Genetic Basis of Kidney Cancer

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National Cancer Institute

Genitourinary Malignancies

Organ Site	Cases/Year*	Deaths/Year*
Prostate	238,590	29,720
Urothelial	75,280	18,910
Kidney	65,150	13,680
Testis	7,920	370
Penile	1,570	310
	388,510	62,990
U.S.	1,660,290 (23.4%)	580,350 (11%)

*Estimated U.S. 2013

Renal Carcinoma

- 271,000 are diagnosed worldwide annually
- 116,000 deaths worldwide annually

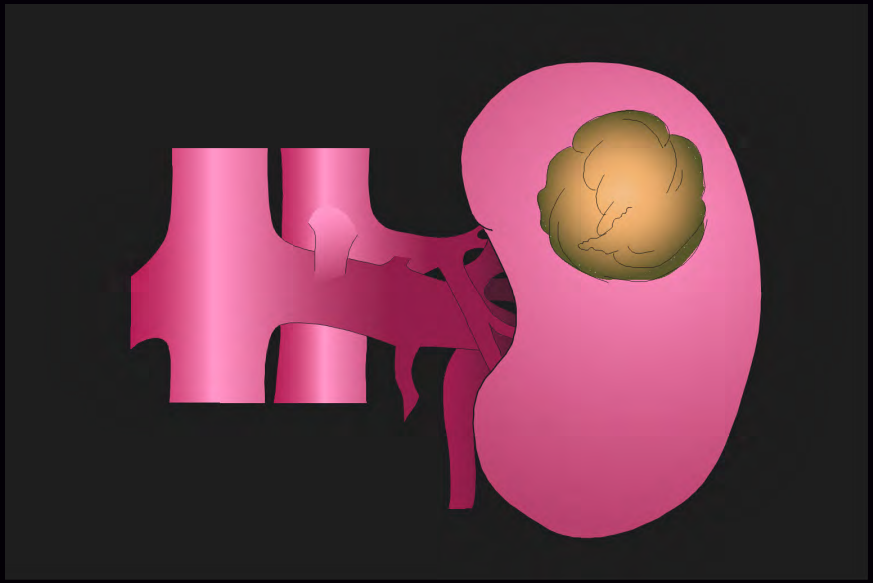
- 65,000 are diagnosed in the U.S. annually
- 13,000 die in the U.S. each year

- There are over 200,000 alive with kidney cancer in the U.S.

Ca Cancer J Clin 62:2012
Int J Cancer 127:2010

Stage I

- Tumor ≤ 7 cm, within the renal capsule
- T1; N0; M0
- 95% 5 year survival



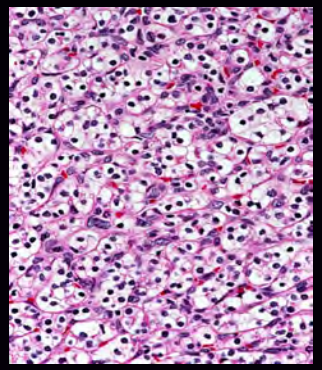
AJCC 7 Cancer Staging Manual 2010

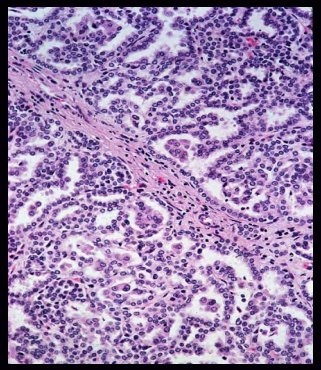
Stage IV

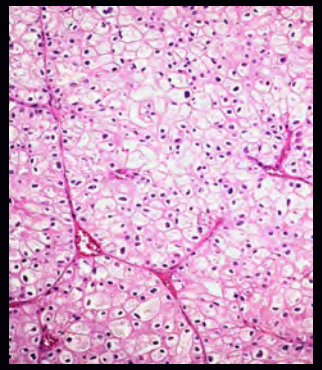
- Adjacent organs or distant metastasis
- T4; M1
- 19% 2 year survival

AJCC 7 Cancer Staging Manual 2010

Human Renal Epithelial Neoplasms


Clear Cell


Papillary Type 1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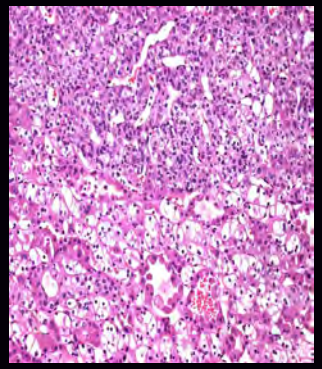
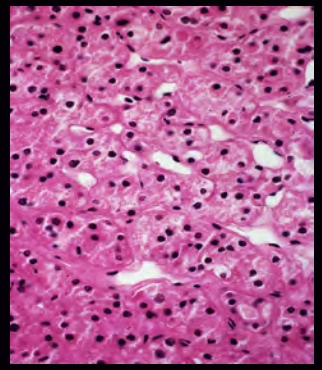
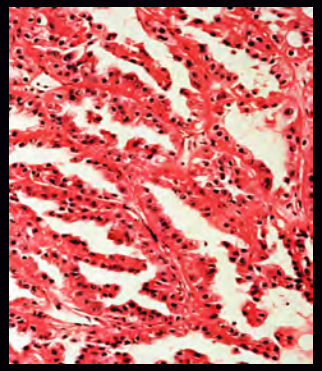
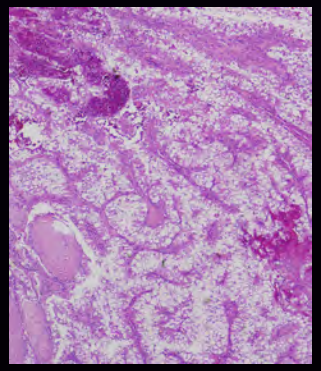

Hybrid


Oncocytoma


Papillary Type 2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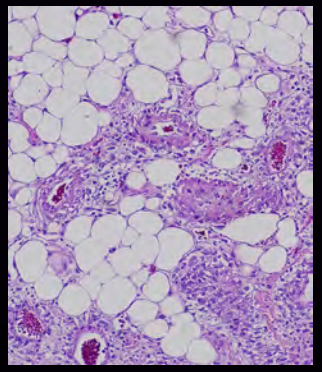
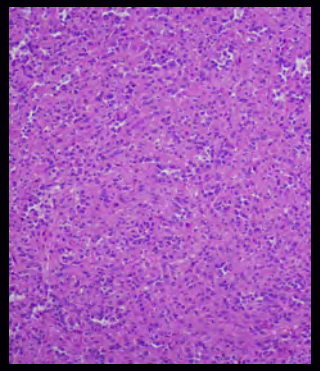
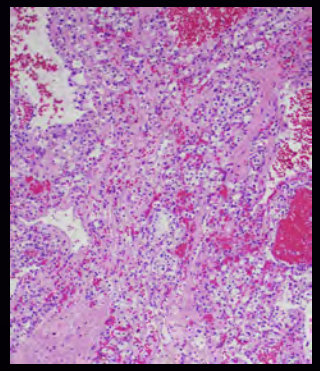
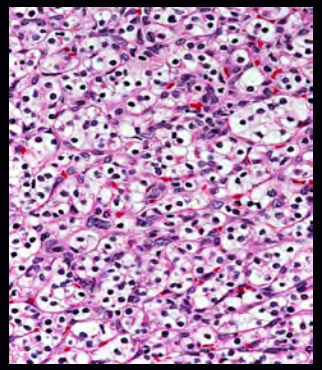

Angiomyolipoma

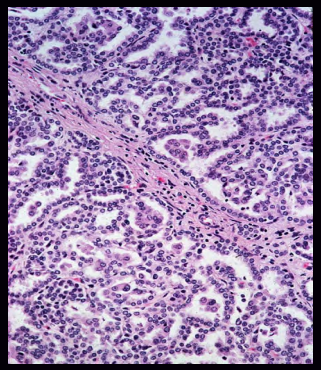

Oncocytic


Clear/Chromophobe

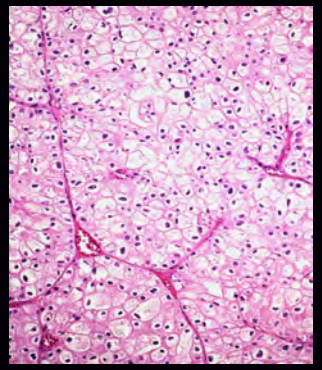
Human Renal Epithelial Neoplasms



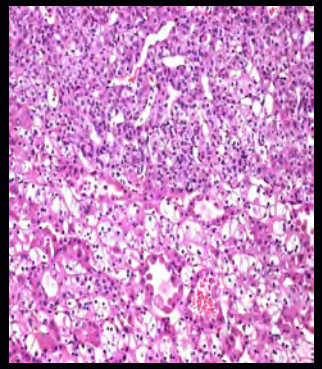
Clear Cell
VHL



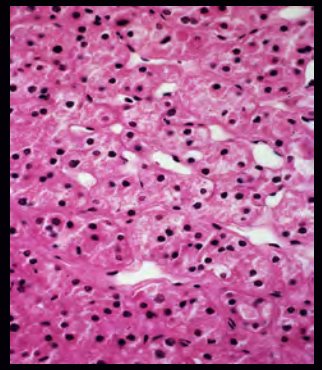
Papillary Type 1
Met



Chromophobe

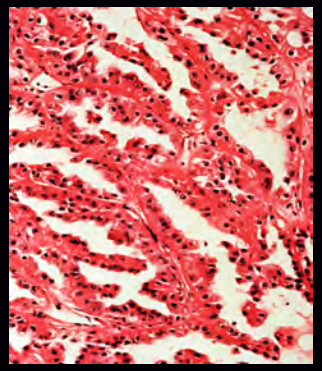


Hybrid

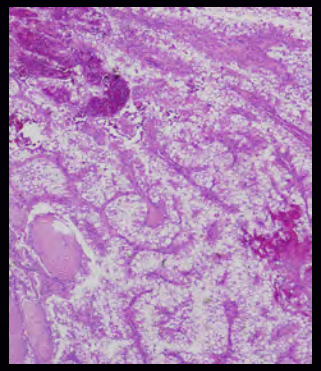


Oncocytoma

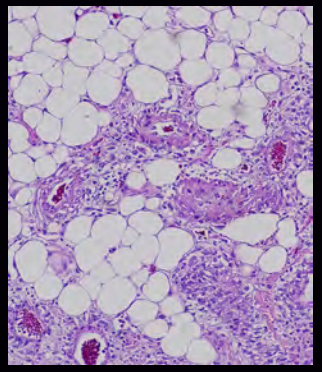
FLCN



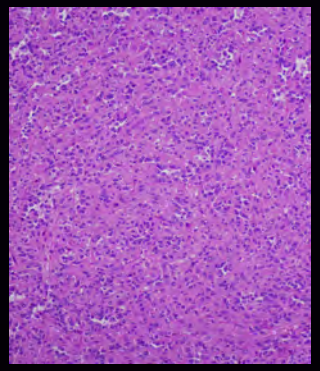
Papillary Type 2
FH



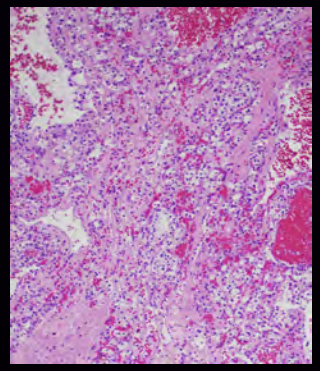
TFE3
TFE3, TFEB, MITF



Angiomyolipoma
TSC1, TSC2



Oncocytic
SDHB, SDHC, SDHD



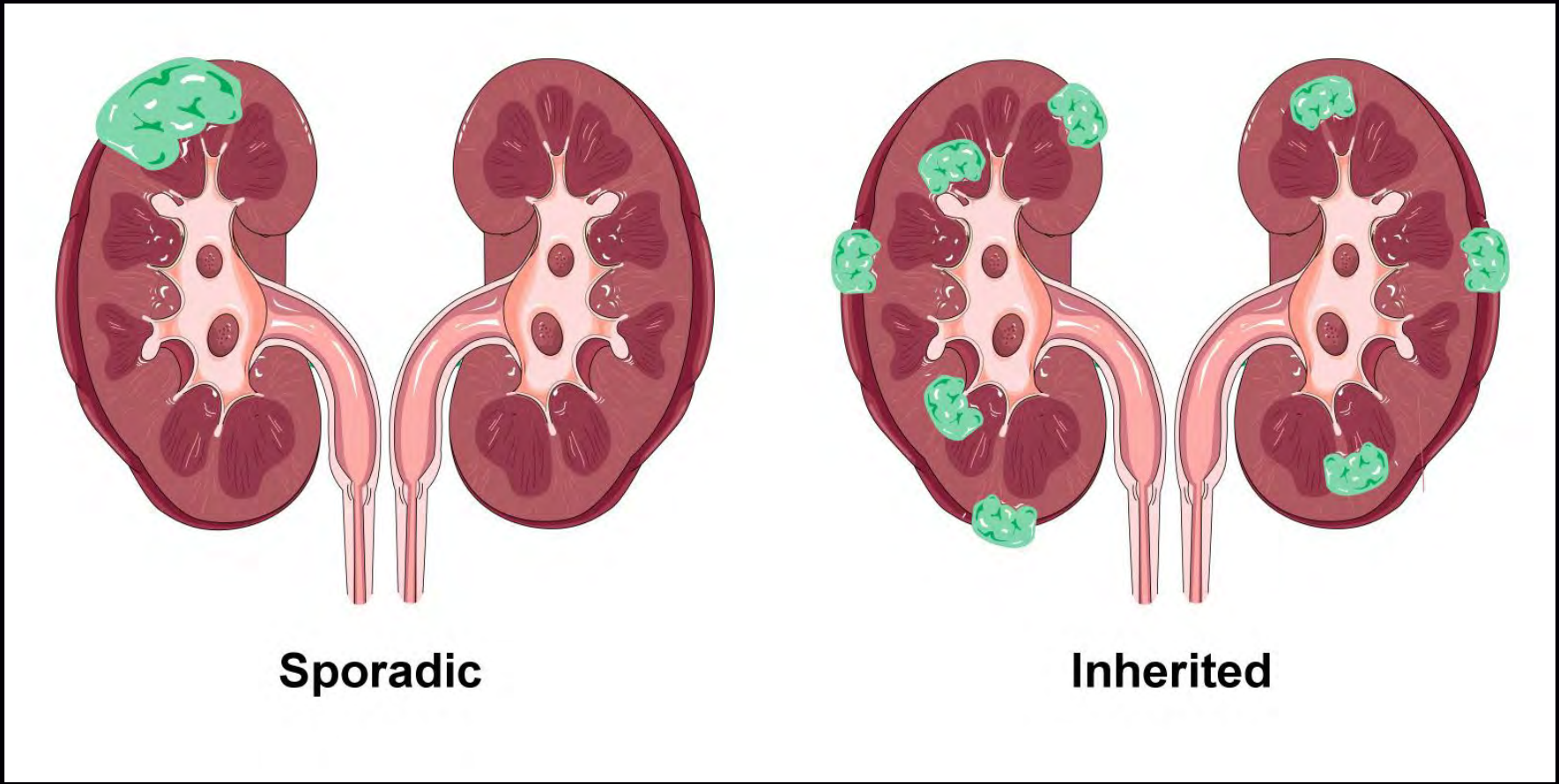
Clear/Chromophobe
PTEN

Studying cancer families to identify renal carcinoma genes

Inherited Forms of Renal Carcinoma

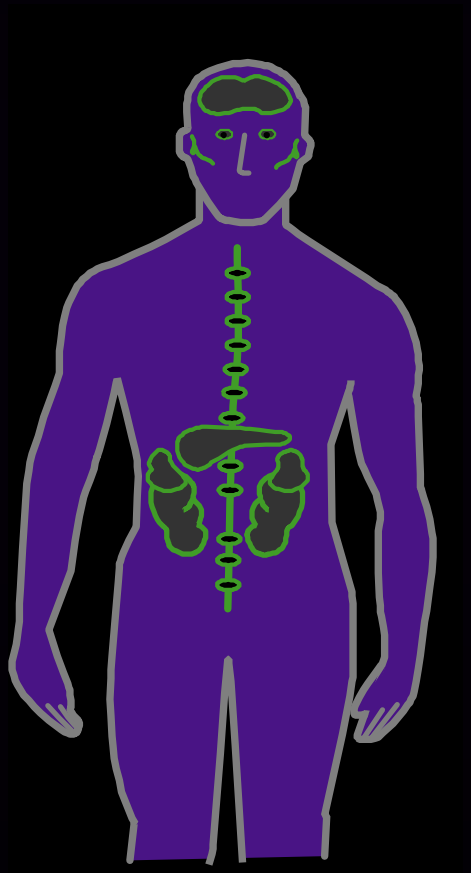
1. **Von Hippel Lindau**
   - **Clear Cell**
2. **Hereditary Papillary Renal Carcinoma**
   - **Papillary Type 1**
3. **Birt Hogg Dubé:**
   - **Chromophobe/Oncocytoma**
4. **Hereditary Leiomyomatosis RCC**
   - **Papillary Type 2**
5. **Succinate Dehydrogenase**
   - **Clear Cell/Chromophobe**

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



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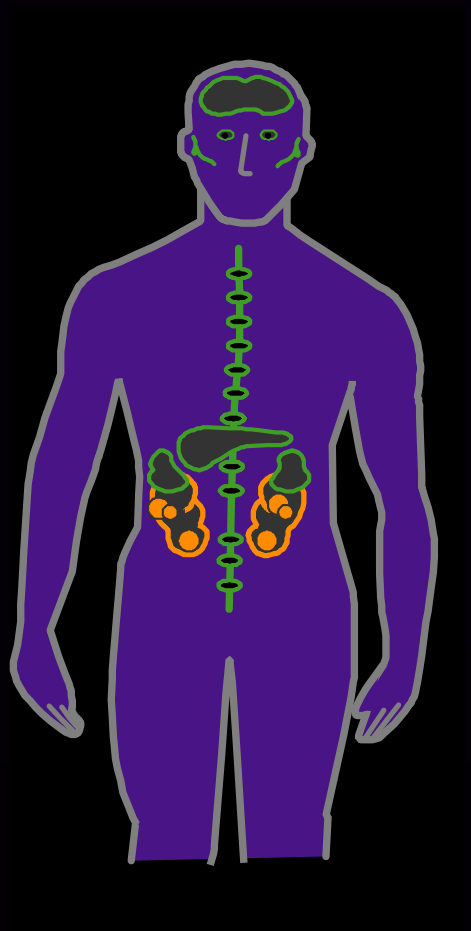
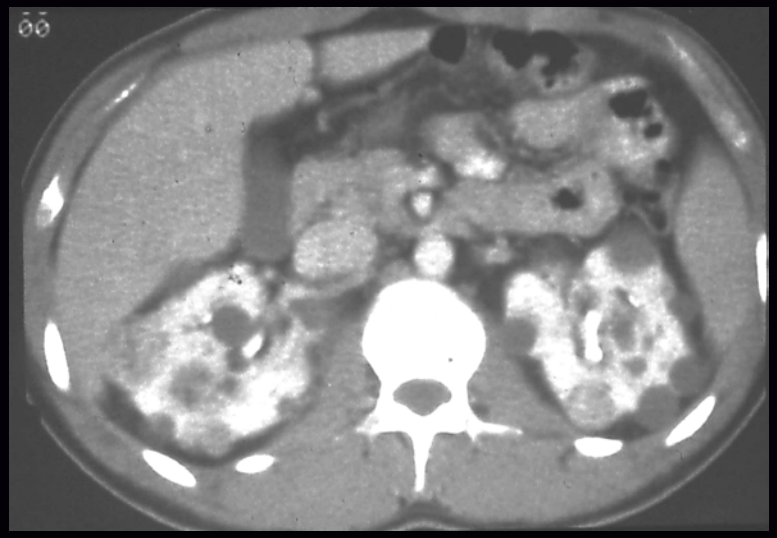


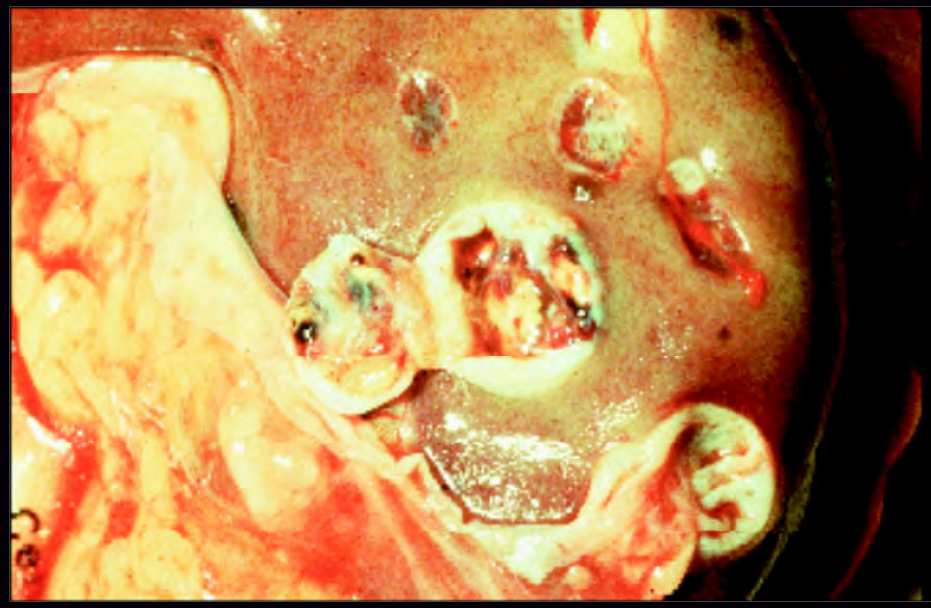
VHL: Renal Cell Carcinoma

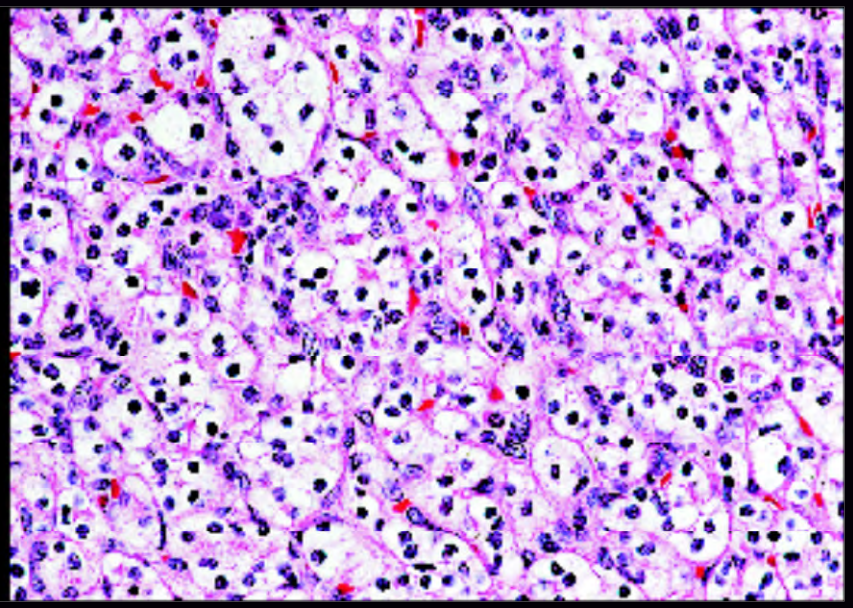


CT Scan: Bilateral, Multifocal RCC

VHL Kidney: Multifocal RCC

von Hippel-Lindau (VHL)
Multiple Clear Cell Renal Carcinomas





Multiple Renal Cysts Containing RCC

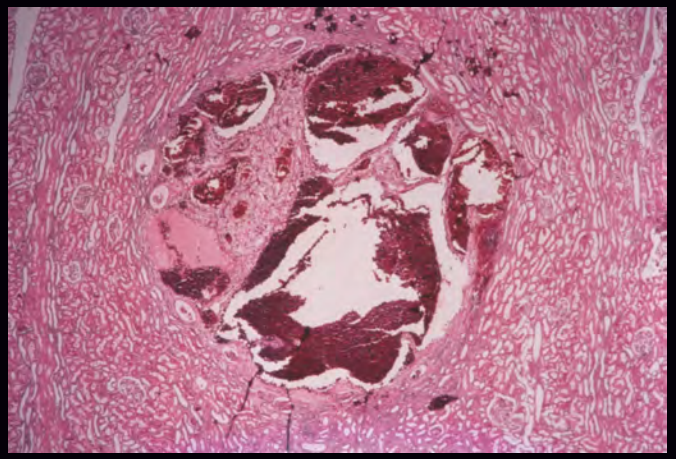
Clear Cell RCC

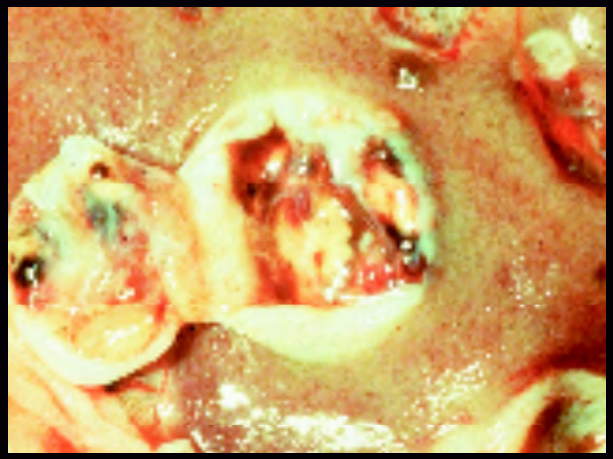
J Urol 153:1995

VHL-Associated RCC
High Persistence Rate

Microscopic Tumors

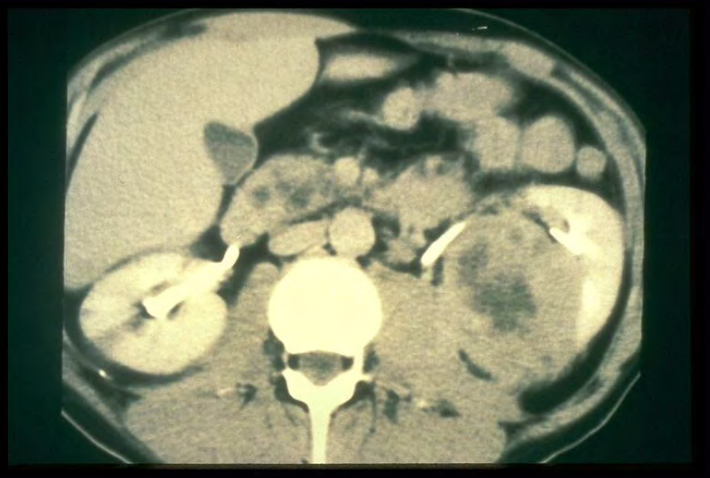
- VHL
  - 600 clear cell RCC/kidney
  - 1300 cysts/kidney

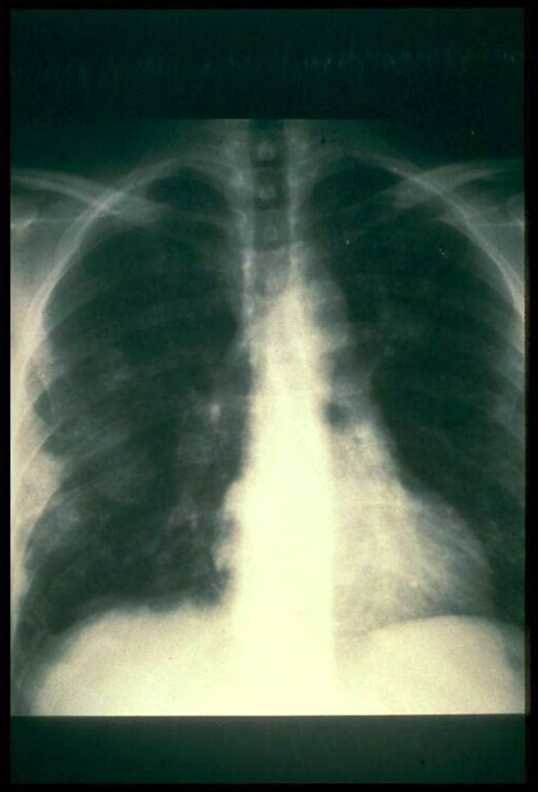




J Urol 154:1995

VHL: Advanced RCC

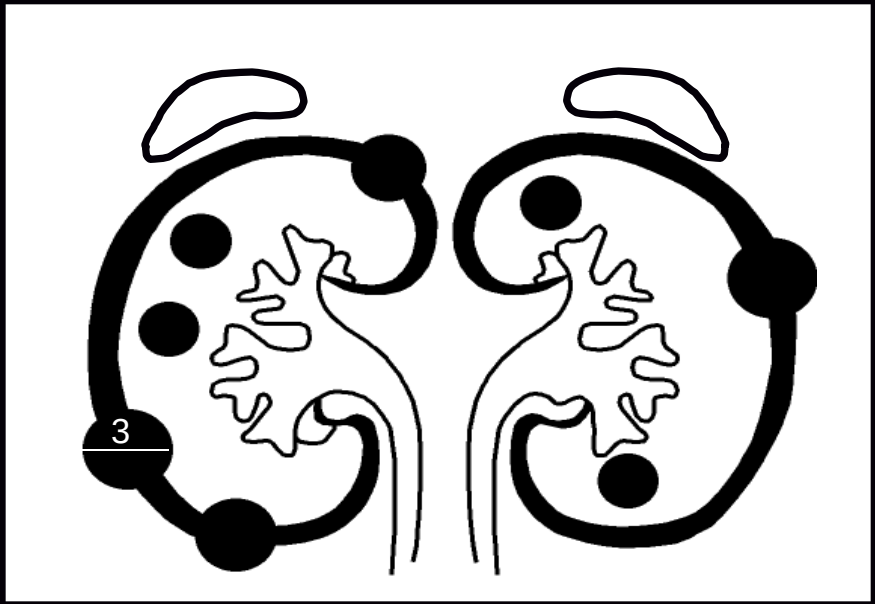




NCI VHL Kindreds N=369

- 972 patients (684 affected) from 369 VHL families have been evaluated
- 338 nephrectomies/partial nephrectomies

Surgical Management of VHL-Associated Renal Carcinoma



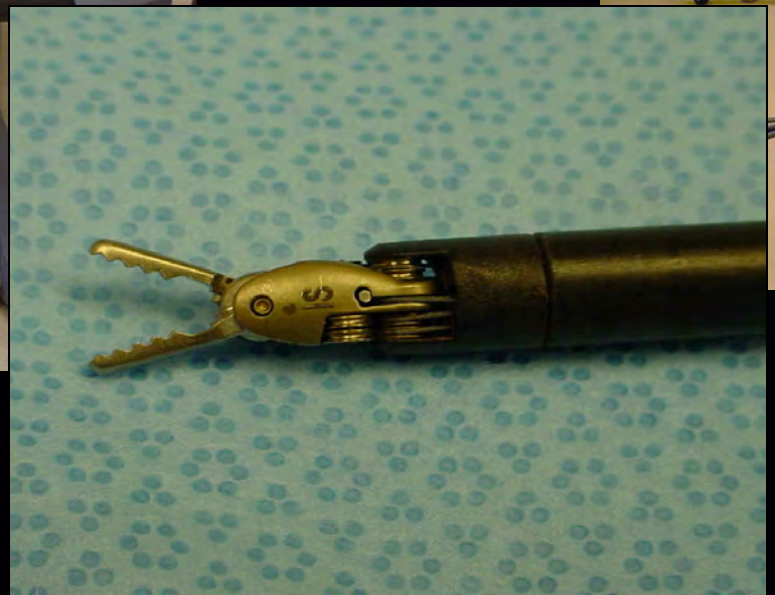
"3 cm rule"

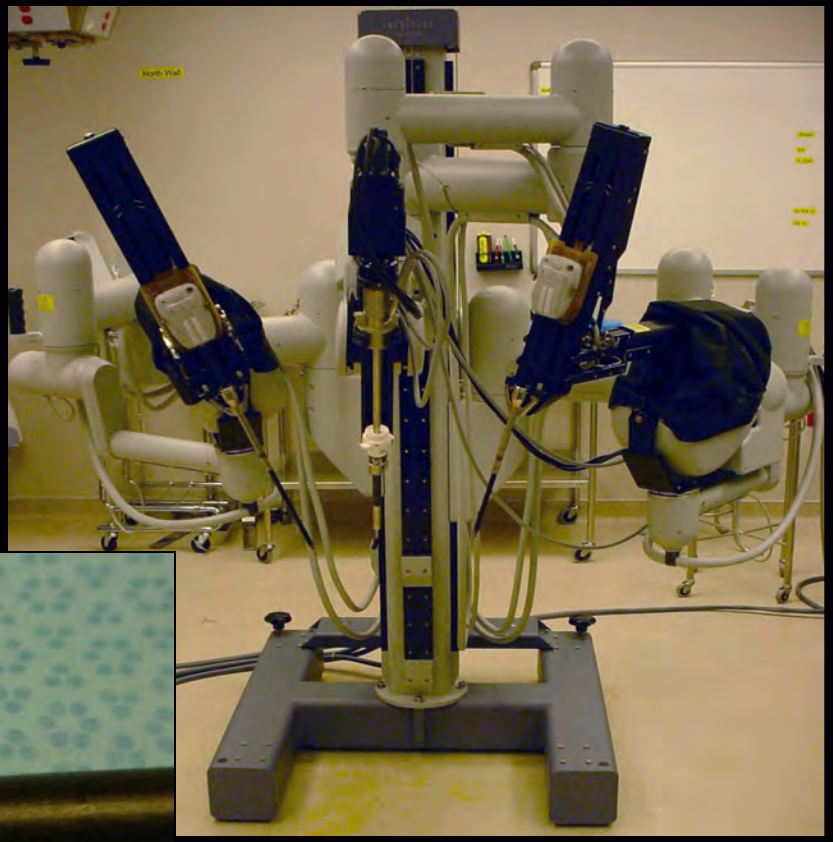
Delay surgery until diameter of largest renal tumor = 3 cm

Surgery = nephron sparing enucleation

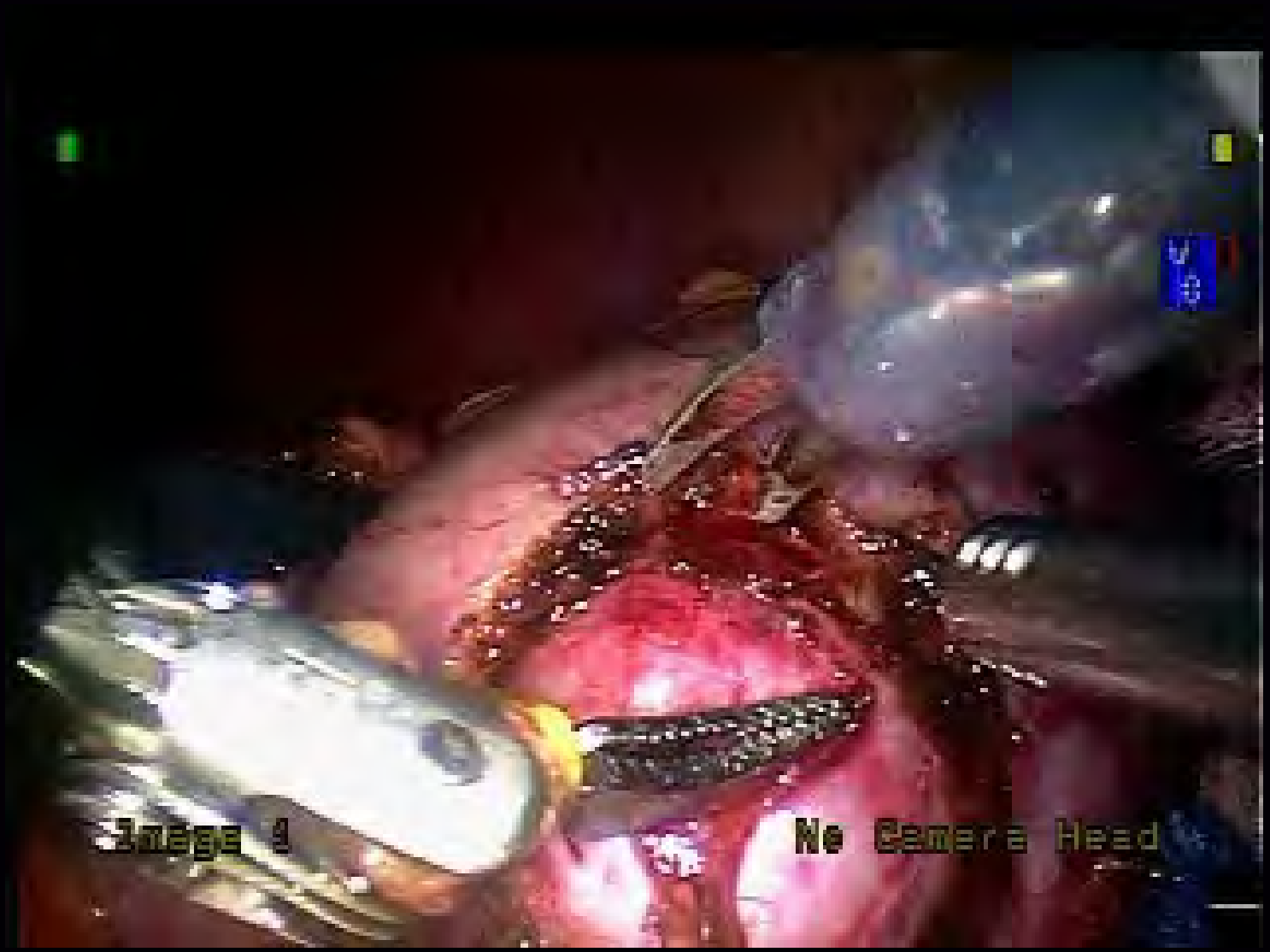
Radiology 174: 1990
J Urol: 153:1995
J Urol 165:2001
J Urol 165:2001
J Urol 172:2004
J Urol 173 2005

Robotic Assisted Partial Nephrectomy

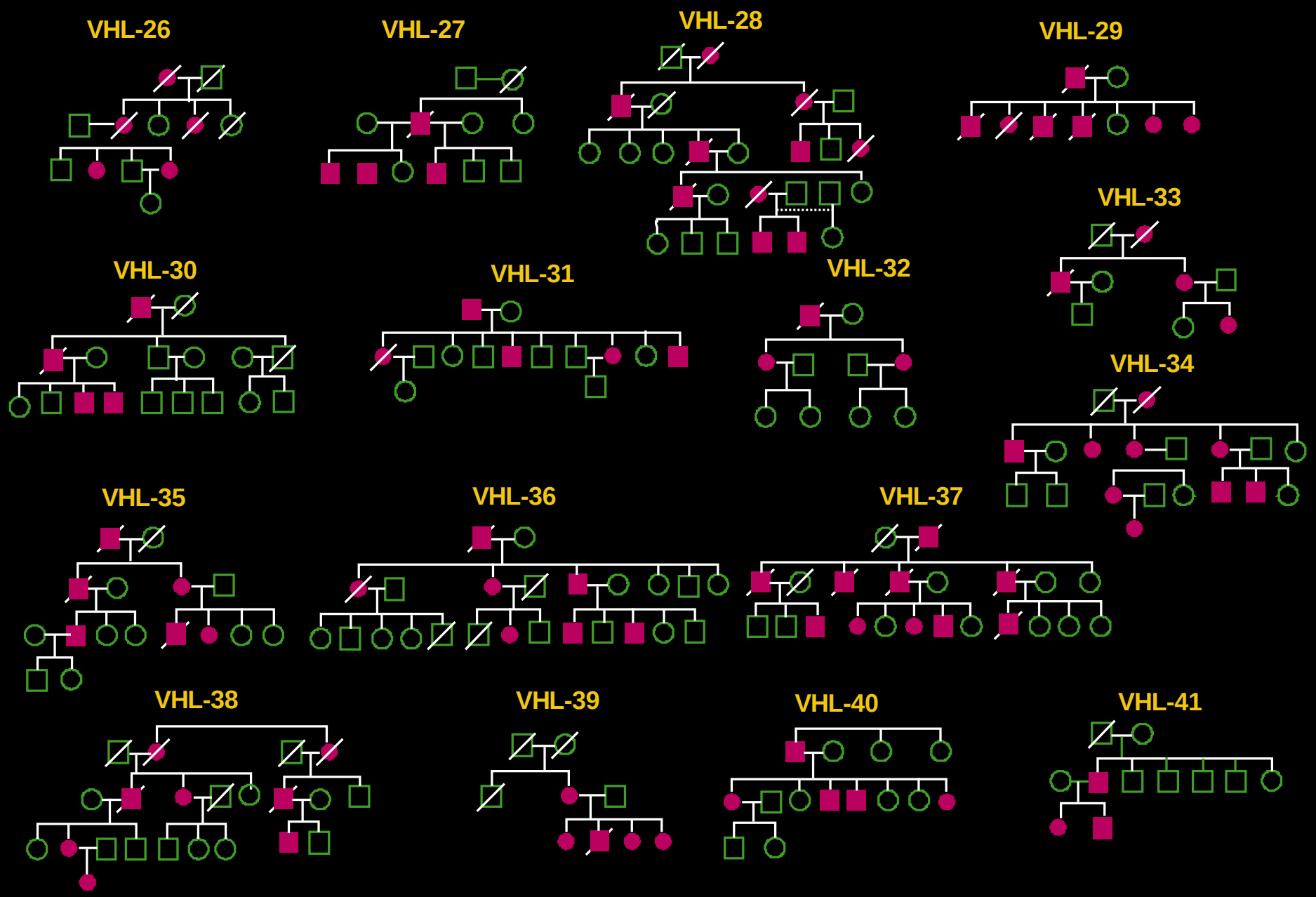




Robotic Assisted Partial Nephrectomy



NIH Clinical Center


VHL-26
VHL-27
VHL-28
VHL-29
VHL-33
VHL-30
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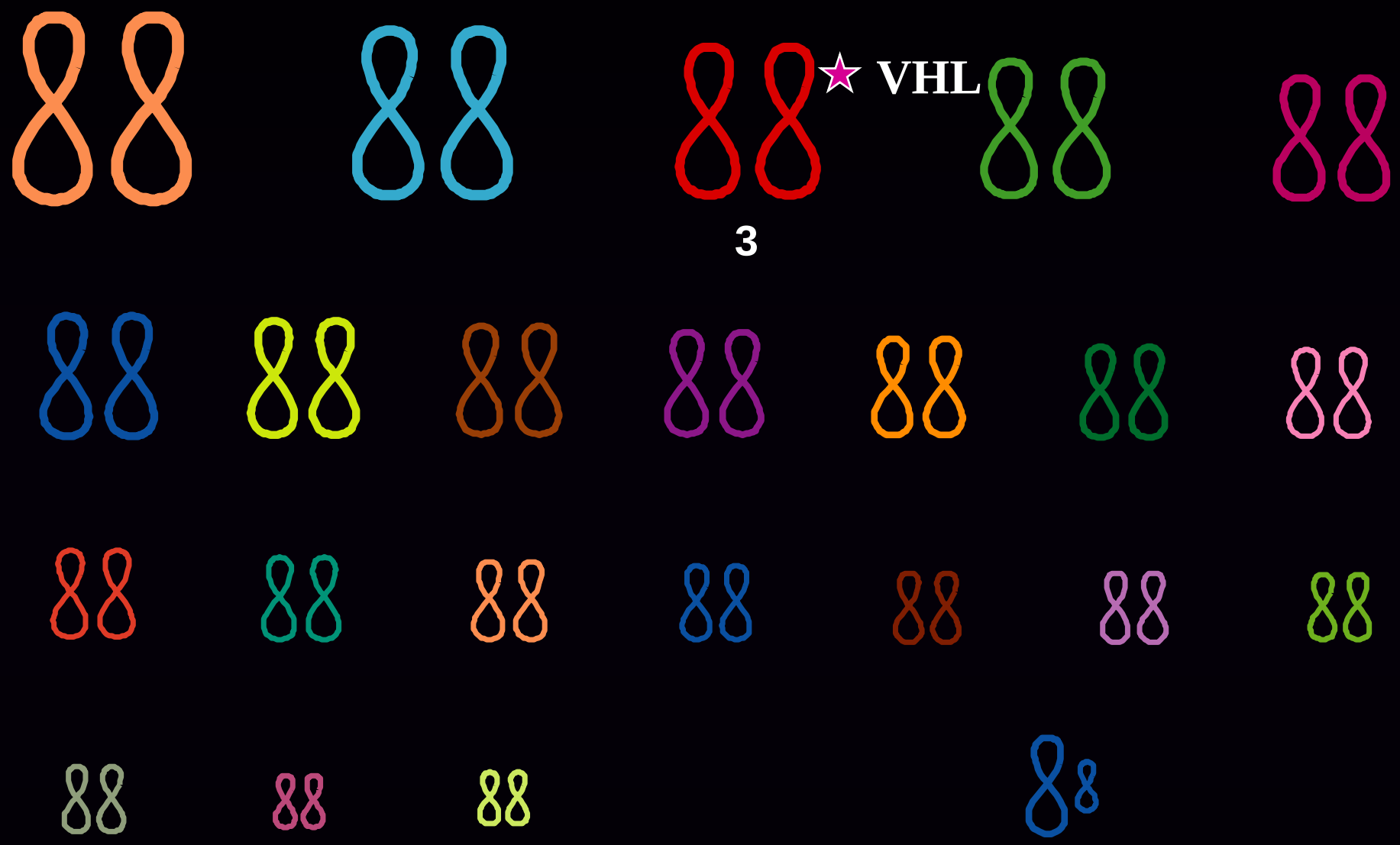
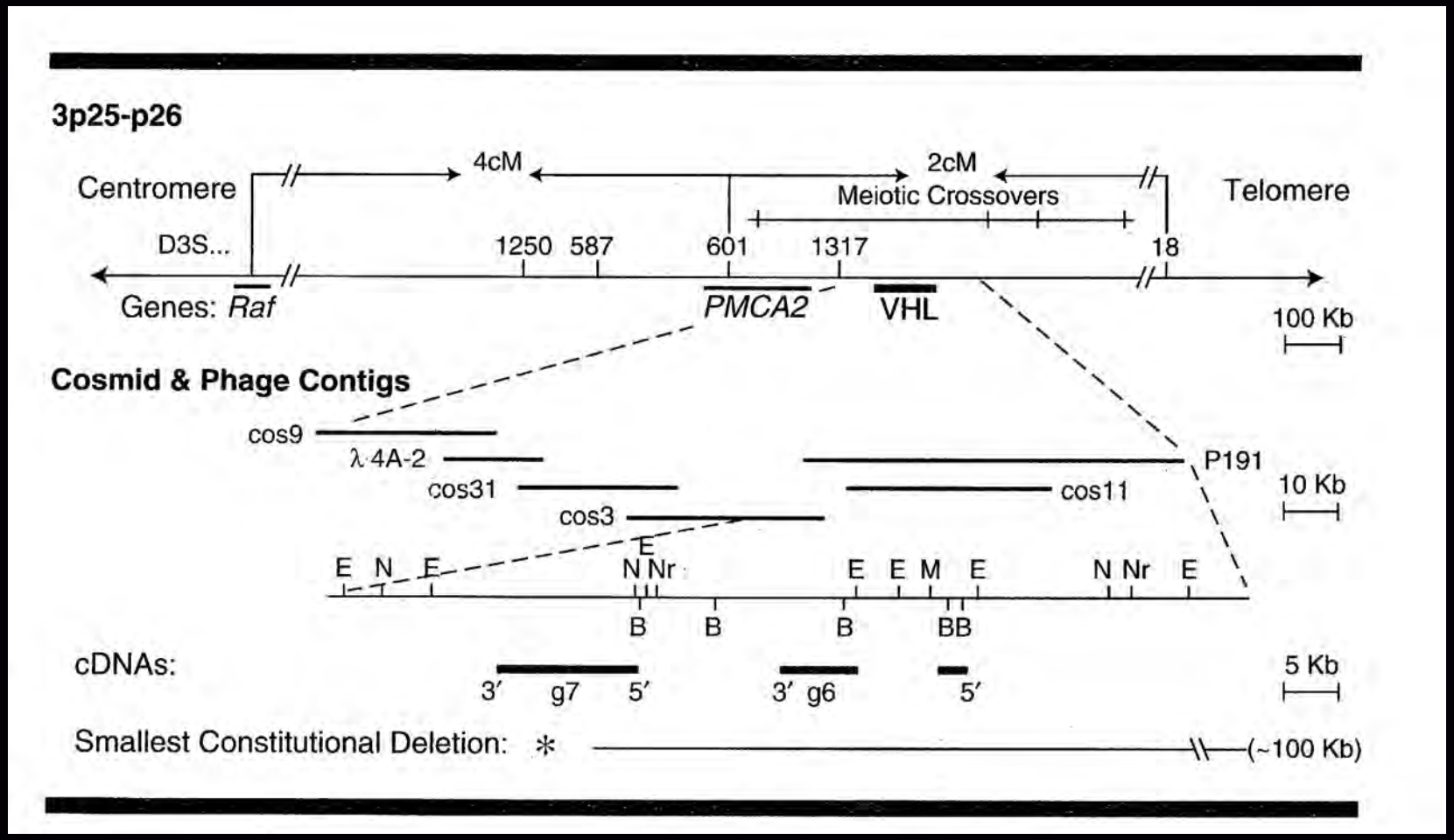
VHL-37
VHL-38
VHL-39
VHL-40
VHL-41



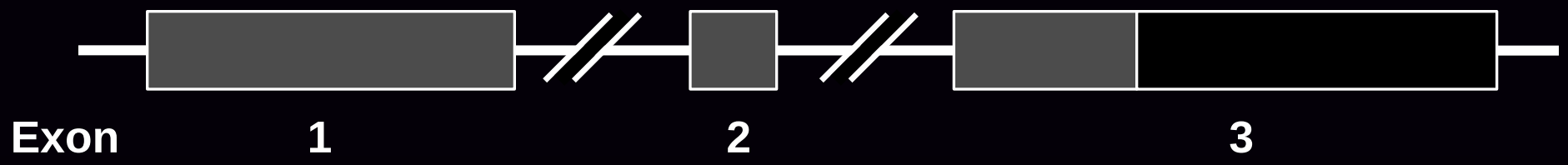
VHL Gene: Clear Cell RCC

VHL Gene Localization Map



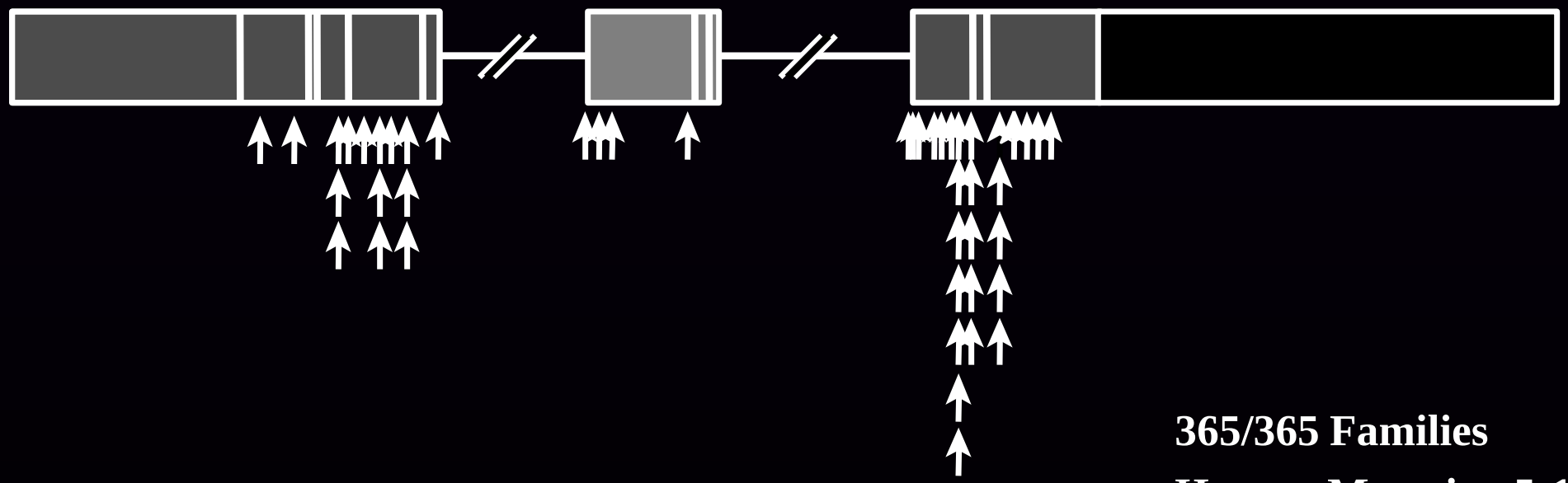
Latif, et al Science 260; 1993

Human VHL Gene



Science 260:1993

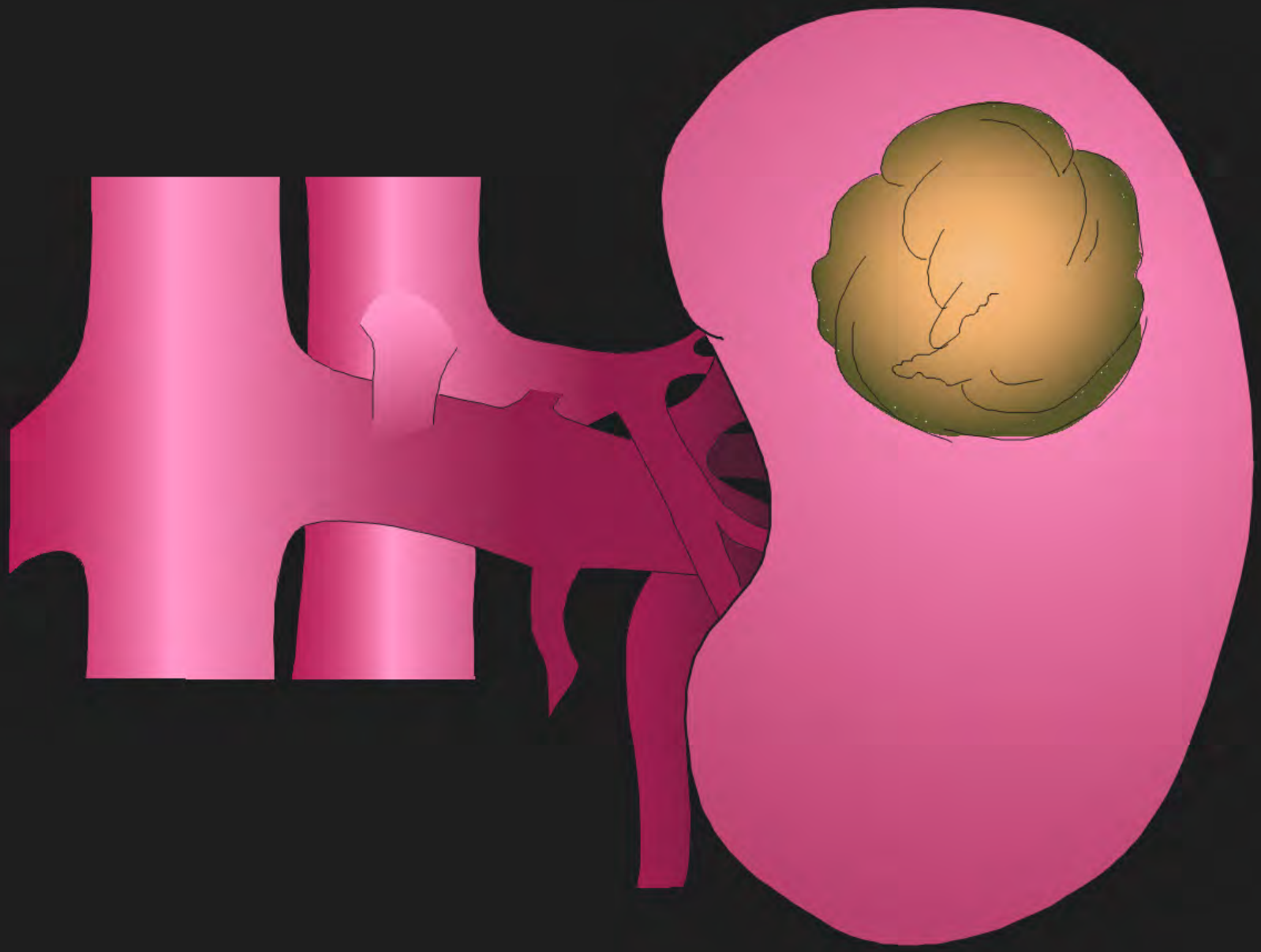
Germline VHL Mutations



365/365 Families

Human Mutation 5:1995

Corbin et al. In Prep



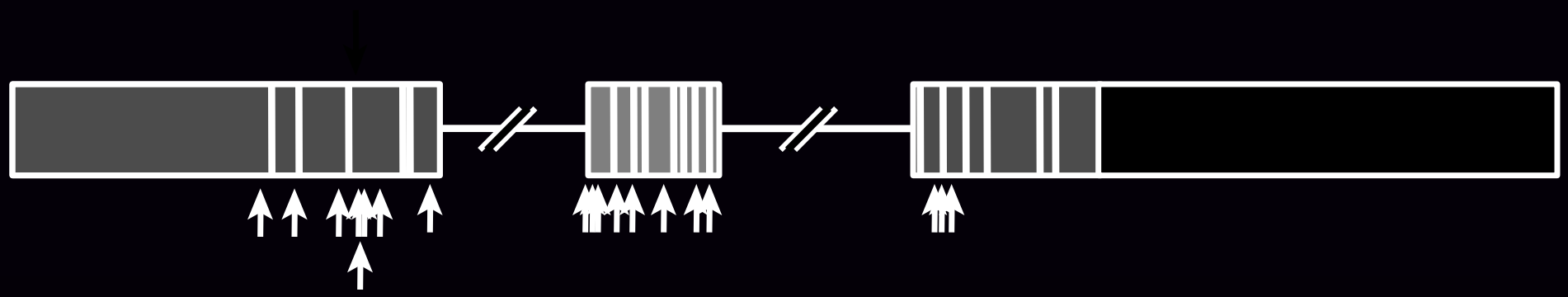
VHL Gene: Sporadic RCC

- Tumor tissues from patients with renal cell carcinoma were evaluated for:

  1. VHL gene mutation

  2. VHL gene deletion (loss)

Sporadic Clear Cell RCC VHL Gene Mutations

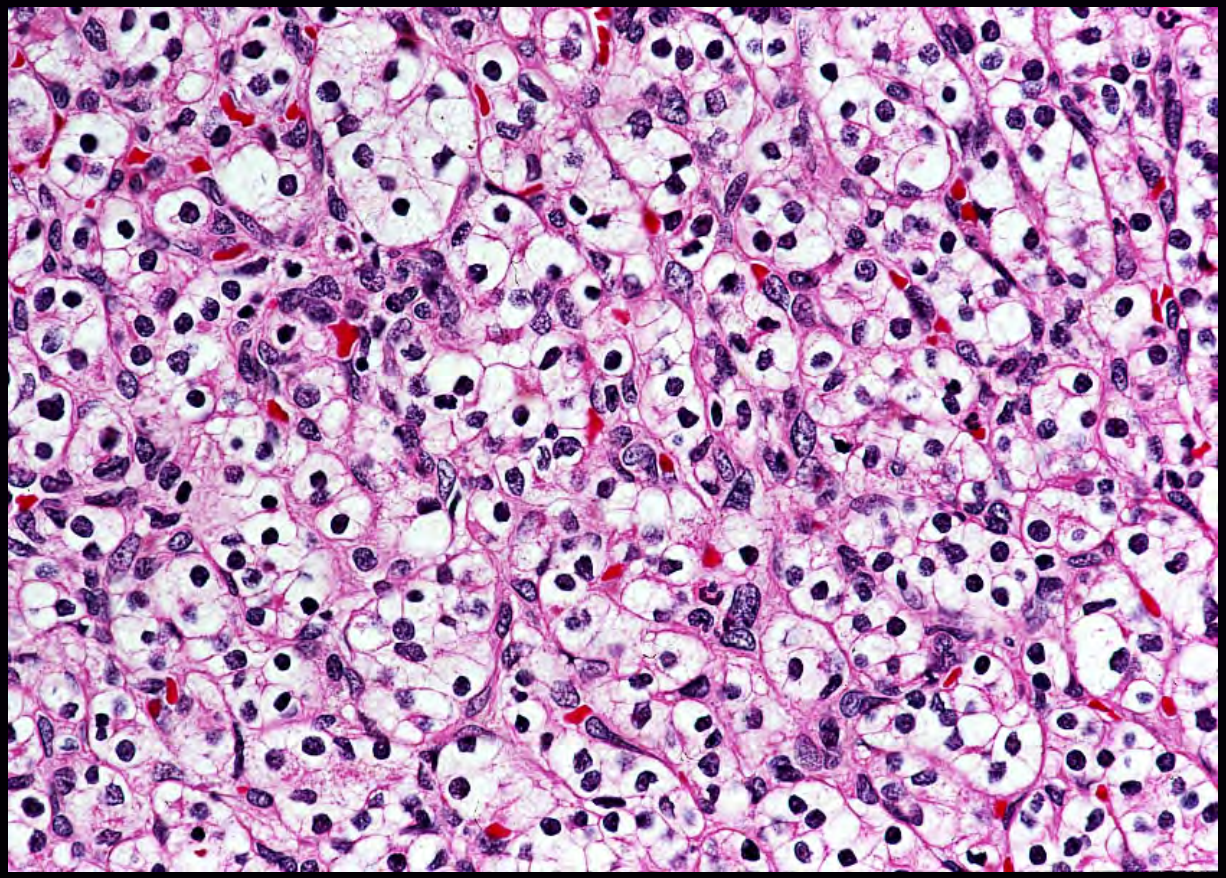


Science 260:1993

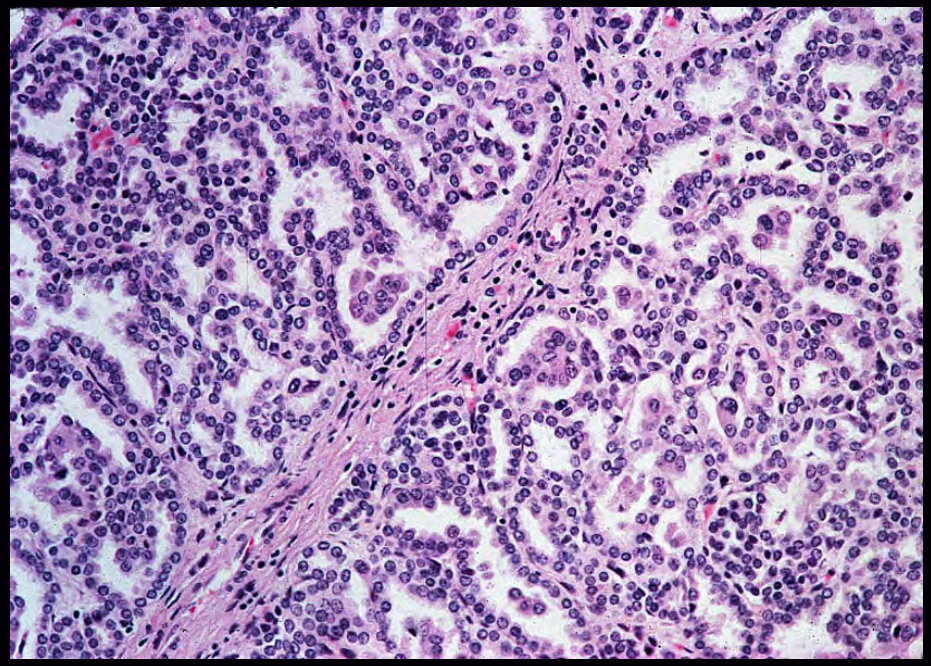
Nature Genetics 7:1994

Clin Cancer Res 14:2008

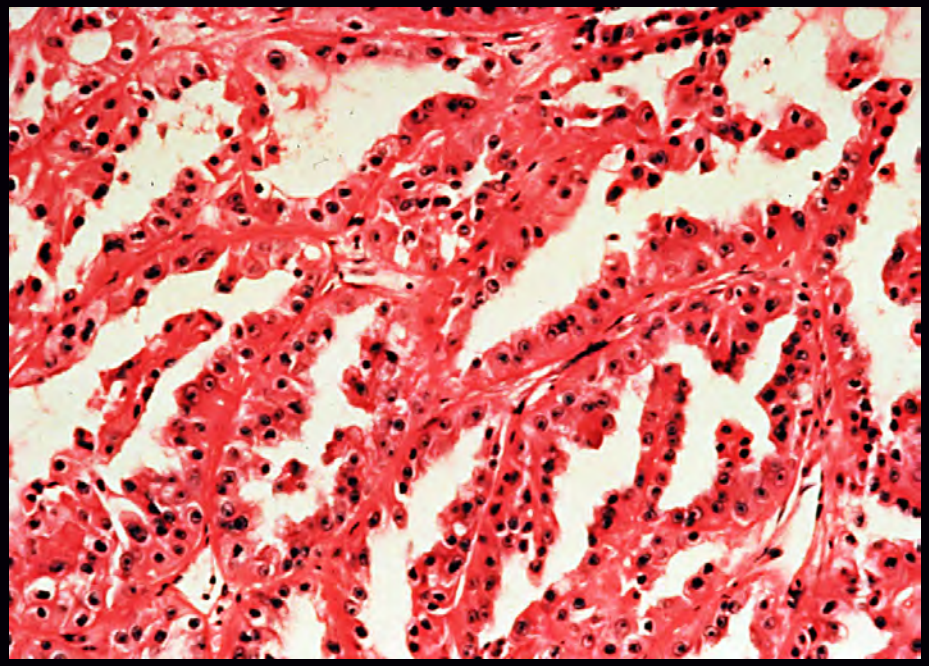
Clear Cell Renal Carcinoma



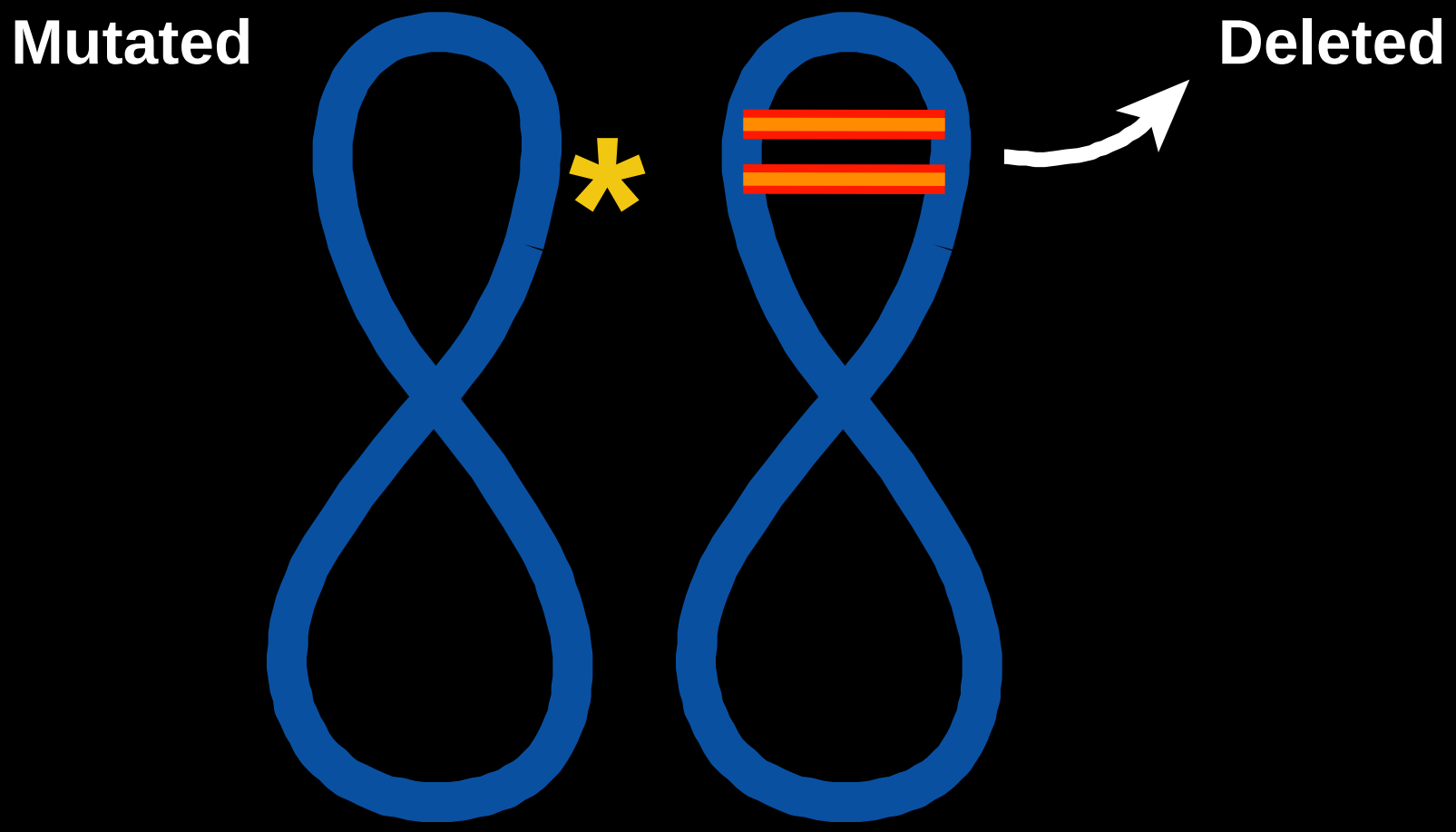
Papillary Renal Carcinoma



Type 1



Type 2



Chromosome 3
Clear Cell Kidney Cancer

Athymic Nude Mouse Bearing Clear Cell RCC (VHL -/-)

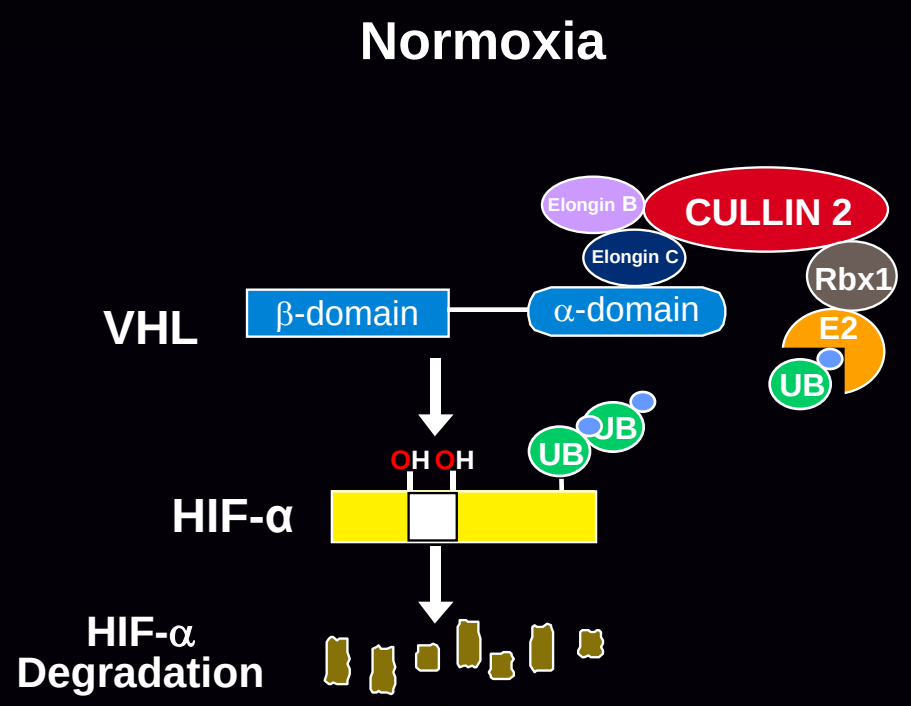
PNAS 93:1996

Mouse With RCC + VHL Gene

PNAS 93:1996

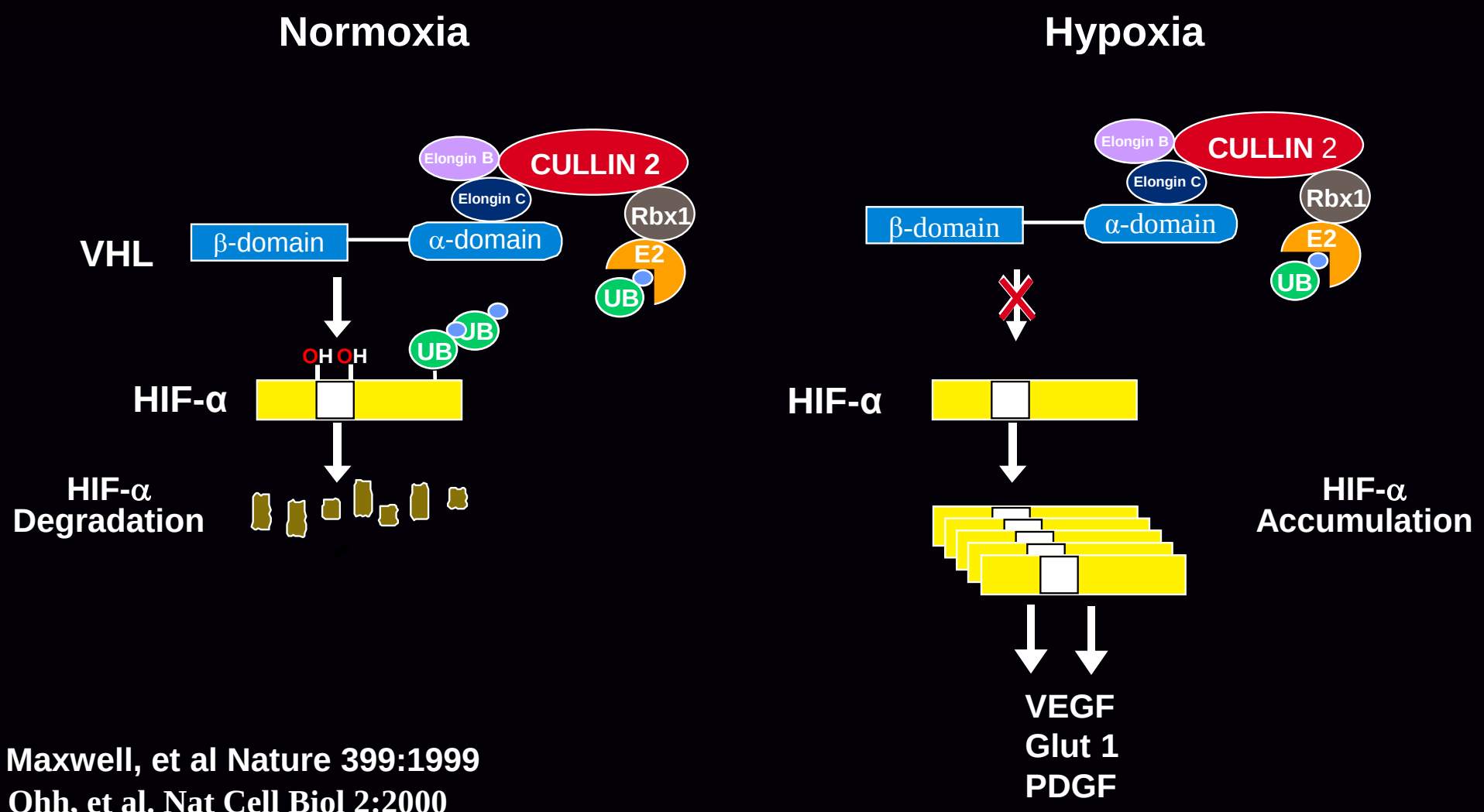
How Does the VHL Gene Function?

