VHL



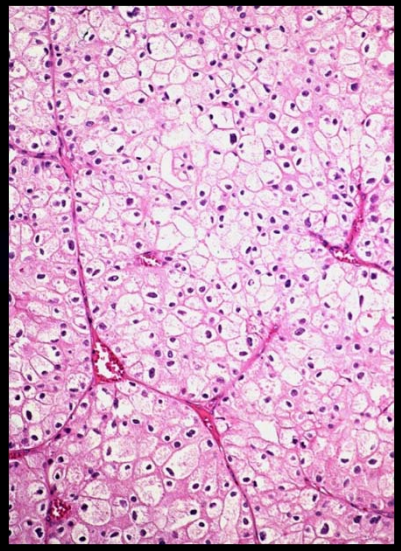
Papillary Type 1

Met

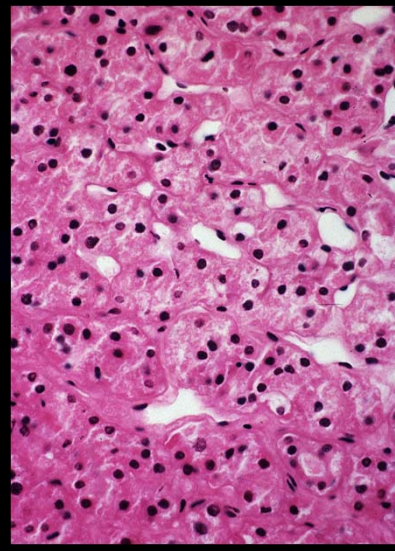


Papillary Type 2

FH



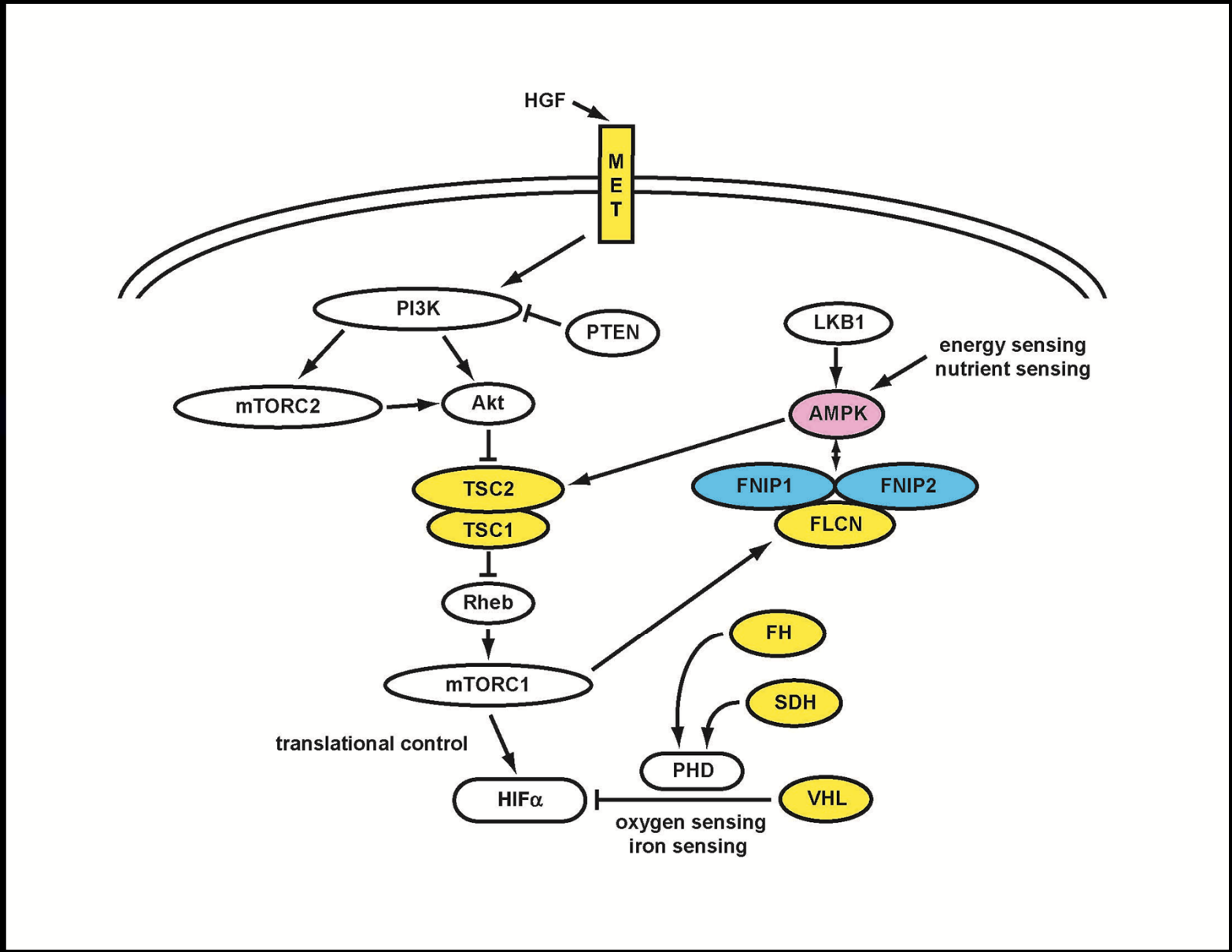
Chromophobe



Oncocytoma

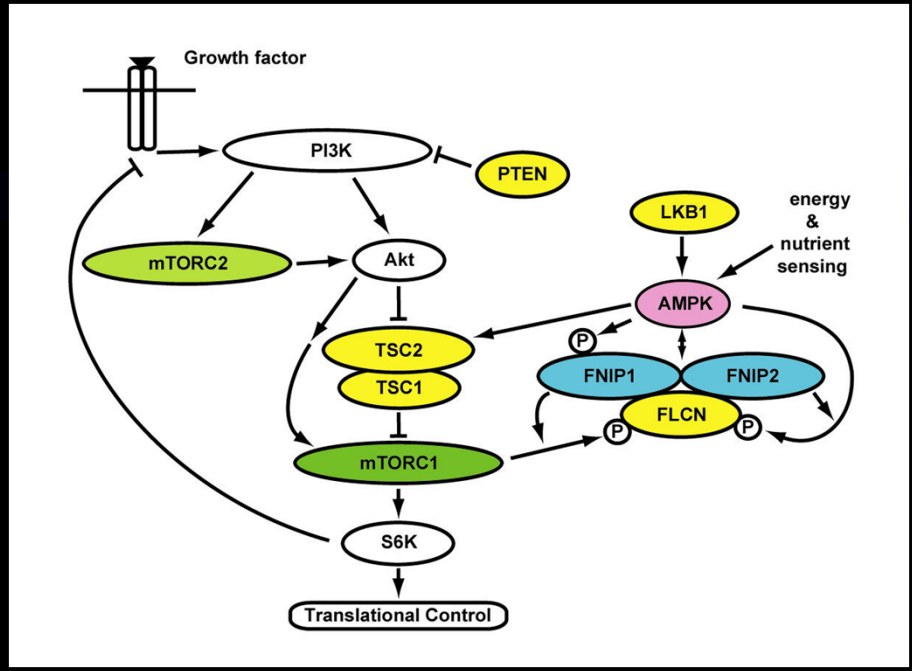
BHD

Kidney Cancer is a Metabolic Disease



Genetics/Biochemistry

- Laura Schmidt, Ph.D.
- Masaya Baba, M.D., Ph.D.
- Seung-Beom Hong, Ph.D.
- Hisashi Hasumi, M.D., Ph.D.
- Yukiko Hasumi, M.D., Ph.D.
- Vladimir Valera, M.D., Ph.D.
- Carole Sourbier, Ph.D.
- Cathy Vocke, Ph.D.
- Robert Worrell, Ph.D.
- Youfeng Yang, M.S.
- Ming Wei, M.S.



Len Neckers, Ph.D.

- Targeting HSP90 in cancer
- Mechanism of inhibition of HIF prolyl hydroxylation by citric acid cycle intermediates & relationship to etiology of hereditary renal cancer
- Molecular therapeutic trials, kidney, and other cancers

Donald P. Bottaro, Ph.D.

- Molecular therapeutic strategies, c-Met associated cancers
- Molecular therapeutic strategies, VHL-HIF pathway

Peter A. Pinto, M.D.

- Management of hereditary forms of kidney cancer
- Surgical & minimally invasive management of localized prostate/kidney cancer
- Molecular therapeutic approaches localized prostate and kidney cancer

Gennady Bratslavsky, M.D.

- Management of hereditary forms of kidney cancer
- Surgical & minimally invasive management of localized/advanced kidney cancer
- Molecular therapeutic approaches kidney cancer

Ramaprasad Srinivasan, MD,Ph.D

- Molecular therapeutic trials, hereditary kidney cancer
- Small molecule natural products targeting the VHL/HIF pathway

Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute