Recent Advances in RCC

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Financial Disclosures

- None

Overview

- Probably more of an update with highlights of some recent changes
- Surgical Advances/Current State
- Individualized Medicine
  - Sequencing
- Immunotherapy

What's Happening in Surgery?

- More Robotics being utilized
  - Partials
  - Radicals
  - Caval Thrombus
- The biopsy debate continues
- Multimodal therapy for recurrences

What's Happening in Surgery?

- Partials
- Off/clamp vs On clamp
- Partial benefits?
- Partial Video

What's Happening in Surgery?

- Advances in technique for vascular control
- Mostly for T3b cases below the hepatics
- Radical/Thrombus Video

What's Happening in Surgery?

- To Biopsy or not to Biopsy
- Different camps
  - Usually ablations supporters biopsy
- What does it change that growth kinetics, patient characteristics and available resources does not?

What's Happening in Surgery?

- Multimodal Therapy for Recurrences

- Recurrent case with IORT and pre-op xrt

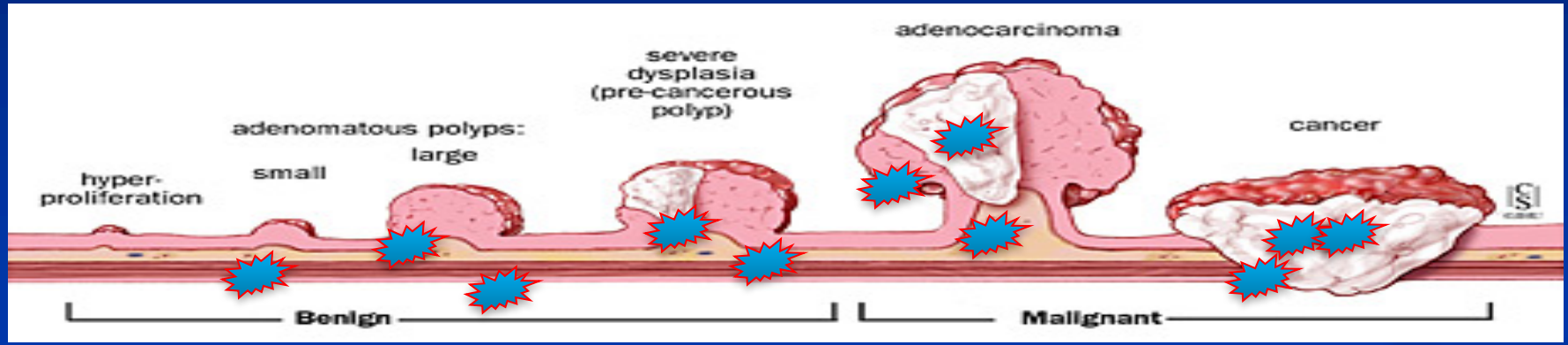
- Recurrent case with IORT and pre-op systemic Rx

Individualizing Medicine

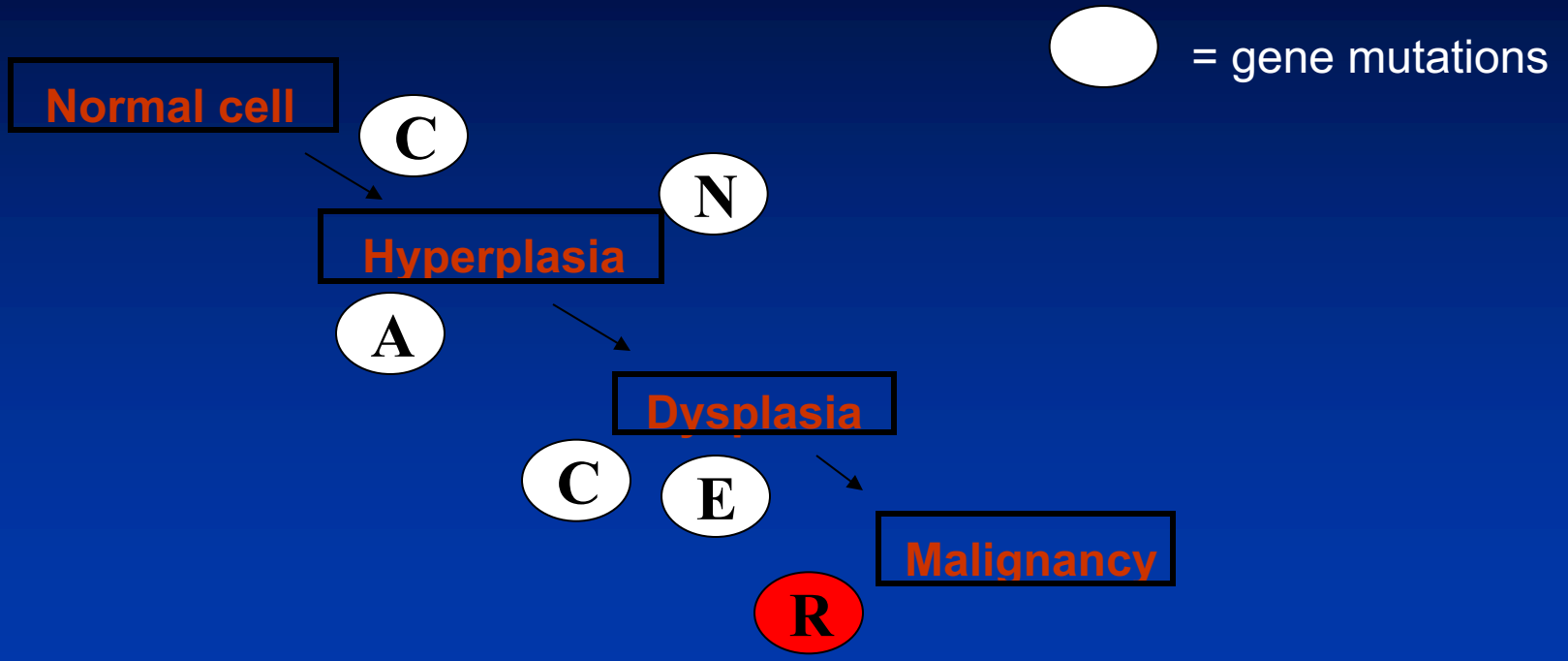
- Genetics and Immunotherapy
- Sequencing
- Assessing via CAMLs
- CAR-T Cell Therapy
- PDL1/PD1

For a cell to transform into a cancer, it acquires mutations in driver genes that promote cell growth

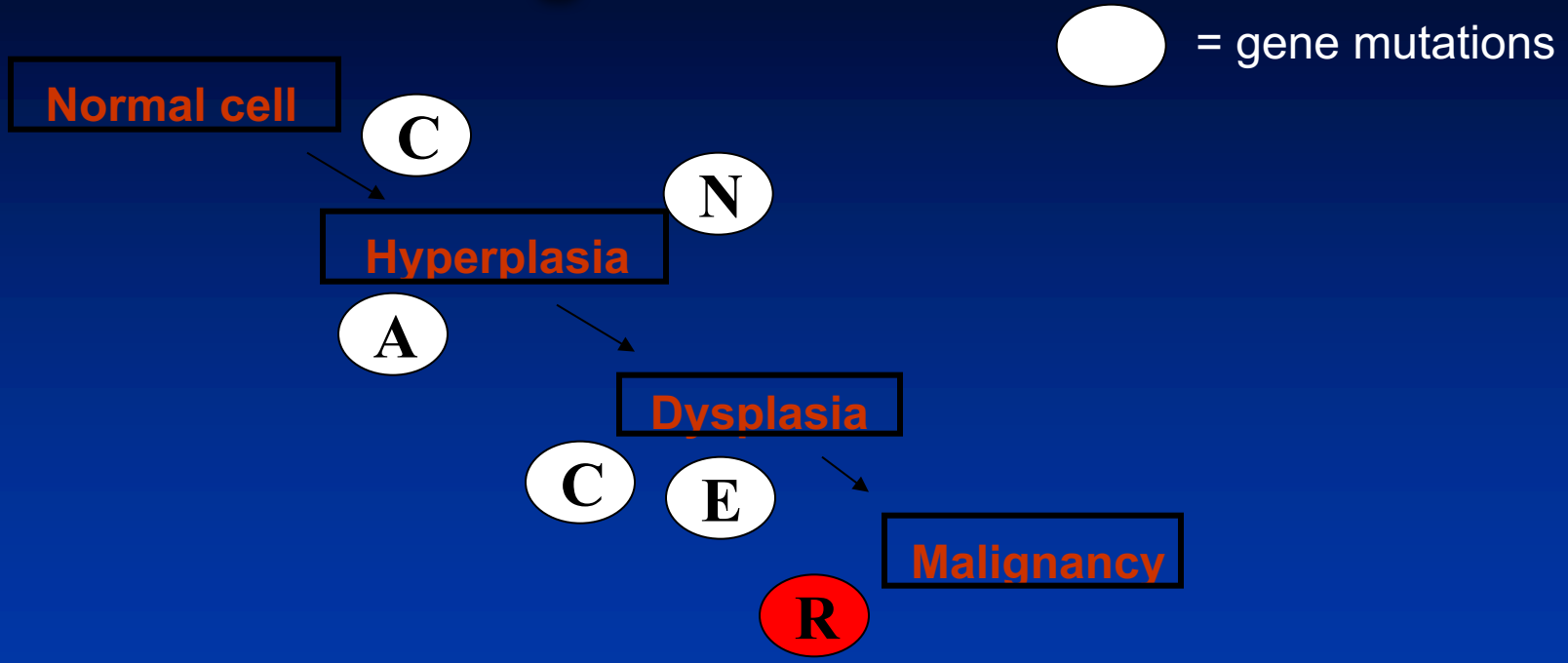
[all cancer is genetic]



Cancer results from random mutations in driver genes over time



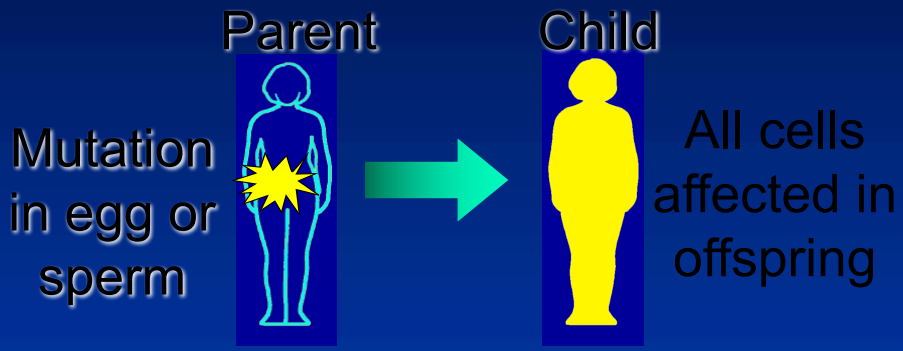
What if all cells started out with one inherited gene mutation?



Makes it **more likely any cell will hit the "Cancer Powerball"** because there is one less event needed

All cancer is genetic.
Most cancer is not hereditary.

Hereditary mutations



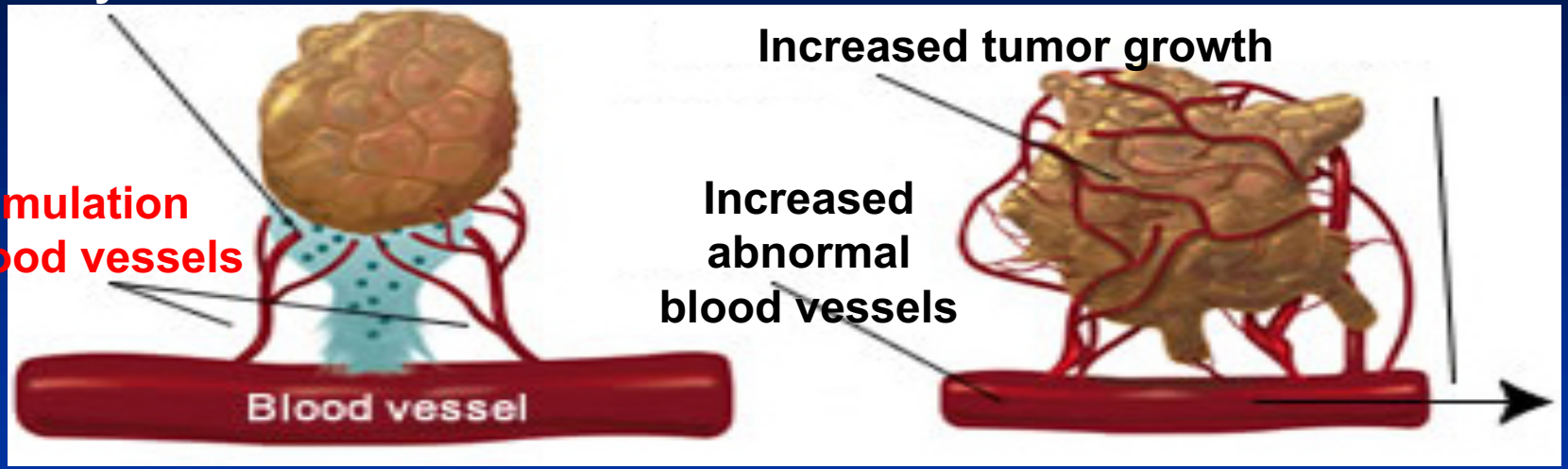
- Present in egg or sperm
- Are heritable
- Cause hereditary cancer syndromes

Somatic mutations

- Occur in tumor tissues
- Are not heritable
- In all cancers

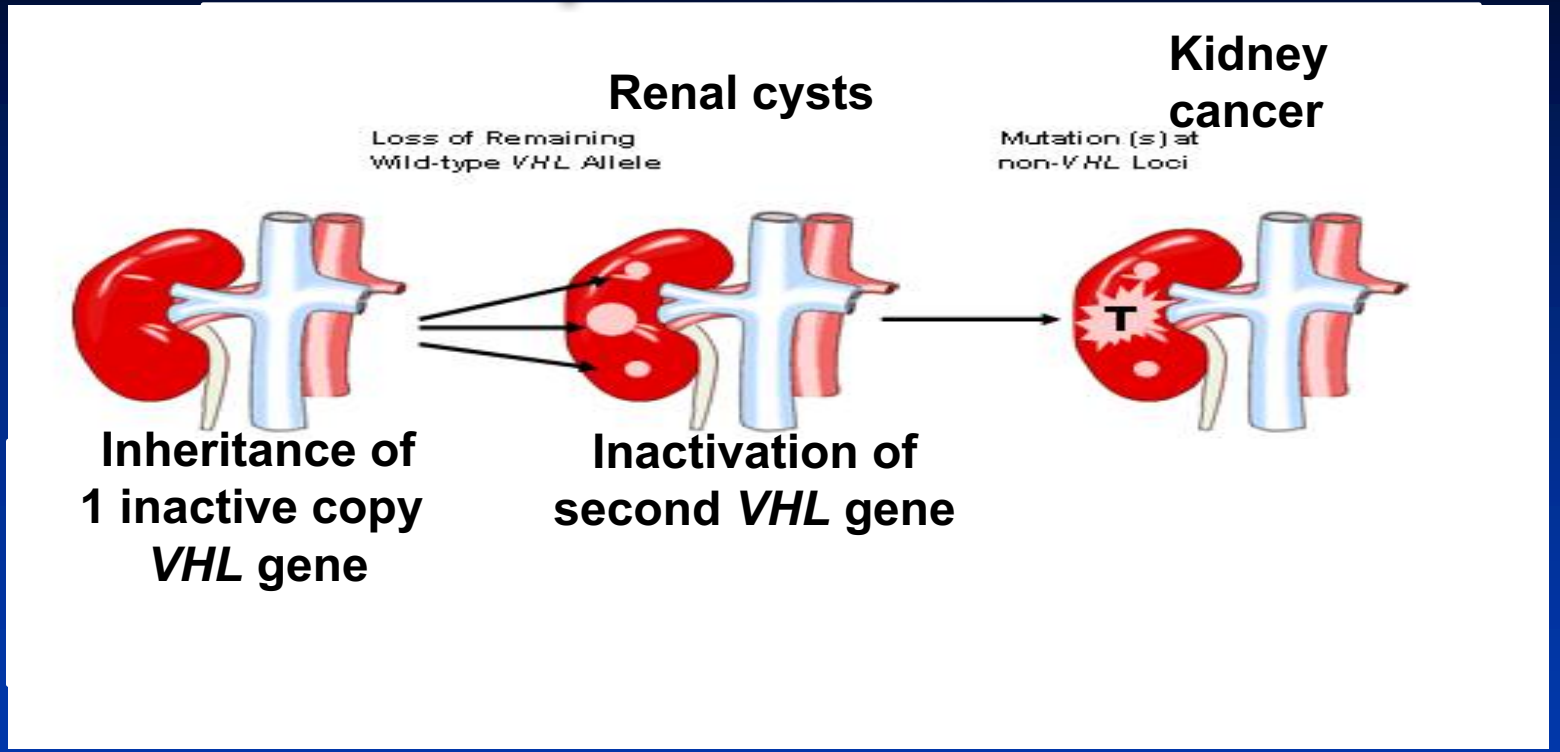
Loss of the *VHL* gene promotes abnormal growth of blood vessels and tumor metastases

Delivery of nutrients to tumor



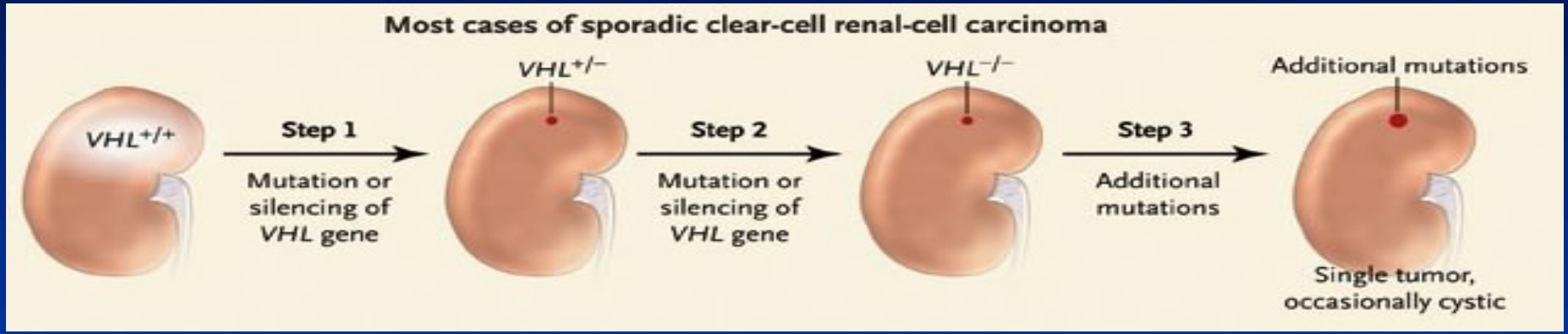
http://www.dana-farber.org/Newsroom/Publications/Gaining-Ground-against-Kidney-Cancer.aspx

The discovery of mutations in the von Hippel-Lindau (*VHL*) gene in VHL syndrome led to a model of tumorigenesis in sporadic ccRCC



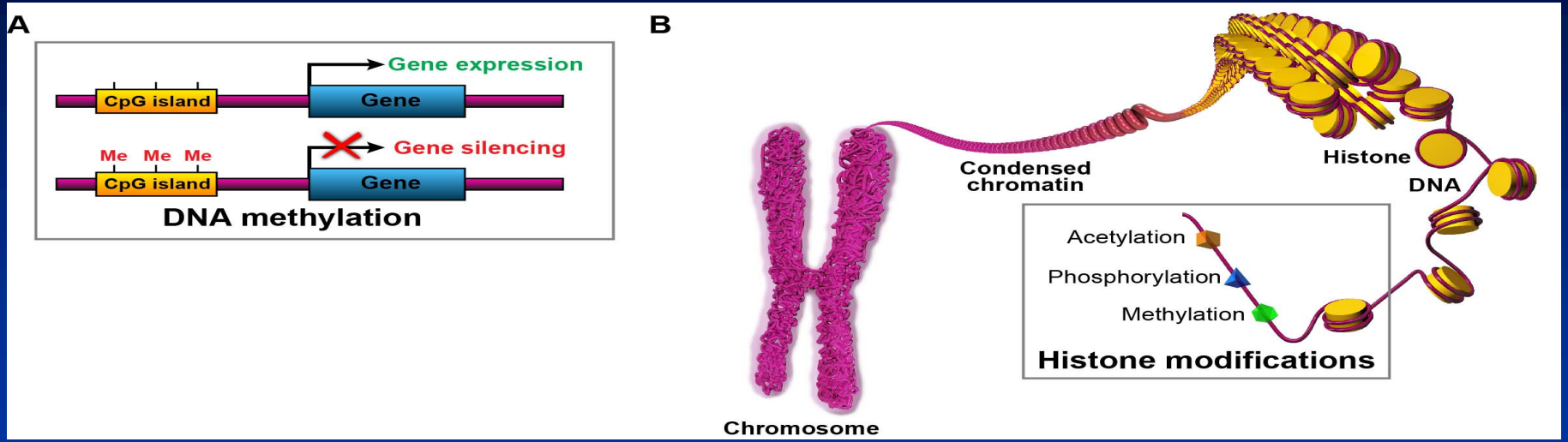
Kaelin, W. "Kidney Cancer: Lessons from VHL Disease" ASCO 2004

Loss of VHL function is insufficient to promote tumorigenesis

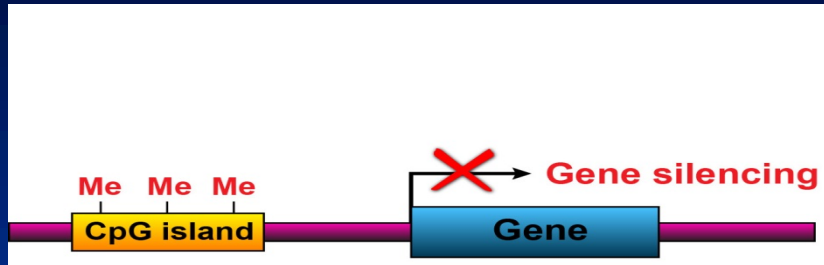


Adapted from Cohen et al. ***NEJM*** 2005, **353**: 2477.

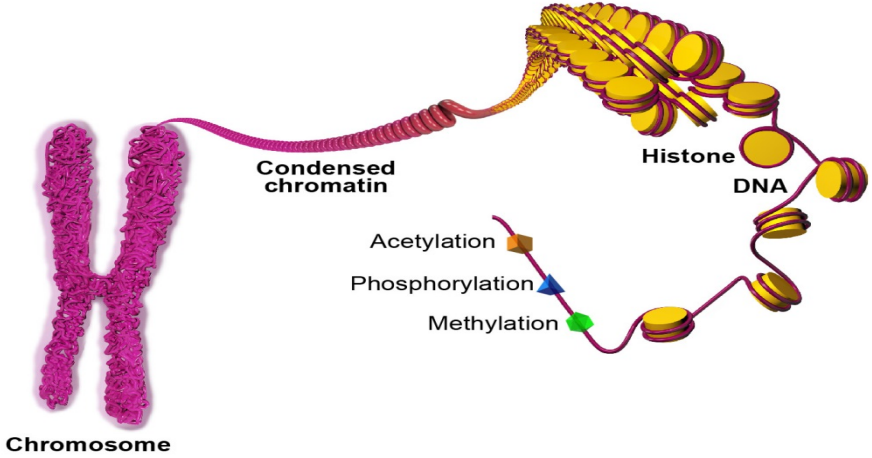
Epigenetic mechanisms modify gene expression without altering DNA sequence



Modifications of both DNA and histone proteins may alter ccRCC biology

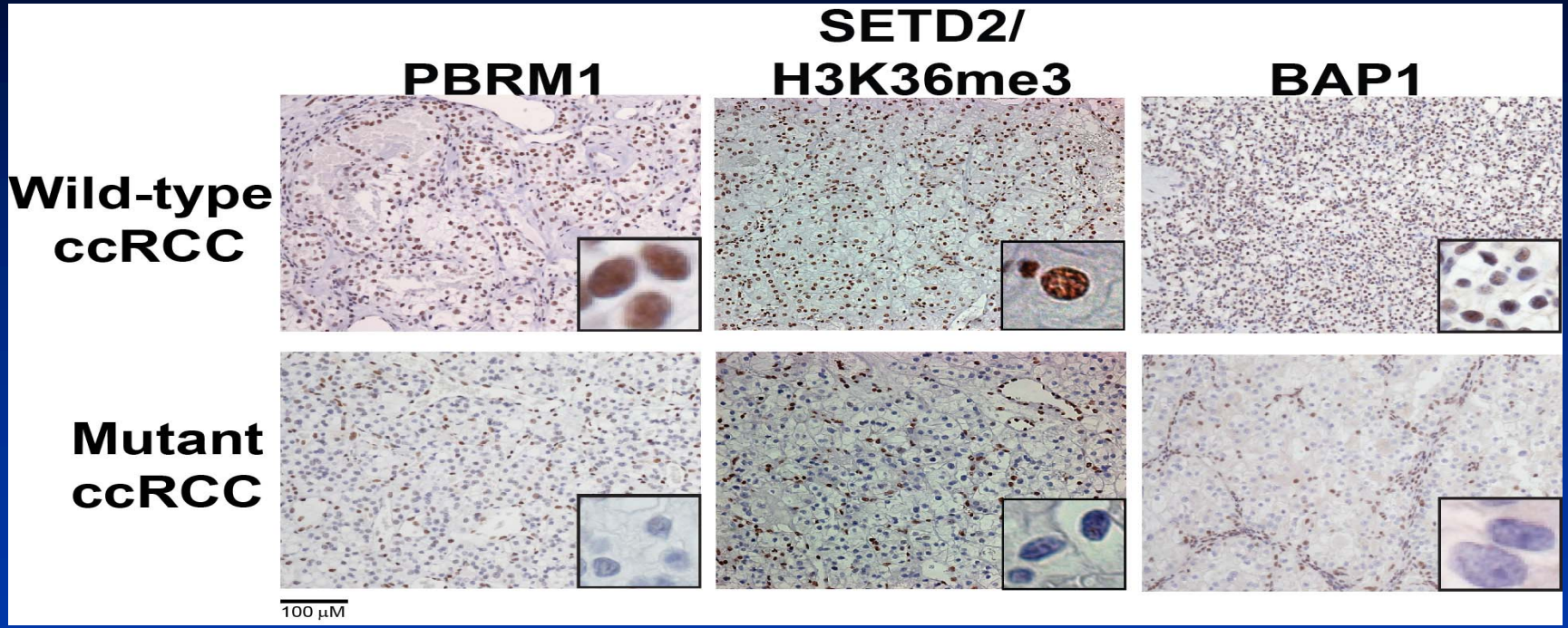


DNA hypermethylation of *VHL* promoter



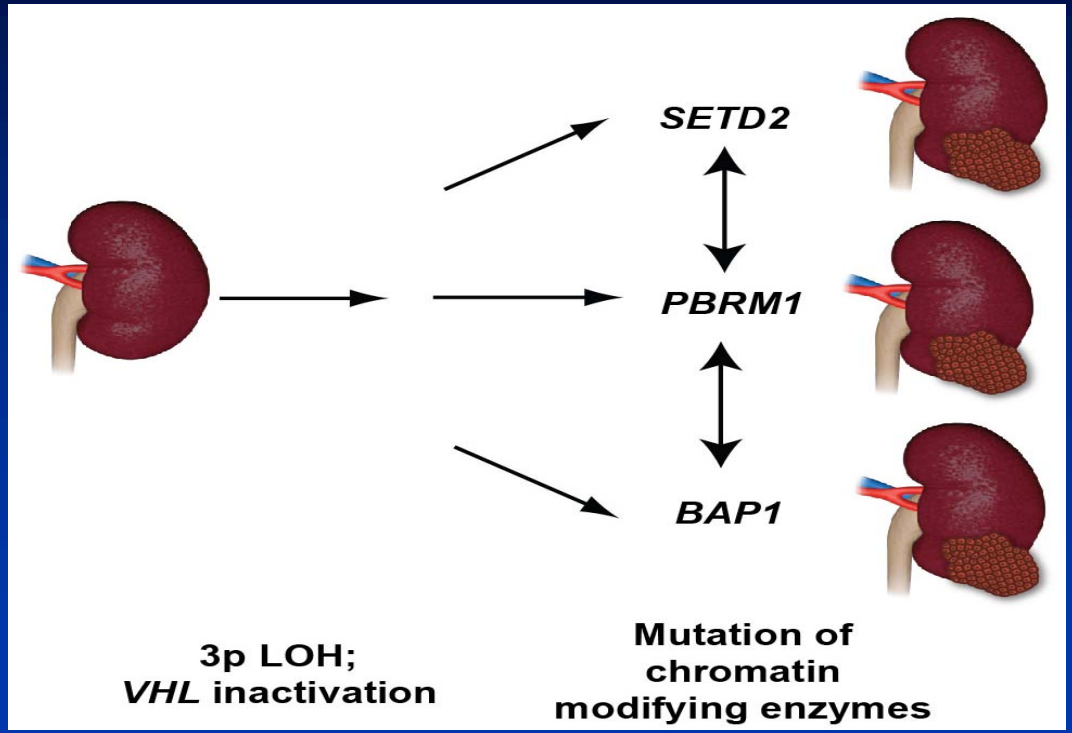
Mutations in chromatin modifying enzymes

Inactivation of chromatin modifying enzymes alters protein expression or histone modifications

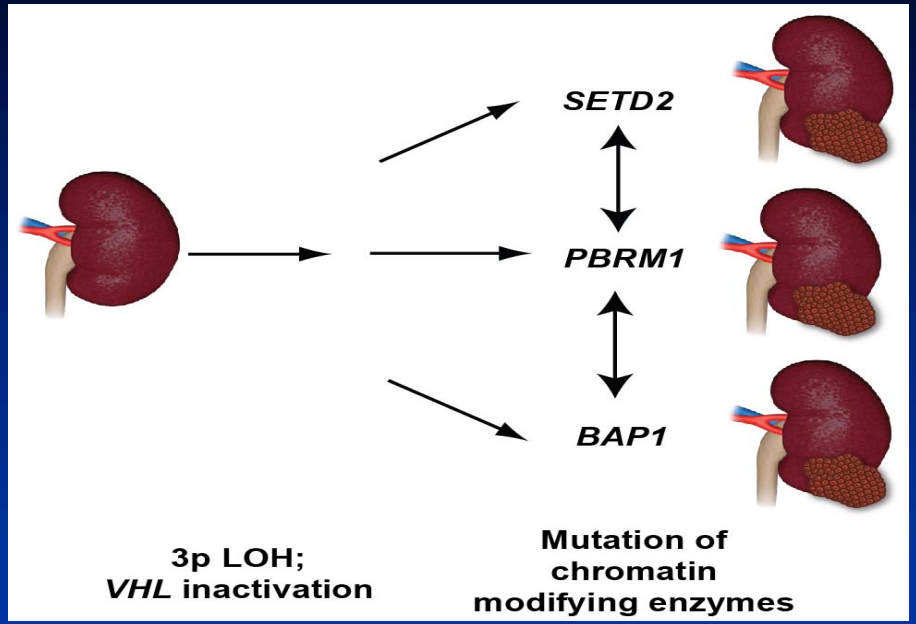


Ho and Kapur et al. Urol. Oncology 2014

Inactivation of *VHL* is an early genetic event followed by secondary mutations in chromatin modifying enzymes

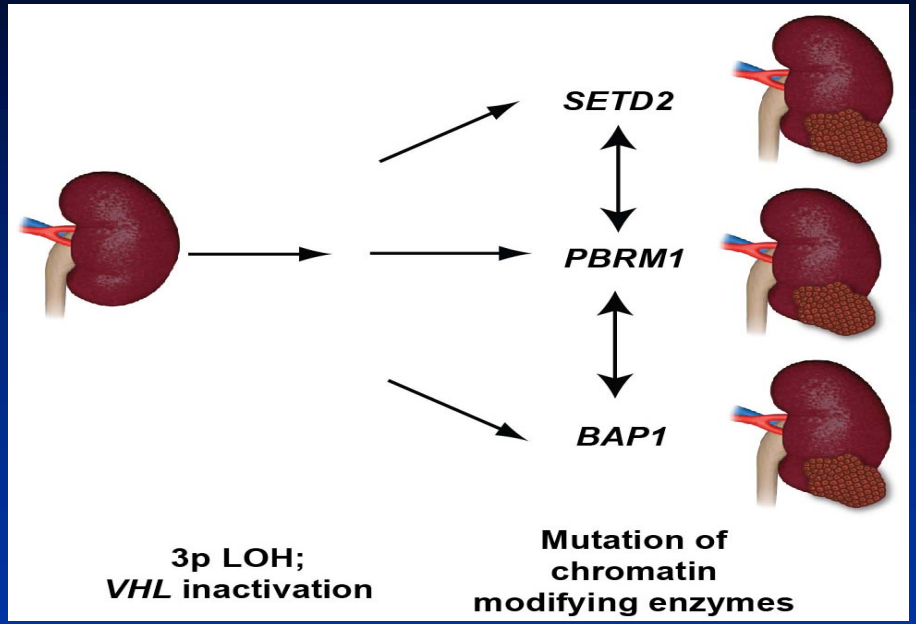


Are these epigenetic mutations predictive or prognostic?



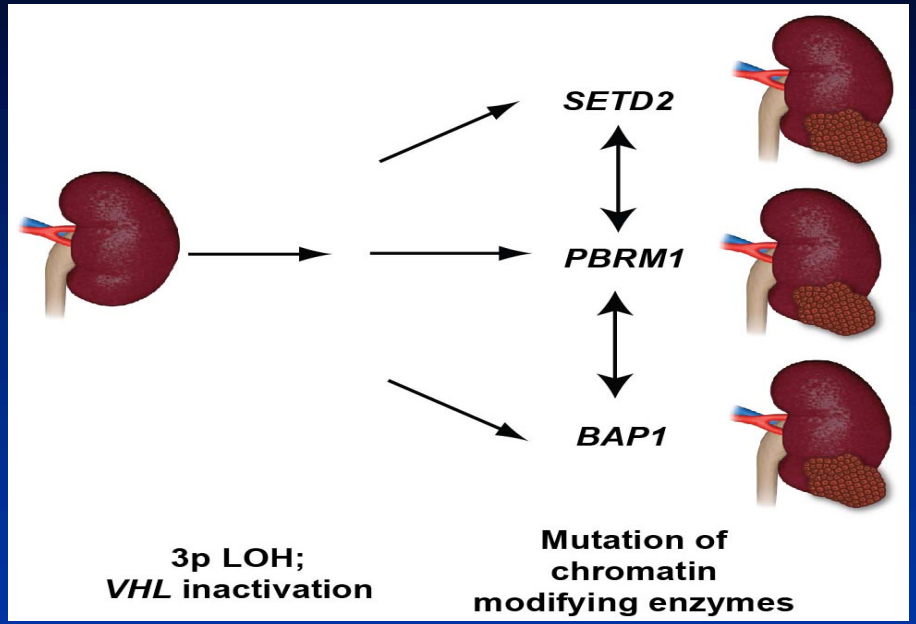
- A prognostic factor is a characteristic that is provides information on the likely outcome of the cancer disease in an untreated individual.
- A predictive factor is a clinical or biologic characteristic that provides information on the likely benefit from treatment.

Are these mutations predictive of response to systemic therapy?



- Current drugs target the microenvironment
- Tumor heterogeneity leads to underestimation of mutations from single tumor-biopsy samples
- Targeted therapies usually inhibit hyperactivated pathways or gain of function mutations

If I order molecular genotyping of a ccRCC what can I expect to find?



- No mutations
- Mutations, no targeted therapies
- Mutations with targeted therapies that are not approved by the FDA for ccRCC
- Mutations associated with hereditary cancer syndromes

"not actionable" mutations; *VHL* mutations are not predictive of response to anti-angiogenic therapy

PATIENT RESULTS

TUMOR TYPE: KIDNEY RENAL CELL CARCINOMA (NOS)

Genomic Alterations Identified†

VHL

PBRM1
SETD2

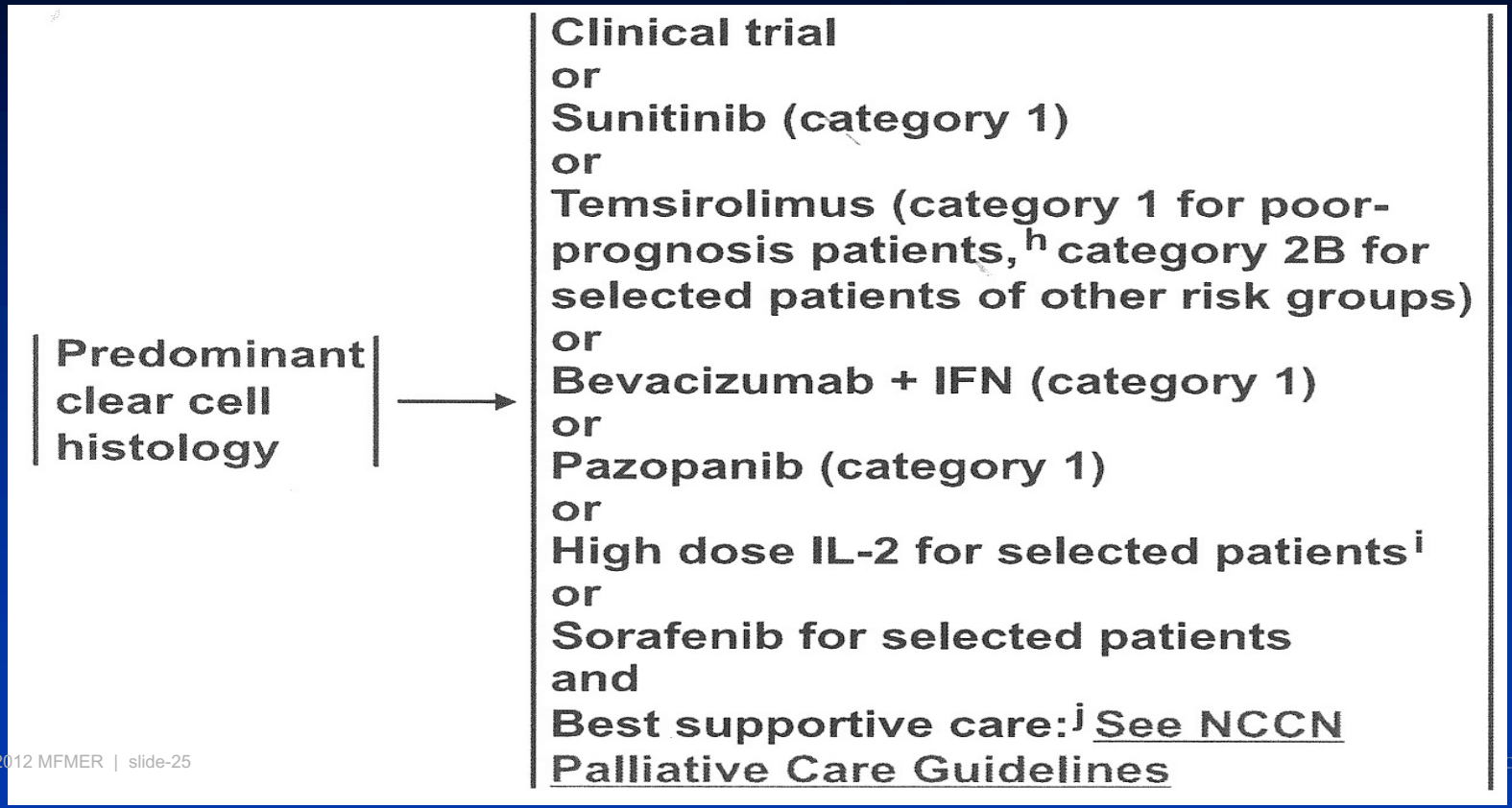
0 therapies associated with lack of response

†For a complete list of the genes assayed, please refer to the Appendix
[36]See Appendix for details