HIFα is targeted for degradation in normoxic,



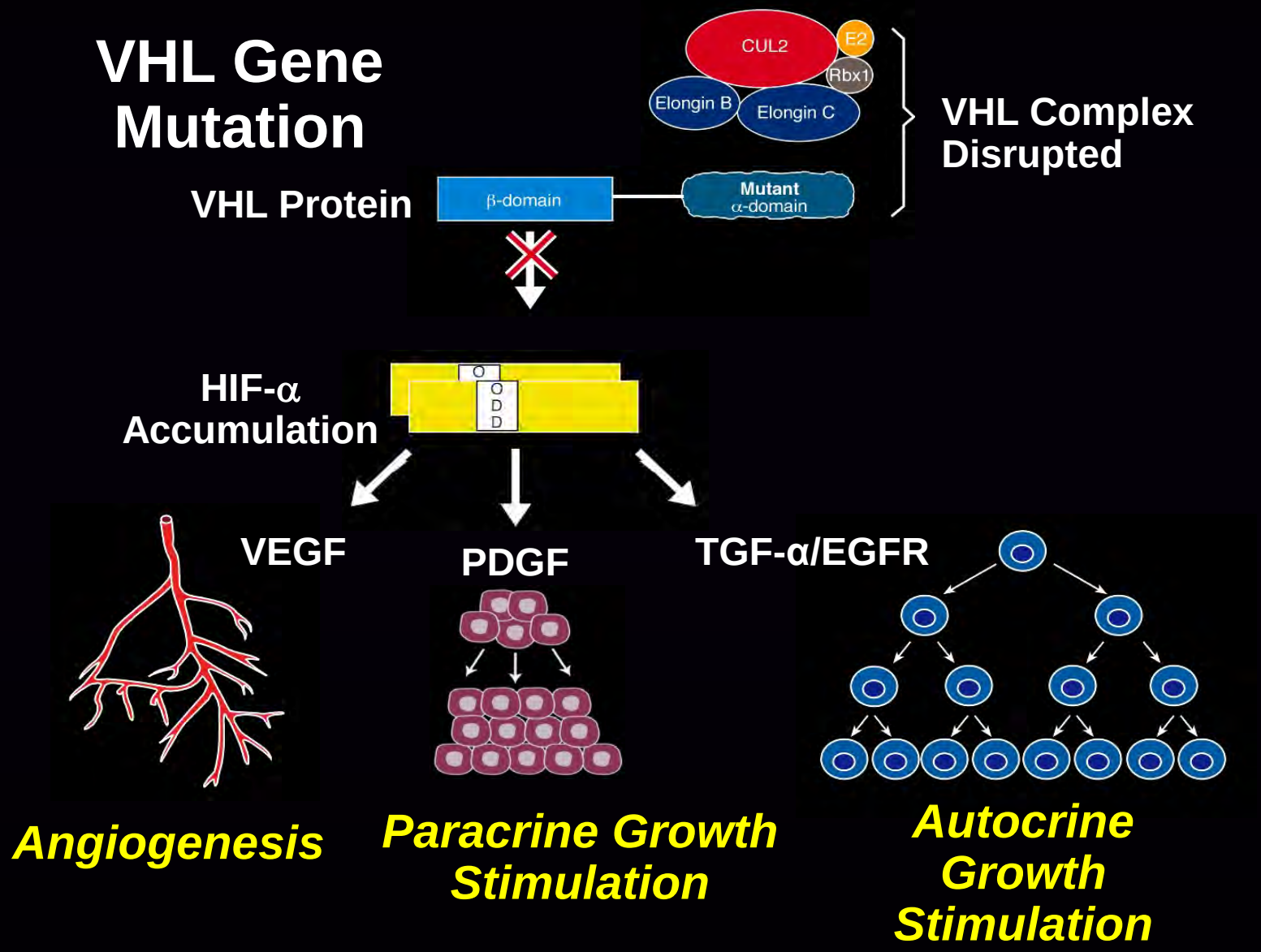
Maxwell, et al Nature 399:1999
Ohh, et al. Nat Cell Biol 2:2000

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

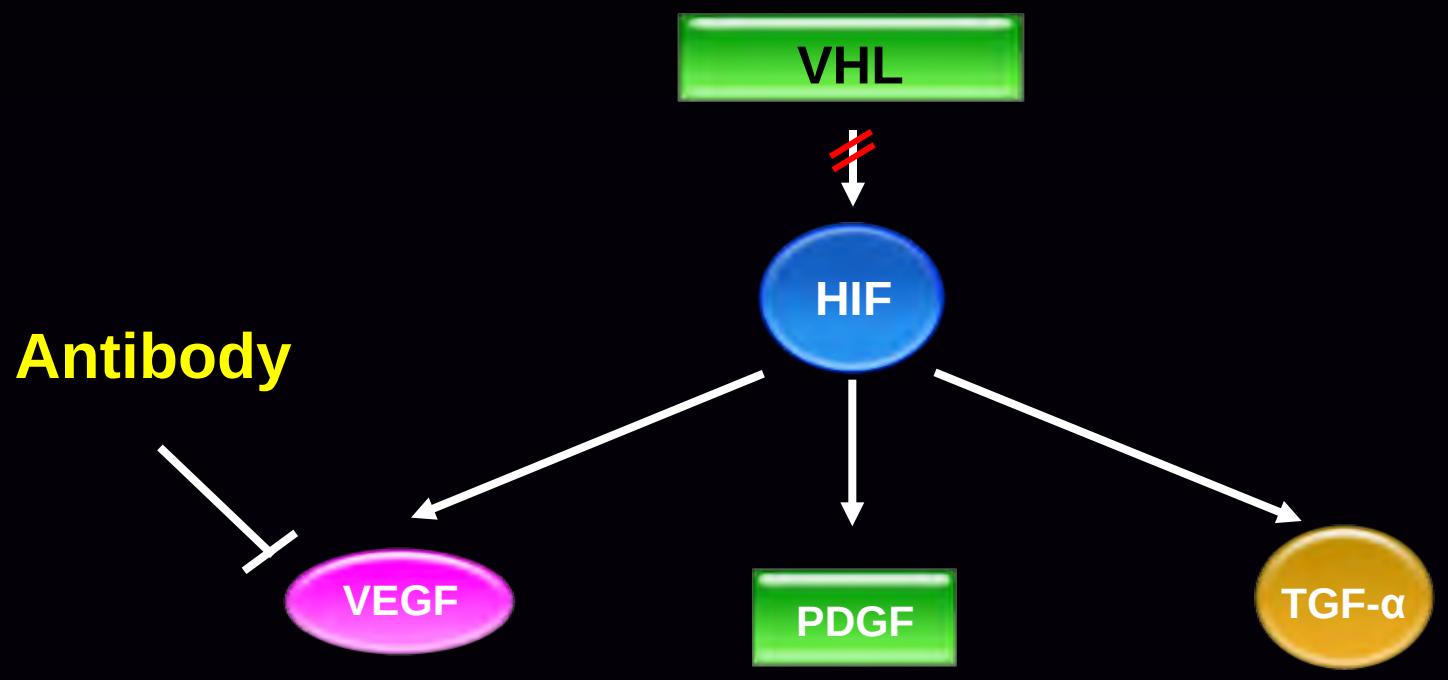


Maxwell, et al Nature 399:1999
Ohh, et al. Nat Cell Biol 2:2000

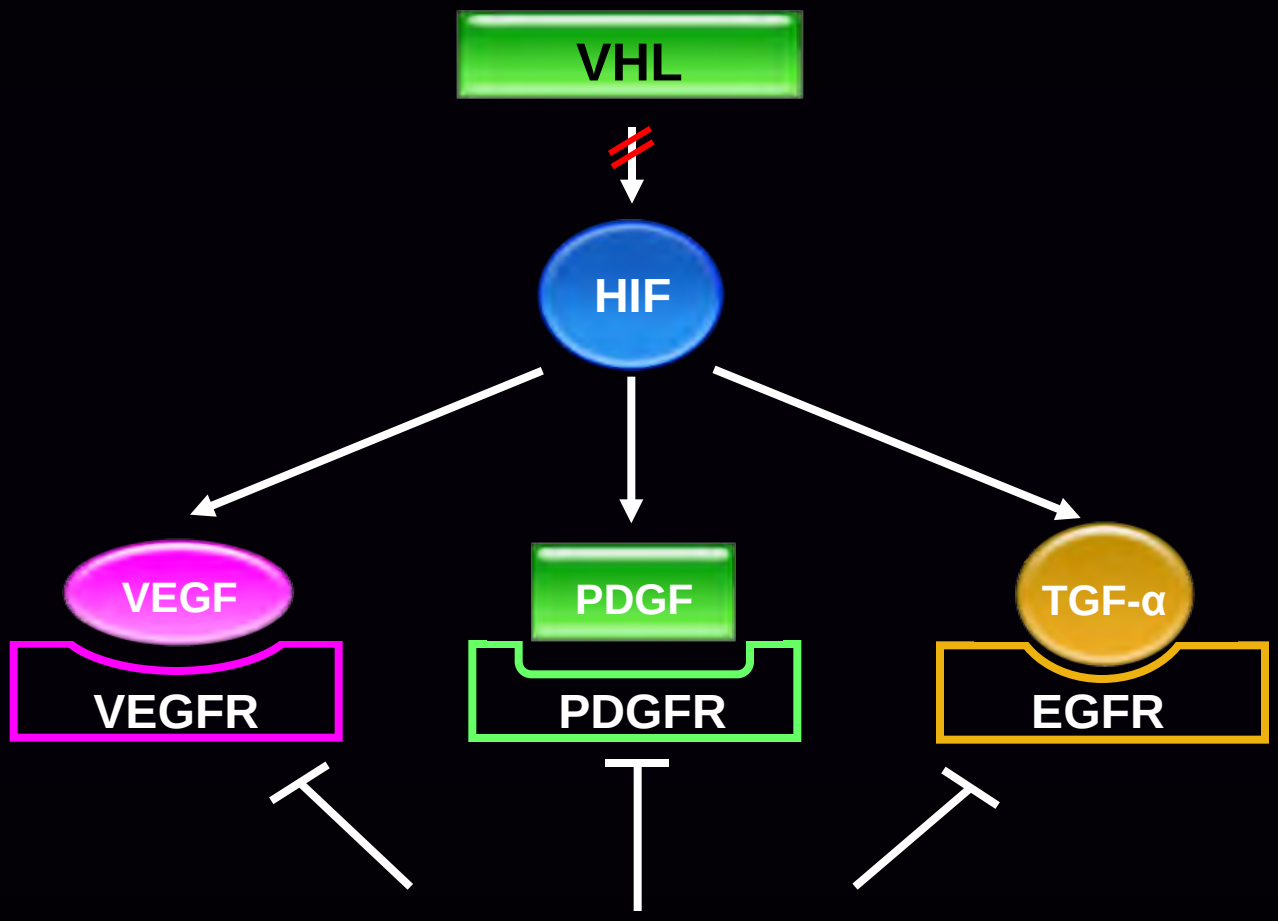
Downstream effects of *VHL* mutation



Targeting VHL/HIF in Clear Cell RCC

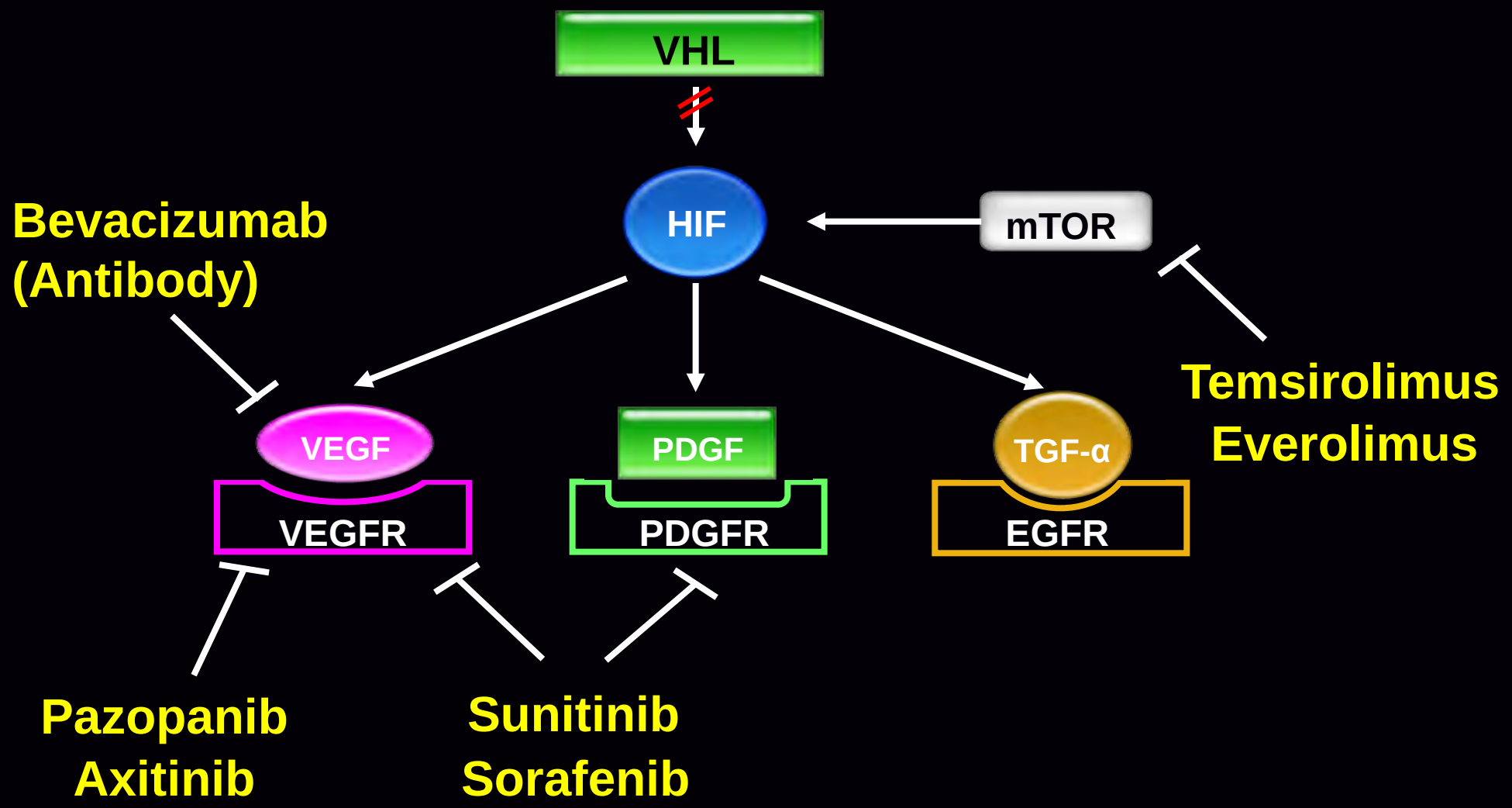


Targeting VHL/HIF in Clear Cell RCC

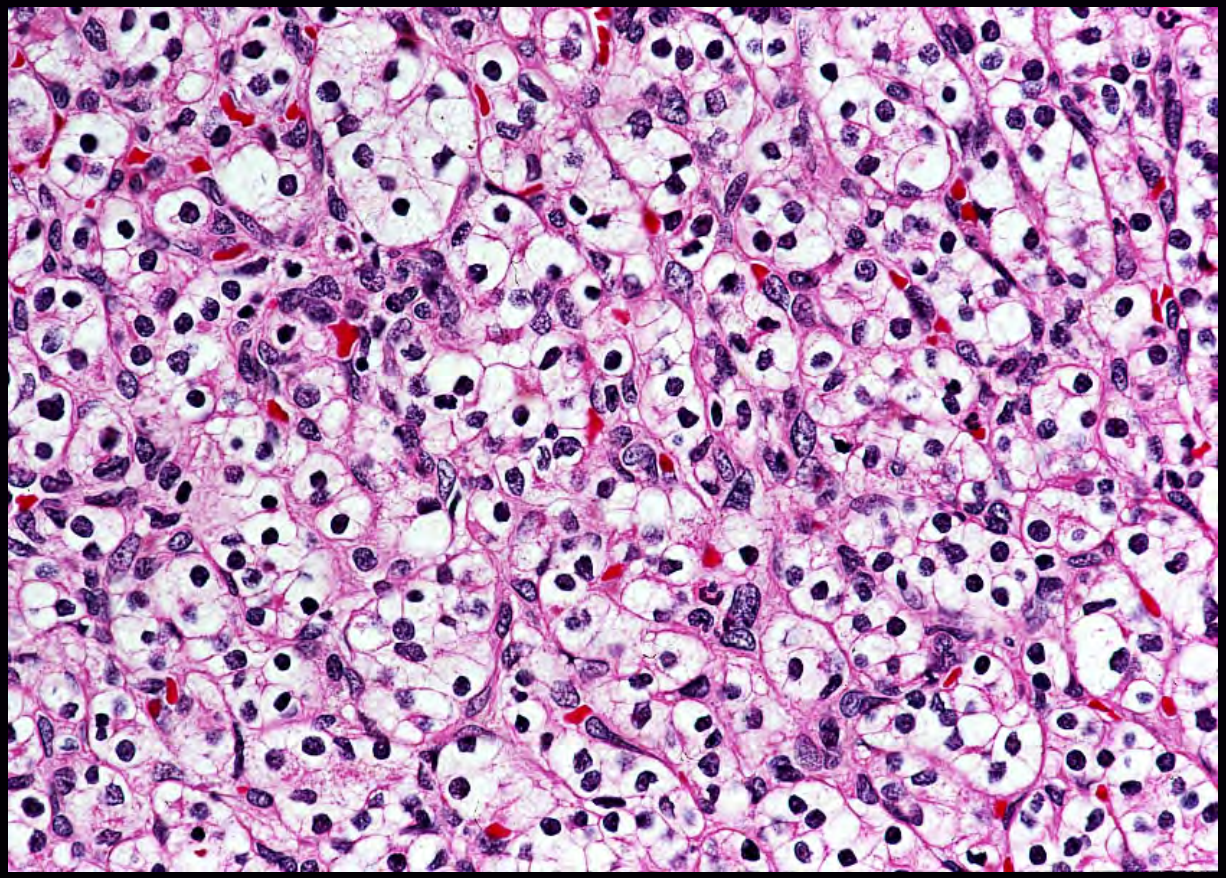


Tyrosine Kinase Inhibitor (TKI)

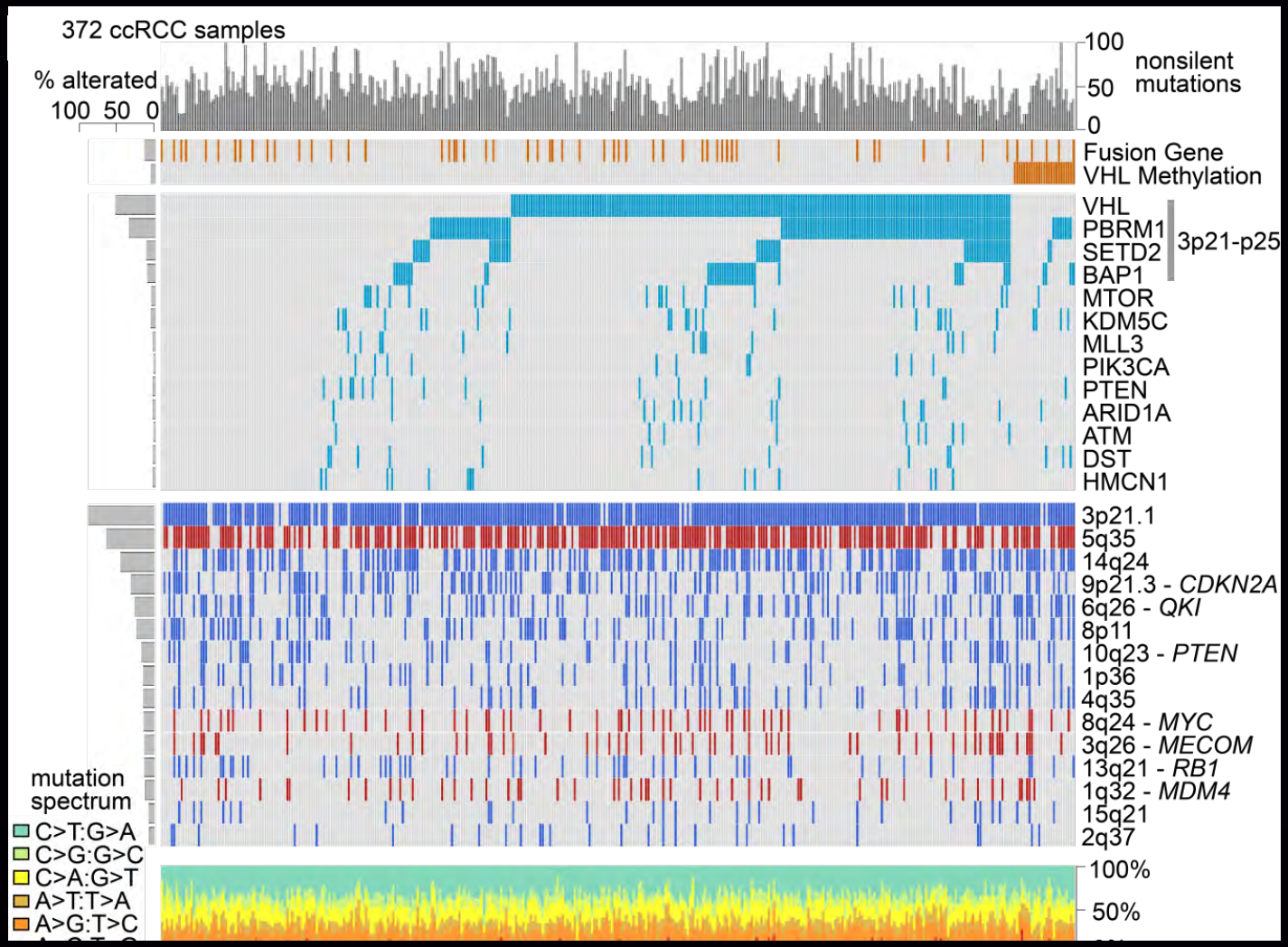
Targeting VHL/HIF in Clear Cell RCC



Clear Cell Renal Carcinoma

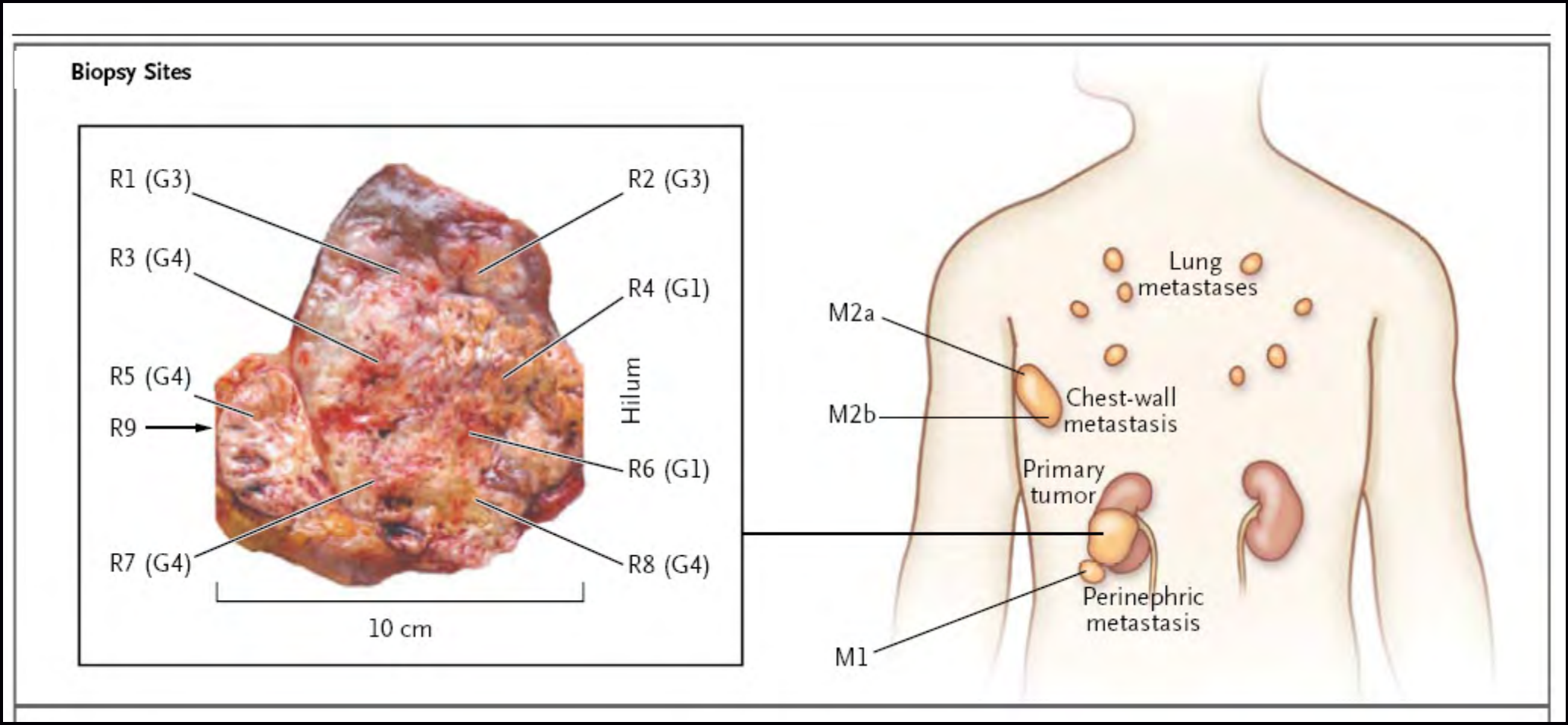


TCGA Clear Cell Kidney Cancer



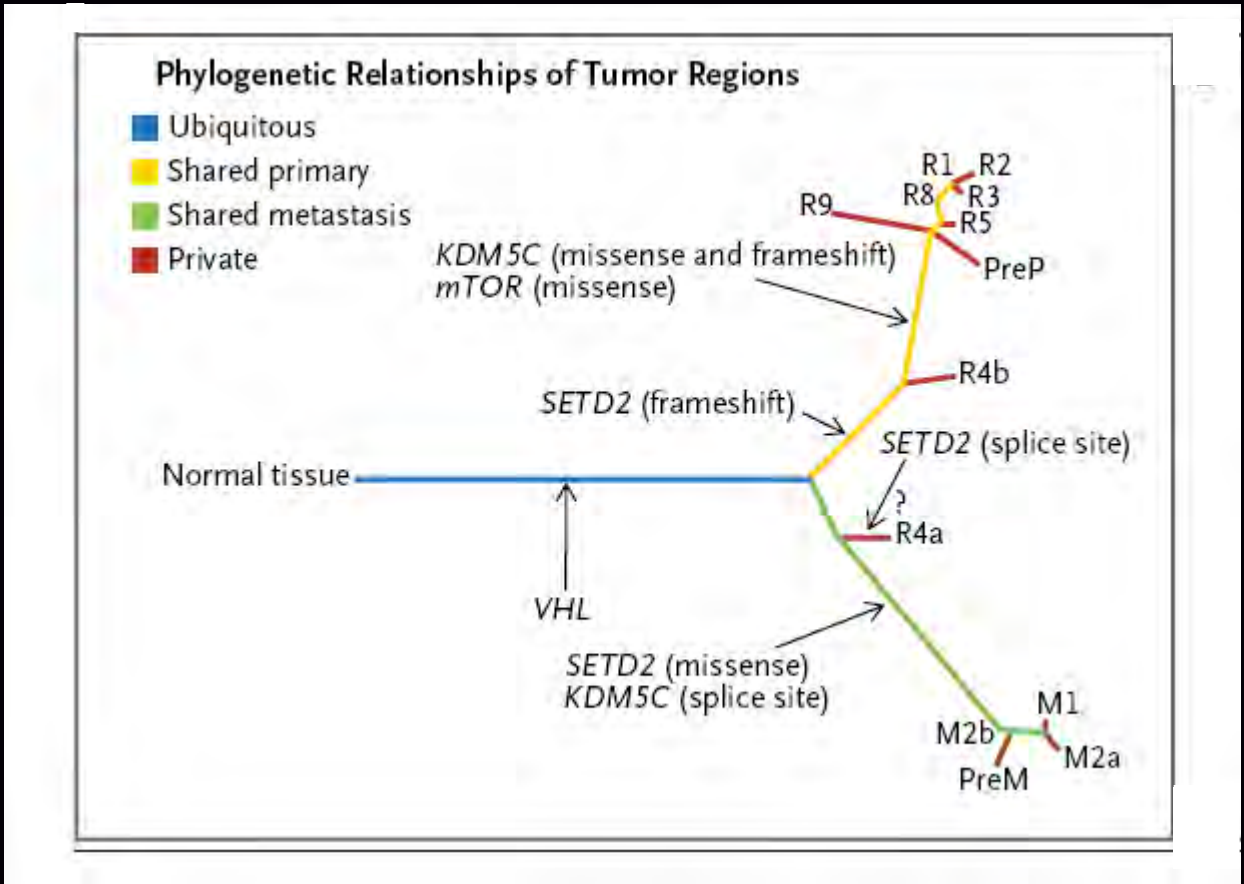
Nature: 2013

Intratumor Heterogeneity

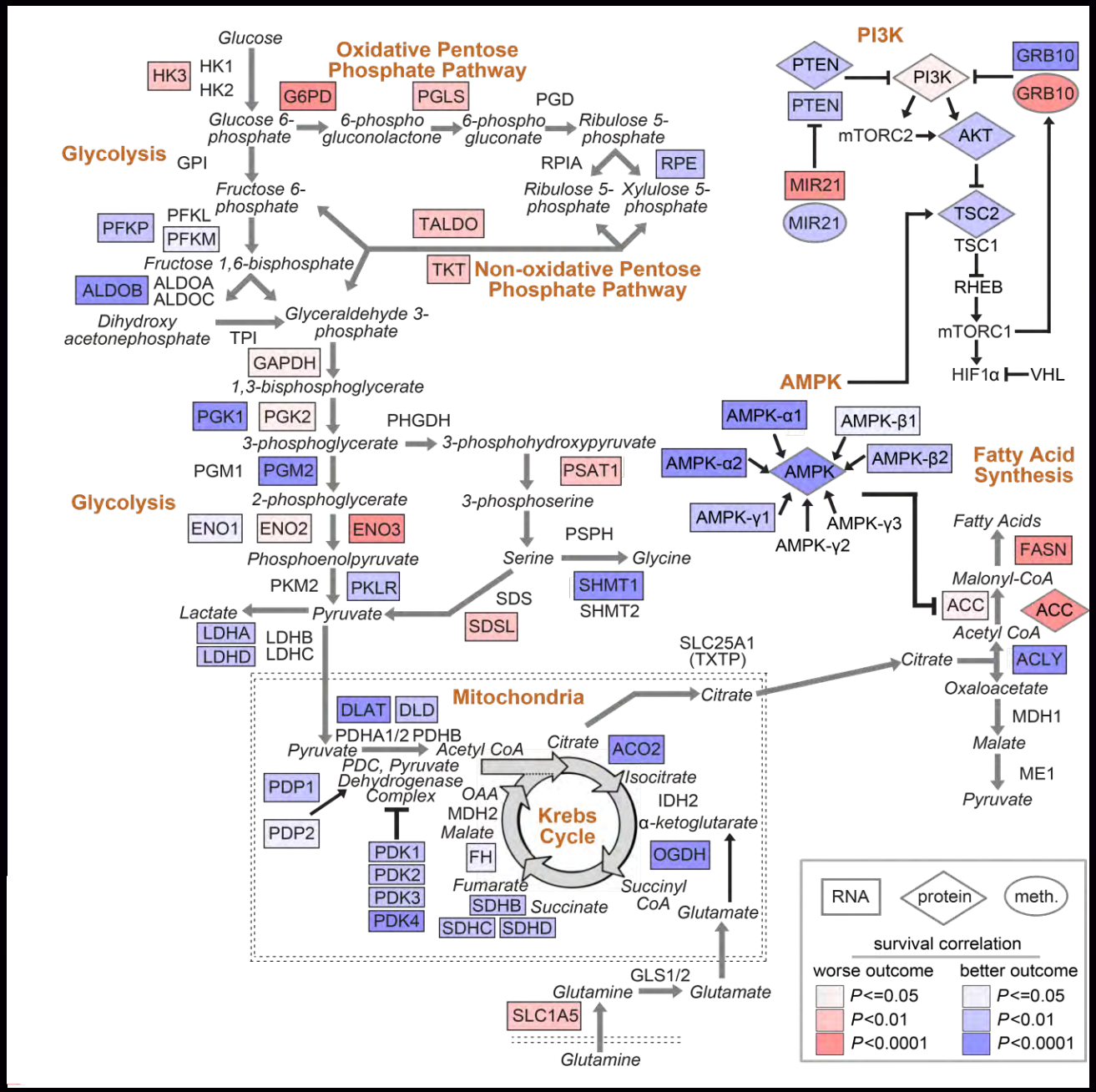


Gerlinger et al *NEJM* 366:2012

Intratumor Heterogeneity

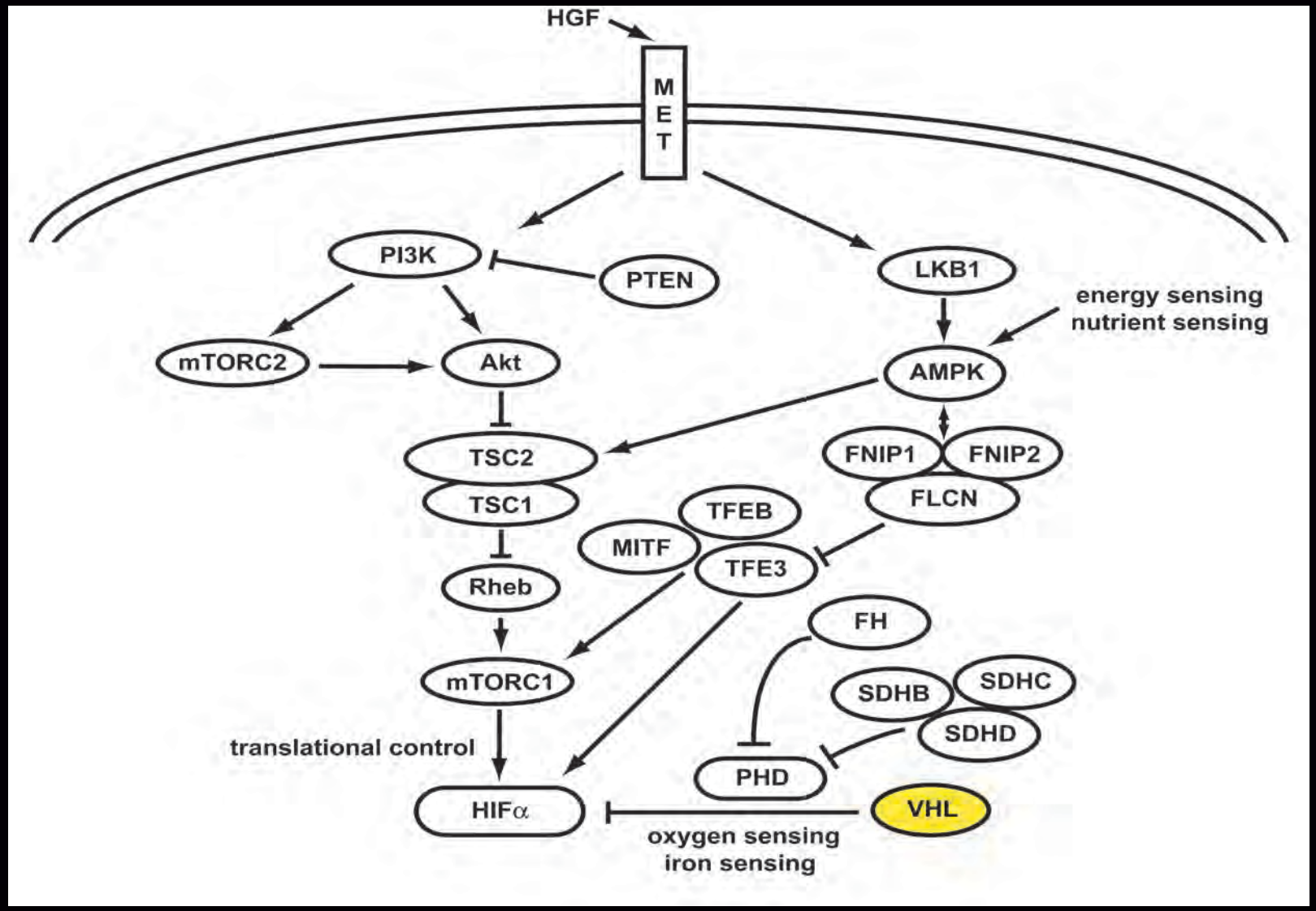


Gerlinger et al *NEJM* 366:2012


Glucose
HK3
HK1
HK2
Oxidative Pentose Phosphate Pathway
G6PD
PGLS
PGD
Glucose 6-phosphate
6-phospho gluconolactone
6-phospho gluconate
Ribulose 5-phosphate
Glycolysis
GPI
RPIA
RPE
Fructose 6-phosphate
Ribulose 5-phosphate
Xylulose 5-phosphate
PFKP
PFKL
PFKM
TALDO
Fructose 1,6-bisphosphate
TKT
Non-oxidative Pentose Phosphate Pathway
ALDOB
ALDOA
ALDOC
Dihydroxy acetonephosphate
TPI
Glyceraldehyde 3-phosphate
GAPDH
1,3-bisphosphoglycerate
PGK1
PGK2
PHGDH
3-phosphoglycerate
3-phosphohydroxypyruvate
PGM1
PGM2
PSAT1
Glycolysis
2-phosphoglycerate
3-phosphoserine
ENO1
ENO2
ENO3
PSPH
Phosphoenolpyruvate
Serine
Glycine
PKM2
PKLR
SHMT1
SDS
SHMT2
Lactate
Pyruvate
SDSL
LDHA
LDHB
LDHD
LDHC
SLC25A1 (TXTP)
Mitochondria
DLAT
DLD
Citrate
PDHA1/2 PDHB
Pyruvate
Acetyl CoA
Citrate
ACO2
PDC, Pyruvate Dehydrogenase Complex
Isocitrate
PDP1
OAA
IDH2
MDH2
Krebs Cycle
α-ketoglutarate
PDP2
Malate
OGDH
PDK1
PDK2
PDK3
PDK4
FH
Fumarate
Succinyl CoA
SDHB
Succinate
Glutamate
SDHC
SDHD
GLS1/2
Glutamine
Glutamate
SLC1A5
Glutamine
PI3K
PTEN
PI3K
GRB10
PTEN
GRB10
mTORC2
AKT
MIR21
MIR21
TSC2
TSC1
RHEB
mTORC1
HIF1α
VHL
AMPK
AMPK-α1
AMPK-β1
AMPK-α2
AMPK
AMPK-β2
Fatty Acid Synthesis
AMPK-γ1
AMPK-γ3
AMPK-γ2
Fatty Acids
FASN
Malonyl-CoA
ACC
ACC
Acetyl CoA
Citrate
ACLY
Oxaloacetate
MDH1
Malate
ME1
Pyruvate
RNA
protein
meth.
survival correlation
worse outcome
better outcome
P<=0.05
P<=0.05
P<0.01
P<0.01
P<0.0001
P<0.0001

Nature: 2013

Kidney Cancer is a Metabolic Disease



Nature Rev Urol: 7 2010

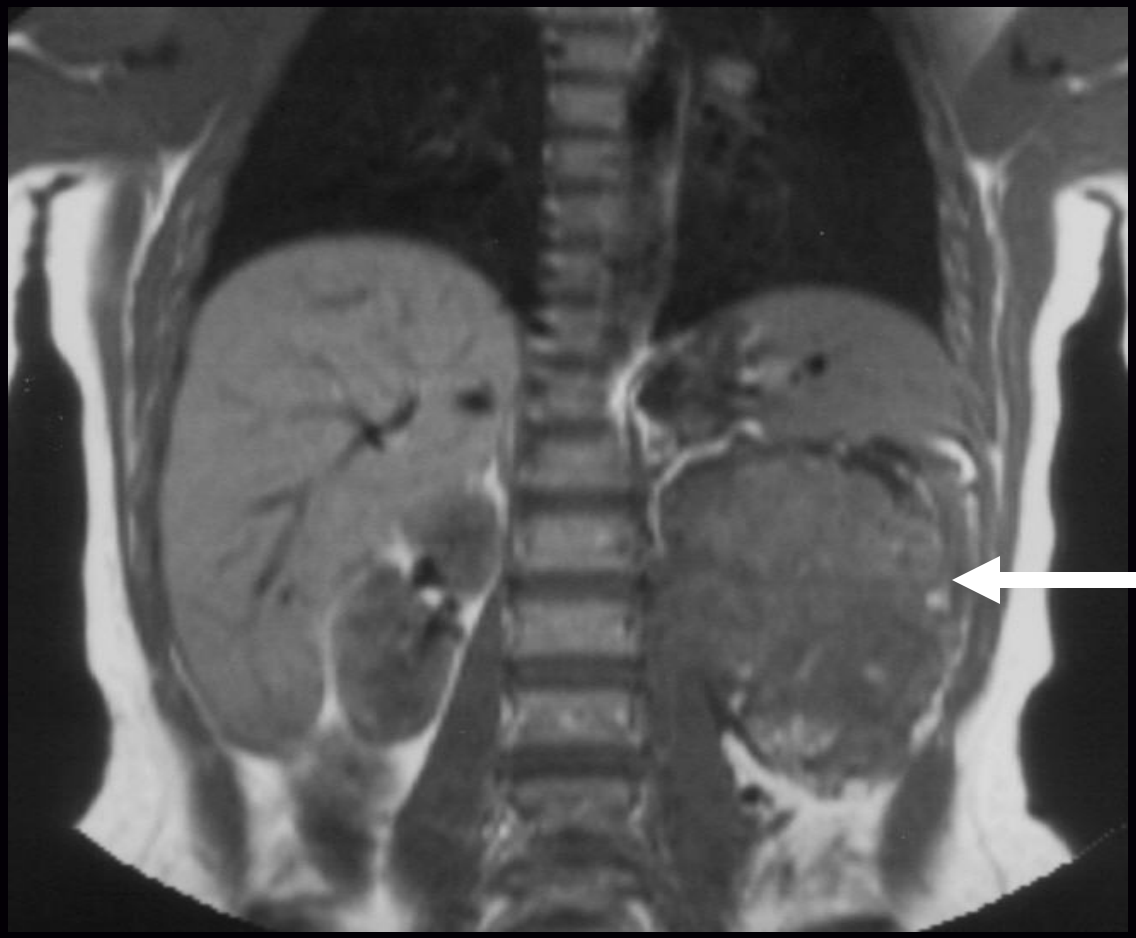
Non-Clear Cell RCC

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. Granular-Clear Cell RCC

Locally Advanced Kidney Cancer

Surgery 4/21/87



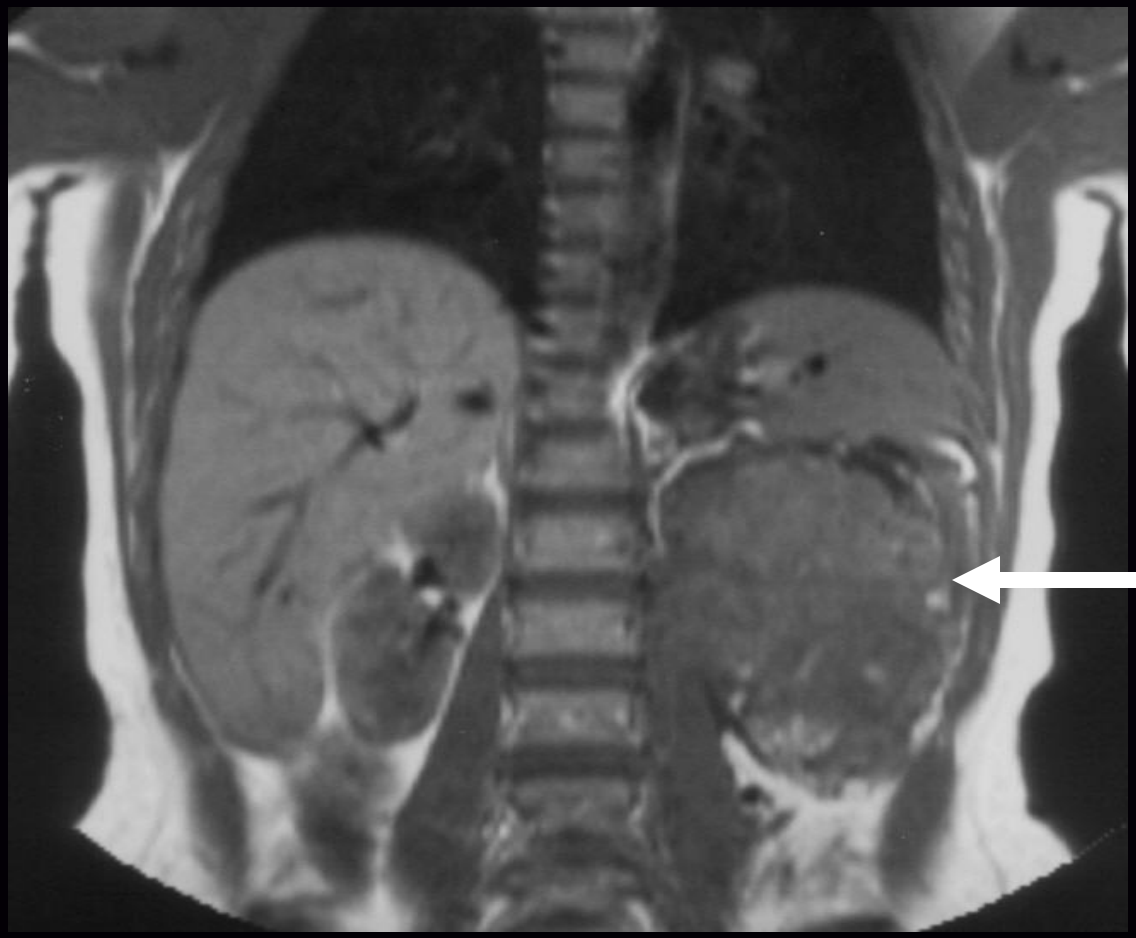
11 cm
T3A

21 Year Old Female

Non-Clear Cell Kidney Cancer Patient 1

Surgery 4/21/87

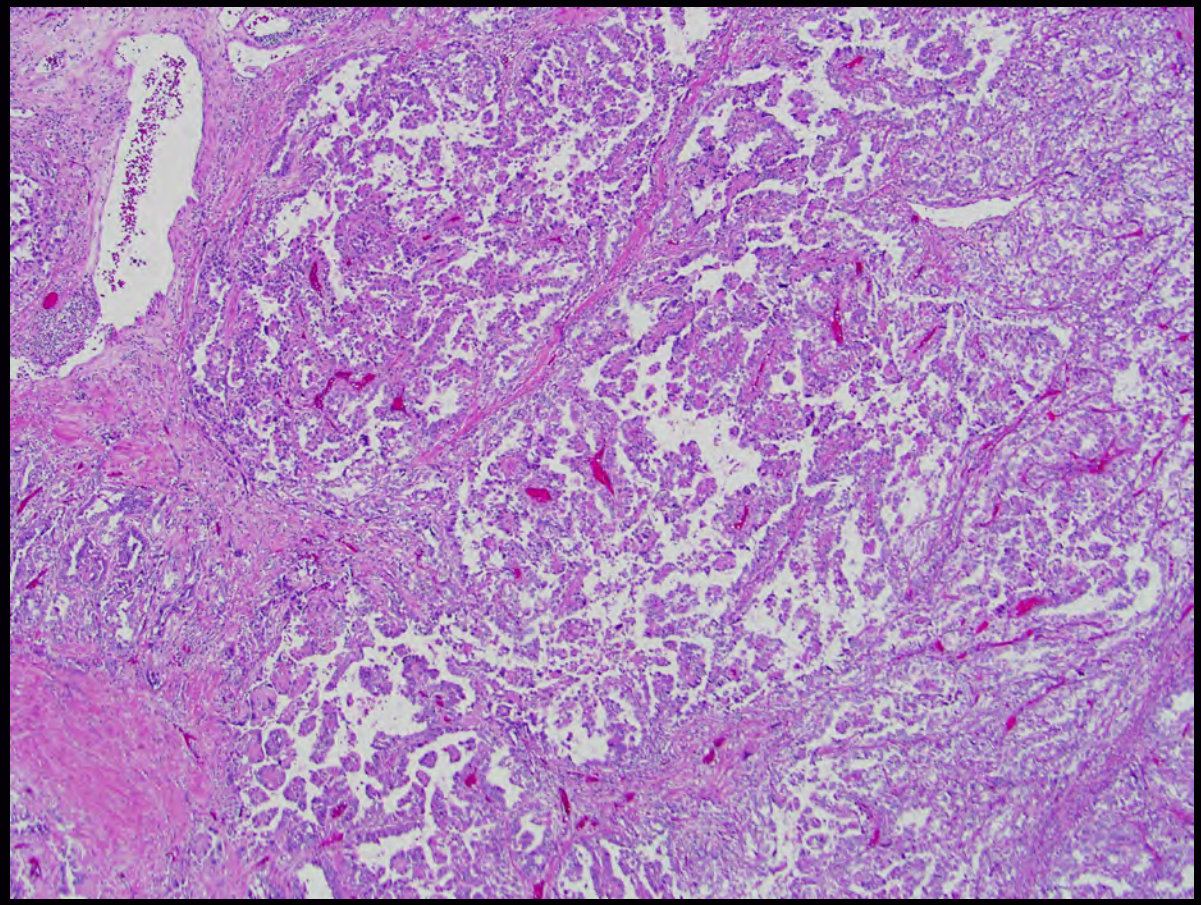
Died 1/08/88



11 cm
T3A

21 Year Old Female

Papillary Kidney Cancer: Patient 1



“Papillary Kidney Cancer”

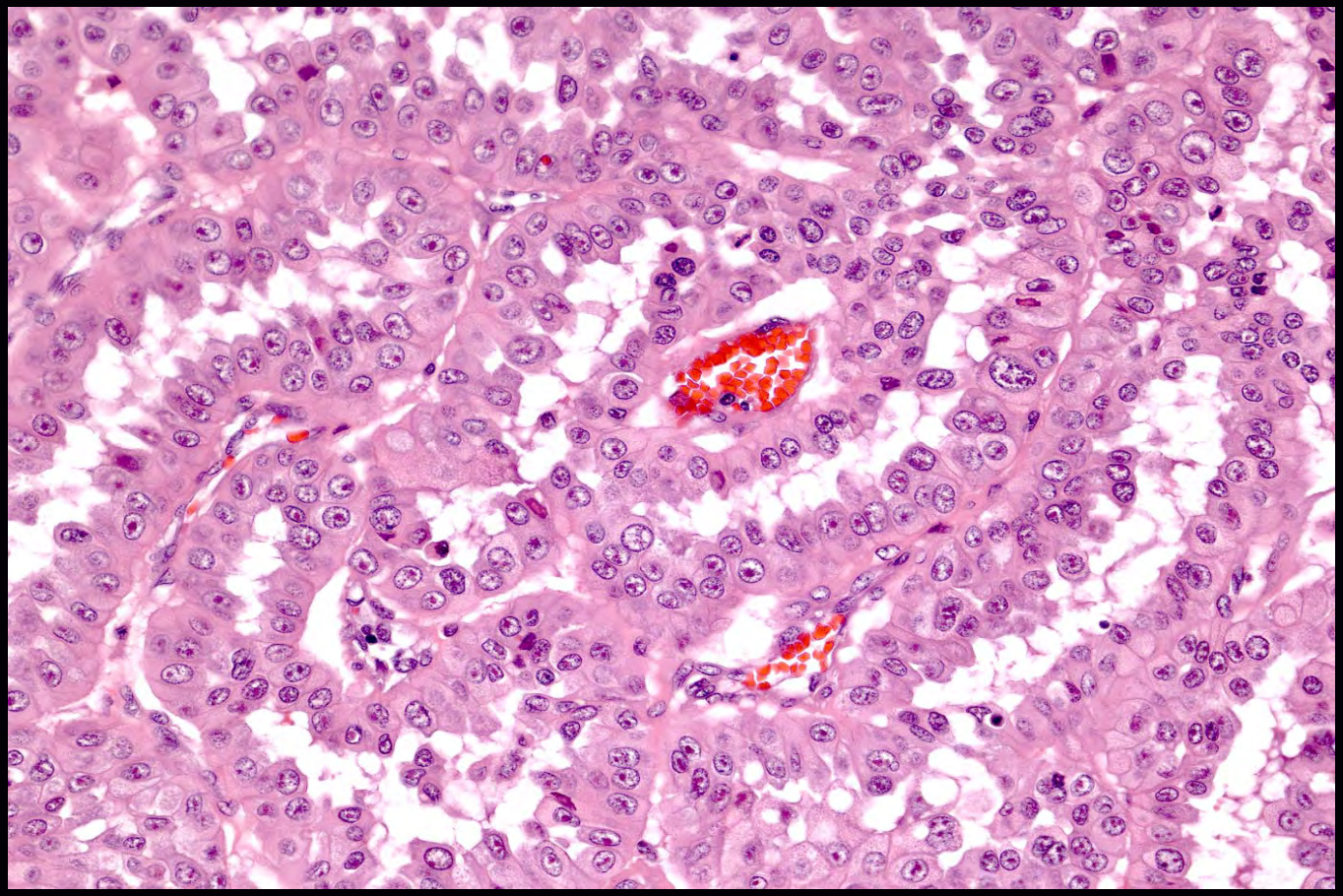
Non-Clear Cell Kidney Cancer: Patient 2

5/23/89

2/01/90

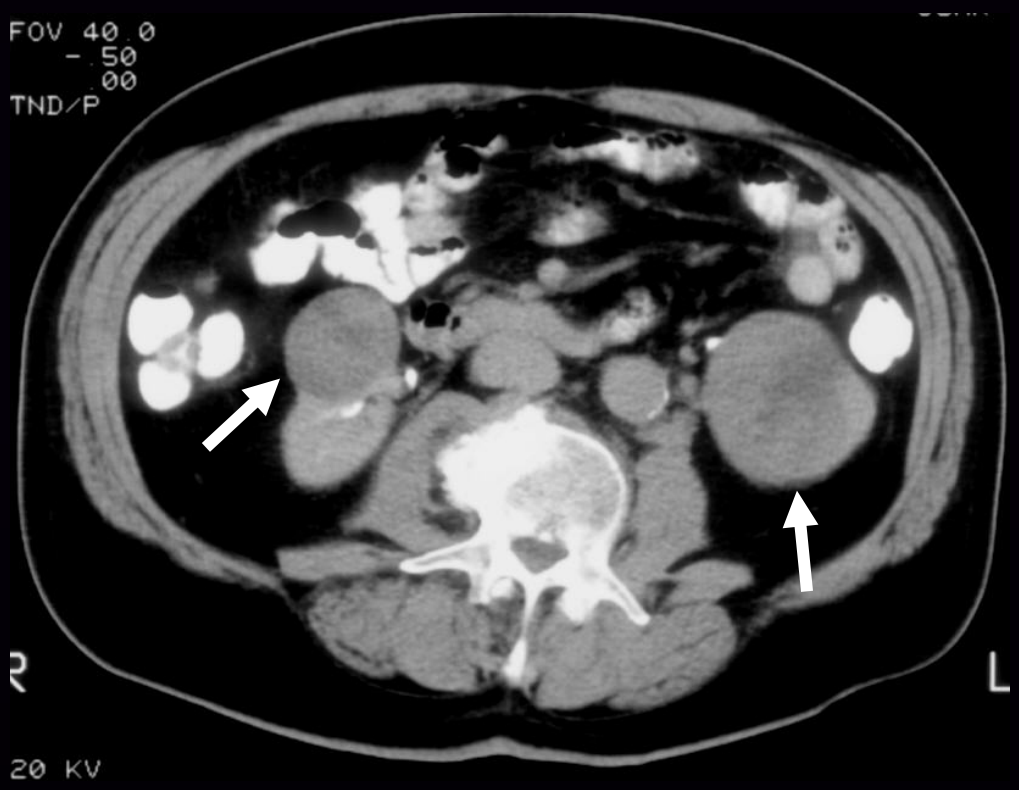
18 Year Old Female

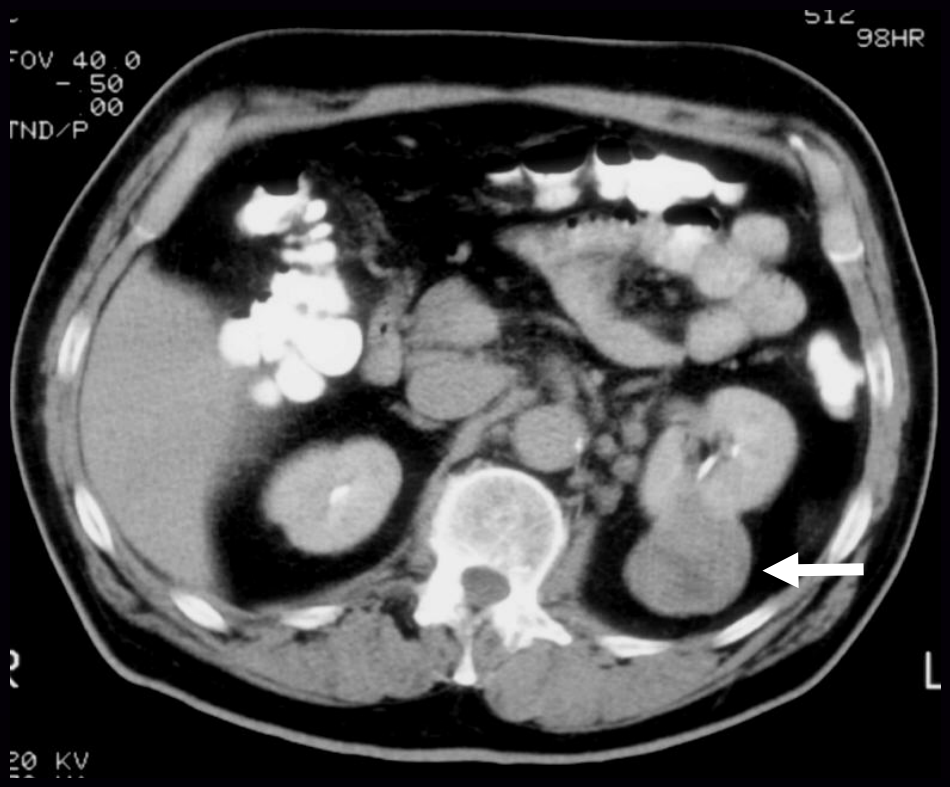
Papillary Kidney Cancer: Patient 2



“Papillary Kidney Cancer”

Non-Clear Cell Kidney Cancer: Patient 3A





3/3/92

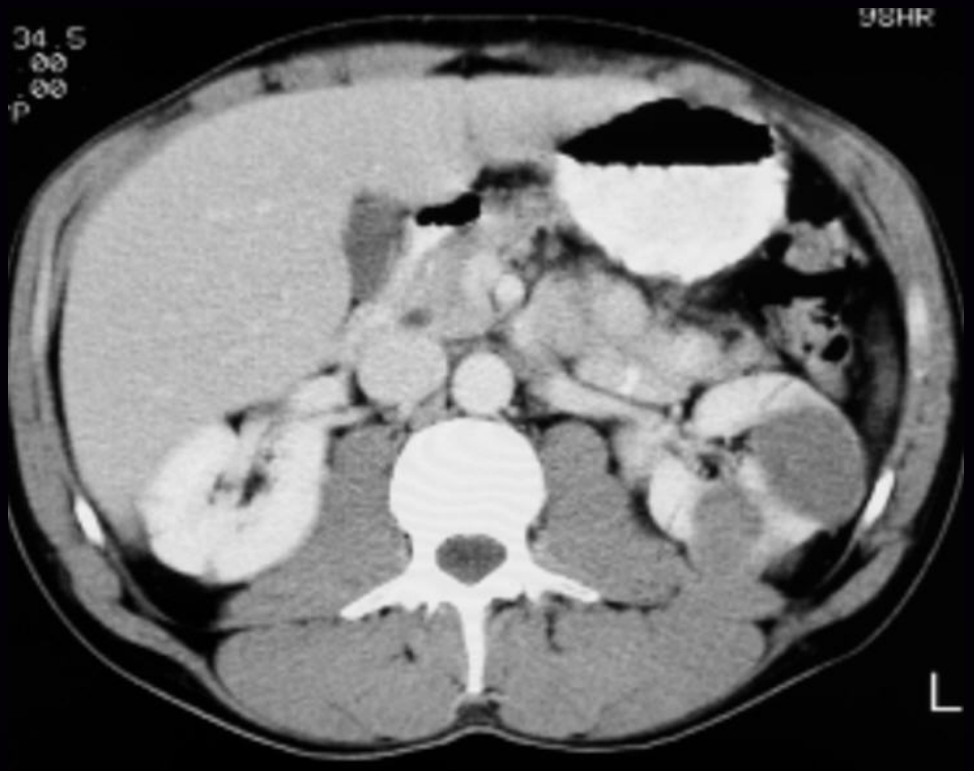
71 year old man

Non-Clear Cell Kidney Cancer: Patient 3B

4/28/92

68 year old female

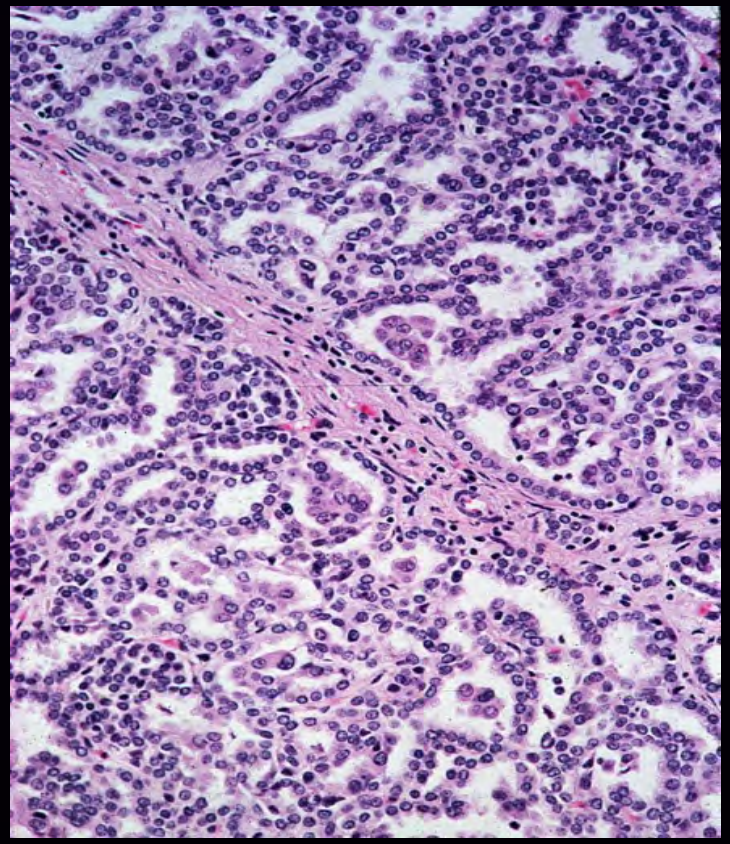
Non-Clear Cell Kidney Cancer: Patient 3C



3/31/92

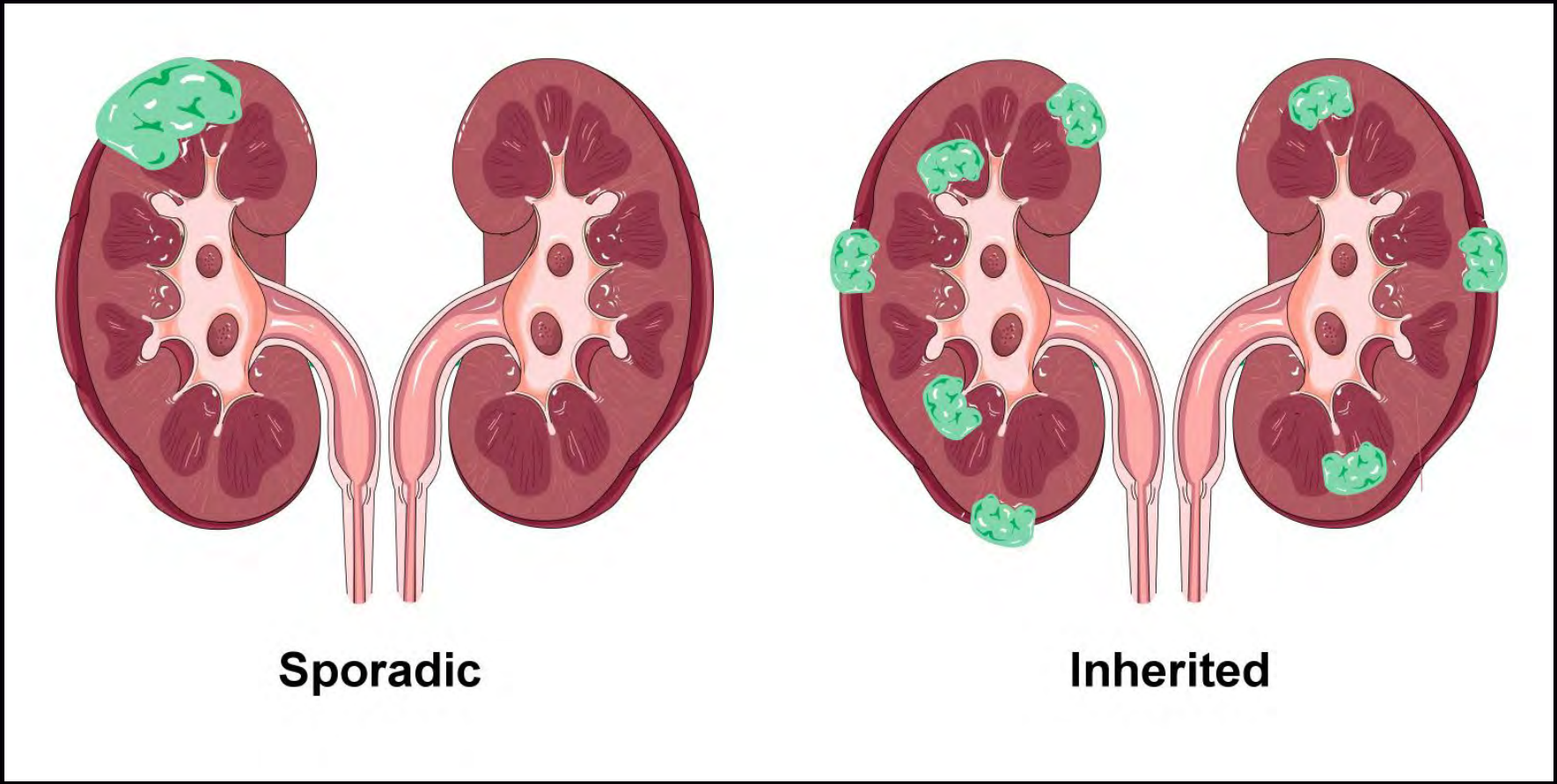
42 year old male

Papillary Kidney Cancer Patient 3

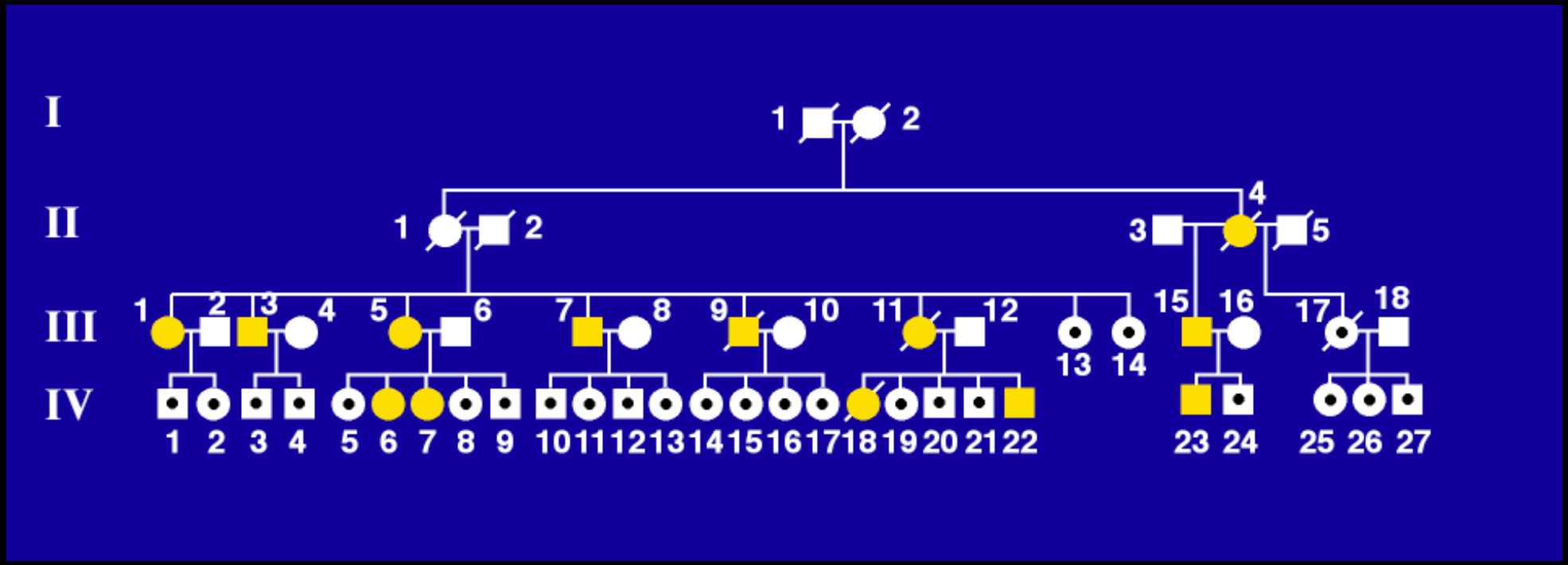


“Papillary Kidney Cancer”

Inherited Renal Carcinoma



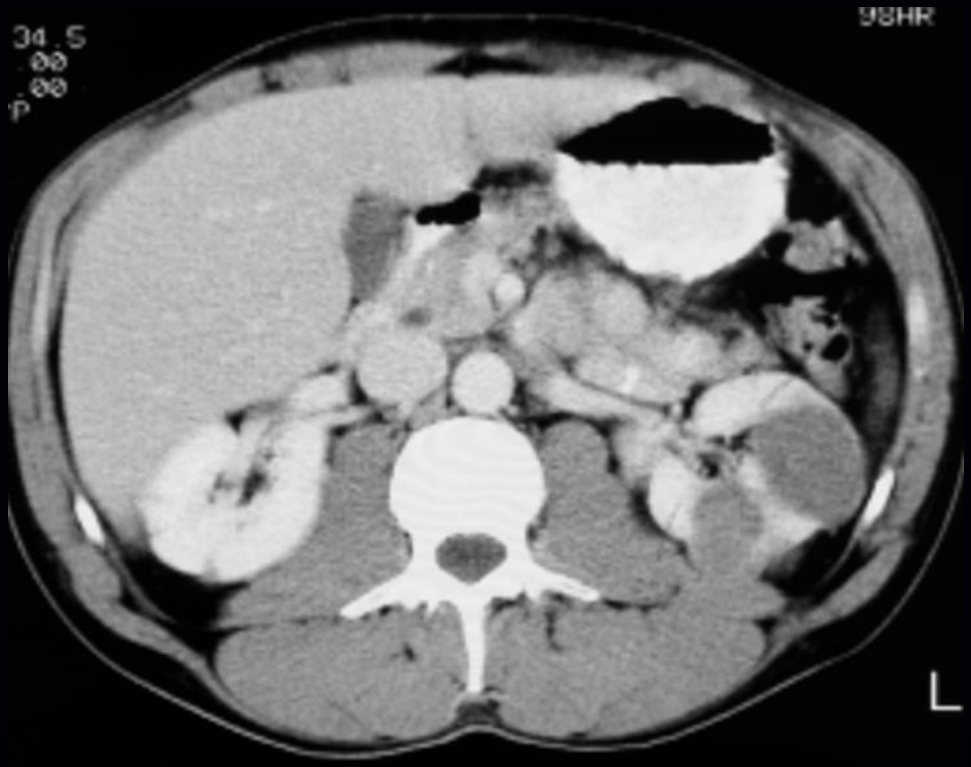
Hereditary Papillary Renal Carcinoma (HPRC)



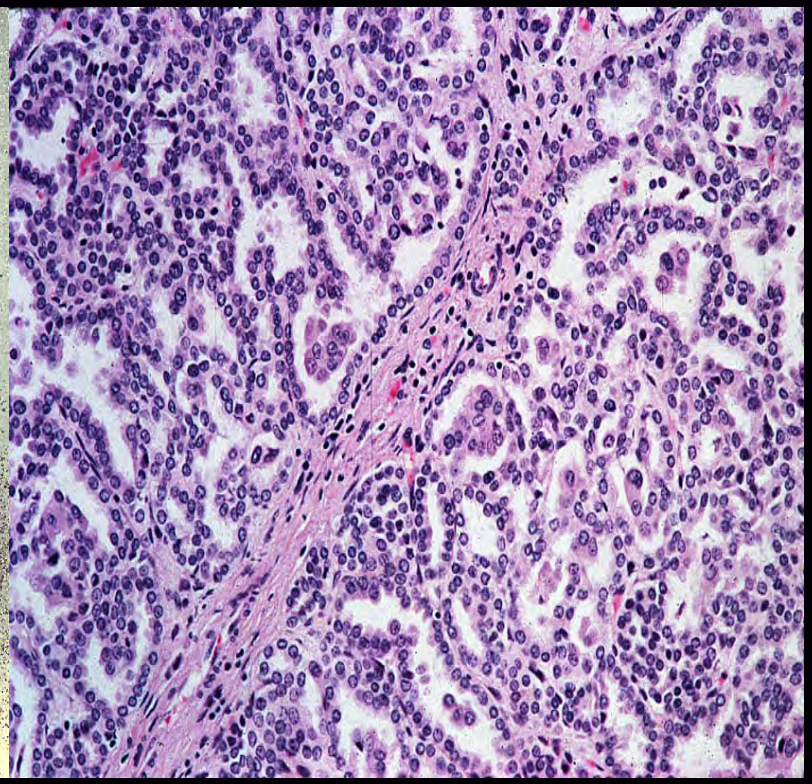
J. Urol 151: 1994

J. Urol 153: 1995

HPRC: Renal Tumors



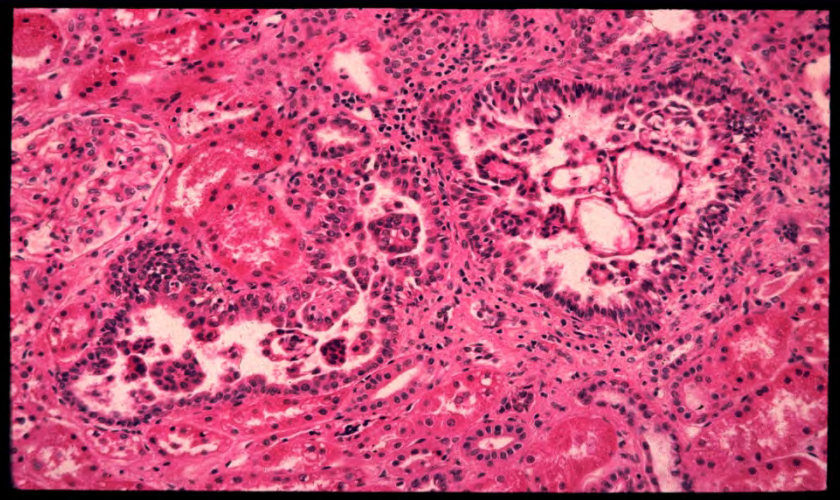
Hereditary Papillary Renal Carcinoma
Type 1 papillary renal carcinoma



Hereditary Papillary Renal Carcinoma High Persistence Rate

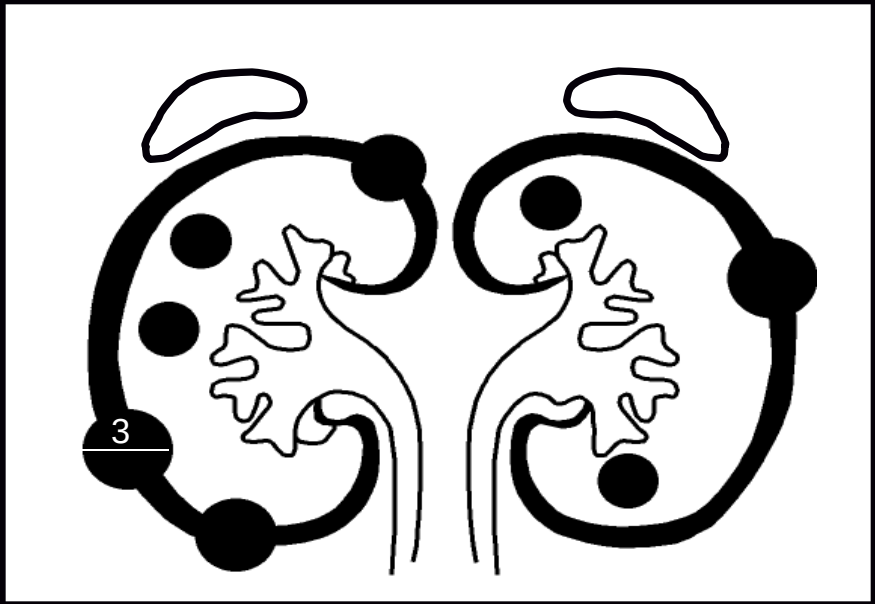
Microscopic Tumors

- **Type 1 Papillary RCC**
  - **1100 basophilic papillary**



J Urol*: 163, 2000*

Surgical Management of HPRC-Associated Renal Carcinoma



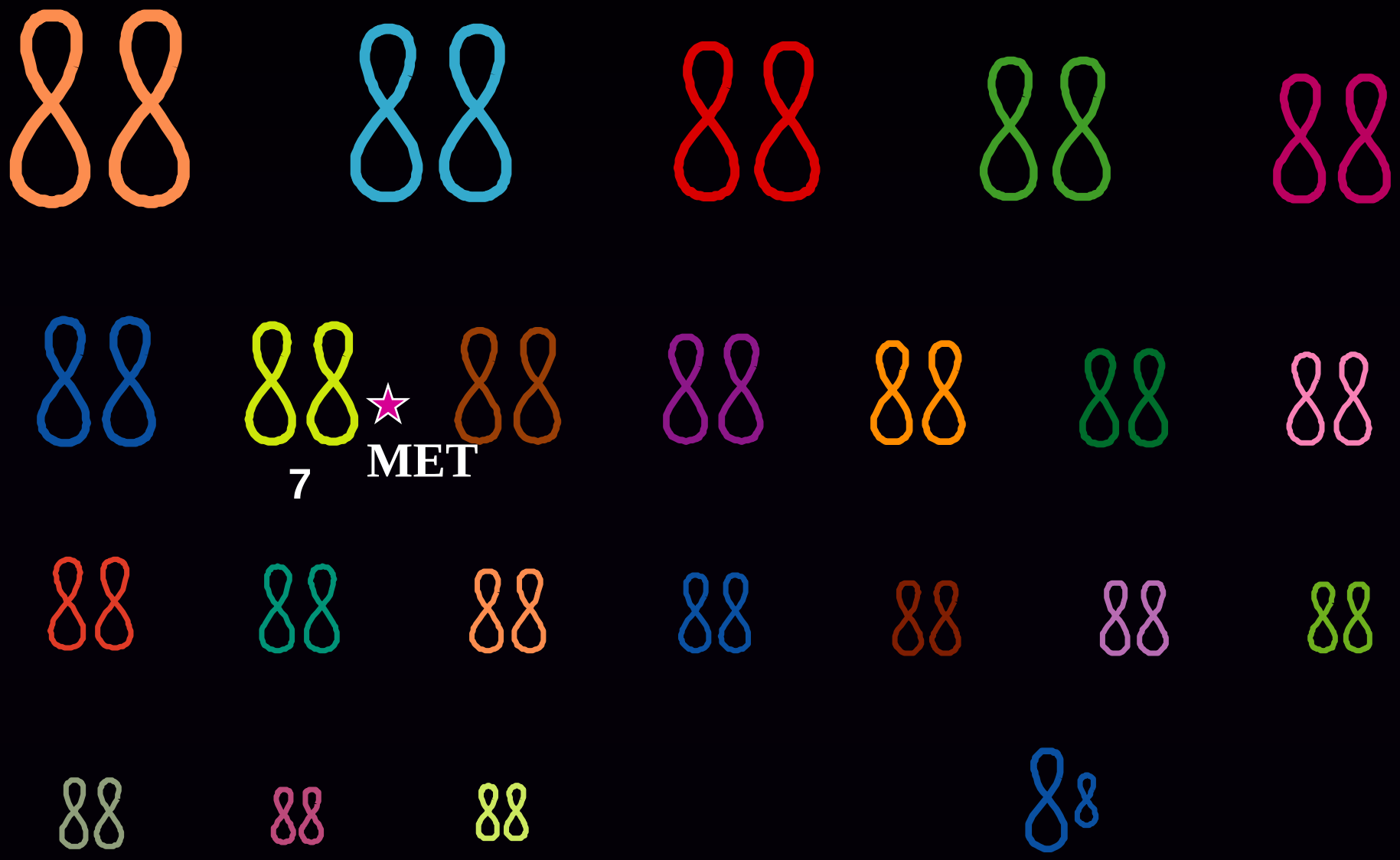
"3 cm rule"

Delay surgery until diameter of largest renal tumor = 3 cm

Surgery = nephron sparing enucleation

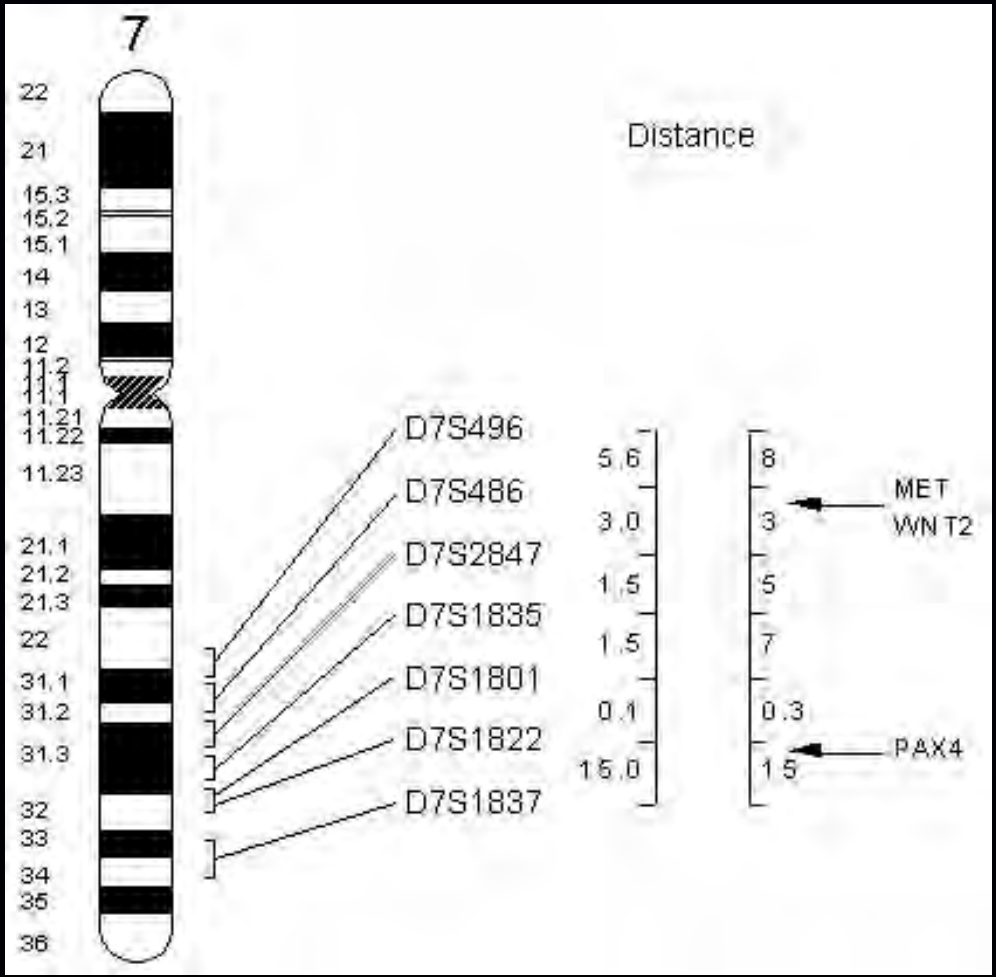
W J Urol 13: 1995
J Urol: 153:1995
J Urol 165:2001
J Urol 165:2001
J Urol 172:2004
J Urol 173 2005

NIH Clinical Center

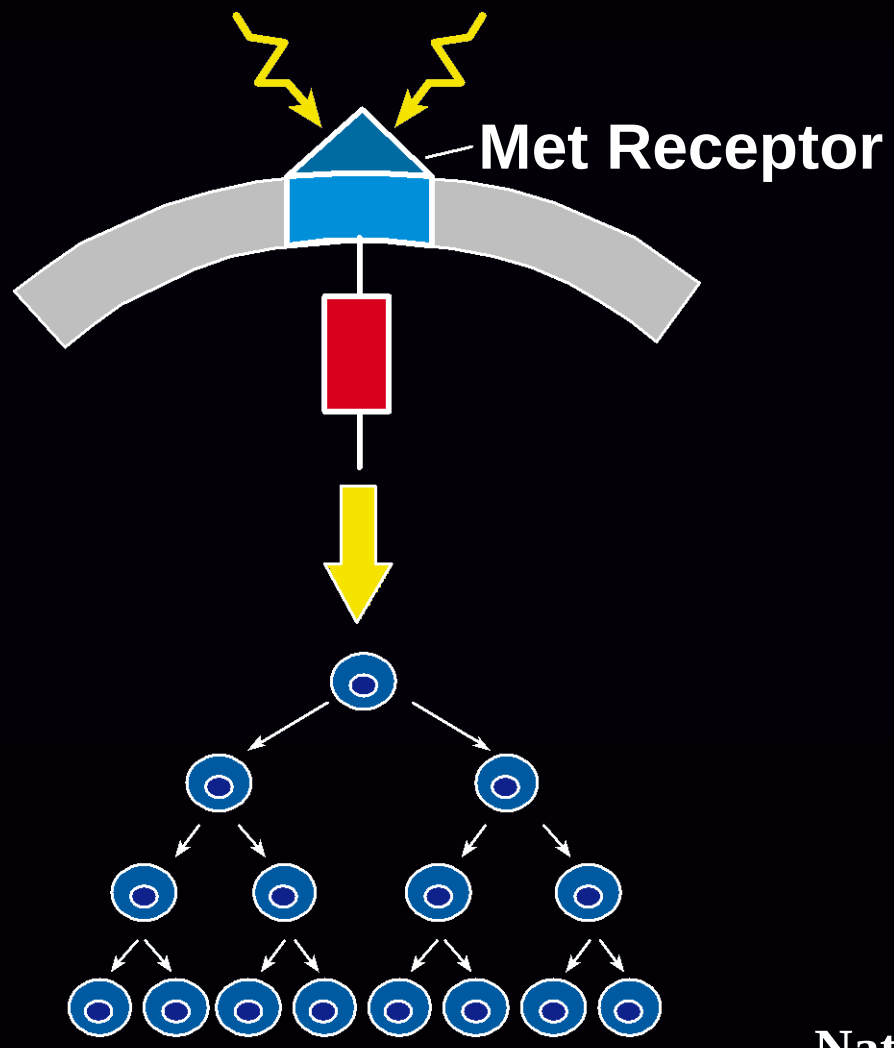


MET Gene: Type 1 Papillary RCC

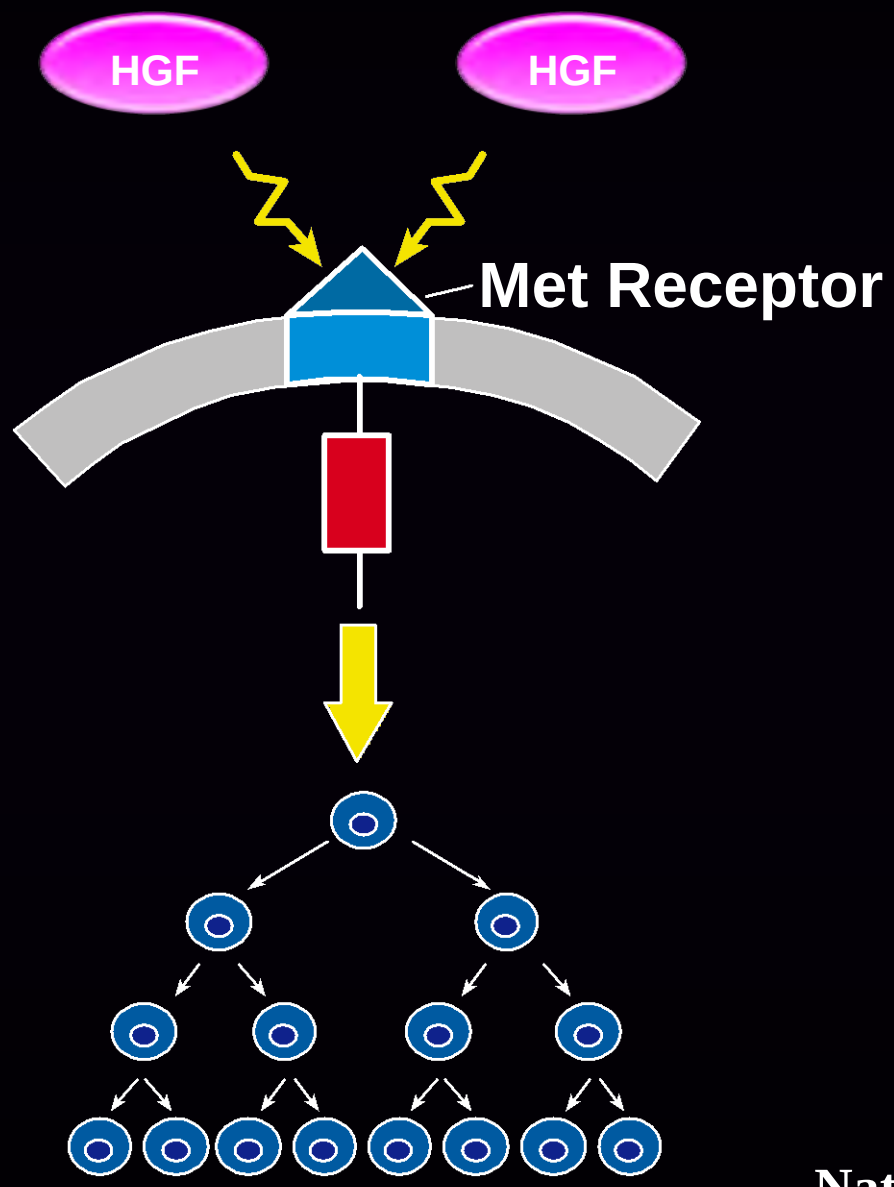
Location of the HPRC Gene



MET is the HPRC Gene

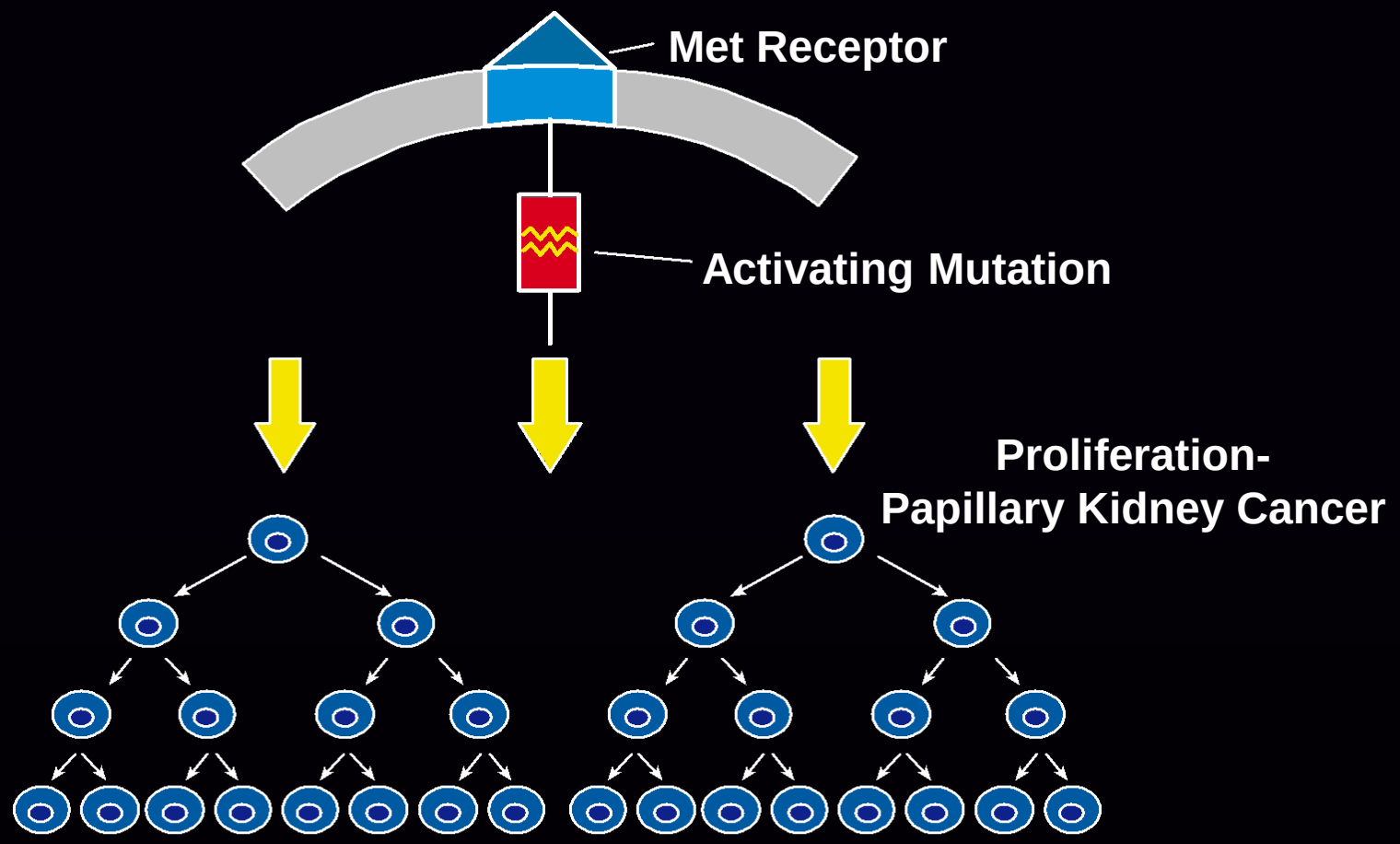


Nature Genetics 16:1997

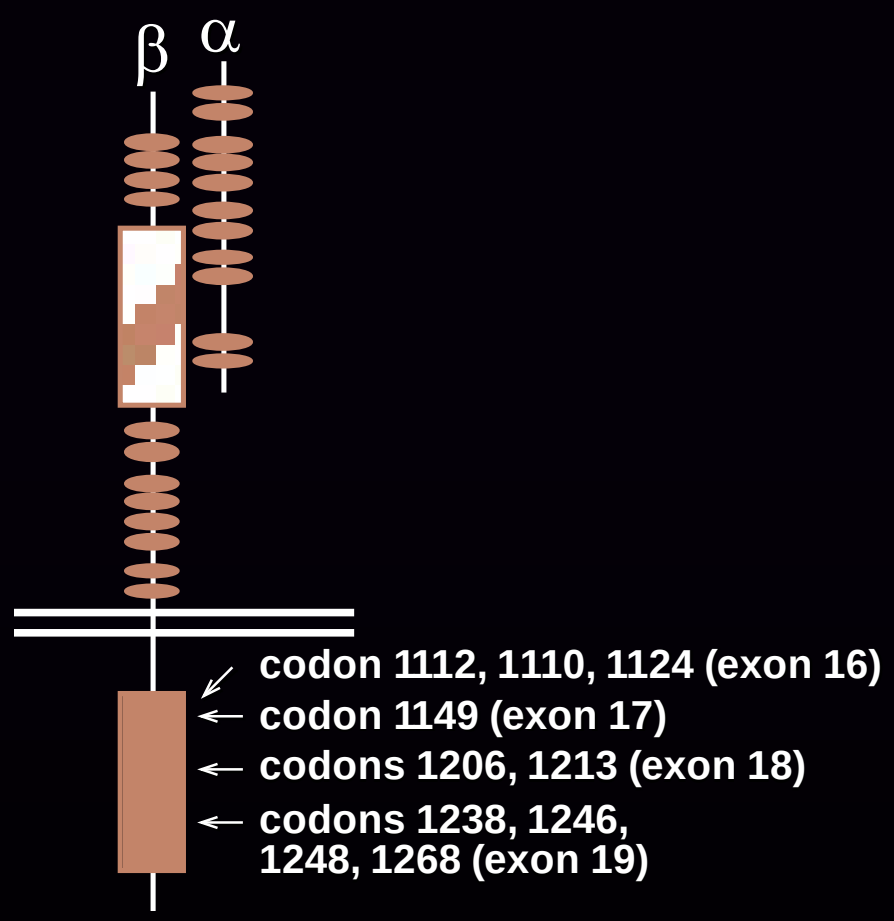


Nature Genetics 16:1997

HPRC: Activating Mutations in the Tyrosine Kinase Domain of *MET*



Location of Met Mutations in the HPRC patients



Nature Genetics 16:1997

Cancer Res 58:1998

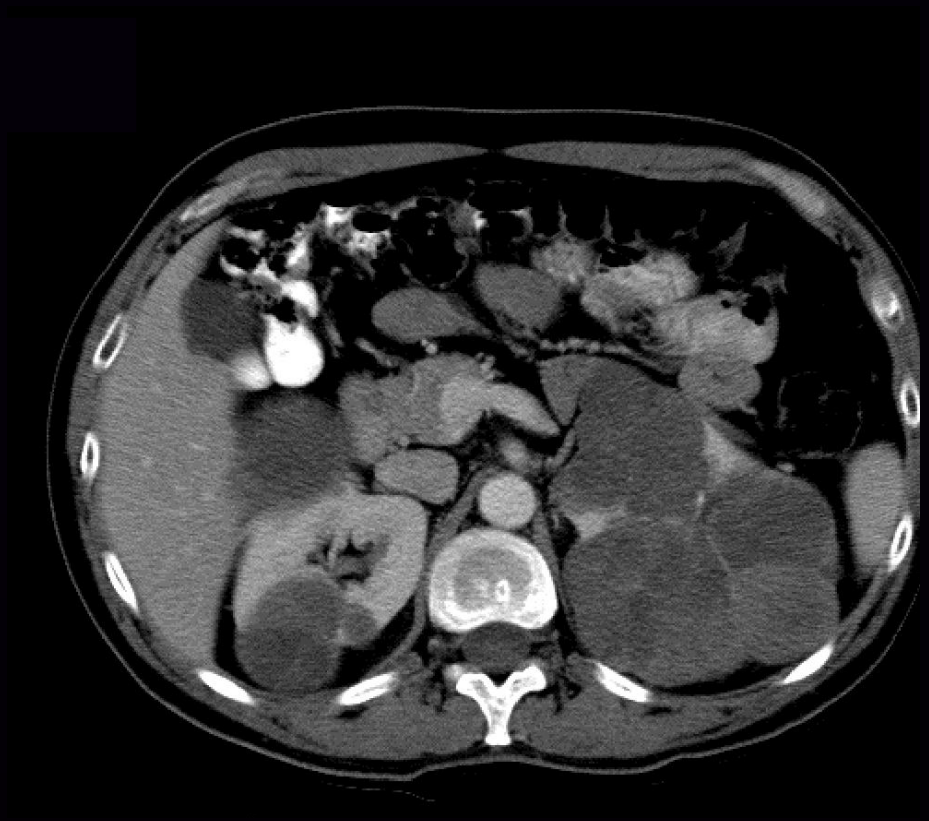
NCI HPRC Kindreds N=10

- 115 patients (66 affected) from 22 HPRC families have been evaluated

- Germline *MET* mutations have been detected in 22/22 (100%) HPRC kindreds.

