

RENAL CANCER PATHOLOGY WHAT REALLY MATTERS?

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- MAJOR PARADIGM SHIFT IN EARLY 1990S IN UNDERSTANDING RENAL CANCER

The impact of genetics on the classification of renal carcinoma

S. FLEMING

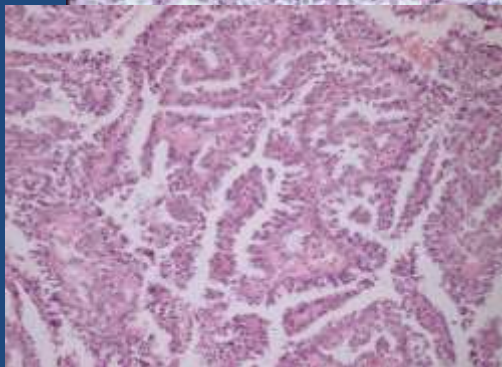
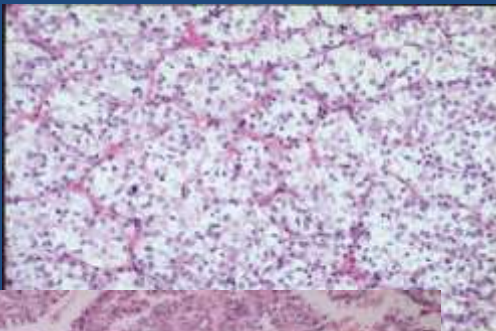
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Molecular differential pathology of renal cell tumours

G. KOVACS

THE HEIDELBERG CLASSIFICATION OF RENAL CELL TUMOURS

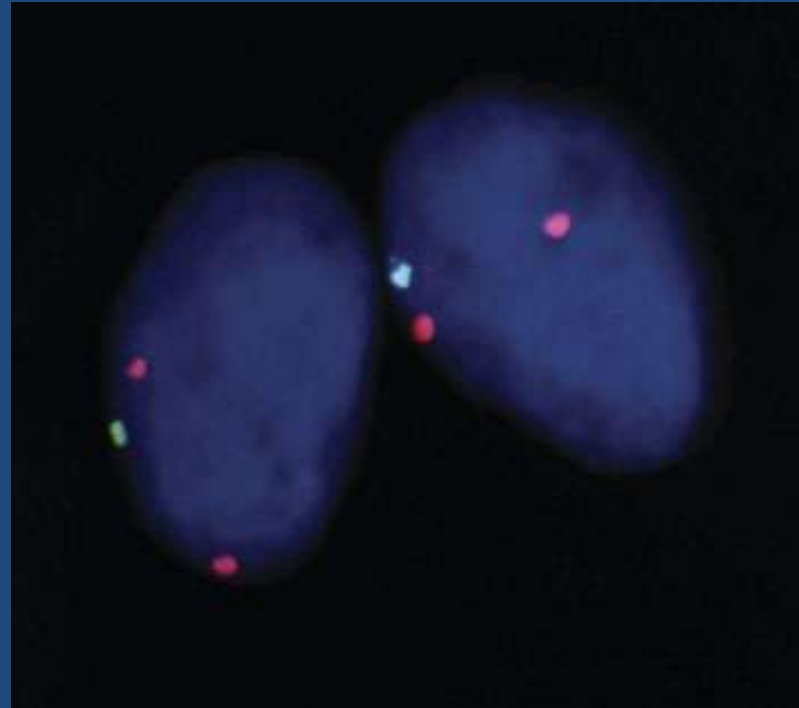
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A CLASSIFICATION ...BASED ON UNDERSTANDING THE GENETIC ABNORMALITIES INVOLVED WILL BE ROBUST IN TERMS OF BIOLOGY, CLINICAL BEHAVIOUR AND RESPONSE TO THERAPY

GENETIC ALTERATION IN RCC CORRELATES STRONGLY WITH MORPHOLOGY

HISTOPATHOLOGY	3p LOSS		VHL MUTATION	
	Y	N	Y	N
CLEAR CELL	25	8	18	25
PAPILLARY	1	7	0	8
ONCOCYTOMA	2	3	0	5
CHROMOPHOBE	0	3	0	3



FOSTER ET AL 1994 Somatic mutations of the von Hippel - Lindau disease tumour suppressor gene in non-familial clear cell renal carcinoma

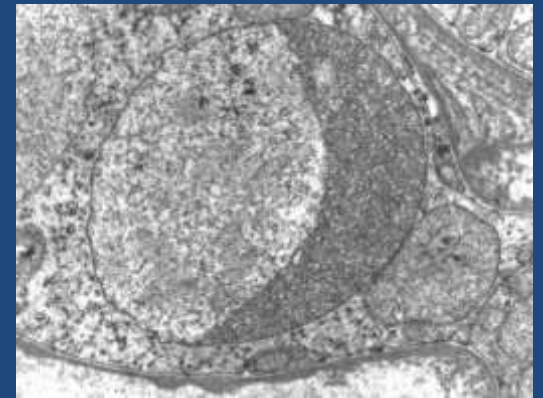
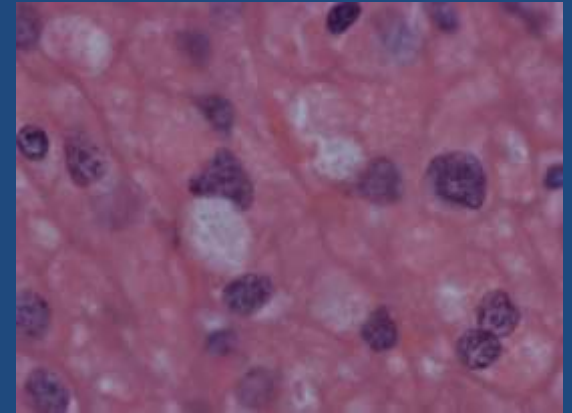
TUMOUR HISTOLOGY MATTERS BECAUSE IT REVEALS THE UNDERLYING GENETICS

WHO v4

- Clear cell renal cell carcinoma **VHL and 3p-**
 - Multilocular clear cell renal cell neoplasm of low malignant potential
- Papillary renal cell carcinoma **c-met and chr 7+; Fumarate hydratase**
- Chromophobe renal cell carcinoma **Multiple chromosome loss**
 - Hybrid oncocytic chromophobe tumour **Folliculin**
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma **IN1 and sickle cell**
- MiT family translocation renal cell carcinoma
 - **Xp11** translocation renal cell carcinoma
 - **t(6;11)** renal cell carcinoma
- Carcinoma associated with neuroblastoma
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic renal cell carcinoma **Fumarate hydratase**
- Acquired cystic disease associated renal cell carcinoma
- Clear cell papillary (tubulopapillary) renal cell carcinoma
- Hereditary leiomyomatosis associated renal cell carcinoma **Fumarate hydratase**
- SDHB associated RCC **SDHB**
- Renal cell carcinoma, unclassified

INHERITED RCC

- VHL
- FAMILIAL PAPILLARY RCC
- BIRT HOGG DUBE SYNDROME
- TUBEROUS SCLEROSIS
- HLRCC
- SDHB
- NON-SYNDROMIC FAMILIAL RCC



STAGING

Identifies biologically aggressive tumours

- **The Robson Staging System of Renal Cell Carcinoma**
 - Stage I - Tumour confined within capsule of kidney
 - Stage II - Tumour invading perinephric fat but still contained within the Gerota fascia
 - Stage III - Tumour invading the renal vein or inferior vena cava (A), or regional lymph-node involvement (B), or both (C)
 - Stage IV - Tumour invading adjacent viscera (excluding ipsilateral adrenal) or distant metastases
- **TNM SYSTEMS ARE A DEVELOPMENT OF THIS CLASSIFICATION**
- **STAGE 1 - 80% 5y AND 65% 10y SURVIVAL**
- **WHY DO SOME KIDNEY CONFINED RCCs PROGRESS?**



DISSECTION AND SAMPLING MATTER

CORRECT DISSECTION OF
NEPHRECTOMY SPECIMENS
WILL REVEAL EXTRA-RENAL
SPREAD

Handling and Staging of Renal Cell Carcinoma
Kiril Trpkov et al 2013 ISUP Consensus