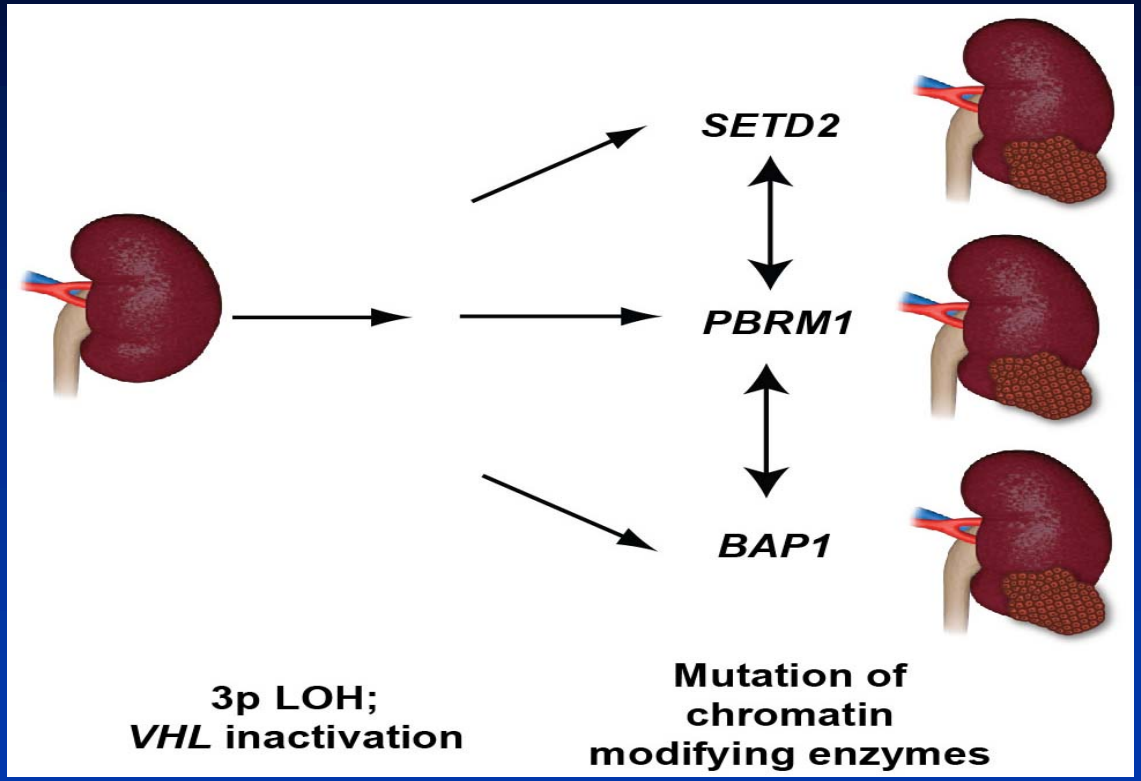
THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
VHL	Axitinib Bevacizumab Everolimus Pazopanib Sorafenib Sunitinib Temsirolimus	Vandetanib	Yes, see clinical trials section
PBRM1	None	None	None
SETD2	None	None	None

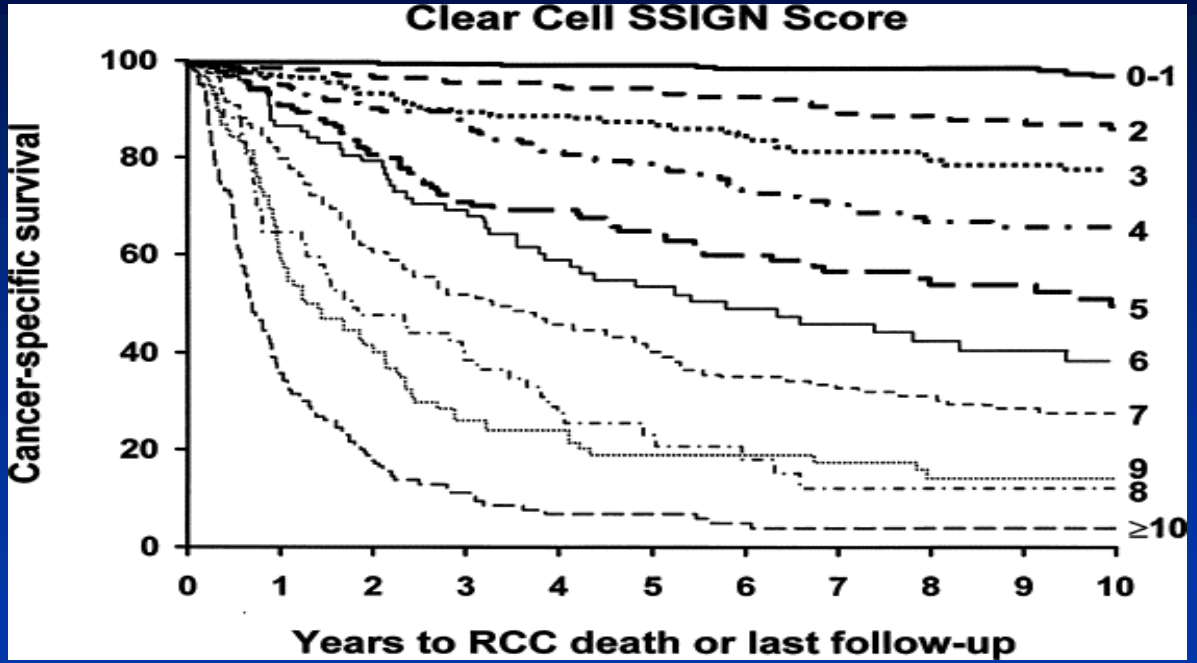
Histology is the primary determinant of first-line therapy



Do epigenetic classifications provide additional prognostic information to existing algorithms?

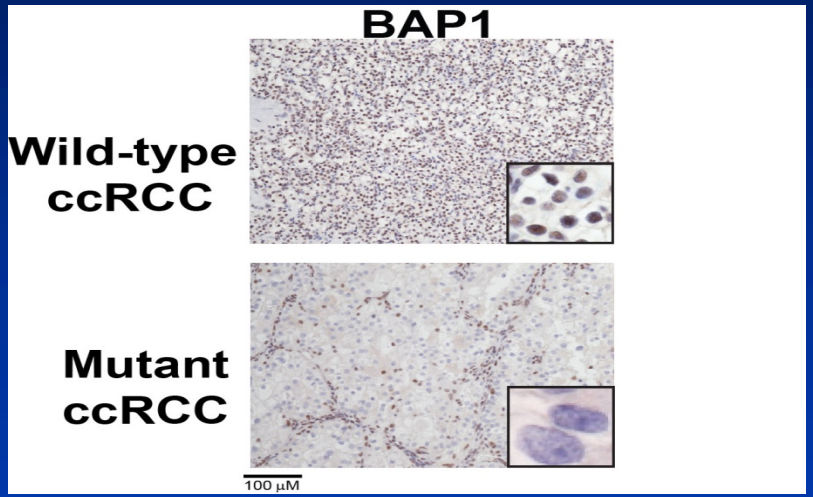


Mayo SSIGN (Stage, Size, Grade, Necrosis) Score stratifies patients into prognostic categories



Frank et al, J. Urol December 2002, Pages 2395–2400

BAP1 loss of expression by IHC is consistent with a BAP1 deficient genotype (as defined by Sanger sequencing)



	Next generation sequencing	IHC
True BAP1 deficient (Sanger)	24/27	25/27
True BAP1 competent (Sanger)	149/149	148/149

Pena-Llopis. et al.
Nature Genetics 2012

Why use immunohistochemistry instead of sequencing to define epigenetic subtypes in RCC?

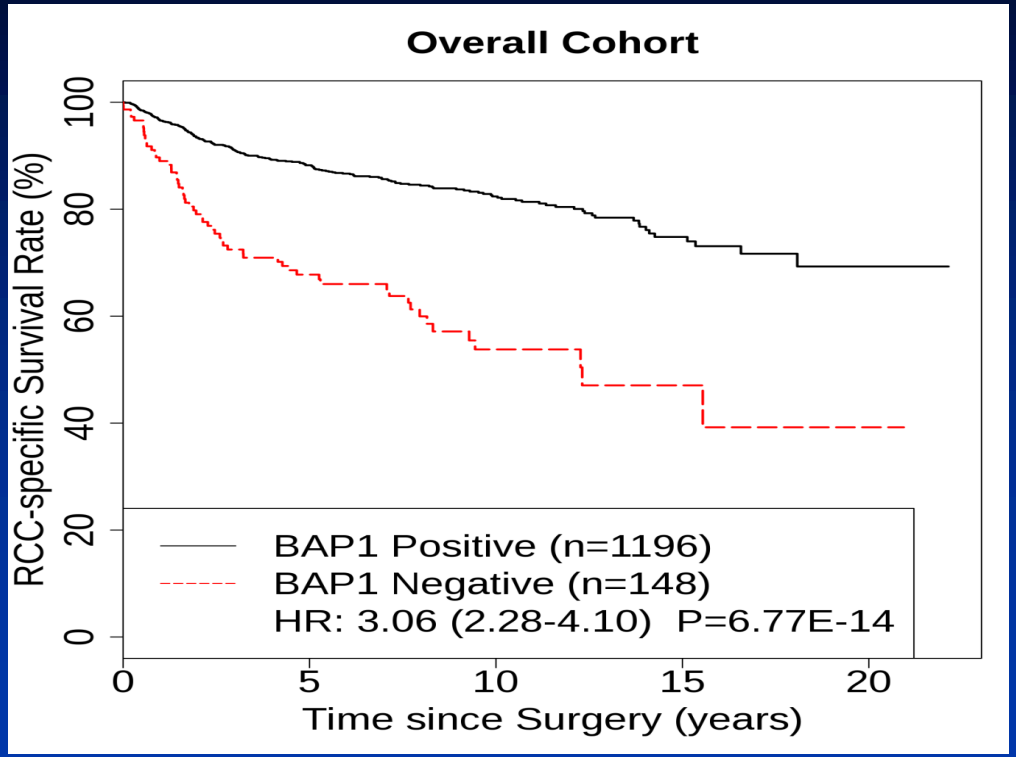
Advantages

- Detects biallelic inactivation leading to loss of protein expression
- Tumor heterogeneity/stromal contamination may reduce sensitivity for mutations
- More cost effective in the current era for large studies ($50 per slide for reagents)

Disadvantages

- Defining IHC cutoffs can be challenging (i.e. focal negative, weak positives)
- May not detect heterozygous mutations
- Each IHC assay has to be optimized for each protein of interest
- Lot to lot variations in antibodies

Loss of BAP1 by IHC is associated with a worse prognosis



Joseph R. et al.
Cancer 2013

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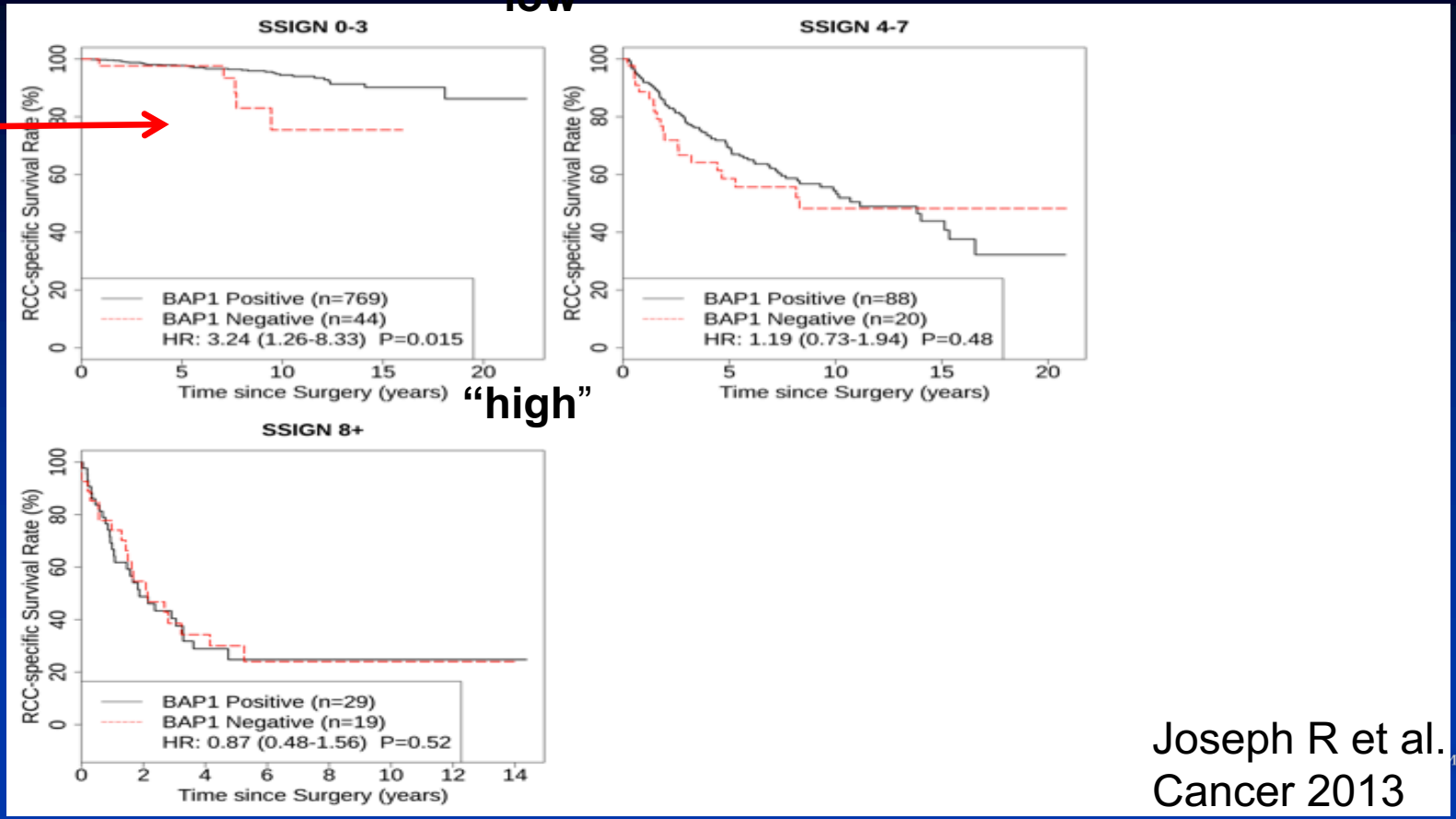
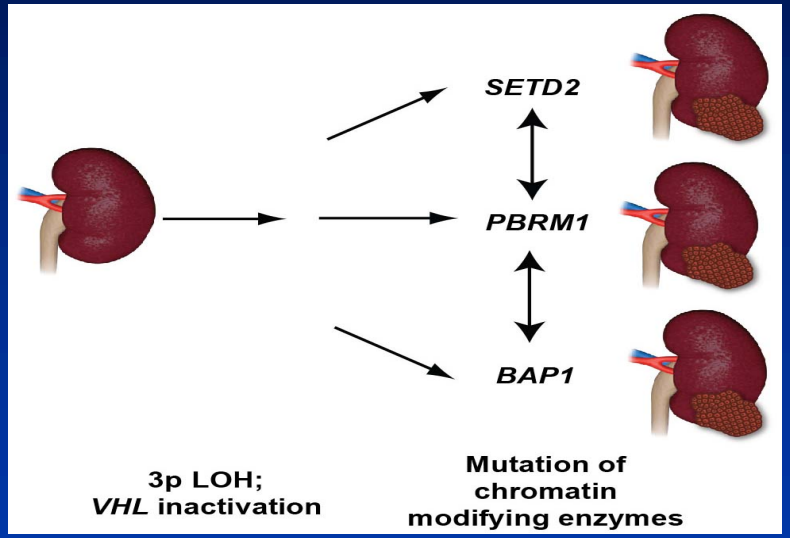
Loss of BAP1 by IHC is associated with a worse prognosis despite a "lower risk" clinicopathological risk score (Mayo SSIGN score)