In Preparation
Nature Genetics 16:1997
Cancer Res 58:1998

Early Onset HPRC

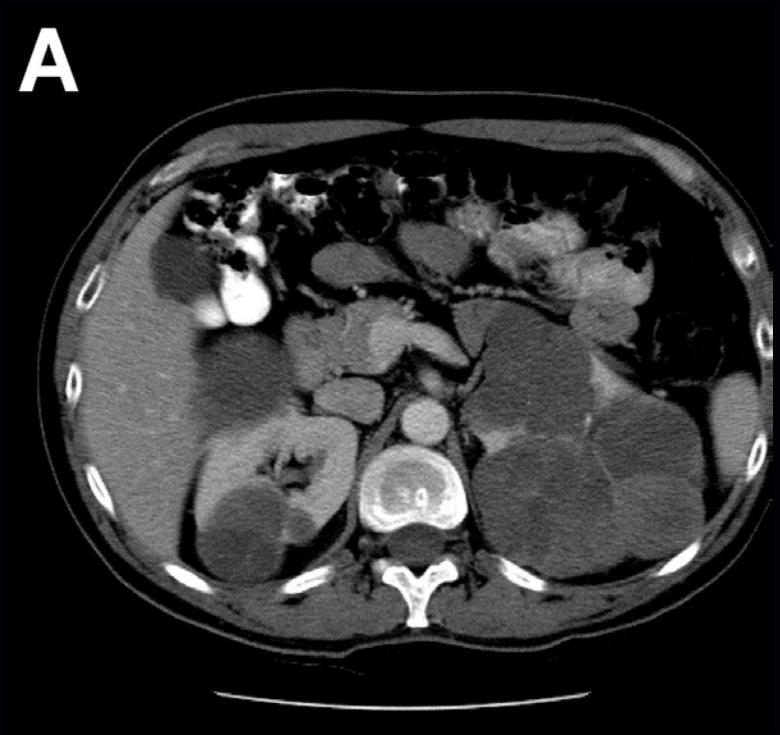


38 year old male

27 year old female

J Urol*: 172, 2004*

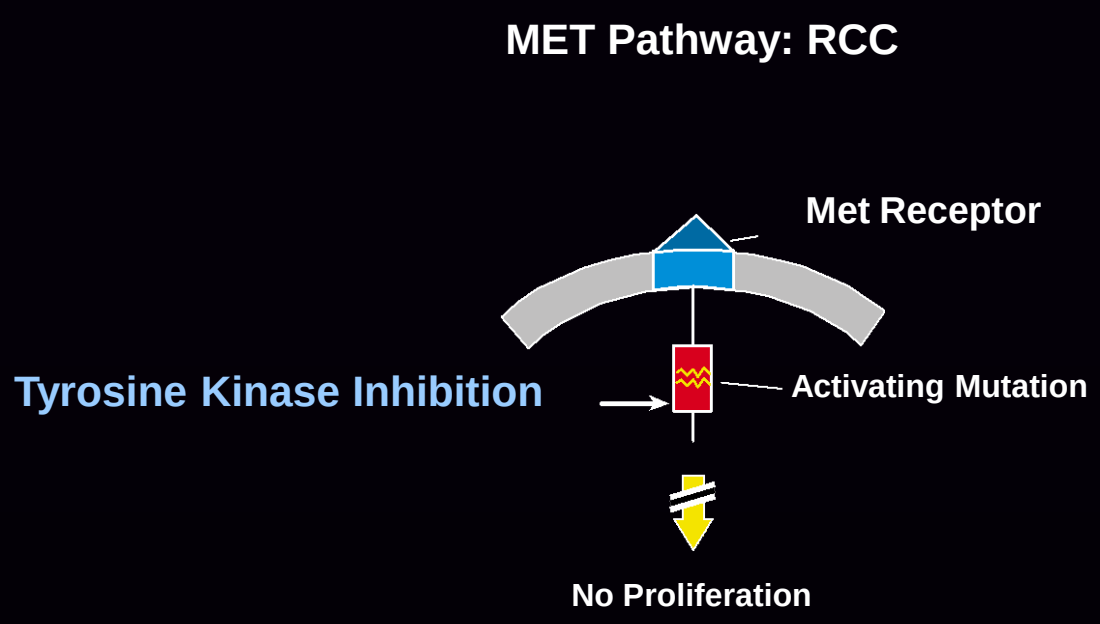
Targeting MET RCC Gene Pathway

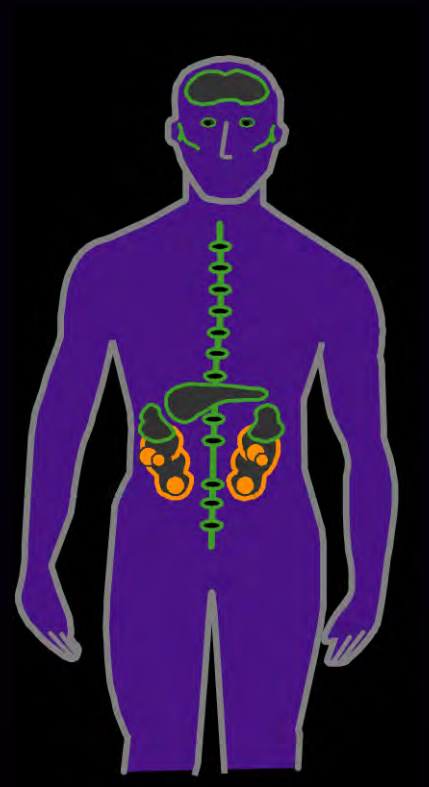


CT Scan: Bilateral, Multifocal RCC

HPRC Kidney: Multifocal RCC

Targeting Met Gene Pathway: Hereditary Papillary Renal Carcinoma

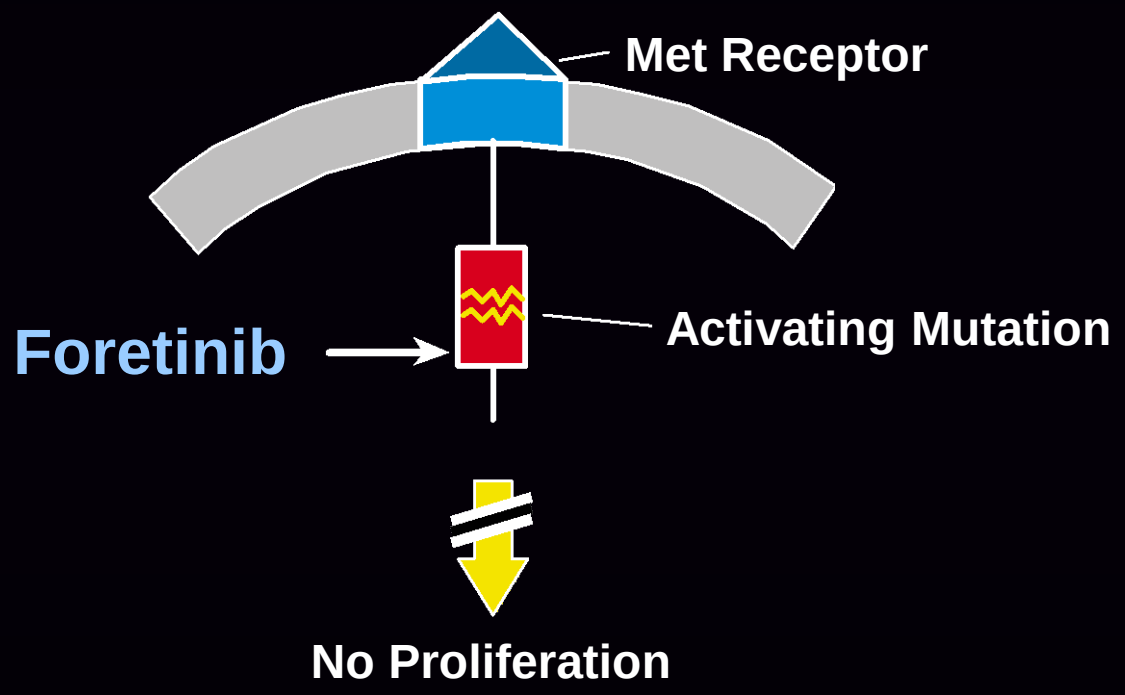




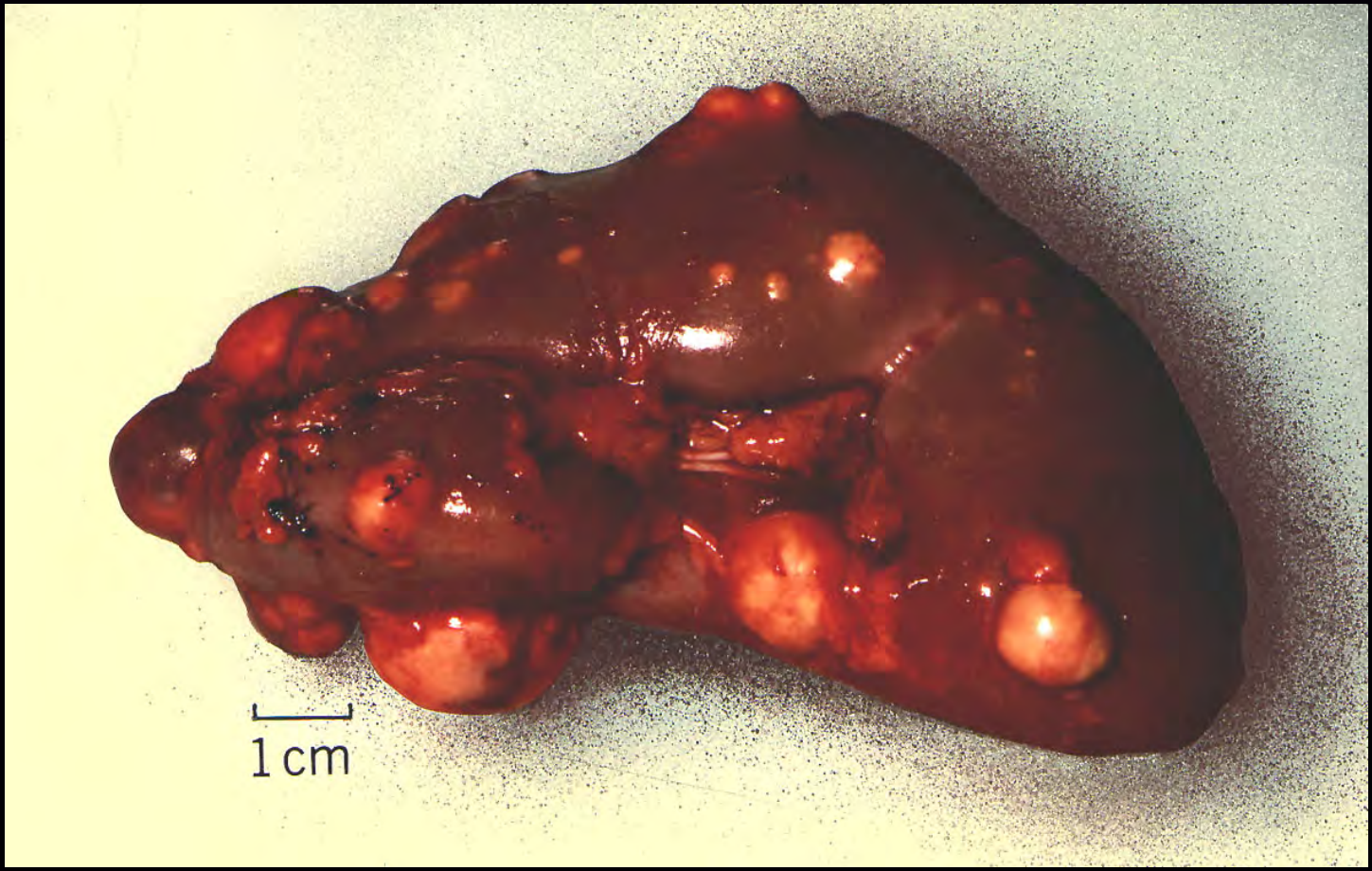
Hereditary Papillary

Renal Cell Carcinoma (HPRC)

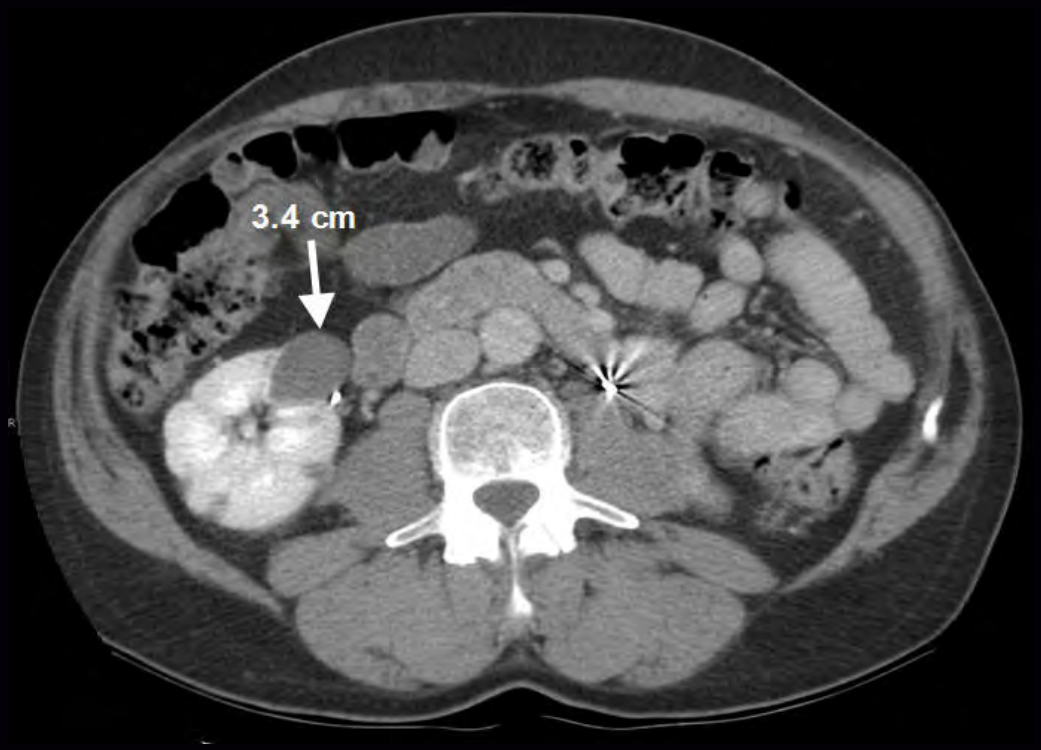
GSK'089:
Dual VEGFR and MET Inhibitor



Hereditary Papillary Renal Carcinoma (HPRC) Type 1



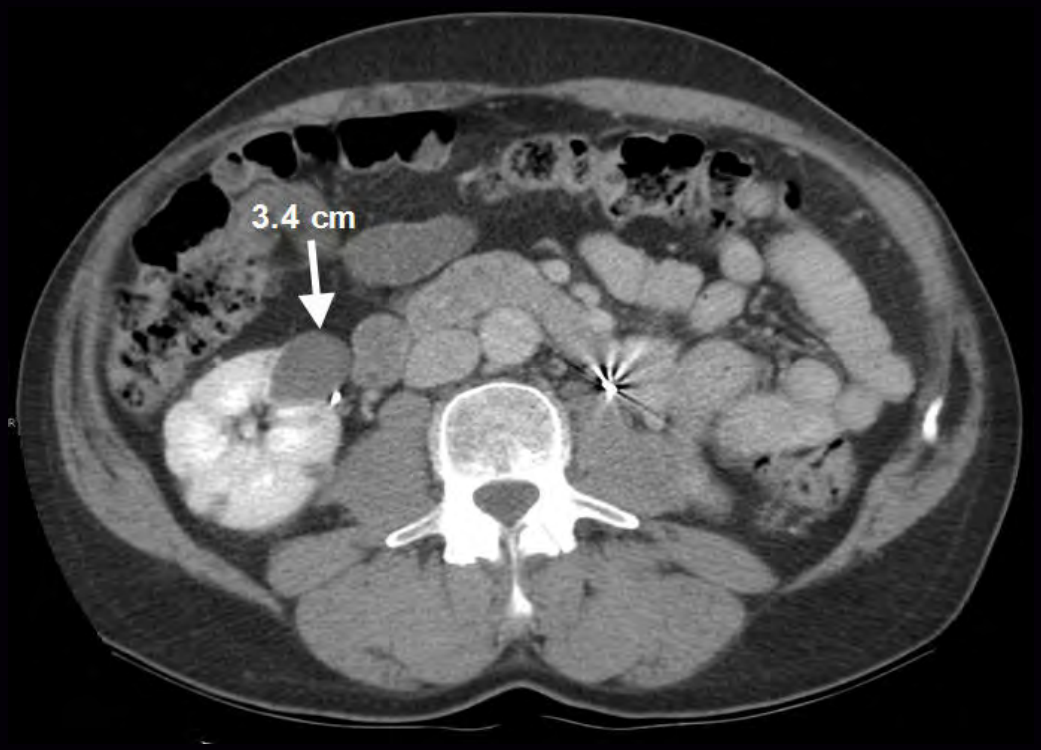
Regression of a renal tumor in a patient with HPRC treated with Foretinib



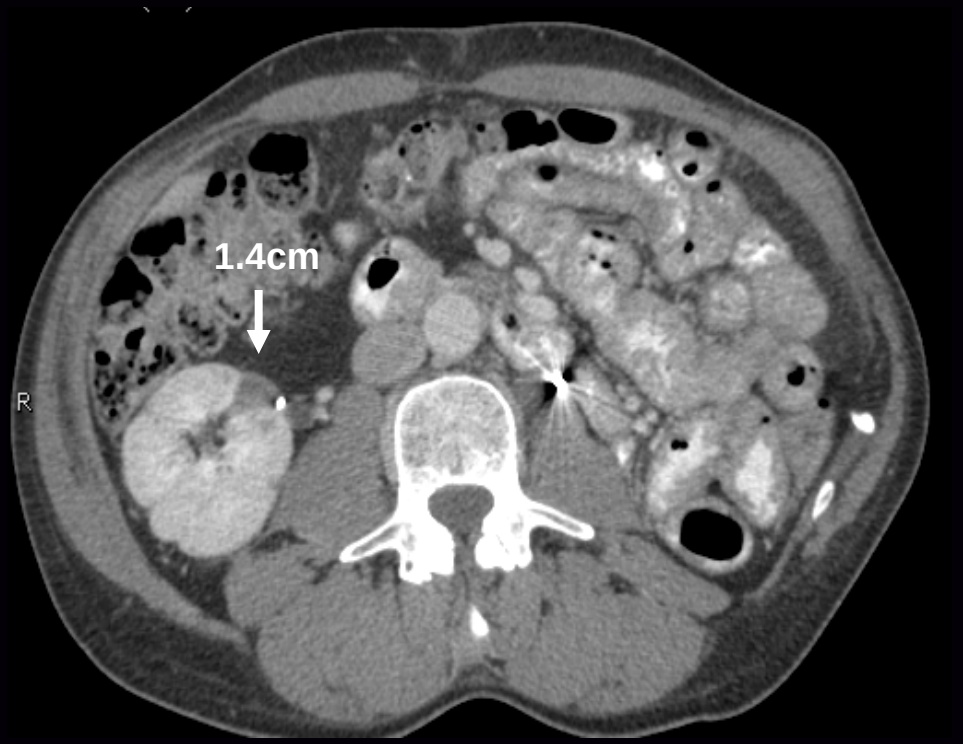
Pre-Treatment

J Clin Oncol 10:2012

Regression of a renal tumor in a patient with HPRC treated with Foretinib



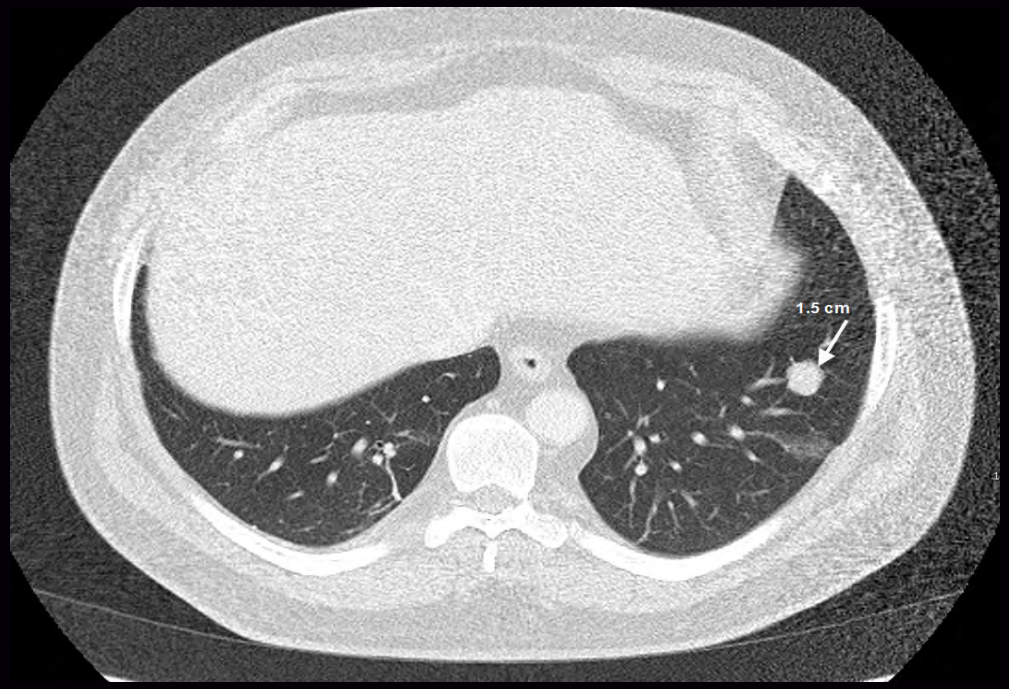
Pre-Treatment



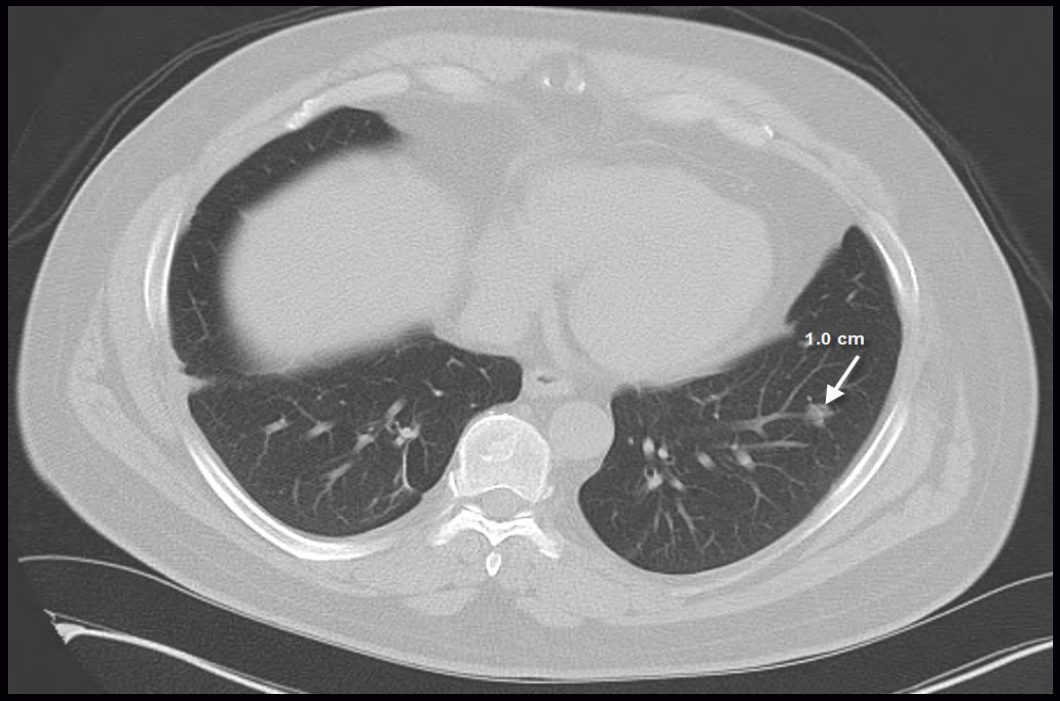
Following 49 cycles of therapy GSK'089

J Clin Oncol 10:2012

Patient #2



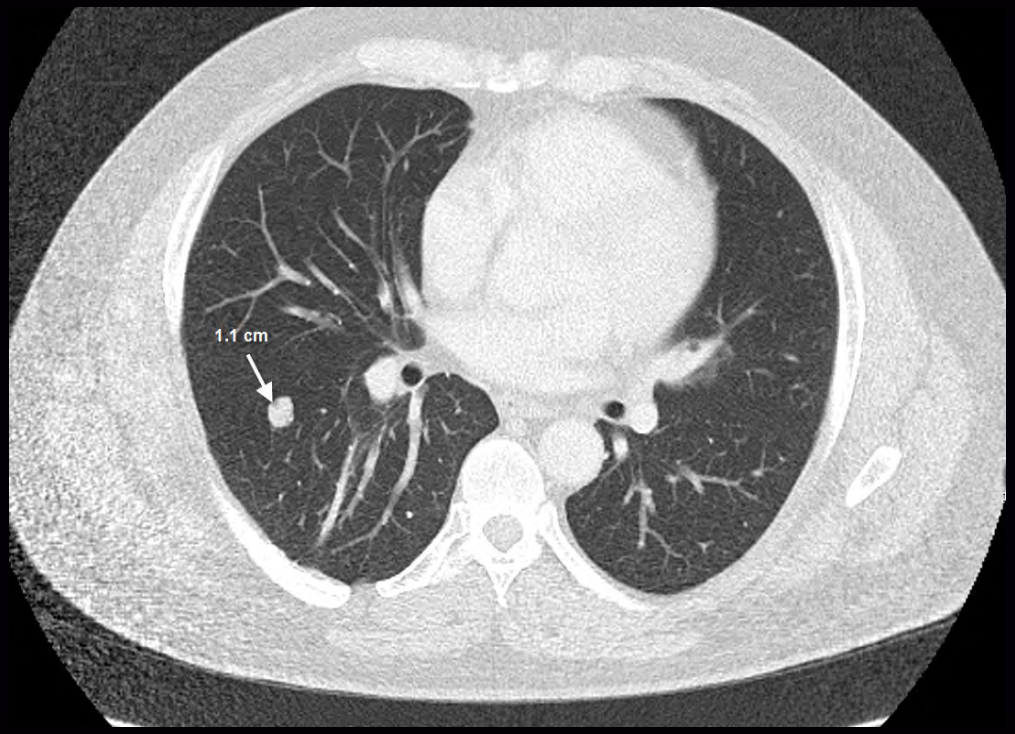
Baseline



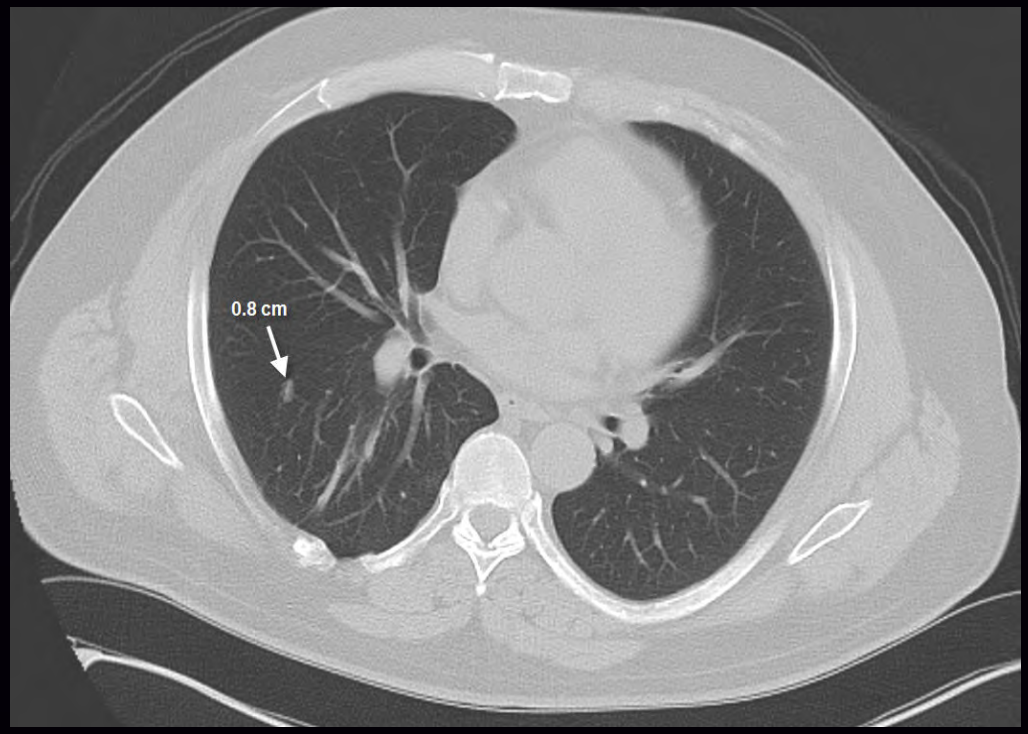
Following 28 cycles

J Clin Oncol 10:2012

Patient #2



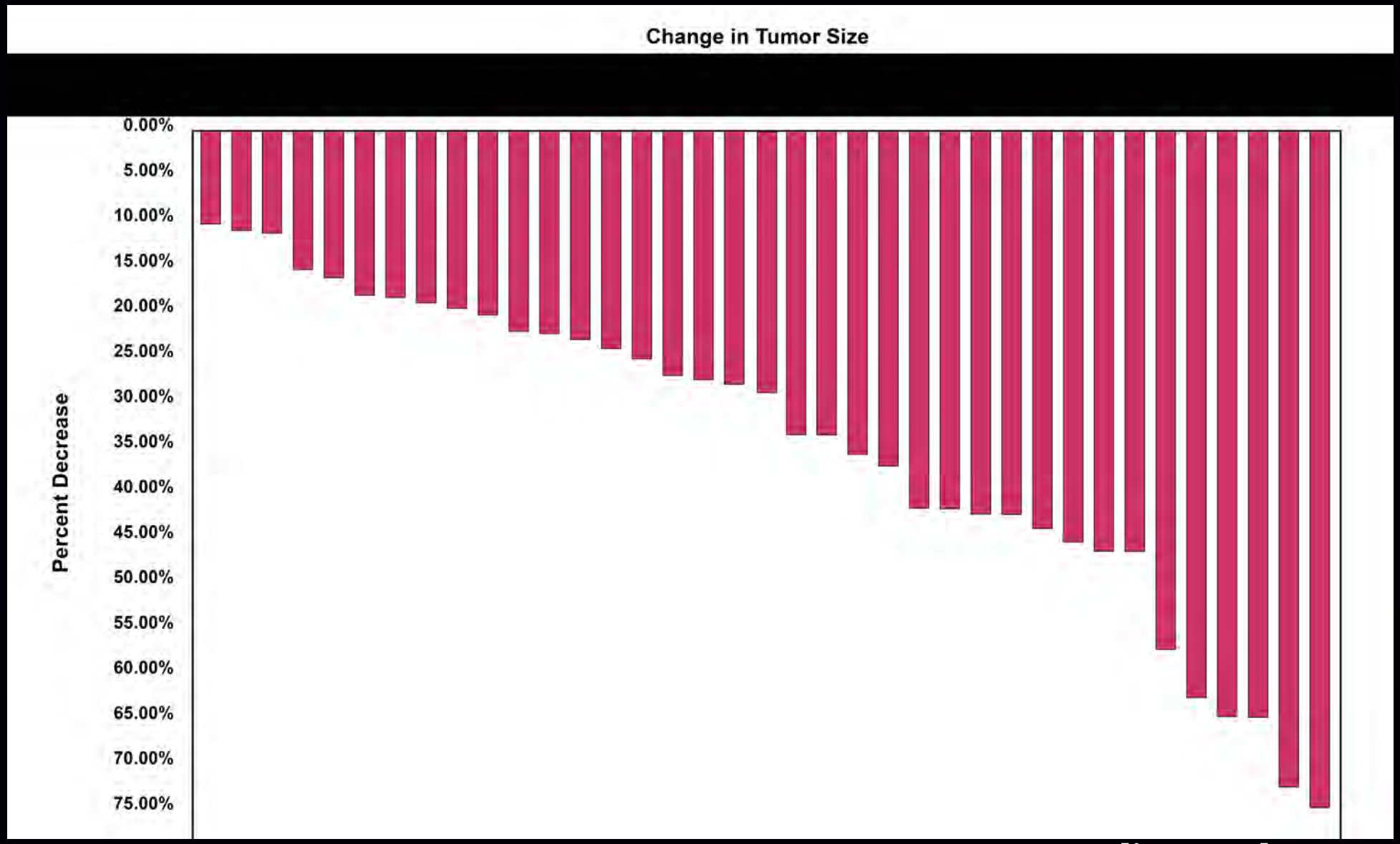
Baseline



Following 28 cycles

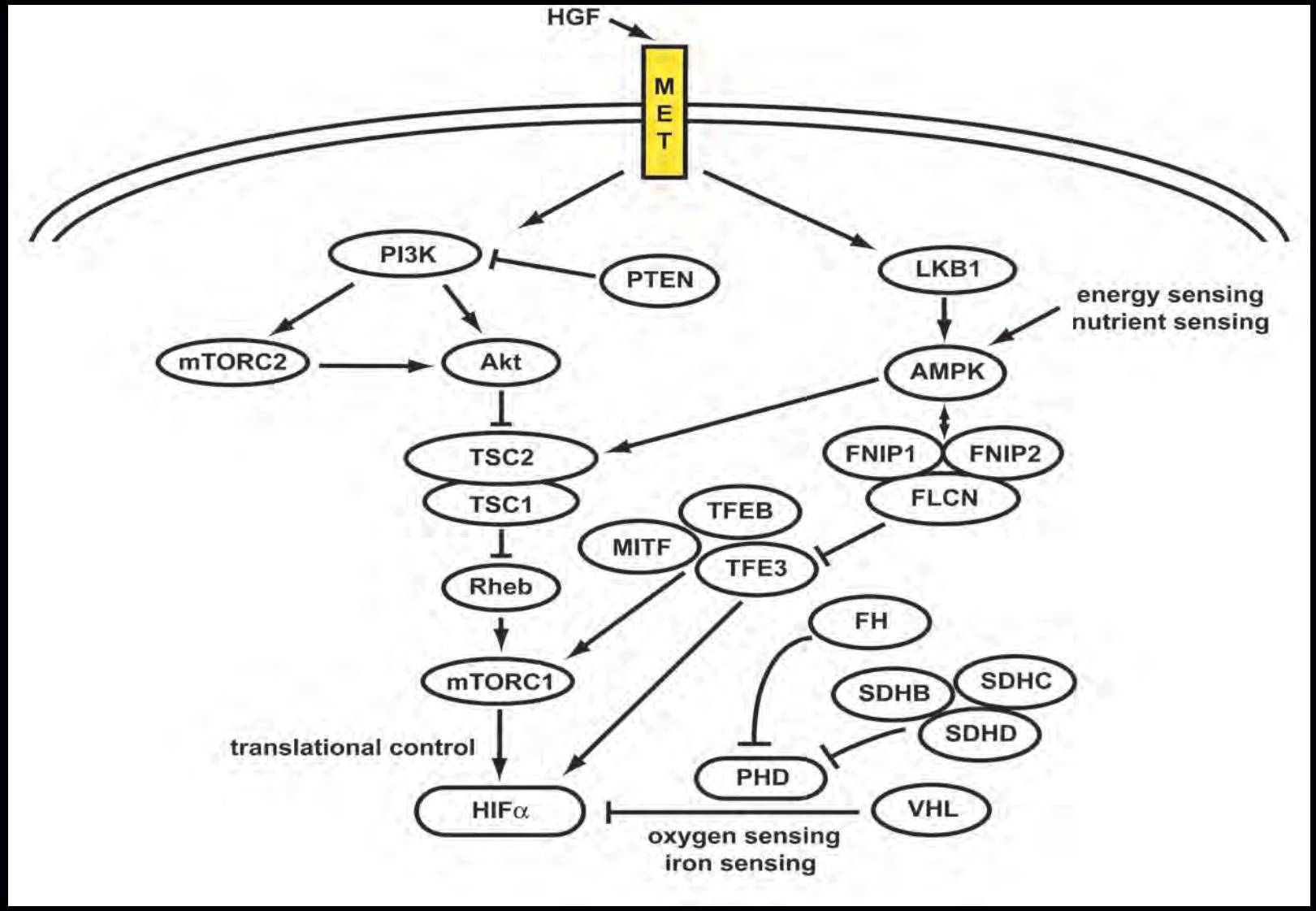
J Clin Oncol 10:2012

Hereditary Papillary Renal Cell Carcinoma: Foretinib 39 Target Lesions from 9 Patients



J Clin Oncol 10:2012

Kidney Cancer is a Metabolic Disease

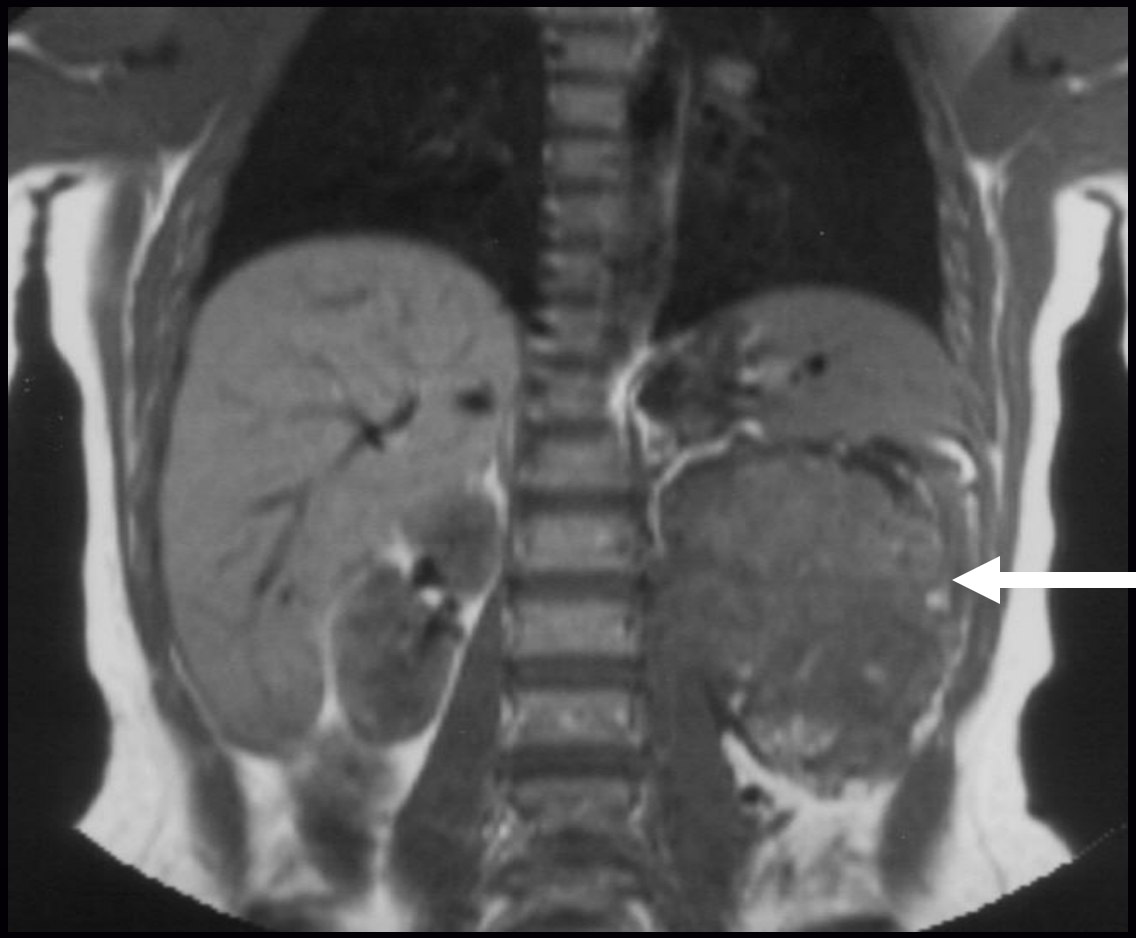


Nature Rev Urol: 7 2010

Locally Advanced Kidney Cancer

Surgery 4/21/87

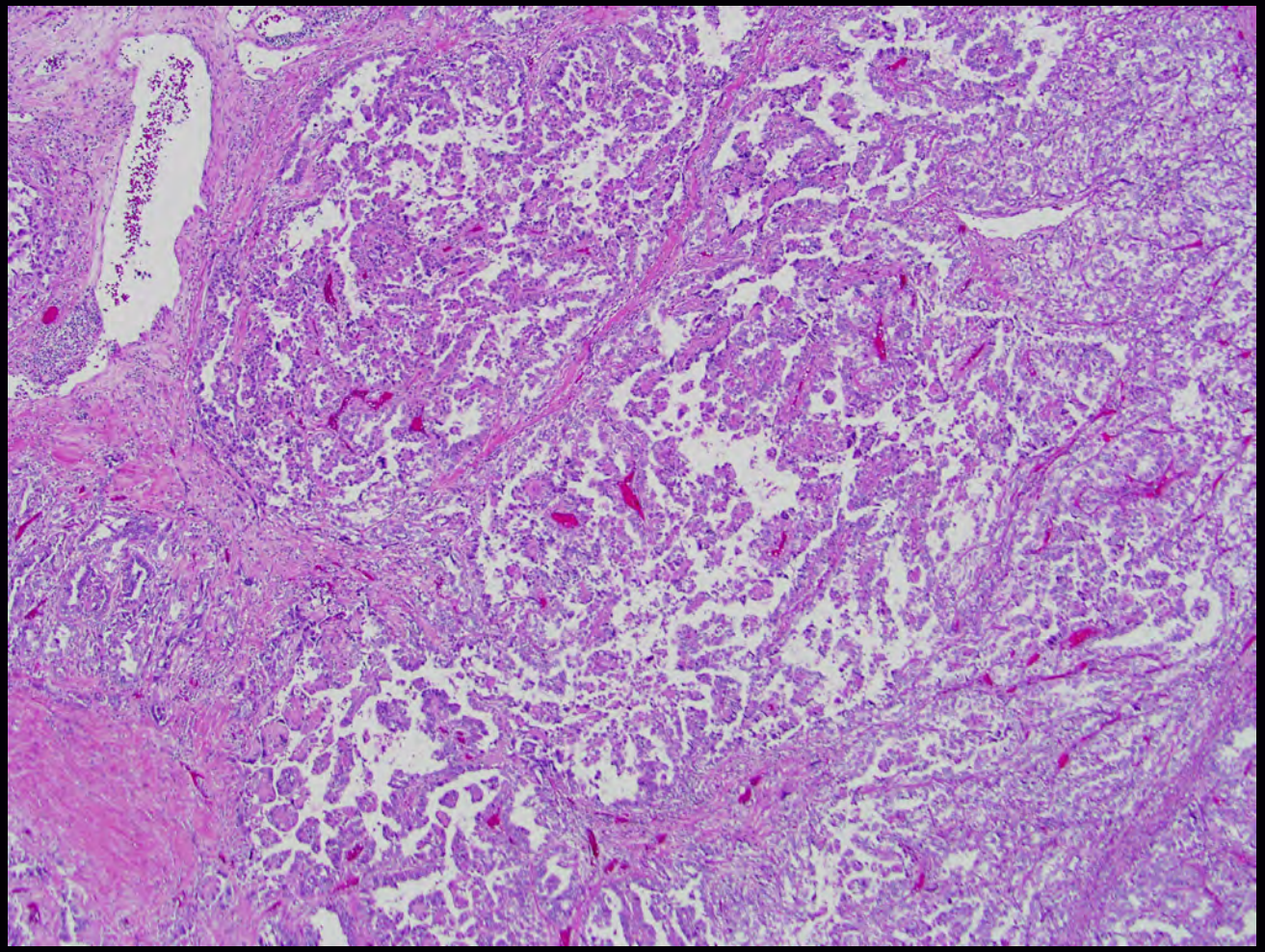
Died 1/08/88



11 cm
T3A

21 Year Old Female

Locally Advanced Kidney Cancer



“Papillary Kidney Cancer”

UOK124
t(X;1)(p11.2;q21.2) Translocation
Papillary Kidney Cancer

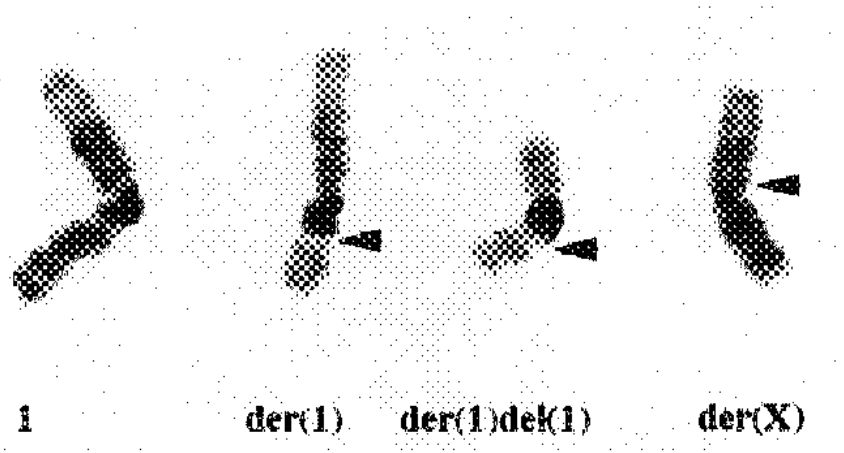
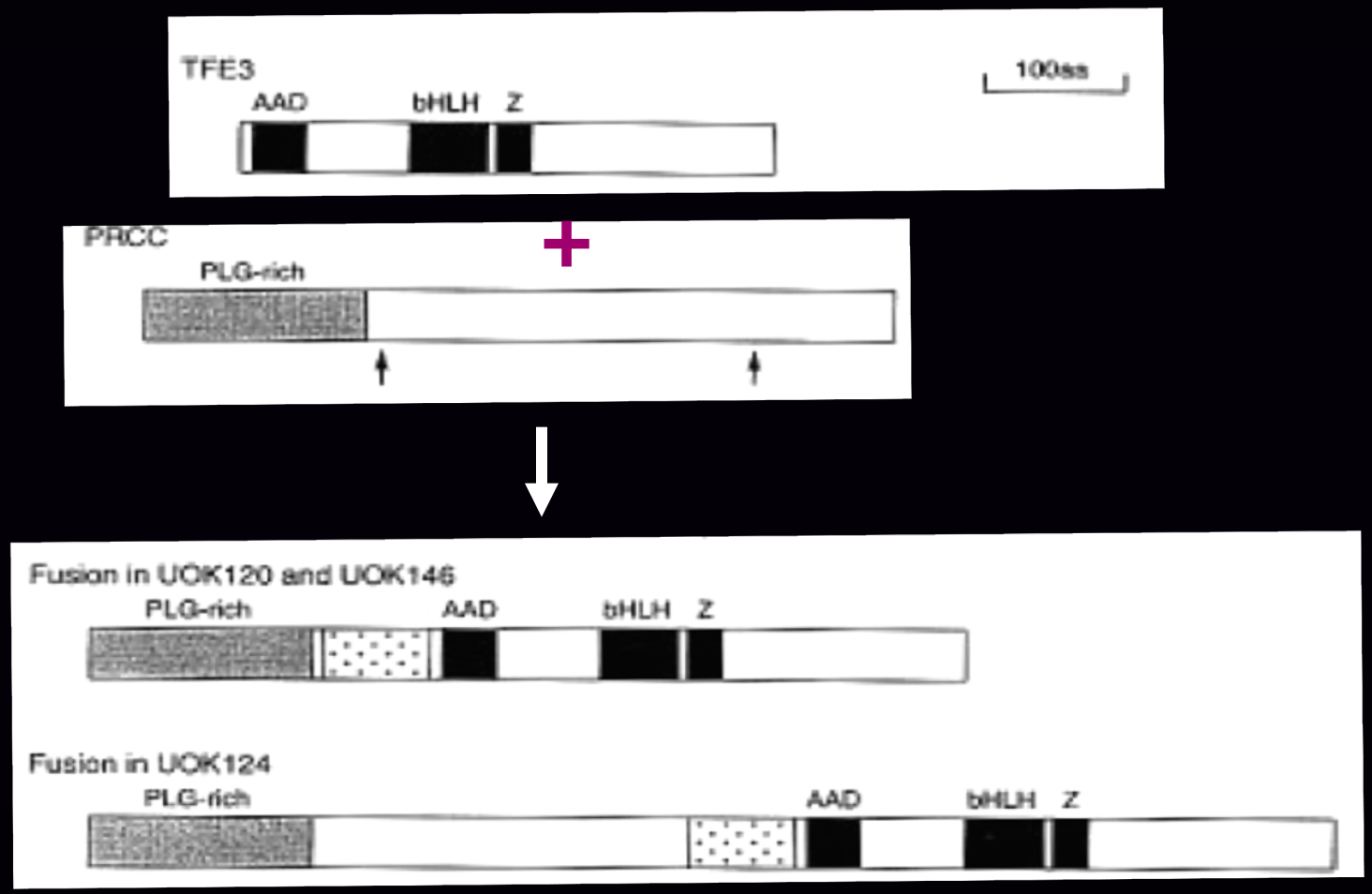


Fig. 1. Partial karyotype of the cell line UOK124 illustrating the rearrangements involving chromosomes X and 1. The karyotype contained a normal chromosome 1 but no normal X. The der(1) and the der(X) result from the t(X;1)(p11.2;q21.2) that is associated with papillary renal cell carcinoma and the der(1)del(1)(p31)t(X;1)(p11.2;q21.2) is thought to be derived by deletion following the duplication of the der(1) chromosome. The arrows indicate the position of the translocation breakpoints.

Cytogenet Cell Genet 71:1995

UOK124, UOK120, UOK 146
TFE3 Kidney Cancer

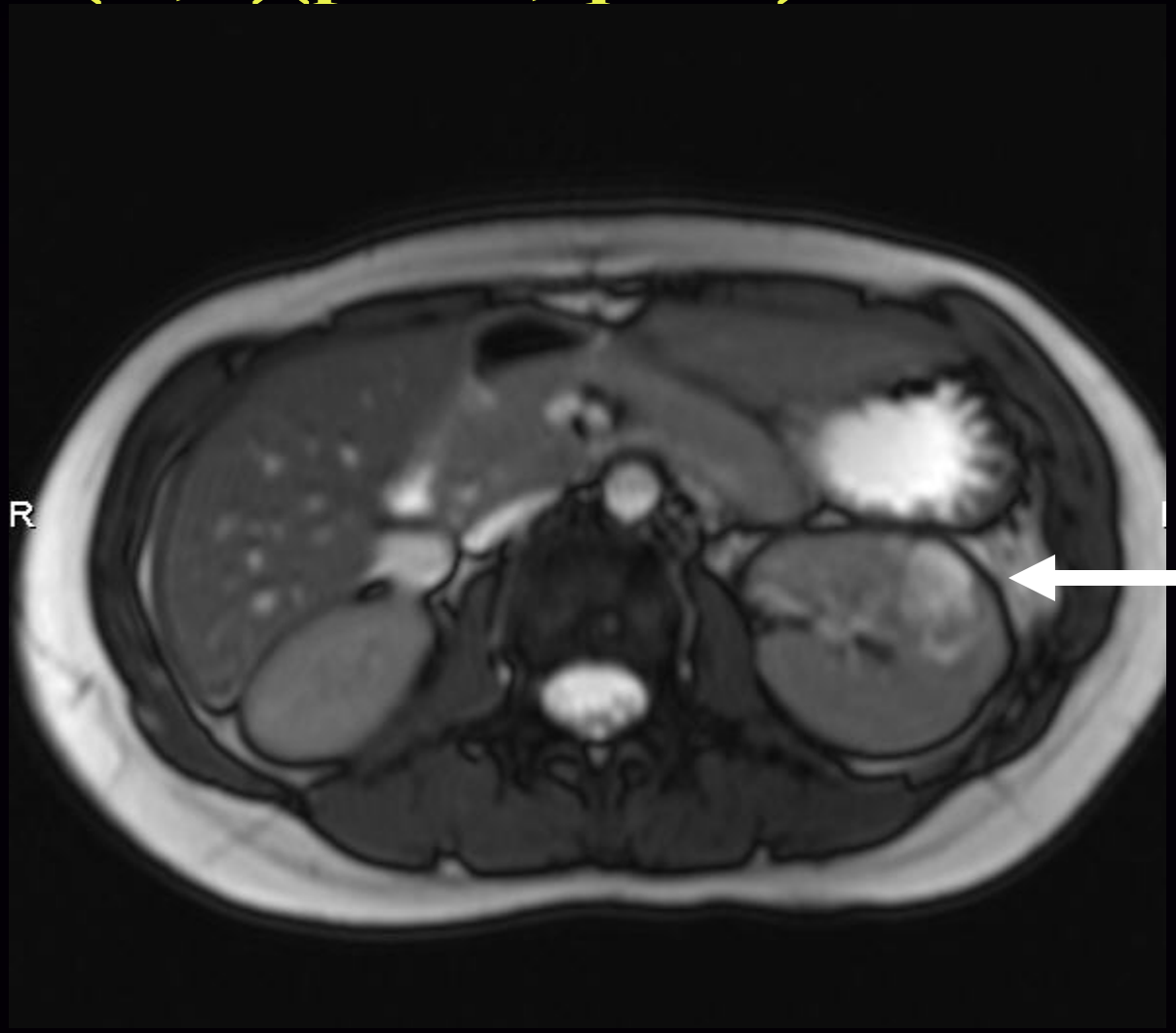


Cell lines
UOK 120, UOK146

Cell line UOK 124

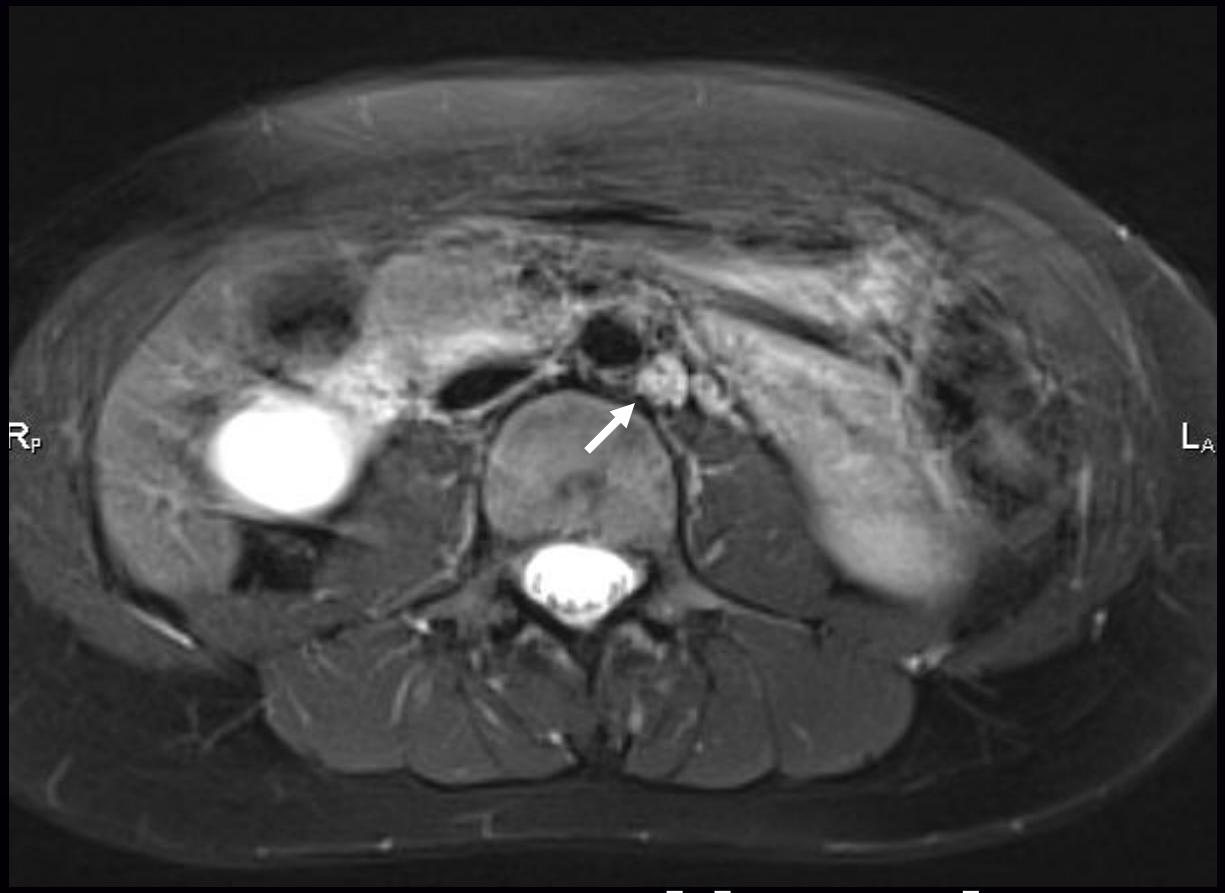
Human Mol Genetics 5:1966

TFE3 t(X;1)(p11.2;q21.2) Translocation



23 Year Old Female

TFE3 t(X;1)(p11.2;q21.2) Translocation Papillary Kidney Cancer



Positive Hilar node

23 Year Old Female

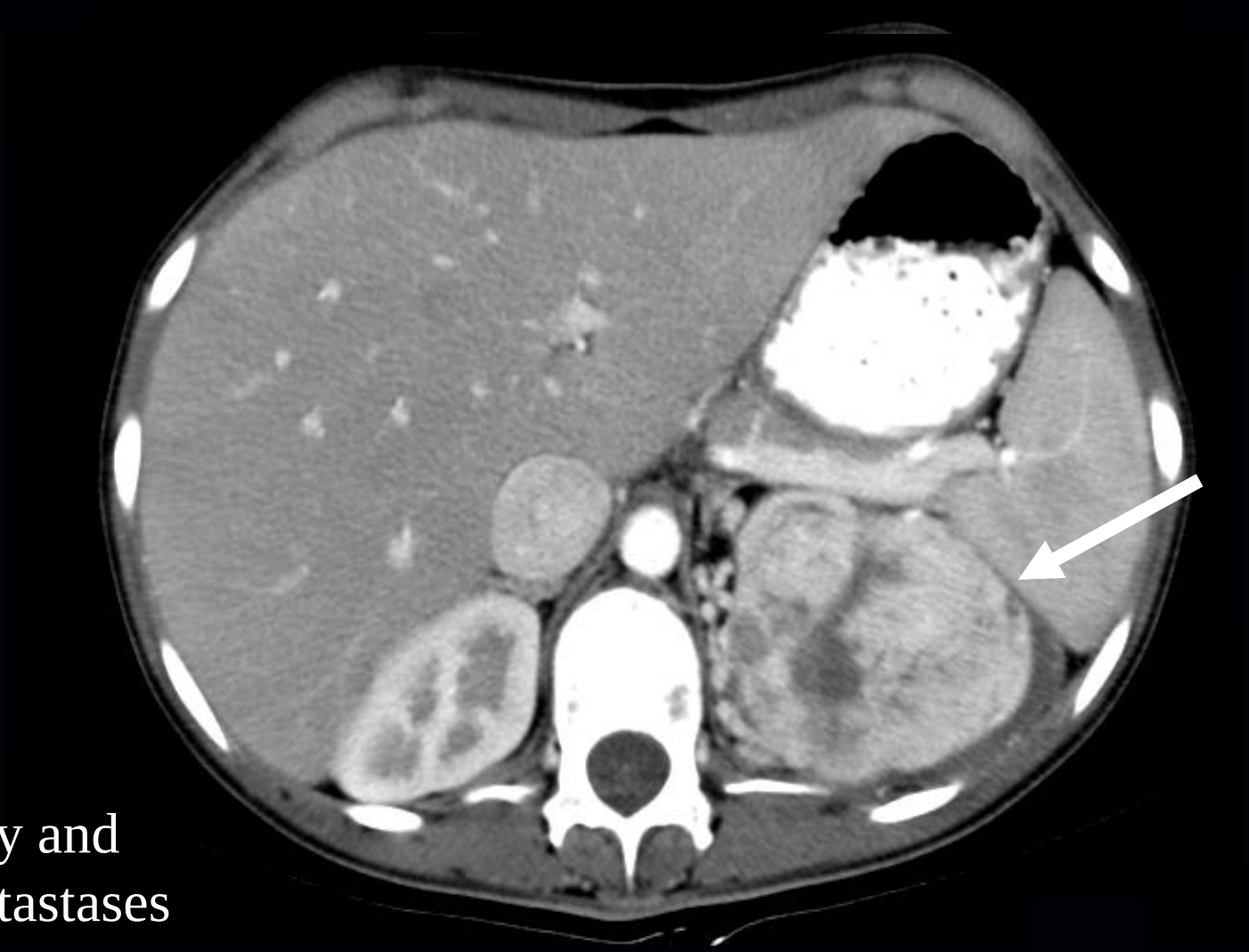
TFE3 Kidney Cancer

1-1.6%	All renal tumors
15%	RCC patients <45 years of age
20-45%	RCC in children and young adults

Micropthalmia Transcription Factor (MITF) Kidney Cancer

- TFE3 kidney cancer
- TFEB kidney cancer
- MITF kidney cancer
  - Kidney cancer and melanoma families

TFEB Kidney Cancer t(6:11)(p21;q13)



Pulmonary and
Osseous metastases

18 Year Old Female

TFEB Kidney Cancer t(6:11)(p21;q13)

14 Year Old Female

MITF Kidney Cancer

LETTER

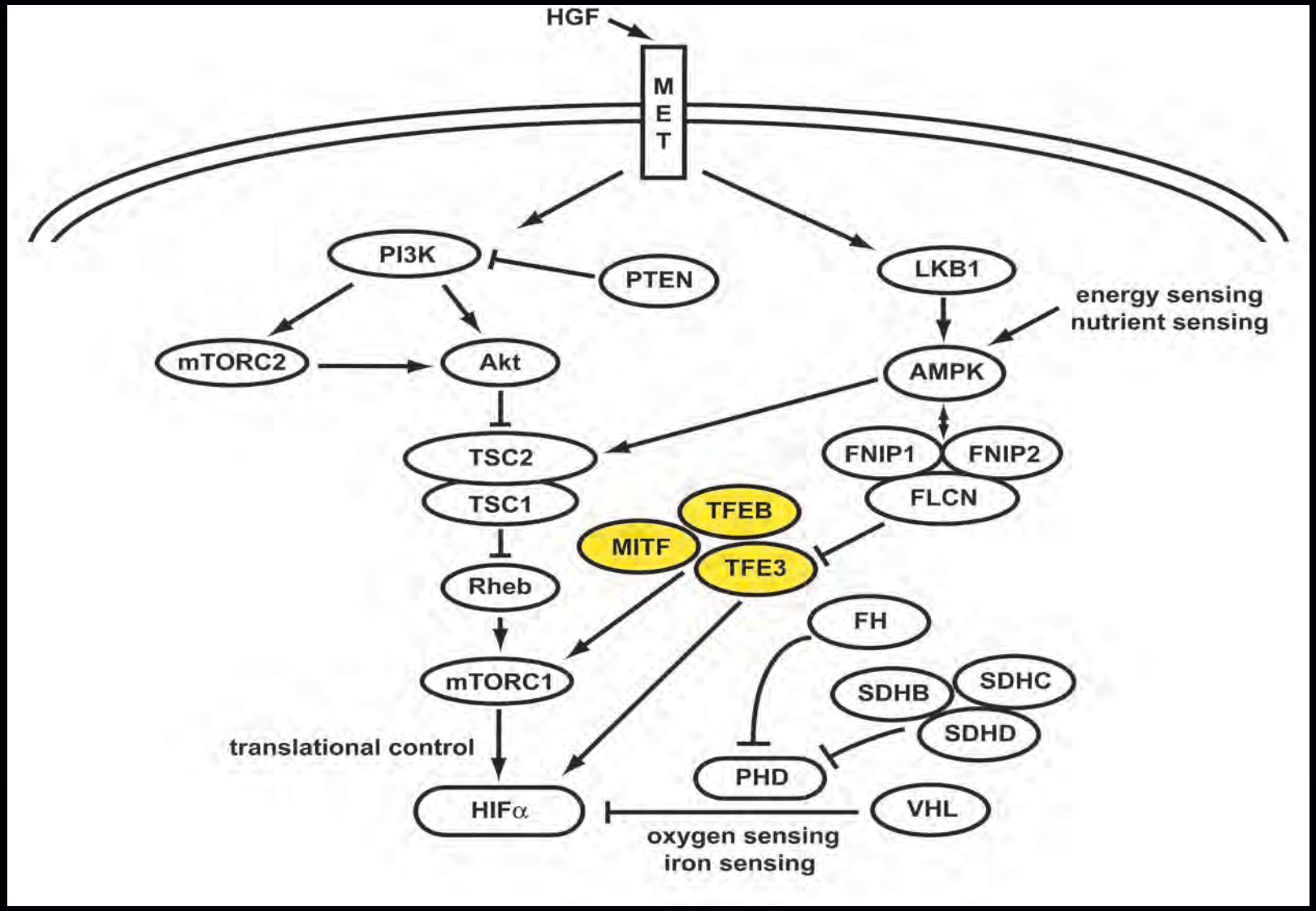
doi:10.1038/nature10539

A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma

Corine Bertolotto[1,2,3]*, Fabienne Lesueur[4]†*, Sandy Giuliano[1,2]*, Thomas Strub[5], Mahaut de Lichy[4], Karine Bille[1], Philippe Dessen[6], Benoit d'Hayer[4], Hamida Mohamdi[7,8,9], Audrey Remenieras[4]†, Eve Maubec[7,10], Arnaud de la Fouchardière[11], Vincent Molinié[12], Pierre Vabres[13], Stéphane Dalle[14], Nicolas Poulalhon[14], Tanguy Martin-Denavit[14], Luc Thomas[14], Pascale Andry-Benzaquen[15], Nicolas Dupin[15], Françoise Boitier[15], Annick Rossi[16], Jean-Luc Perrot[17], Bruno Labeille[17], Caroline Robert[18], Bernard Escudier[18], Olivier Caron[18], Laurence Brugières[19], Simon Saule[20], Betty Gardie[21], Sophie Gad[21], Stéphane Richard[21,22], Jérôme Couturier[23], Bin Tean Teh[24,25], Paola Ghiorzo[26], Lorenza Pastorino[26], Susana Puig[27], Celia Badenas[27], Hakan Olsson[28], Christian Ingvar[29], Etienne Rouleau[30], Rosette Lidereau[30], Philippe Bahadoran[3], Philippe Vielh[31], Eve Corda[7,9], Hélène Blanché[9], Diana Zelenika[32], Pilar Galan[33], The French Familial Melanoma Study Group‡, Valérie Chaudru[7,9,34], Gilbert M. Lenoir[4,35], Mark Lathrop[9,32], Irwin Davidson[5], Marie-Françoise Avril[15], Florence Demenais[7,8,9], Robert Ballotti[1,2,3]* & Brigitte Bressac-de Paillerets[4,7]*

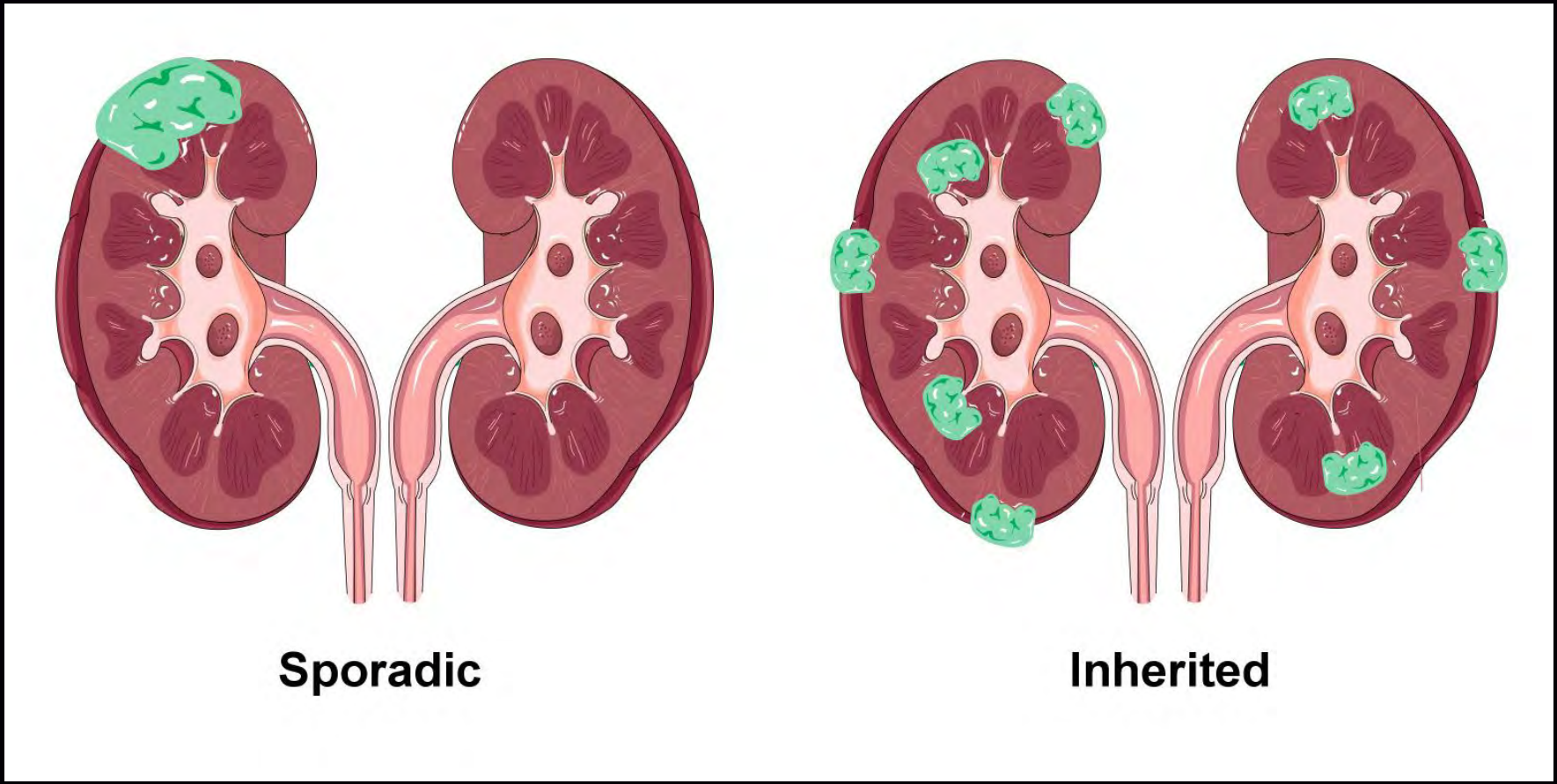
Nature 480:2011

Kidney Cancer is a Metabolic Disease

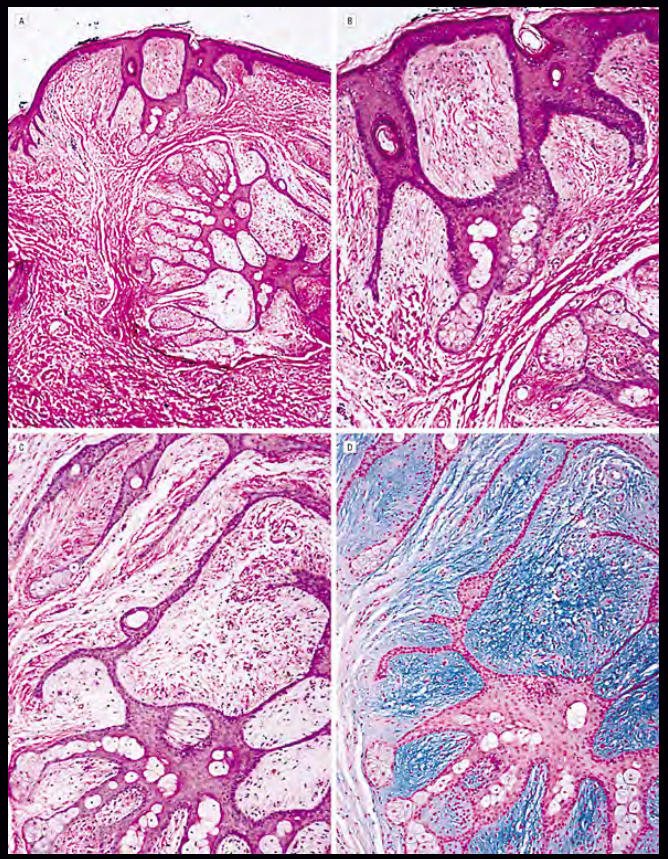


Nature Rev Urol: 7 2010

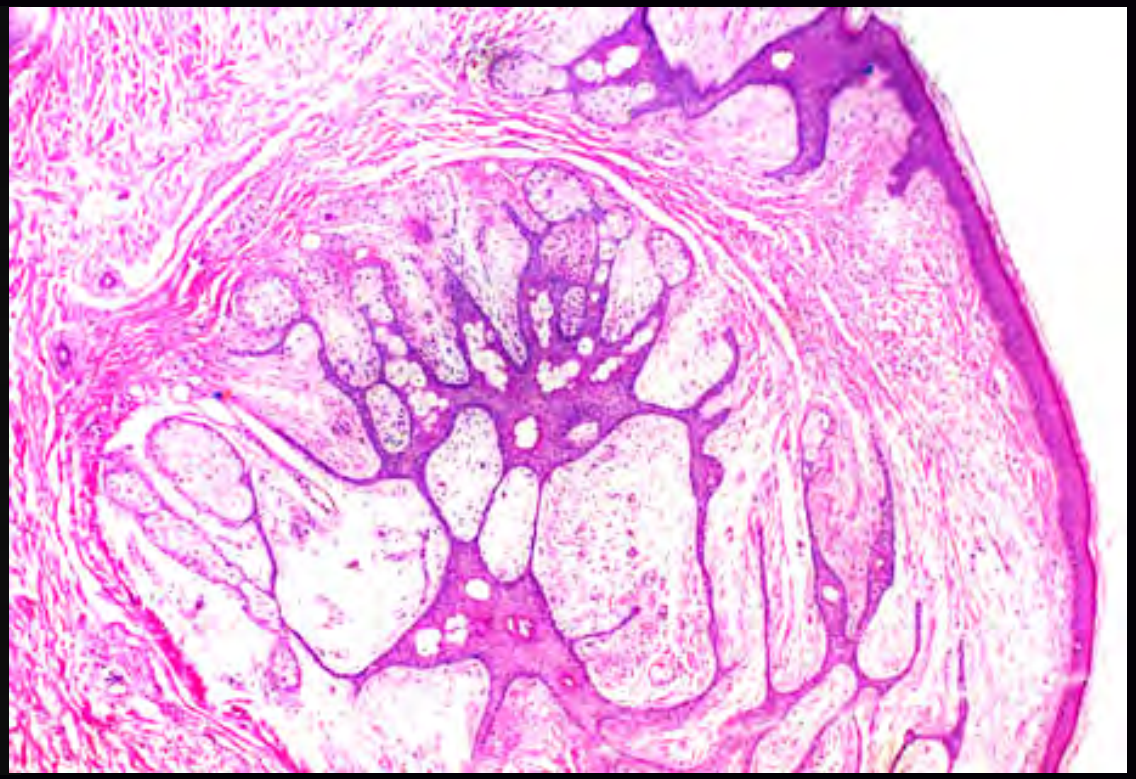
Inherited Renal Carcinoma
Birt-Hogg-Dubé (BHD)



Birt Hogg Dubé
Cutaneous Manifestations



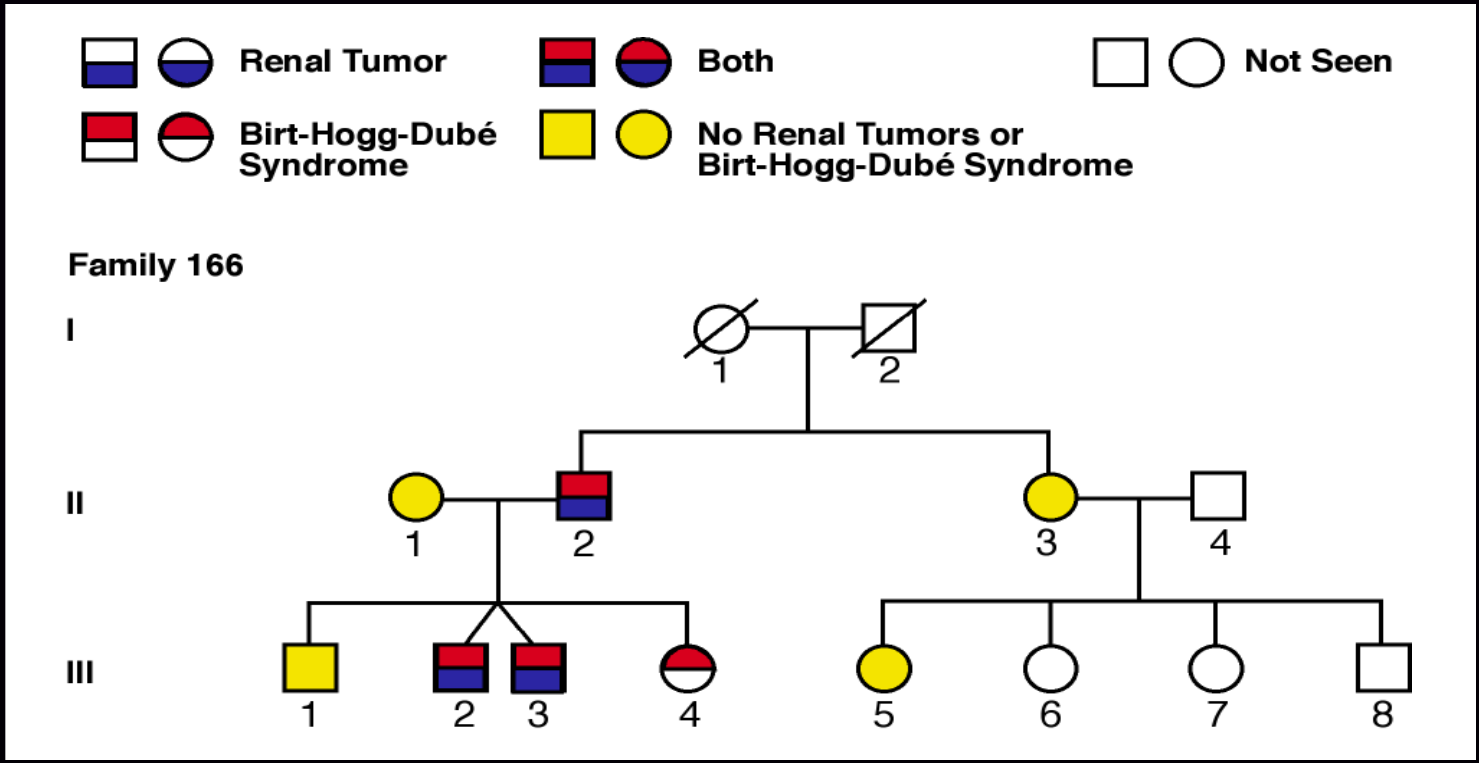
Birt Hogg Dubé
Cutaneous Manifestations



Kidney Tumors in BHD:

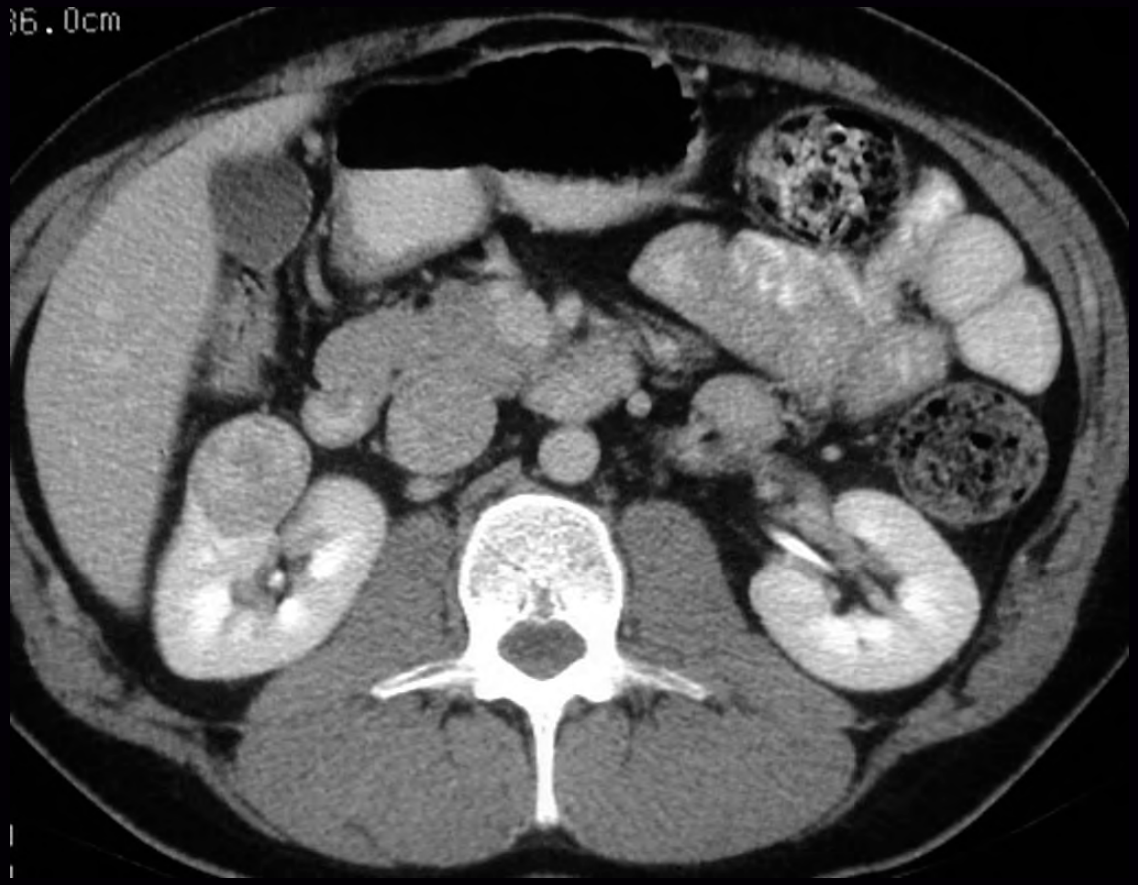
Risk of Renal and Colonic Neoplasms and Spontaneous Pneumothorax in the Birt-Hogg- Dubé Syndrome

B Zbar, G Alford, G Glenn, M Turner, C Pavlovich, L. Schmidt, M Walther, P Choyke, F Gabril, C Greenberg, M Merino, J Toro and W M Linehan