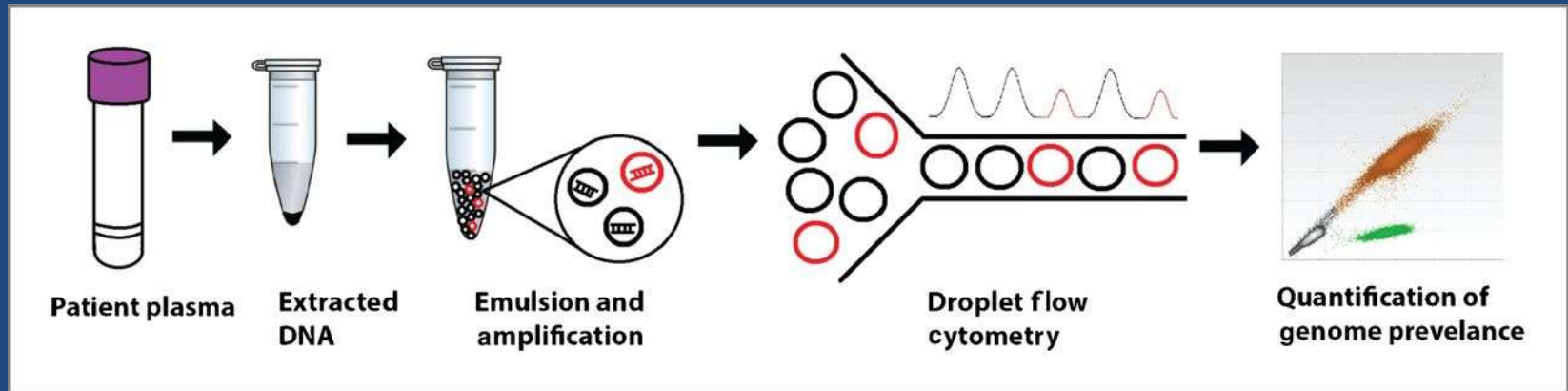
CARDIFF METHOD

MACROSCOPIC EXTENT OF TUMOUR SPREAD

- MACROSCOPIC DATA IS REQUIRED FOR ACCURATE TNM 7 STAGING
 - T3: Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
 - T3a Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic) fat but not beyond Gerota fascia
 - T3b Tumour grossly extends into vena cava below diaphragm
 - T3c Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava



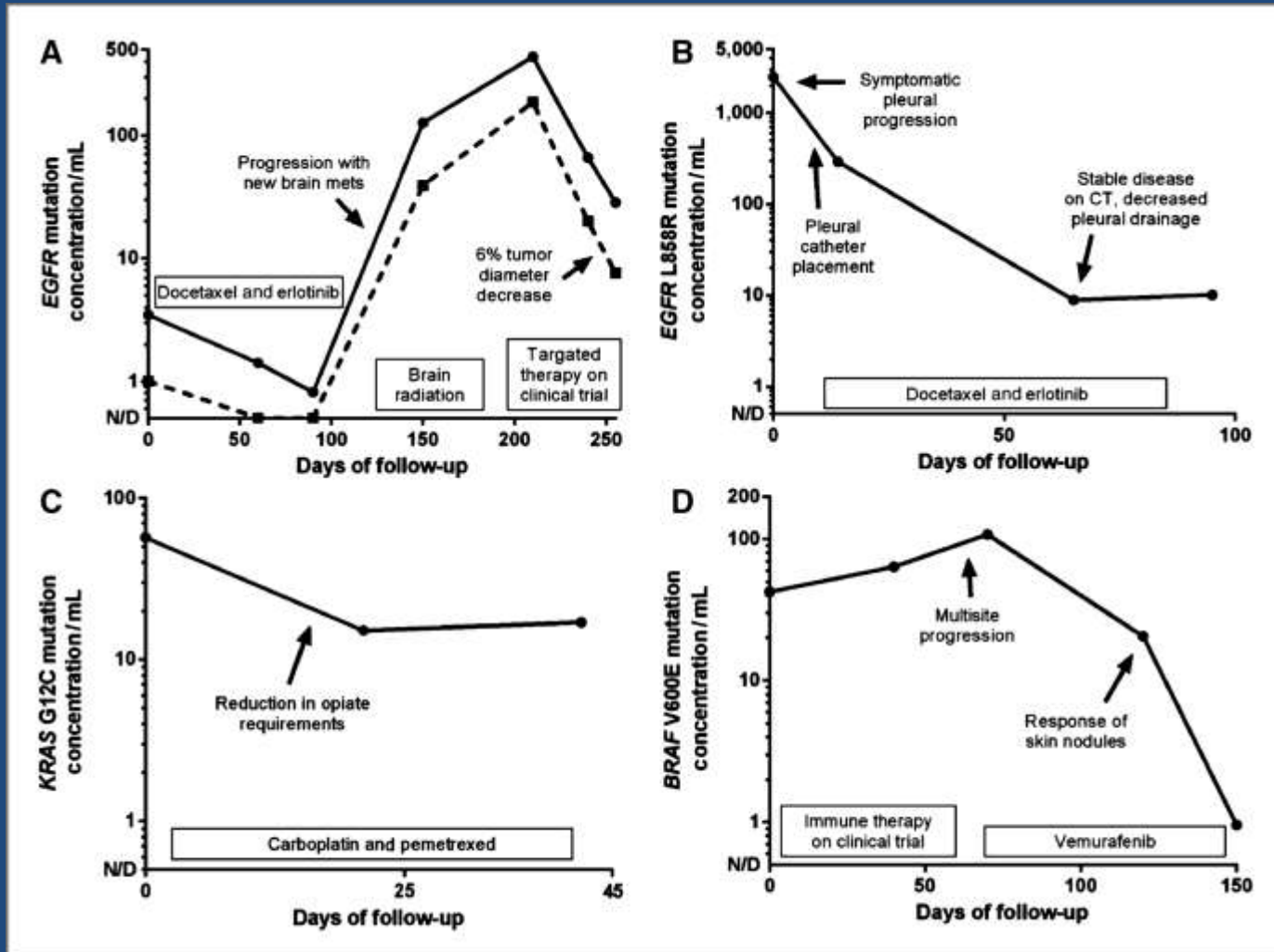
FOUNDER MUTATIONS OFFER AN OPPORTUNITY FOR LIQUID BIOPSY STAGING



Plasma genotyping using ddPCR.