"low"



Joseph R et al. Cancer 2013

Although sequencing tumors identifies epigenetic classifications, it does not improve upon patient outcomes



- IHC may be a more cost-effective assay than sequencing for determining epigenetic classifications
- The predictive impact of epigenetic classifications in metastatic ccRCC is unknown
- Although epigenetic classifications add prognostic information for localized ccRCC, there are no guidelines for intervention

72 F with stage II ccRCC

PATIENT RESULTS

0 therapies associated with lack of response

TUMOR TYPE: KIDNEY RENAL CELL CARCINOMA (NOS)

Genomic Alterations Identified†

VHL

†For a complete list of the genes assayed, please refer to the Appendix
‡See Appendix for details

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VHL	Axitinib Bevacizumab Everolimus Pazopanib Sorafenib Sunitinib Temsirolimus	Vandetanib	Yes, see clinical trials section

Sequencing analyses identifies recurrent mutations in additional genes *(PBRM1, SETD2, BAP1)* in sporadic RCC; *BAP1* was later identified in familial syndromes of RCC

Gene	MSKCC, % (n=188)	TCGA, % (n=446)	U. Of Tokyo, % (n=106)
VHL	51	52	40
PBRM1	30	33	26
SETD2	7	12	11
BAP1	6	10	8

Hakimi, A. *et al.* Clin Cancer Res. Apr 1;20(7):1955-64
Cancer Genome Atlas Research Network. Nature. 2013 Jul 4;499(7456):43-9.
Sato Y. *et al.* Nat Genet. 2013 Aug;45(8):860-7.

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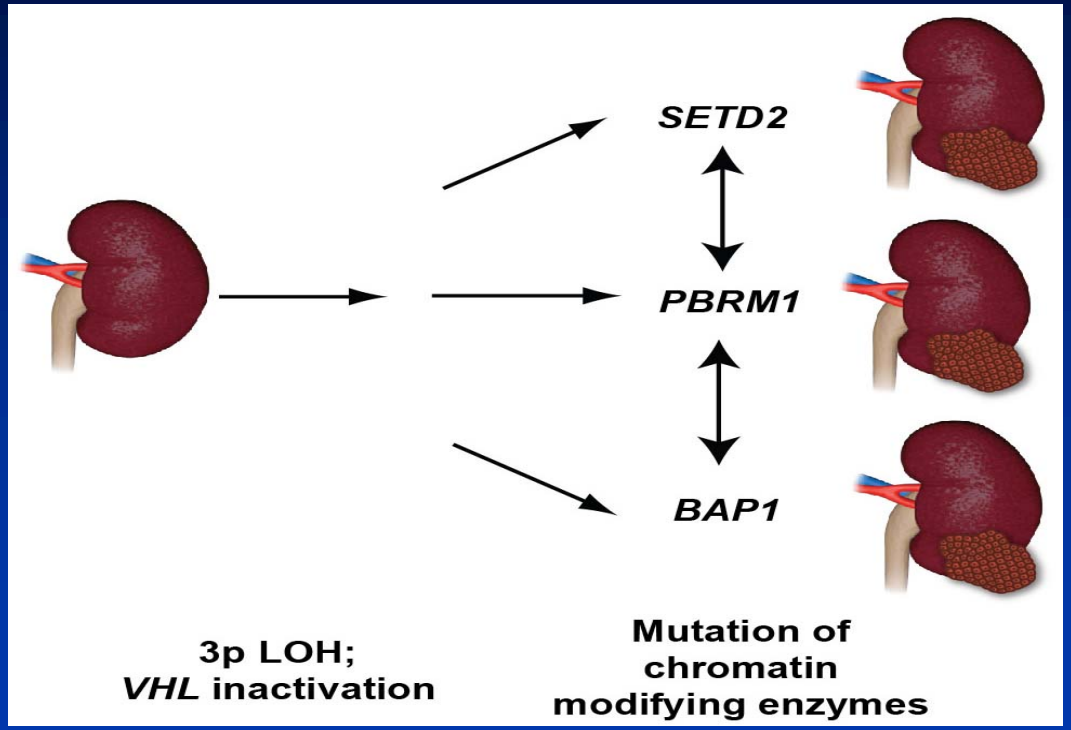
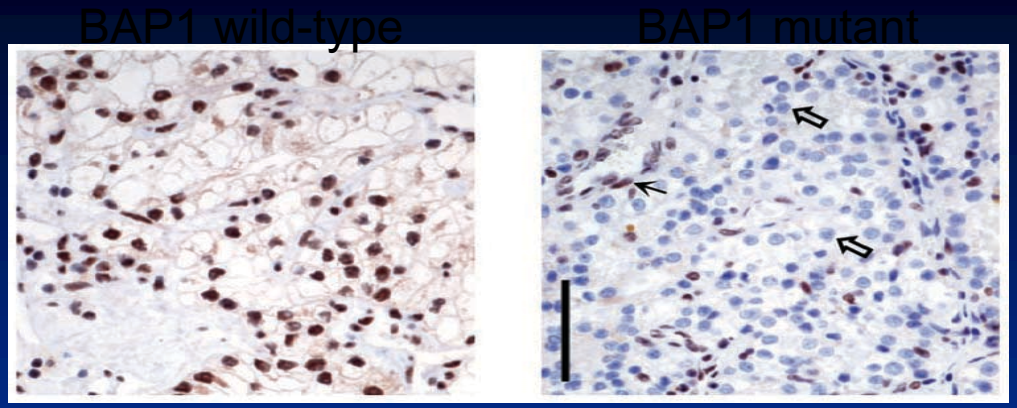
Inactivation of *VHL* is an early genetic event followed by secondary mutations in chromatin modifying enzymes



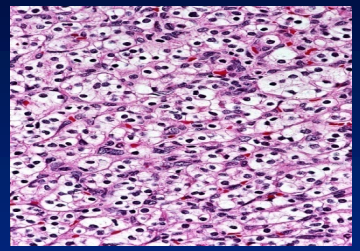
BAP1 predisposition for familial ccRCC



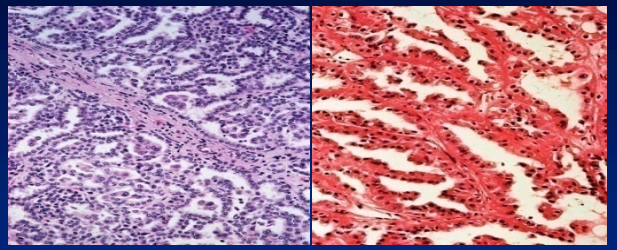
- *BAP1* mutations disrupt expression of BAP1 protein
- Mutated in ~10% of sporadic RCC, also mutated in familial syndromes of uveal melanoma
- Germline mutations associated with 8-fold increase in risk of RCC

Samuel Peña-LLopis et al., Nature Genetics 2012

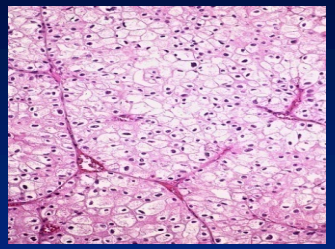
Kidney Cancer: RCC is a heterogenous disease



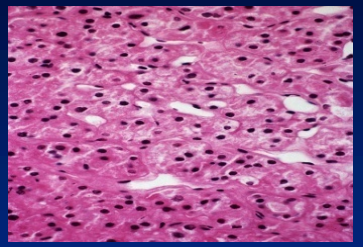
Clear Cell Carcinoma (ccRCC) (75%)



Papillary Carcinoma, Type I and II, (15%)



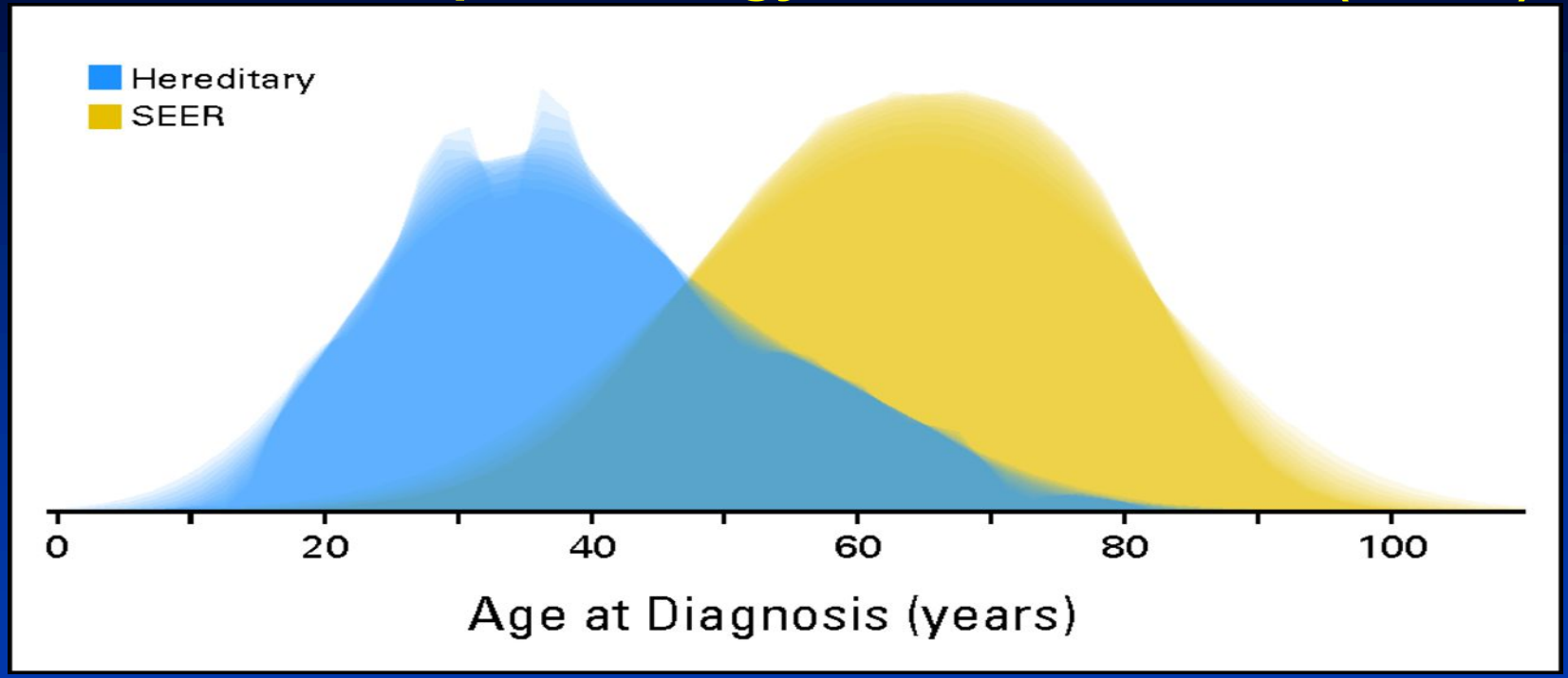
Chromophobe (5%)



Oncocytoma (5%)