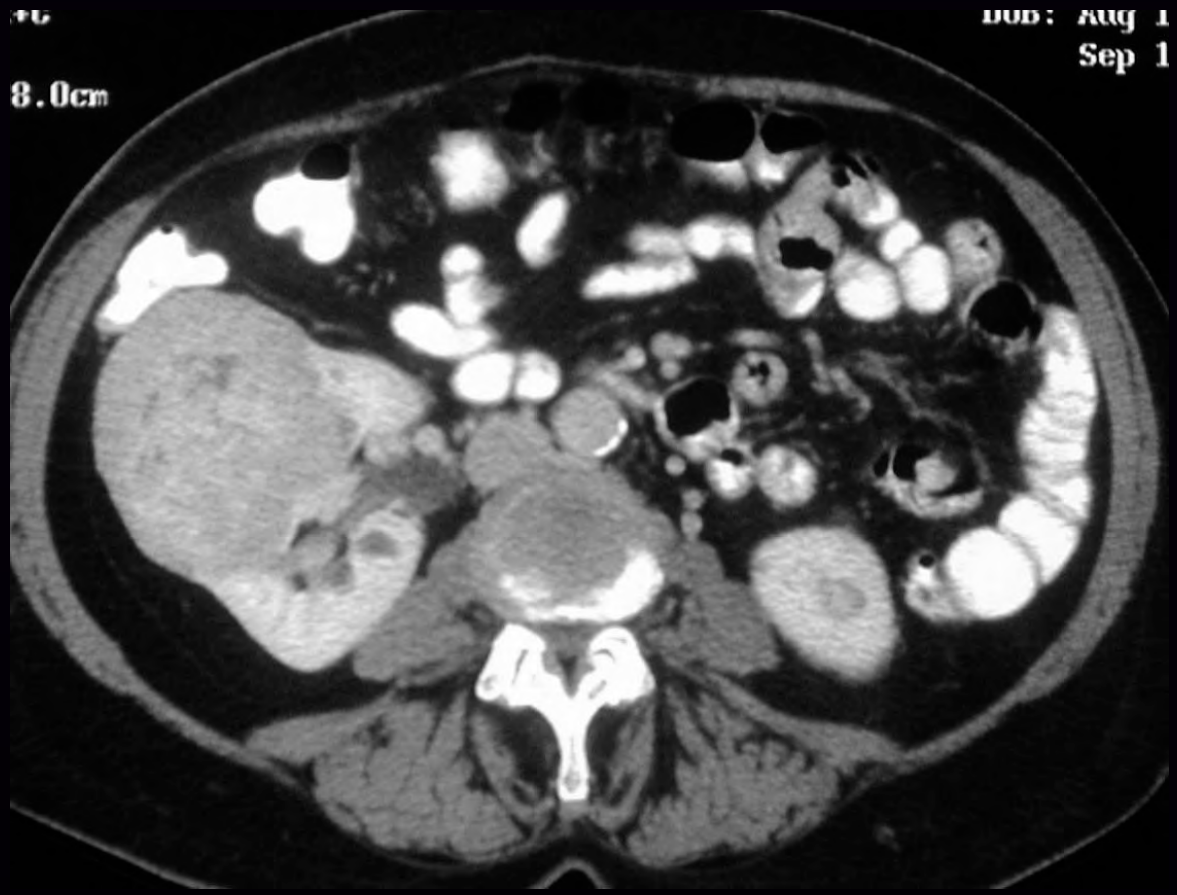
Cancer Epi, Biomarkers & Prev 11:2002

Kidney Tumors in Birt Hogg Dubé

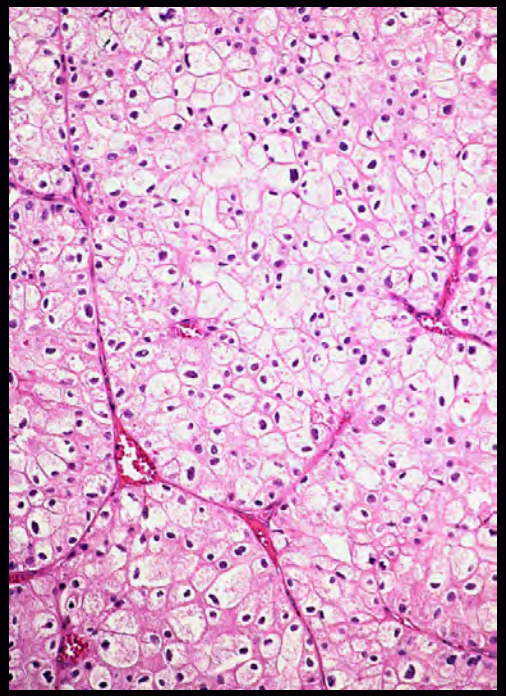


Kidney Tumors in Birt Hogg Dubé

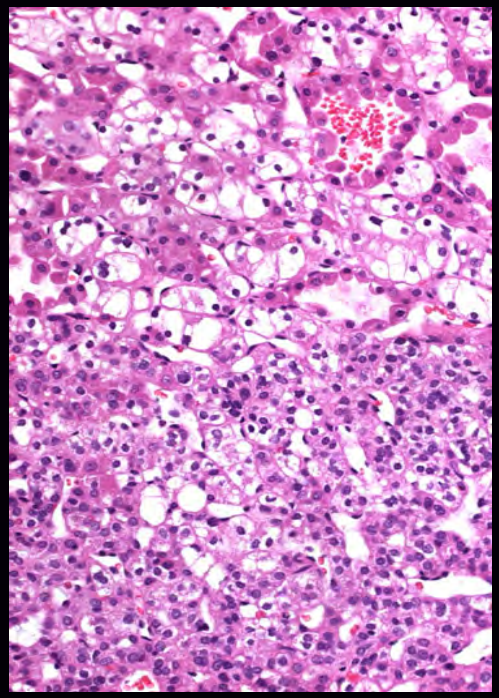
Kidney Tumors in Birt Hogg Dubé



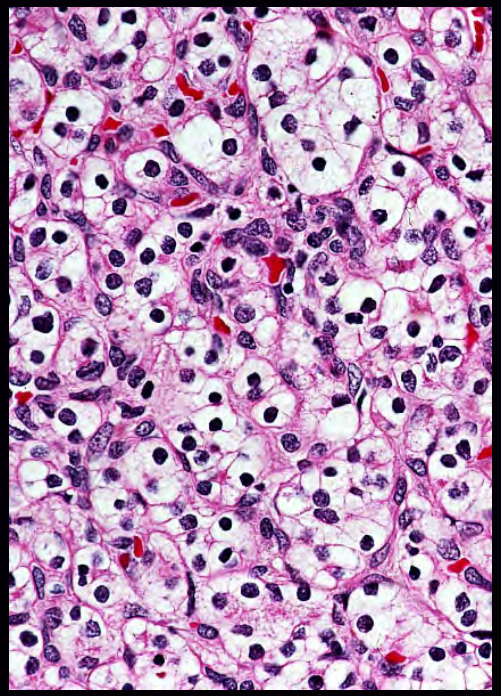
Birt Hogg Dubé Renal Tumors



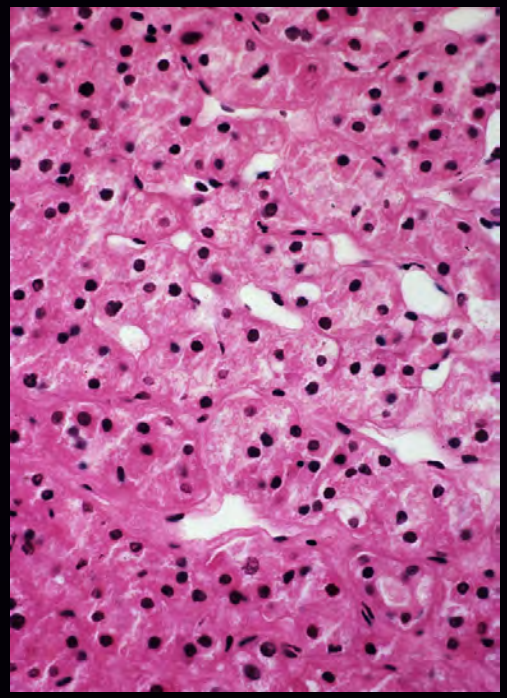
Chromophobe RCC



Hybrid RCC

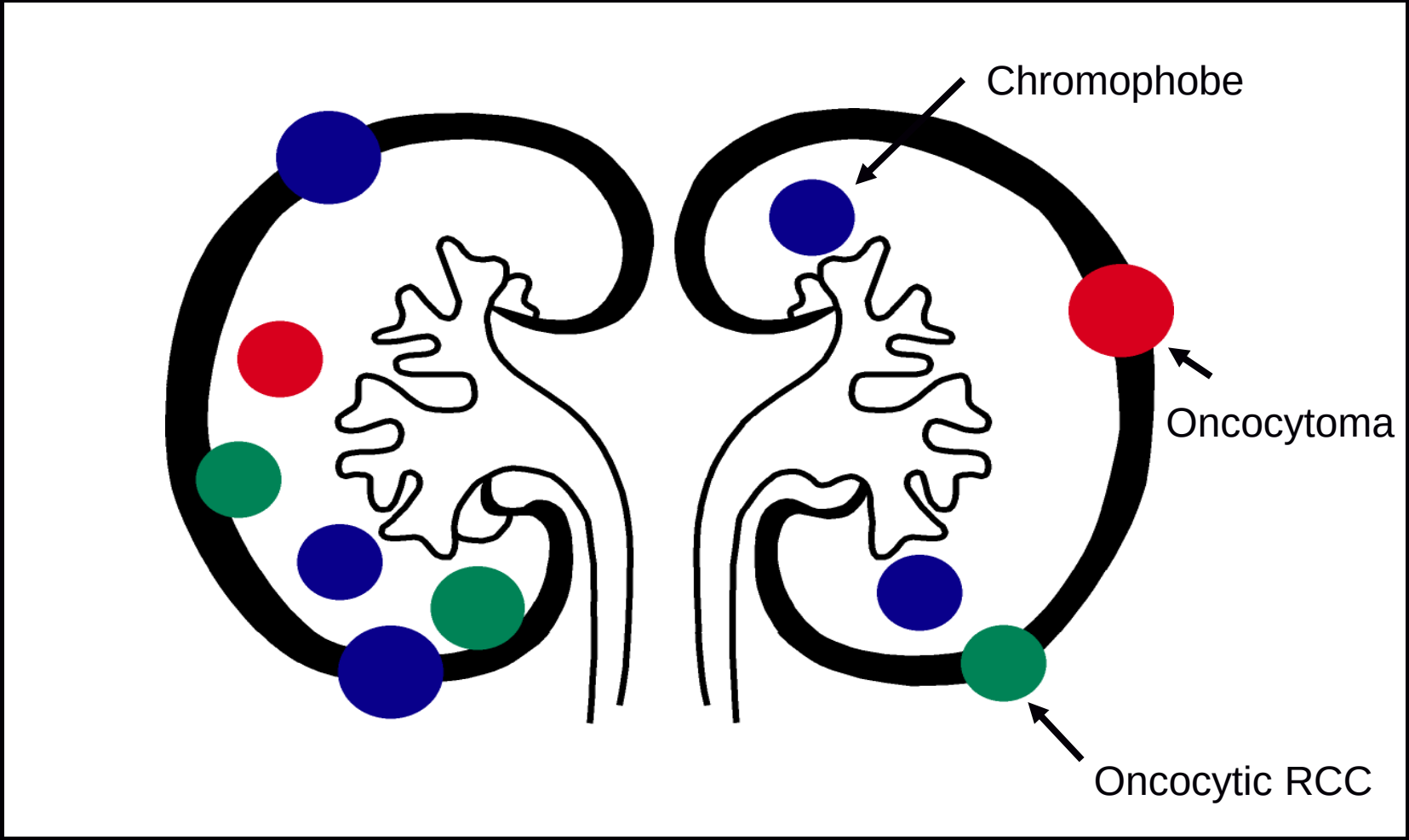


Clear Cell RCC



Oncocytoma

BHD Renal Tumor Pathology

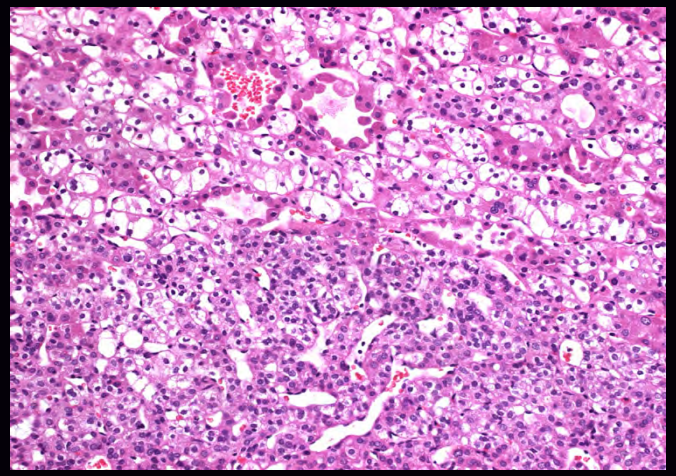


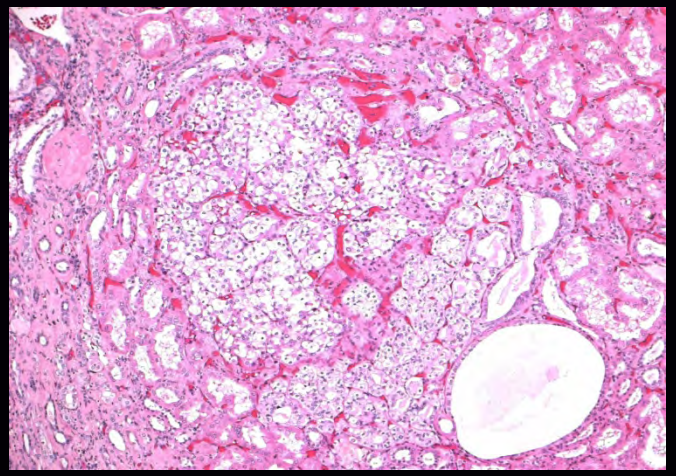
High Persistence Rate

Microscopic Tumors

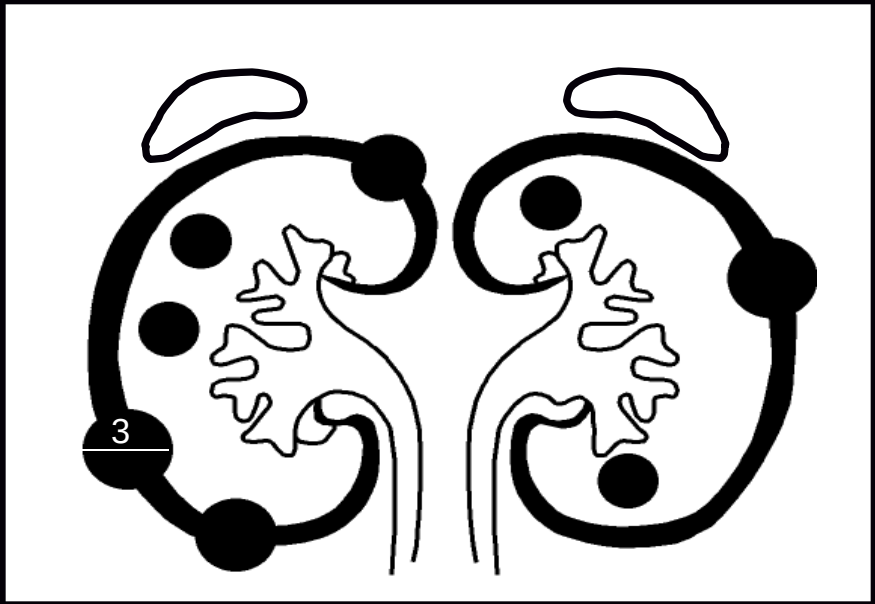
- **BHD**

  3,000 Chromophobe,
  Chromo-Hybrid





Surgical Management of BHD-Associated Renal Carcinoma



"3 cm rule"

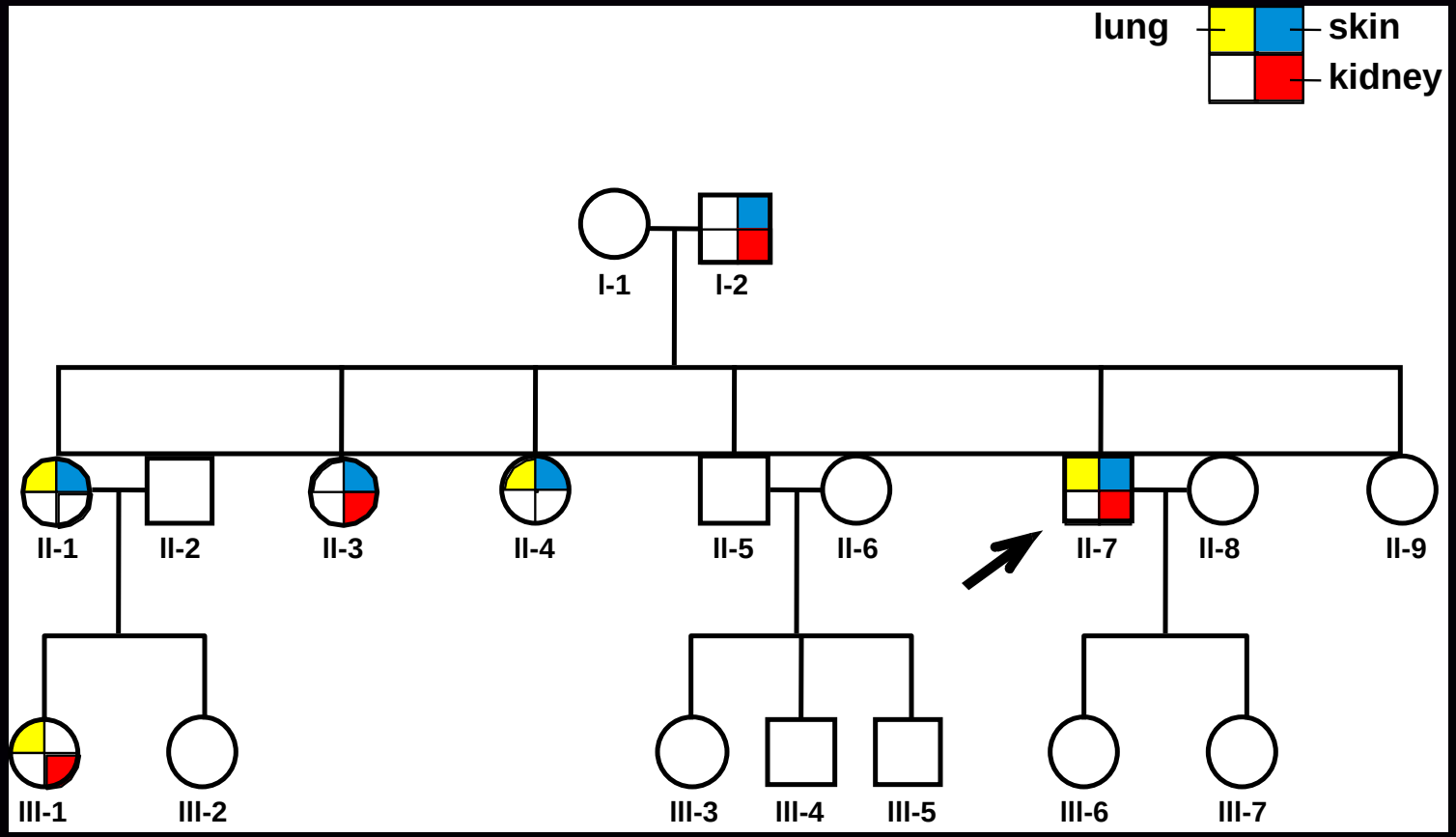
Delay surgery until diameter of largest renal tumor = 3 cm

Surgery = nephron sparing enucleation

J Urol 173 2005

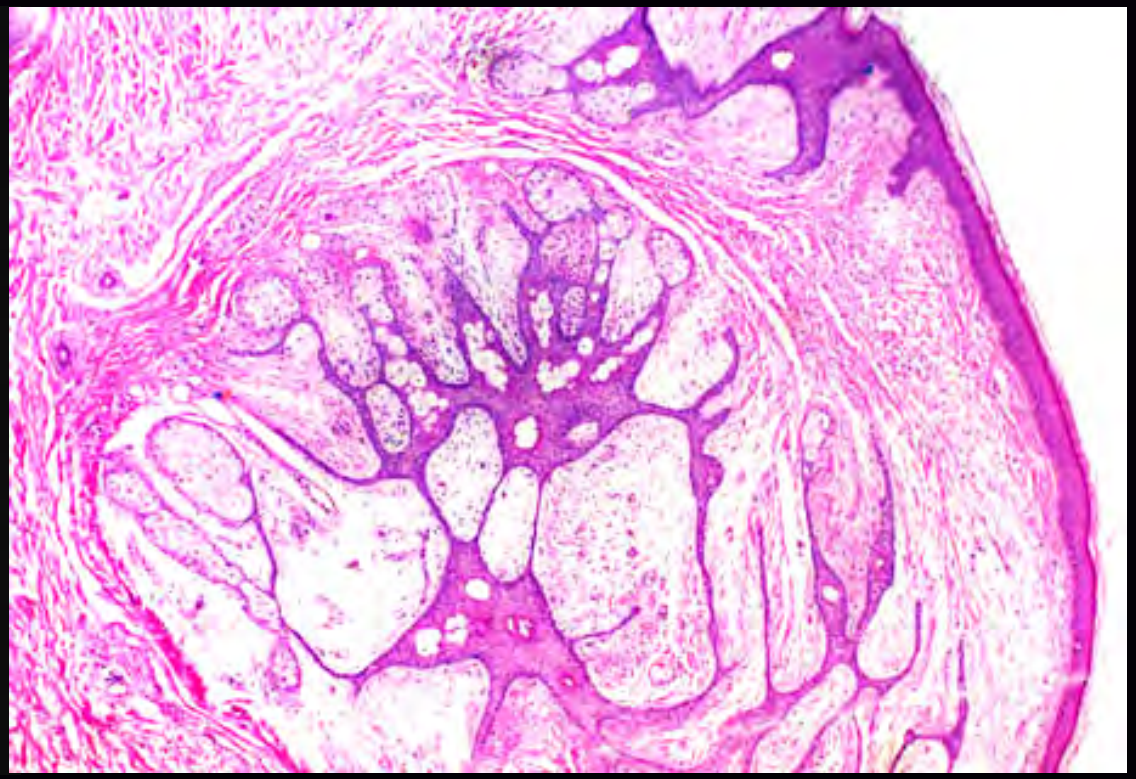
Am J Hum Genet 76: 2005

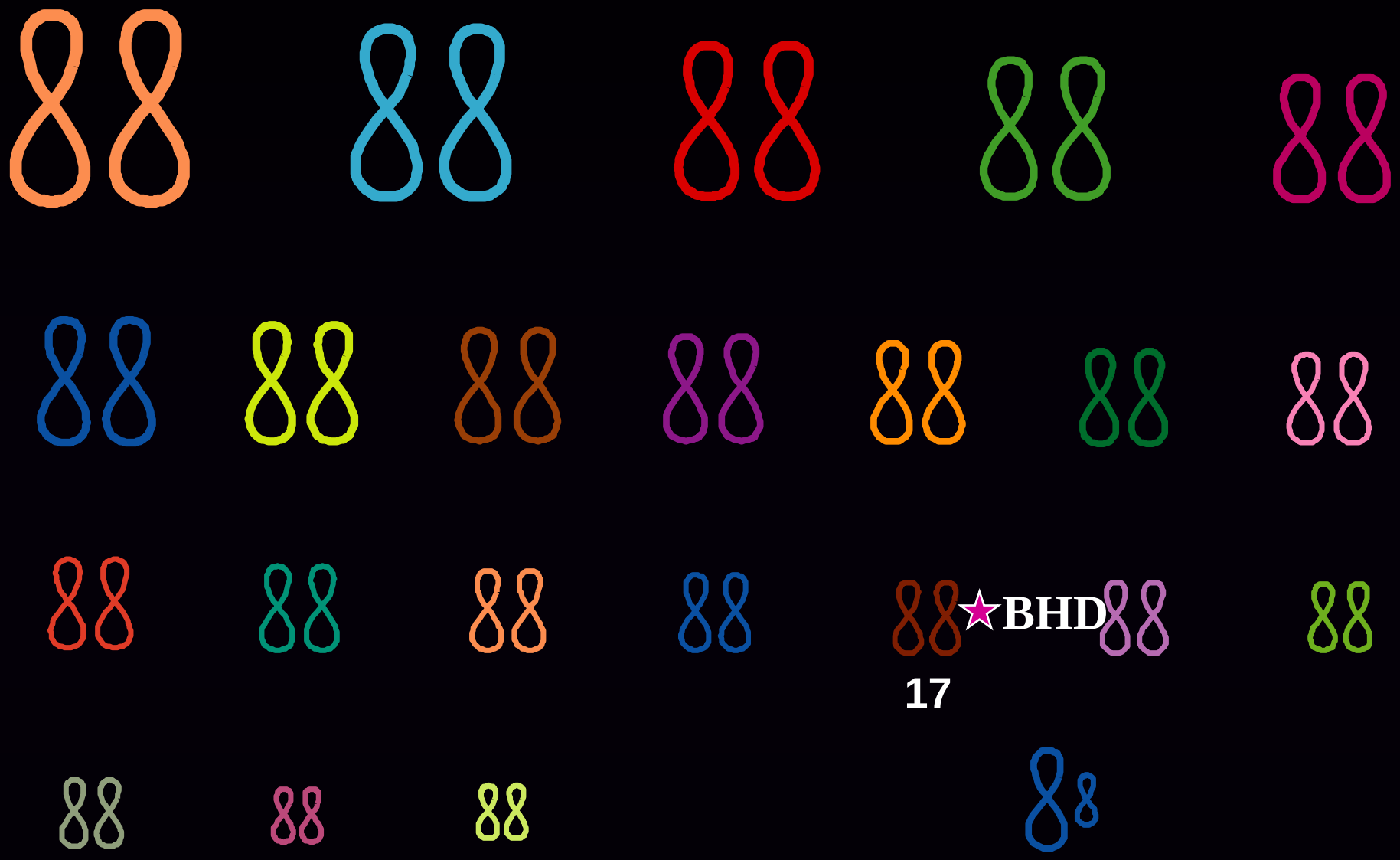
Identification of the BHD Gene



NIH Clinical Center

Cutaneous Fibrofolliculomas

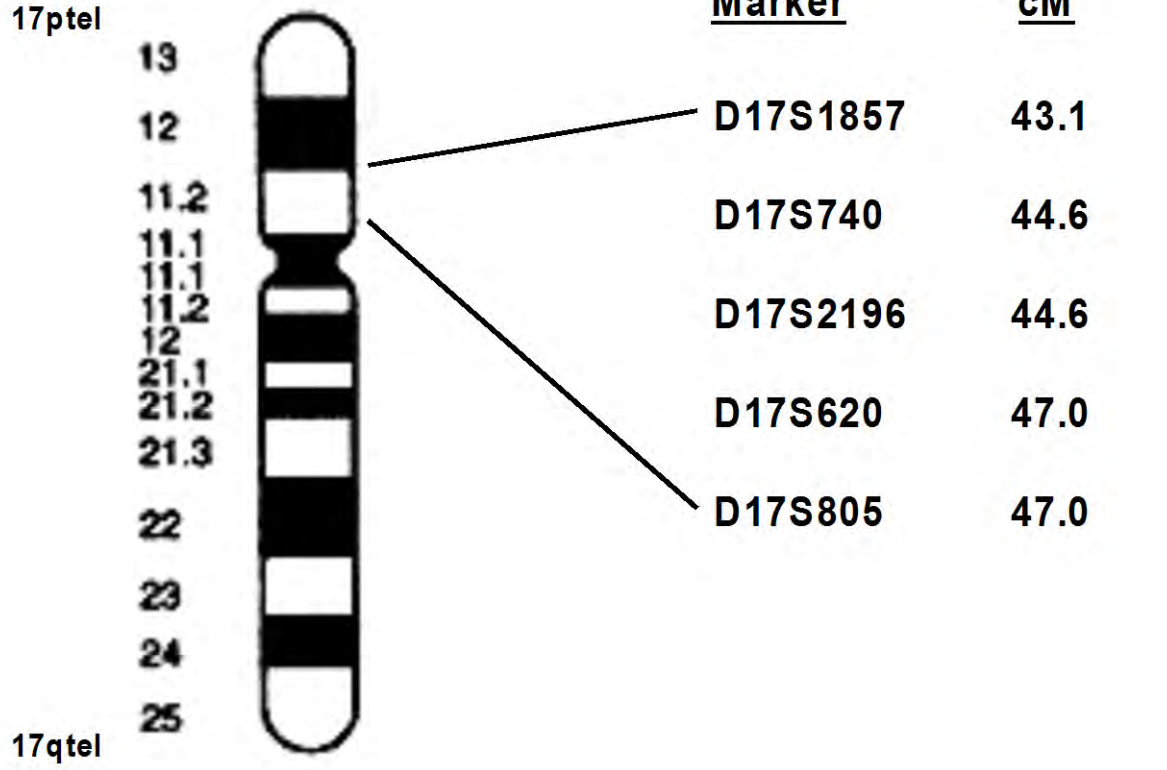




BHD Gene: Chromophobe RCC

Am J Hum Genetics 69:2001

BHD1 Gene Locus Chromosome 17



Am J Hum Genetics 69:2001

BHD Protein Sequence

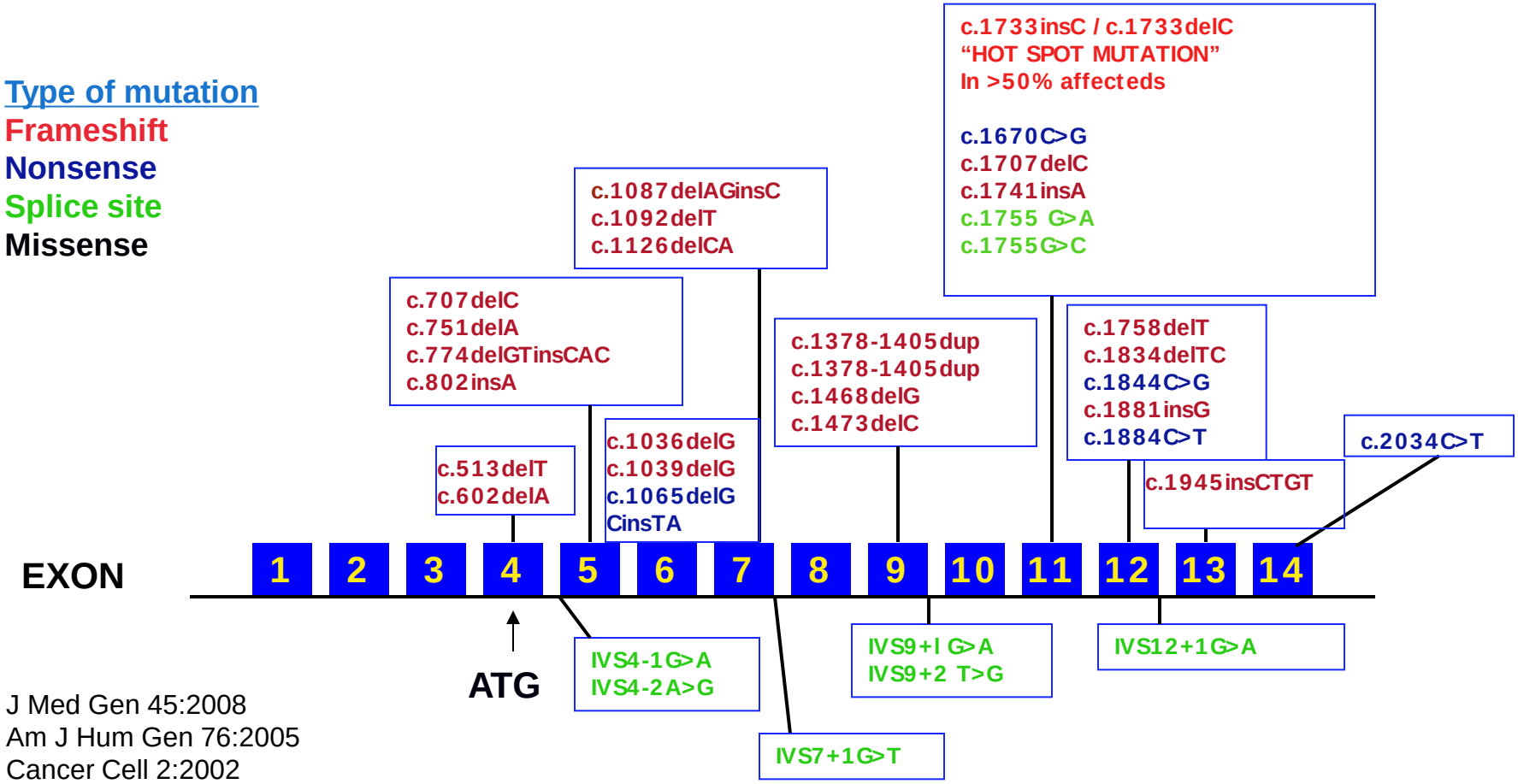
b)

```
1   MNAIVALCHFCELHGPRTLFCTEVLHAPLPQGDGNEDSPGQGEQAEEEEGGIQMNSRMRA
61  HSPAEGASVESSSPGPKKSDMCEGCRSLAAGHPGYISHDKETSIKYVSHQHPSHPQLFSI
121 VRQACVRSLSCEVCPGREGPIFFGDEQHGFVFSHTFFIKDSLARGFQRWYSIITIMMDRI
181 YLINSWPFLLGKVRGIIDELQGKALKVFEAEQFGCPQRAQRMNTAFTPFLHQRNGNAARS
241 LTSLTSDDNLWACLHTSFAWLLKACGSRLTEKLLEGAPTEDTLVQMEKLADLEEESESWD
301 NSEAEEEEKAPVLPESTEGRELTQGPAESSSLSGCGSWQPRKLPVFKSLRHMRQVLGAPS
361 FRMLAWHVLMGNQVIWKSRDVDLVQSAFEVLRTMLPVGCVRIIPYSSQYEEAYRCNFLGL
421 SPHVQIPPHVLSSEFAVIVEVHAAARSTLHPVGCEDDQSLSKYEFVVTSGSPVAADRVGP
481 TILNKIEAALTNQNLSVDVVDQCLVCLKEEWMNKVKVLFKFTKVDSRPKEDTQKLLSILG
561 ASEEDNVKLLKFWMTGLSKTYKSHLMSTVRSPTASESRN.
```

Cancer Cell: 2002

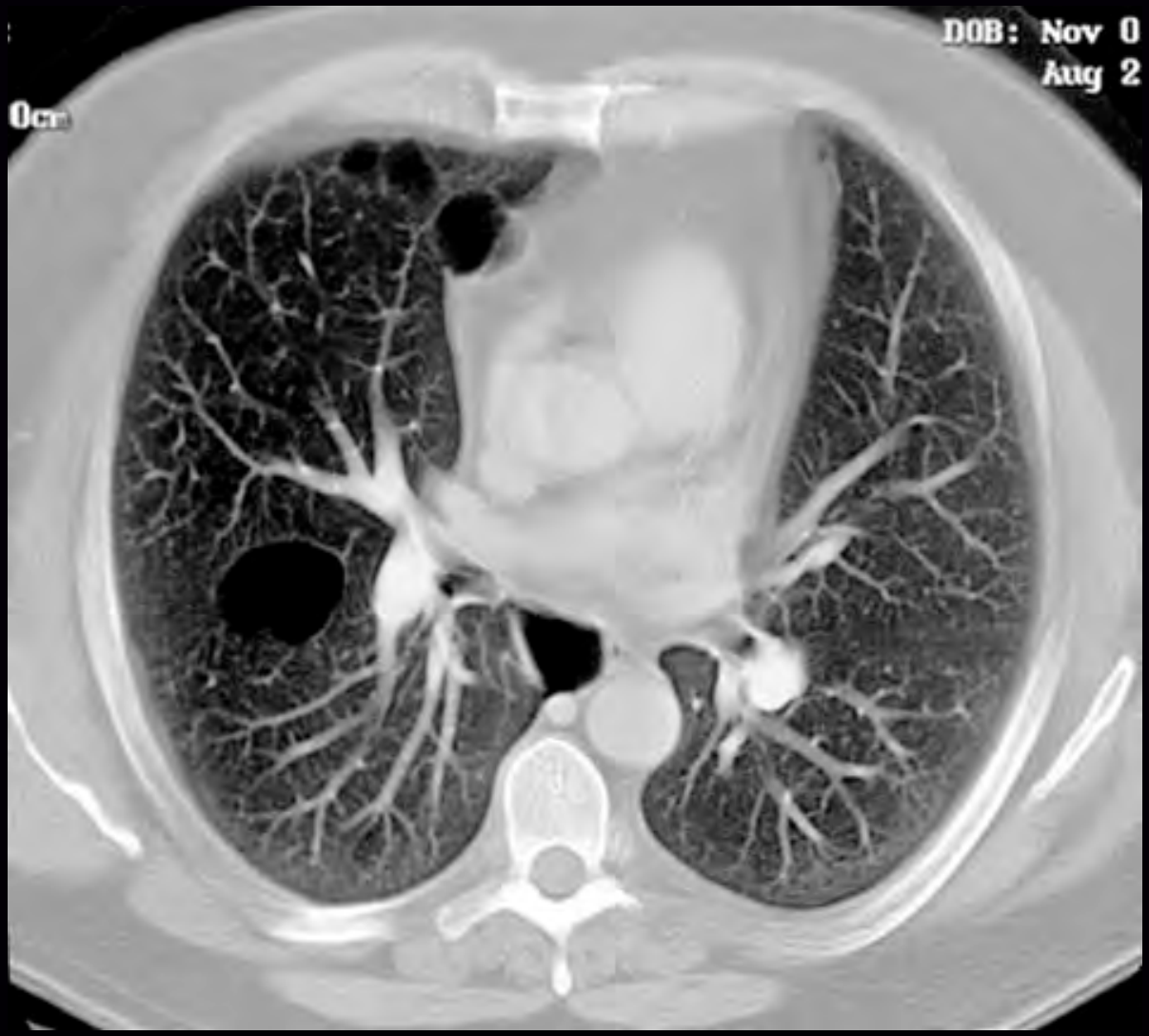
FLCN mutation spectrum

FLCN mutations across the entire gene
97% detection rate in 176 NCI BHD families

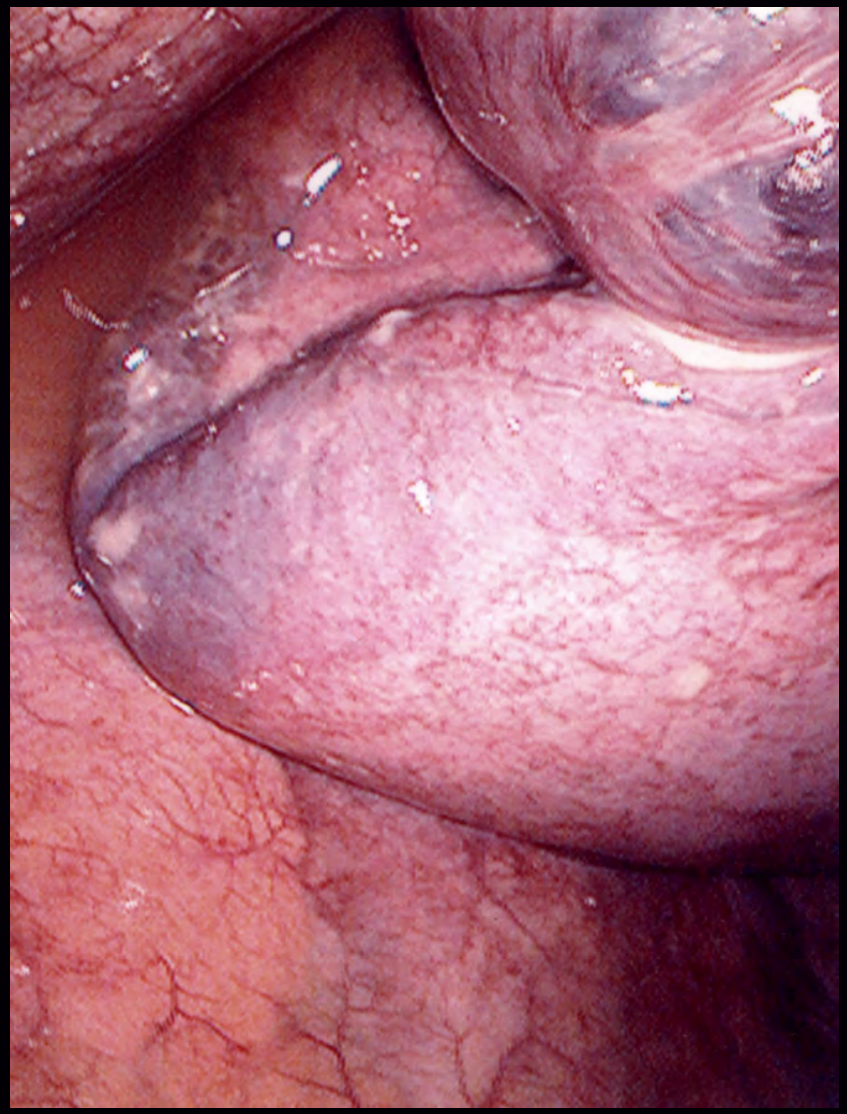


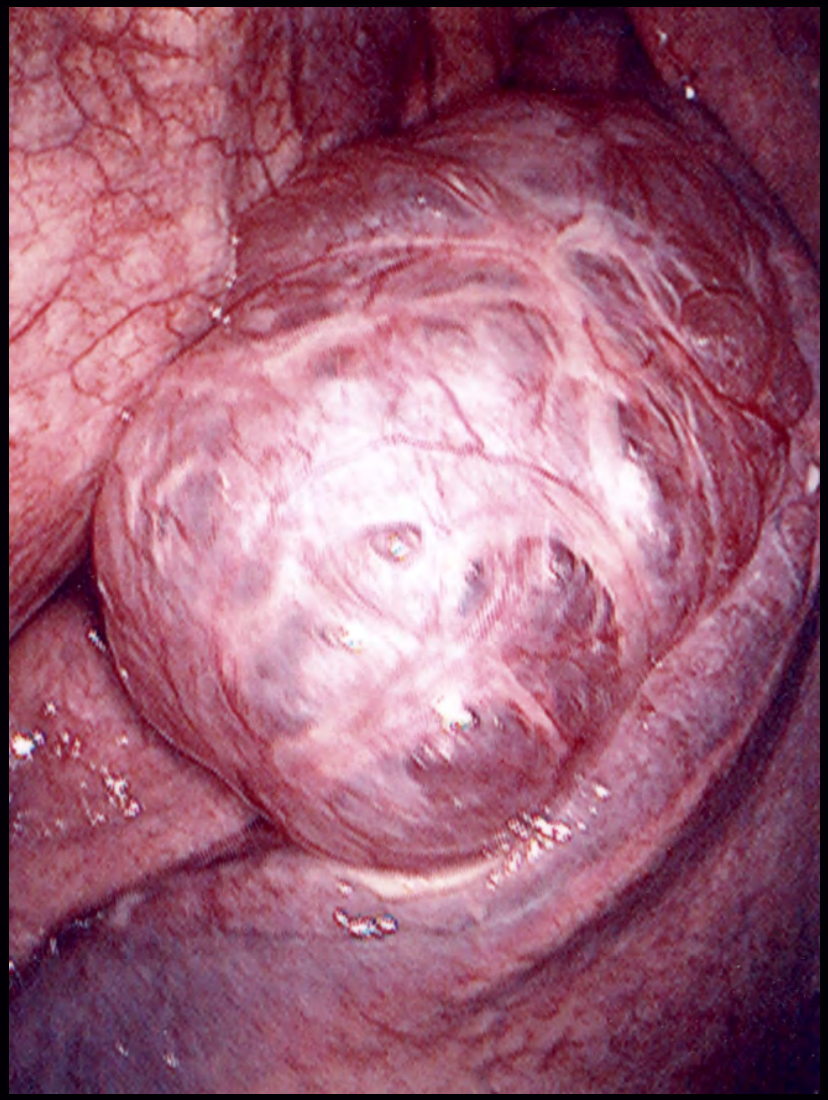
J Med Gen 45:2008
Am J Hum Gen 76:2005
Cancer Cell 2:2002

BHD Lung Cysts

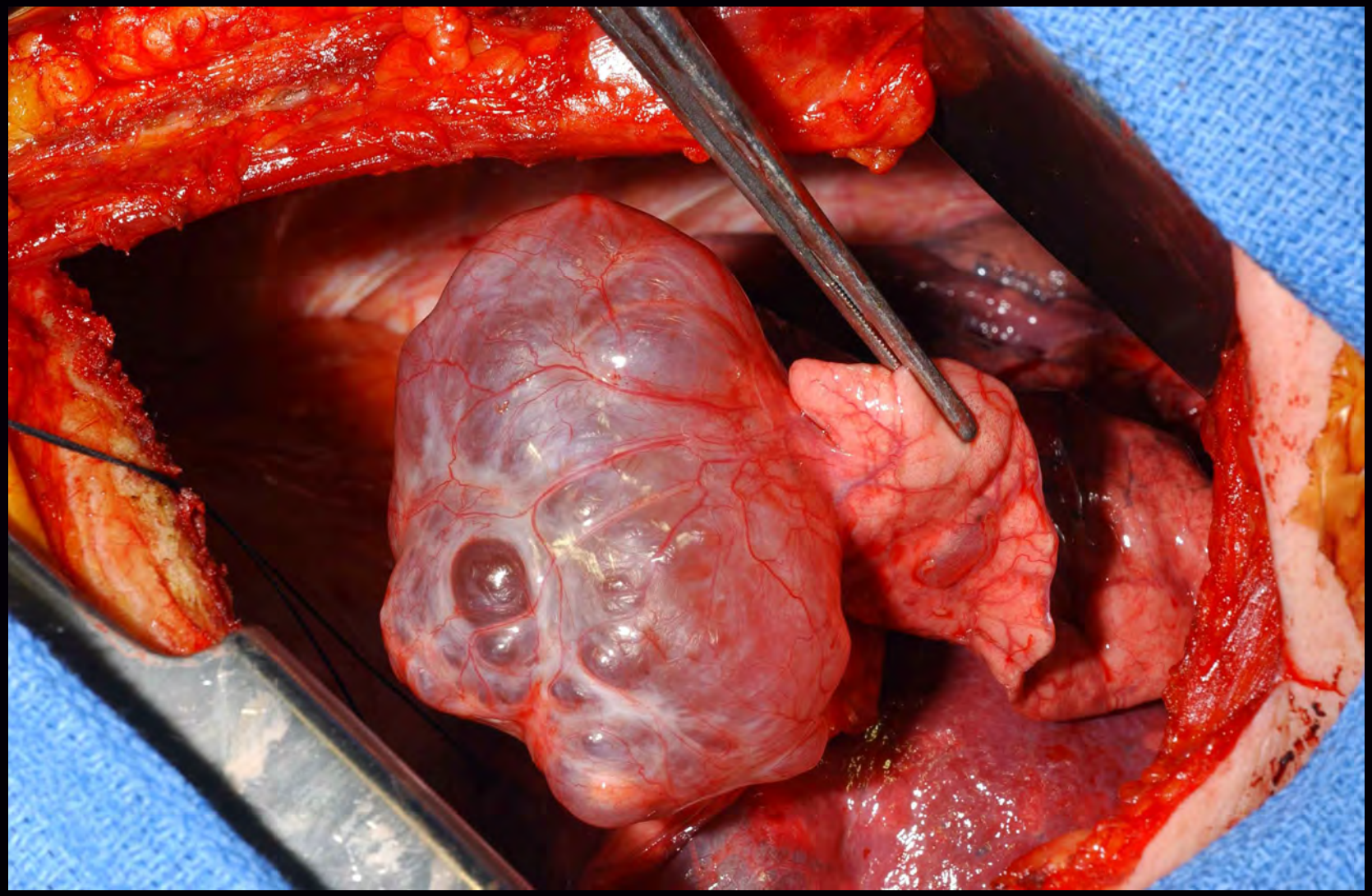


BHD Lung Cysts





BHD Lung Cysts



Therapeutic Approach: What Kind of Gene is FLCN?

BHD Gene Analysis in BHD-Associated RCC

- Tumor tissues from patients with BHD renal cell carcinoma were evaluated for:

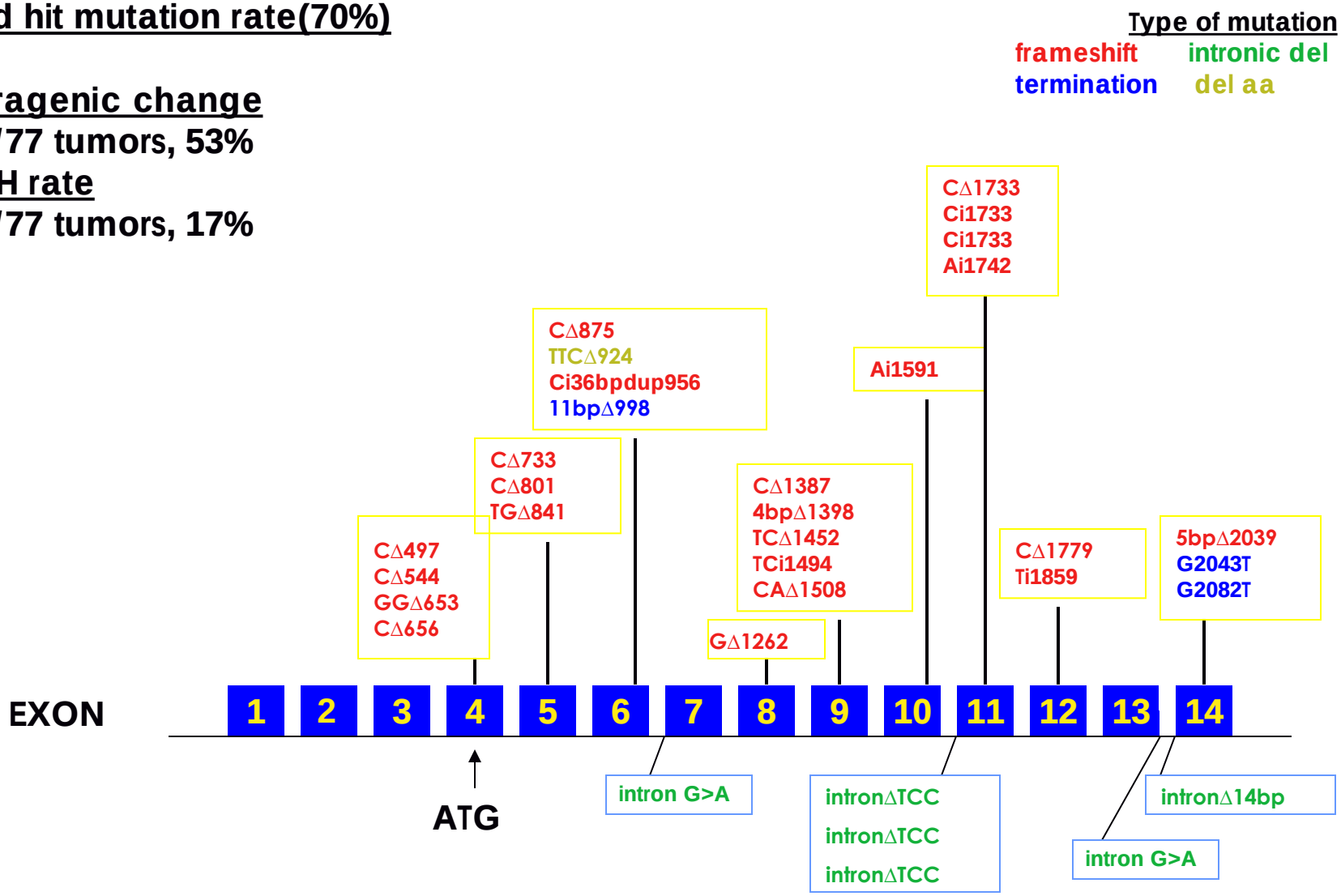
  1. BHD gene mutation

  2. BHD gene deletion (loss)

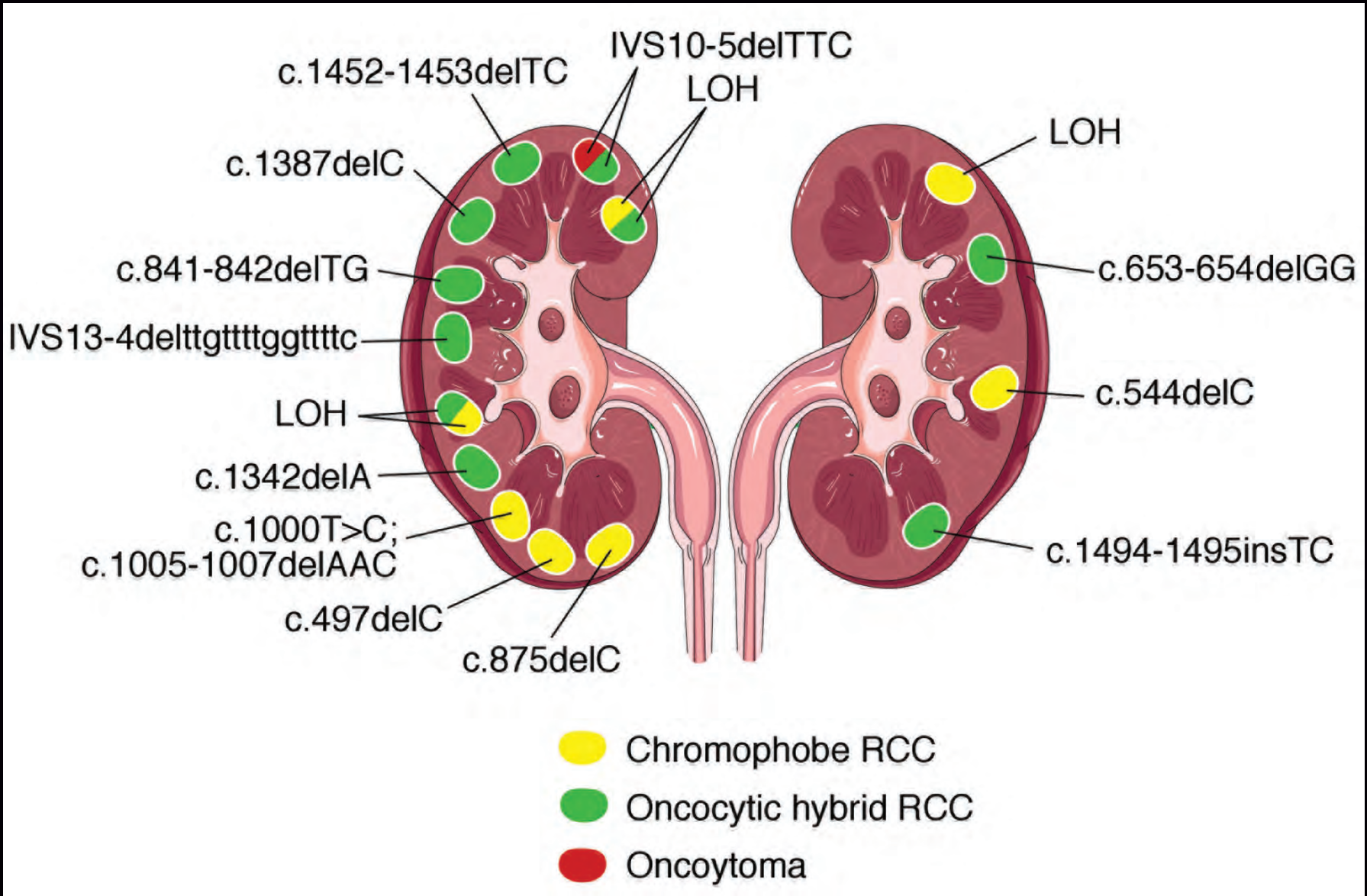
Somatic mutations in renal tumors from BHD patients

2nd hit mutation rate(70%)

Intragenic change
41/77 tumors, 53%
LOH rate
13/77 tumors, 17%



Somatic mutations in tumors from a single BHD patient



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

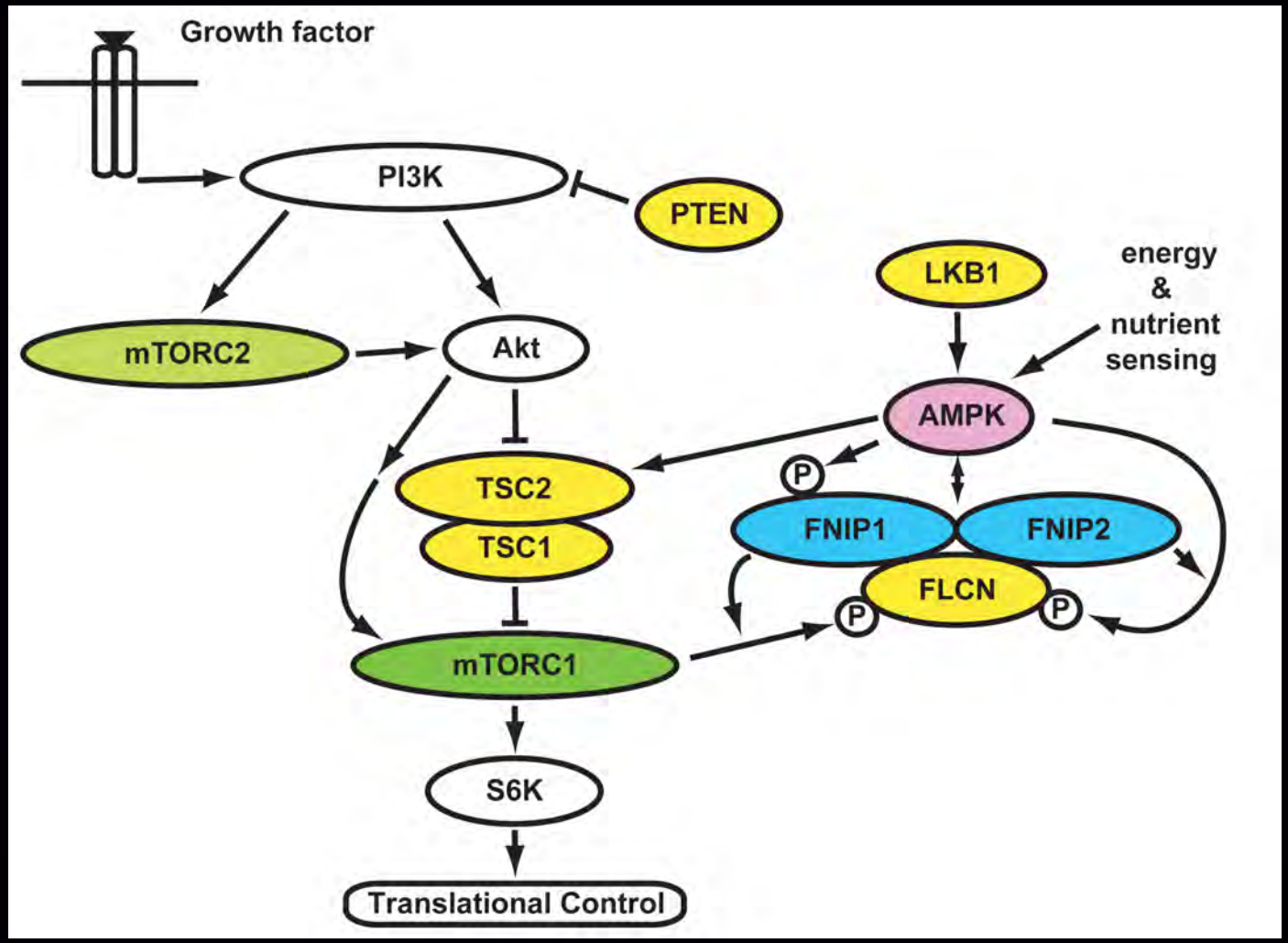
UOK257

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

UOK257-2

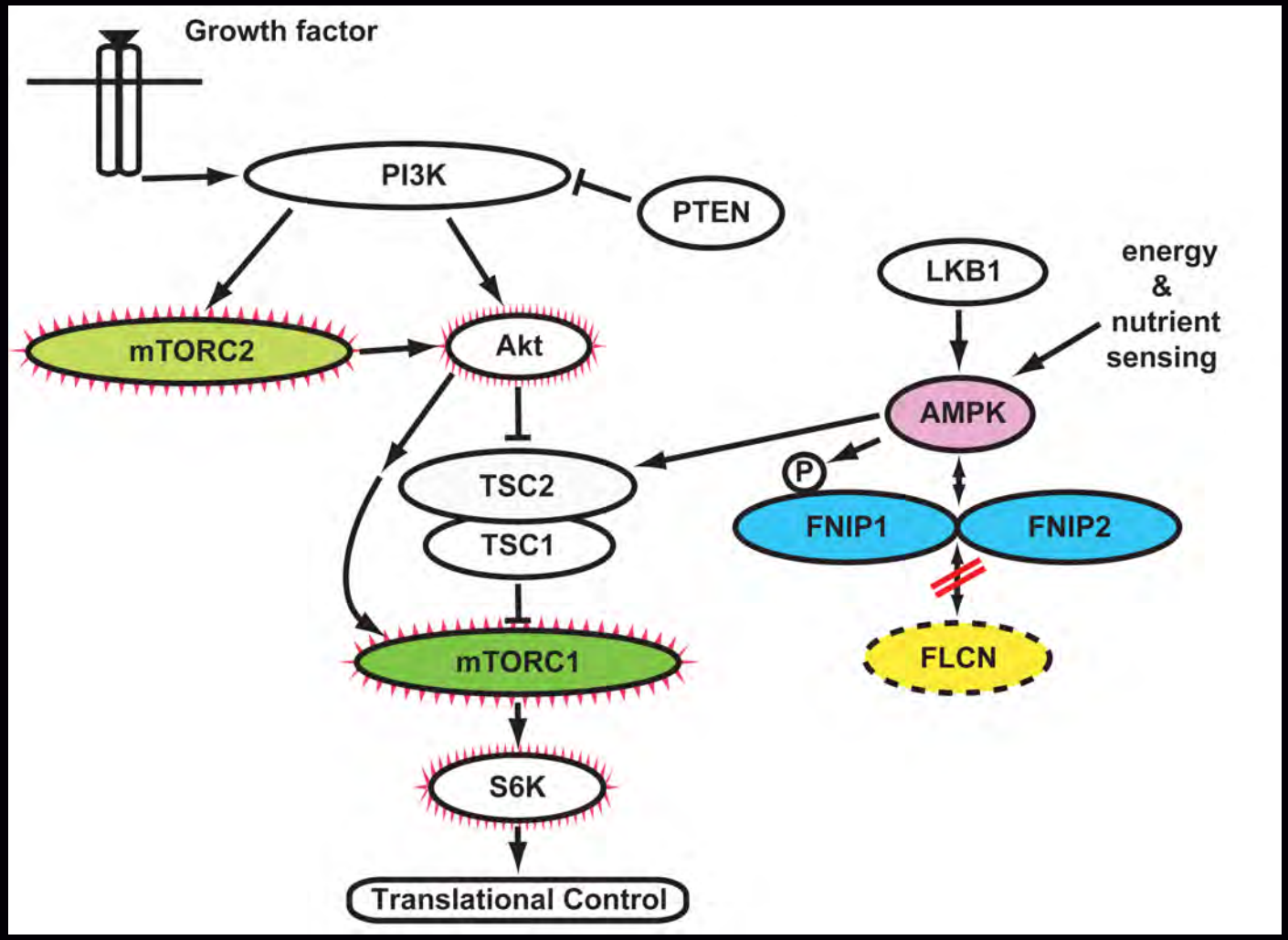
How Does the *FLCN* Gene Function?

Folliculin-FNIP1/2-AMPK Interactions



PNAS 103:2006
Gene 415:2008

mTORC1/mTORC2 Activation: FLCN-Deficient Kidney Cancer



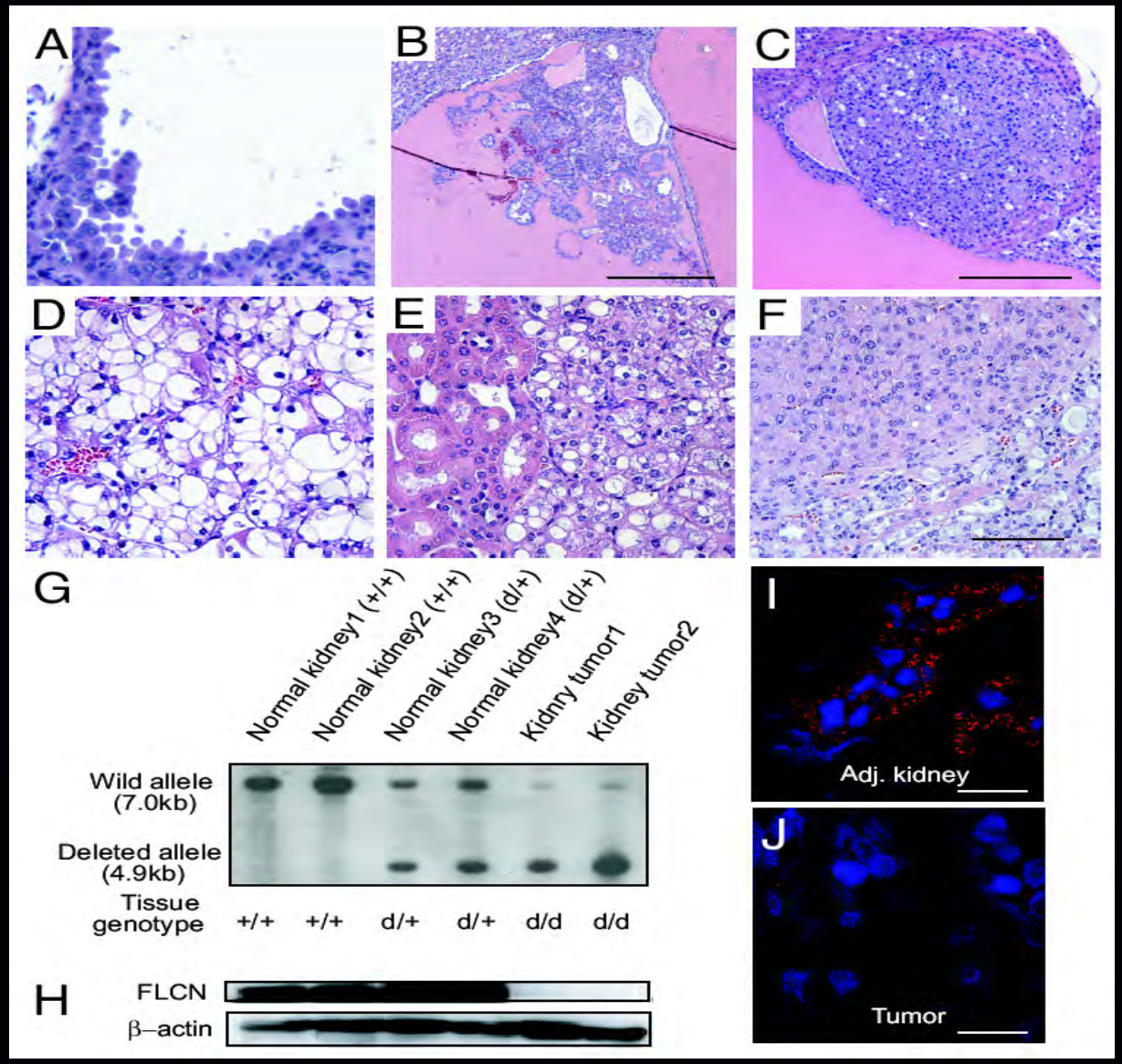
PNAS 106:2009
PNAS 103:2006

Tumors from *BHD*$^{d/+}$ mice show histology and LOH at *BHD* locus similar to human BHD tumors

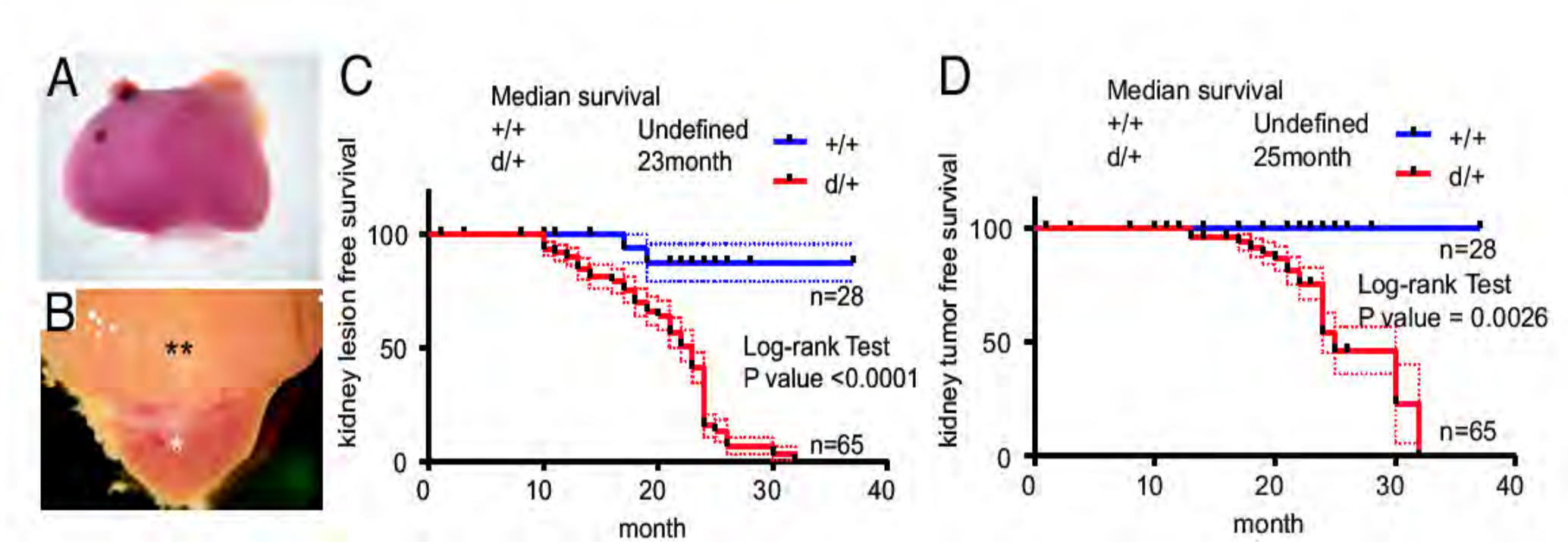
Clear cell, oncocytic hybrid and oncocytoma histology

Southern blot shows loss of *BHD* wt allele

WB & Duolink immunostaining show loss of FLCN expression

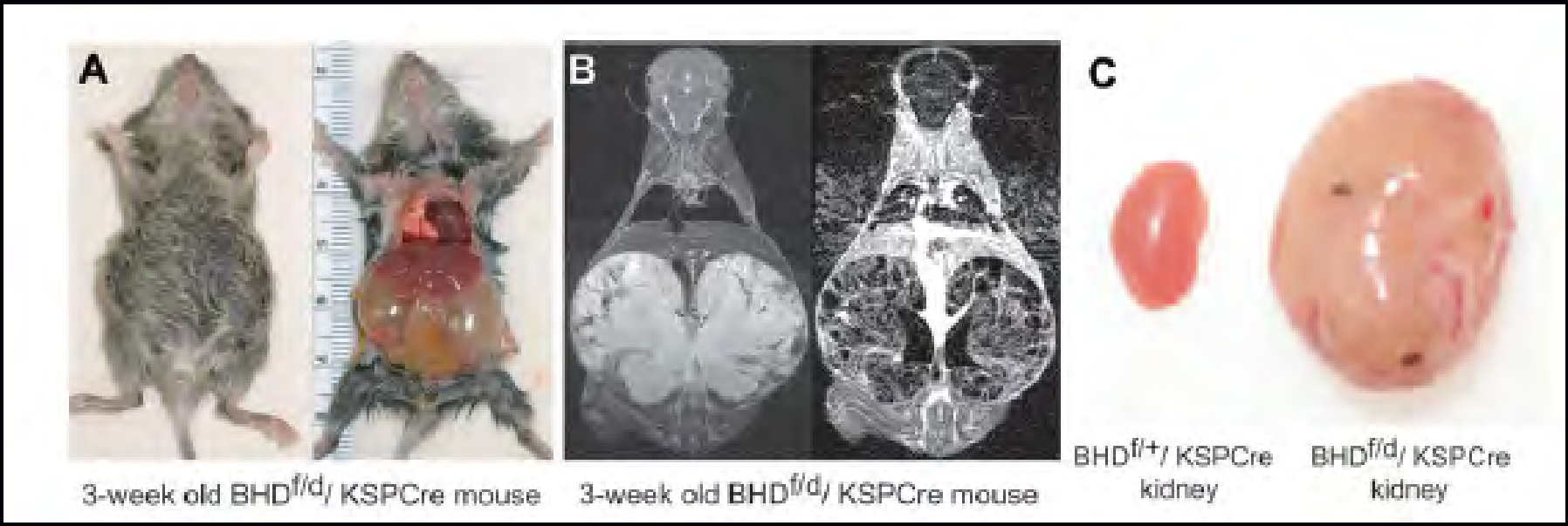


Tumor development in a *BHD* heterozygous null mouse model



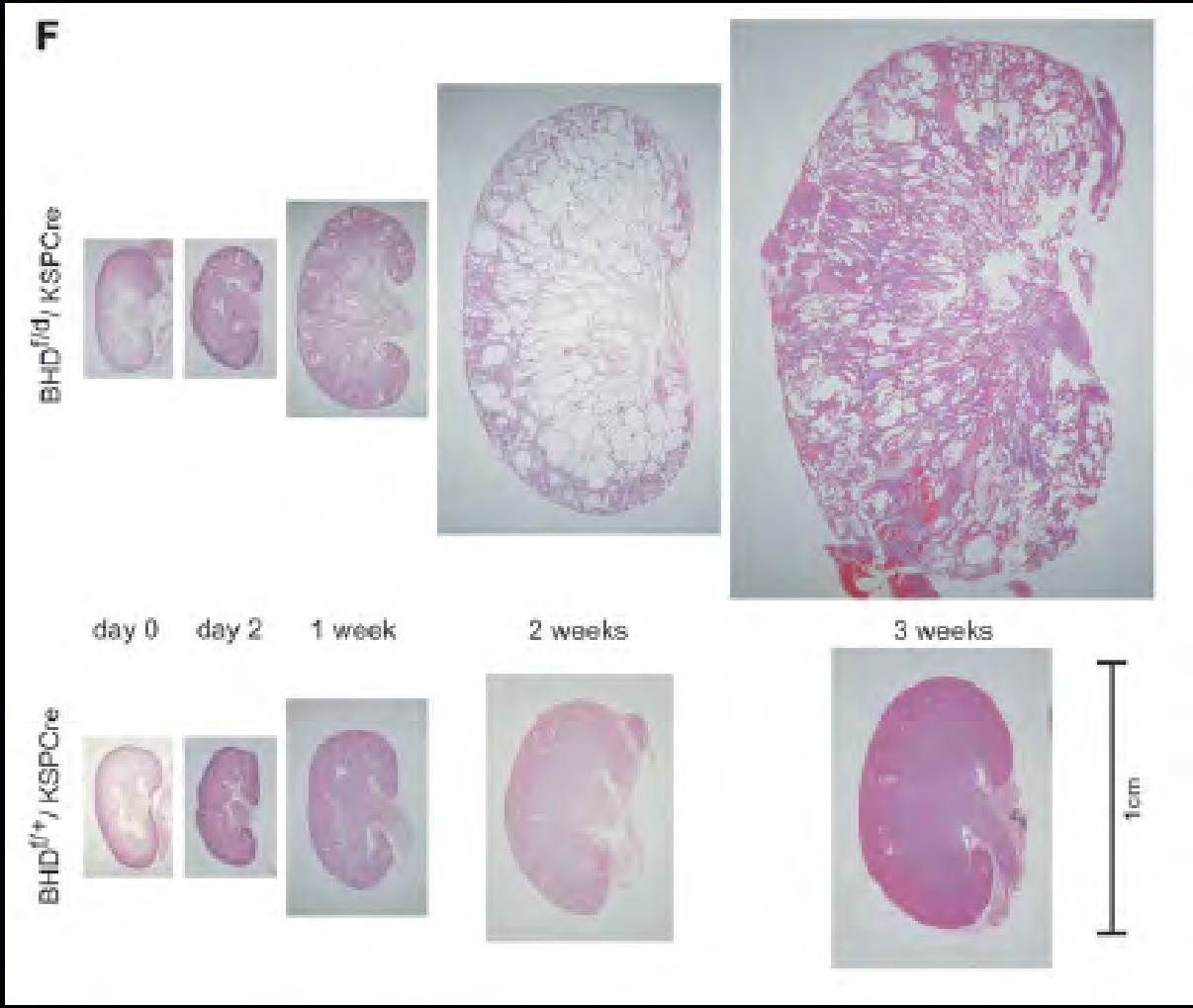
Aged *BHD*$^{d/+}$ mice develop renal tumors by 24 months

BHD Deletion Specifically in the Kidney



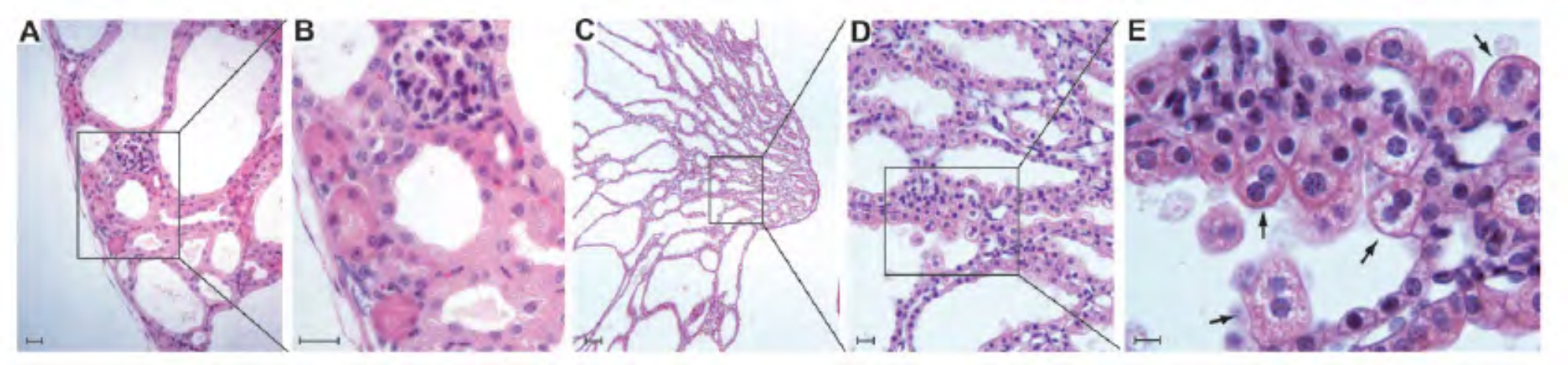
Baba, *JNCI* 100:2008

BHDf/d/KSPCre Mouse Kidney Histology



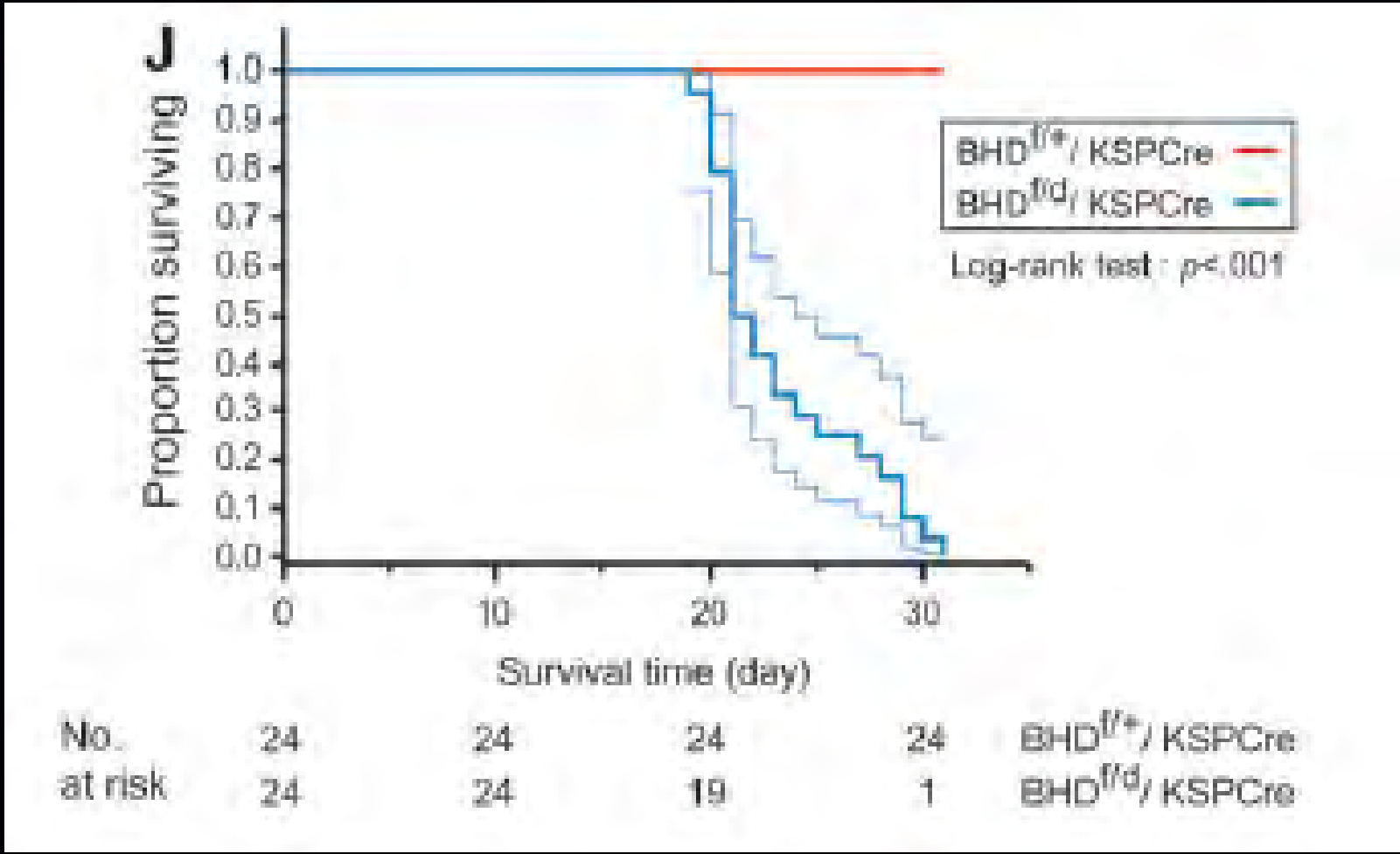
Baba, *JNCI* 100:2008

BHD$^{f/d}$/KSPCre Mouse Microscopic Kidney Histology



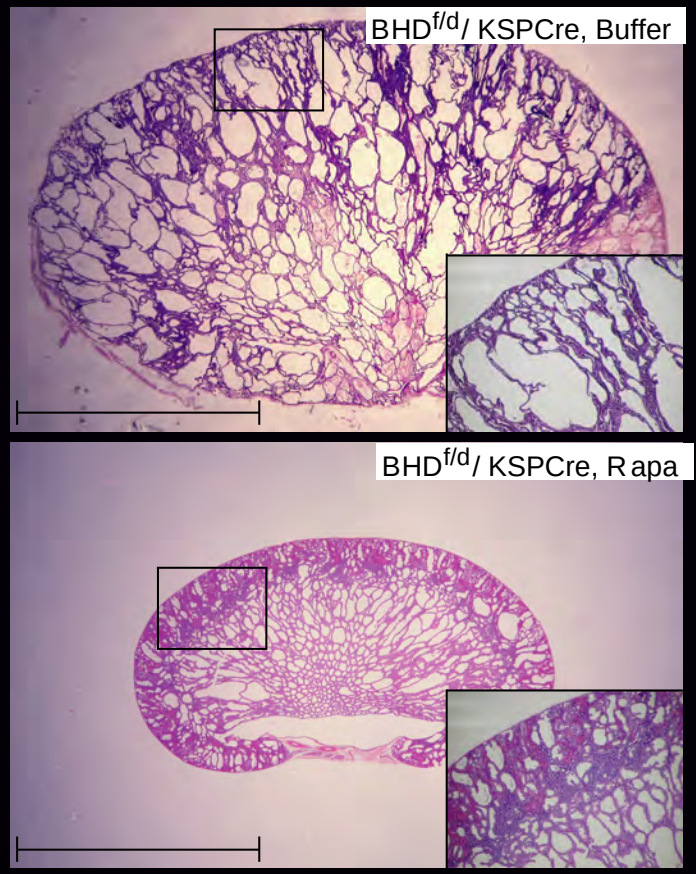
Baba, *JNCI* 100:2008

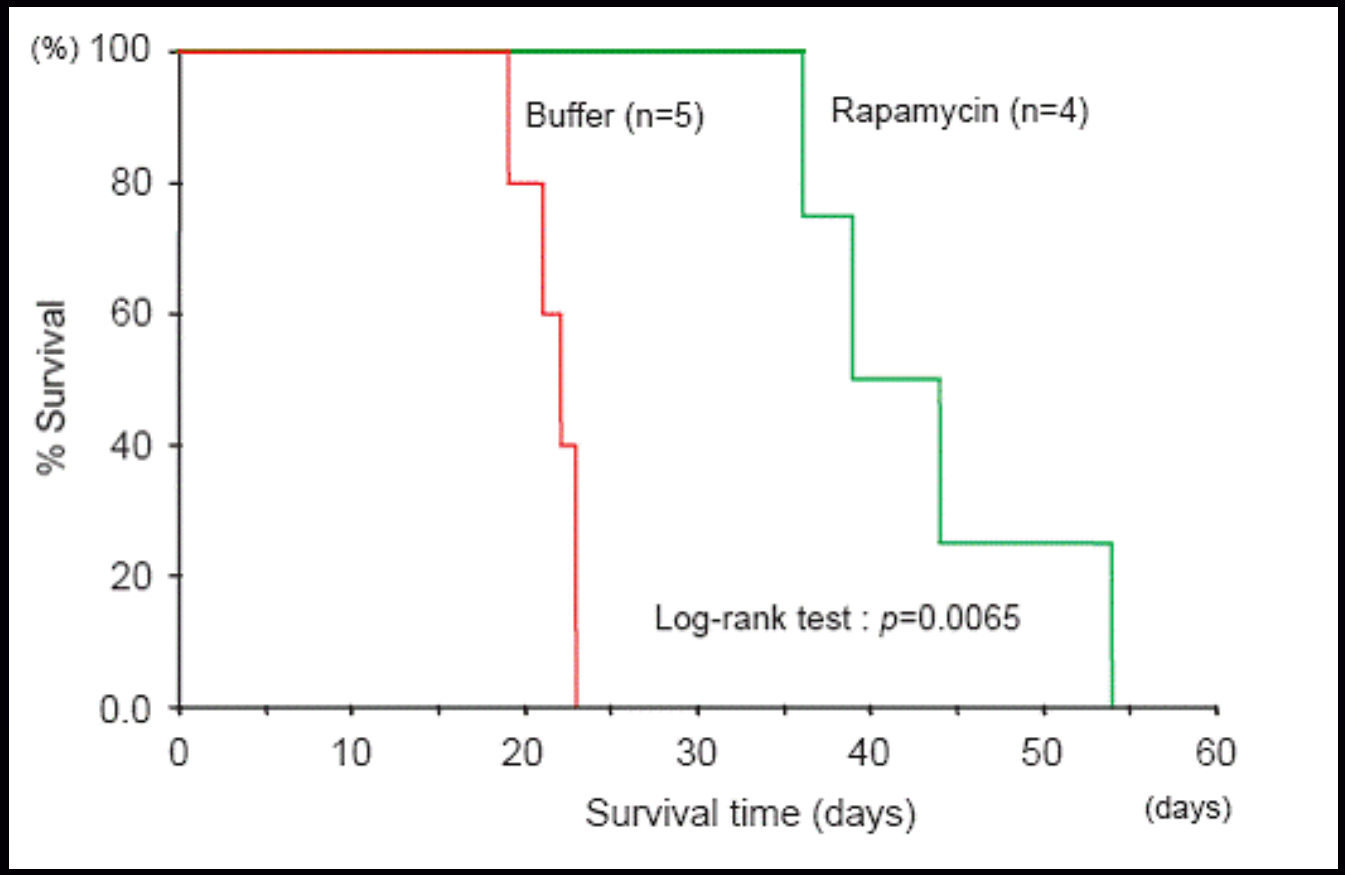
BHD Deletion Specifically in the Kidney



Baba, *JNCI* 100:2008

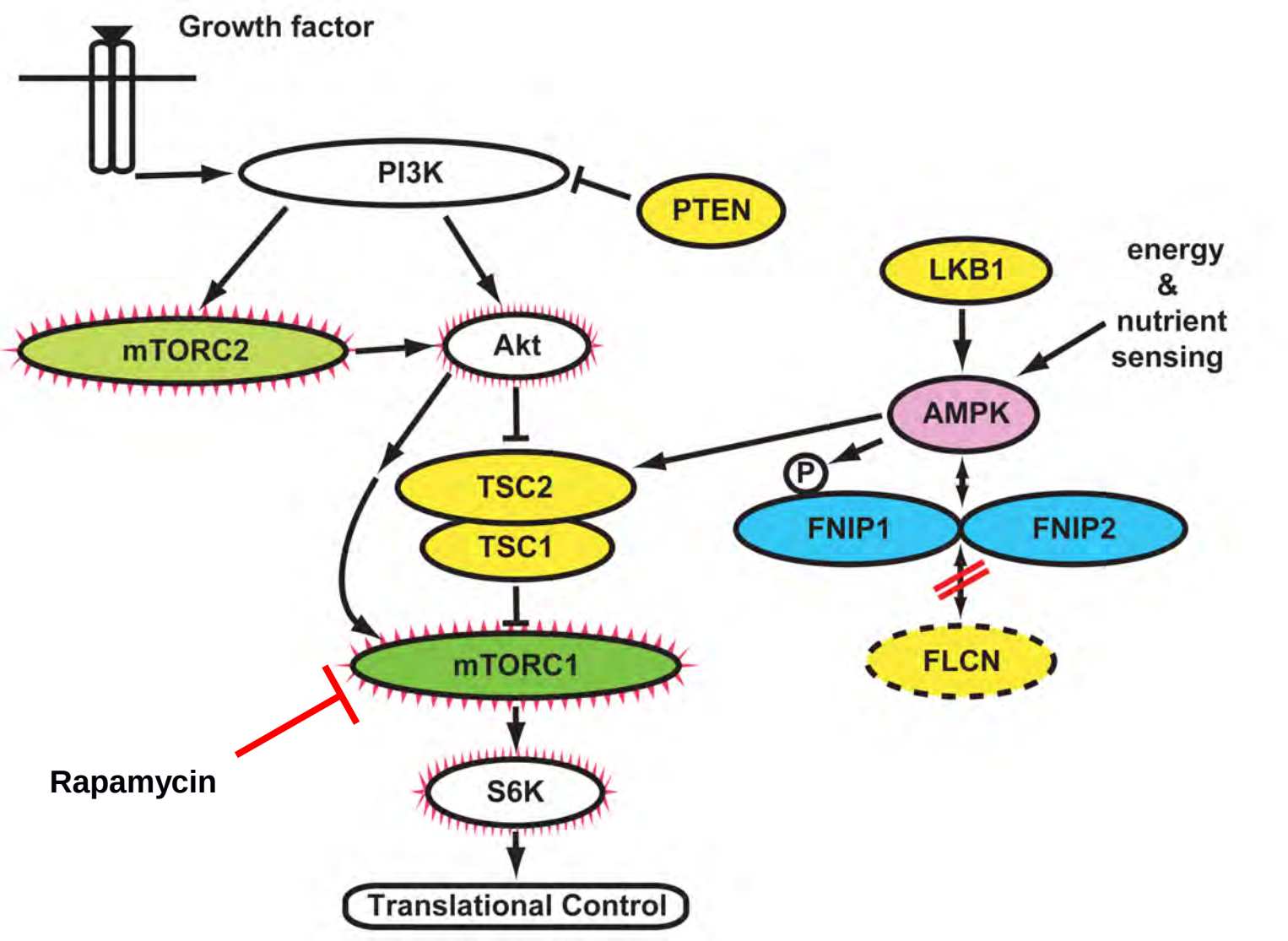
BHD Flox/Delete KspCre
Renal Phenotype & Survival +/- Rapamycin