Allele specific amplification allows separate identification of wild type and mutant DNA eg VHL mutant DNA

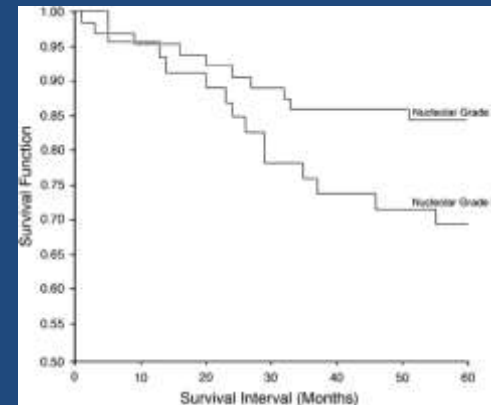
Serial measurement of plasma genotype for disease monitoring.



TUMOUR GRADE PREDICTS BIOLOGY

ISUP NUCLEOLAR GRADE

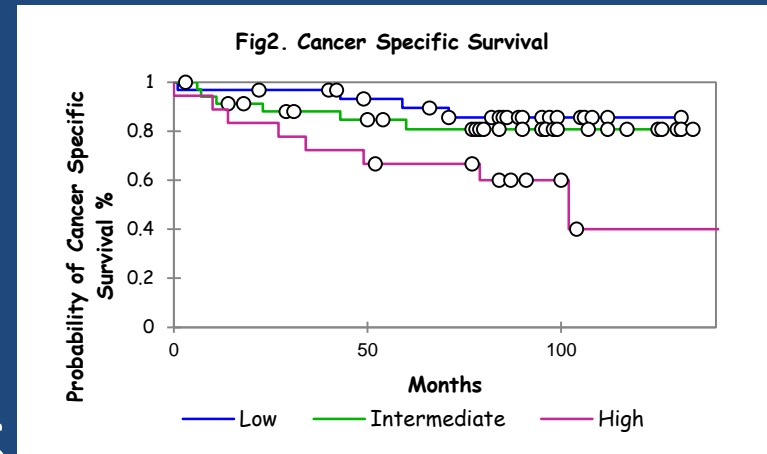
- Not applicable
 - Grade X - Cannot be assessed
 - Grade 1 - Nucleoli inconspicuous or absent at high power magnification
 - Grade 2 - Nucleoli evident at high power magnification
 - Grade 3 - Nucleoli large and prominent at low power magnification
 - Grade 4 - Nuclei bizarre and/or multilobated, sarcomatoid or rhabdoid morphology
-
- Grade should be assigned according to the worst grade regardless of extent.
 - This system has been validated for clear cell and papillary renal cell carcinoma. It has not been validated for chromophobe and other types of renal cell carcinoma.