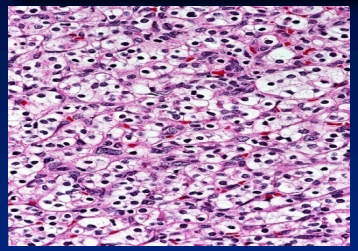
Collecting Duct/Renal Medullary (rare)

The age of onset of patients with hereditary RCC syndromes (NCI Genetics Clinic) is lower than in the Surveillance, Epidemiology, and End Results (SEER)



Shuch B et al. JCO 2014;32:431-437

The histology of an early-onset RCC may be linked to an underlying genetic syndrome



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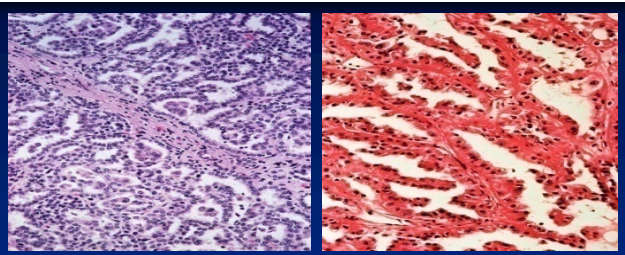

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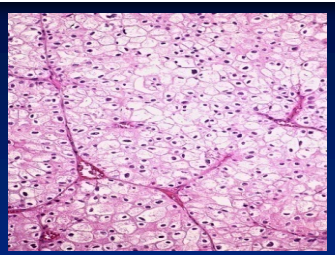
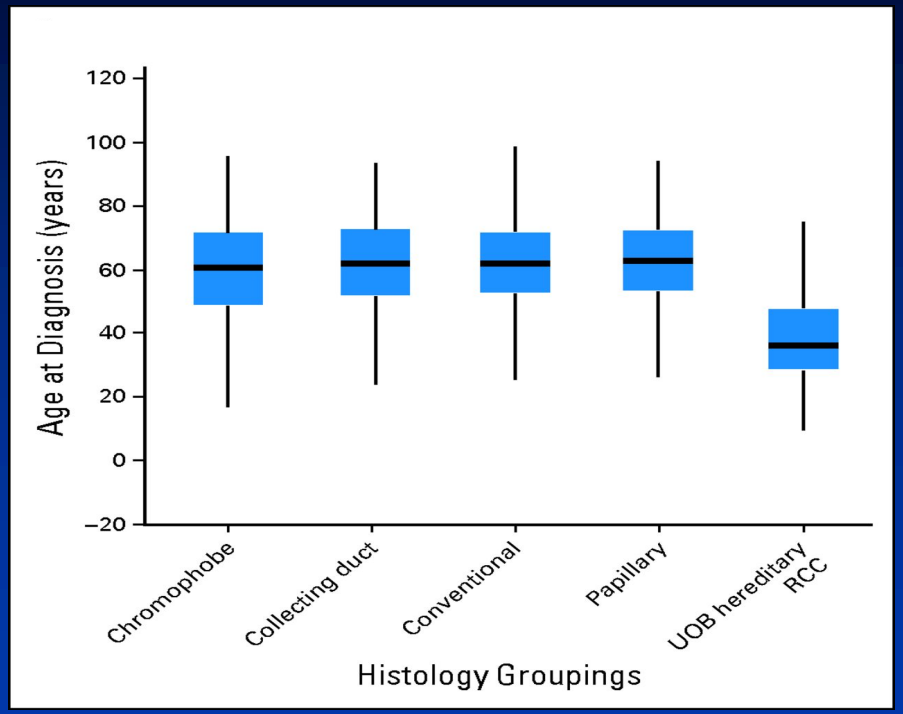


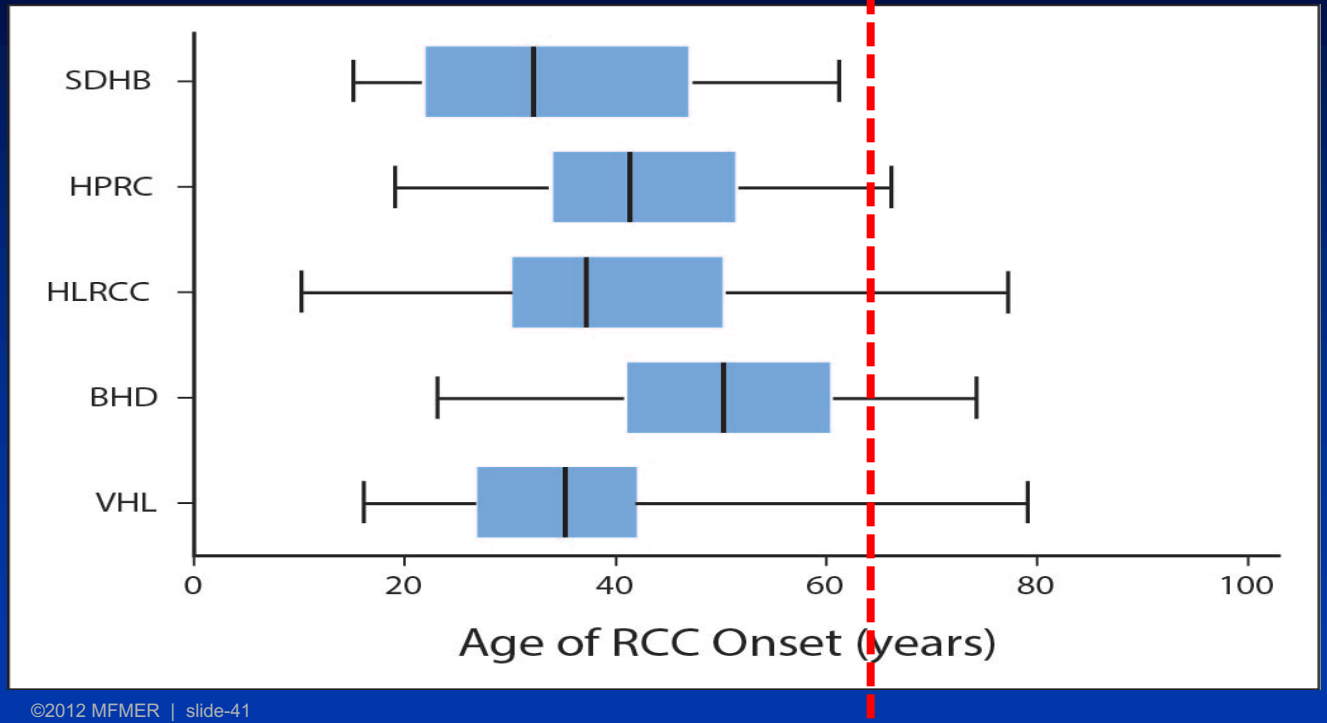
Chromophobe (5%)

The age of onset of patients with hereditary RCC syndromes (NCI clinic) is lower than sporadic non-ccRCC histologies



Shuch B et al. JCO 2014;32:431-437

Age of onset of hereditary RCC syndromes; SEER database mean age of 64



SDHB, succinate dehydrogenase B (ccRCC)

HPRC, hereditary papillary RCC (pRCC)

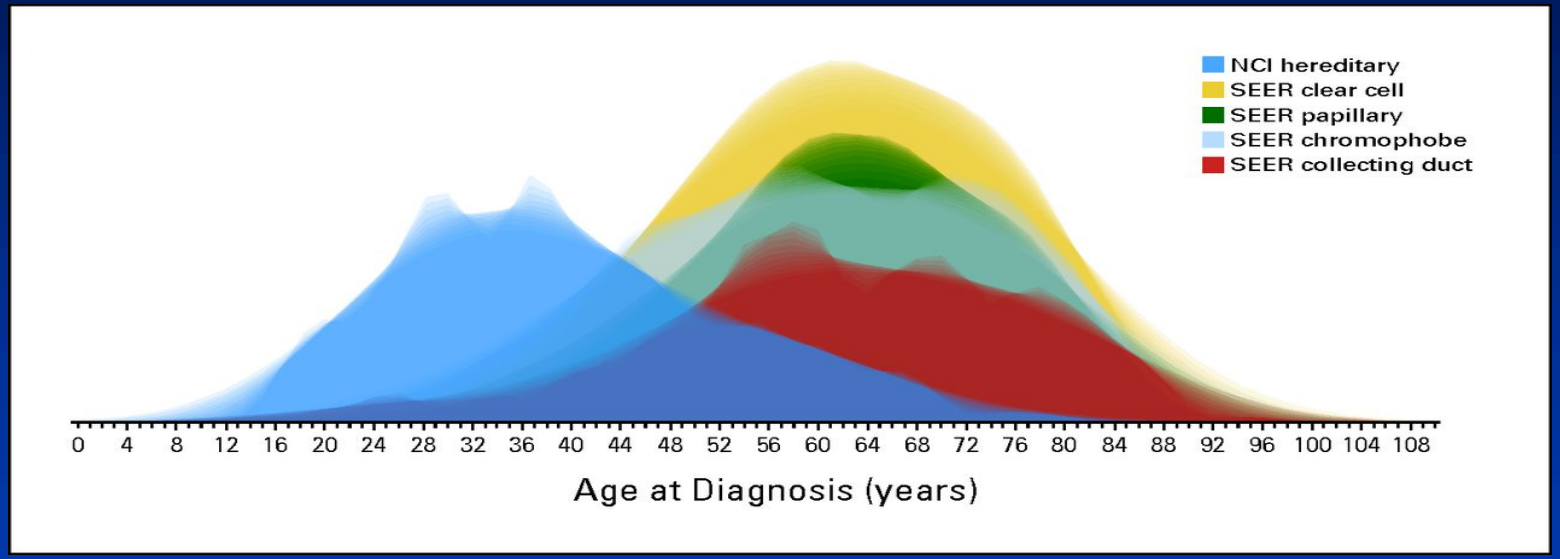
HLRCC, hereditary leiomyomatosis and RCC (pRCC)

BHD, Birt-Hogg-Dubé (oncocytoma /chromophobe)

VHL, von Hippel-Lindau (ccRCC)

Shuch B et al. JCO 2014;32:431-437

The age of onset of patients with hereditary RCC syndromes (NCI clinic) is lower than sporadic non-ccRCC histologies



Shuch B et al. JCO 2014;32:431-437

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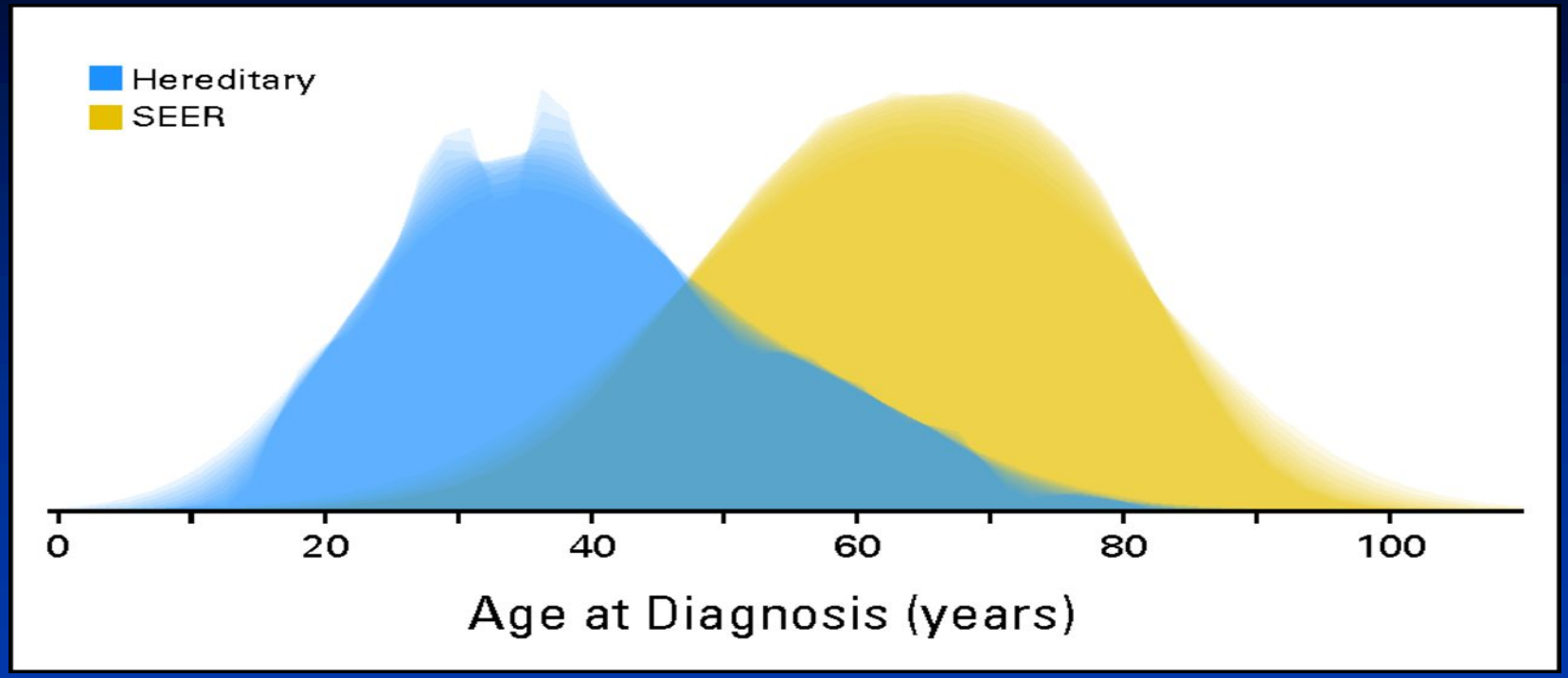
An age of onset of 46 years or younger may serve as a clinical guide for referral for genetic testing