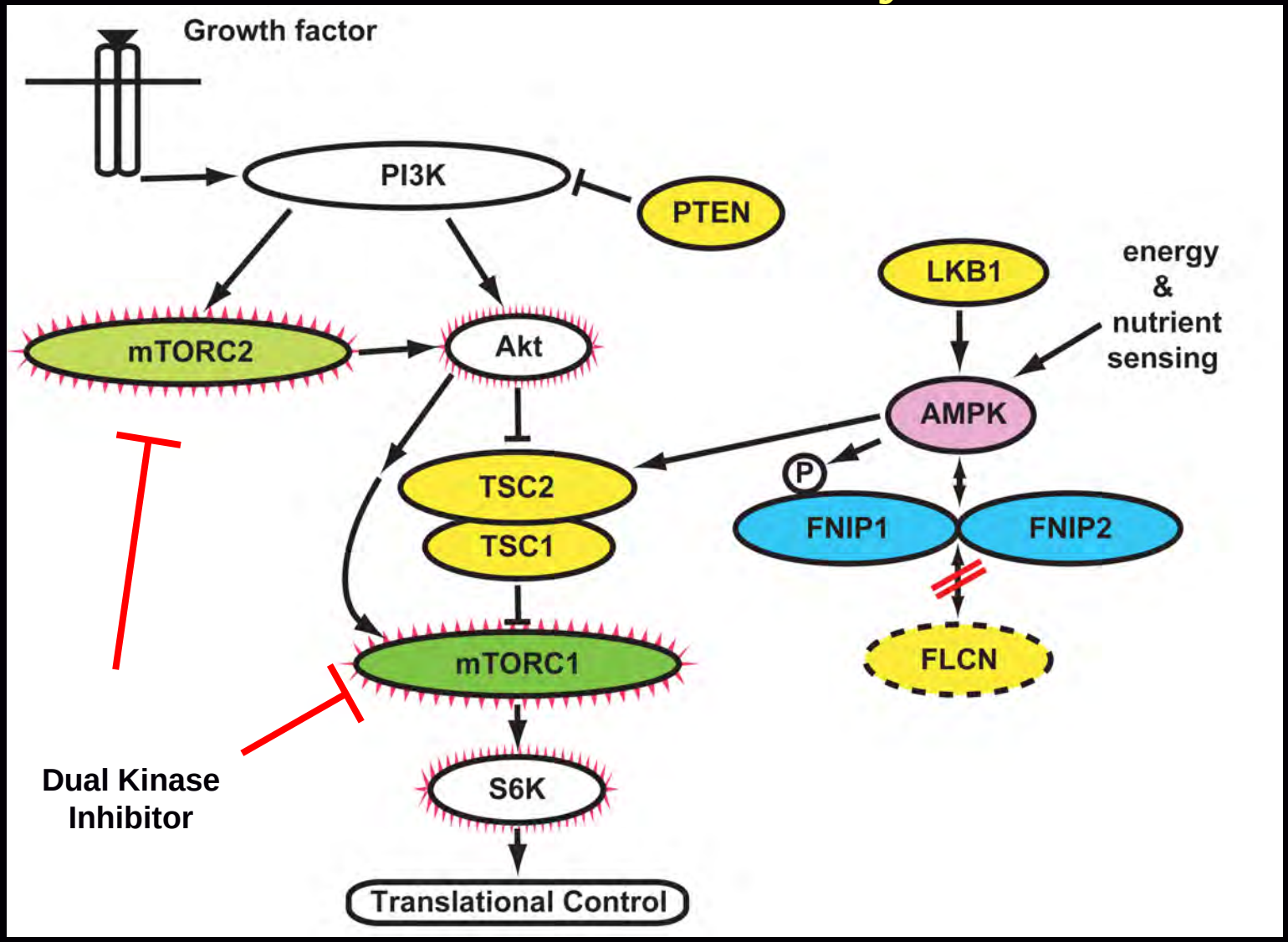
Baba, *JNCI* 100:2008

mTORC1/mTORC2 Activation: FLCN-Deficient Kidney Cancer



JNCI 100:2008

mTORC1/mTORC2 Activation: FLCN-Deficient Kidney Cancer



In preparation

HLRCC Kidney Cancer

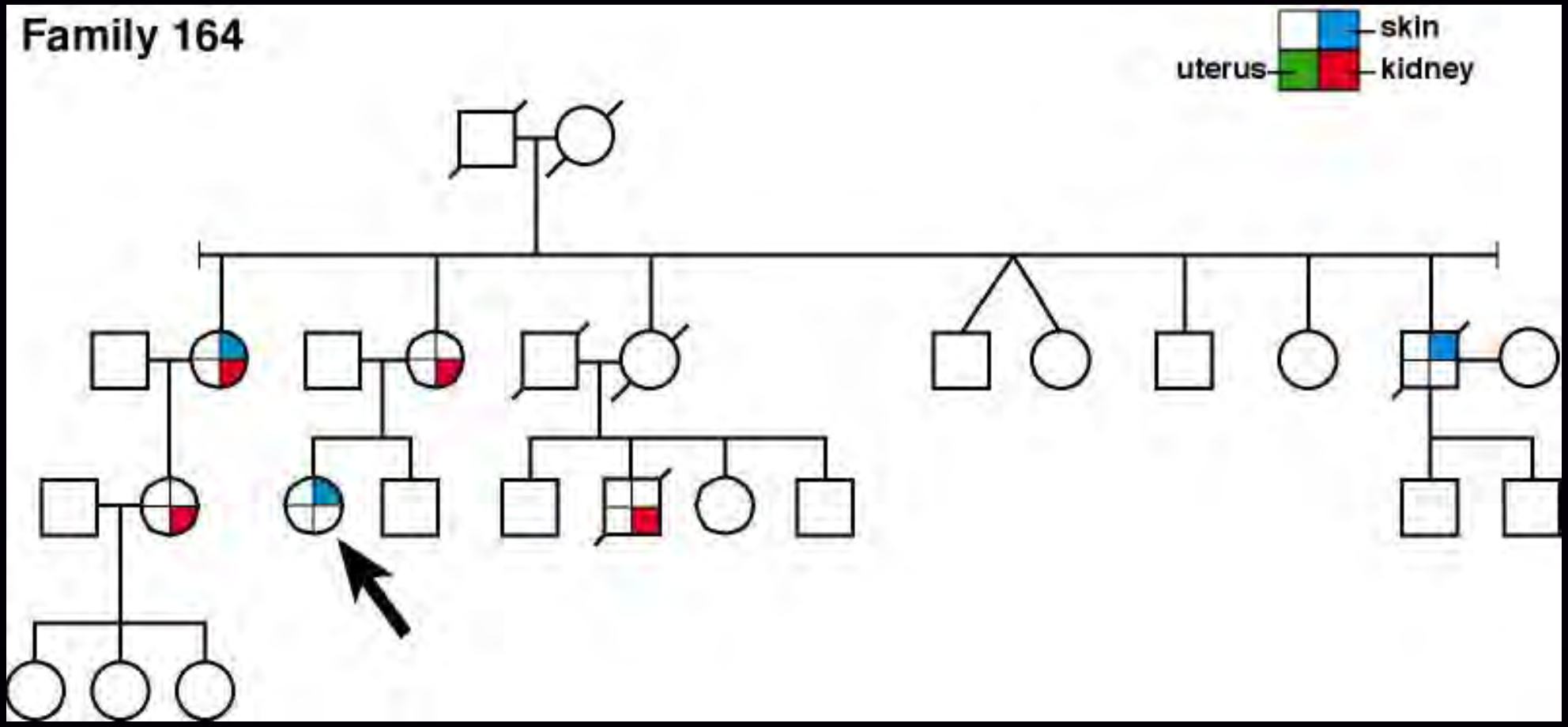
18 y.o.
Female

Germline FH Mutation: c.240dupA, NT 110, p.Ile81AspfsX14 , AA# 38, Exon 1, Frameshift

Hereditary Leiomyomatosis Renal Cell Carcinoma: HLRCC

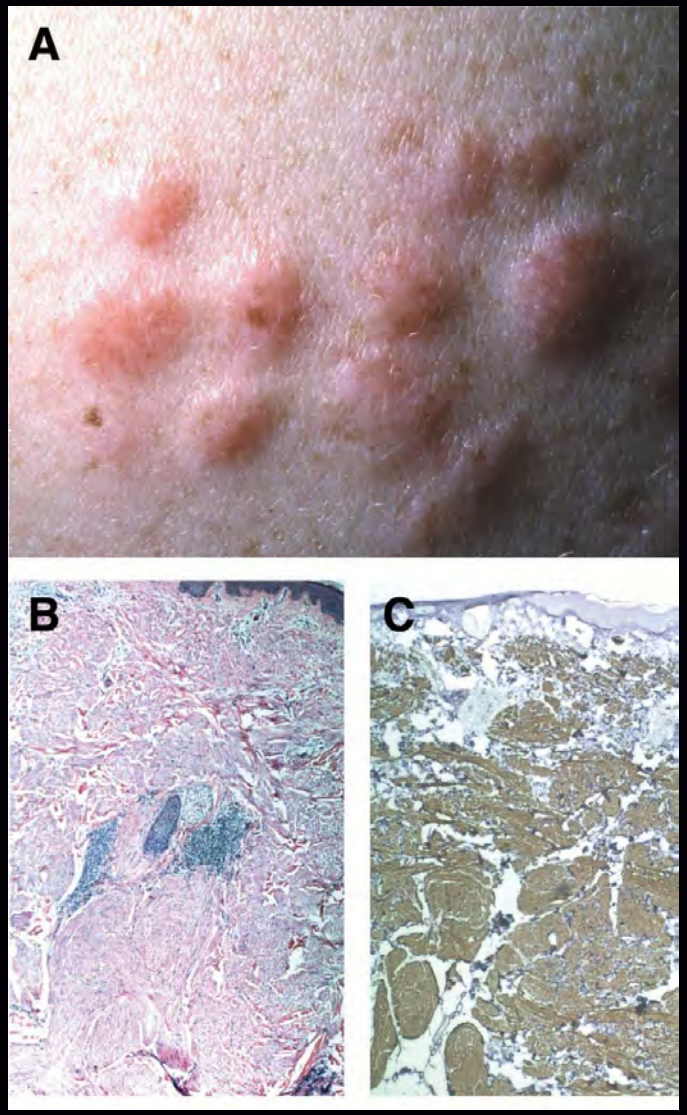
- Cutaneous leiomyomas
- Uterine leiomyomas (fibroids)
- Renal cell carcinoma

HLRCC Kindred



J Urol:153 1995

HLRCC: Cutaneous Manifestations

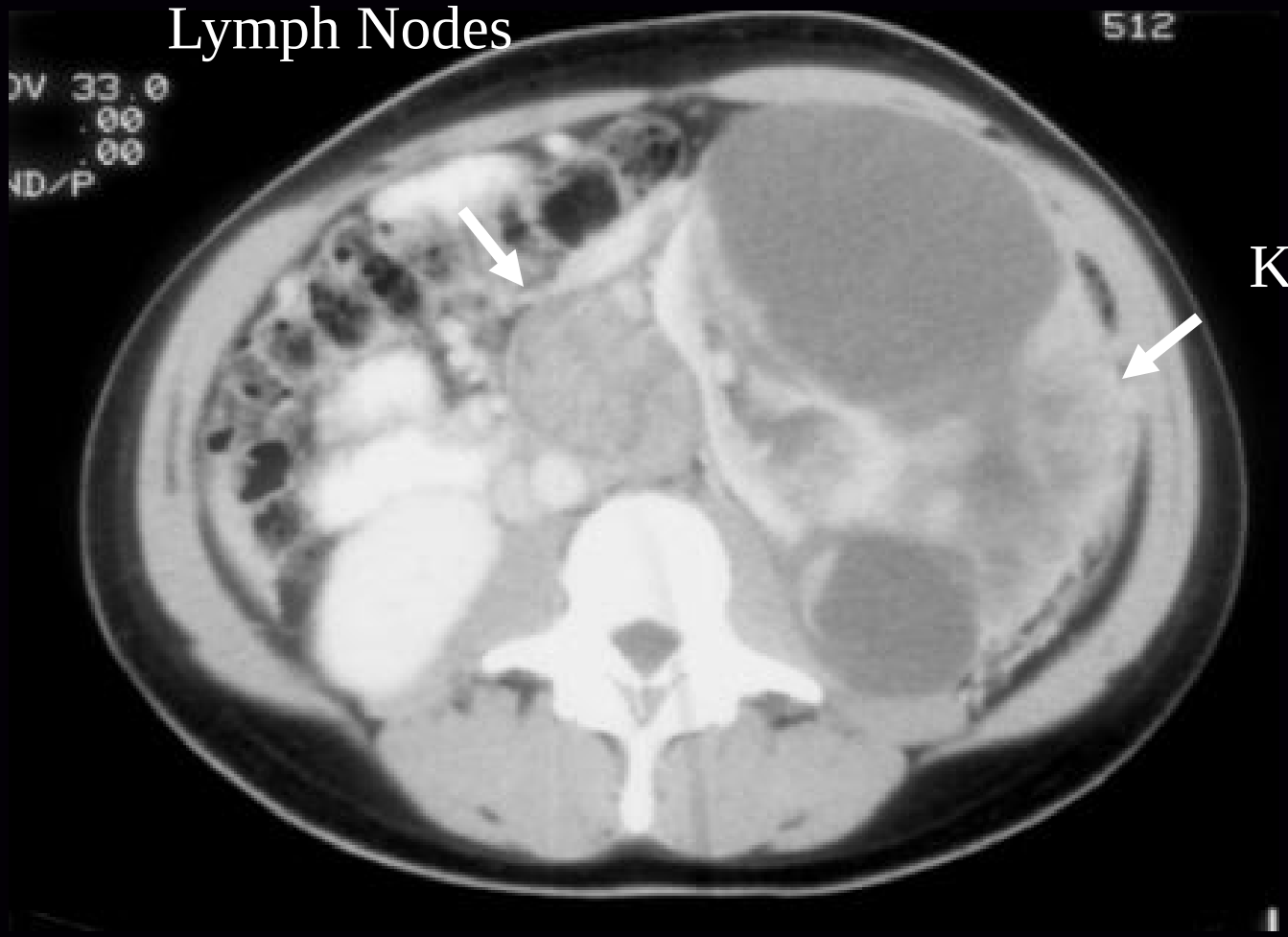


HLRCC: Cutaneous Manifestations

HLRCC: Uterine leiomyomas

Am J Hum Genet 71:2003

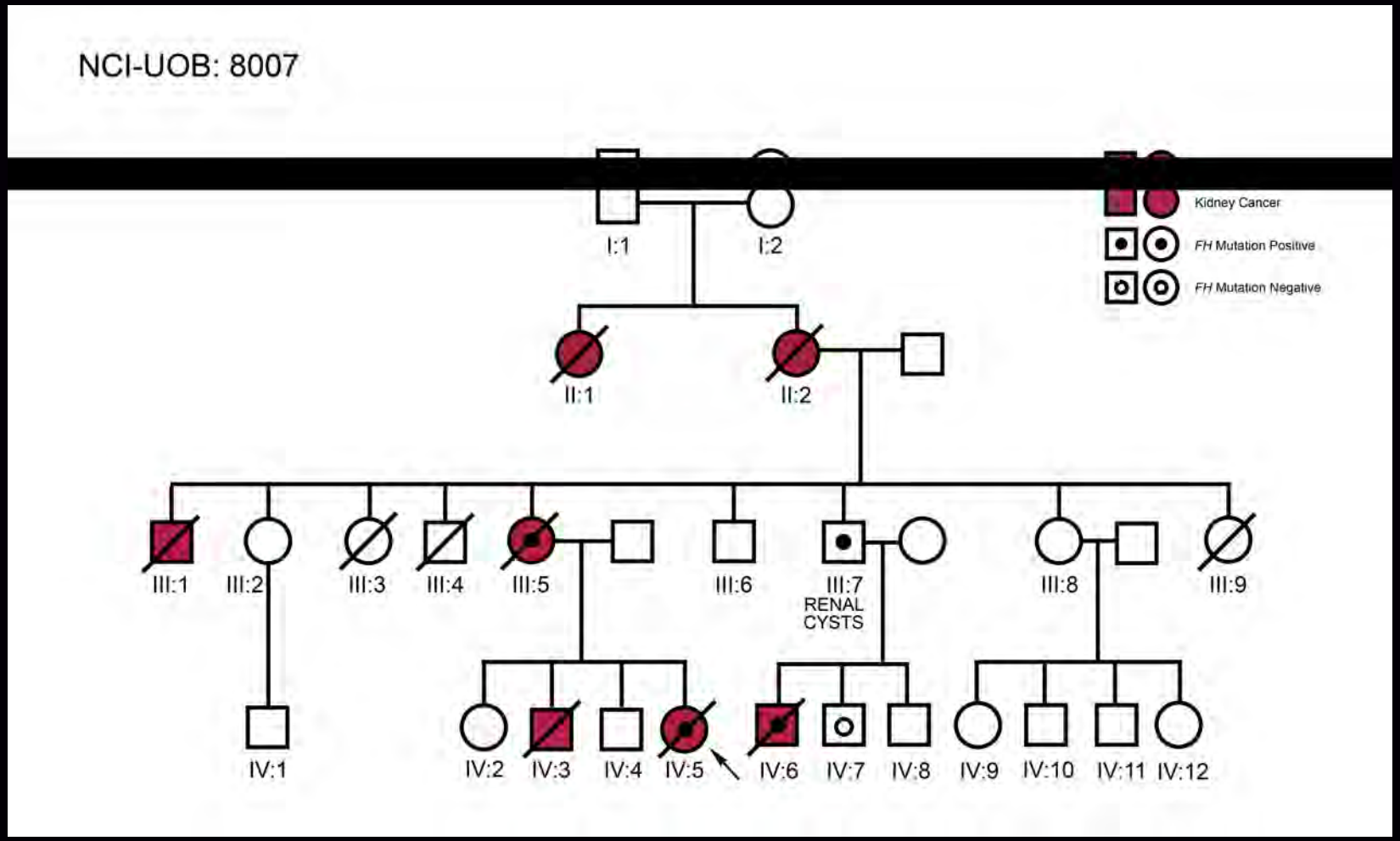
HLRCC Kidney Cancer



18 y.o.
Female

Germline FH Mutation: c.240dupA, NT 110, p.Ile81AspfsX14 , AA# 38, Exon 1, Frameshift

HLRCC Kidney Cancer



Germline FH Mutation: c.240dupA, NT 110, p.Ile81AspfsX14 , AA# 38, Exon 1, Frameshift

HLRCC Kidney Cancer
21 Year Old Male

HLRCC Patient

32 Year Old Male

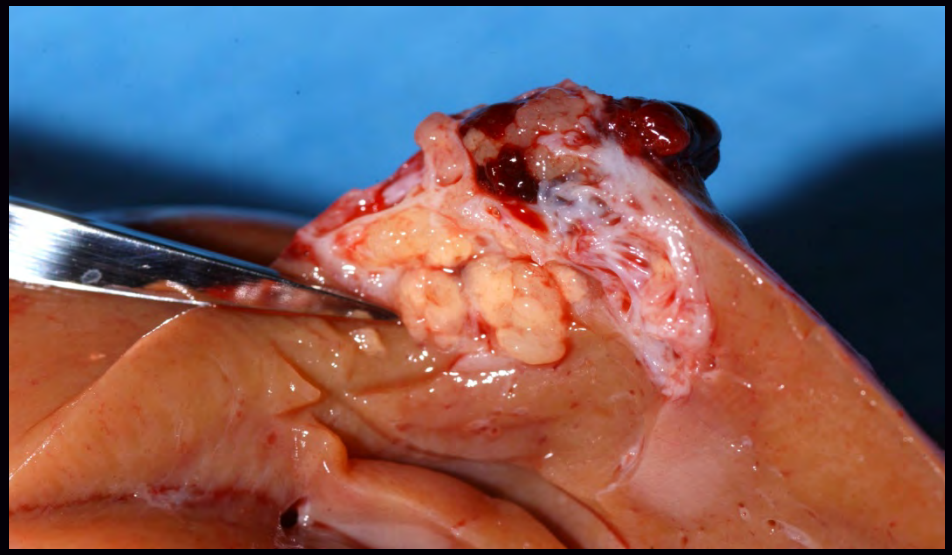
J Urol:177 2007

HLRCC Renal Mass
2/22/02

2.5 Cm Renal Cyst

HLRCC Renal Mass
2/22/02

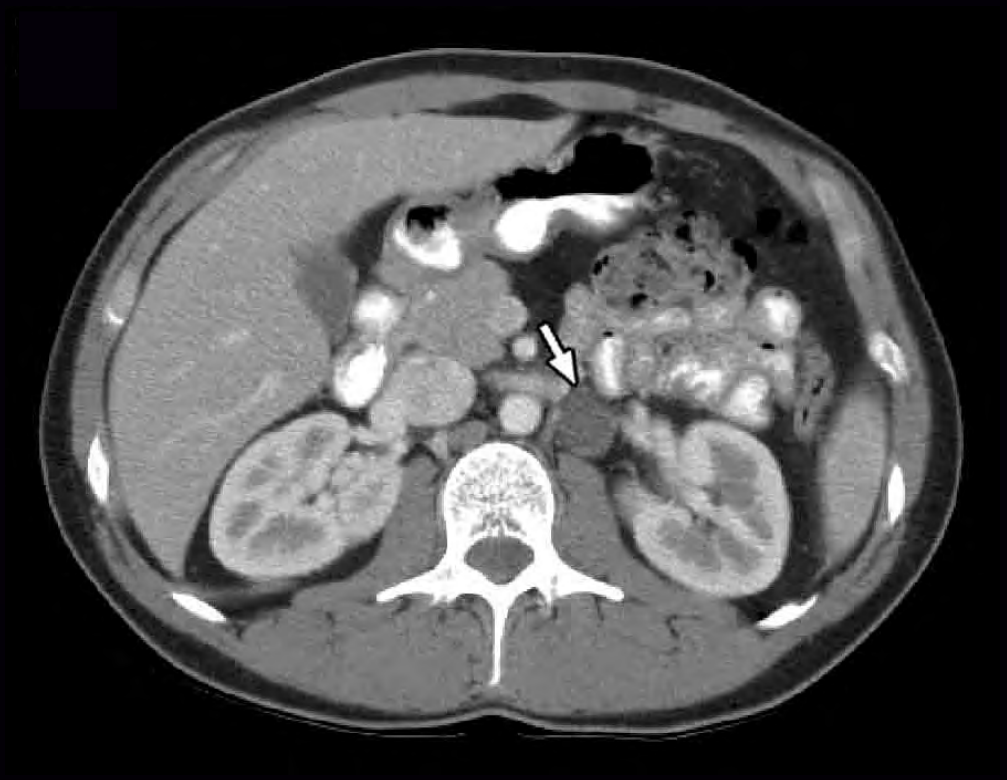
2.5 Cm Renal Cyst



½ cm Renal Tumor

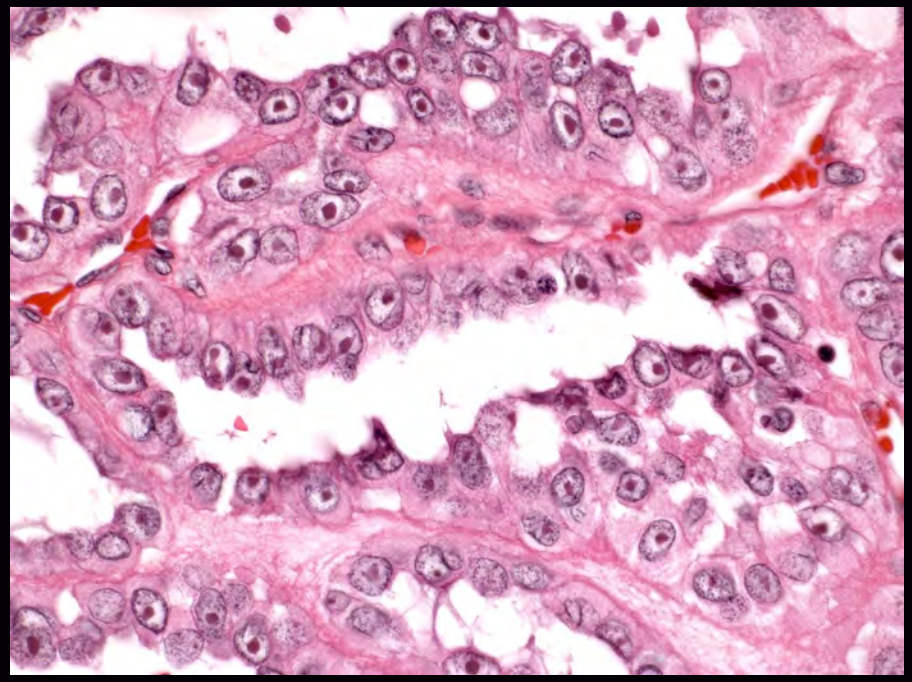
HLRCC Renal Mass
2/22/02

2.5 Cm Renal Cyst

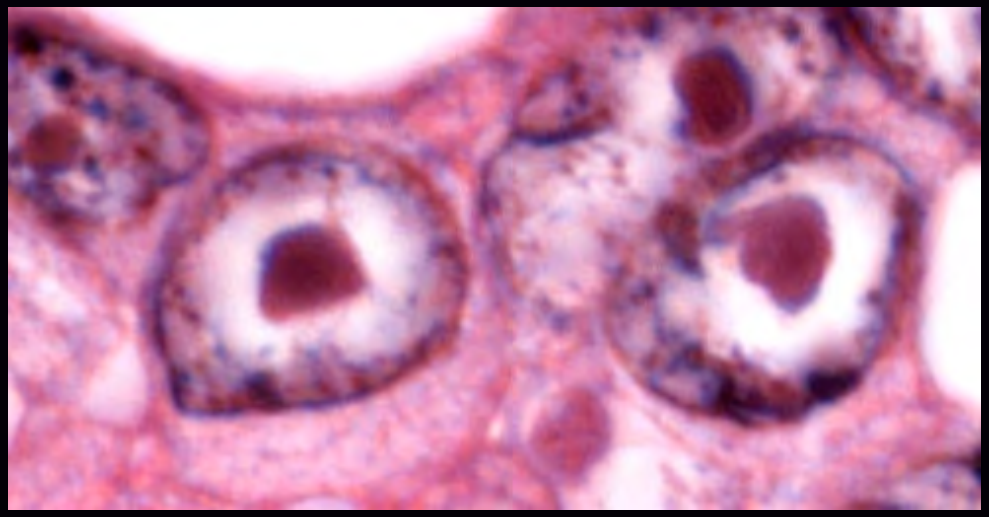


2 cm Hilar Node

HLRCC Kidney Cancer: Orangophilic Nucleoli + Perinucleolar Halos



40X

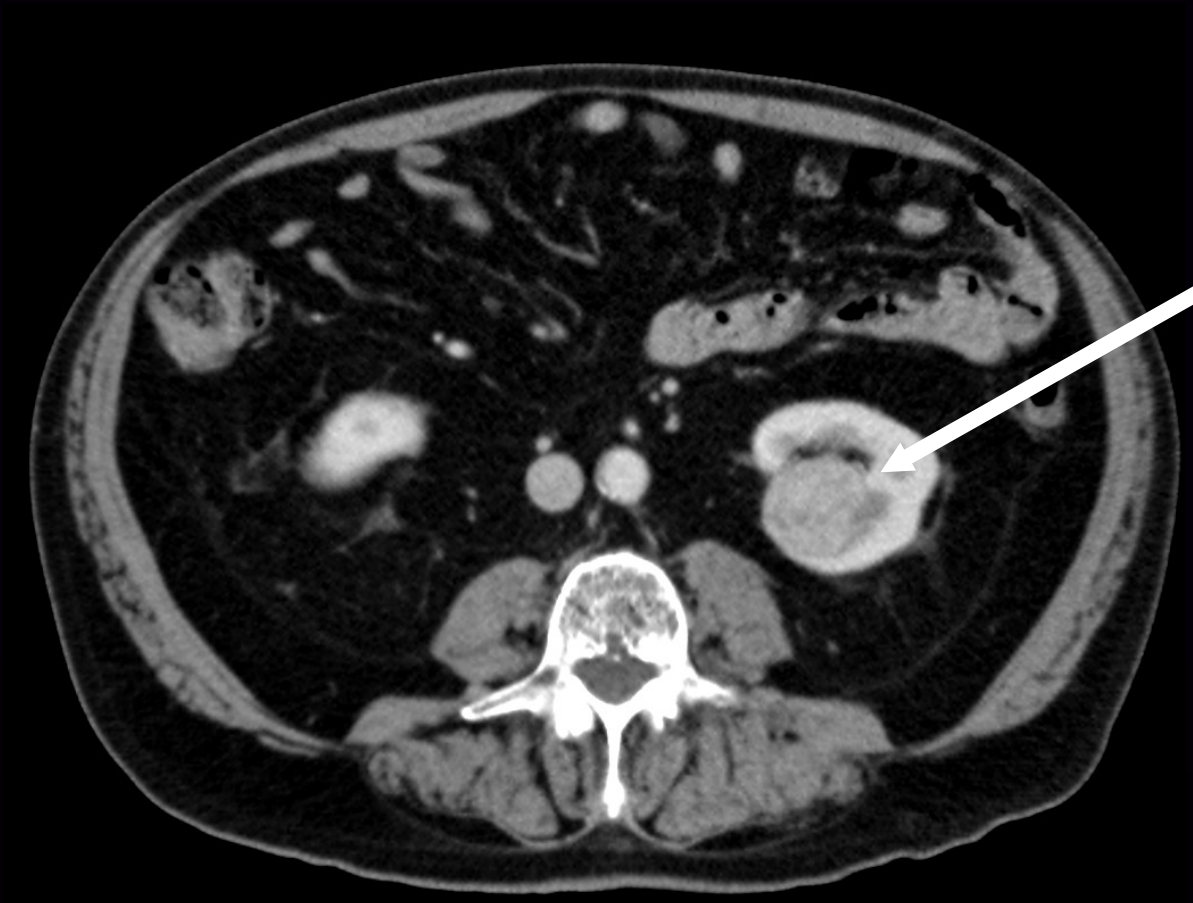


100X

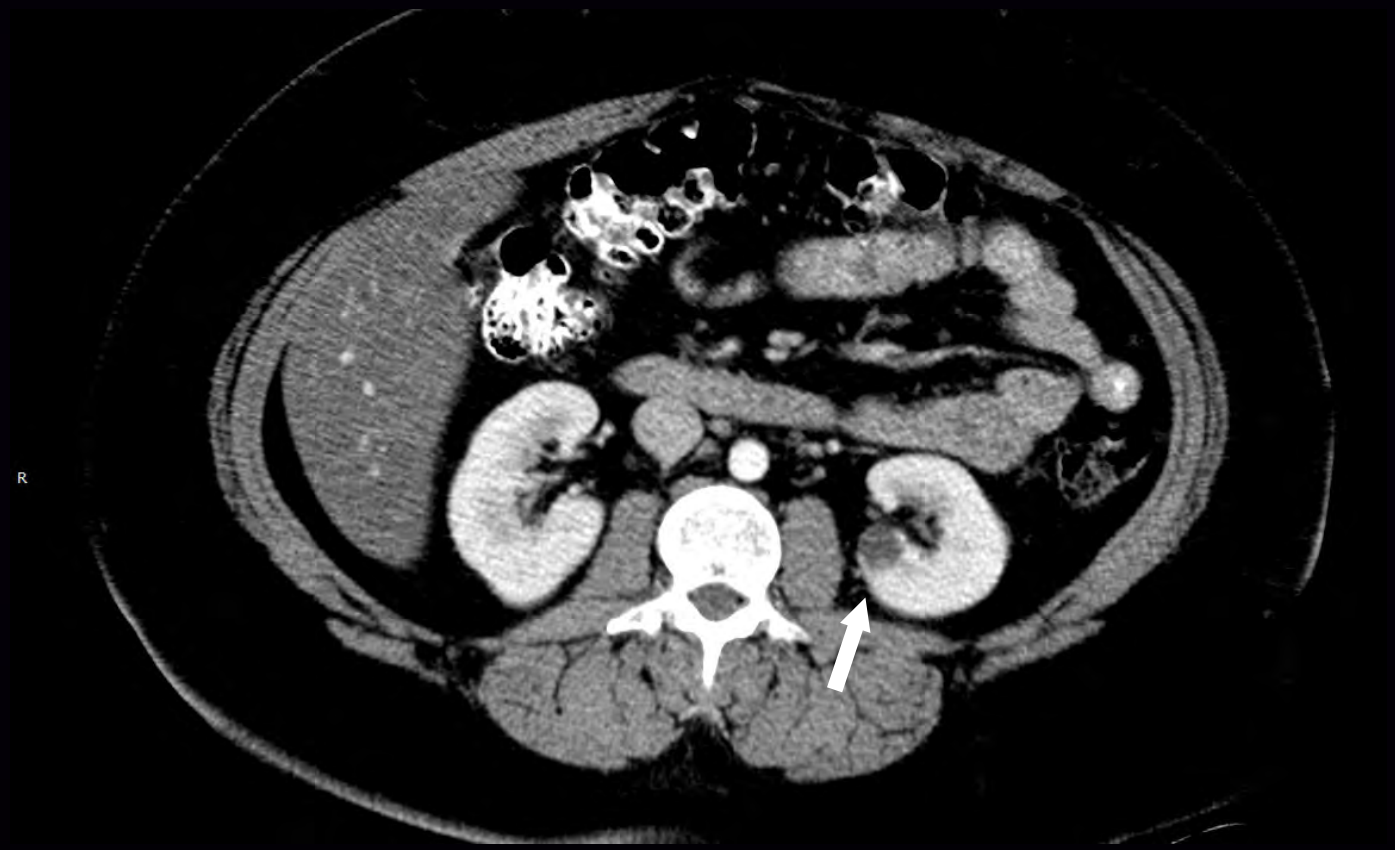
Am J Surg Path 31:2007

HLRCC Kidney Cancer
10 Year Old Female

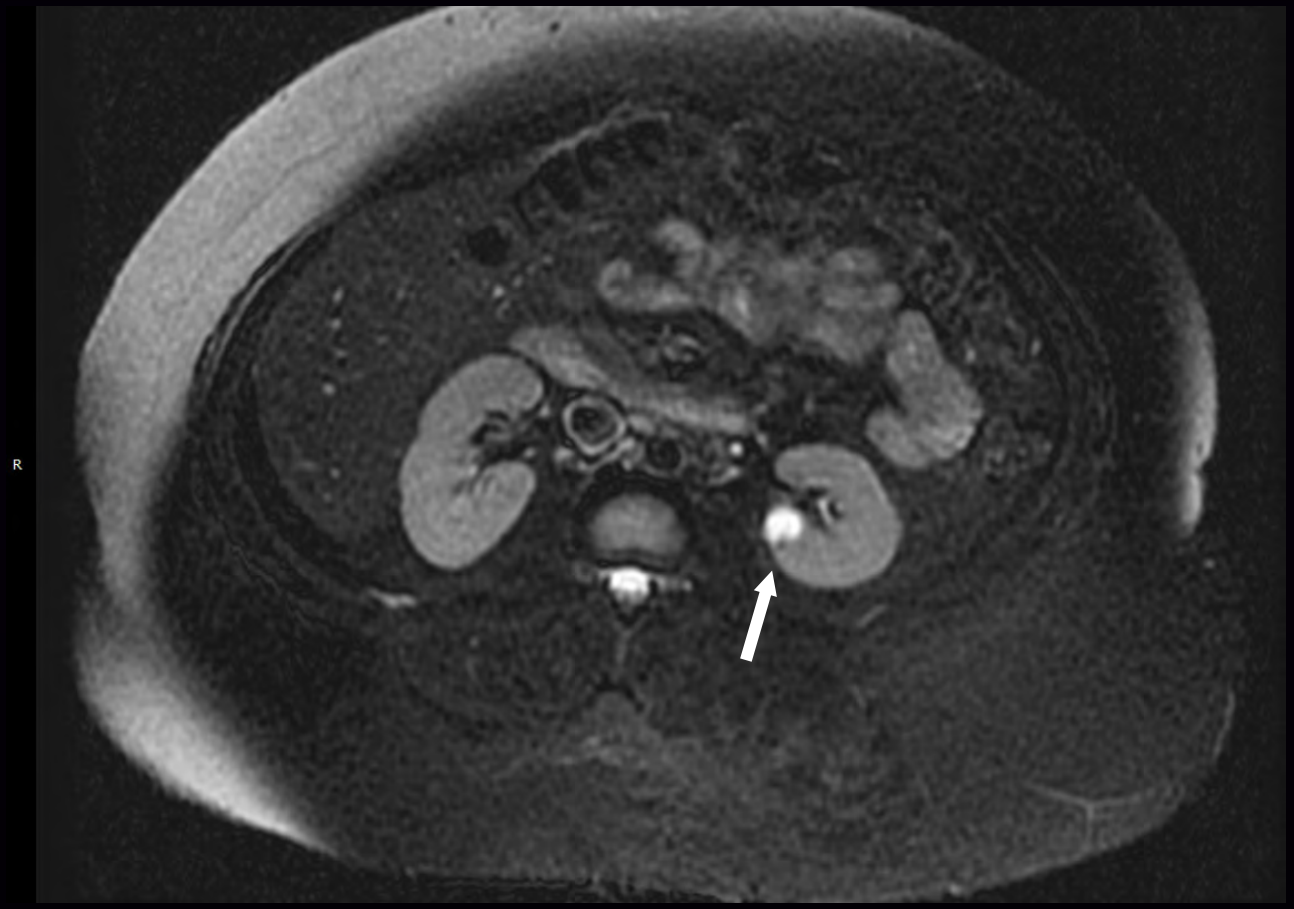
HLRCC Kidney Cancer
77 Year Old Male



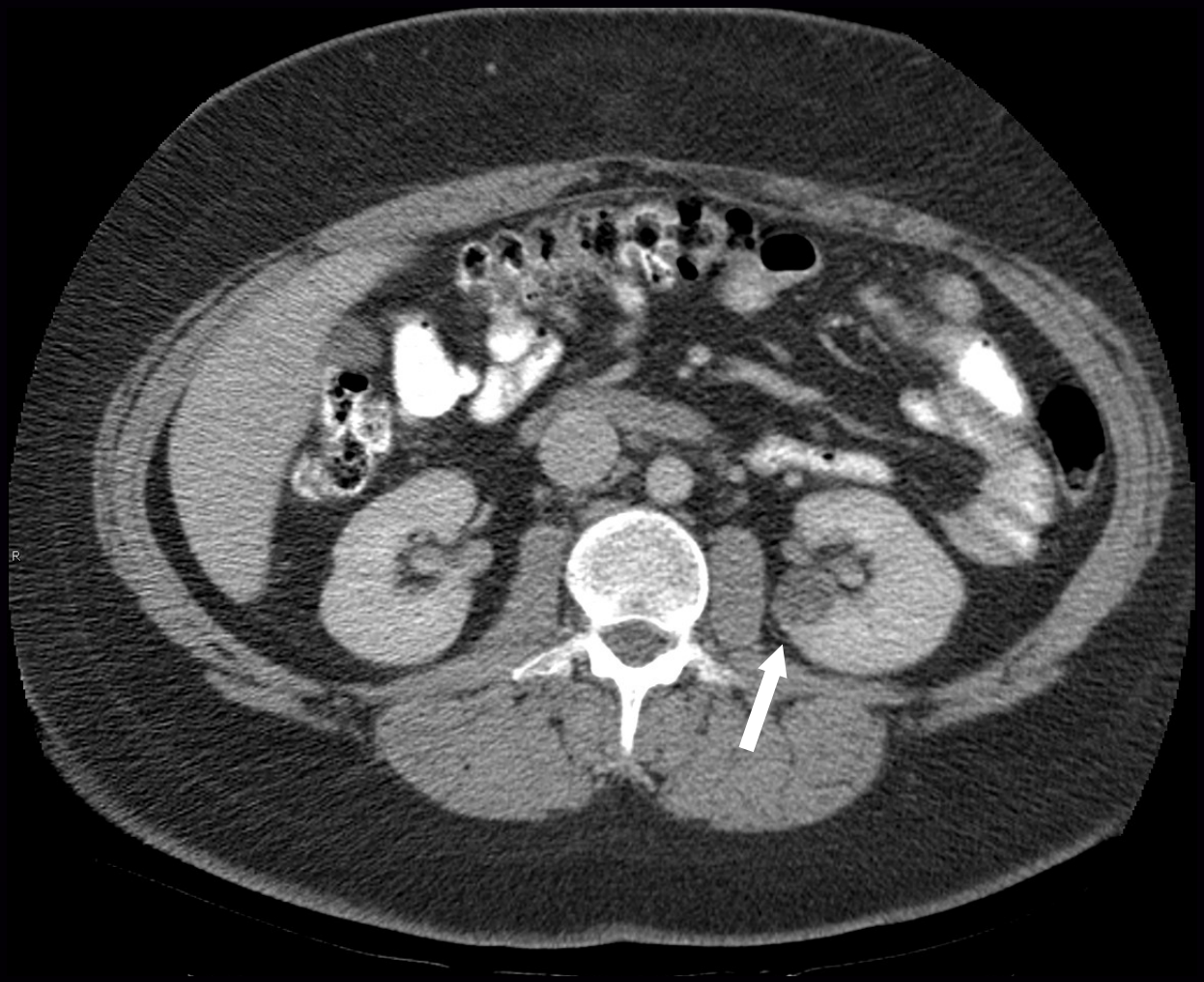
24 Year Old Female HLRCC Patient
4/11/2007



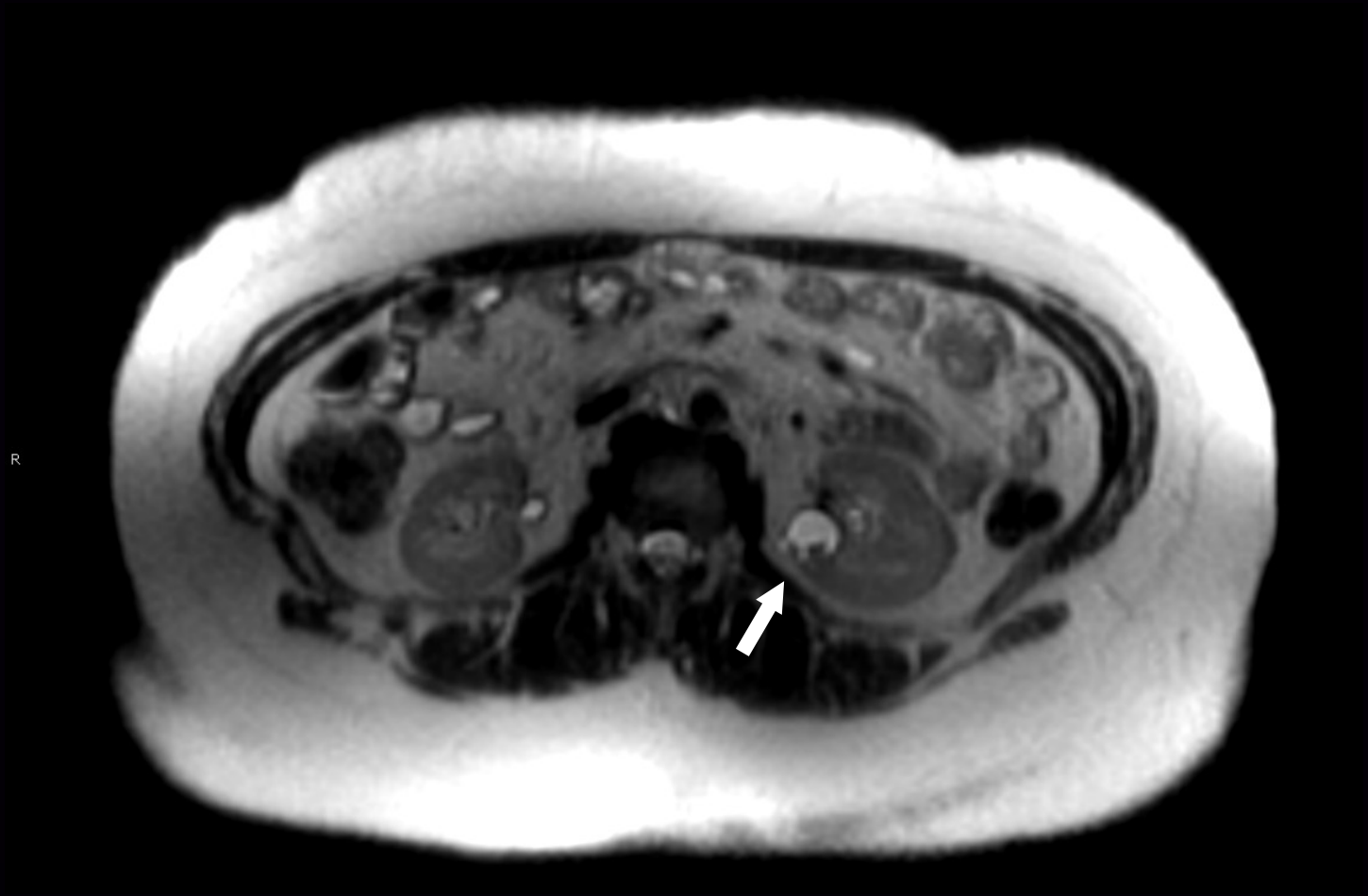
24 Year Old Female HLRCC Patient
07/18/07



24 Year Old Female HLRCC Patient
04/09/08

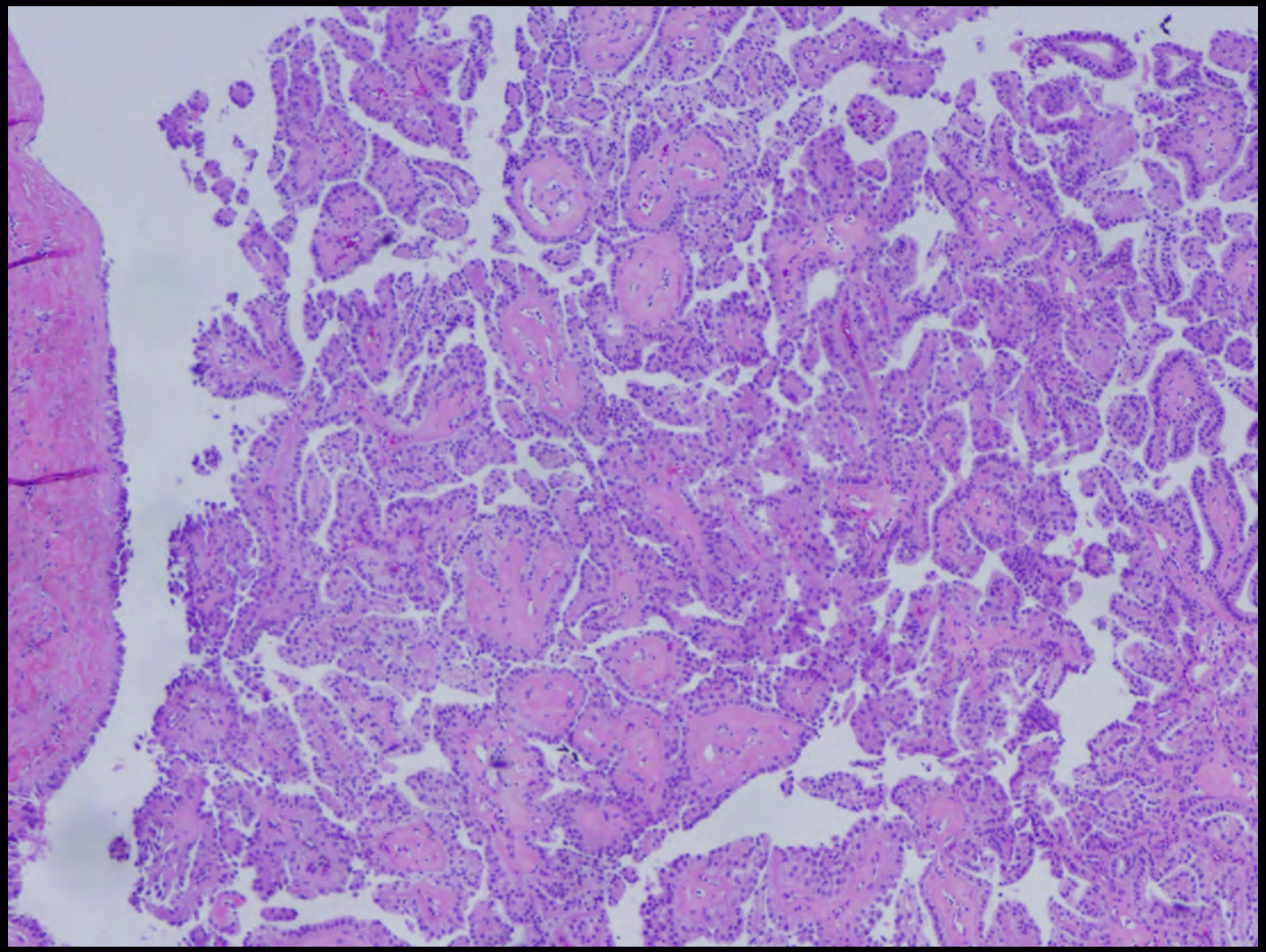


24 Year Old Female HLRCC Patient
04/09/08

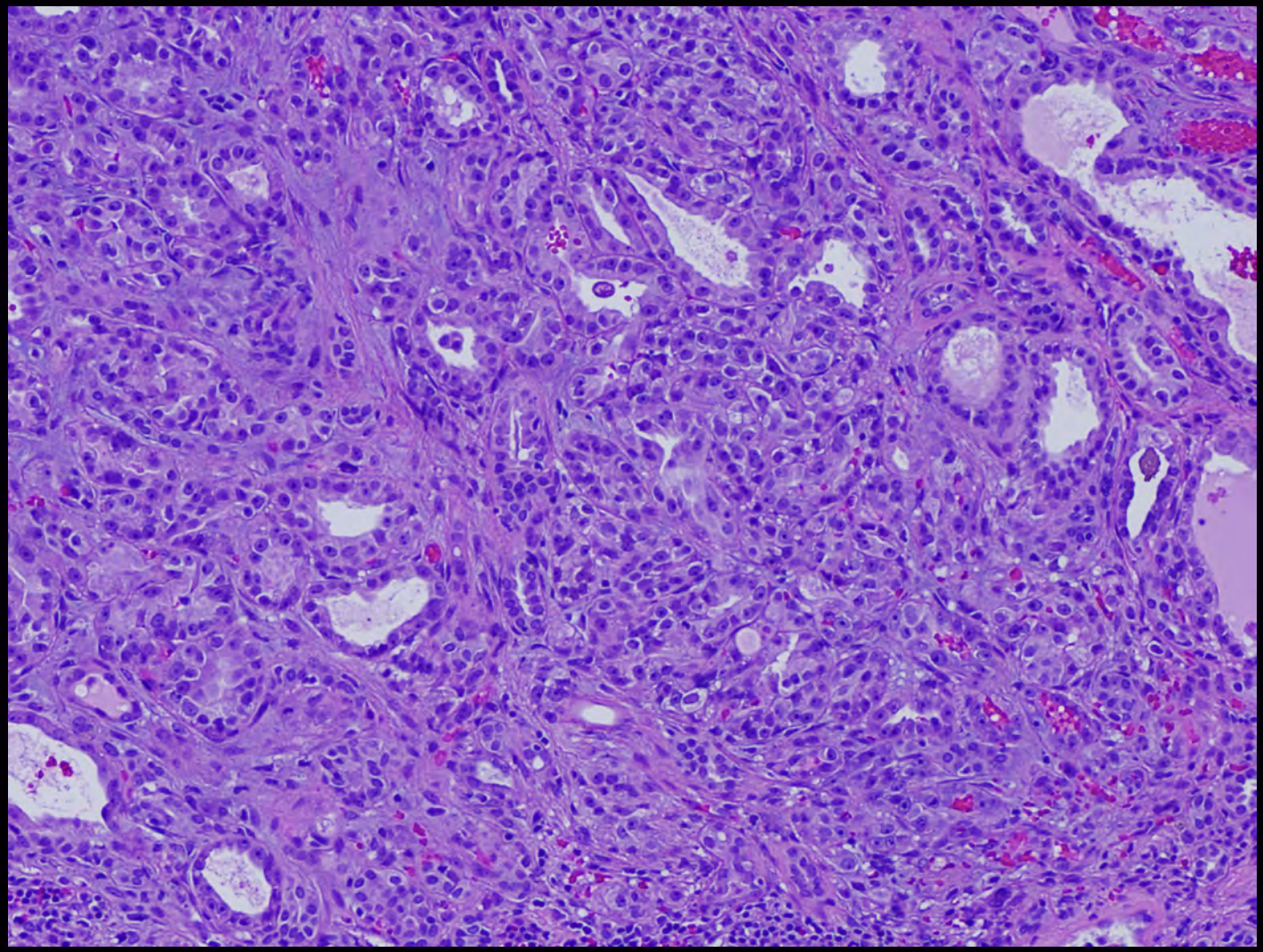


24 Year Old Female HLRCC Patient
04/09/08

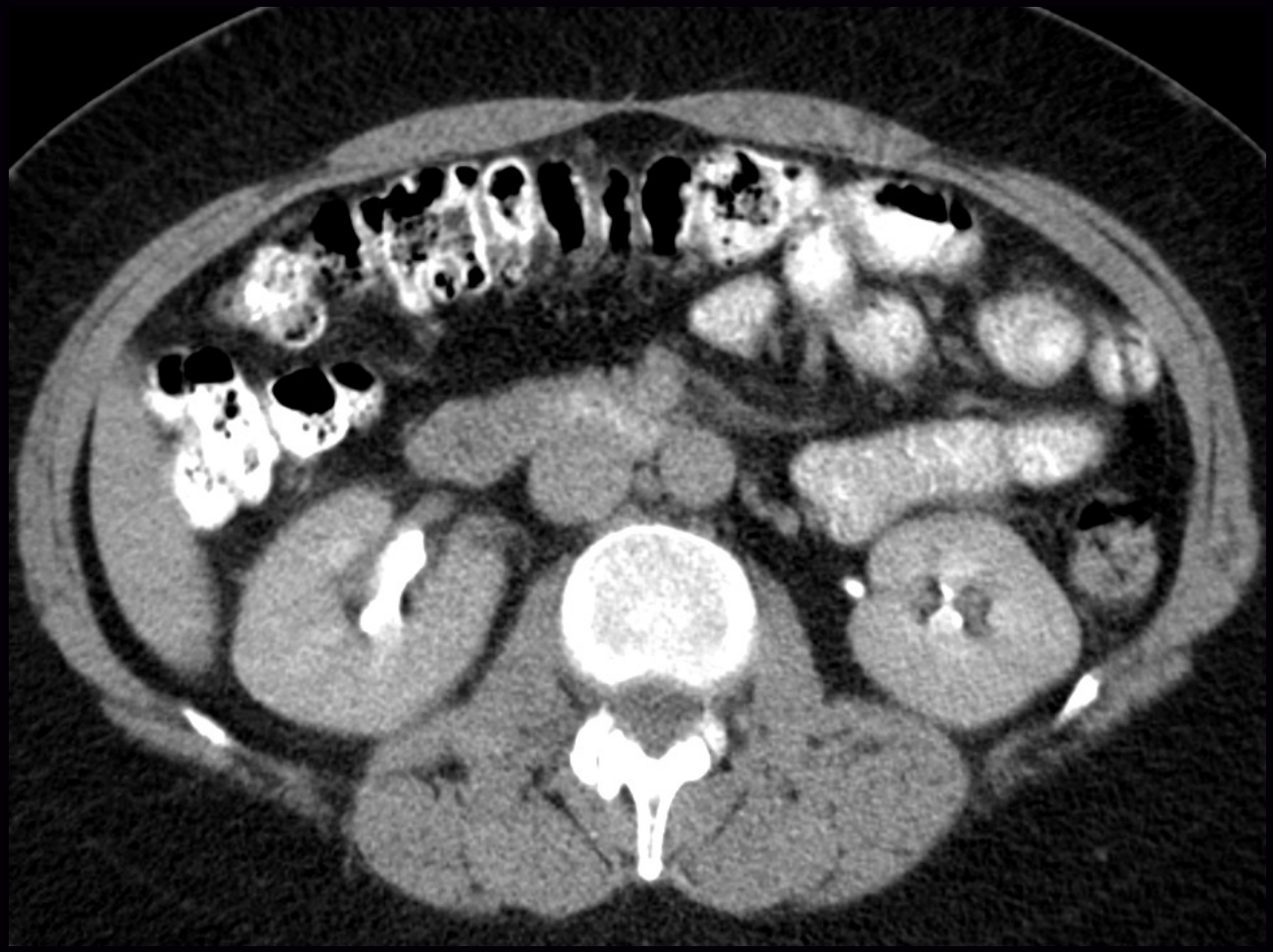
24 Year Old Female HLRCC Patient 06/06/08



24 Year Old Female HLRCC Patient 06/06/08

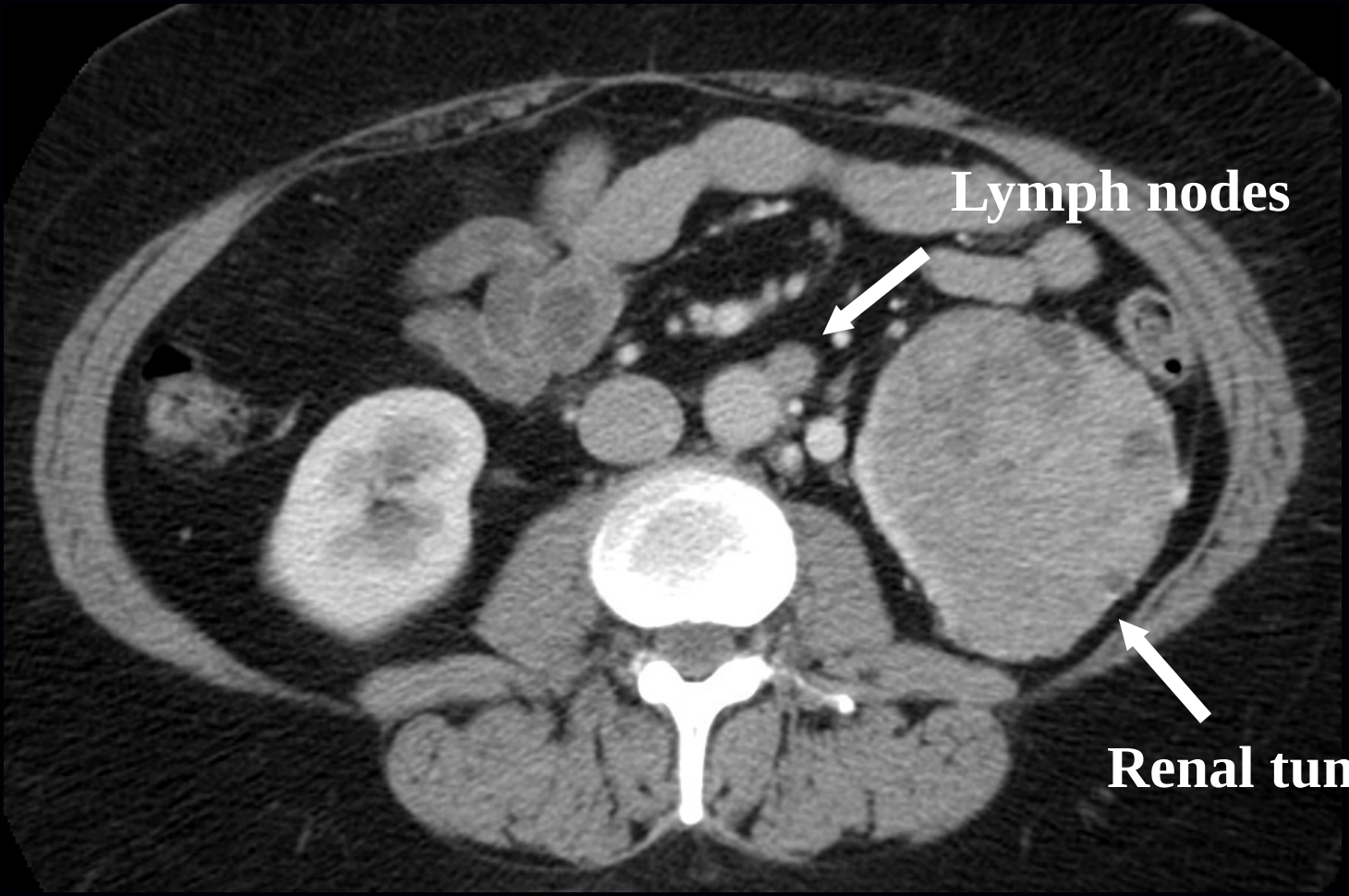


46 Year Old Female HLRCC Patient
September 2006



FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

50 Year Old Female HLRCC Patient
December 2010

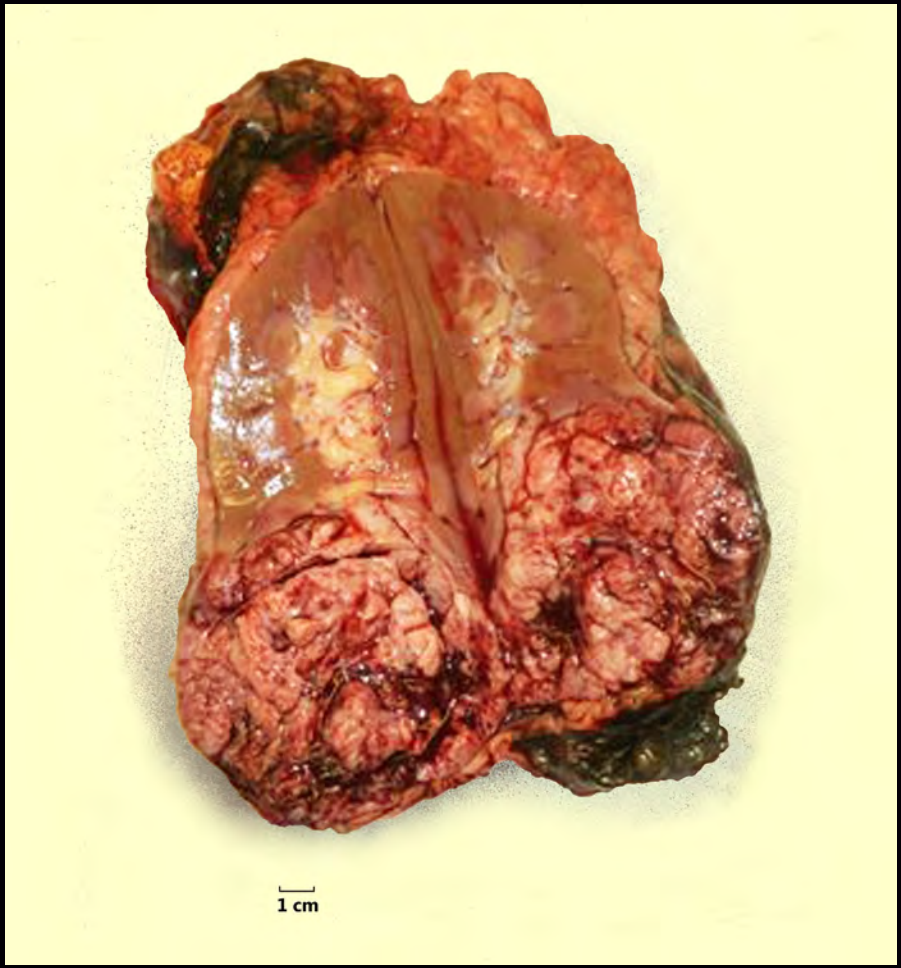


FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

50 Year Old Female HLRCC Patient
December 2010

FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

50 Year Old Female HLRCC Patient

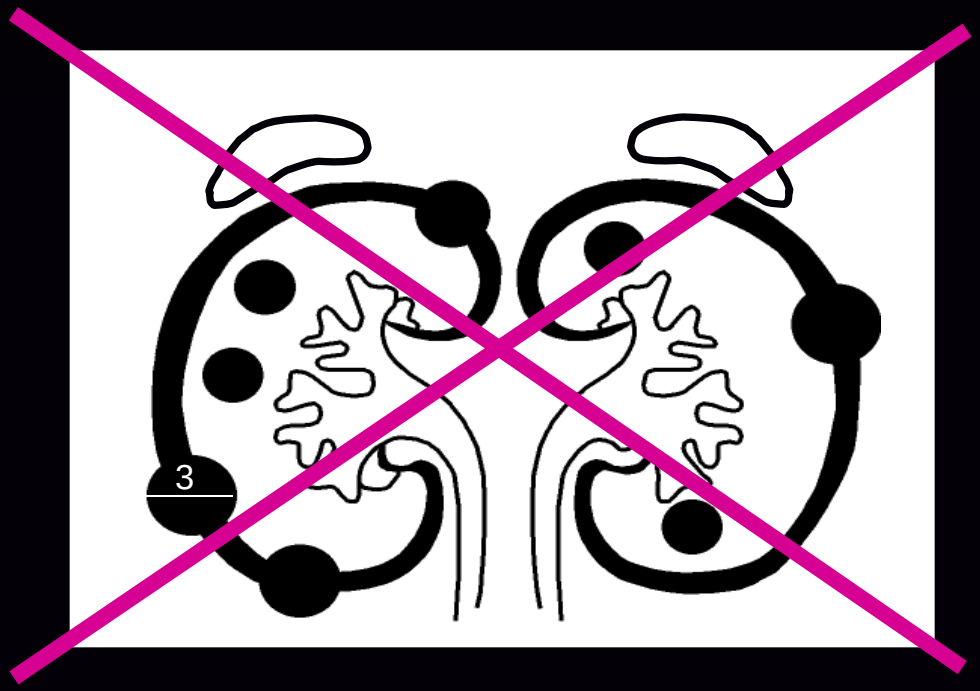


9 cm Type 2 Papillary Renal Cancer

10/59 lymph nodes positive

FH: T>G, NT 602, Leu201Arg, Exon 4, Missense

Surgical Management of HLRCC-Associated Renal Carcinoma



"3 cm rule"

Delay surgery until diameter of largest renal tumor = 3 cm

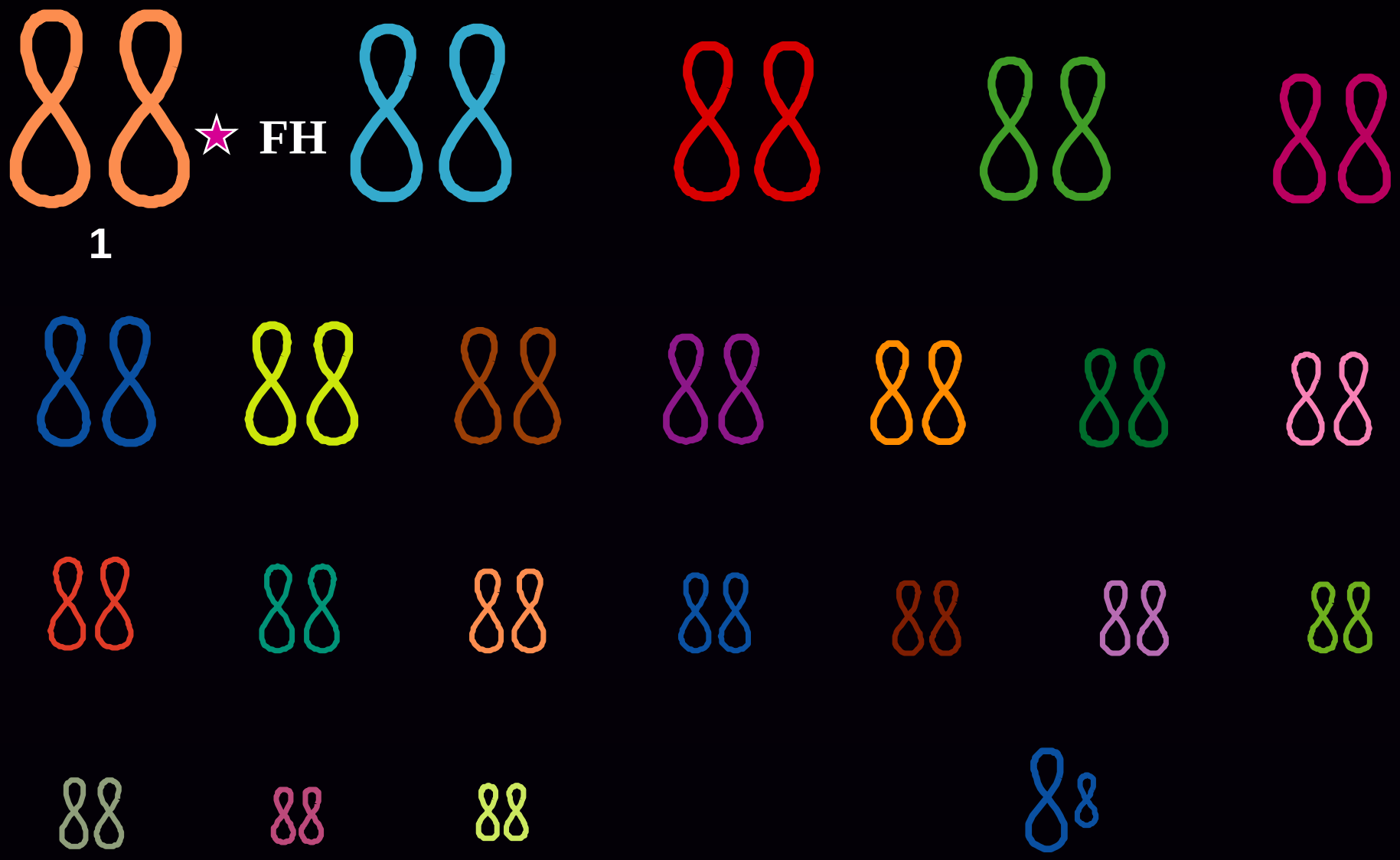
Surgical management should NOT be delayed

Wide Surgical Margins

Mostly Open Procedures

Can be bilateral and multifocal

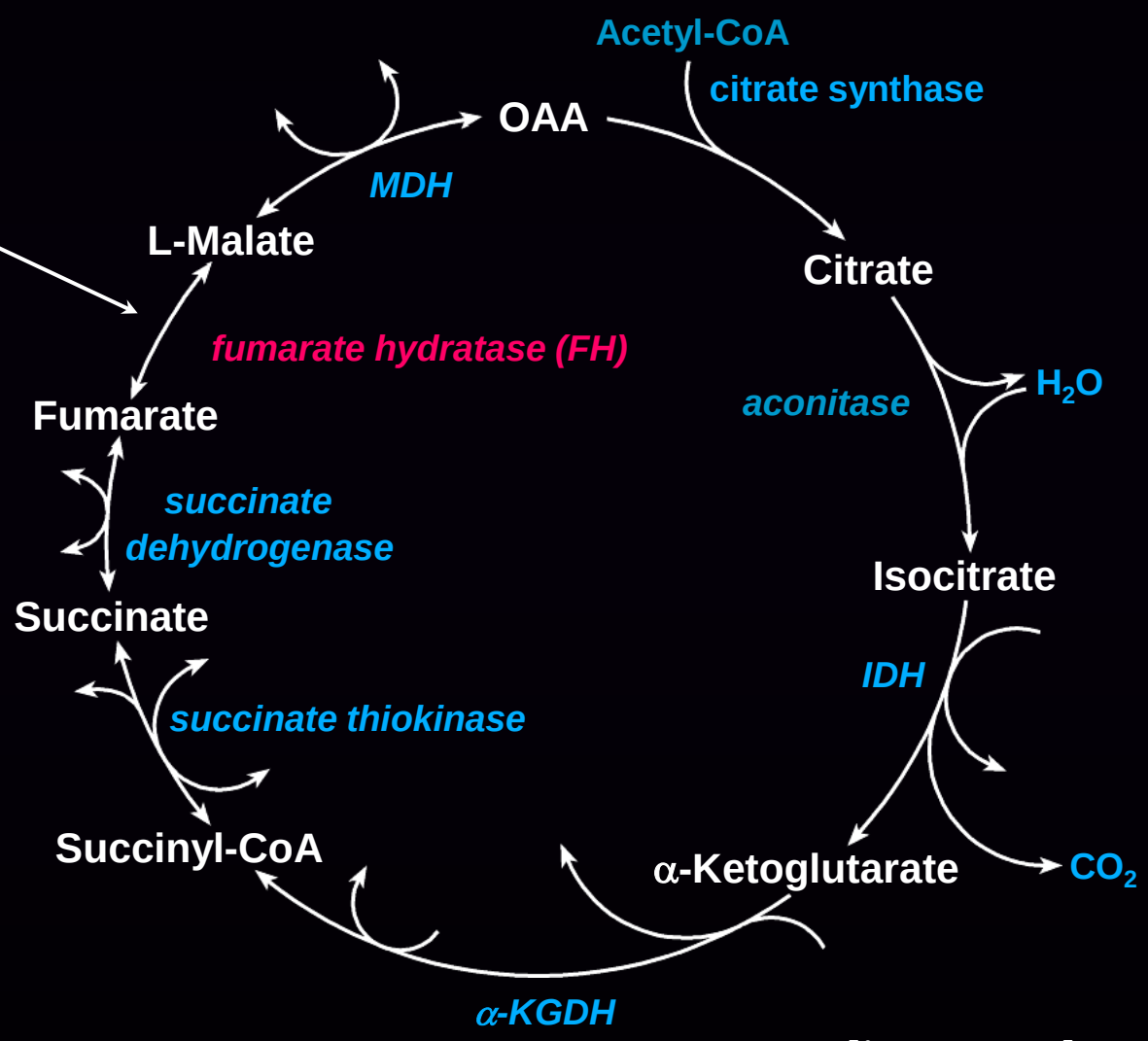
Nature CPU 3:2007
J Urol 177:2007



Fumarate Hydratase Gene: HLRCC

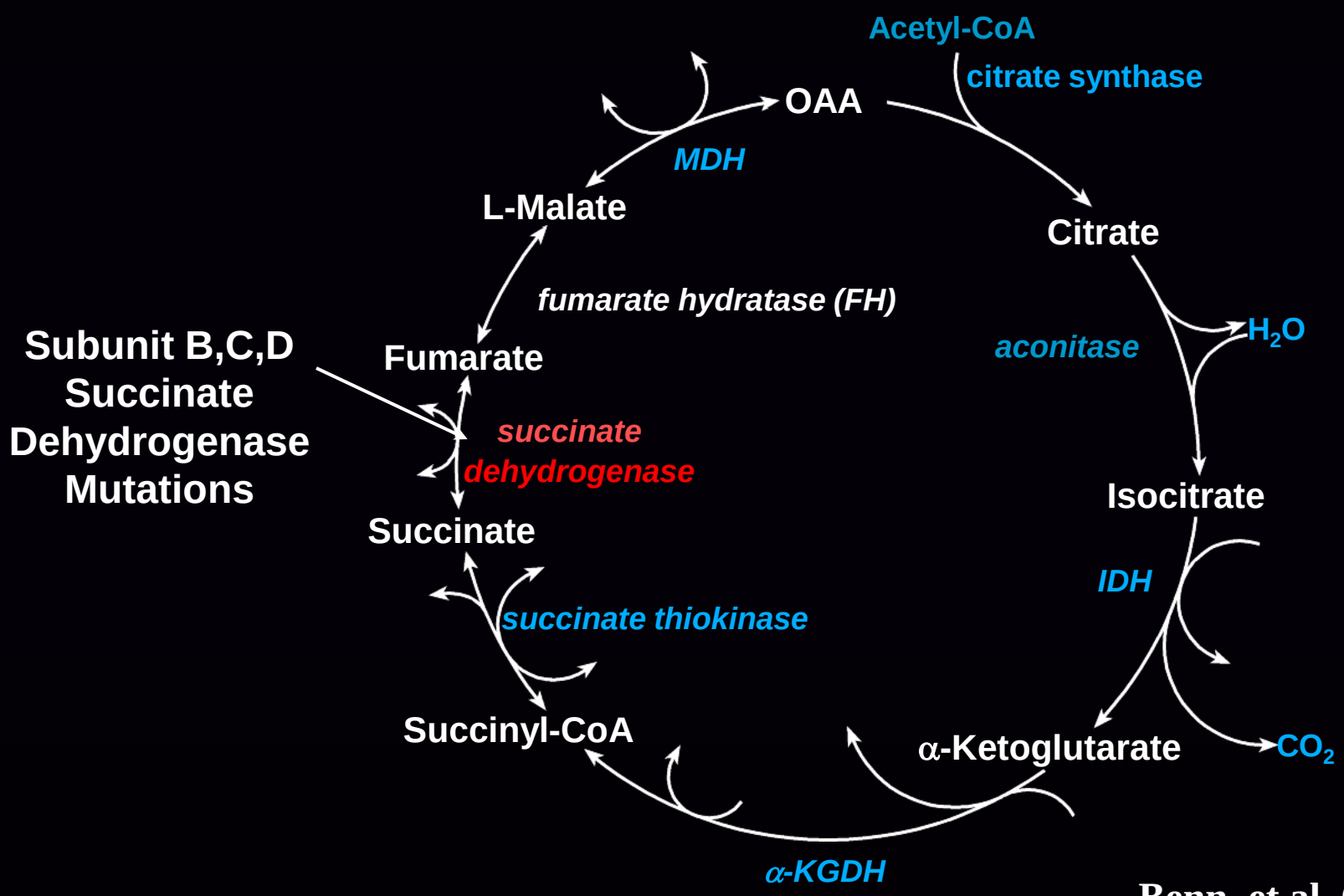
Fumarate Hydratase (FH): HLRCC Gene

FH catalyzes the conversion of fumarate to malate

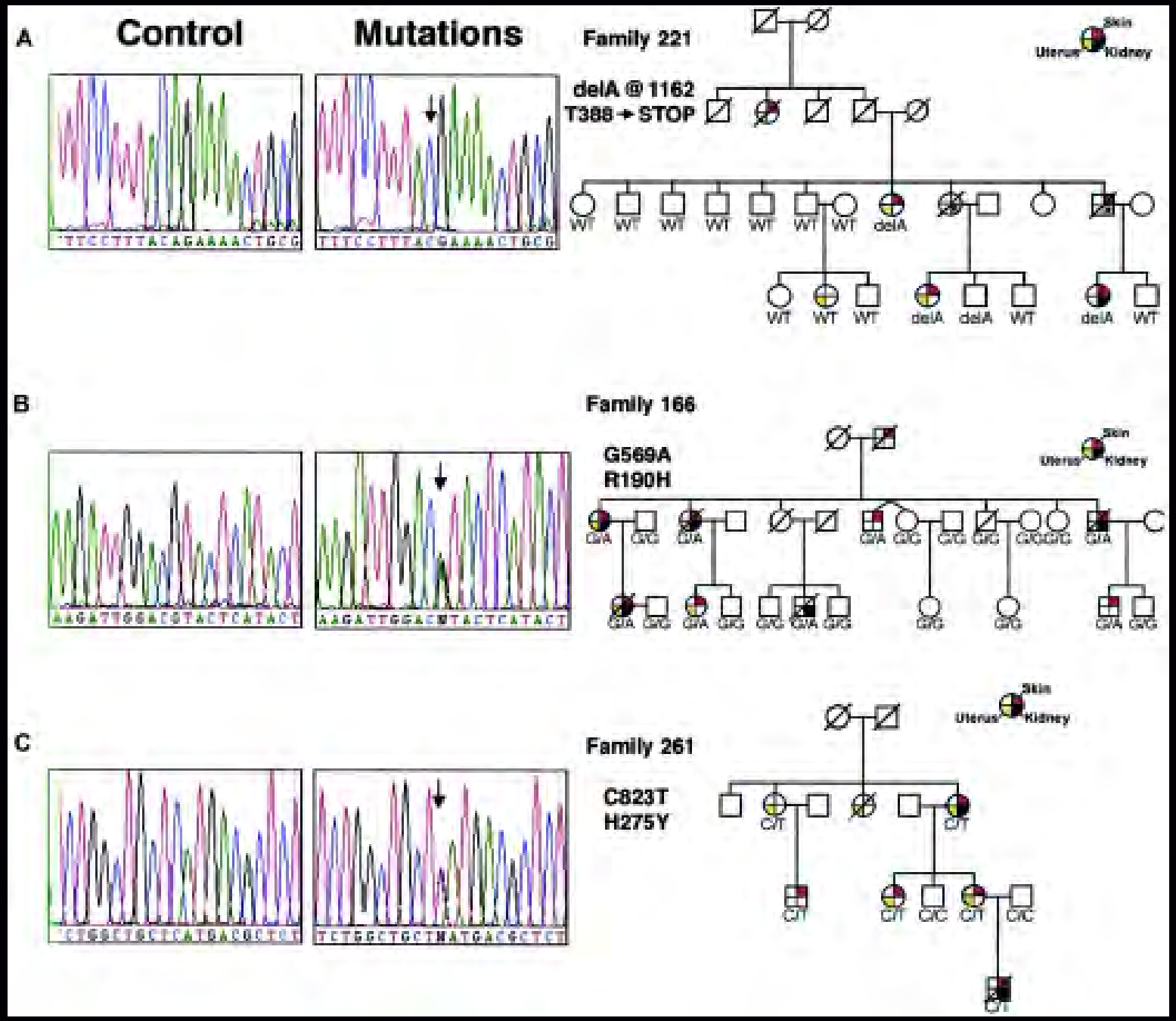


Tomlinson, et al. Nature Genetics:30 2002

Succinate Dehydrogenase: CBT Gene



Benn, et al. Oncogene 22:2003

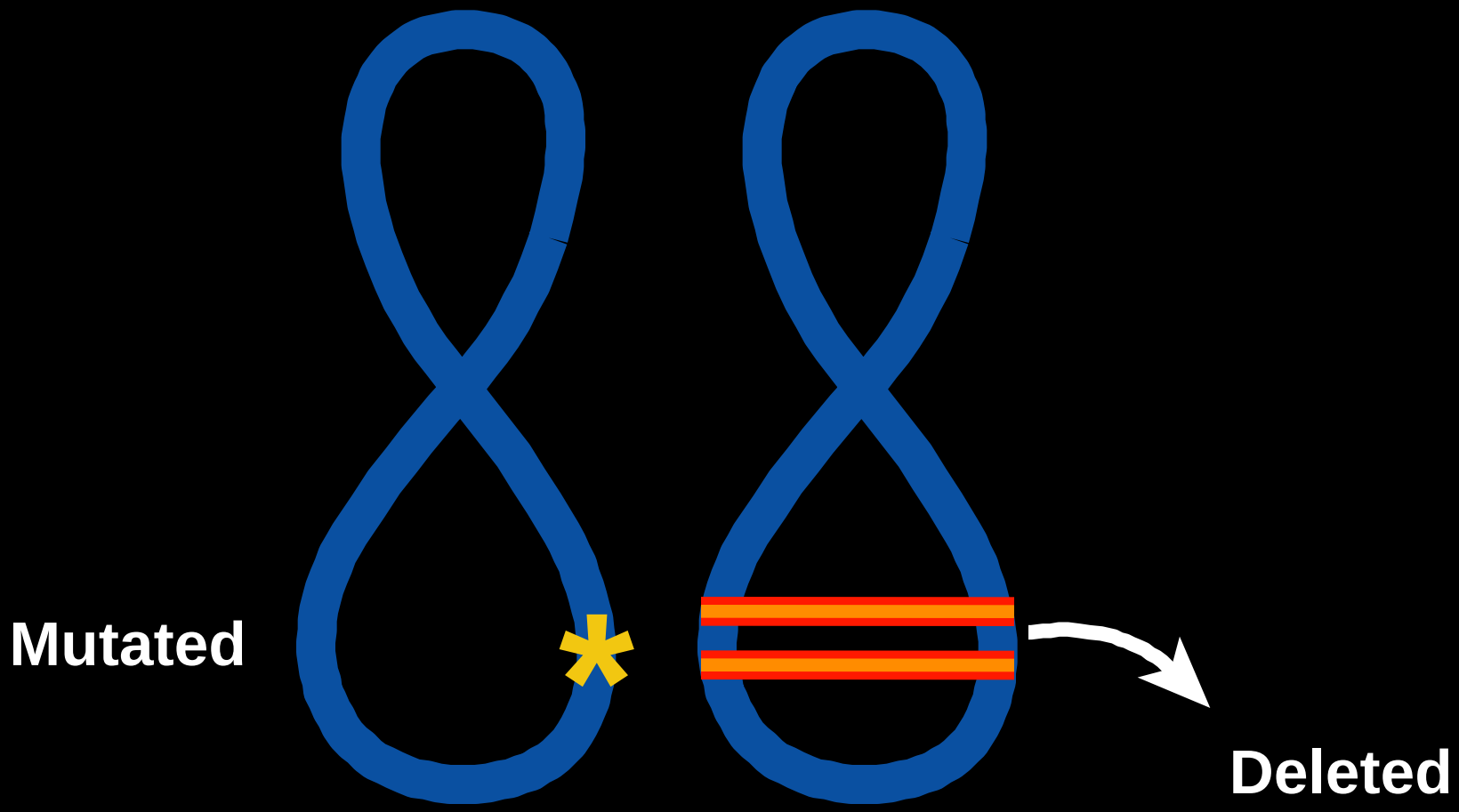

A
Control
Mutations
Family 221
delA @ 1162
T388 → STOP
Skin
Uterus
Kidney
WT
delA
B
Family 166
G569A
R190H
G/A
G/G
C
Family 261
C823T
H275Y
C/T
C/C

NCI HLRCC Kindreds N=141

- 269 affected individuals from 141 families have been evaluated
- Germline FH mutations have been detected in 135/138 (98%) HLRCC kindreds.