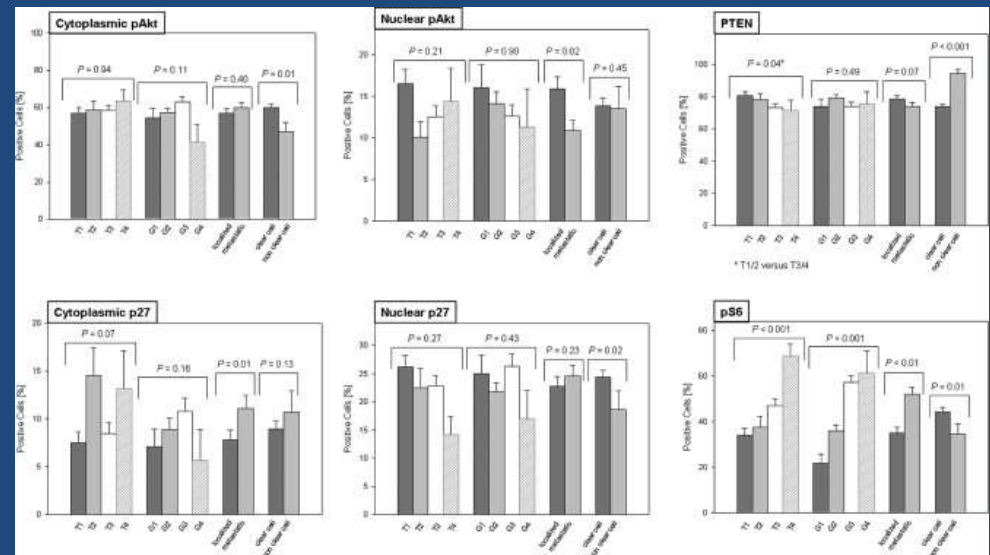
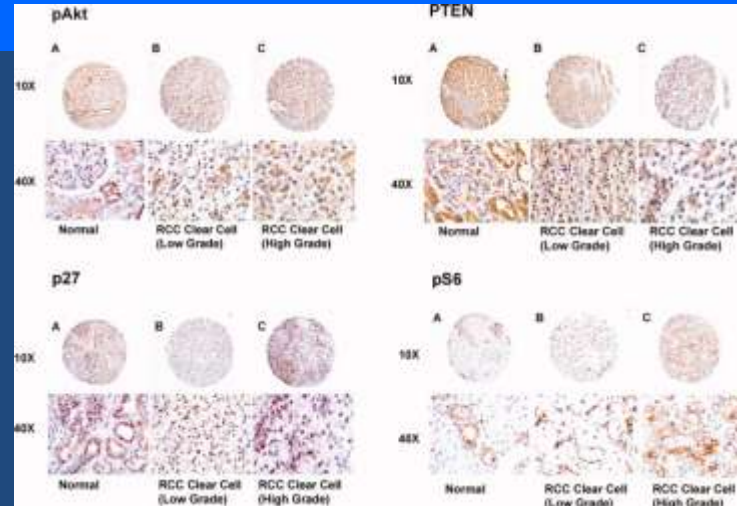
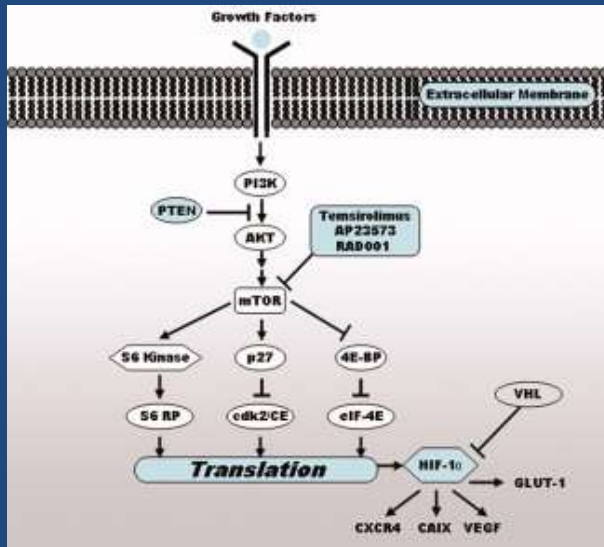
HOW DOES IT REFLECT GENETICS?

CHROMOSOMAL CHANGES ARE IMPORTANT PROGNOSTIC MARKERS

- 3p LOSS IS MORE THAN LOSS OF wtVHL
 - PBRM1
 - FHIT
 - RASSF1A
 - miRNA
- 9P LOSS POOR PROGNOSIS



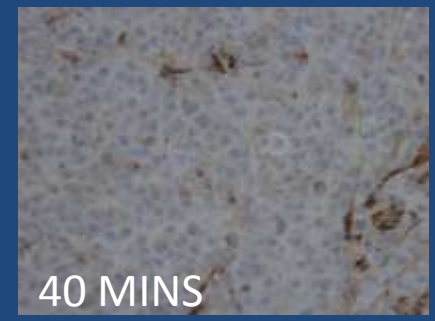
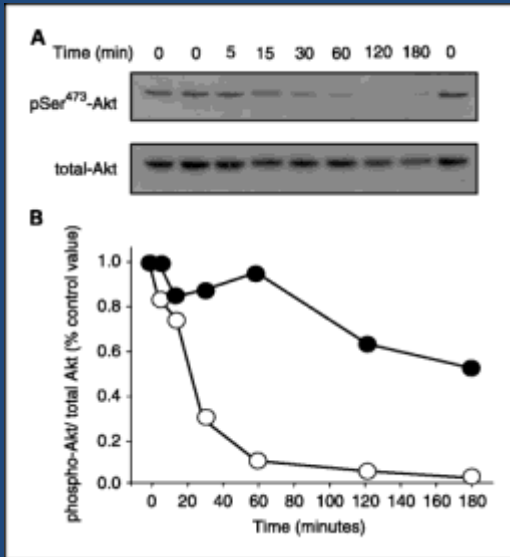
KINASE PROFILING



CELL SIGNALLING IS DYNAMIC – IHC STATIC

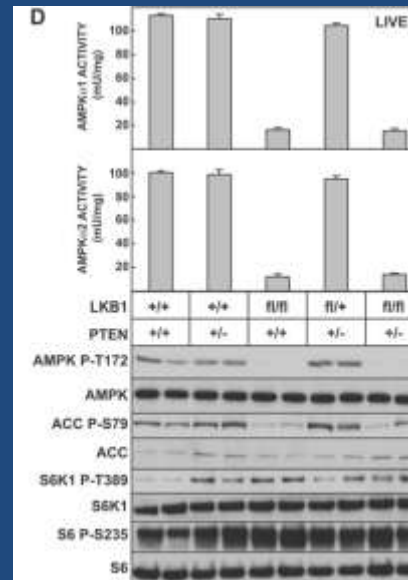
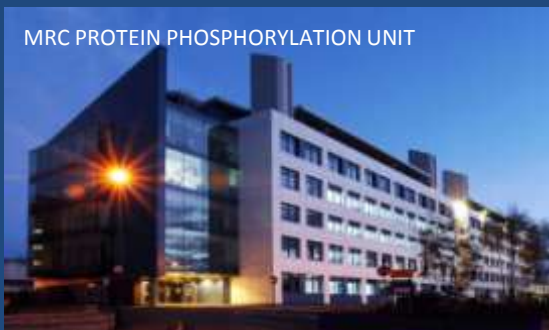