Shuch B et al. JCO 2014;32:431-437

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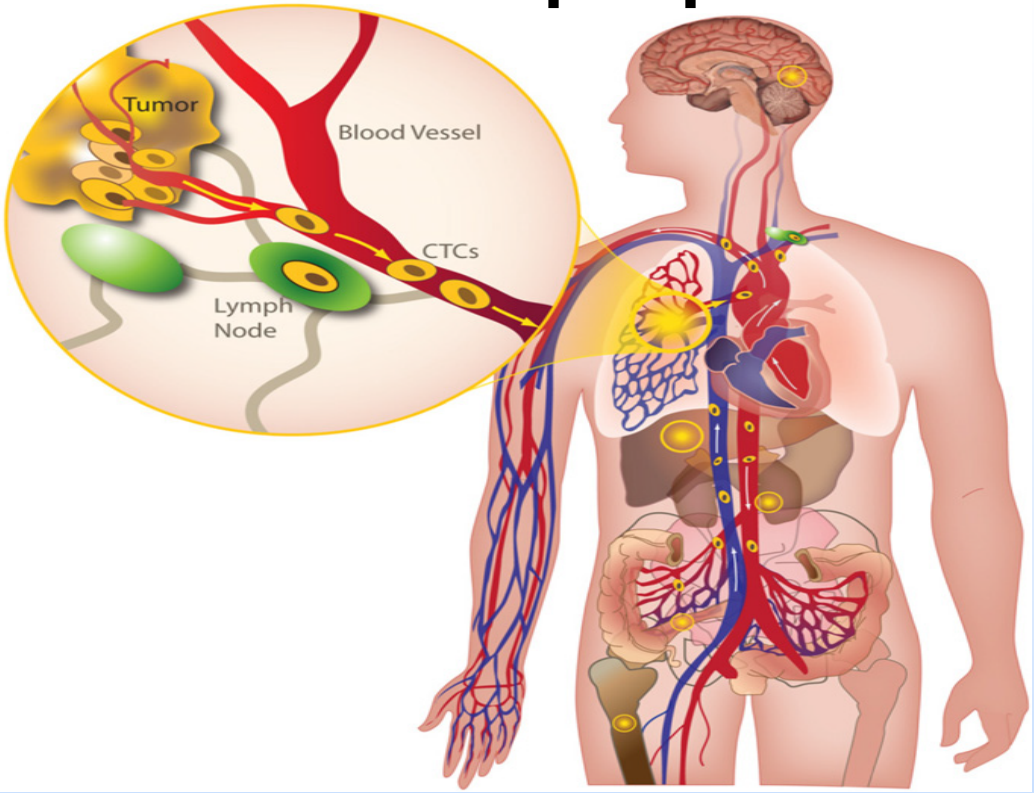
Individualizing Medicine

- Genetics and Immunotherapy
- Sequencing
- Assessing via CAMLs
- CAR-T Cell Therapy
- PDL1/PD1

What cancer-associated cells are present in the peripheral circulation?



Cell capture methods

- **Label-dependent** (antibody capture)
- **Label-independent** (cell size, cell density)

P. Kuhn and K Bethel, Phys. Biol. 9 (2012).

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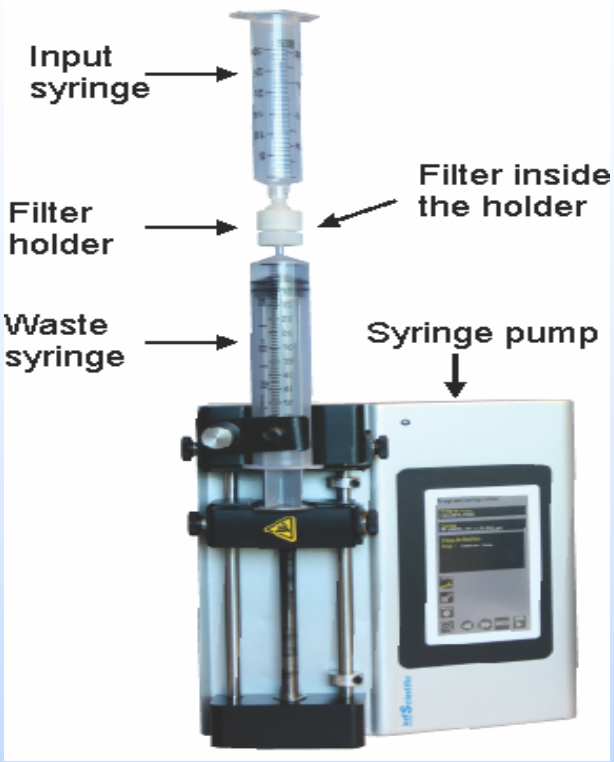
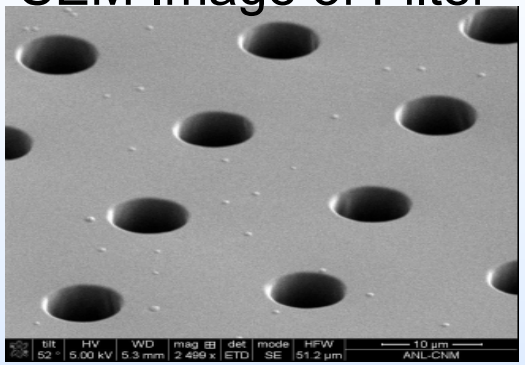
Microfiltration assay based on size exclusion



SEM Image of Filter



Pore diameter: 7 μm

Thickness: 10 μm

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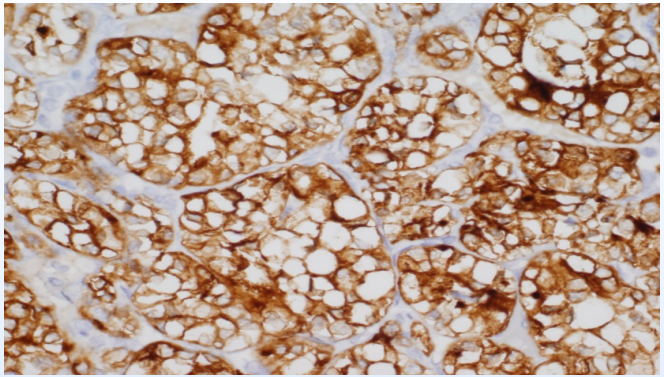
CD10 and vimentin (A) IHC in ccRCC and (B) IF in 786-O RCC cell line

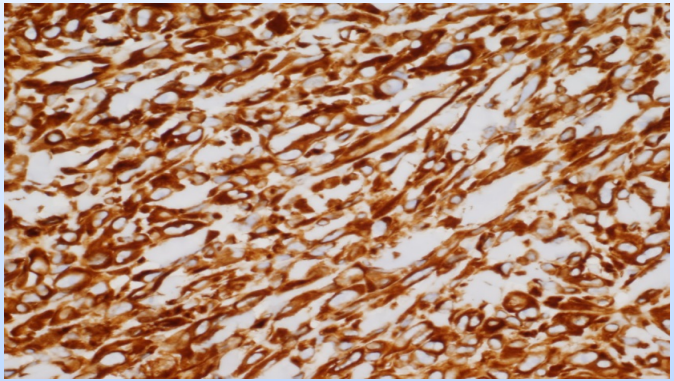
A

ccRCC

CD10

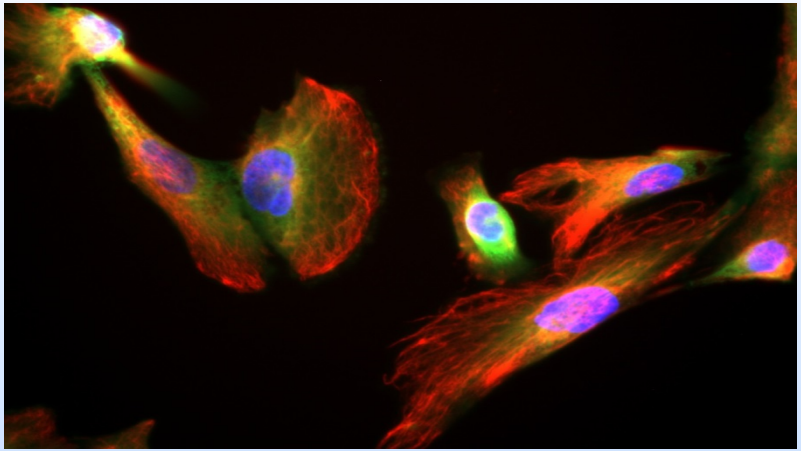


Vimentin



B

786-O RCC cell line
(green-CD10,
red-vimentin, blue-nucleus)



MAYO CLINIC

Individualizing Medicine

- Genetics and Immunotherapy
- Sequencing
- Assessing via CAMLs
- CAR-T Cell Therapy
- PDL1/PD1

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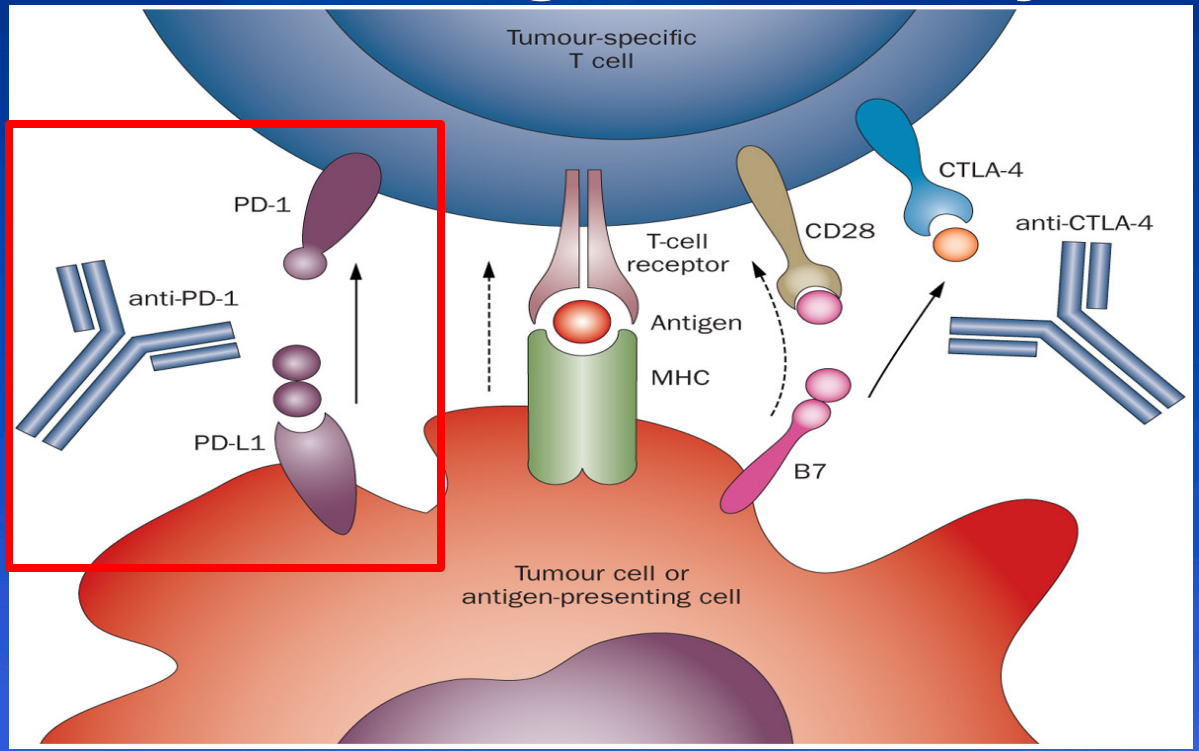
Emerging role of immune checkpoints in genitourinary cancer



- T-cell activation requires secondary cell surface signals in addition to MHC/antigen complexes
- Tumors have evolved mechanisms that evade immune-mediated destruction by aberrant cell surface receptors (PD-L1)
- Therapeutic antibodies that block PD-1 restore proper immune-mediated destruction

Drake, C. G. *et al.* (2013) Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2013.208