Am J Hum Genet 71:2003

J. Med Genet 6: 2005



Chromosome 1

Fumarate Hydratase-Deficient Kidney Cancer

UOK-262 EV (Empty Vector)

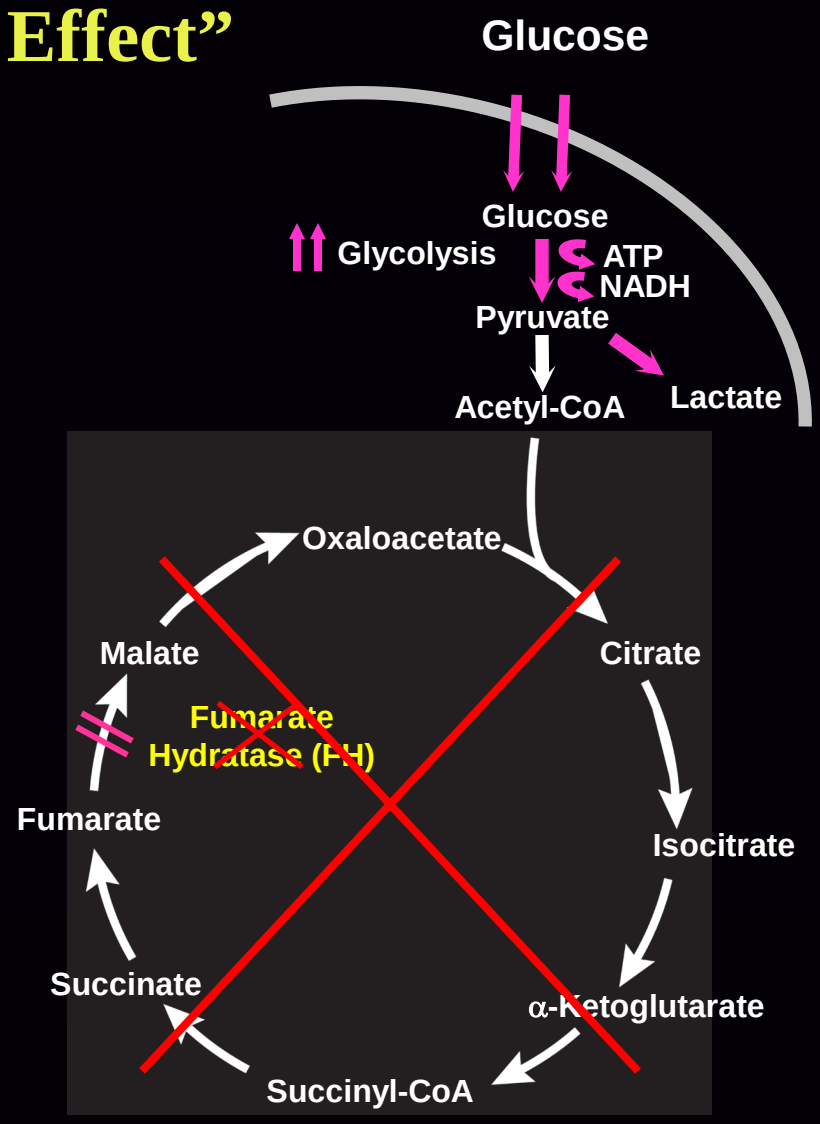
Cancer Cell 20:2011

UOK-262 FHWT (Wild-type replaced)

Cancer Cell 20:2011

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

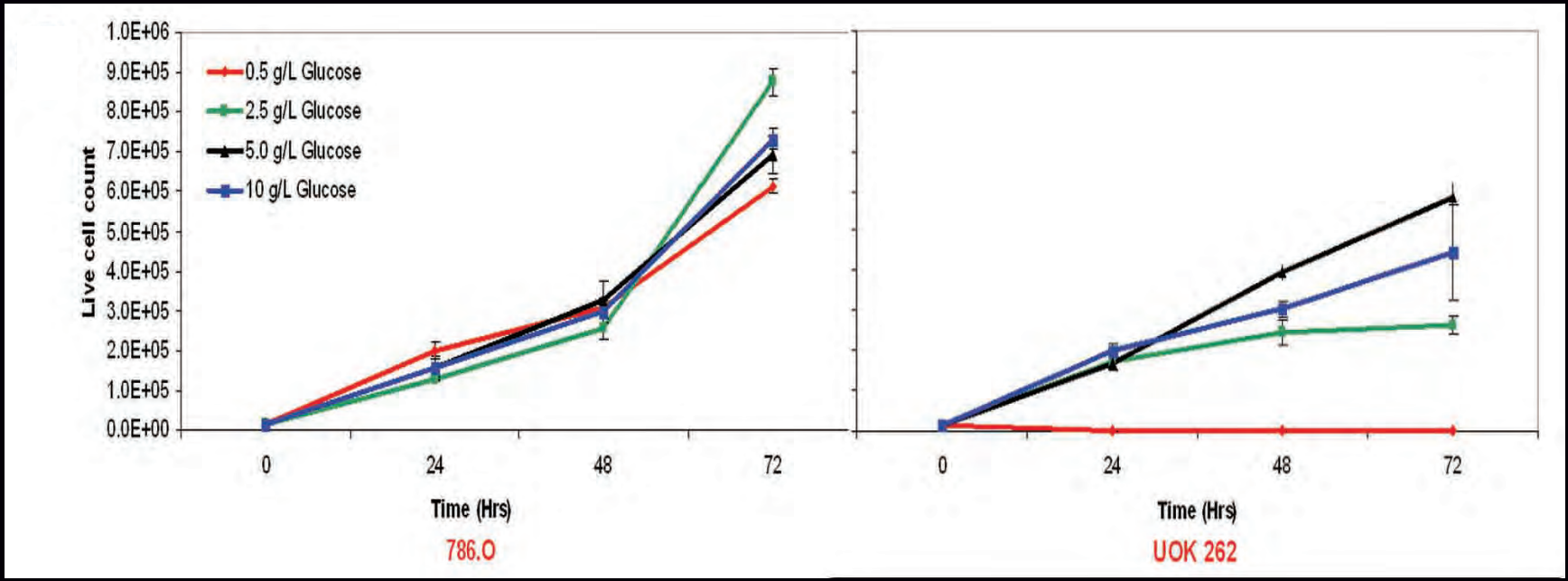
HLRCC Kidney Cancer
Glucose Dependent-“Warburg Effect”



Citric Acid Cycle

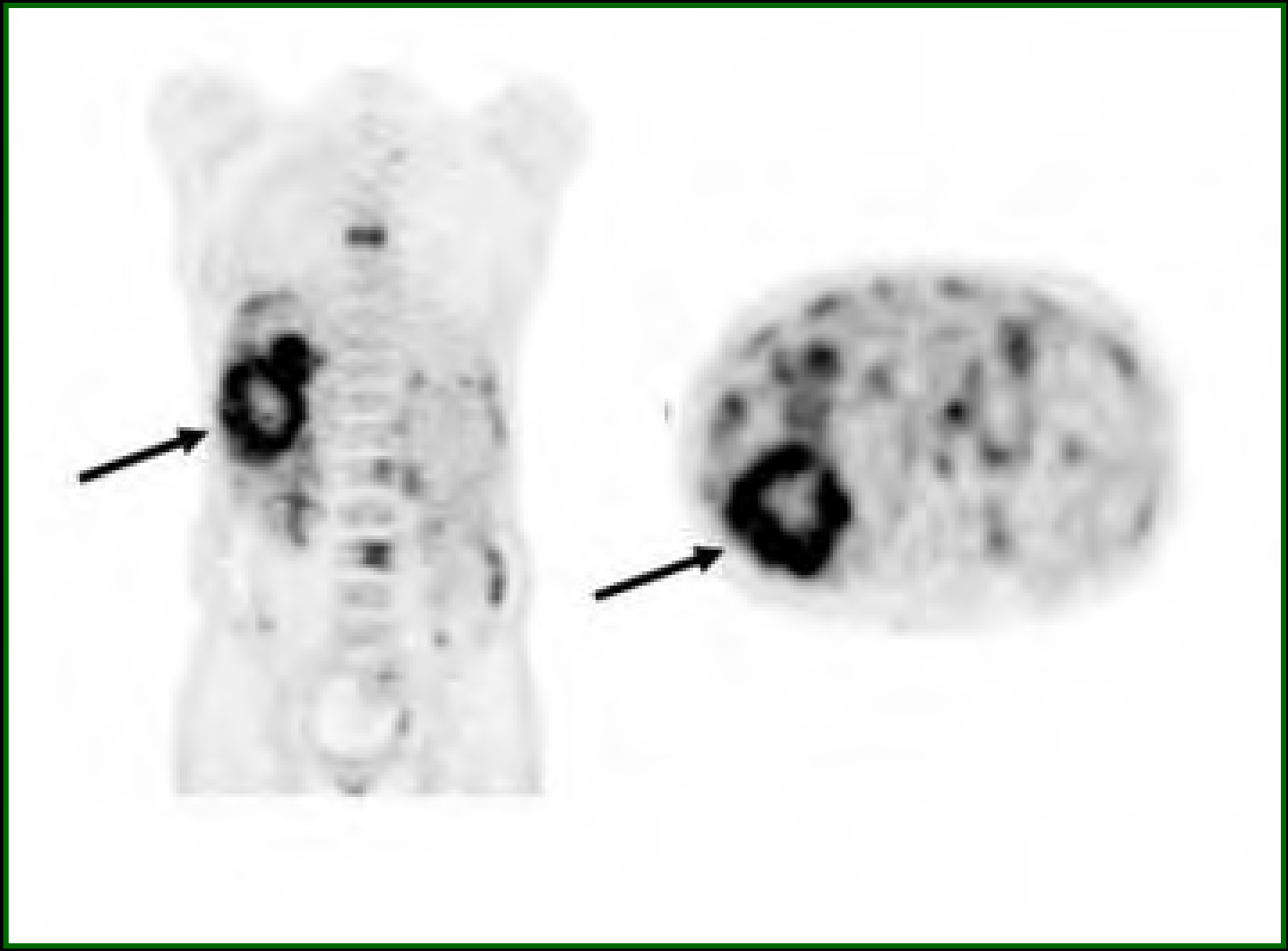
Cancer Cell 20:2011
Cancer Cell: 2005

HLRCC-Renal Cancer: Glucose-Dependent

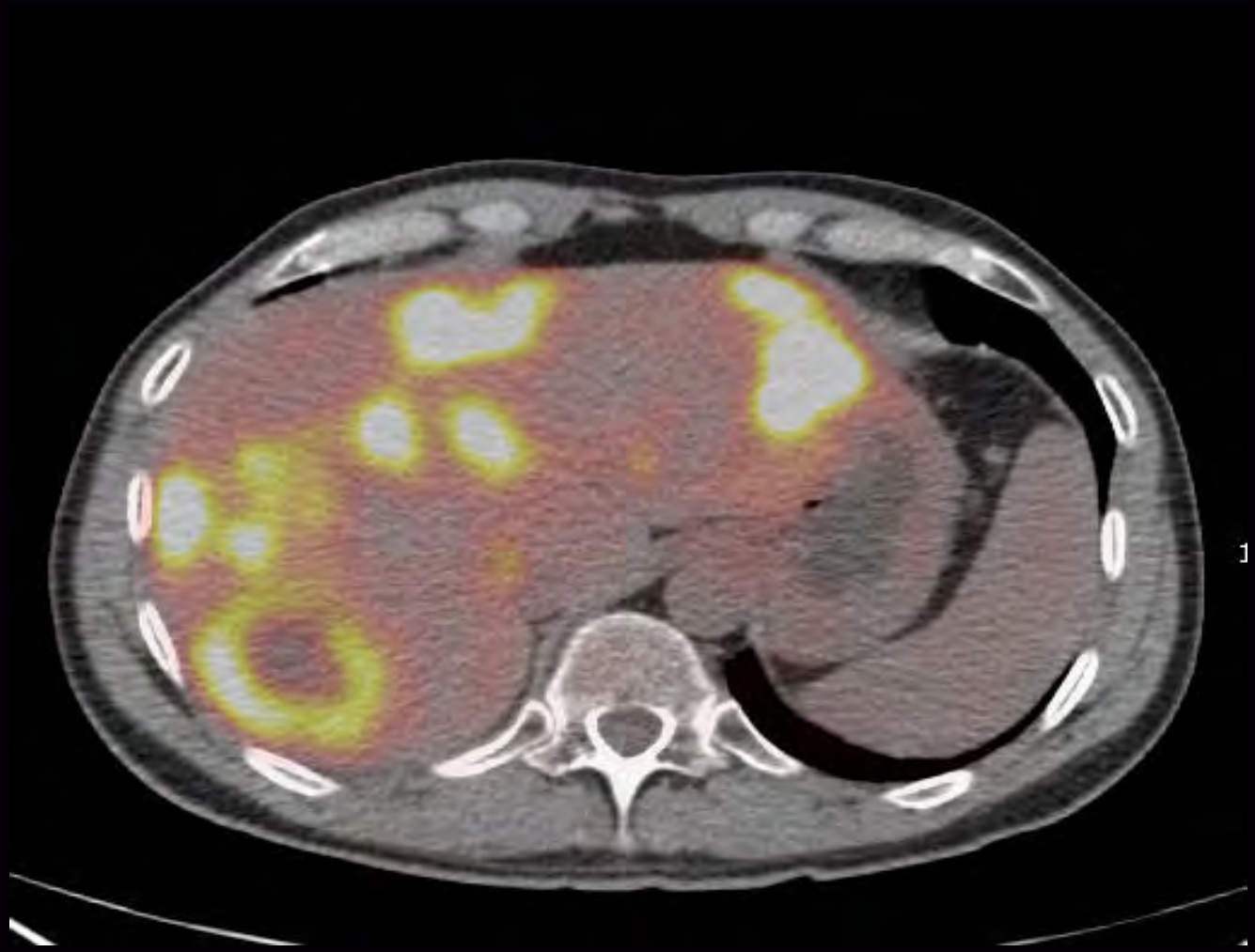


Cancer Gen Cytogenet 196:2010

HLRCC Tumors *In Vivo* are Readily Detected by [18]Fluoro-deoxyglucose-based PET Scan



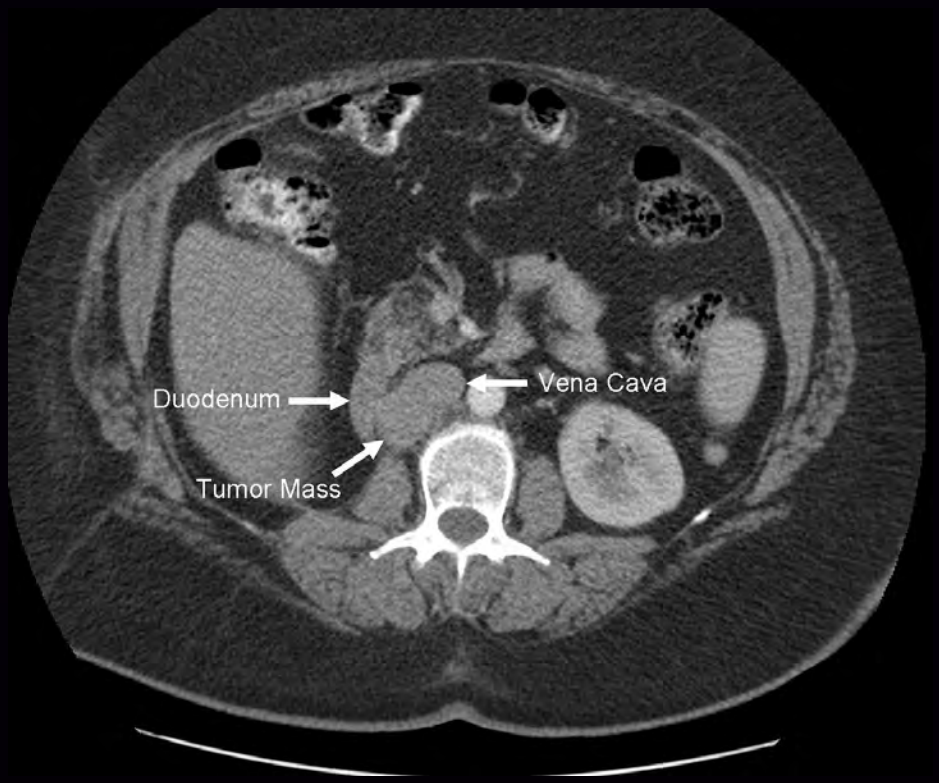
HLRCC Tumors *In Vivo* are Readily Detected by [18]Fluoro-deoxyglucose-based PET Scan



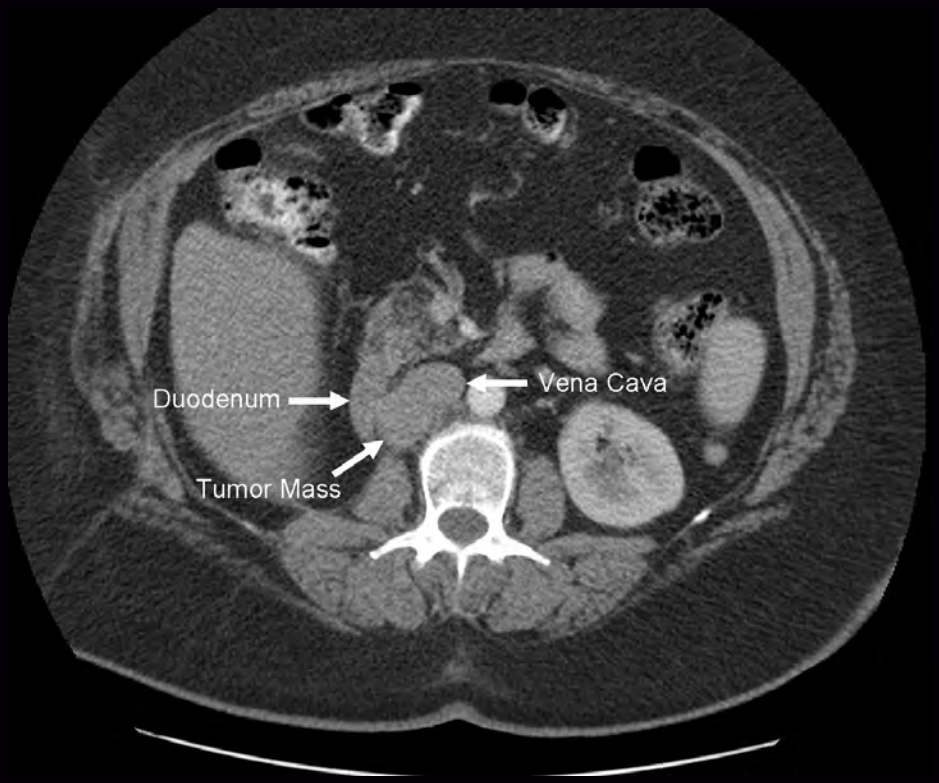
HLRCC Liver Tumor: CT Scan

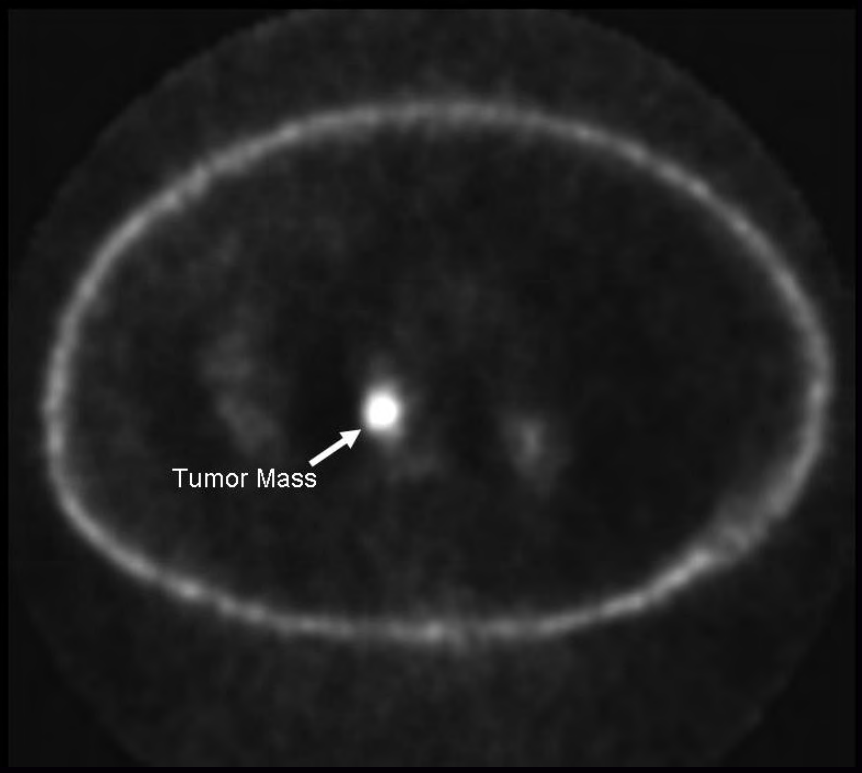
HLRCC Tumors *In Vivo* are Readily Detected by [18]Fluoro-deoxyglucose-based PET Scan

HLRCC Retroperitonal Tumor: PET Scan

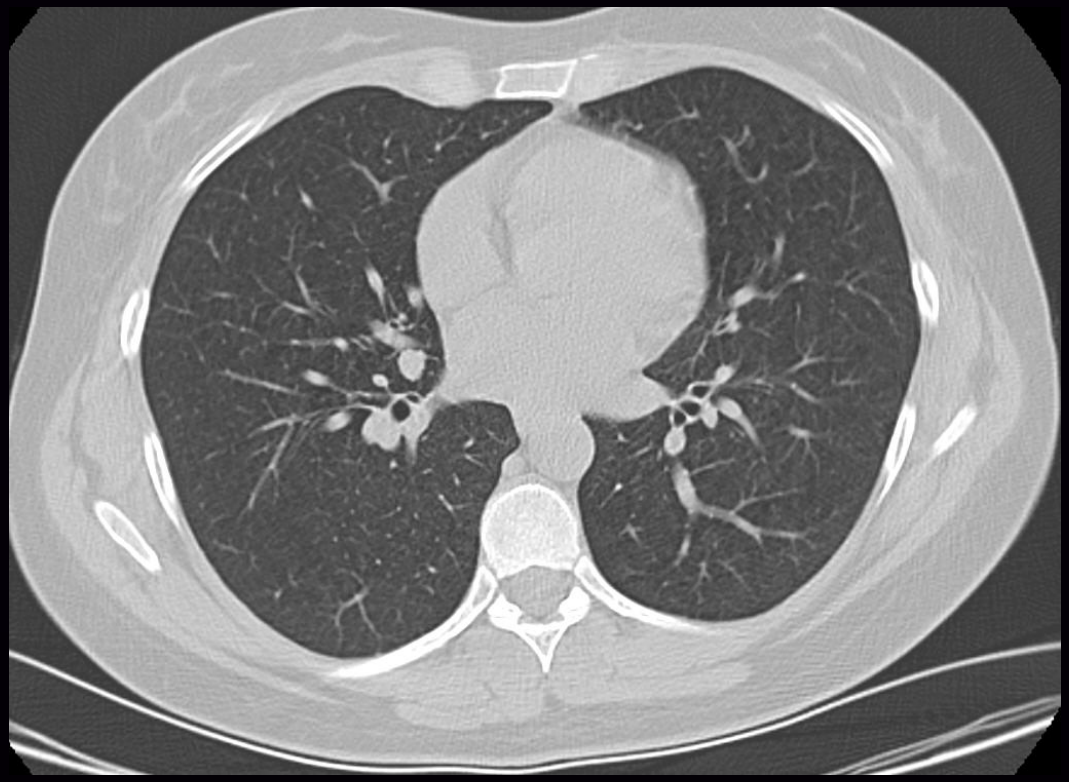


HLRCC Retroperitonal Tumor: PET Scan



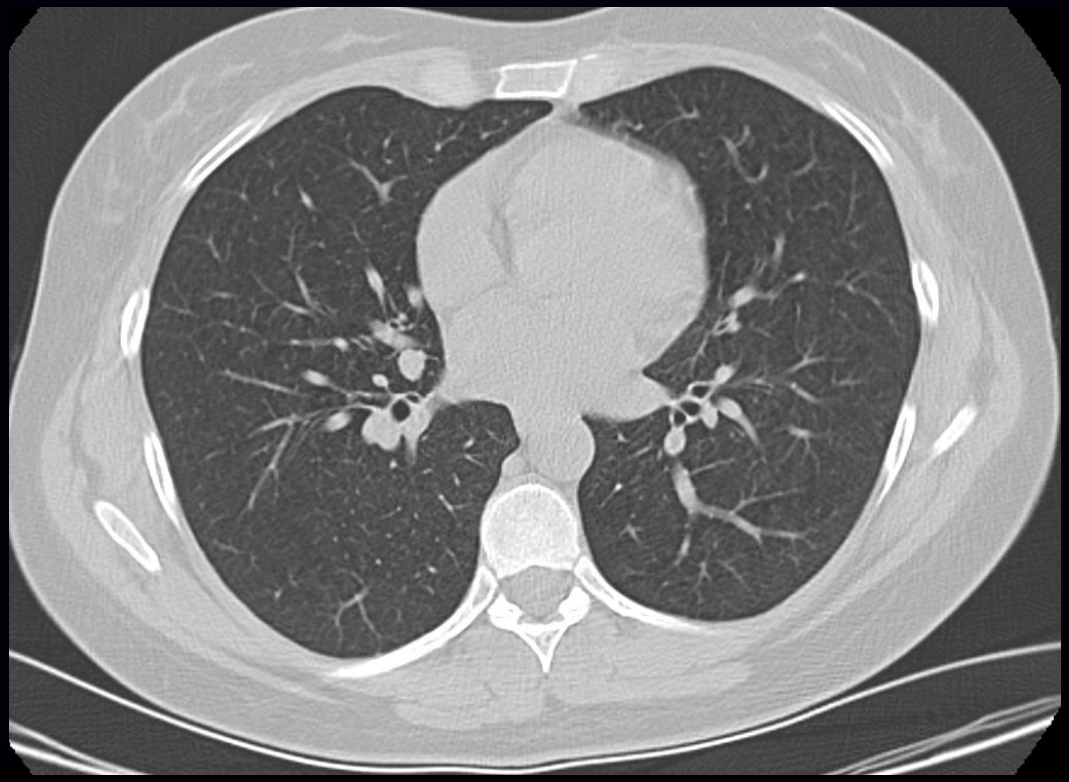


HLRCC Chest Tumor: PET Scan

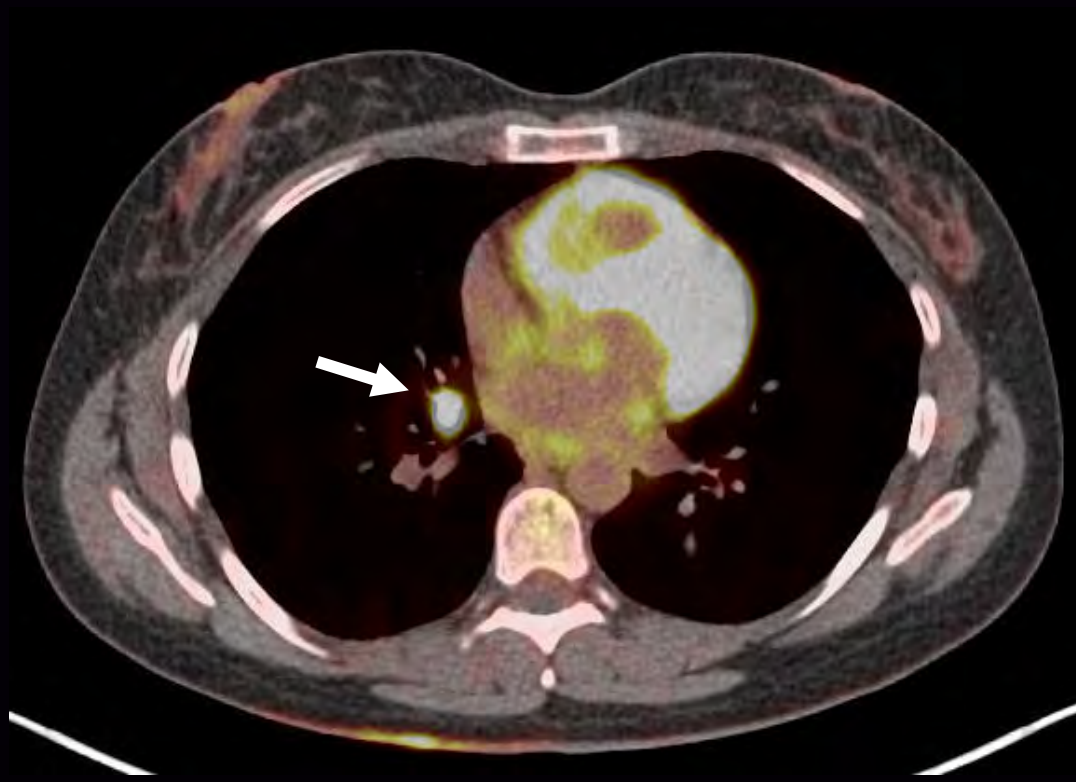


Chest CT

HLRCC Chest Tumor: PET Scan

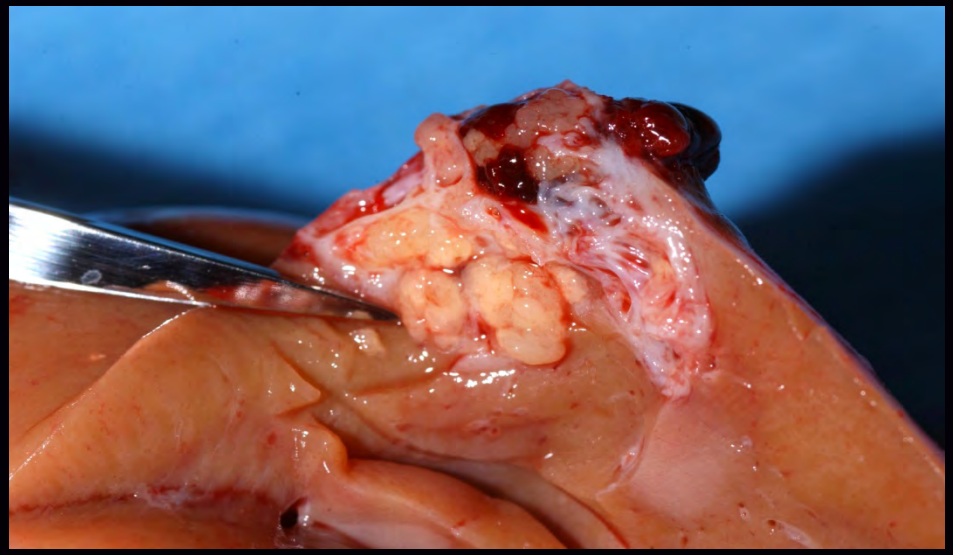


Chest CT



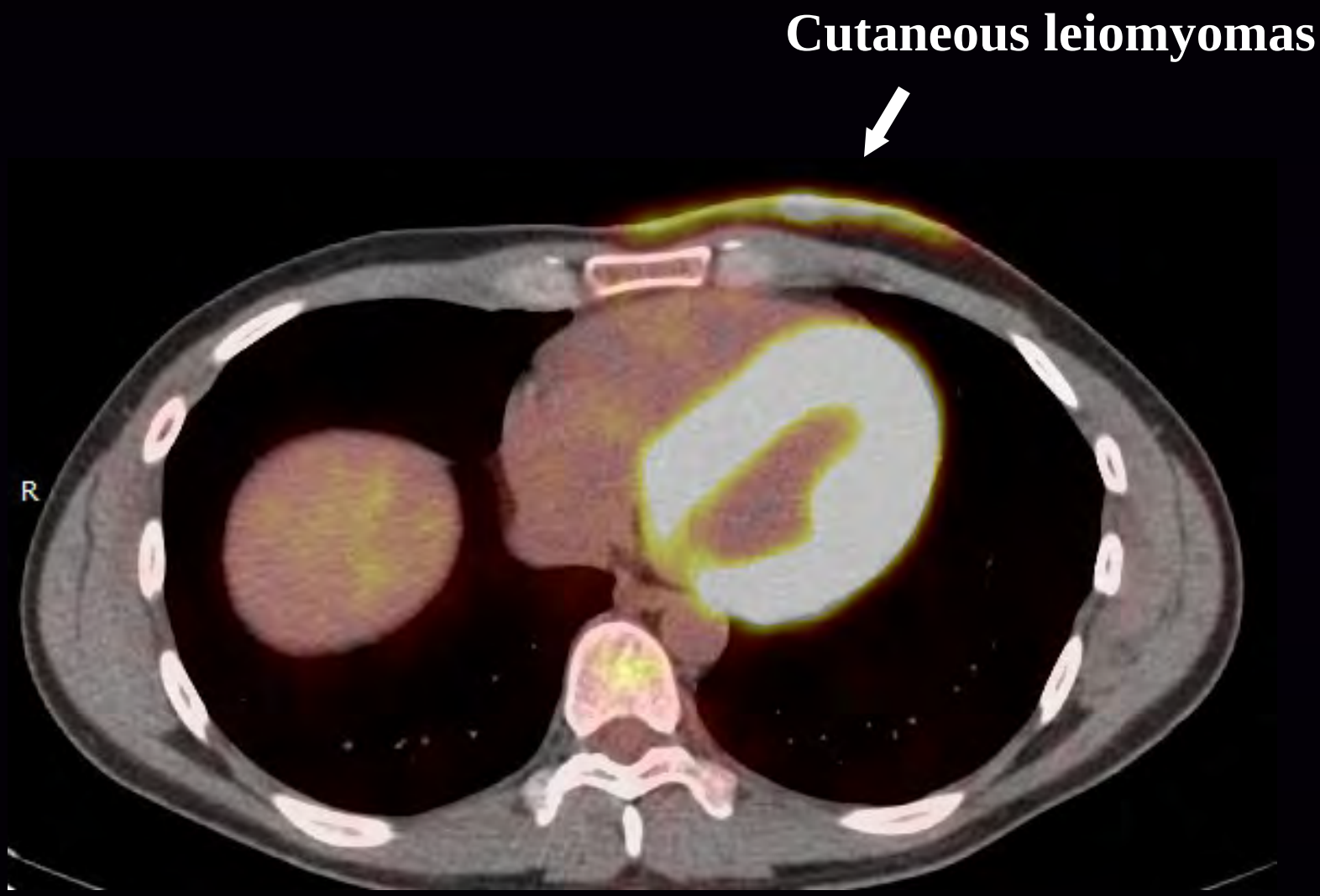
FDG PET

HLRCC Patient

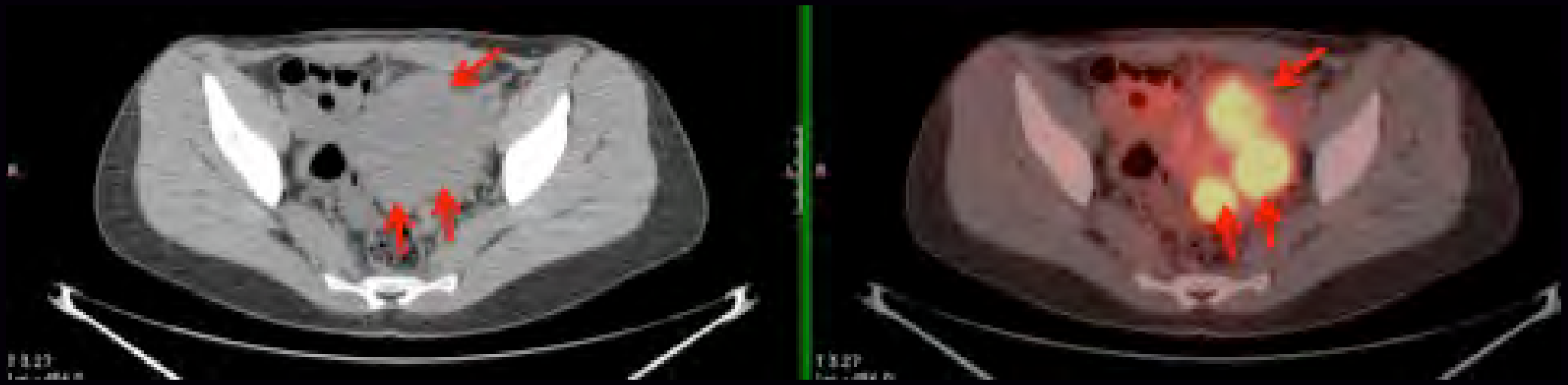


J Urol:177 2007

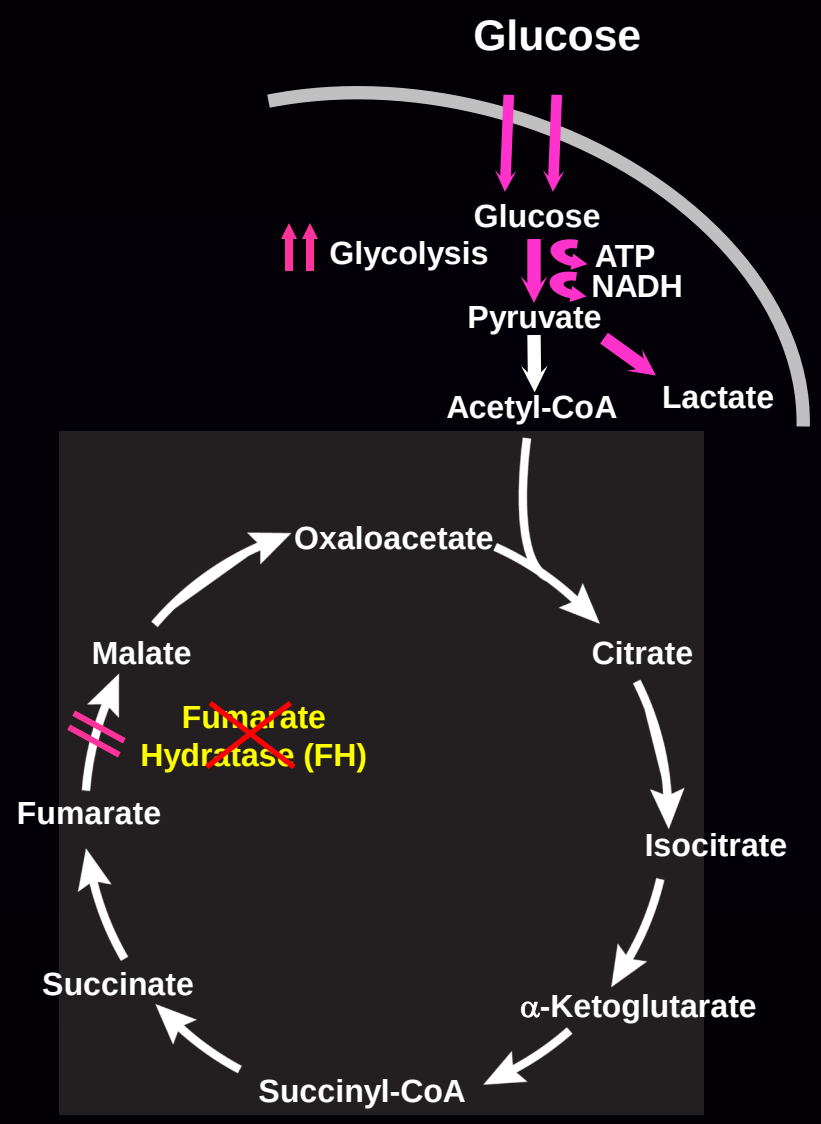
Cutaneous Leioymyomas *In Vivo* are Readily Detected by [18]Fluoro-deoxyglucose-based PET Scan



Uterine Leiomyomas



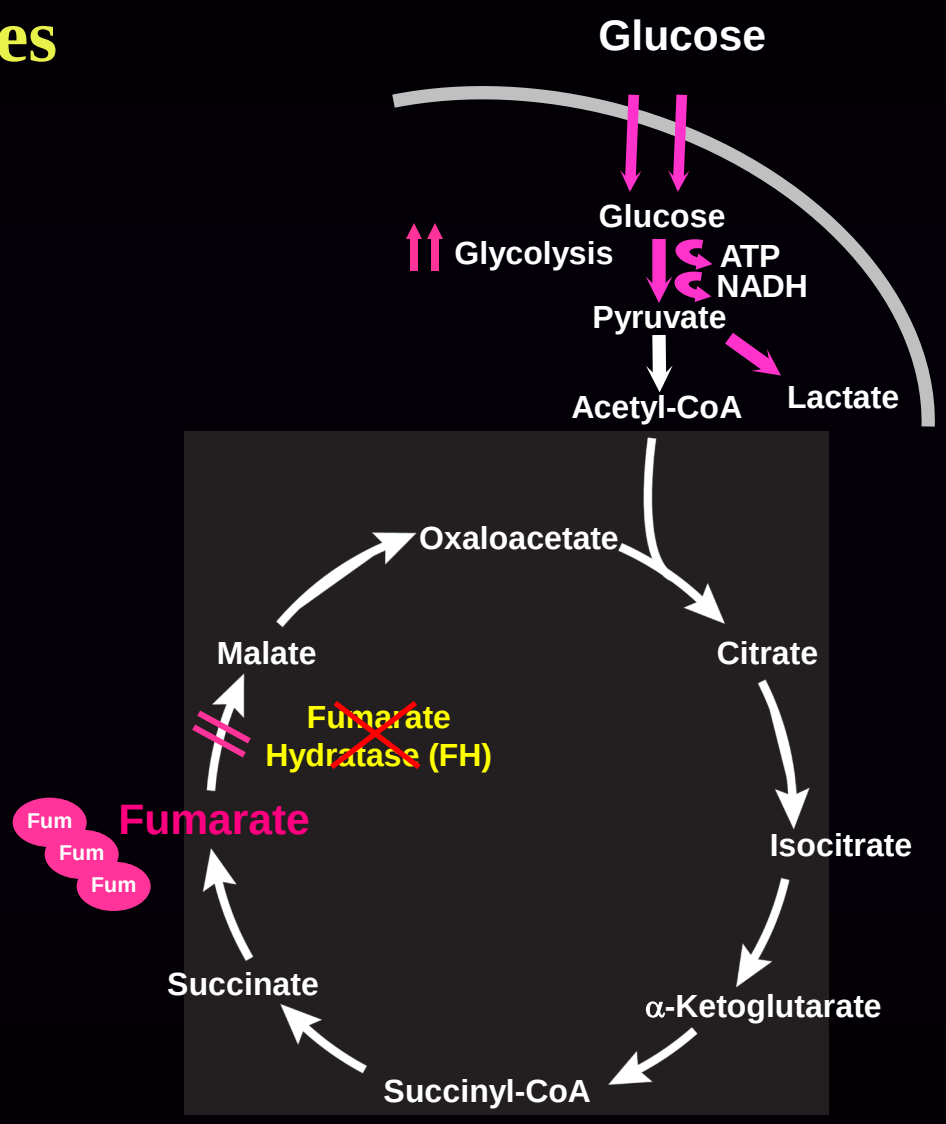
HLRCC
Fumarate Increases



Citric Acid Cycle

Cancer Cell 20:2011
Cancer Cell: 2005

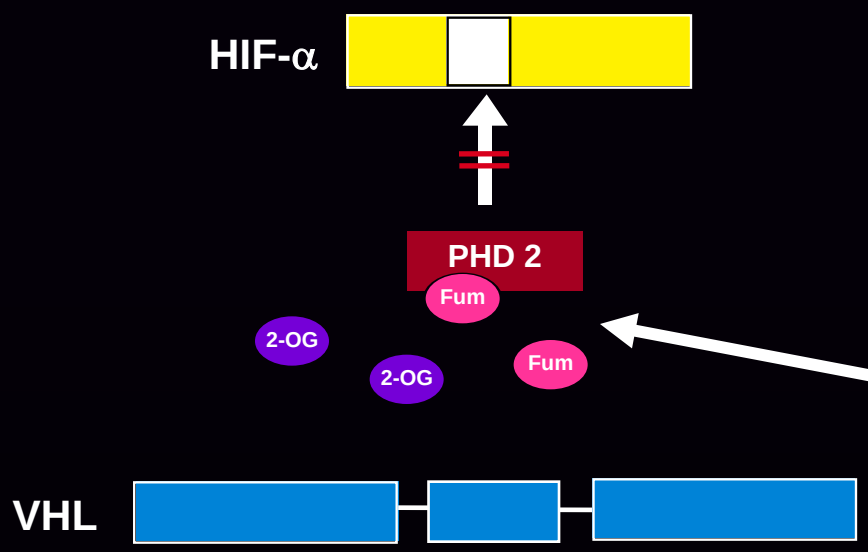
HLRCC
Fumarate Increases

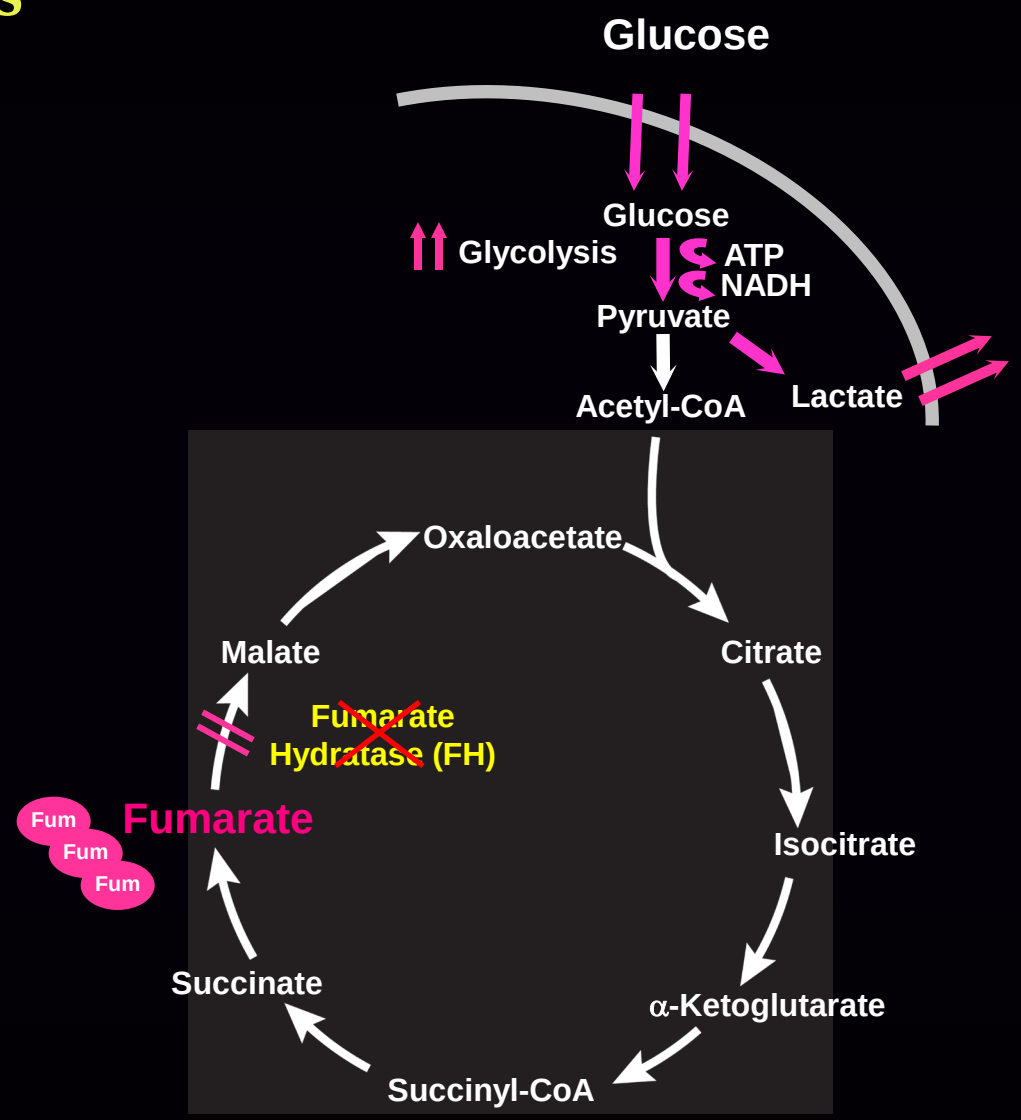


Citric Acid Cycle

Cancer Cell 20:2011
Cancer Cell: 2005

HIF Accumulates

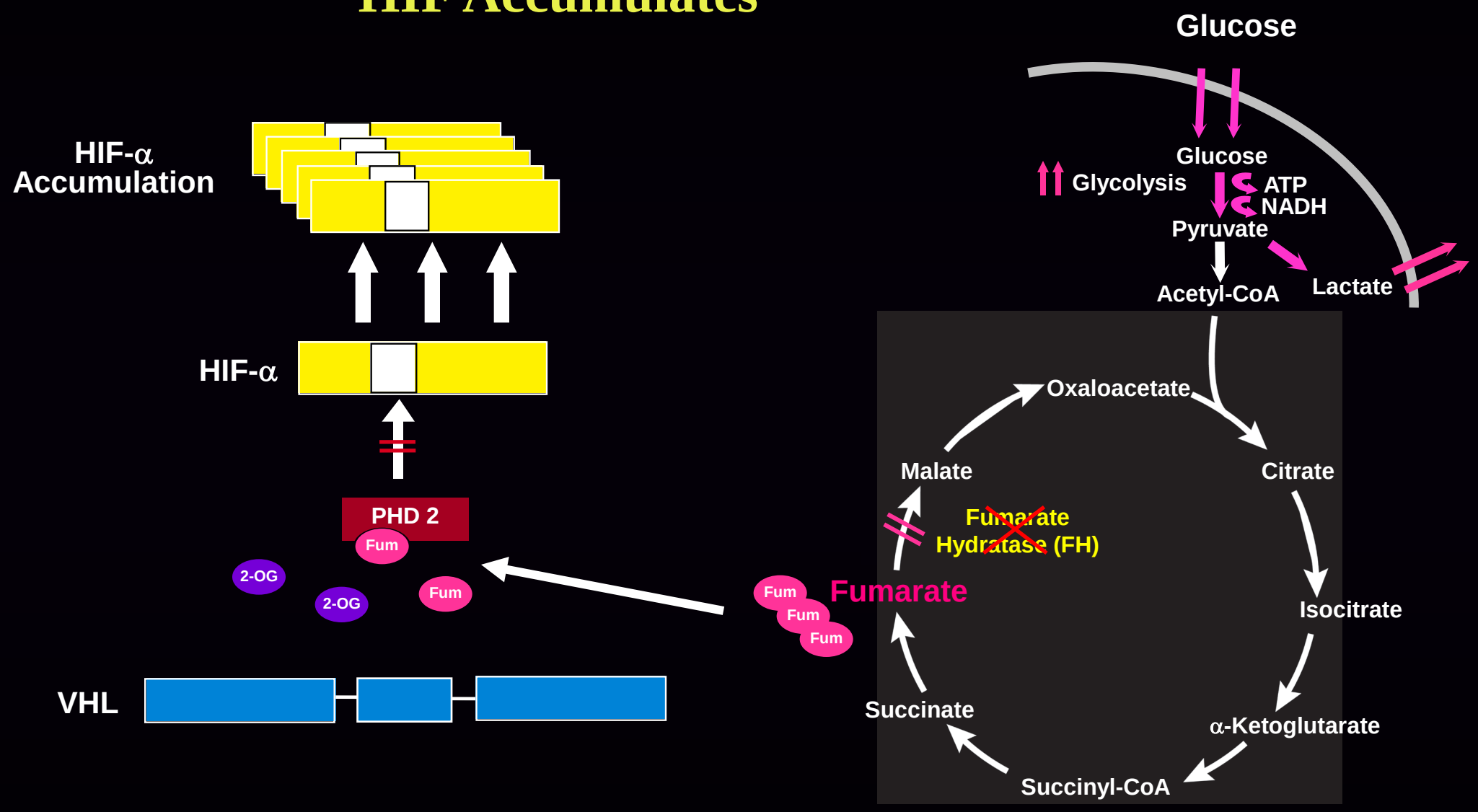




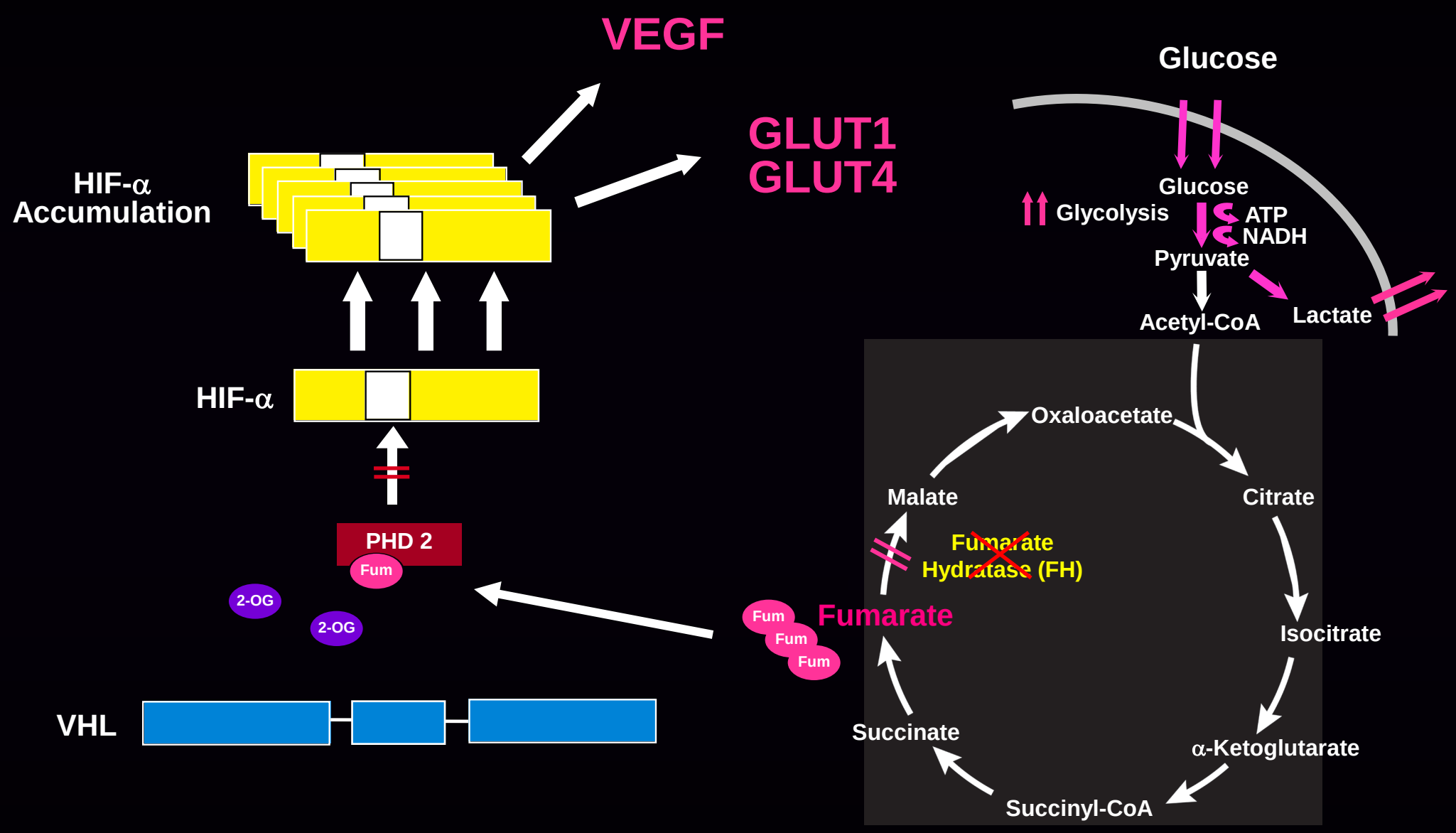
Citric Acid Cycle

Cancer Cell 20:2011
Cancer Cell: 2005

HIF Accumulates

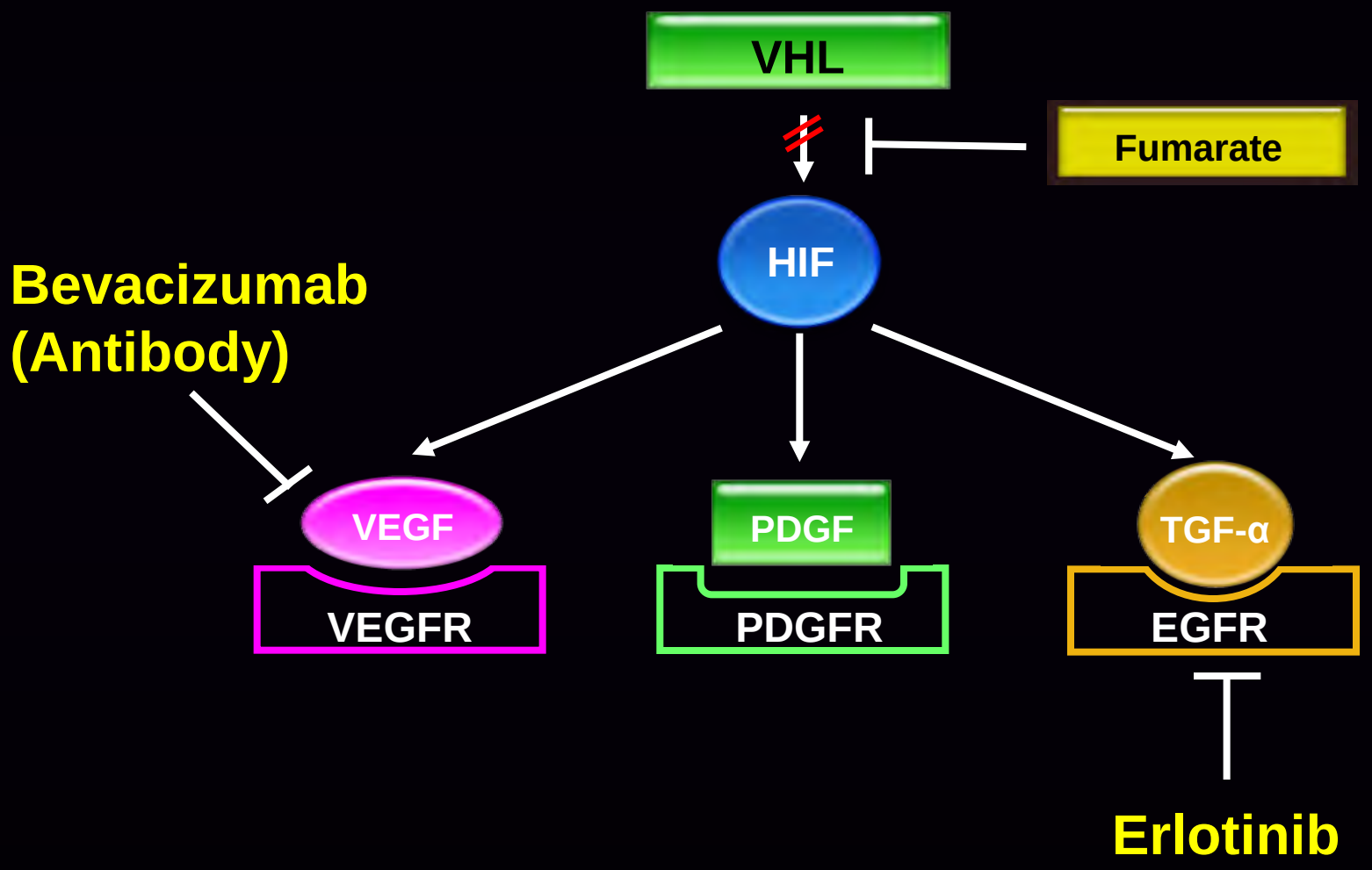


Cancer Cell 20:2011
Cancer Cell: 2005



Cancer Cell 20:2011
Cancer Cell: 2005

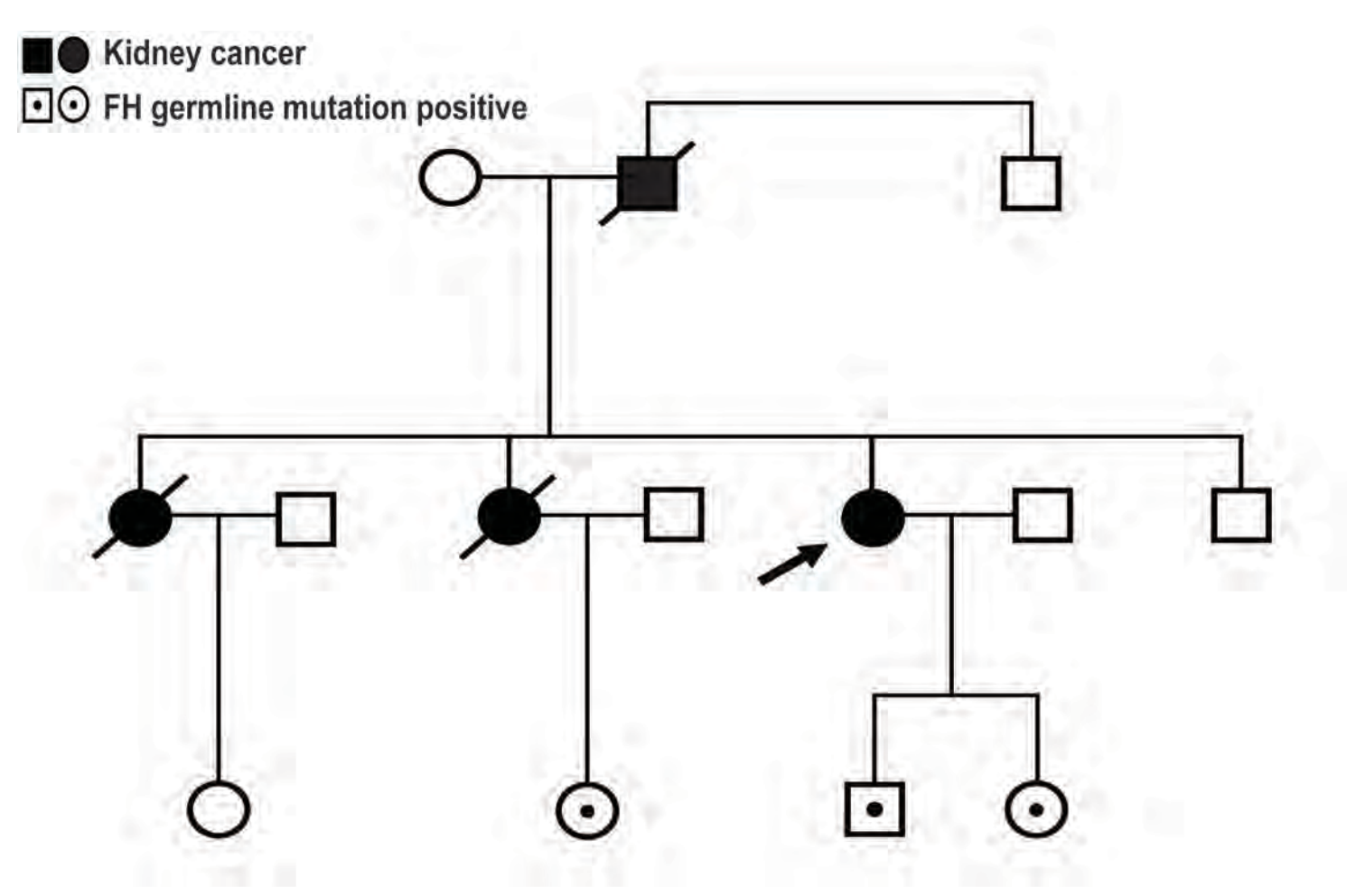
Targeting VEGF/EGFR in HLRCC



Pre-Therapy

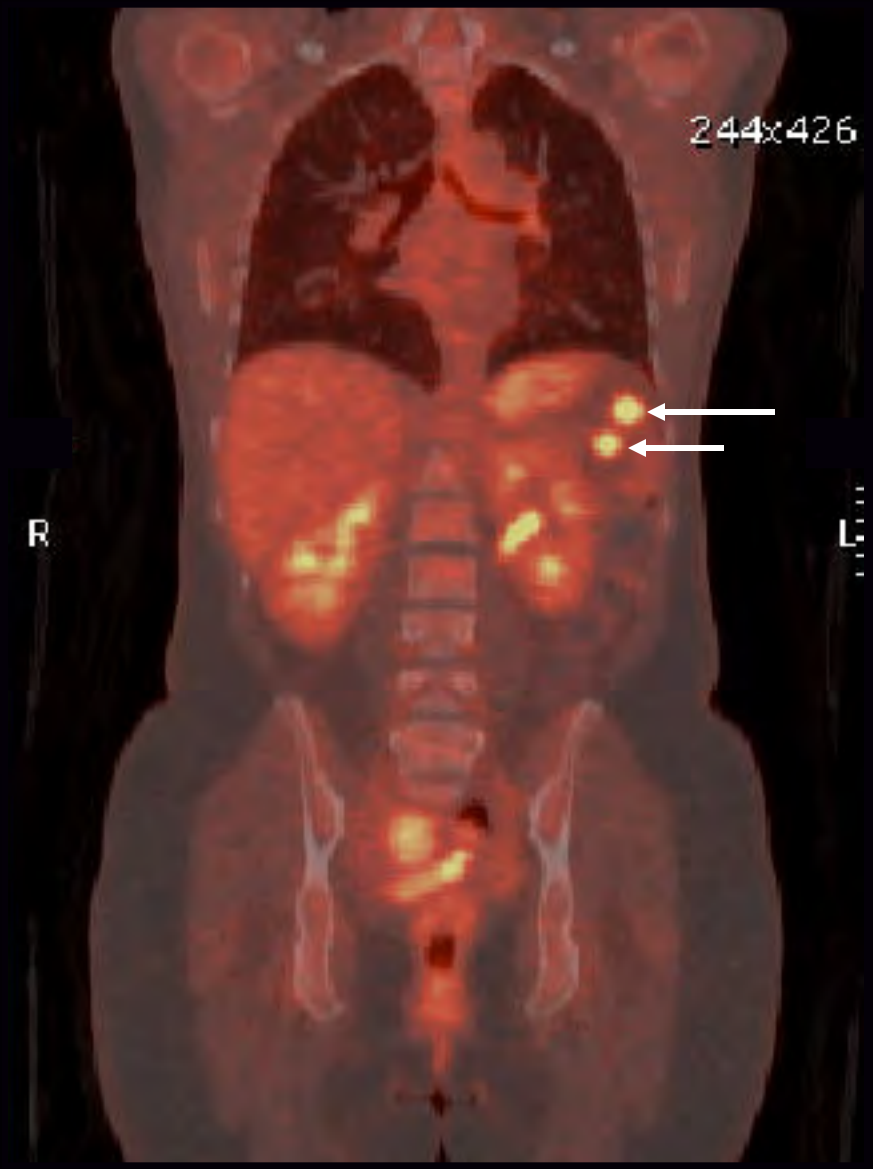
A partial response following 18 months of therapy with bevacizumab + erlotinib

HLRCC



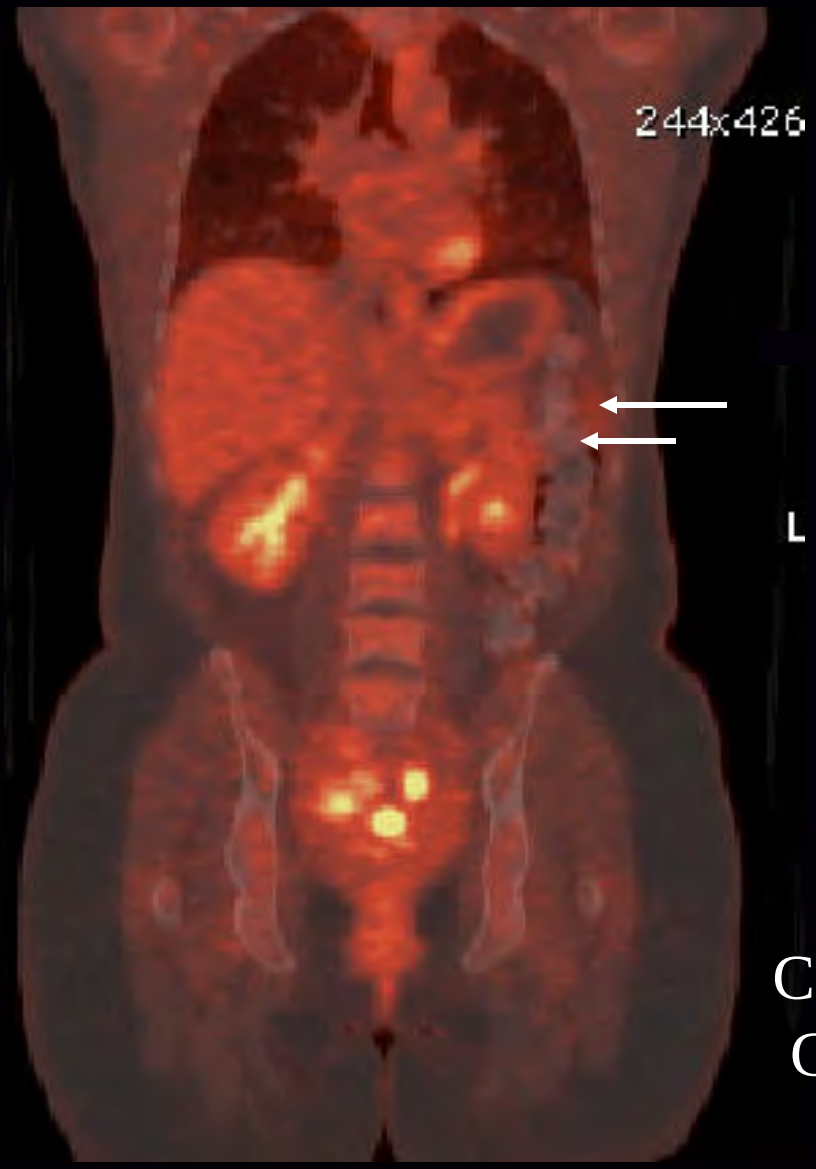
Germline FH Mutation: Del TC, NT 1346-1347, AA# 449, Exon 9, Frameshift

HLRCC Patient with Metastatic RCC
Pre-Therapy



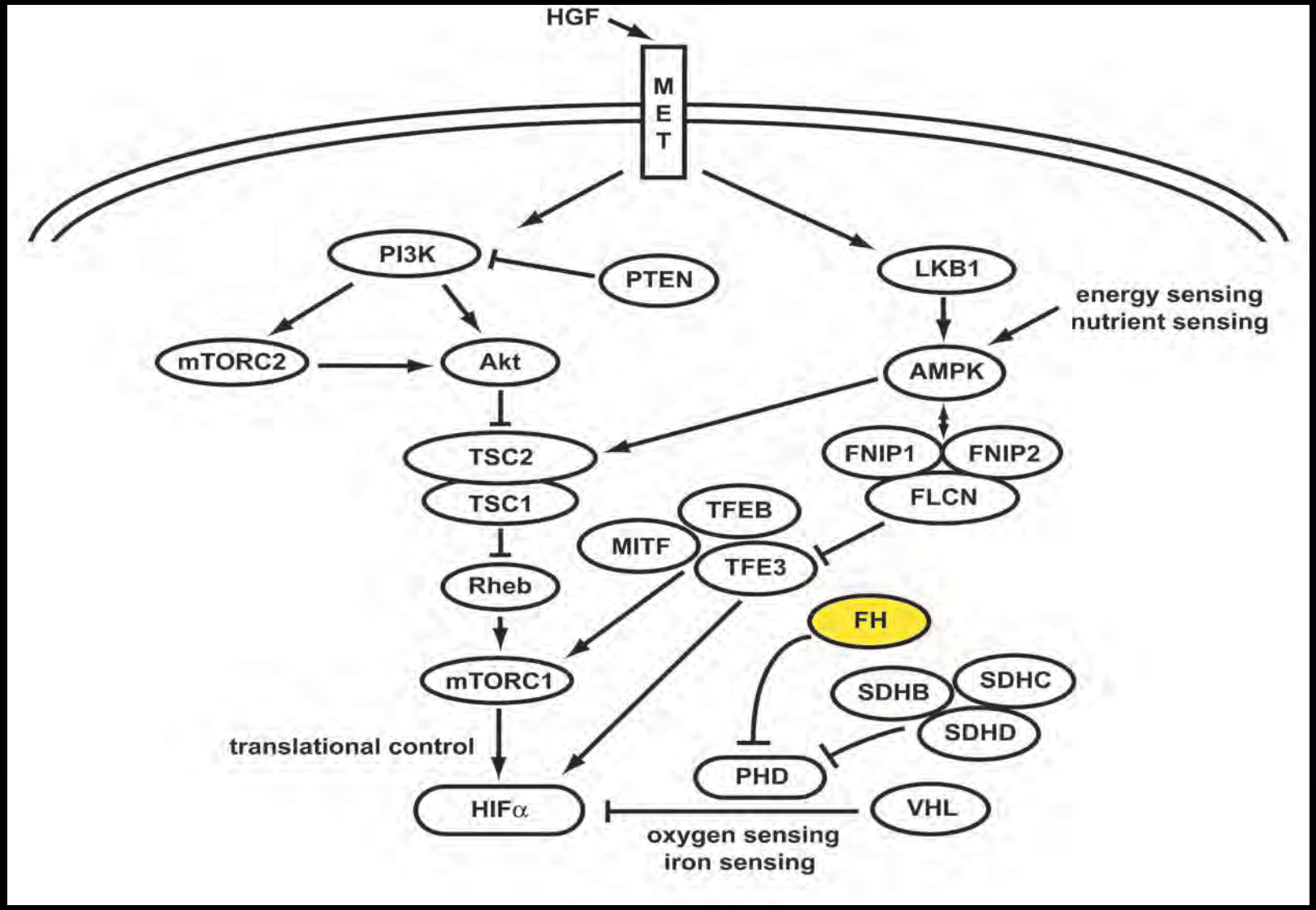
Complete Response Following 3 Months Following Bevacizumab and Erlotinib

Complete Response Following 3 Months Following Bevacizumab and Erlotinib



On Therapy 9/05
Complete Response 12/05
Continued CR as of 4/12
6 years

Kidney Cancer is a Metabolic Disease

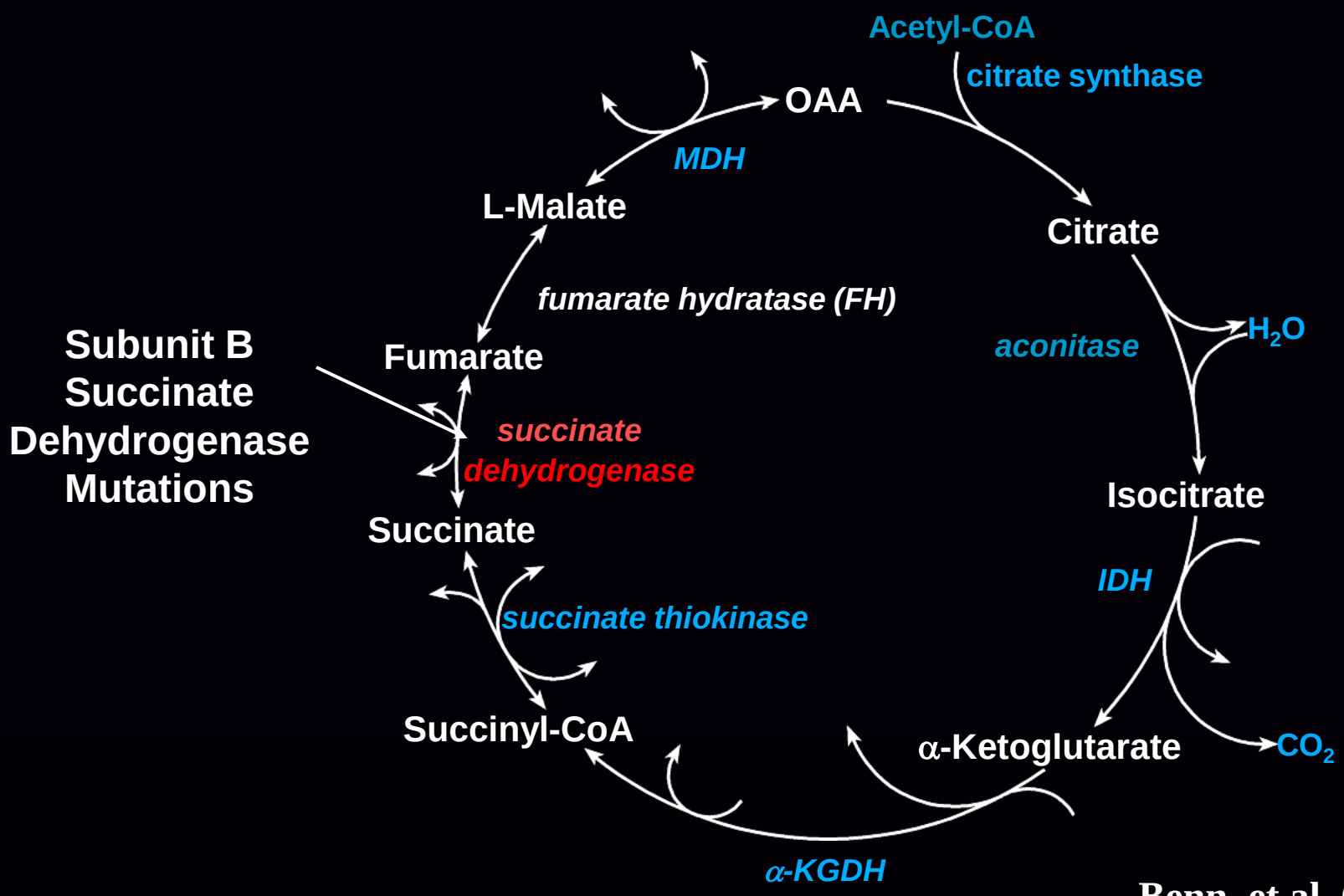


Nature Rev Urol: 7 2010

SDH-RCC
Succinate Dehydrogenase Kidney Cancer

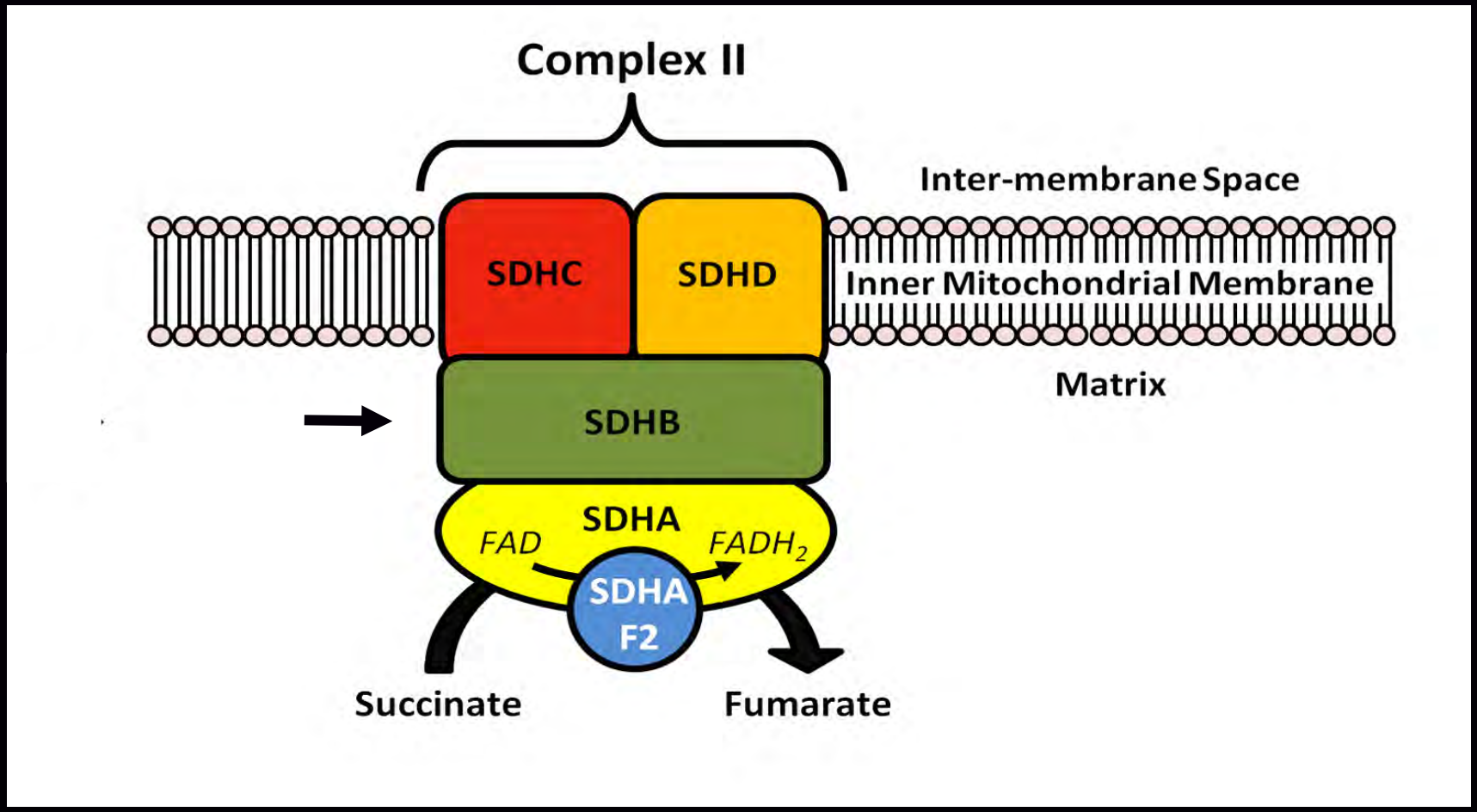
- Pheochromocytoma
- Paraganglioma
- Renal cell carcinoma