IHC USEFUL FOR LOCALISING BUT UNRELIABLE FOR QUANTIFYING PHOSPHO-PROTEIN



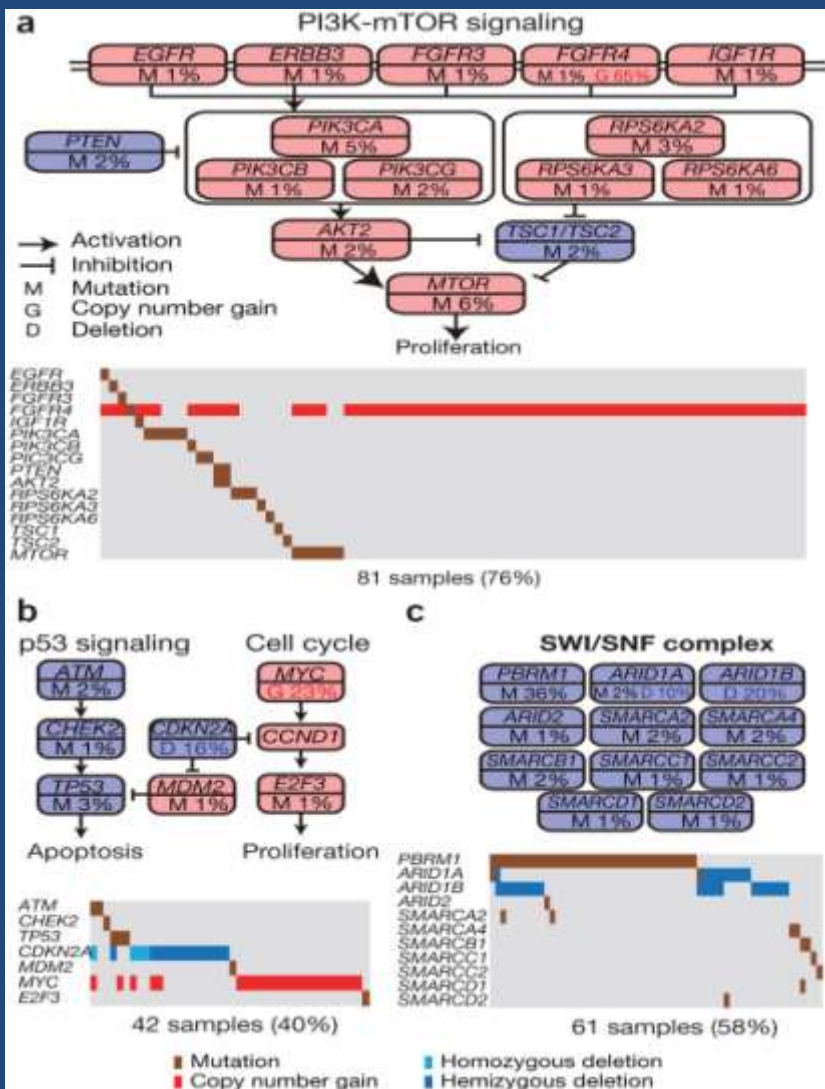
GLIOMA XENOGRAFT AKT-P473

BAKER ET AL CLIN. CANCER RES 2005



USE FRESH TISSUE COLLECTED IN PHOSPHATASE INHIBITORS AND ASSAYED BY BIOCHEMICAL AND WESTERN BLOT METHODS

HUANG ET AL
BIOCHEM J 2008

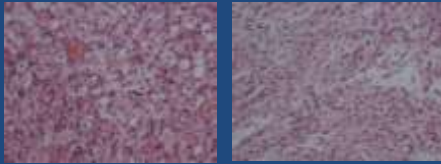


CAN WE DEFINE TREATMENT PATHWAYS BY IDENTIFICATION OF DRIVER MUTATIONS?

DOES TUMOUR EVOLUTION CONFOUND THAT AIM?