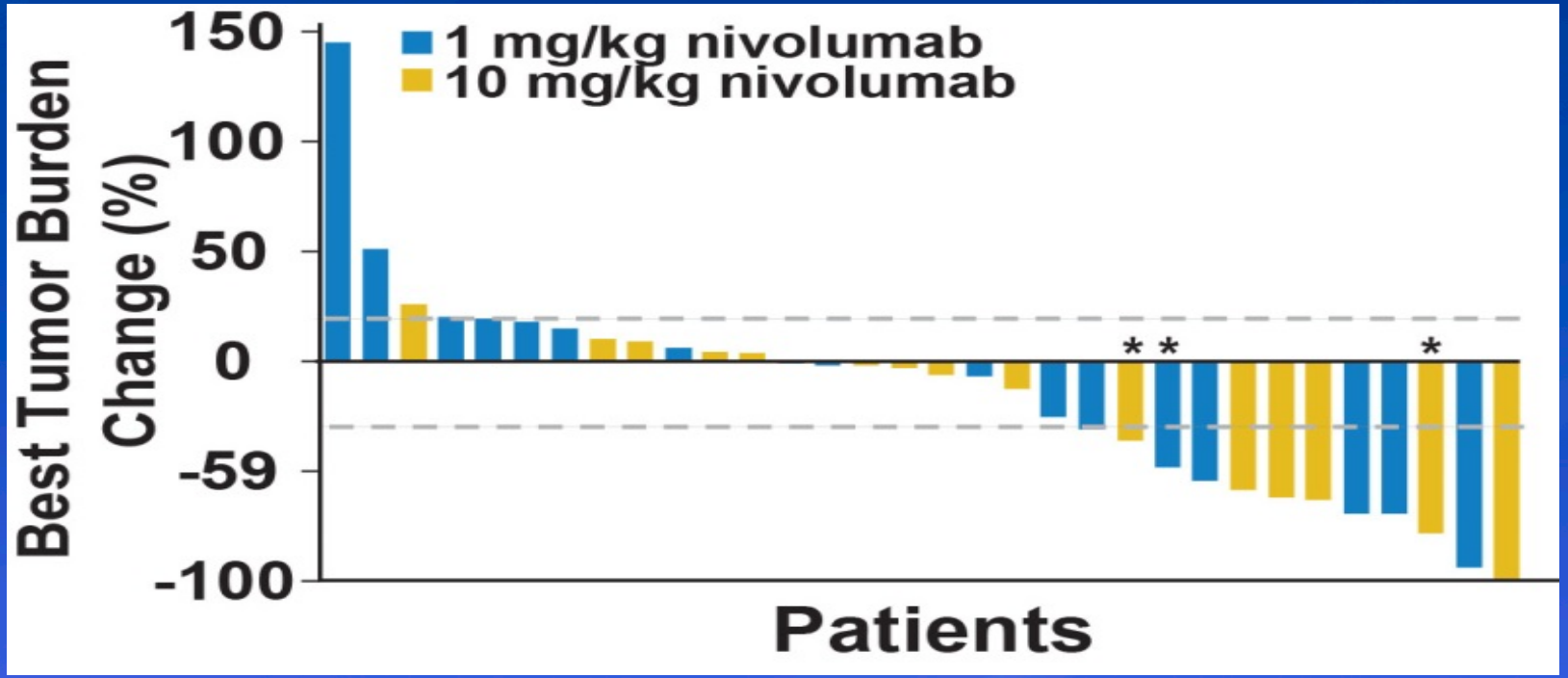
Phase I dose-escalation of nivolumab in cohort-expansion of metastatic RCC

Advanced/ metastatic RCC

1,3 or 10 mg/kg nivolumab IV Q2 weeks (*N*=34)

McDermott DF, et al. (2015) Survival, Durable Response, and Long-Term Safety in Patients with Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab. JCO June 2015.

Nivolumab has an objective response rate of 29% in metastatic RCC with prior treatment



McDermott DF, et al. (2015) Survival, Durable Response, and Long-Term Safety in Patients with Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab. JCO June 2015.

Phase I of MPDL3280A in cohort-expansion of metastatic urothelial carcinoma

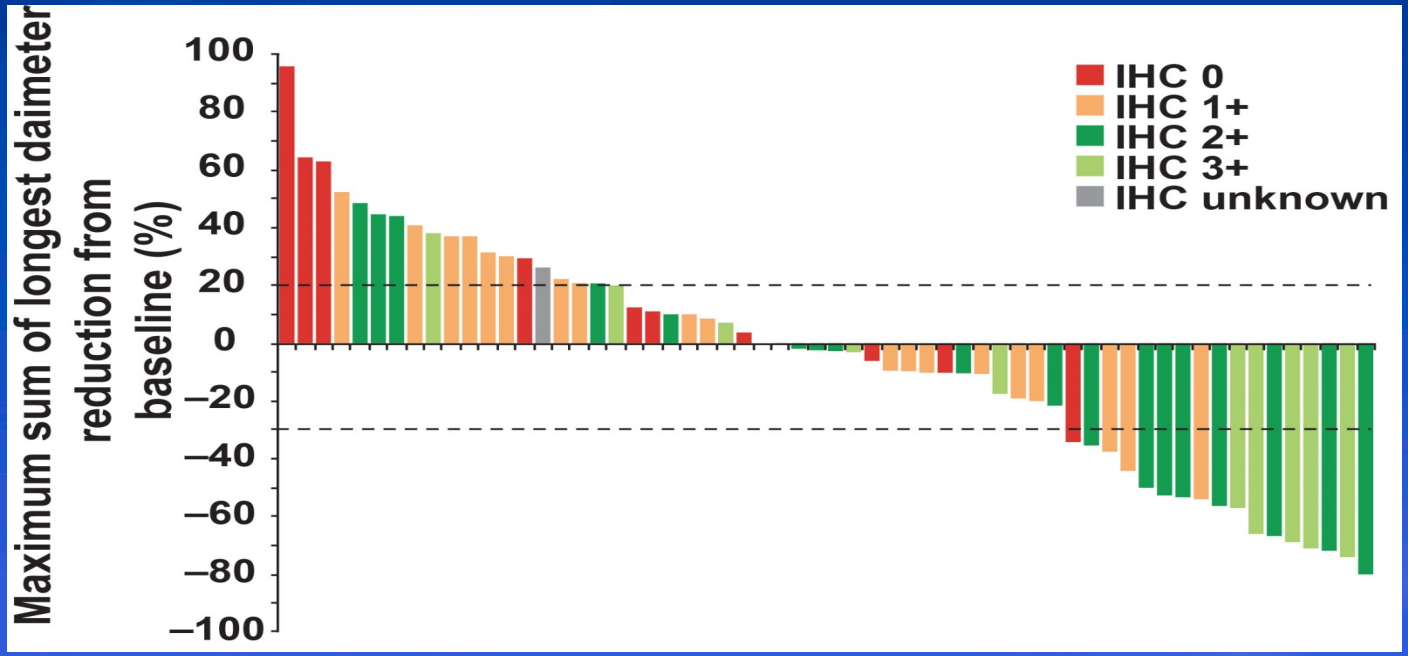
Metastatic urothelial

Initial cohort restricted to IHC 2+/3+ (≥5%), then expanded to all pts

15 mg/kg MPDL3280A IV Q3 weeks (*N*=68)

T Powles *et al. Nature* **515**, 558-562 (2014) doi:10.1038/nature13904

MPDL3280 has an objective response rate of 11-43% in metastatic urothelial with prior treatment



- ORR for IHC2/3 (43%) and IHC0/1 (11%)
- 18.5% with CrCl <60
- Historical ORR of 27.7 for pemetrexed (Sweeney C. JCO)

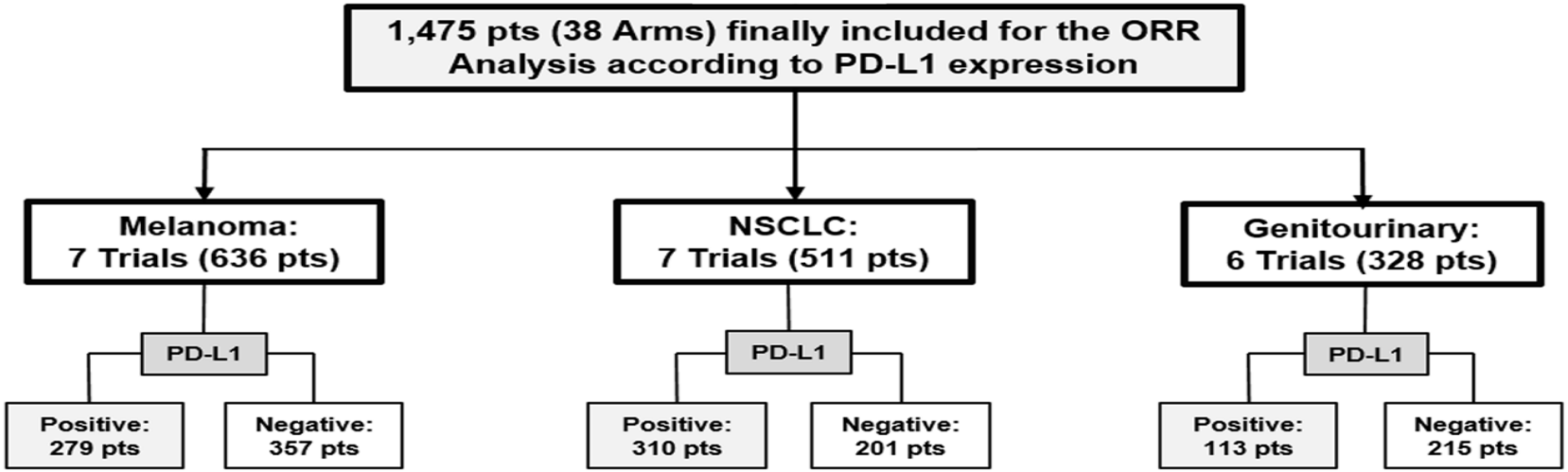
MAYO CLINIC

T Powles *et al. Nature* **515**, 558-562 (2014) doi:10.1038/nature13904

What is the predictive role of PD-L1 expression on genitourinary cancers?

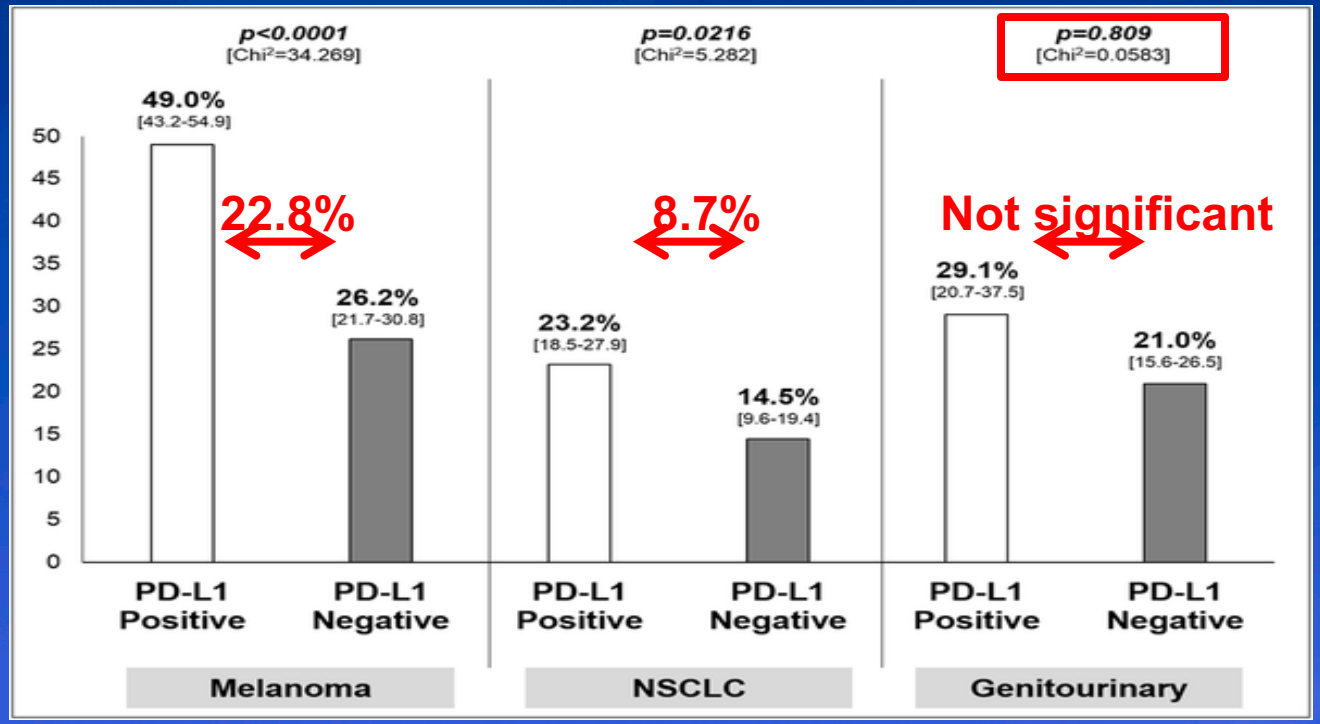
Literature Search using keywords and bibliographies of relevant articles (n=4,755):
- Database: PubMed (n=2,930)
- Meeting Abstracts: ASCO (n=1,060), ESMO (n=483), WLCC (n=170), CMSTO (n=112)

Limits: English-language articles only



Carbognin L, et al. (2015) Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1):PLoS ONE 10(6): e0130142.

The overall response rate is higher in PD-L1 (+) melanomas and NSCLC, but was not linked to IHC intensity in bladder/kidney tumors



- PD-L1 (+) expression cut-off ≥ 1% or 5%
- Includes trials of pembroluzimab, nivolumab, and MPDL3280A

Carbognin L, et al. (2015) Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1):PLoS ONE 10(6): e0130142.

Key points

- An age of onset of ≤ 46 may be used as a guide for genetics referral even in the absence of extrarenal manifestations
- The presence of a hereditary RCC syndrome is associated with recurrent and multiple tumors in a lifetime
- Immune checkpoint blockade has activity in phase I clinical trials for metastatic RCC and urothelial carcinoma
- Meta-analyses suggest that PD-L1 IHC negative GU cancers respond to immune checkpoint blockade

Conclusions

- Patients 45 or younger with diagnosis of RCC should be considered for genetic testing
- Primary genetic profiling of renal cell carcinoma is unlikely to provide information that will alter therapeutic approaches at this time
- Many of the key genetic information can be inferred or obtained from IHC studies for additional mutations
- Use of CAMLs being developed and refined

Conclusions

- CAR-T cell therapy is the hot topic now
  - We may find a combination of “immuno targeting”with a patient derived cells the next frontier

- PDL1/PD1
  - Ultimately found its origin in RCC
  - Will see more use of medications in the future

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Assoc. Professor Pathology
Mayo Clinic Arizona