SDH-RCC
Succinate Dehydrogenase Kidney Cancer

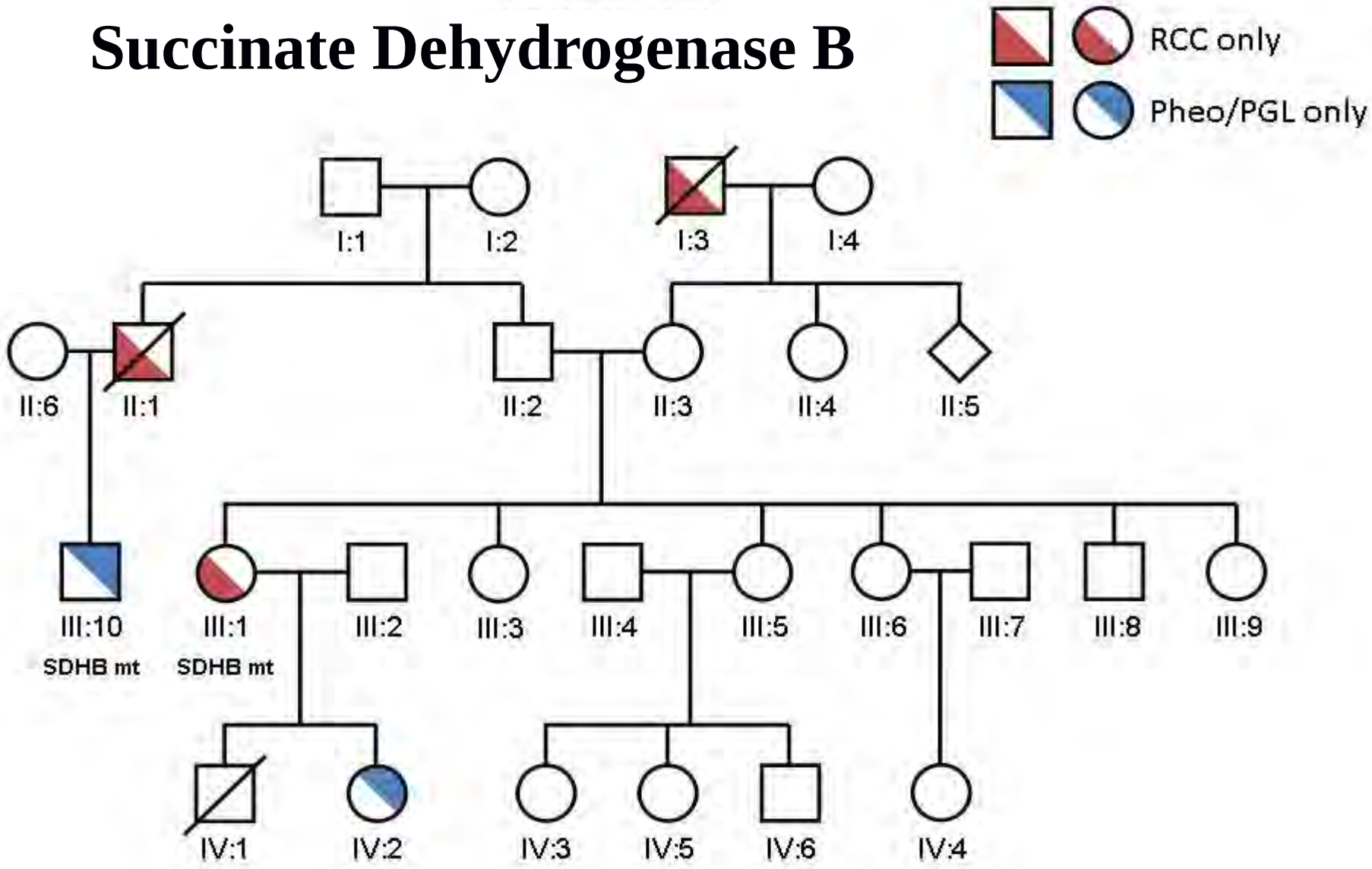


Benn, et al. Oncogene 22:2003

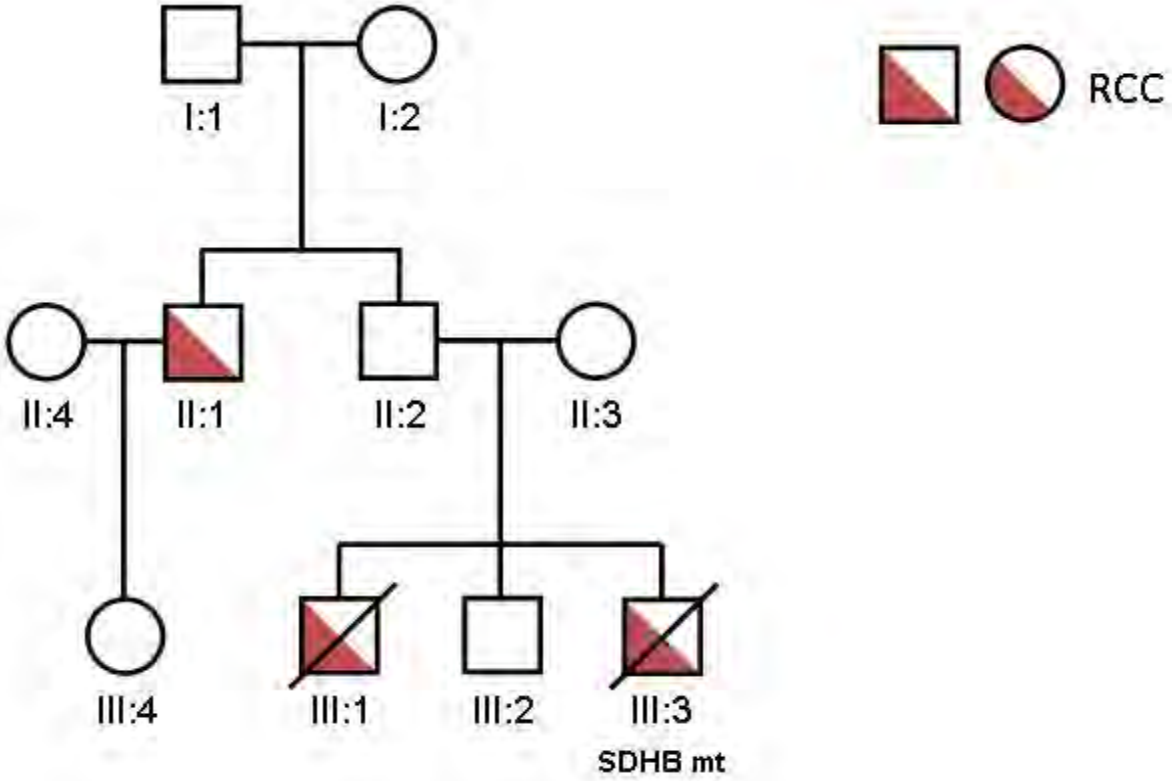
Succinate Dehydrogenase



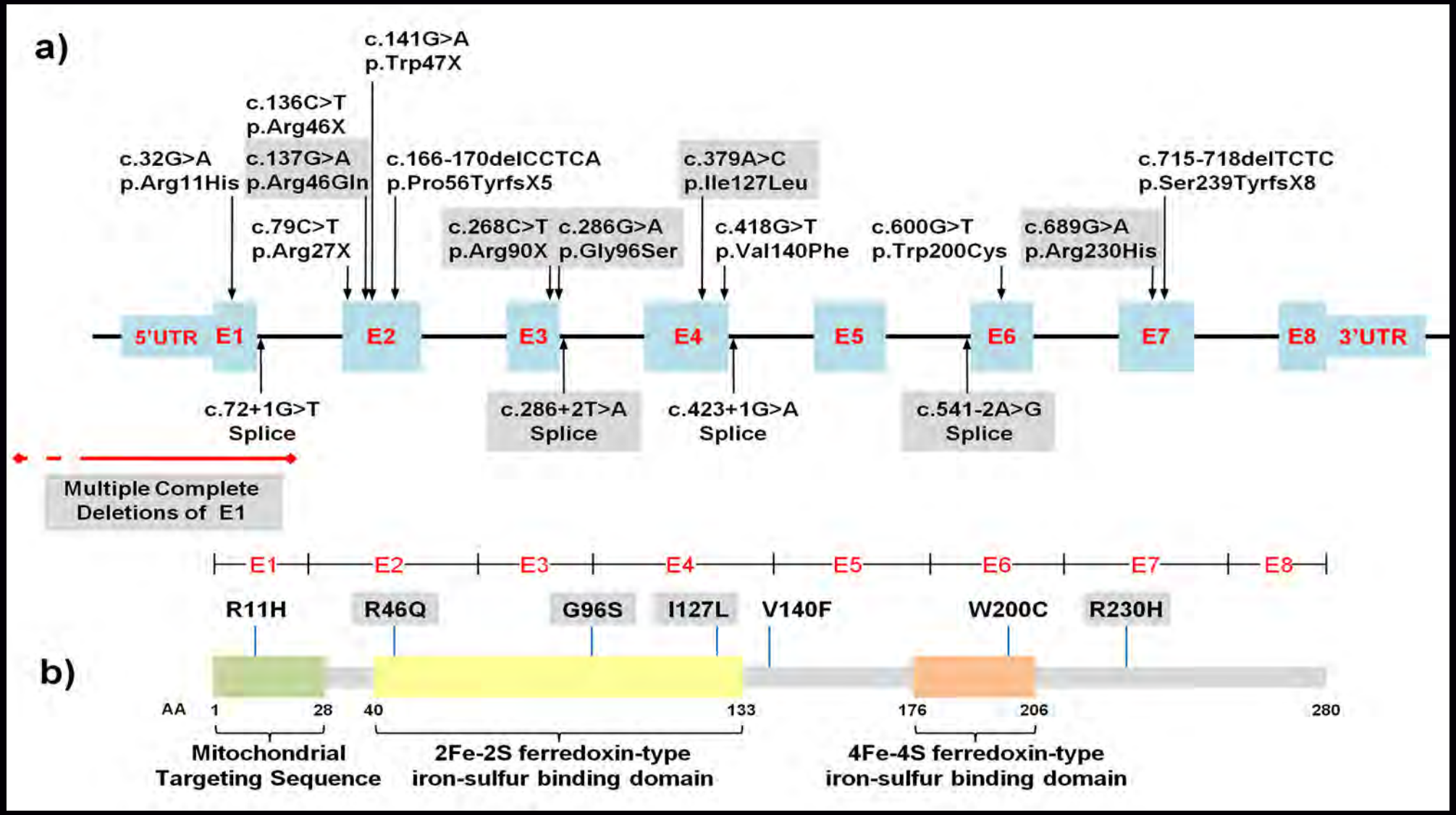
SDH-RCC
Succinate Dehydrogenase B



SDH-RCC
Succinate Dehydrogenase B

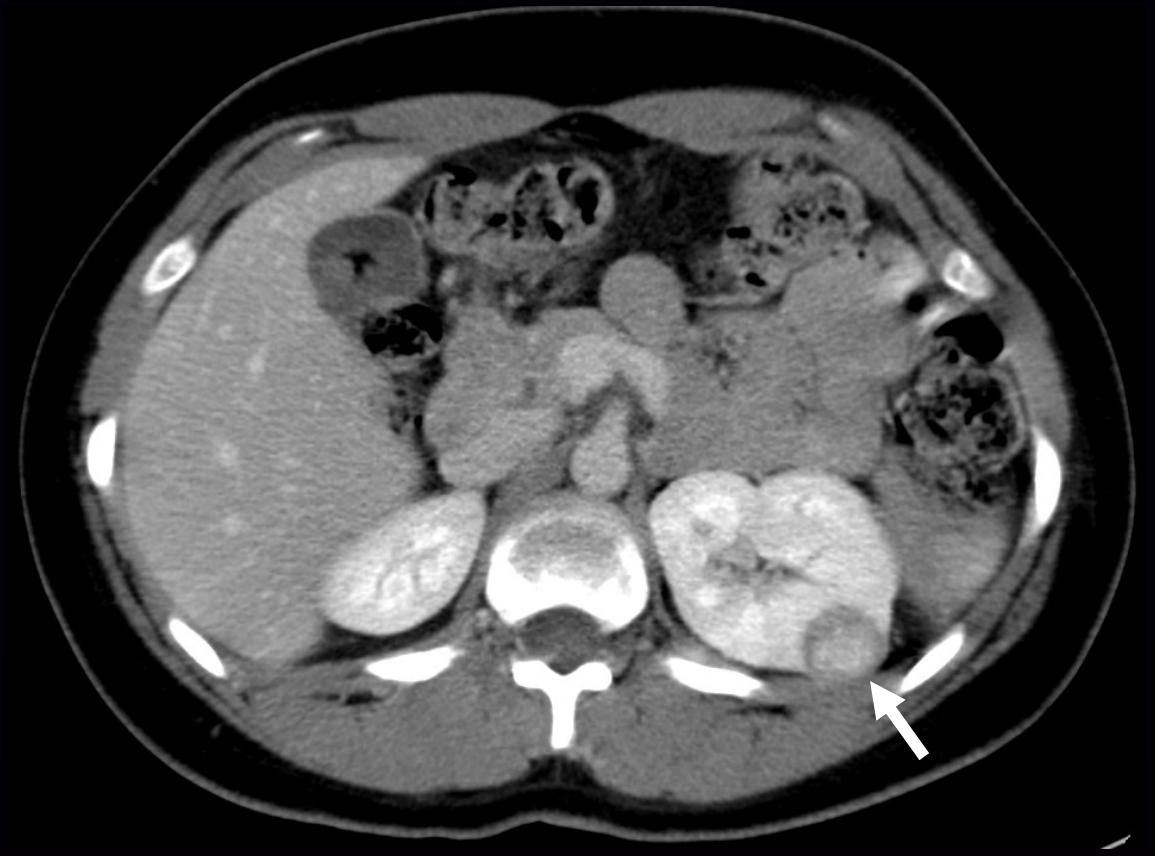


SDHB-RCC


a)
c.141G>A
p.Trp47X
c.136C>T
p.Arg46X
c.32G>A
p.Arg11His
c.137G>A
p.Arg46Gln
c.166-170delCCTCA
p.Pro56TyrfsX5
c.379A>C
p.Ile127Leu
c.715-718delTCTC
p.Ser239TyrfsX8
c.79C>T
p.Arg27X
c.268C>T
p.Arg90X
c.286G>A
p.Gly96Ser
c.418G>T
p.Val140Phe
c.600G>T
p.Trp200Cys
c.689G>A
p.Arg230His
5'UTR
E1
E2
E3
E4
E5
E6
E7
E8
3'UTR
c.72+1G>T
Splice
c.286+2T>A
Splice
c.423+1G>A
Splice
c.541-2A>G
Splice
Multiple Complete
Deletions of E1
E1
E2
E3
E4
E5
E6
E7
E8
R11H
R46Q
G96S
I127L
V140F
W200C
R230H
b)
AA
1
28
40
133
176
206
280
Mitochondrial
Targeting Sequence
2Fe-2S ferredoxin-type
iron-sulfur binding domain
4Fe-4S ferredoxin-type
iron-sulfur binding domain

SDH-RCC
Succinate Dehydrogenase B

19 y.o. female

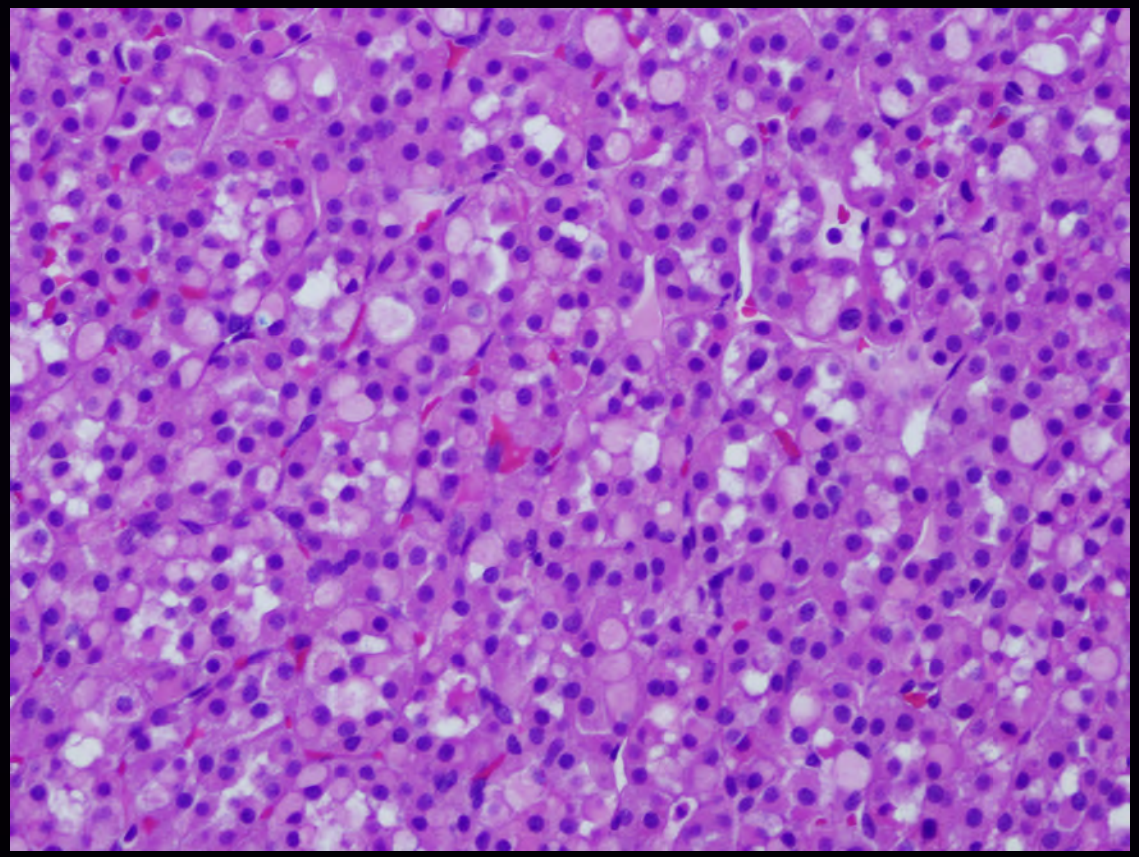


SDHB Mutation: c.541-2A>G, IVS5-2A>G, Splice Acceptor

SDH-RCC
Succinate Dehydrogenase B

19 y.o. female

"Oncocytic"
+ mitochondria



SDHB Mutation: c.541-2A>G, IVS5-2A>G, Splice Acceptor

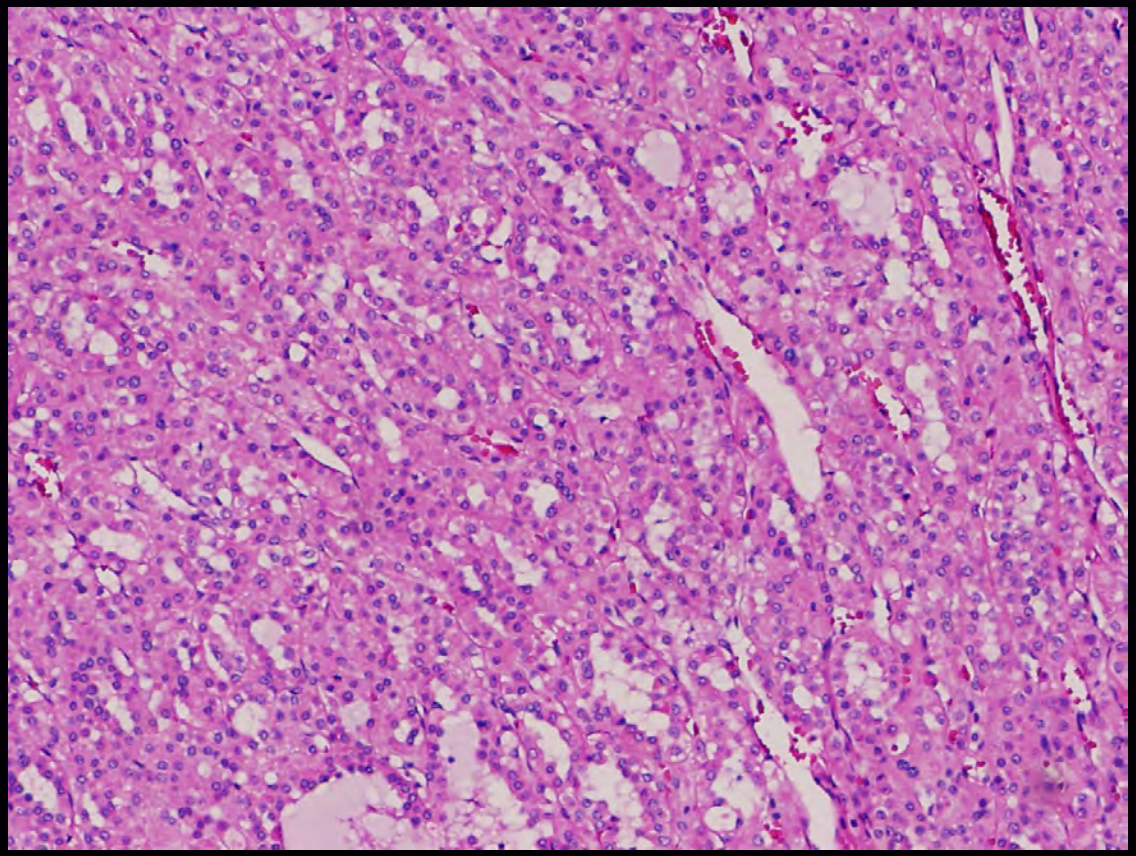
SDH-RCC
Succinate Dehydrogenase B

17 y.o. Male

Germline SDHB mutation: c.137G>A

SDH-RCC
Succinate Dehydrogenase B

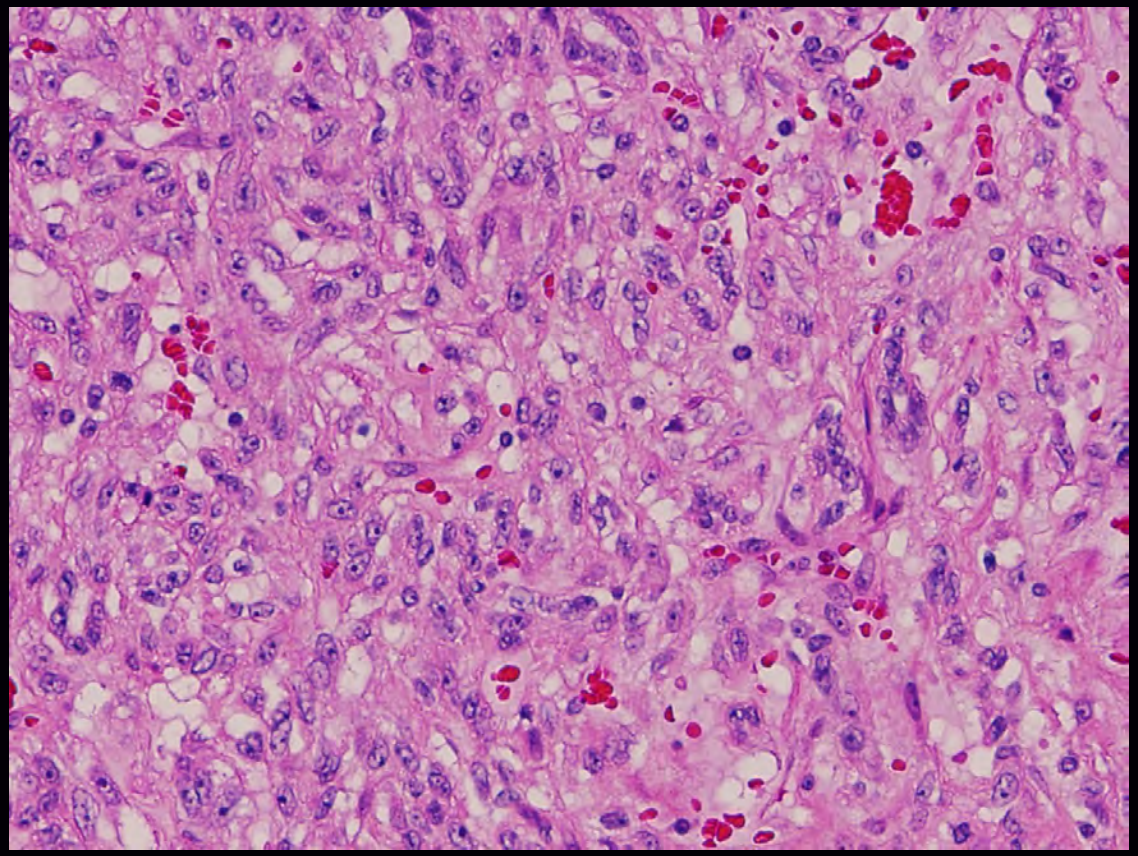
17 y.o. Male
“Oncocytic”
Kidney Cancer



Germline SDHB mutation: c.137G>A

SDH-RCC
Succinate Dehydrogenase B

17 y.o. Male
"Oncocytic"
Kidney Cancer
With
"Spindle
Features"



Germline SDHB mutation: c.137G>A

SDH-RCC
Succinate Dehydrogenase B

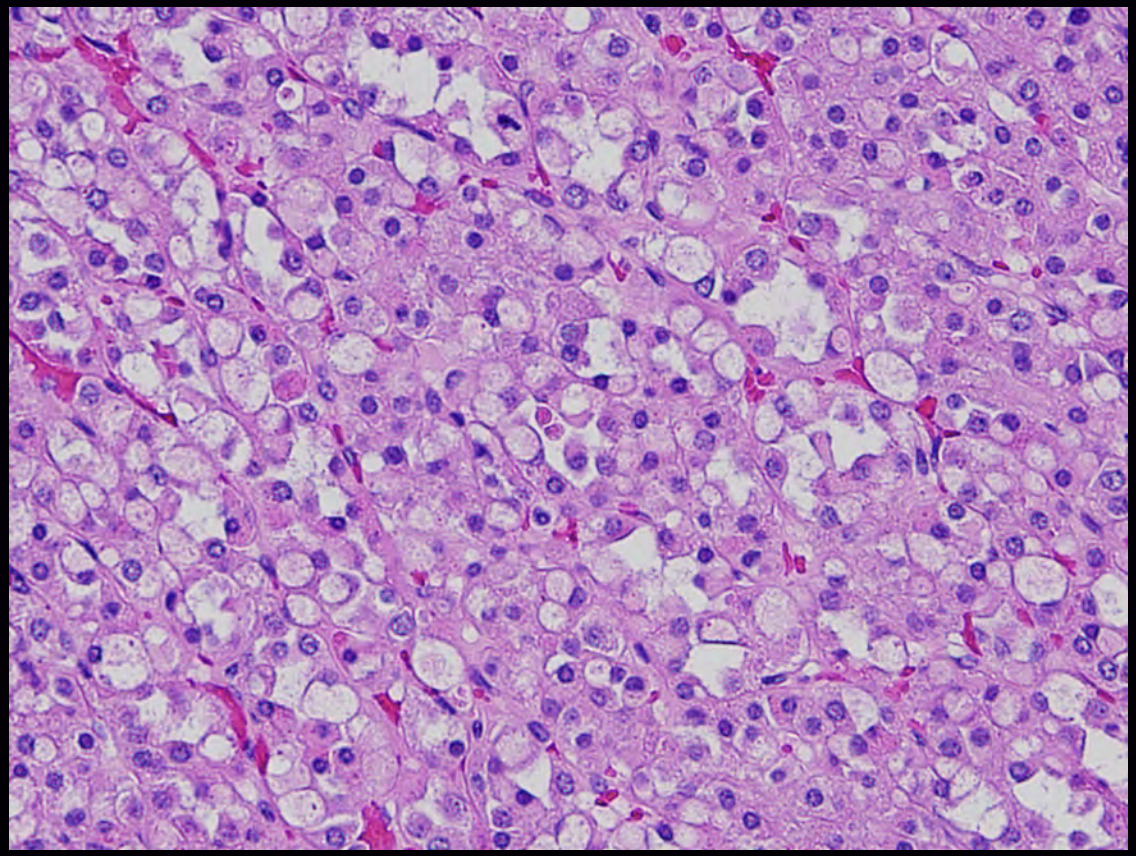
27 y.o. female

SDHB Mutation: Partial Deletion

SDH-RCC
Succinate Dehydrogenase B

27 y.o. female

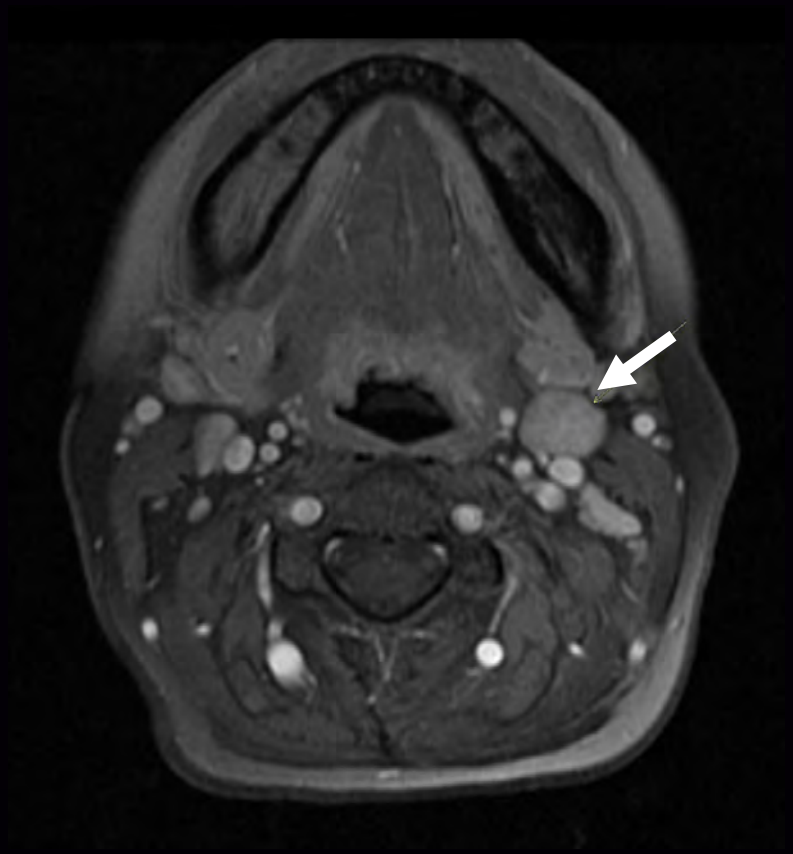
"Oncocytic"
Kidney Cancer



SDHB Mutation: Partial Deletion

SDH-RCC
Succinate Dehydrogenase B

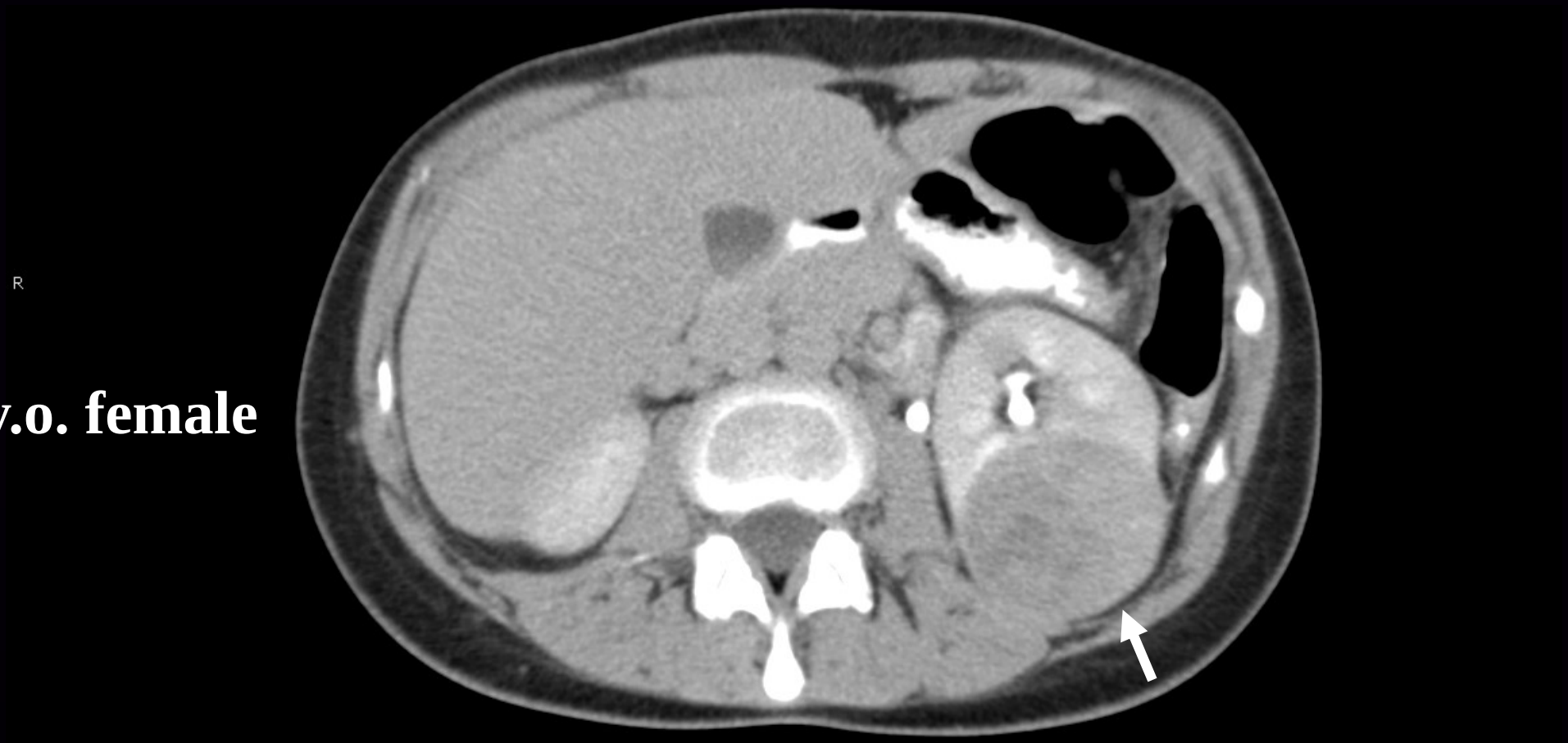
27 y.o. female



Carotid body Tumor (CBT)

SDHB Mutation: Partial Deletion

SDH-RCC
Succinate Dehydrogenase B



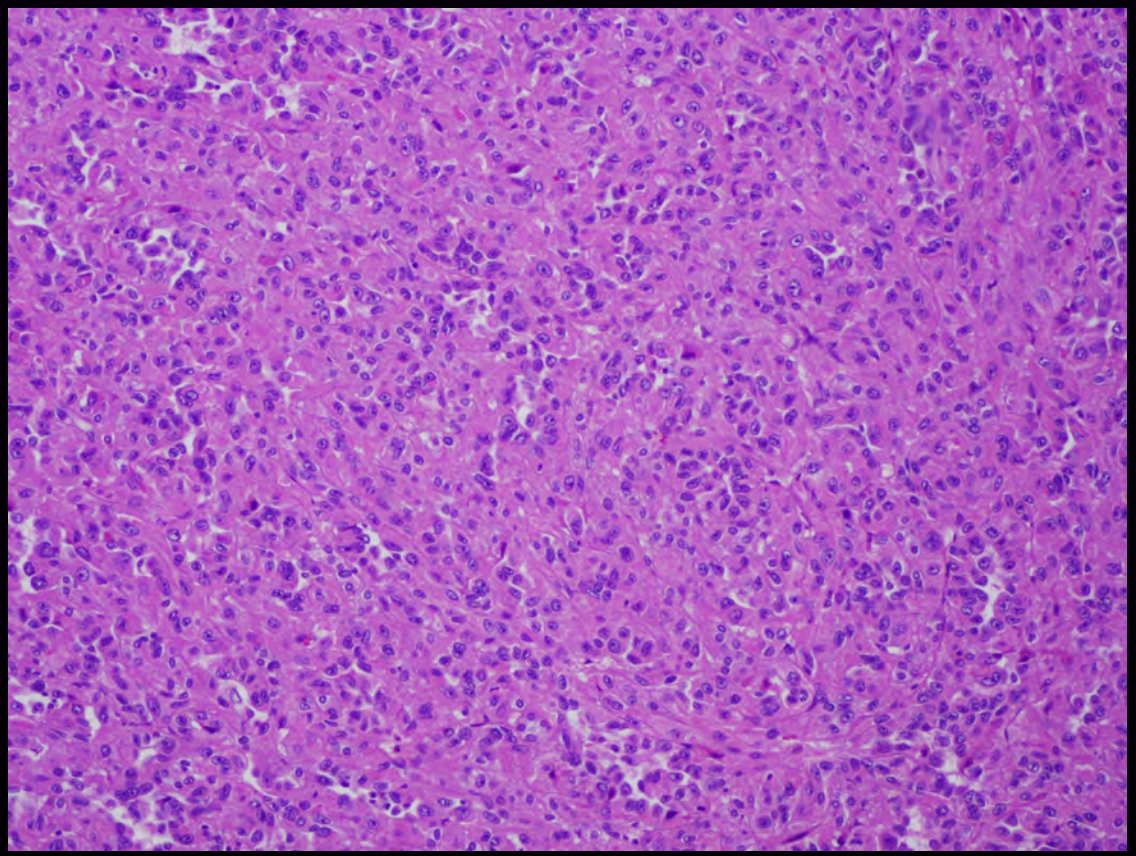
33 y.o. female

SDHB Mutation: G>A, NT 137, Arg46Gln, Missense

SDH-RCC
Succinate Dehydrogenase B

33 y.o. female

"Oncocytic"
Kidney Cancer



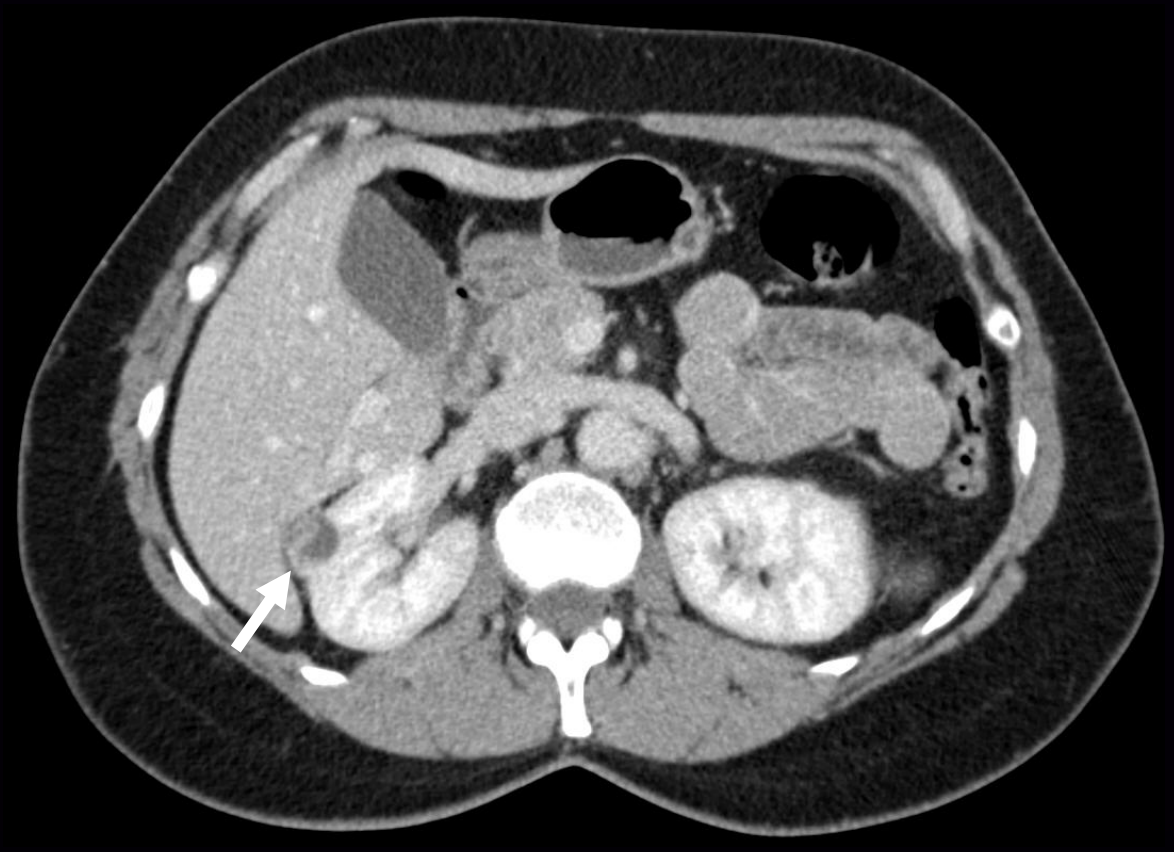
→ UOK269
SDHB -/-
RCC cell line

SDHB Mutation: G>A, NT 137, Arg46Gln, Missense

SDH-RCC
Succinate Dehydrogenase B

55 y.o. female

1.8 cm tumor

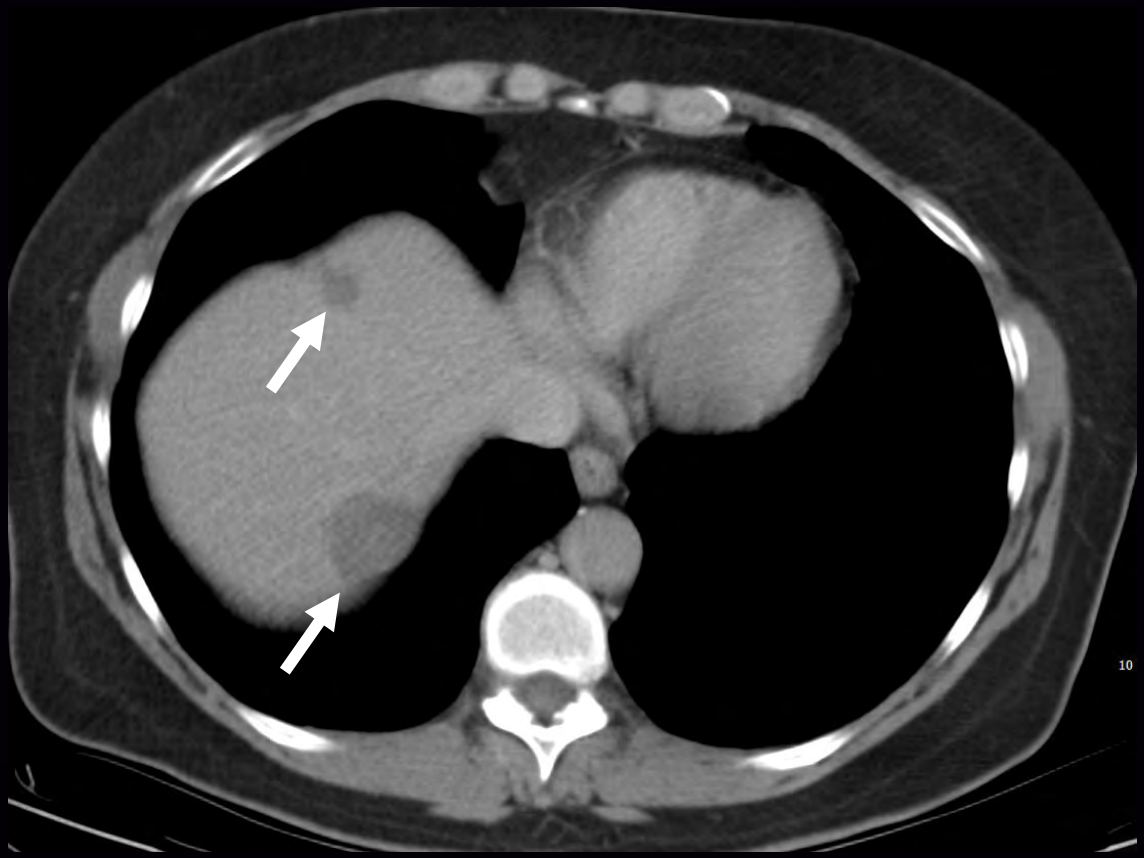


SDHB Mutation: G>A, NT 286, Gly96Ser, Missense

SDH-RCC
Succinate Dehydrogenase B

55 y.o. female

Hepatic Metastases

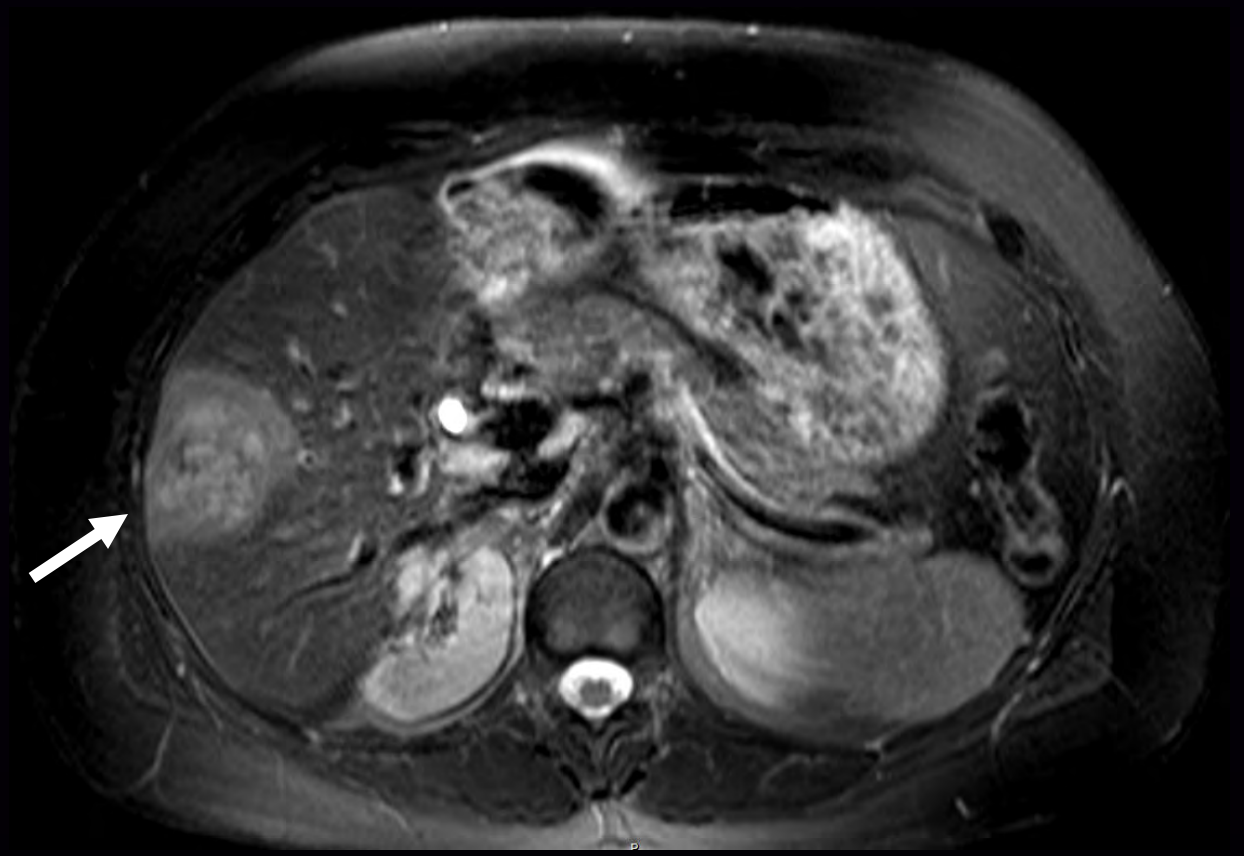


SDHB Mutation: G>A, NT 286, Gly96Ser, Missense

SDH-RCC
Succinate Dehydrogenase B

55 y.o. female

Hepatic Metastases

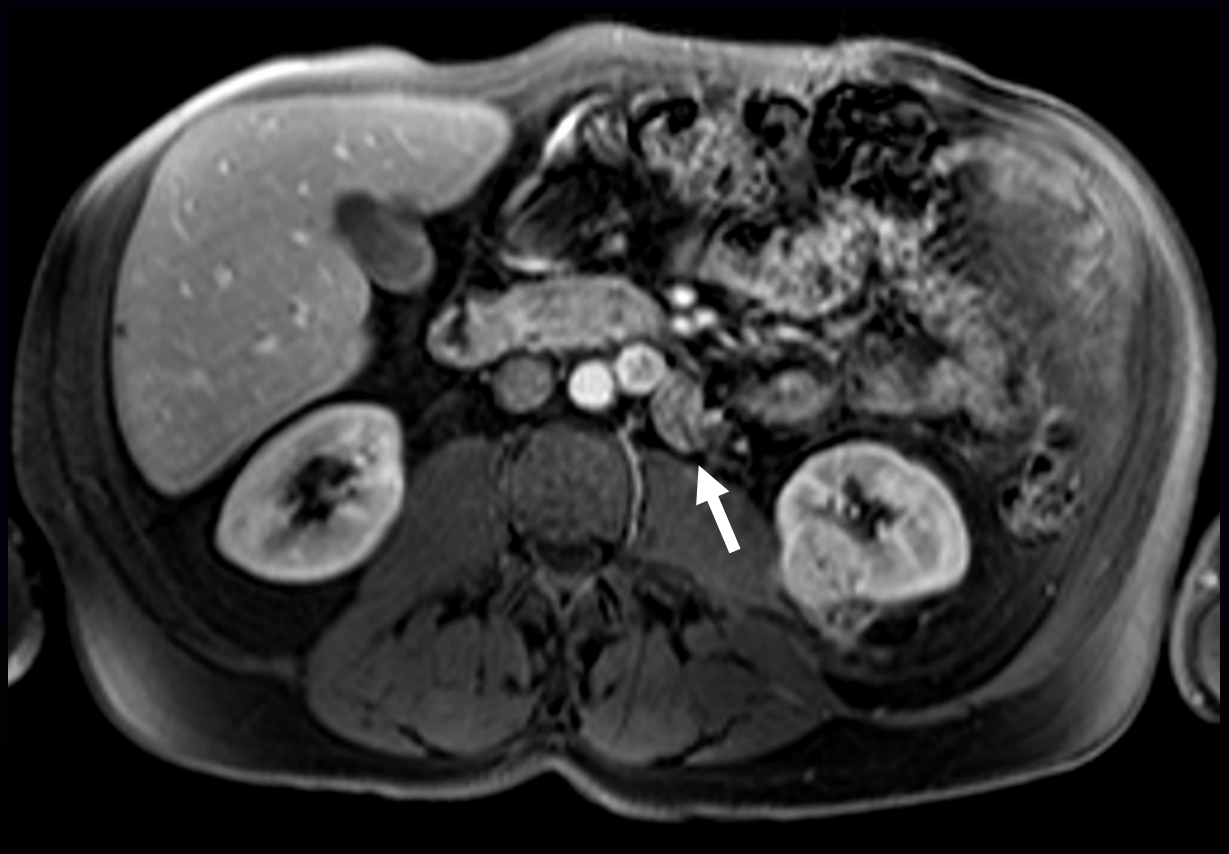


SDHB Mutation: G>A, NT 286, Gly96Ser, Missense

SDH-RCC
Succinate Dehydrogenase B

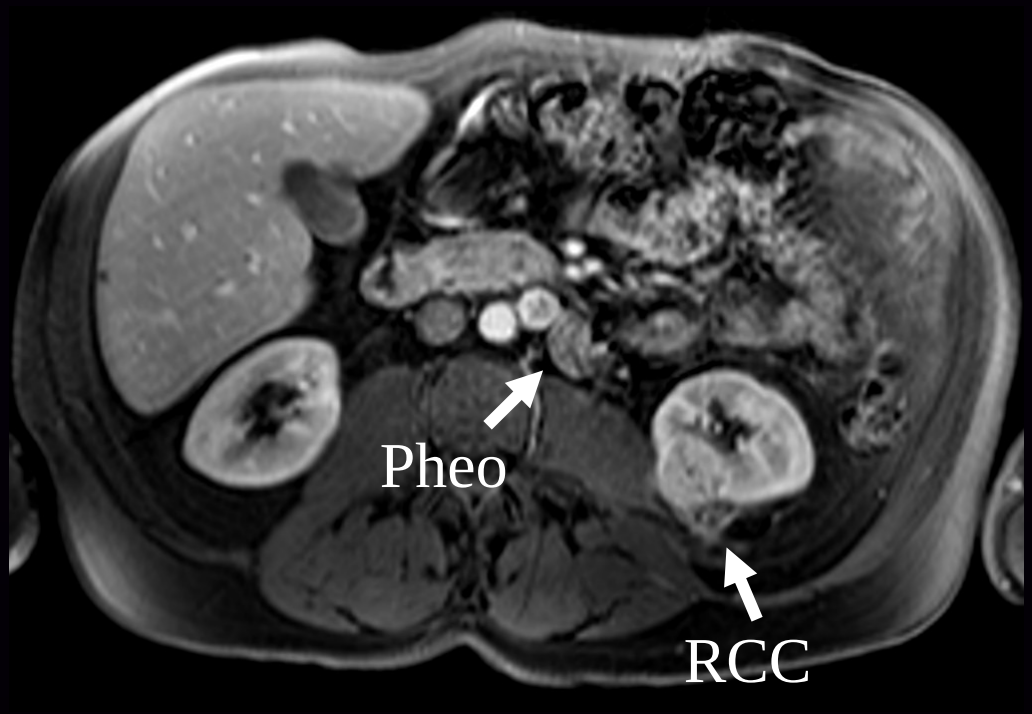
61 y.o. male

Pheochromocytoma

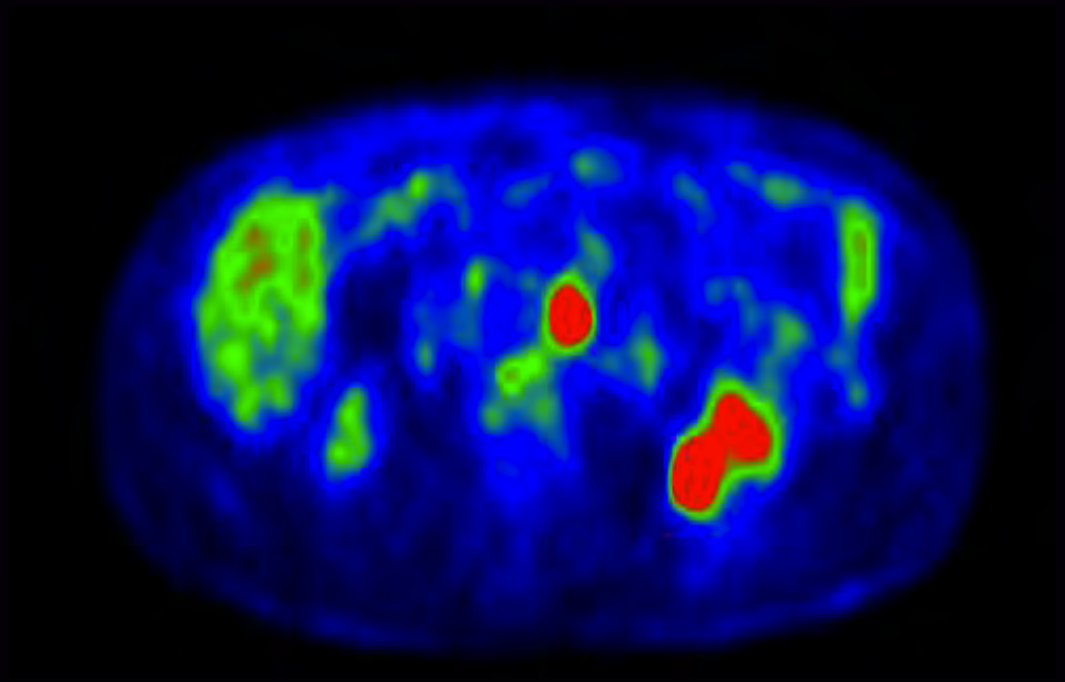


SDHB Mutation: C>T, NT 268, p.Arg90X, AA# = 90, Nonsense

SDHB-RCC
Glucose Uptake: FDG PET Scan

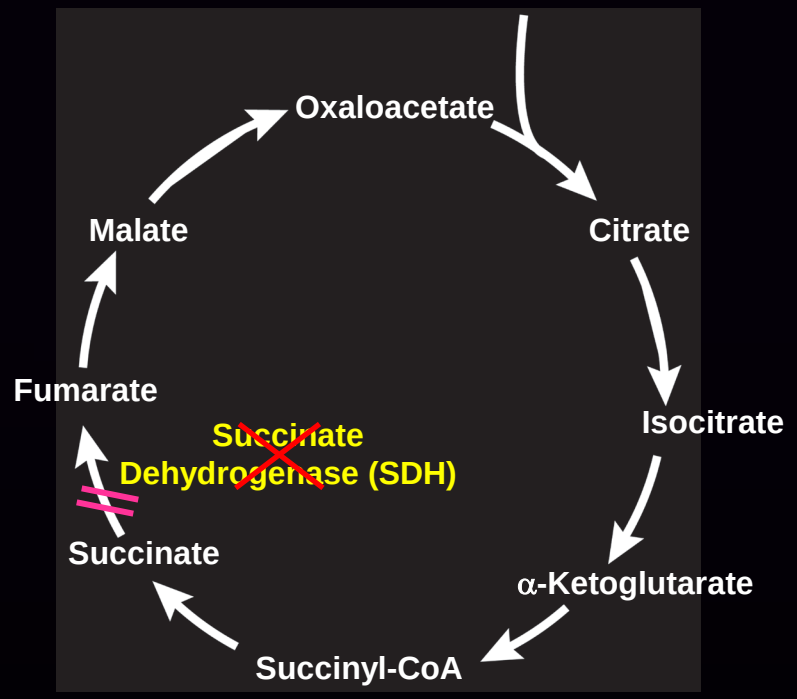


CT SCAN



FDG PET SCAN

Familial Renal Carcinoma
Succinate Dehydrogenase B

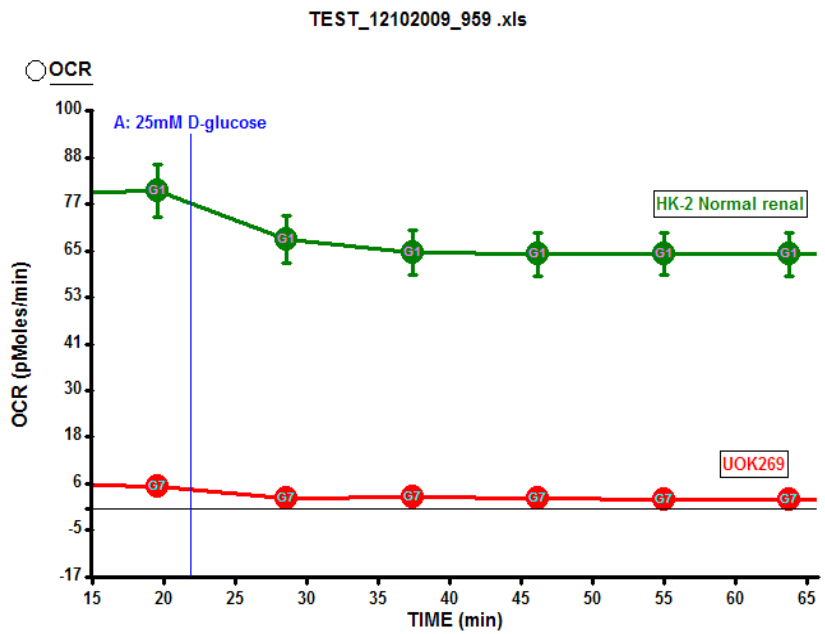


Citric Acid Cycle

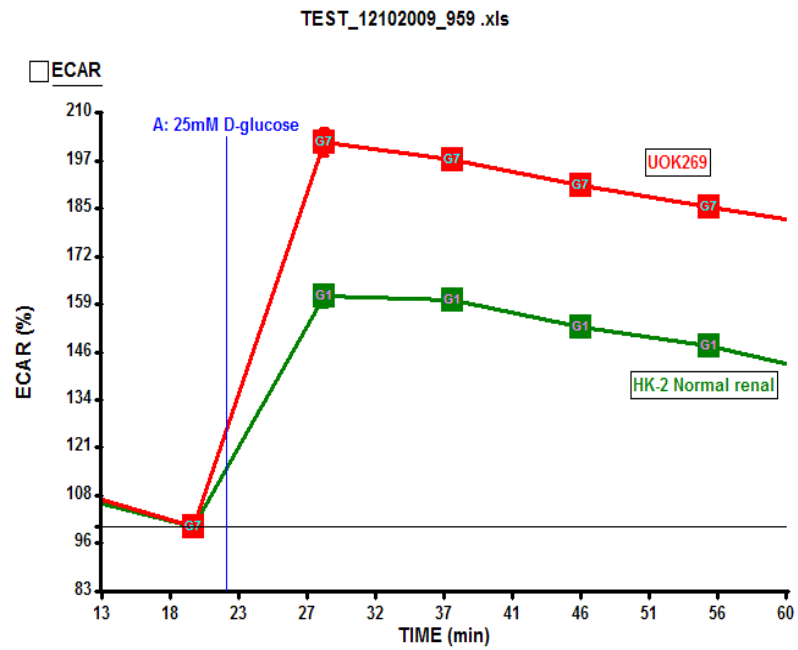
Benn, et al. Oncogene 22:2003

SDH-deficient Kidney Cancer (UOK-269) Characterized by Aerobic Glycolysis

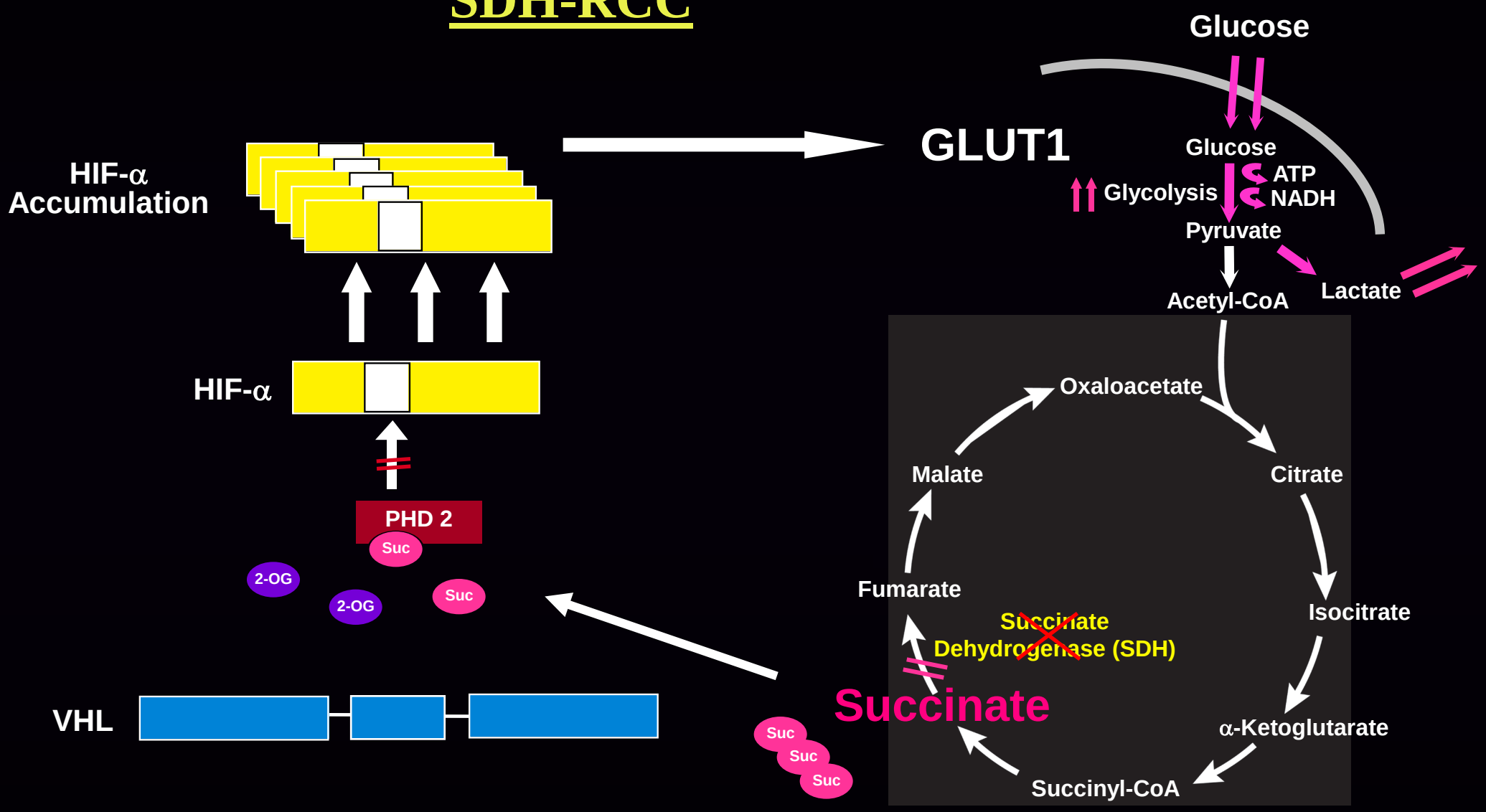
O2 Consumption Rate (OCR)



Extracellular Acidification Rate (ECAR-Glycolysis)



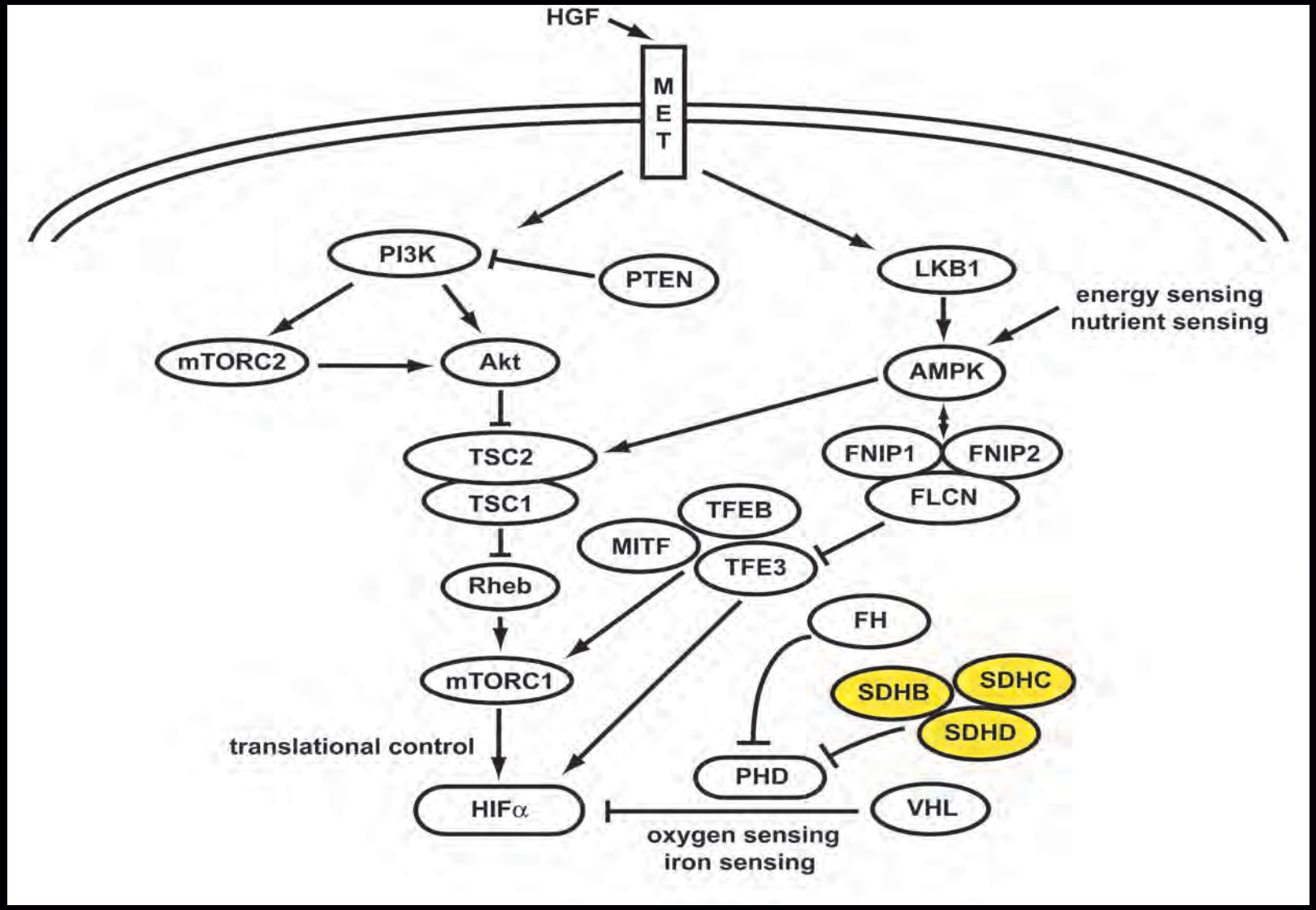
SDH-RCC



Yang, et al. In prep

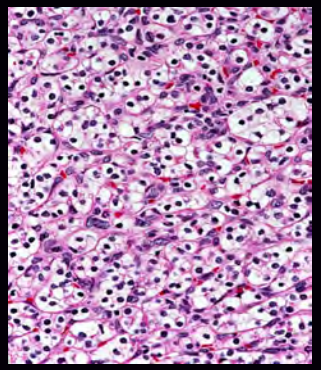
Citric Acid Cycle

Kidney Cancer is a Metabolic Disease

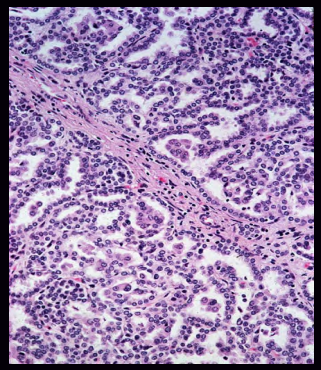


Nature Rev Urol: 7 2010

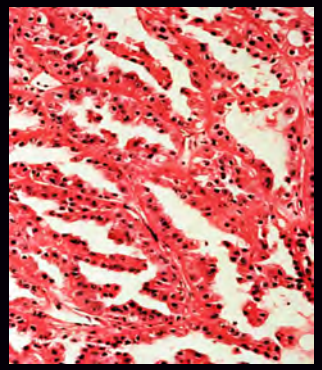
Human Renal Epithelial Neoplasms



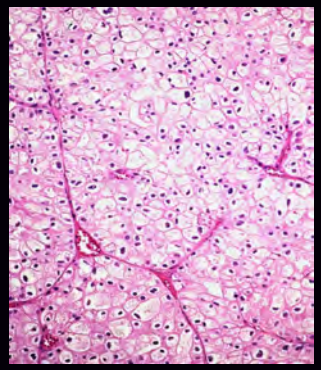
Clear Cell
VHL



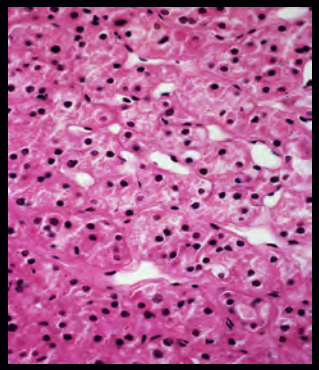
Papillary Type 1
Met



Papillary Type 2
FH

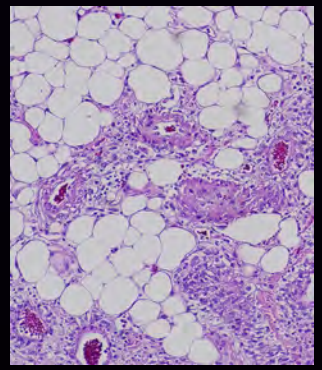


Chromophobe

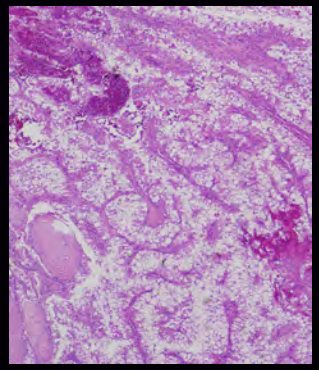


Oncocytoma

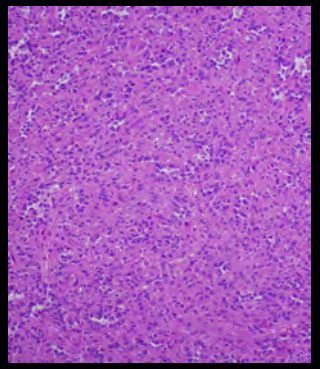
FLCN



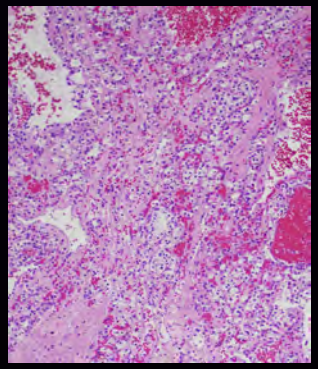
Angiomyolipoma
TSC1, TSC2



TFE3
TFE3, TFEB, MITF

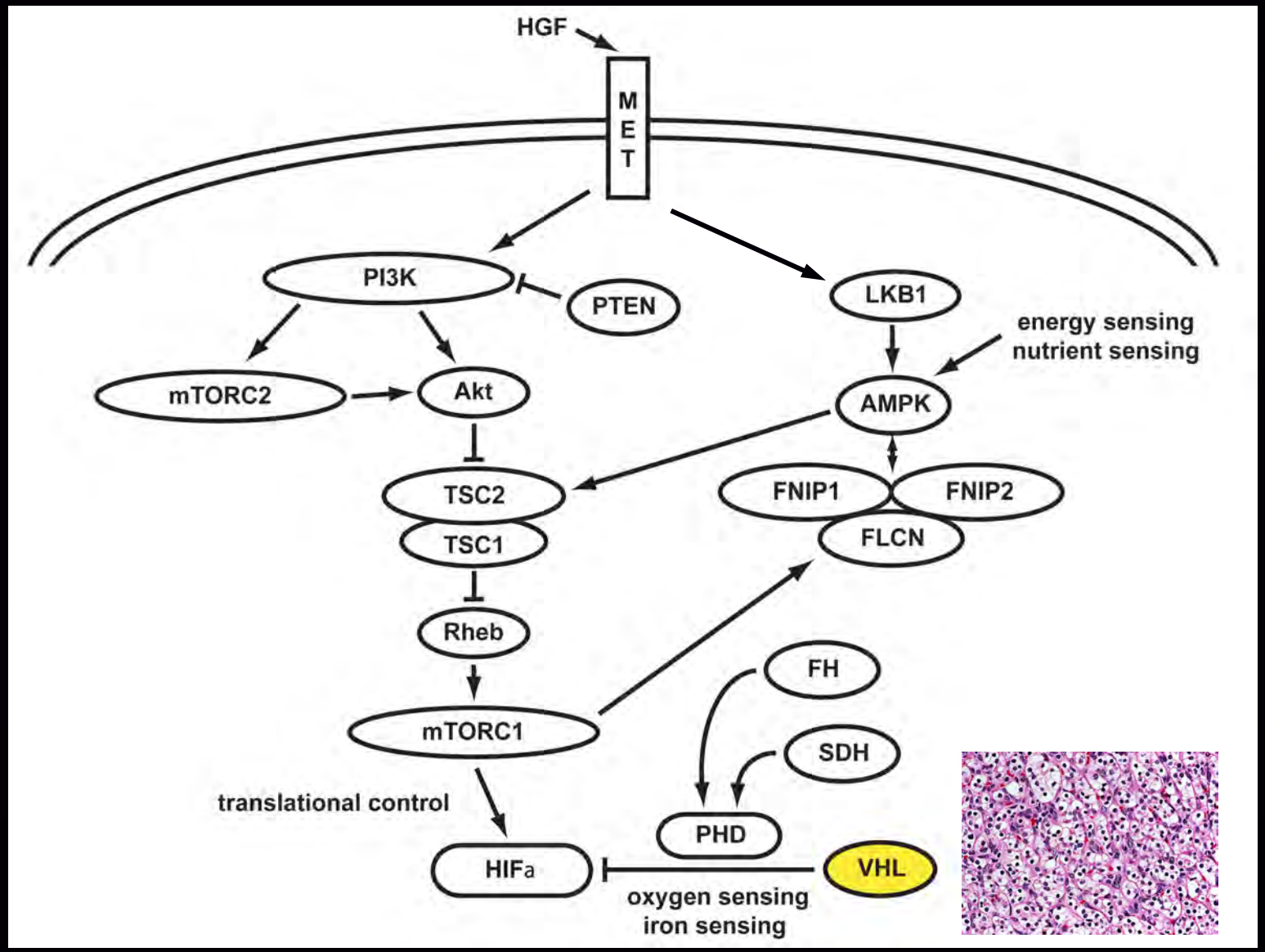


Oncocytic
SDHB, SDHC, SDHD



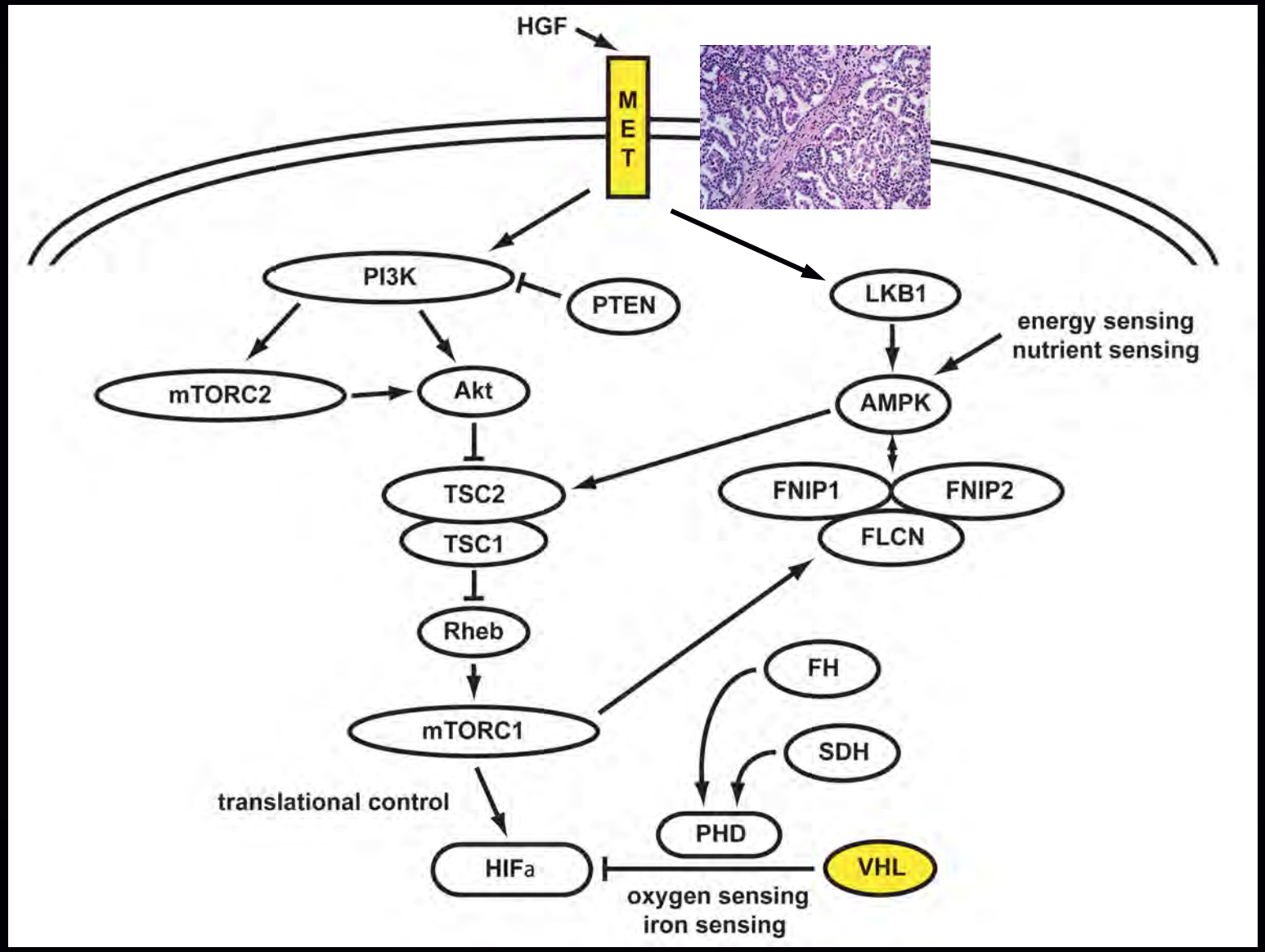
Clear/Chromophobe
PTEN

Kidney Cancer is a Metabolic Disease



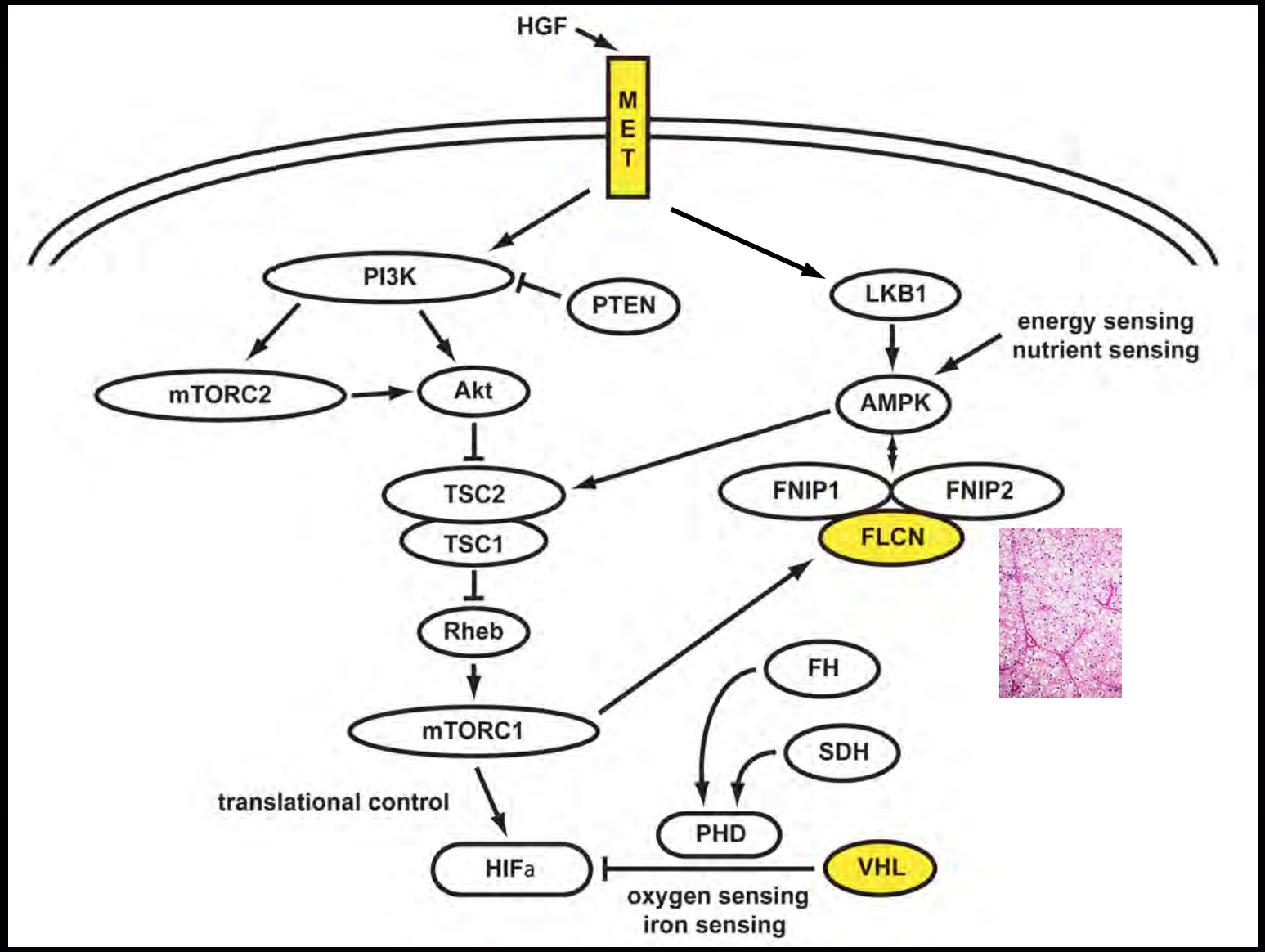
Nature Rev Urol: 7 2010

Kidney Cancer is a Metabolic Disease



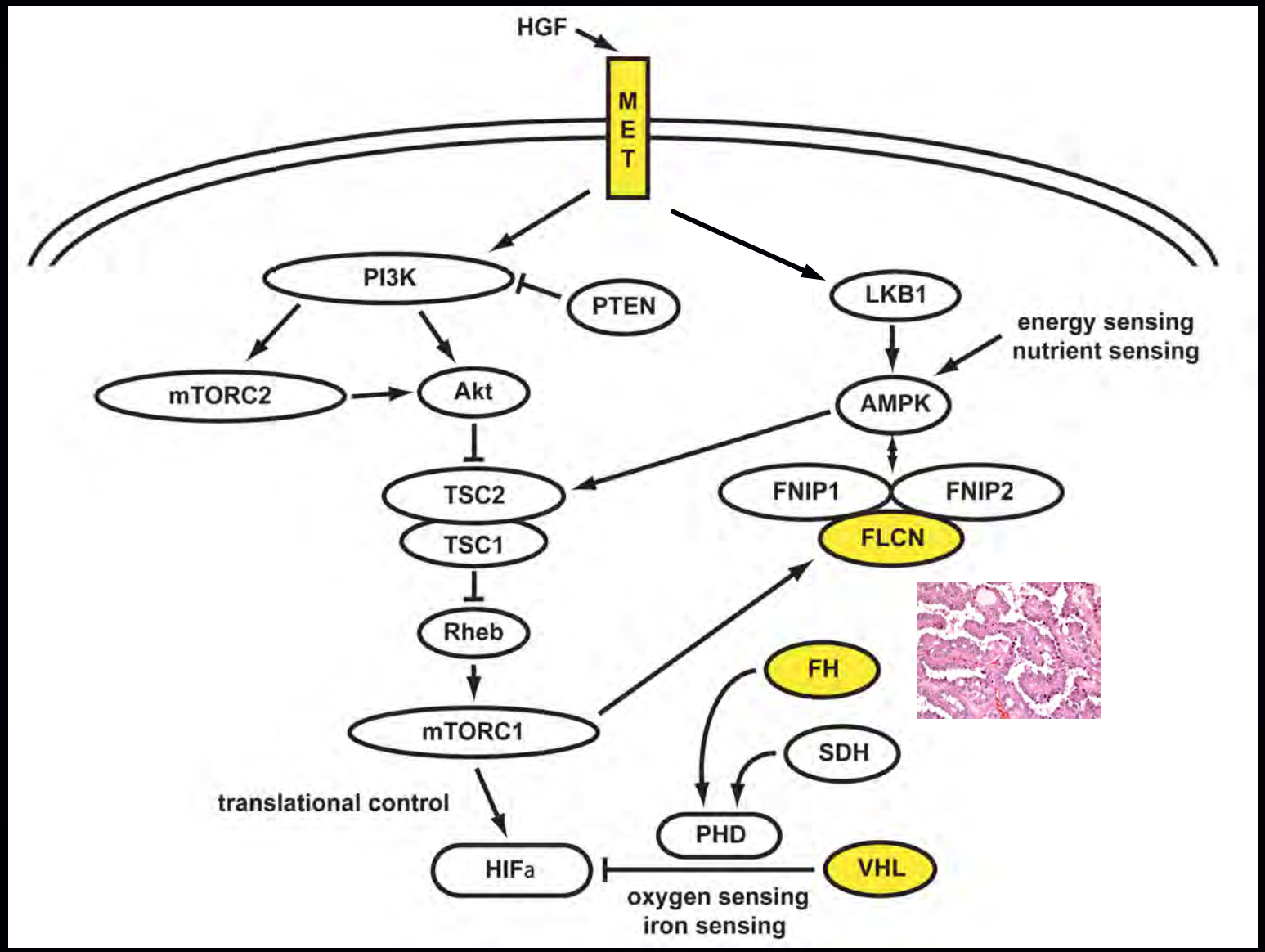
Nature Rev Urol: 7 2010

Kidney Cancer is a Metabolic Disease



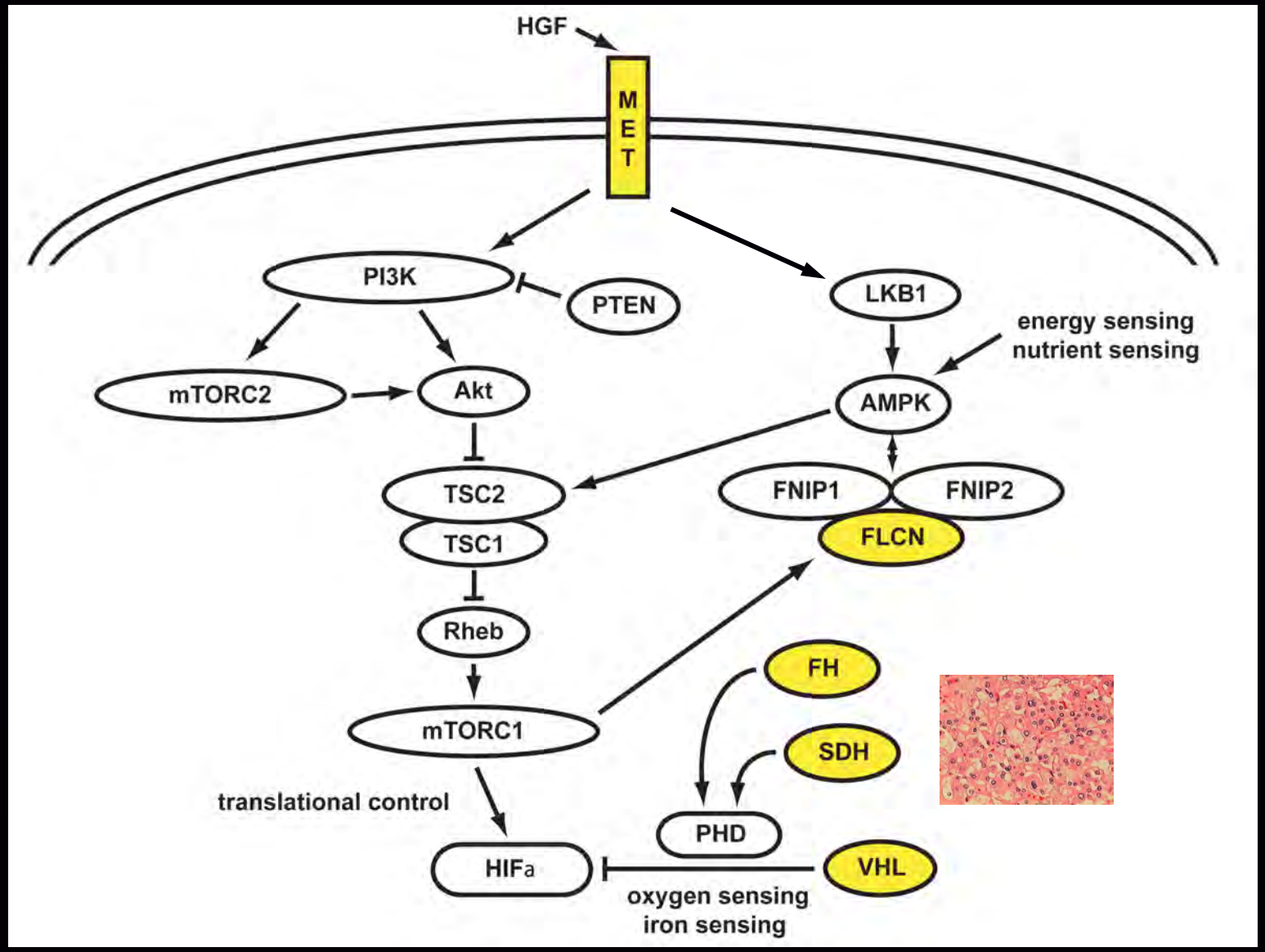
Nature Rev Urol: 7 2010

Kidney Cancer is a Metabolic Disease



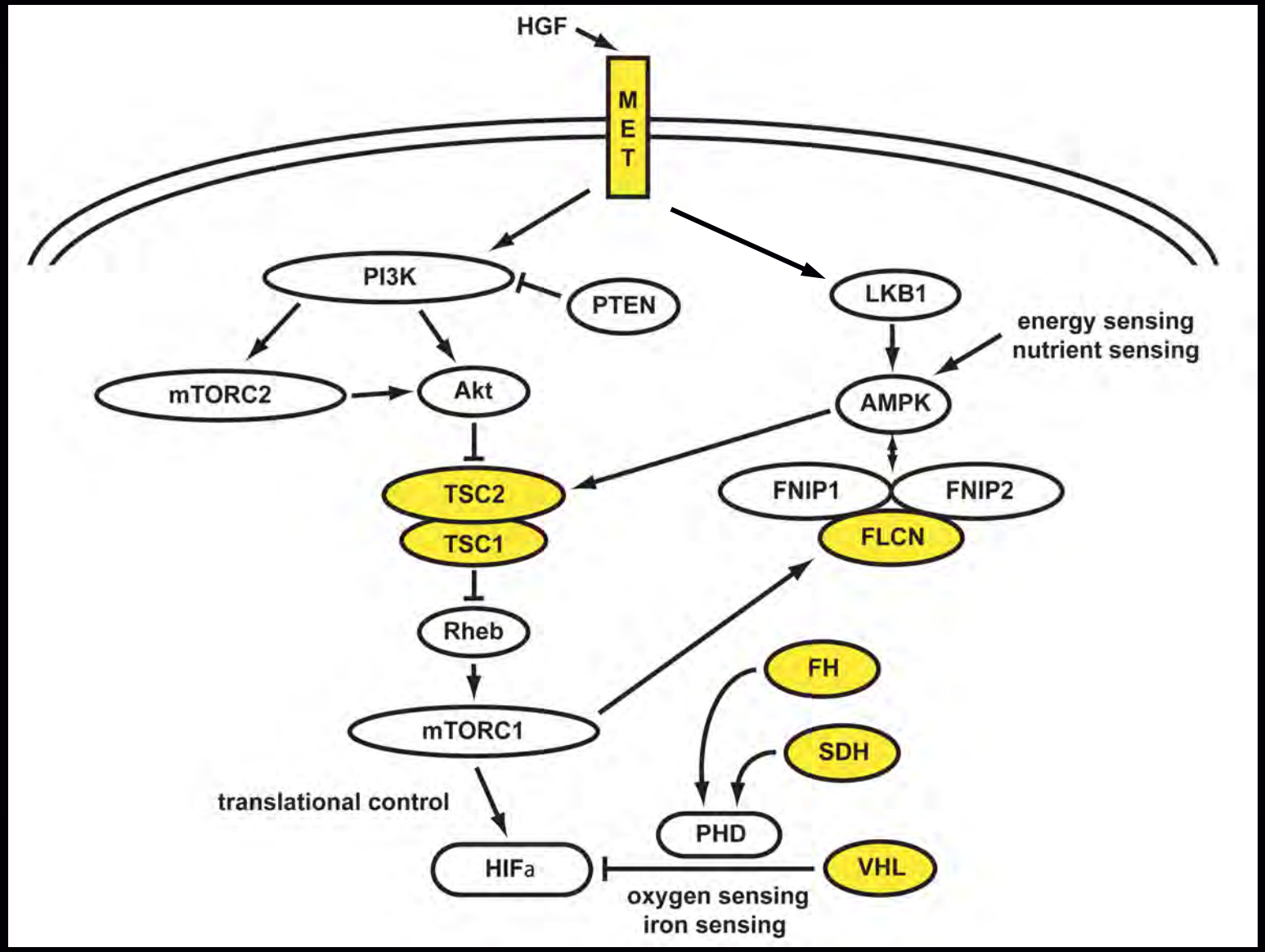
Nature Rev Urol: 7 2010

Kidney Cancer is a Metabolic Disease



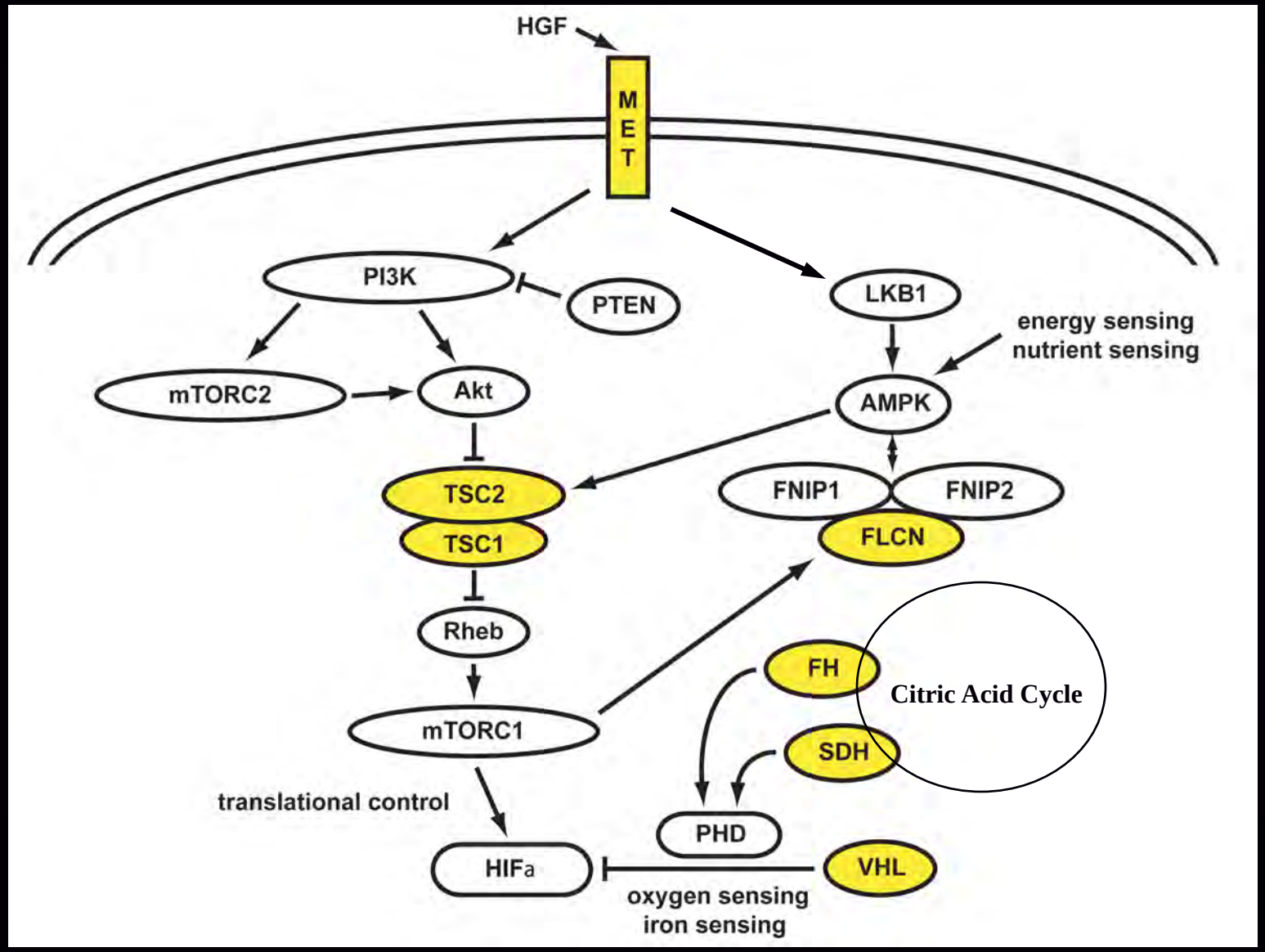
Nature Rev Urol: 7 2010

Kidney Cancer is a Metabolic Disease



Nature Rev Urol: 7 2010

Kidney Cancer is a Metabolic Disease



Nature Rev Urol: 7 2010

Peter A. Pinto, M.D.