SATO ET AL Nat Genet.
 Aug;45:860-7 (2013)

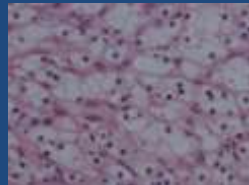
TUMOUR HETEROGENEITY



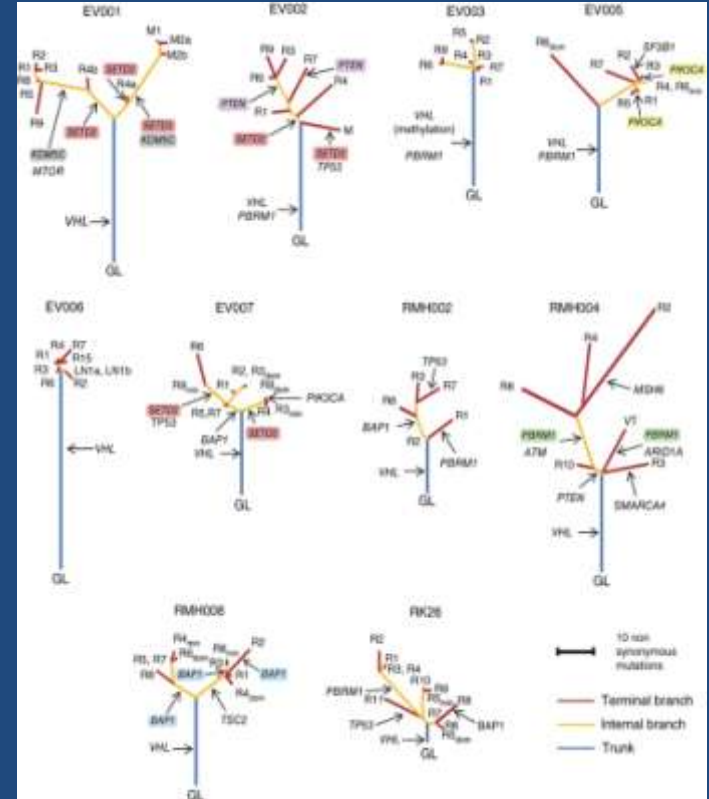
MORPHOLOGY



IMMUNOHISTOCHEMISTRY



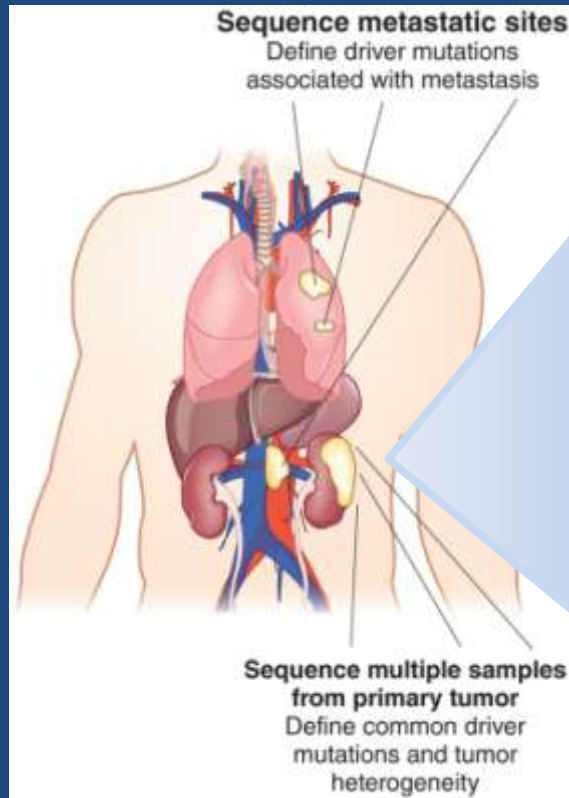
GRADE



- STUDY OF MOLECULAR ALTERATIONS HAS CONFIRMED THAT TUMOUR EVOLUTION IS A BETTER TERM

GERLINGER ET AL Nat Genet 46, 225–233, (2014)