- **Prostate Cancer**
- **Surgical & minimally invasive management of localized prostate cancer**
- **MRI/image guided biopsy localized prostate cancer**
- **Molecular therapeutic approaches localized prostate cancer**

Adam Metwalli, M.D.

- **Kidney Cancer**
- **Surgical & minimally invasive management of localized/advanced kidney cancer**
- **Molecular therapeutic approaches kidney cancer**

Piyush Agarwal, M.D.

- **Bladder Cancer**
- **Surgical & minimally invasive management of localized/advanced bladder cancer**
- **Molecular therapeutic approaches bladder cancer**

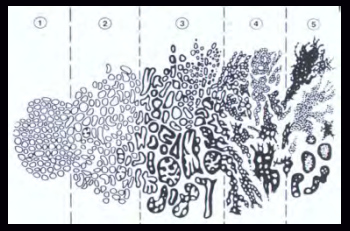
Ramaprasad Srinivasan, MD,Ph.D

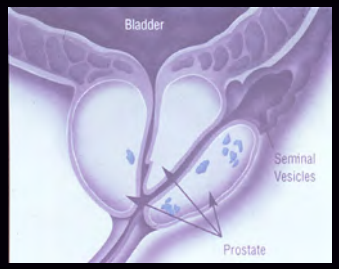
- **Molecular therapeutic trials, hereditary and sporadic kidney cancer**

- **Small molecule natural products targeting the kidney cancer gene pathways**

Urologic Oncology Fellows 2012-2013

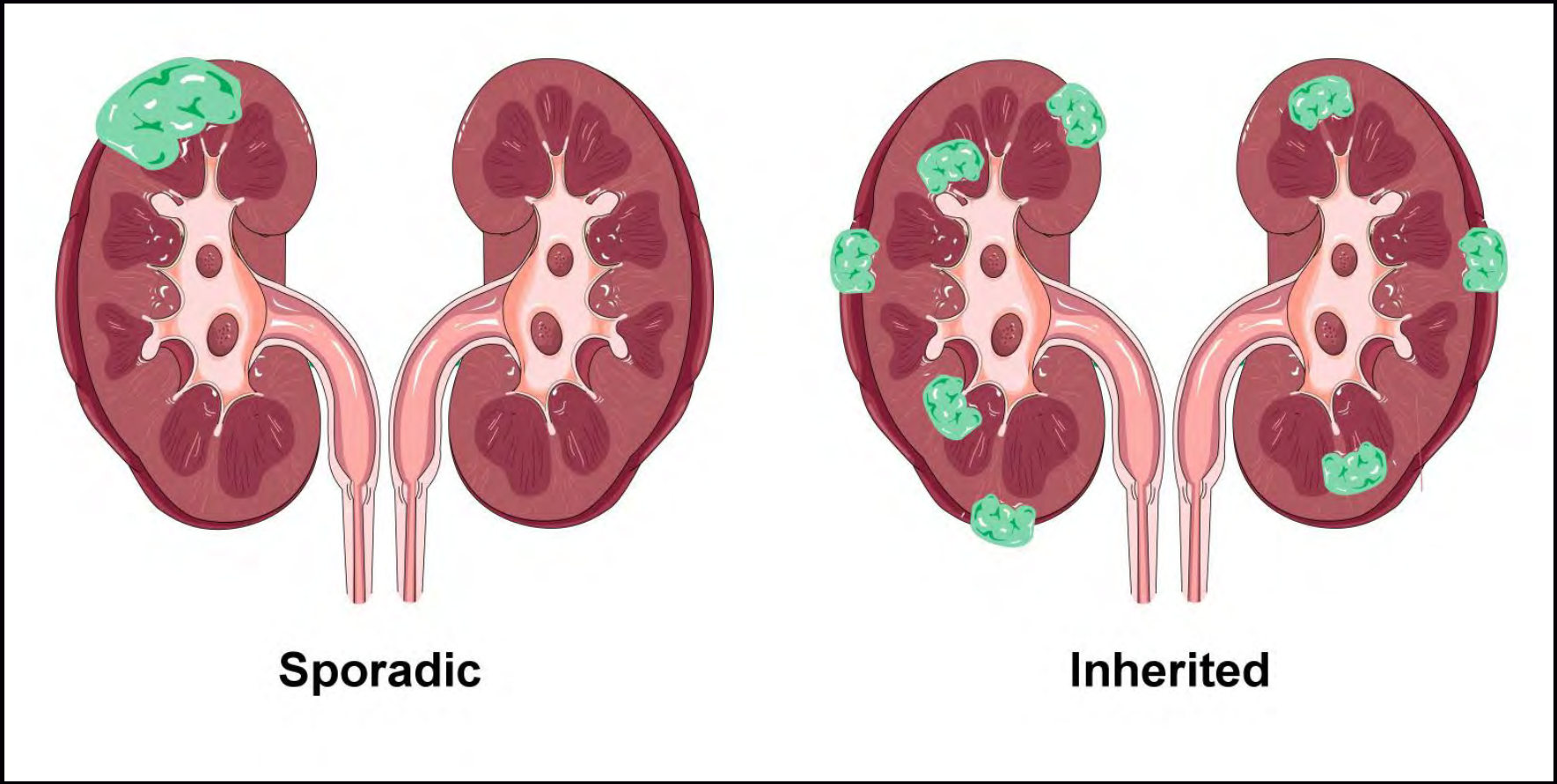
- Brain Shuch, M.D.
- Srinivas Vourganti, M.D.
- Armine Smith, M.D.
- Anthony Huang, M.D.
- Jeffery Nix, M.D.
- Soroush Rais Bahrami, M.D.
- Minhaj Siddiqui, M.D.
- Lambros Stamatakis, M.D.





Urologic Oncology Branch
National Cancer Institute

Inherited Renal Carcinoma: Tuberous Sclerosis Complex (TSC)



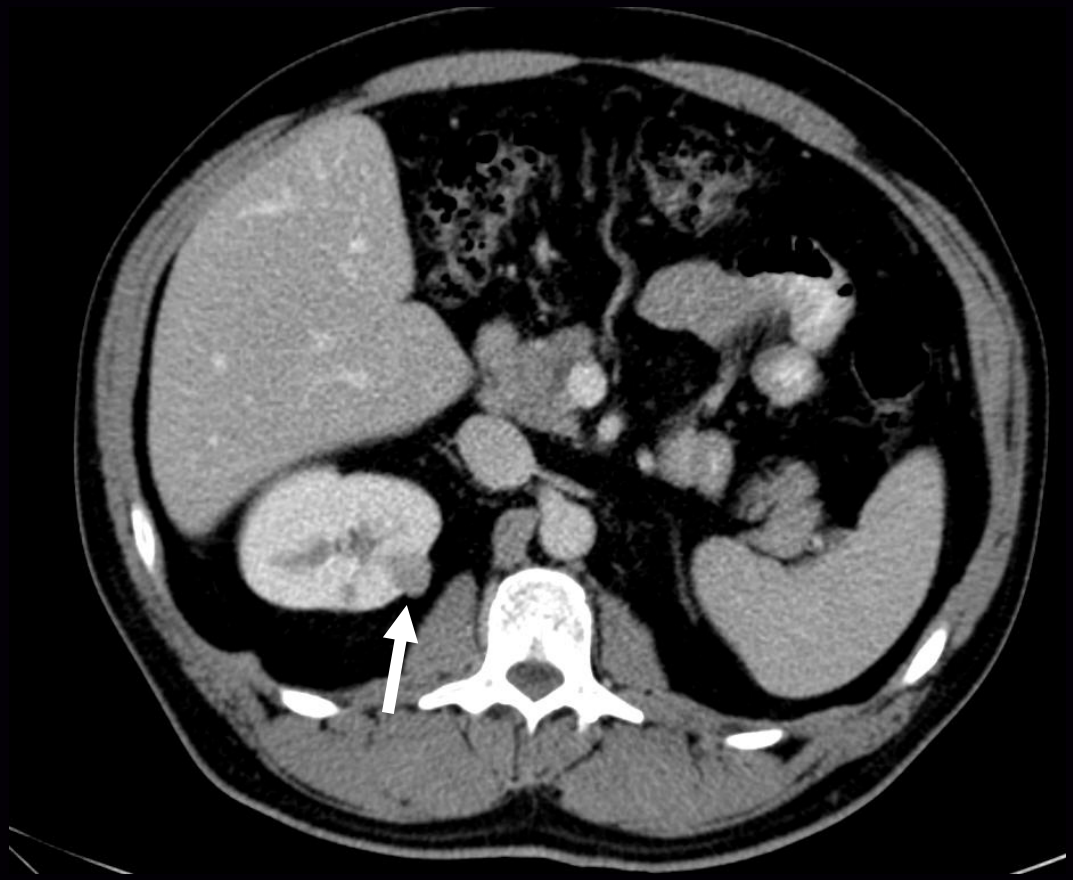
TSC: Angiomyolipoma

49 Year Old Male

TSC: “Fat Poor AML”

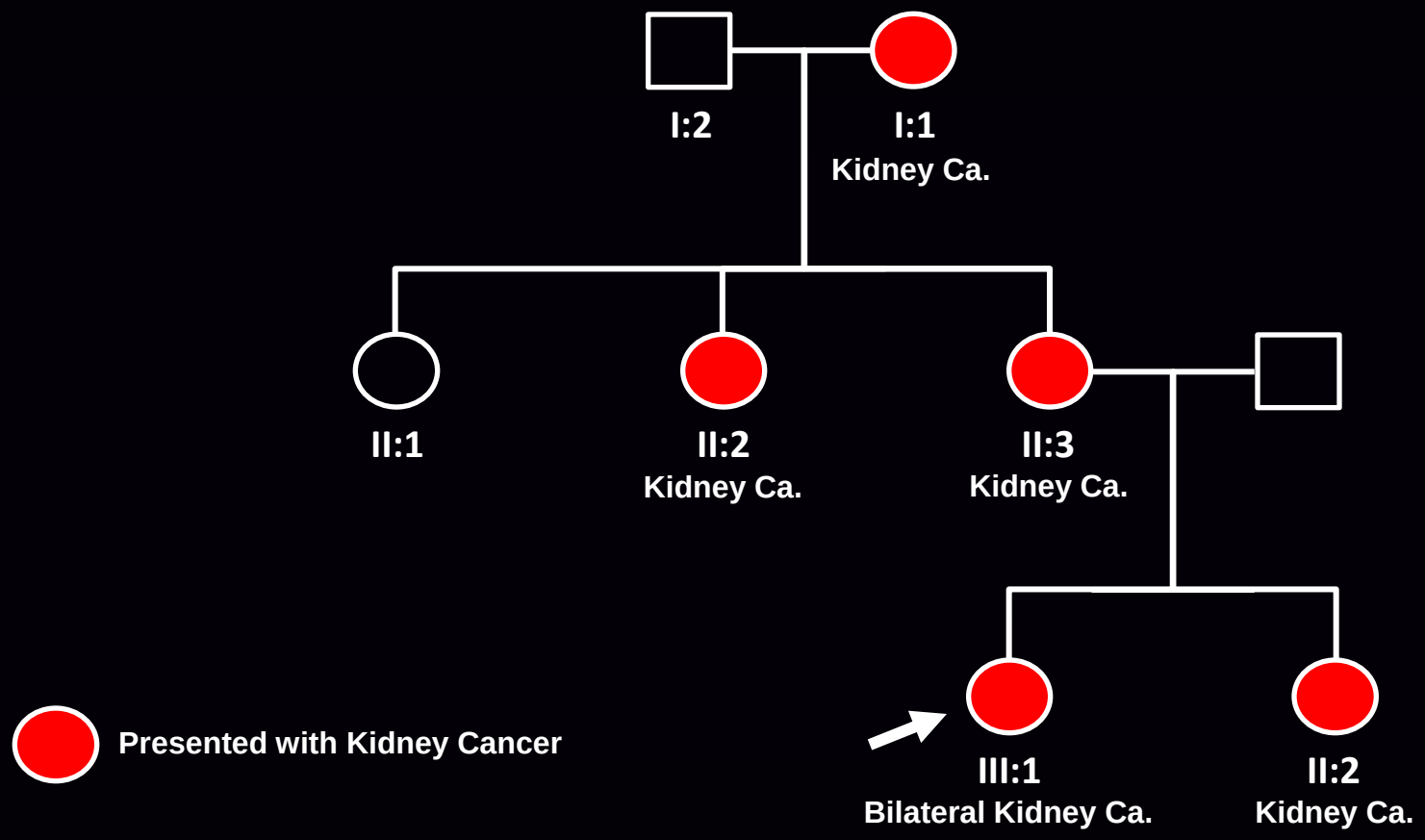
49 Year Old Male

TSC: “Fat Poor AML”

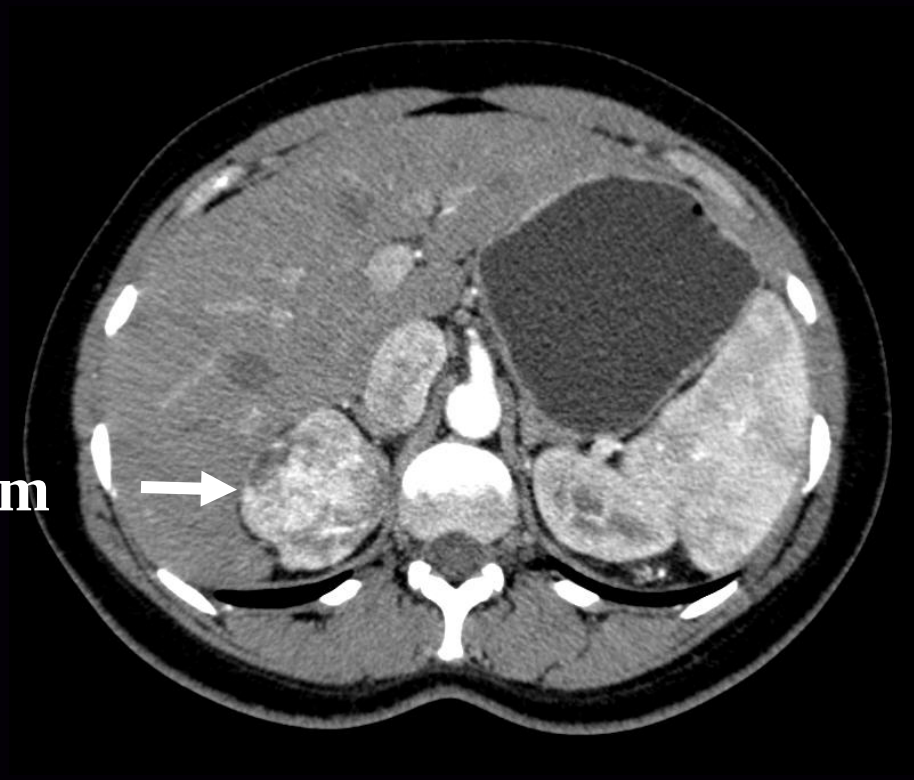


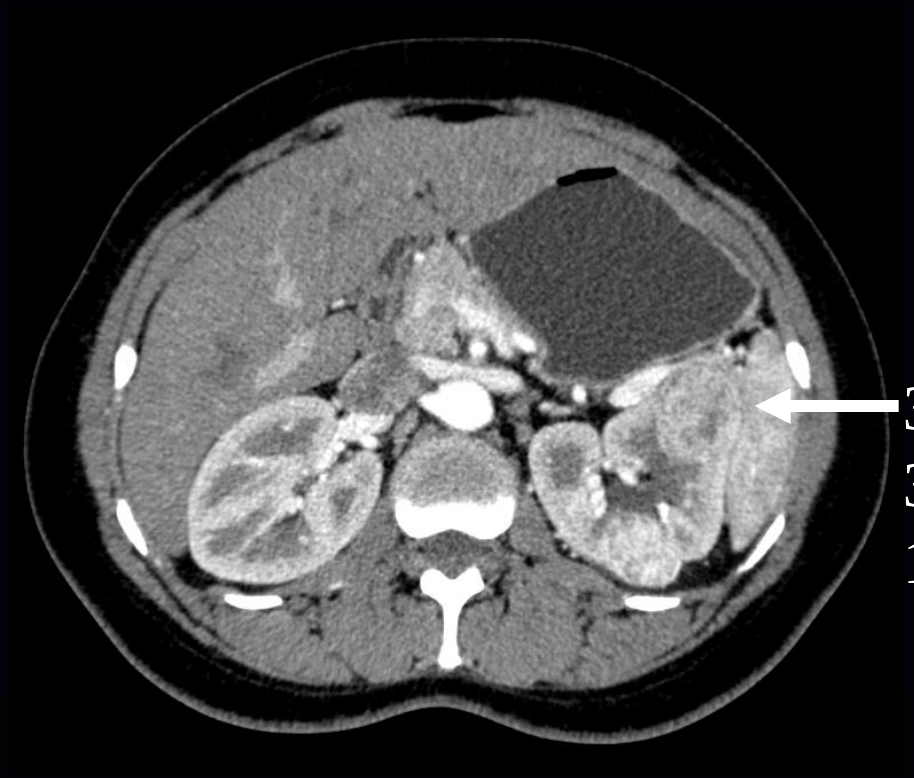
49 Year Old Male

Familial Renal Cancer (FRC)



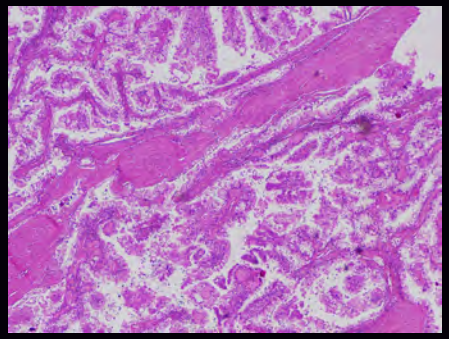
Familial RCC
Bilateral, Multifocal



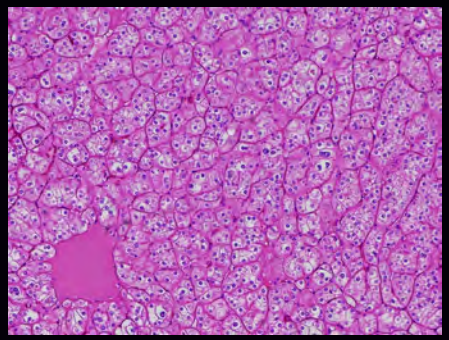


44 Year Old Female

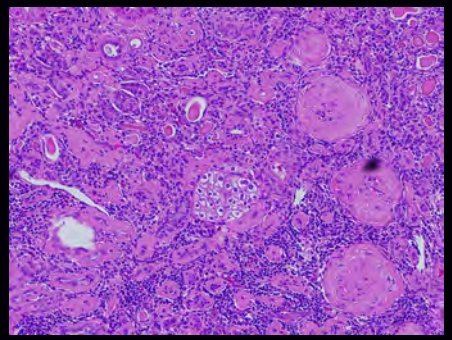
Familial RCC
Bilateral, Multifocal



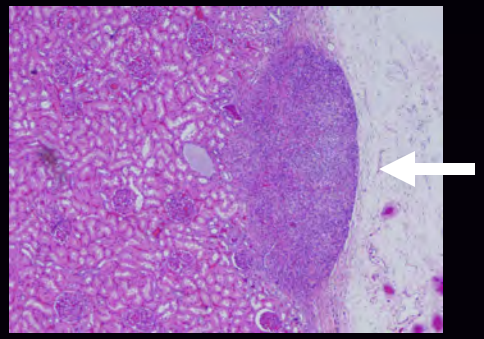
Clear cell with papillary RCC



Chromophobe RCC



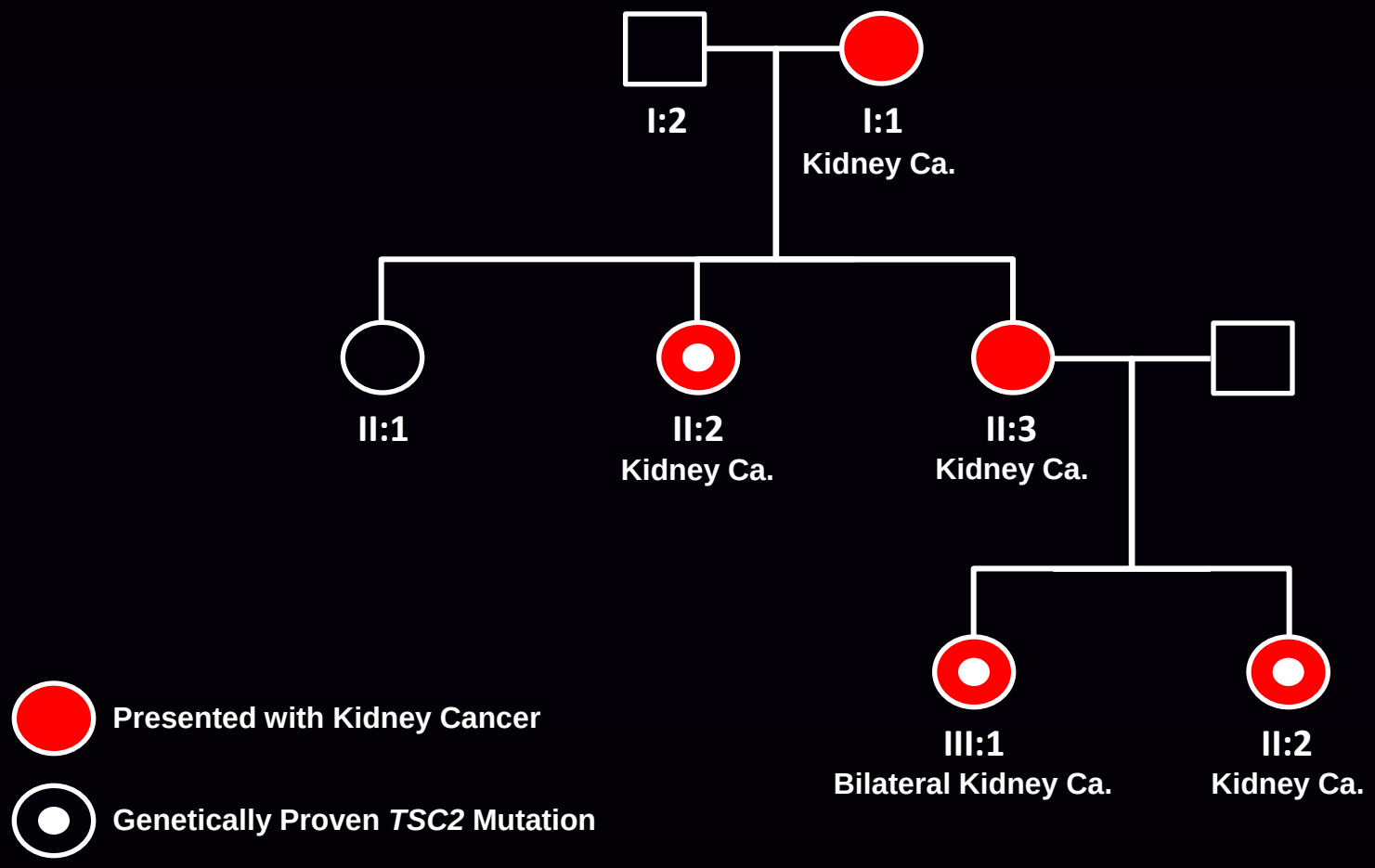
Oncocytosis



Leiomyoma

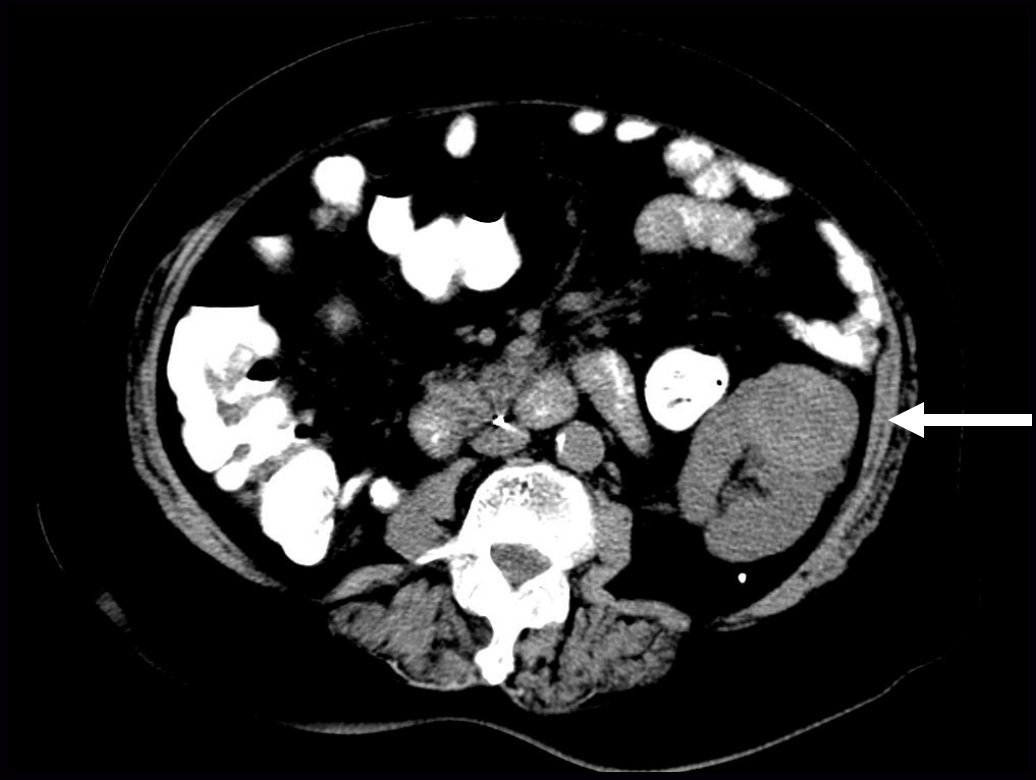
44 Year Old Female

Tuberous Sclerosis Complex (TSC)



TSC2: c.3598C>T, p.Arg1200Trp, Missense

Tuberous Sclerosis Complex (TSC)



RCC with clear cell and tubular features

47 Year Old Female

TSC2: c.1946T>C, p.Met649Thr

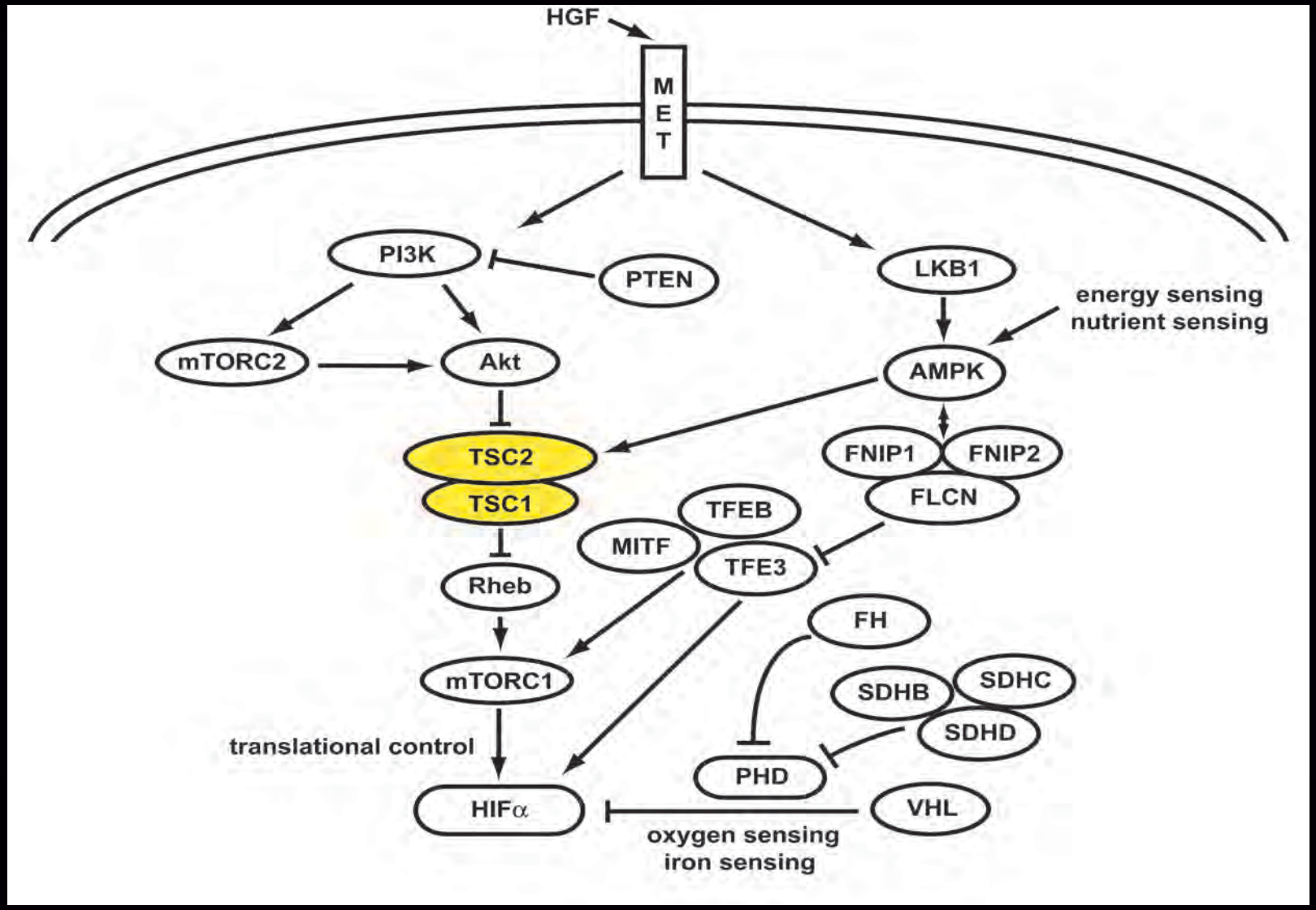
Tuberous Sclerosis Complex (TSC)

RCC with clear cell and tubular features
Capsular leiomyoma

51 Year Old Female

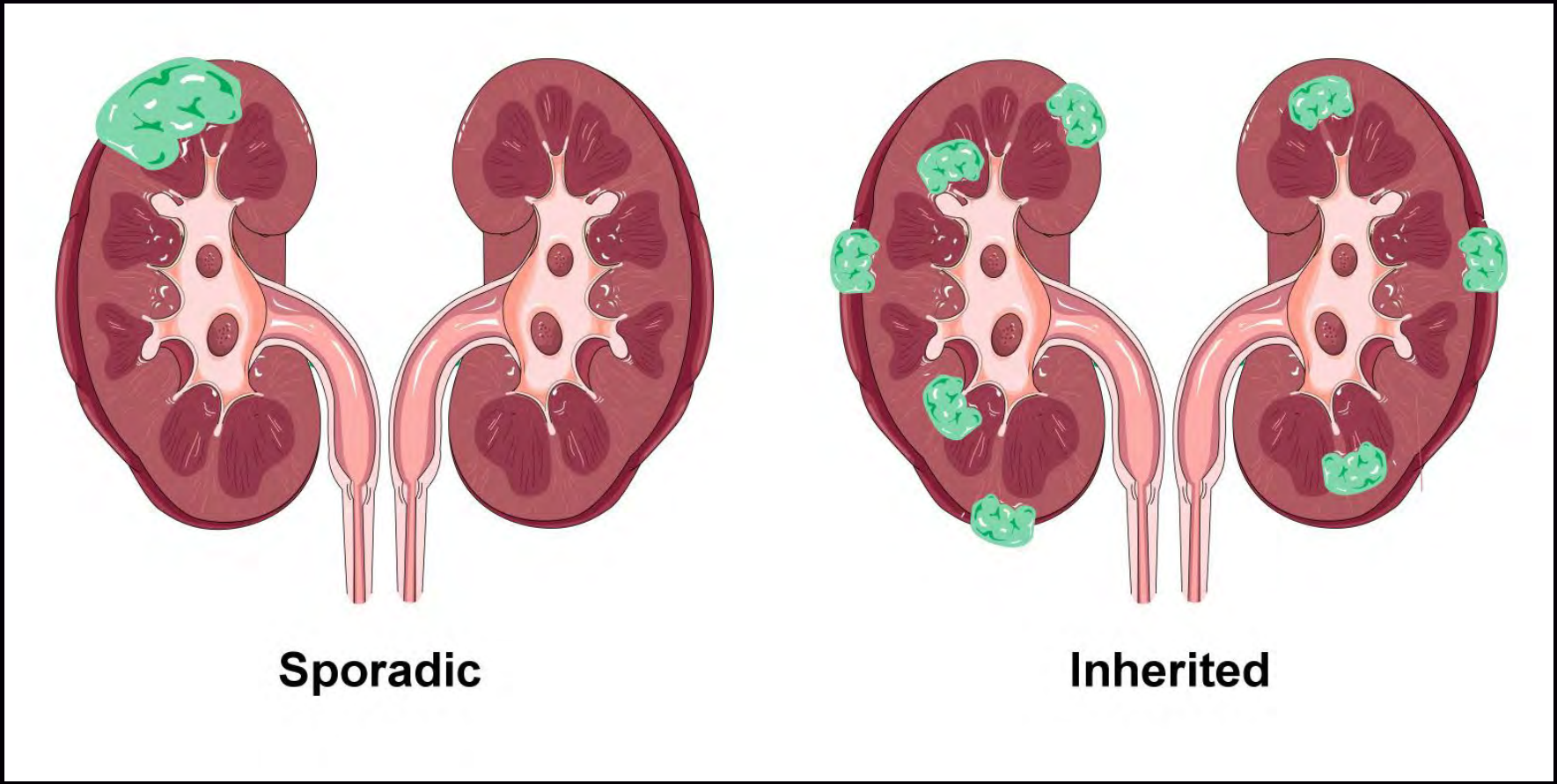
TSC1: del 4 bp (GAGA), Frameshift

Kidney Cancer is a Metabolic Disease



Nature Rev Urol: 7 2010

Inherited Renal Carcinoma: Cowden's Disease



Cowden's Disease

56 Year Old Male

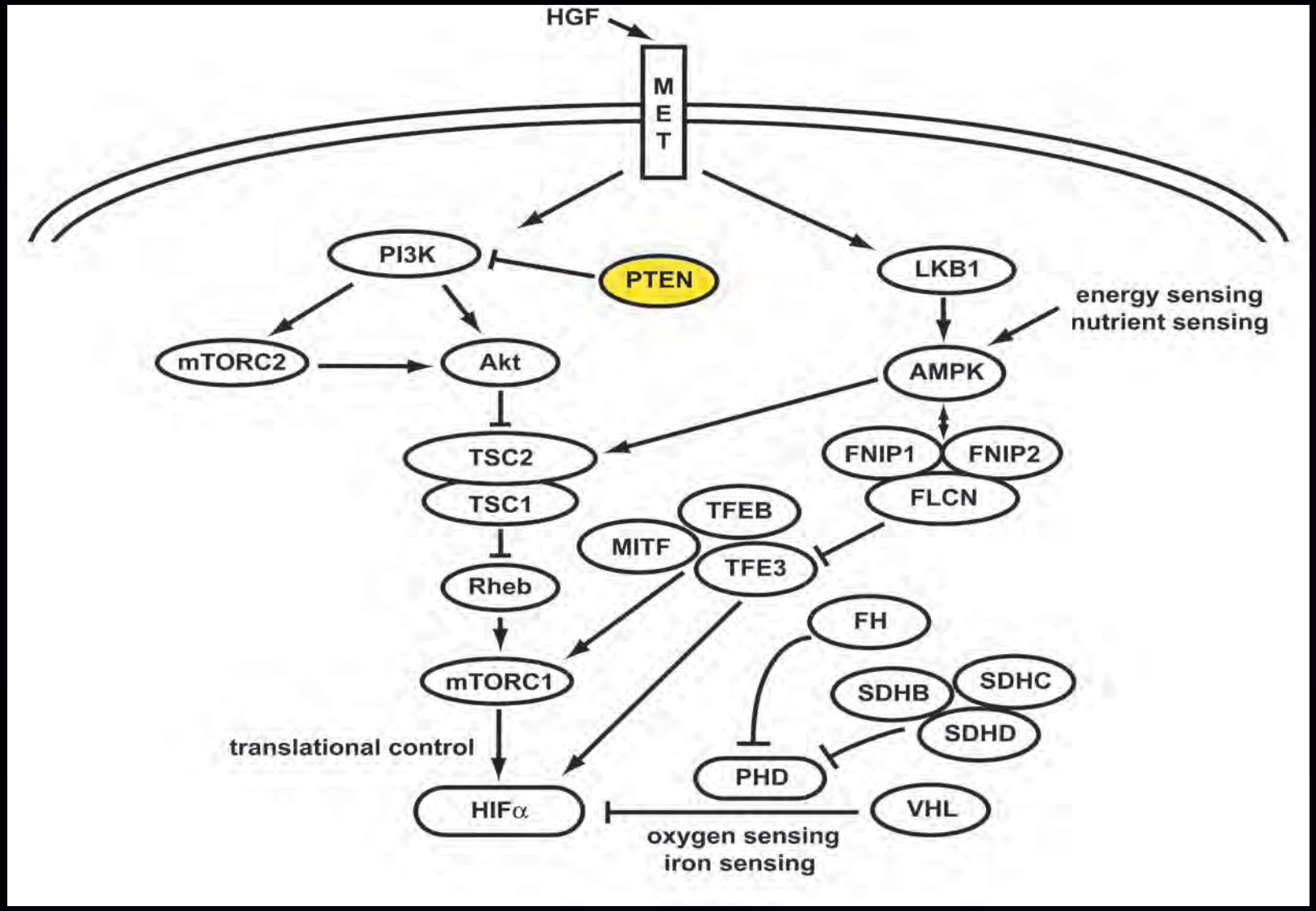
PTEN: 388 C>T, R130X

Cowden's Disease

32 Year Old Female

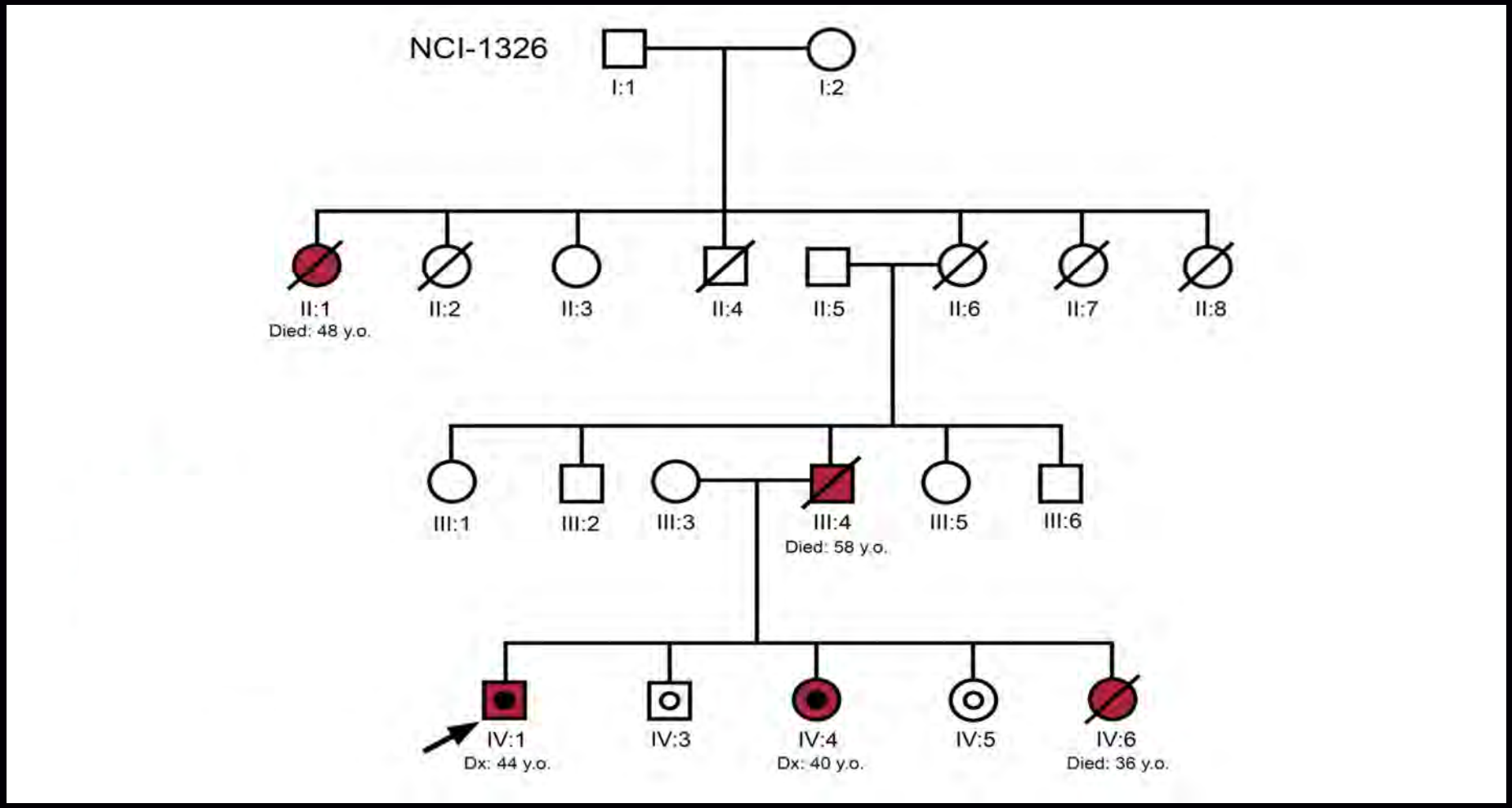
PTEN: 210-1G>A

Kidney Cancer is a Metabolic Disease



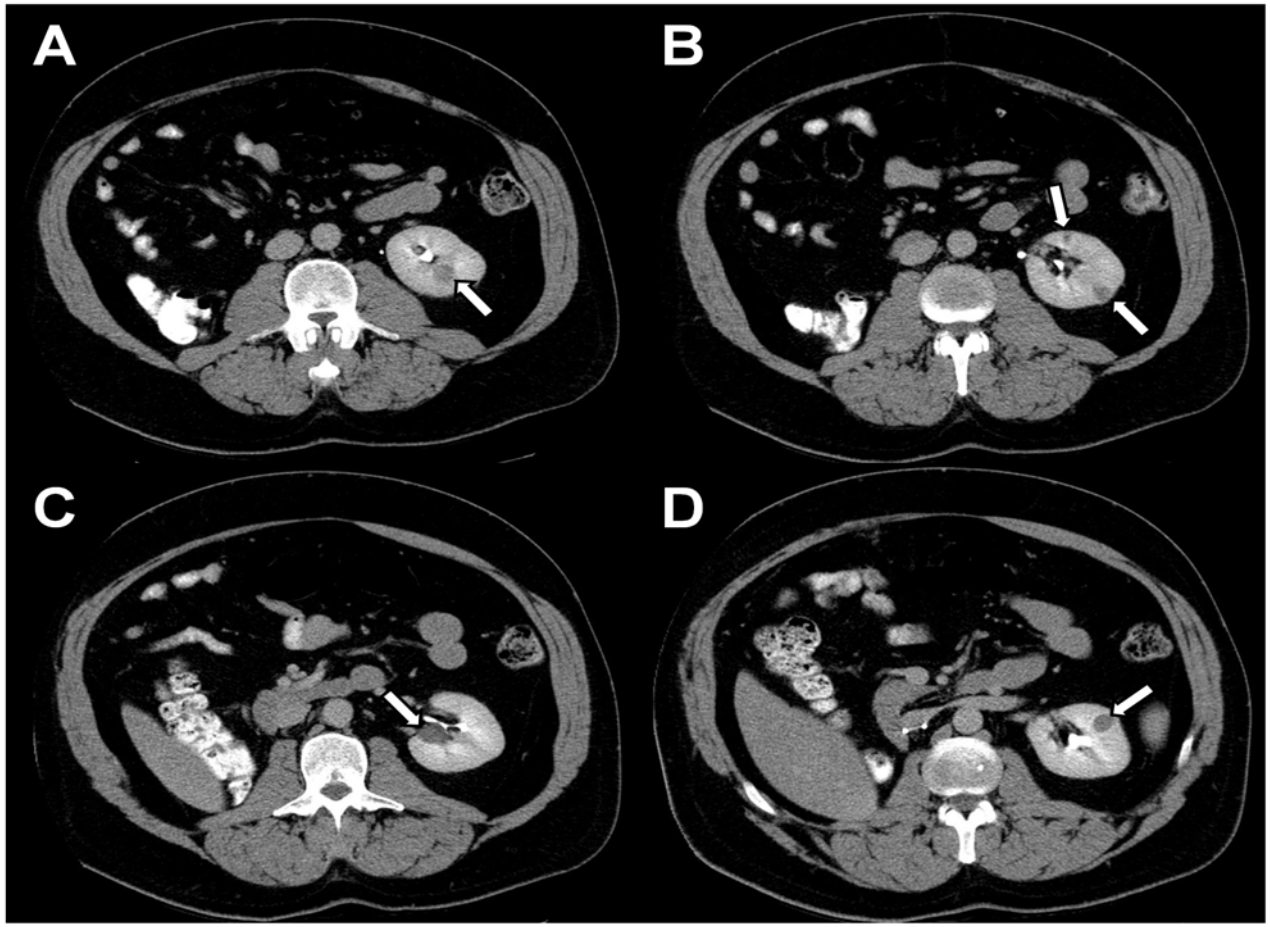
Nature Rev Urol: 7 2010

Familial Renal Cancer



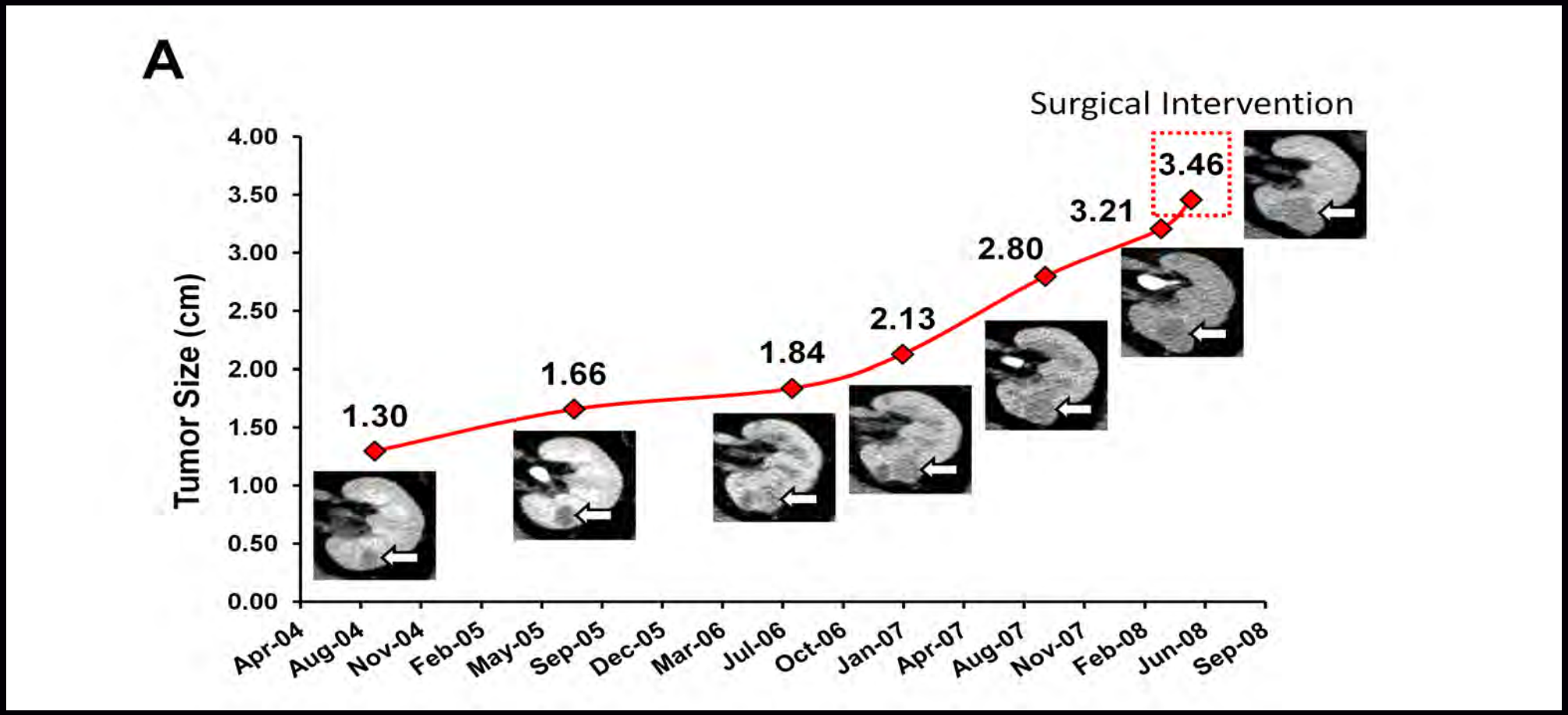
Mol Cancer Res: **In Press**

Familial Renal Cancer



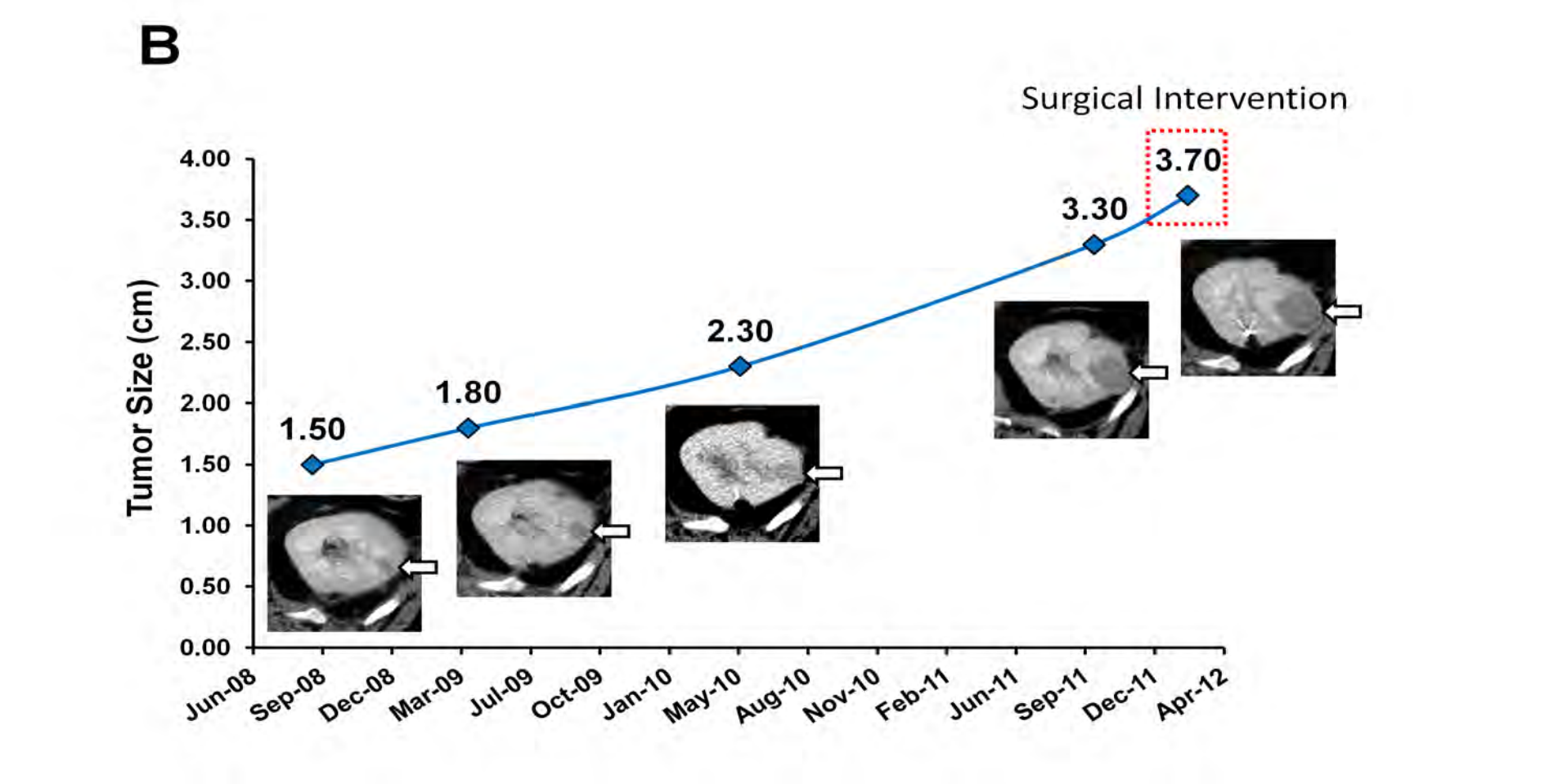
Mol Cancer Res: In Press

Familial Renal Cancer



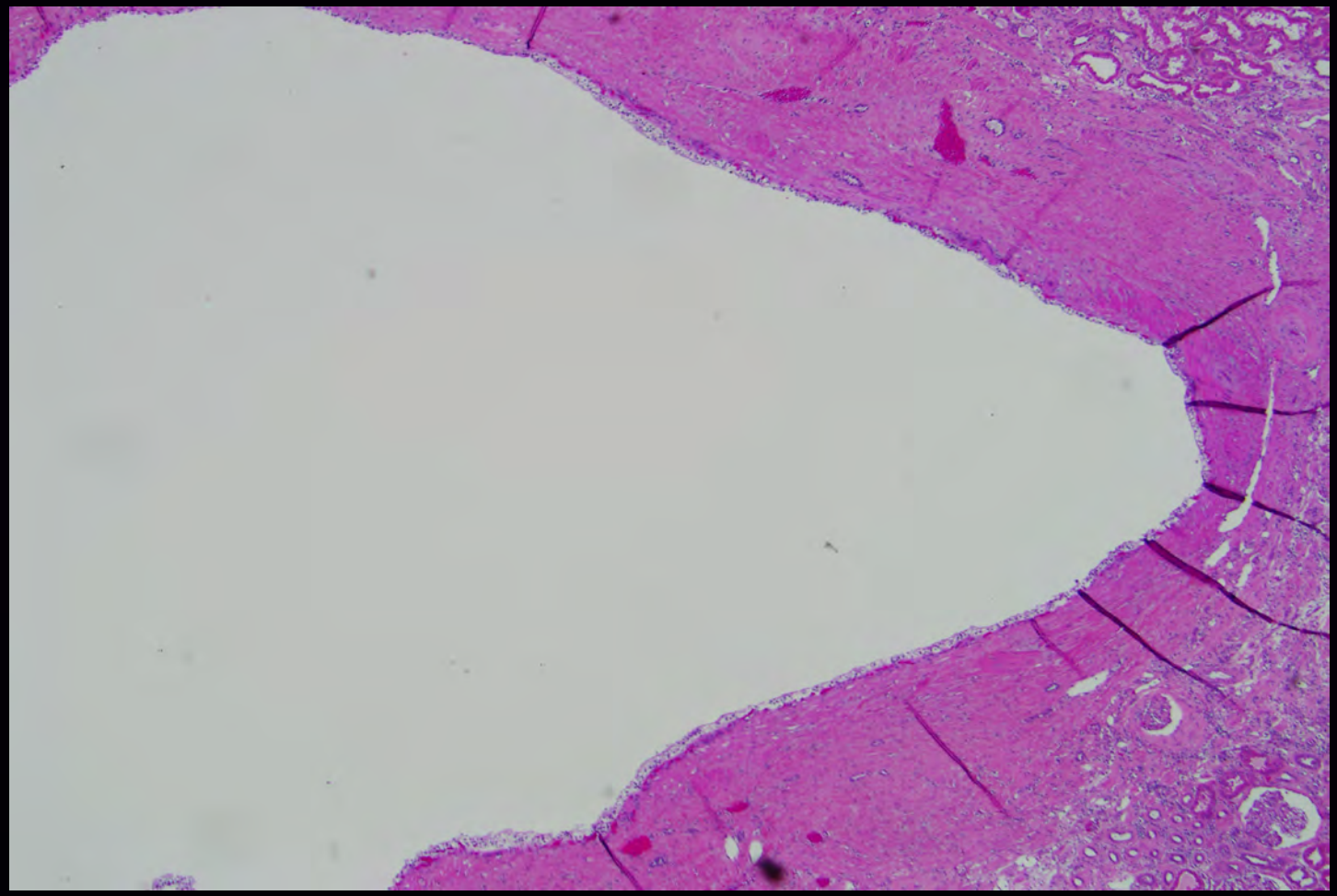
Mol Cancer Res: In Press

Familial Renal Cancer



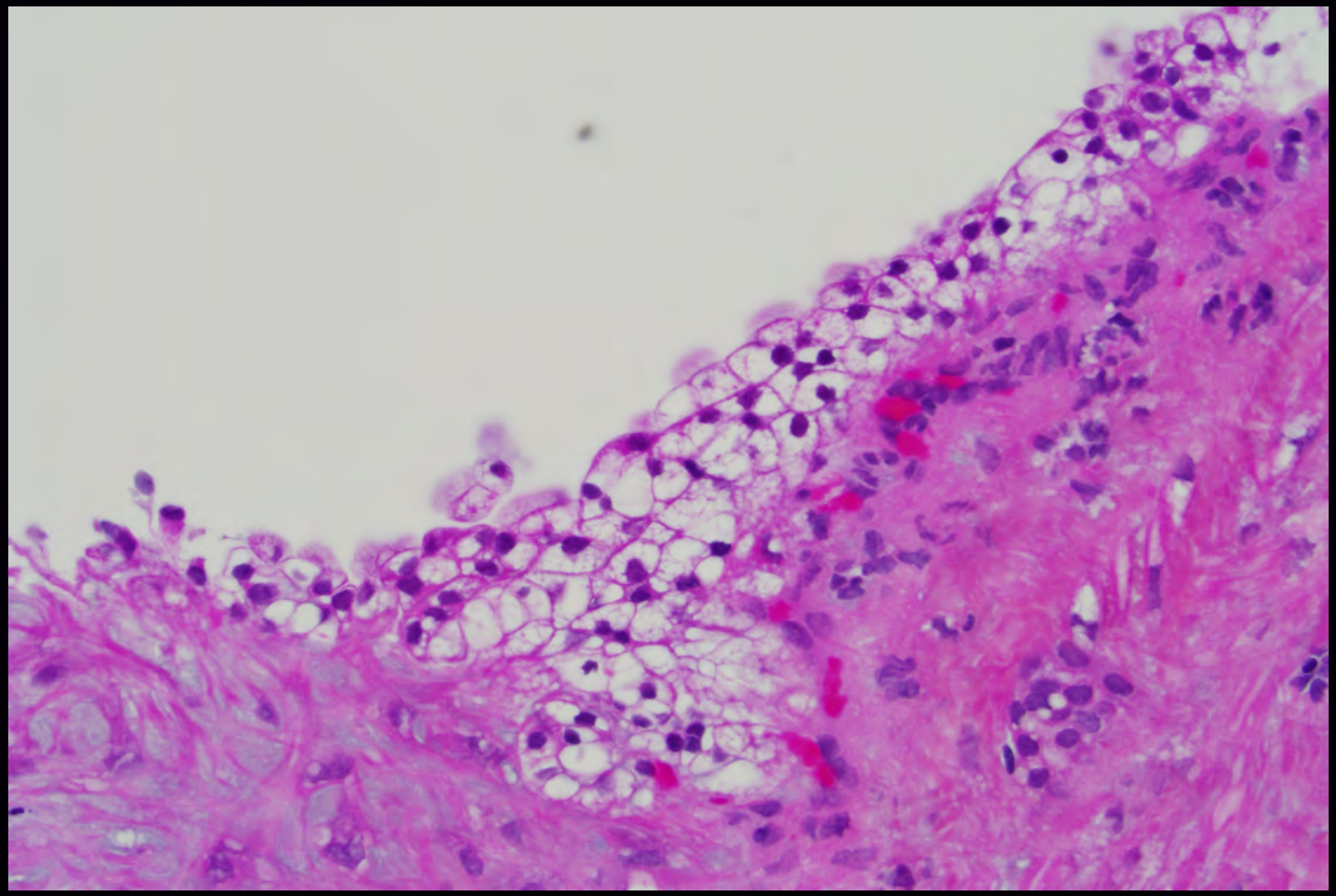
Mol Cancer Res: In Press

FRC: Renal Cyst



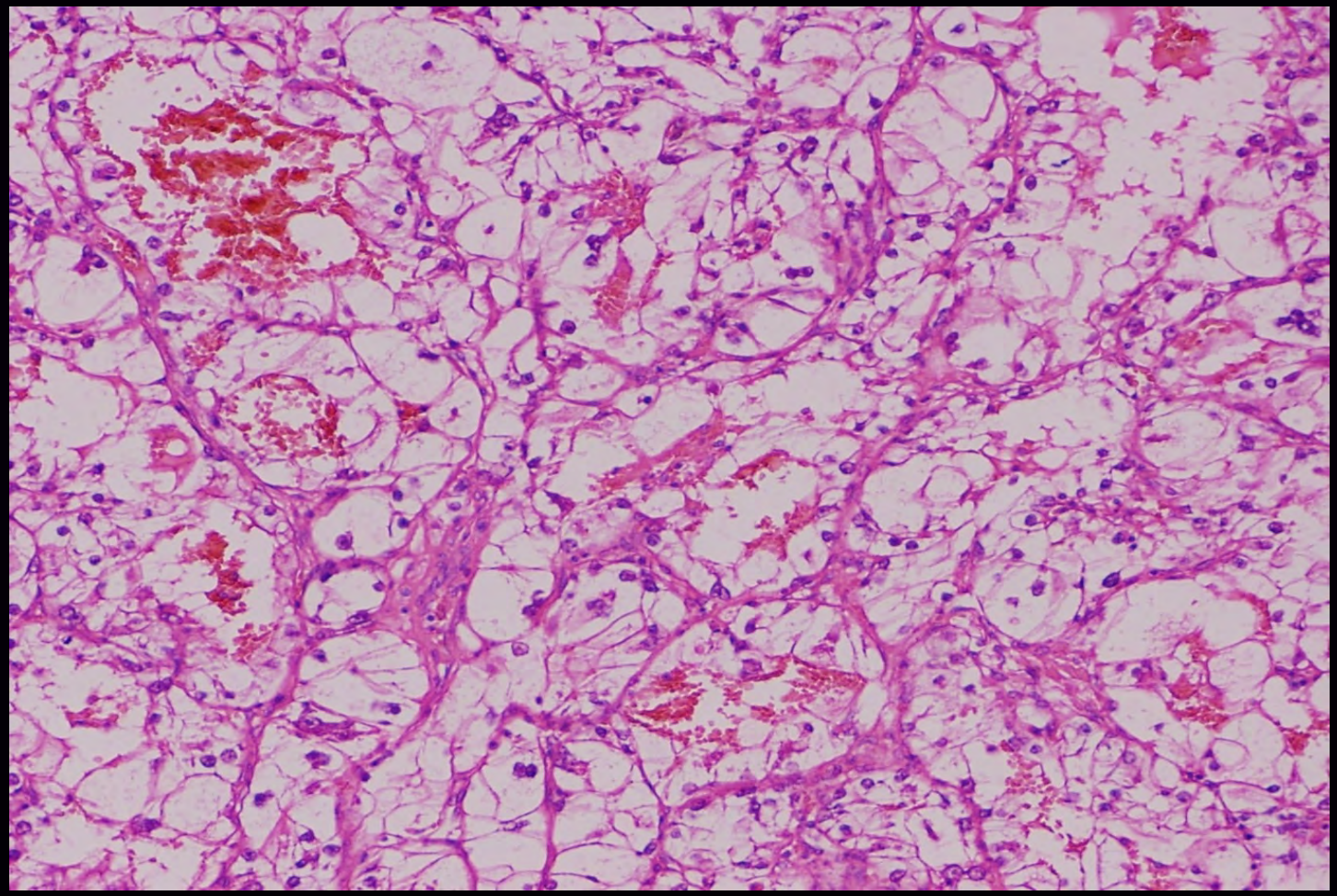
Mol Cancer Res: In Press

FRC: Cystic Clear Cell RCC



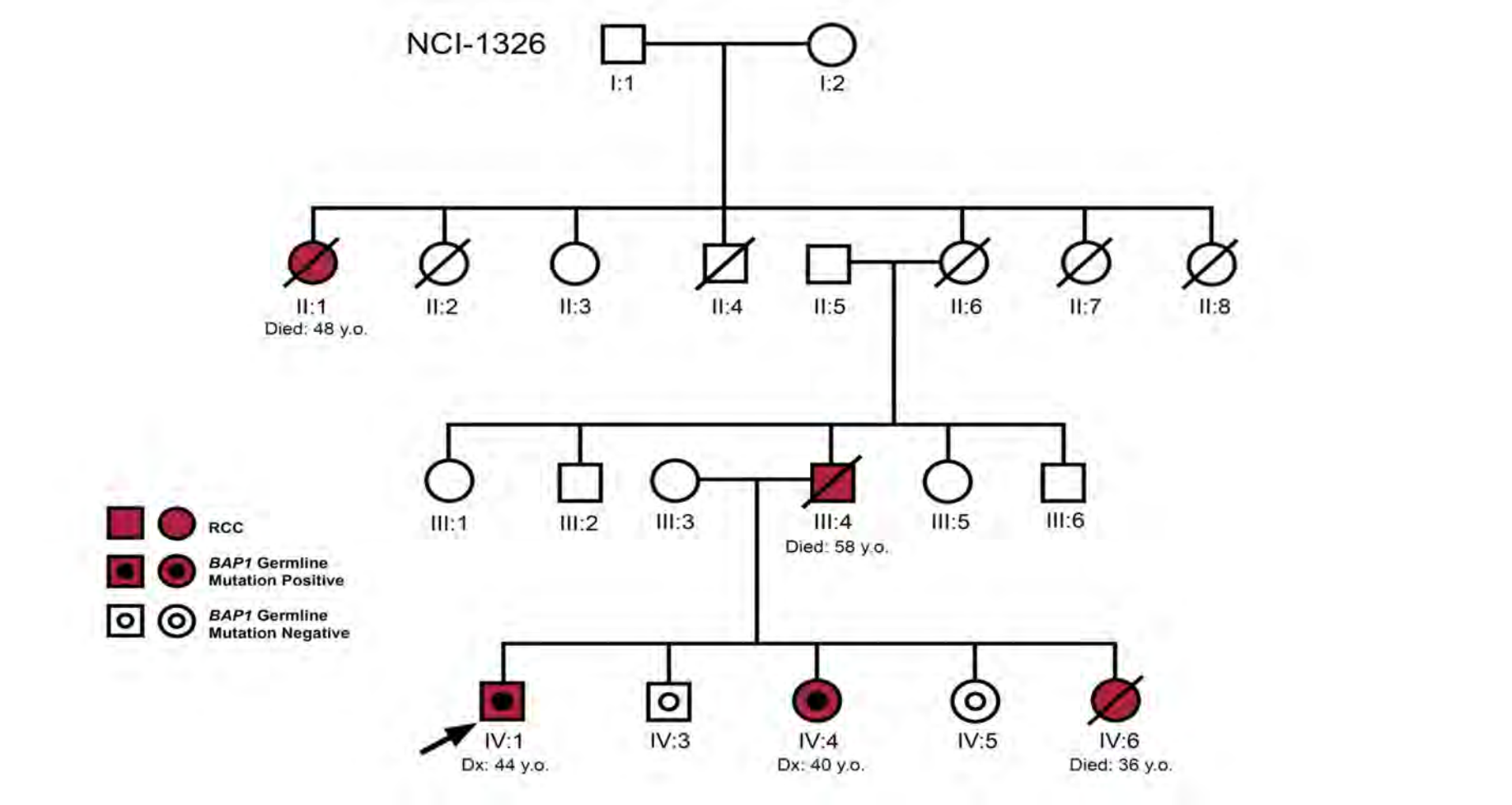
Mol Cancer Res: In Press

FRC: High Grade Clear Cell RCC



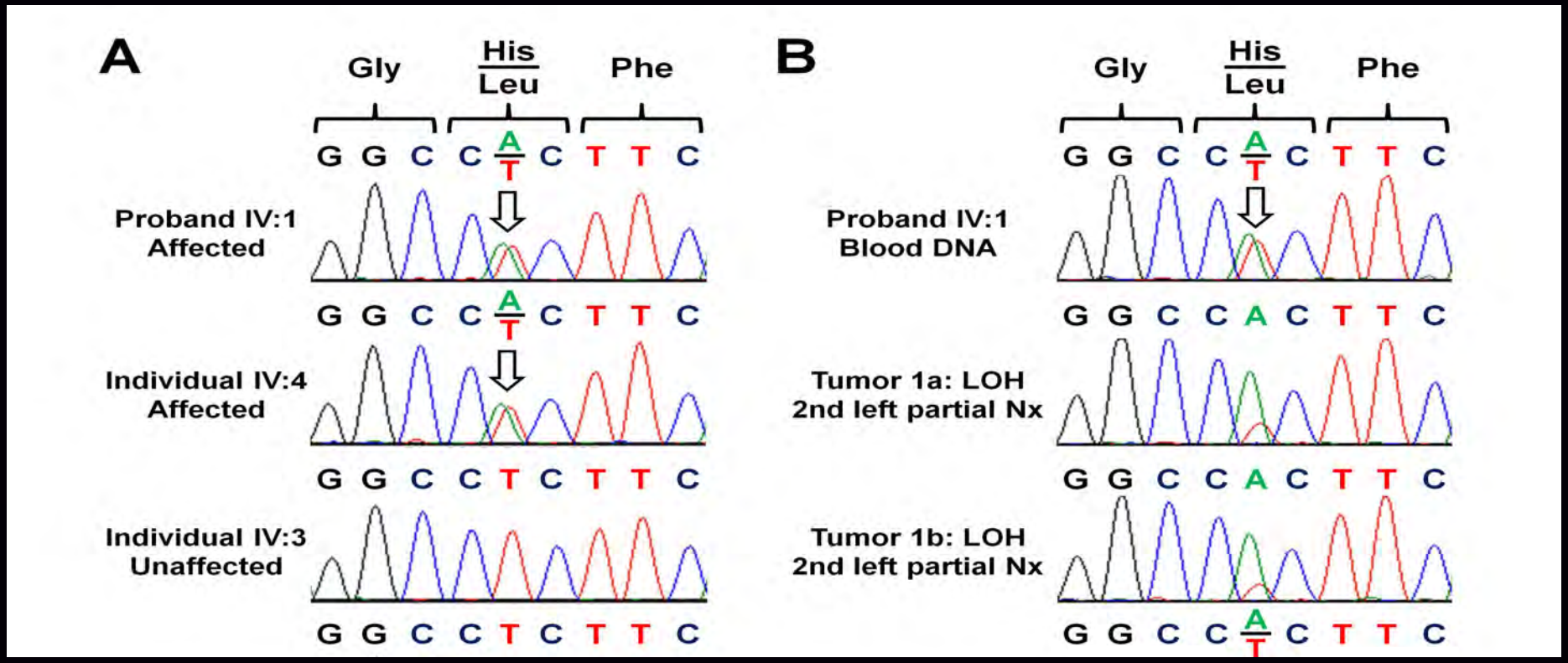
Mol Cancer Res: In Press

BAP1 Familial Renal Cancer



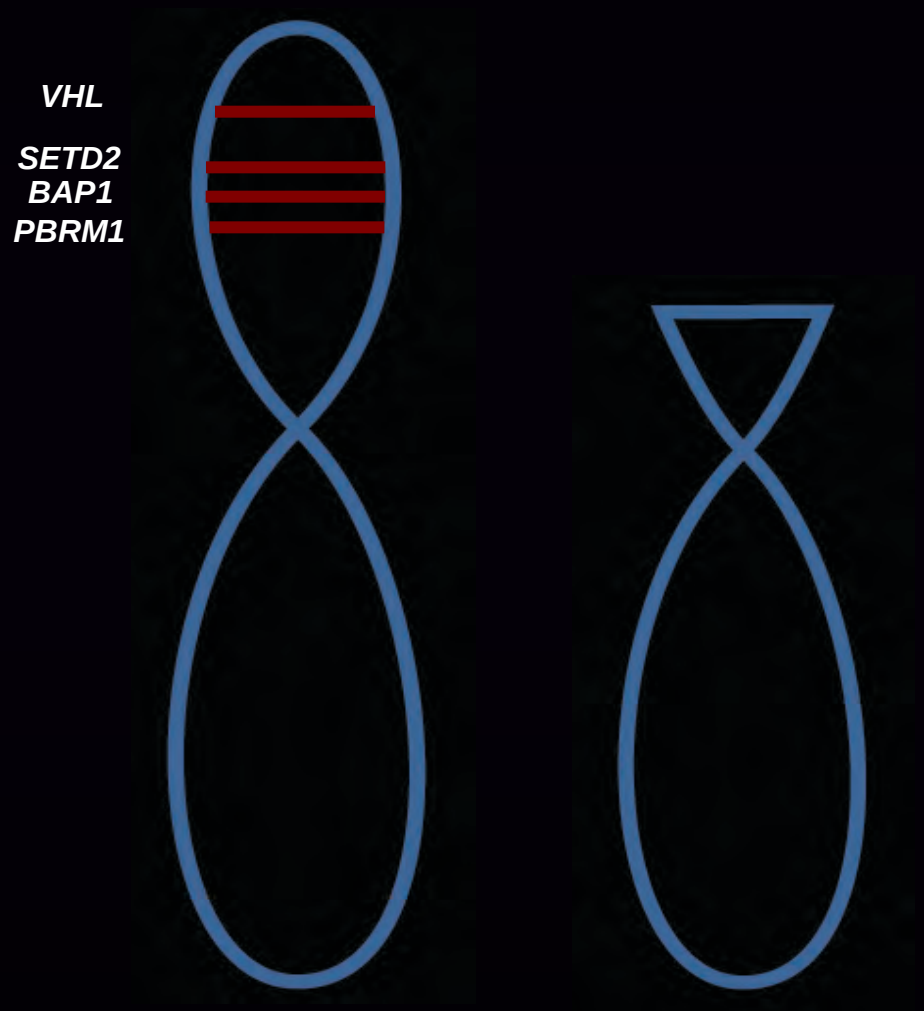
Mol Cancer Res: **In Press**

Germline *BAP1* p.L14H Mutation Familial Renal Cancer



Mol Cancer Res: In Press

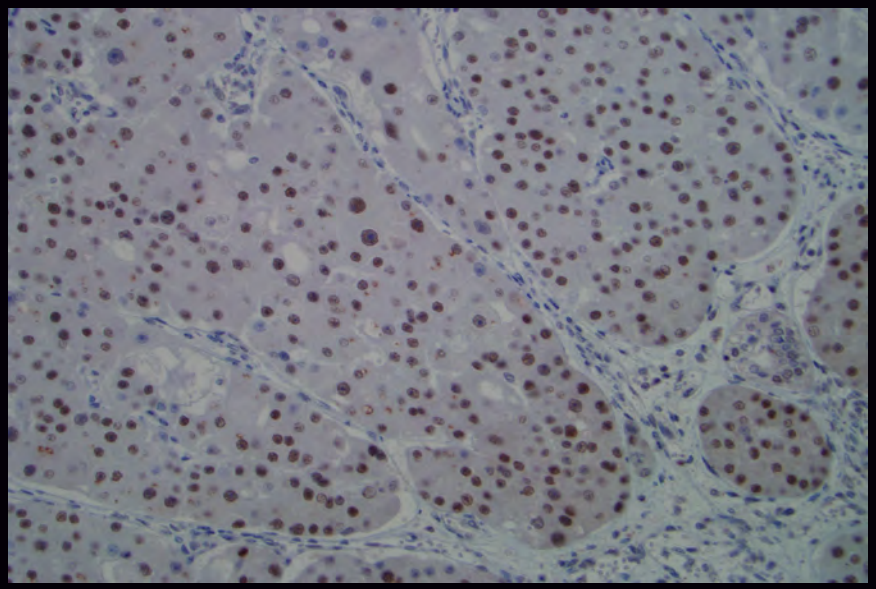
Clear Cell Kidney Cancer



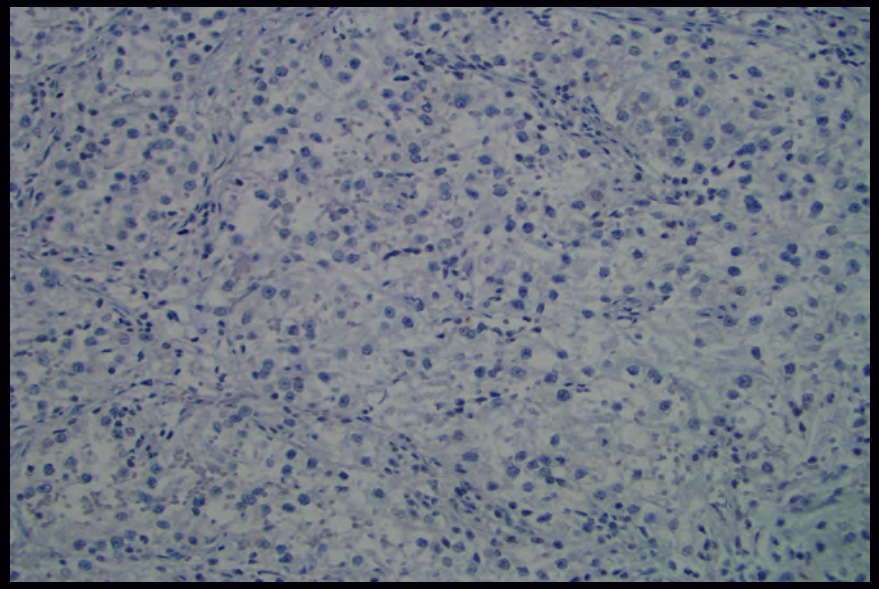
Chromosome 3

Nature: In Press

BAP1 Staining



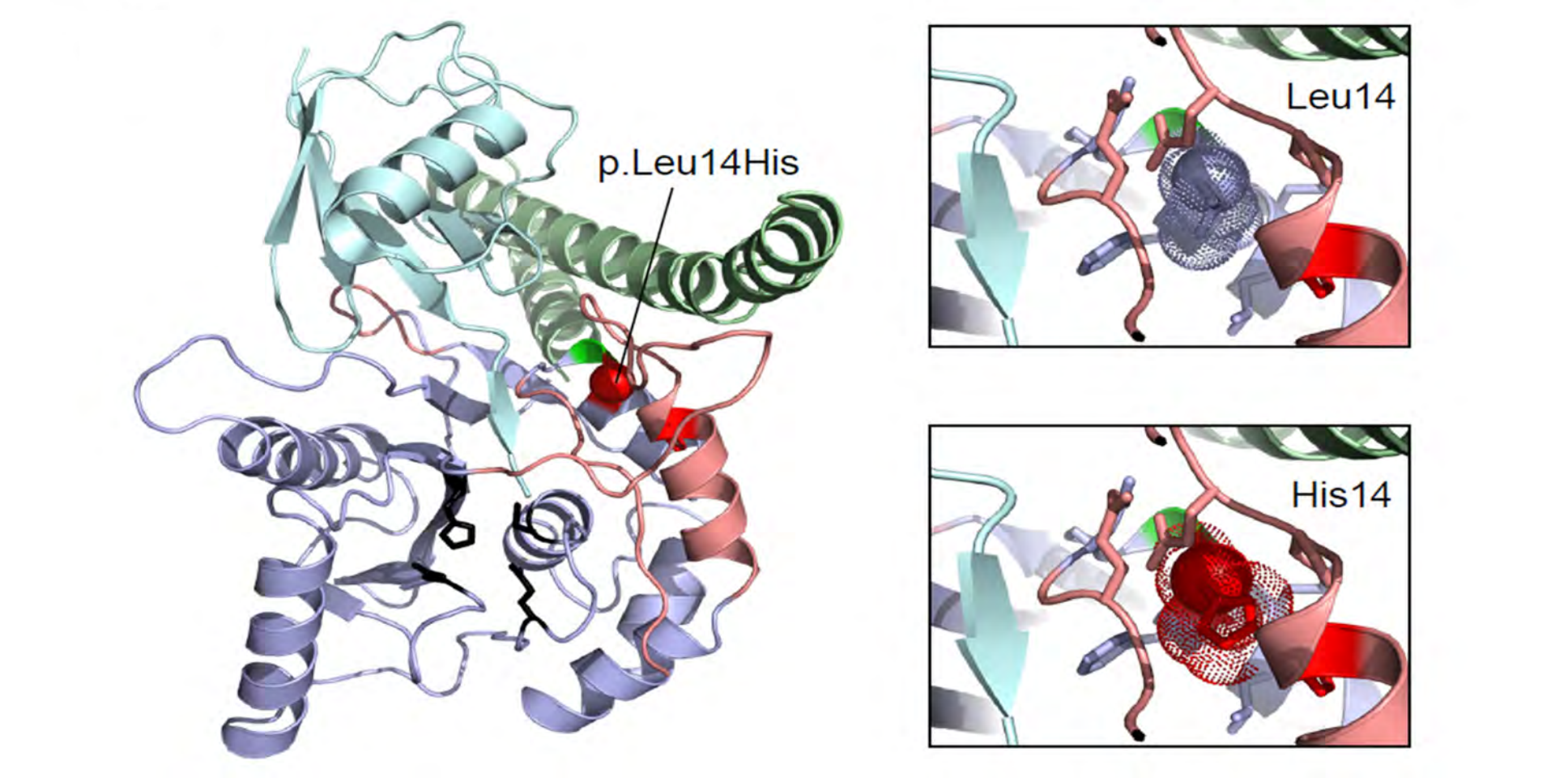
Normal (positive)



Tumor (negative)

***Mol Cancer Res*: In Press**

BAP1 Familial Renal Cancer



Mol Cancer Res: **In Press**