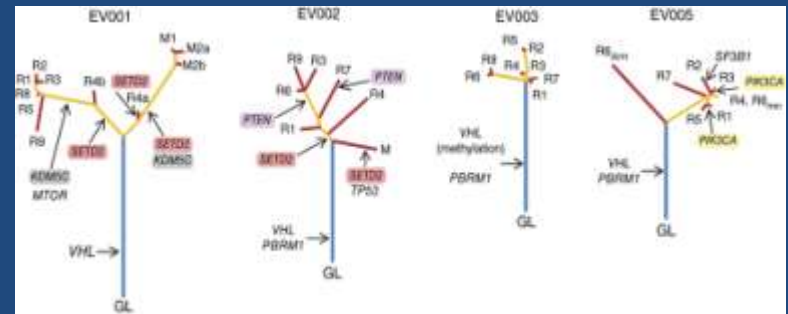
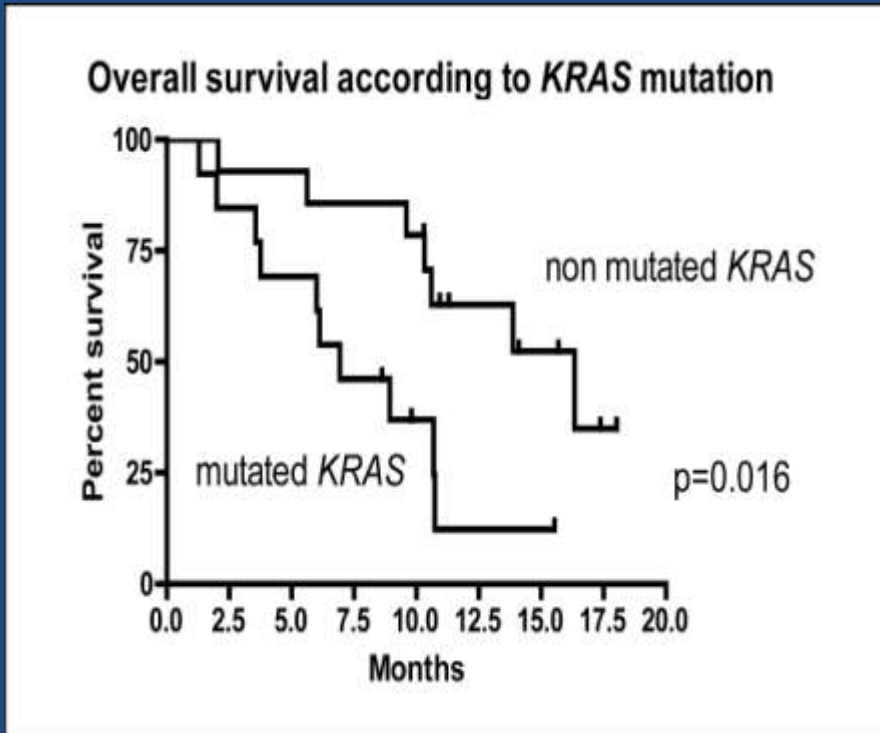
HOW ARE WE TO IDENTIFY DRIVER MUTATIONS TO PLAN TREATMENT?



LEARNING FROM FAILURES



Overall survival curves of patients with a KRAS-mutated and nonmutated tumor.



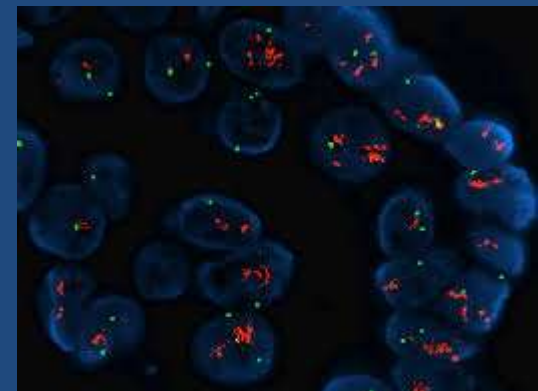
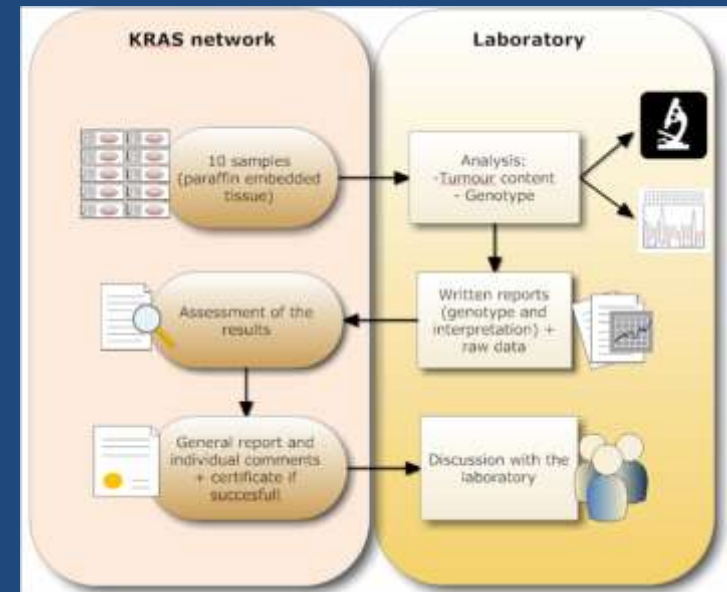
Responders 0/13 had KiRas mutation
 Non-responders 13/19 has KiRas mutation

Lièvre A et al. Cancer Res 2006;66:3992-3995

WHAT IS THE BIOLOGY OF TREATMENT FAILURE IN RCC?

MOLECULAR PATHOLOGY

- Protocols for molecular genetic techniques need to be standardized, thresholds agreed upon, sampling of tissues needs to be assessed and inter-observer agreement reported.
- The results of new and emerging molecular genetic techniques need to be validated including appropriate use of negative and positive controls.



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